MONASH University

Facilitation of Atrial Fibrillation screening by risk assessment using clinical, echocardiographic and strain variables.

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MBBS/B Med Sci/MMed

A thesis submitted for the degree of Doctor of Philosophy at

Monash University in 2020

Baker Heart and Diabetes Institute

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Supervision

The research work presented in this thesis was supervised by:

Primary supervisor

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Abstract

Atrial Fibrillation (AF) is increasing in incidence and prevalence and places a significant burden on the healthcare system. AF screening may be associated with reduced complications and hospitalisations because early diagnosis allows for risk factor modification and initiation of anticoagulation. However, the potential risks include false positives from screening, patient anxiety and potential healthcare costs. The success of AF screening is dependent on improved risk assessment. The aims of the research were to; 1/ determine the most appropriate monitoring technology to use for AF screening, 2/ identify factors that would help predict risk of AF (and thereby selection for screening), 3/ determine the use of previous imaging data (including left atrial (LA) strain) for AF risk stratification and 4/ assess whether this echo-guided AF screening strategy was cost-effective compared to a community-wide approach..

This thesis is based on results from a community cardiac screening program which was conducted in Tasmania (Tas-ELF) and Victoria (Vic-ELF) of individuals ≥65 years with 1 or more risk factor for AF or heart failure (HF). Patients with previous AF, HF or mitral-valve disease were excluded. AF risk was determined by the CHARGE-AF score. Functional capacity was assessed using the six-minute walk test and quality of life (QoL) scores (Duke Activity Status Index, Minnesota Living with Heart Failure score, Charlson-Index and EuroQoL5D Visual-Analog Scale). Regional SES was assessed using the SEIFA indices. A transthoracic echocardiogram (TTE) was performed. LA/LV strain analysis was performed offline using a third-party software program. Patients were followed up for incident AF during the follow up period (clinically diagnosed AF from specialists/GP and AF screening performed by a single lead ECG device–5x 60 sec recordings for 2 weeks). The analysis performed included:

1/ A systematic review/meta-analysis to compare AF detection rates between single lead ECG monitoring devices and Holter monitoring.

2/ Studies designed to better understand which groups in the community should be considered for screening;

a) Cross-sectional studies to assess the association between AF risk and functional capacity, and between the three components of LA strain.

b) Cross-sectional study to observe the relationship between BP and LA function to determine the most sensitive BP parameter to assess LA dysfunction.
c) Longitudinal study to determine the association between incident AF and regional social determinants of health,

3/ Evaluation of LA strain as a predictor of incident AF. Longitudinal studies to determine the association between incident AF and LA/LV strain and LA mechanical dispersion.

4/ A decision analytic model to compare the cost-effectiveness of an echo-guided AF screening model to an age-based screening strategy.

5/ Feasibility and optimal pathway to screening. Cross sectional study based on questionnaires sent to a pilot group of 180 participants addressing some of the practical issues related to AF screening.

The highlights of this research are; 1/ the utility of single lead ECG devices used for AF detection, 2/ AF risk is associated with reduced exercise capacity and socioeconomic deprivation, 3/ LA pump strain is independent of LV function and may provide incremental information about LA function, 4/ CBP may be more closely related with LV/LA function than brachial BP and may help identify patients at earlier disease stages of the path to AF, 5/ LA strain and LA mechanical dispersion are associated with AF and 6/ targeting patients who have had a previous echocardiogram is a cost-effective method for AF screening.

In conclusion, selection is important in AF screening, and should combine clinical, socioeconomic and imaging markers of risk. Many patients at risk of AF have echocardiograms for other reasons, and LA and LA mechanical dispersion are useful markers for AF risk assessment. Practical issues such as patient compliance and cognition must be addressed for AF screening programs to be successful.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature:

Print Name: Dr. Satish Ramkumar

Date: 12 April 2020

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 5 original papers published in peer reviewed journals and 4 submitted publications. The core theme of the thesis is facilitation of atrial fibrillation screening using clinical and echocardiographic variables including LA strain. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Baker Heart and Diabetes Institute under the supervision of Prof. Thomas Marwick.

(The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research).

Chapter 10 of this thesis is a narrative describing a novel imaging parameter which can be used in AF risk assessment. In the case of chapters 3-12 (excluding chapter 10) my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status *(published, in press, accepted or returned for revision, submitted)*	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
3	*Ramkumar et. al. Atrial fibrillation detection using single lead portable electrocardiographic monitoring: A systematic review and meta-analysis.*	Published *BMJ Open* 2018	• 70% • Involved in project concept and design. • Performed literature search and analysis of individual studies • Statistical analysis, manuscript preparation and editing	1. Nitesh Nerlekar – involved with statistical analysis and manuscript preparation - 5% 2. Daniel D'Souza – involved with literature search and analysis of induvial studies - 5% 3. Derek Pol – involved with data analysis and manuscript preparation and editing - 5% 4. Johnathan Kalman – involved in manuscript preparation and editing - 5% 5. Thomas Marwick – developed project concept, involved in statistical analysis, manuscript preparation and editing - 10%	Nitesh Nerlekar – Y Daniel D'Souza – N Derek Pol – N Jonathan Kalman – N Thomas – Marwick - N
4	*Ramkumar et. al. Relation of Functional Status to Risk of Development of Atrial Fibrillation.*"	Published *Am J Cardiol* 2017	• 65% • Involved in project design. • Involved with data analysis, manuscript	1. Hong Yang – involved in data analysis and manuscript editing - 5% 2. Ying Wang – involved in data analysis and manuscript editing - 5%	Hong Yang – N Ying Wang – N Mark Nolan – N Kazuaki Negishi – N

			preparation and editing	3. Mark Nolan – involved in data analysis and manuscript editing - 5% 4. Kazuaki Negishi – involved in data analysis and manuscript editing - 5% 5. Prashanthan Sanders – involved with manuscript preparation and editing - 5% 6. Thomas Marwick – developed project rationale. Involved in data analysis, manuscript preparation and editing - 10%	Prashanthan Sanders – N Thomas Marwick - N
5	*Ramkumar et. al. Association between low socio-economic status and risk of incident atrial fibrillation.*	Published *IMJ* 2019	• 60% • Involved in project design and patient recruitment. • Involved with data analysis, manuscript preparation and editing	1. Ayame Ochi – involved in patient recruitment, data collection and analysis and manuscript editing – 5% 2. Hong Yang – Performed echocardiograms. Involved in data collection, patient reviews, data analysis and manuscript editing - 5% 3. Nitesh Nerlekar – Involved in data and statistical analysis as well as manuscript editing - 5% 4. Nicholas D'Elia – Involved in data collection, patient reviews, data analysis and manuscript editing - 4% 5. Elizabeth Potter – Involved in data collection, patient reviews, data analysis and manuscript editing - 2% 6. Isabella Murray – Involved in data collection, ECG analysis, data analysis and manuscript editing - 2% 7. Nishee Nattraj – Involved in data collection, ECG analysis, data	Ayame Ochi – N Hong Yang – N Nitesh Nerlekar – Y Nicholas D'Elia – N Elizabeth Potter – Y Isabella Murray – N Nishee Nattraj – N Ying Wang – N Thomas Marwick - N

				analysis and manuscript editing - 2% 8. Ying Wang – Involved in data collection, patient reviews, data analysis and manuscript editing - 5% 9. Thomas Marwick – Developed project concept. Involved in study design, data analysis, manuscript preparation/editing and overall project supervision - 10%	
6	*Ramkumar et. al. Association of the Active and Passive Components of Left Atrial Deformation with Left Ventricular Function.*	Published *JASE* 2017	• 65% • Involved in project design. • Involved in strain analysis and data collection. • Involved with data analysis, manuscript preparation and editing	1. Hong Yang – Performed echocardiograms. Involved in data collection, patient reviews, data analysis and manuscript editing - 5% 2. Ying Wang – Involved in data collection, patient reviews, data analysis and manuscript editing - 4% 3. Mark Nolan – Involved with patient reviews and in manuscript editing - 3% 4. Tomoko Negishi – Performed strain analysis and involved in data collection - 3% 5. Kazuaki Negishi – involved with patient review and manuscript editing - 5% 6. Thomas Marwick – Developed project concept. Involved in study design, data analysis, manuscript preparation/editing and overall project supervision - 15%	Hong Yang – N Ying Wang – N Mark Nolan – N Tomoko Negishi – N Kazuaki Negishi – N Thomas Marwick – N

7	*The Importance of Calibration Method in Determining the Association between Central Blood Pressure with Left Ventricular and Left Atrial Strain.*	Under Review by *Am J Hypertension*	• 60% • Involved in project design. • Involved in strain analysis and data collection. • Involved with data analysis, manuscript preparation and editing	1. Hong Yang – Performed echocardiograms. Involved in data collection, patient reviews, data analysis and manuscript editing - 5% 2. Ying Wang – Involved in data collection, patient reviews, data analysis and manuscript editing - 4% 3. Ynez Howlett-Jansen – Involved with patient reviews and in data collection - 2% 4. Mark Nolan – Involved with patient reviews and in manuscript editing - 2% 5. Tomoko Negishi – Performed strain analysis and involved in data collection - 2% 6. James Sharman – Involved with project design, data analysis and manuscript editing - 5% 7. Thomas Marwick – Involved in study design, data analysis, manuscript preparation/editing and project supervision - 10% 8. Kazuaki Negishi – Developed project concept. Involved in study design, data analysis, manuscript preparation/editing and project supervision - 10%	Hong Yang – N Ying Wang – N Ynez Howlett-Jansen – N Mark Nolan – N Tomoko Negishi – N James Sharman – N Thomas Marwick – N Kazuaki Negishi - N
8	*Ramkumar et. al. "Echocardiographic risk assessment to guide screening for atrial fibrillation."*	Published *JASE* 2019	• 60% • Involved in project design. • Involved in strain analysis and data collection.	1. Ayame Ochi – Involved in patient recruitment, data collection and manuscript editing - 5% 2. Hiroshi Kawakami – Performed strain analysis. Involved in data analysis and manuscript editing - 5% 3. Hong Yang – Performed echocardiograms. Involved in data	Ayame Ochi – N Hiroshi Kawakami – N Hong Yang – N Elizabeth Potter – Y Nicholas D'Elia – N

			• Involved with data analysis, manuscript preparation and editing	collection, patient reviews, data analysis and manuscript editing - 3% 4. Elizabeth Potter – Involved in patient follow up, data collection and manuscript editing - 3% 5. Nicholas D'Elia – Involved in patient recruitment, data collection and manuscript editing - 2% 6. Tomoko Negishi – Performed strain analysis and involved in data collection - 2% 7. Kazuaki Negishi – involved with patient review and manuscript editing - 5% 8. Thomas Marwick – Developed project concept. Involved in study design, data analysis, manuscript preparation/editing and overall project supervision - 15%	Tomoko Negishi – N Kazuaki Negishi - N Thomas Marwick - N
9	*Impact of disease stage on the performance of strain markers in the prediction of atrial fibrillation.* *This project also relates in part to another published manuscript* Kawakami, H, Ramkumar S, Pathan F, Wright L, Marwick TH. *"Use of echocardiography to stratify the risk of atrial fibrillation: Comparison of left atrial and ventricular strain."* European Heart	Under review by *JASE*	• 58% • Involved in project design. • Involved in strain analysis and data collection. • Involved with data analysis, manuscript preparation and editing	1. Faraz Pathan – involved in project design, data collection/analysis. Involved in manuscript editing - 7% 2. Hiroshi Kawakami –Performed strain analysis. Involved in data analysis and manuscript editing - 18% 3. Ayame Ochi – involved in patient recruitment and data collection - 3% 4. Hong Yang – Performed echocardiograms. Involved in data collection, patient reviews and data analysis - 2% 5. Elizabeth Potter – Involved in patient follow up, data collection and manuscript editing - 2%	Faraz Pathan – N Hiroshi Kawakami – N Ayame Ochi – N Hong Yang – N Elizabeth Potter – Y Thomas Marwick – N

	Journal – Cardiovascular Imaging 2020 Apr 1;21(4):399-407. DOI: https://doi.org/10.1093/ehjci/jez240			6. Thomas Marwick – Developed project concept. Involved in study design, data analysis, manuscript preparation/editing and overall project supervision - 10%	
11	*Ramkumar et. al. Cost-effectiveness of Screening for Paroxysmal Atrial Fibrillation in Patients undergoing Echocardiography*	Under Review by *JASE*	• 68% • Developed project design • Designed markov model • Involved in data analysis, manuscript preparation and editing	1. Hiroshi Kawakami – involved with data analysis and manuscript editing - 3% 2. Edmond Wong – involved with literature review and data collection - 2% 3. Mark Nolan – involved with data collection and manuscript editing - 2% 4. Thomas Marwick – Developed project concept. Involved in study design, data analysis, manuscript preparation/editing and project supervision - 25%	Hiroshi Kawakami – N Edmond Wong – N Mark Nolan – N Thomas Marwick - N
12	*Atrial Fibrillation Screening – Practical considerations and the impact on recruitment site on detection rates.*	Under Review by *Eur J Prev Cardiol*.	• 60% • Developed project rationale • Involved in data analysis and manuscript preparation/editing	1. Ayame Ochi – Involved in patient recruitment, data collection and manuscript editing - 10% 2. Hong Yang – Performed echocardiograms. Involved in data collection, patient reviews, data analysis and manuscript editing - 5% 3. Elizabeth Potter – Involved in patient follow up, data collection and manuscript editing - 5% 4. Thomas Marwick – Developed project concept. Involved in study design, data analysis, manuscript preparation/editing and overall project supervision - 20%	Aymae Ochi – N Hong Yang – N Elizabeth Potter – Y Thomas Marwick - N

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: **Date:** 12 April 2020

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature: **Date:** 12 April 2020

Acknowledgements

This research was kindly supported by a Research Training Program stipend from Monash University from 2017-2018 and from the National Heart Foundation of Australia, through their Health Professional Scholarship from 2018. I would like to thank the support of Avant who supported me with a Doctor in Training scholarship in 2017 and the Baker Heart and Diabetes Institute who supported me with a Bright Sparks top up scholarship and travel grants. I would also like to thank the Cardiac Society of Australia and New Zealand and the School of Public Health and Preventative Medicine who have provided me with travel grants to fund conference travel.

I would like to acknowledge the work of the staff involved in the Tas-ELF and Vic-ELF studies who have helped me with my PhD. Dr Faraz Pathan and Dr Kaz Negishi who spent time teaching me strain analysis. Thank you to Prof. Peter Kistler and Prof. John Kalman for helping me with my research projects. I would like to thank Hilda Yang, Ying Wang and Leah Wright, with whom I spent a lot of time doing outpatient clinics and who supported me throughout my PhD. Jasmine Pritchard has been a tremendous support throughout my PhD and I fondly remember all the times we spent travelling to clinics and to CT scanning whilst at the Baker. I acknowledge the work of Ayame Ochi and Nic D'Elia who helped me setting up the AF screening study and helped with tracking the ECG devices. In Melbourne the staff at the Baker Heart and Diabetes Institute have helped me a great deal with my research. A big thank you to Lisa Riddell who co-ordinated posters for conferences and my appointments with Prof. Marwick and was a great support throughout. I would also like to acknowledge the staff at Monash Heart and my clinical supervisor A/Prof. Arthur Nasis who have always been supportive of my research commitments whilst I have completed my clinical cardiology training.

Thank you to my parents, in-laws, my sister Sudha and brother in law Ajay for always being supportive of my career, helping me deal with stress and helping me conquer the challenges during my PhD. To my wife Sudha who has been incredibly supportive of my training and career, thank you for putting up

with my late nights, stress, research discussions and grumpy moods! I hope to support you in your PhD research as well as you have done for me.

Finally, to my supervisor Prof. Marwick who has been my mentor and guided me throughout the past 4 years, thank you for giving me the opportunity to work with you and learn about medical research. I still remember fondly our first meeting in Hobart. It gave me a first real taste of cardiology, a career which I hope will continue for many years to come. You have always been supportive and have inspired me throughout my PhD. I hope in the future to use the skills I have learnt during my PhD.

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Abbreviations

ACE – Angiotensin Converting Enzyme

ACE-I - Angiotensin Converting Enzyme Inhibitors

AF – Atrial Fibrillation

AgeScreen – Age based screening

ANOVA – Analysis of Variance

ARB – Angiotensin Receptor Blocker

ARIC – Atherosclerosis Risk in Communities

AUC – Area under the Curve

BMI – Body Mass Index

BP – Blood Pressure

BSA – Body Surface Area

CART - Classification and Regression Tree

CBP – Central Blood Pressure

CHARGE-AF – Cohorts for Heart and Aging Research in Genomic Epidemiology – Atrial Fibrillation

DASI – Duke Activity Status Index

DBP – Diastolic Blood Pressure

DOAC – Direct oral anticoagulant

ECG – Electrocardiogram

EQ-VAS – EuroQoL 5D Visual Analog Scale

GCS – Global Circumferential Strain

GLS – Global Longitudinal Strain

HF – Heart Failure

HFpEF – Heart Failure with Preserved Ejection Fraction

HFrEF – Heart Failure with Reduced Ejection Fraction

HR – Hazard Ratio

IAD – Index of Advantage/Disadvantage

ICER – Incremental Cost-Effectiveness Ratio

IEO – Index of Education/Occupation

IER – Index of Economic Resources

ImagingScreen – Imaging based screening

LA – Left Atrium

LARS – Left atrial reservoir strain

LAVi - LA volume indexed to body surface area

LV – Left Ventricle

LVEF – Left Ventricular Ejection Fraction

LVH – Left Ventricular Hypertrophy

LVM – Left Ventricular Mass

MAP – Mean Arterial Pressure

MLHF – Minnesota Living with Heart Failure Score

PP – Primary Prevention

QALY – Quality adjusted life years

ROC – Receiver Operator Characteristic

SBP – Systolic Blood Pressure

SD-TPS – Standard Deviation of the Time of Peak Strain

SEIFA – Socio-Economic Indices for Areas

SES – Socioeconomic status

SMWT – Six Minute Walk Test

SP – Secondary Prevention

T2DM – Type II Diabetes Mellitus

Tas-ELF – Tasmanian AF Screening Cohort

TTE – Transthoracic echocardiography

USD – United States of America dollars

Vic-ELF – Victorian AF Screening Cohort

WTP – Willingness to Pay

Publications relating to thesis

Published/accepted/submitted papers to peer-reviewed journals

Chapter	Publication	Study Design	Status
1. Introduction	*N/A*	-	-
2. Methods	*N/A*	-	-
3. Deciding on the most appropriate technology for screening	*Ramkumar et. al. Atrial fibrillation detection using single lead portable electrocardiographic monitoring: A systematic review and meta-analysis. BMJ Open 2018;8;e024178. DOI: http://dx.doi.org/10.1136/bmjopen-2018-024178*	Systematic Review	Published BMJ Open 2018
4. Selection of patients for AF screening	*Ramkumar et. al. Relation of Functional Status to Risk of Development of Atrial Fibrillation." Am J Cardiol. 2017;119;572-578. DOI: http://dx.doi.org/10.1016/j.amjcard.2016.10.043*	Cross Sectional	Published Am J Cardiol 2017
5. Selection of patients for AF screening – importance of regional SES	*Ramkumar et. al. Association between low socio-economic status and risk of incident atrial fibrillation. IMJ 2019 Oct;49(10);1244-51 DOI: https://doi.org/10.1111/imj.14214*	Longitudinal	Published IMJ 2019
6. Using imaging to assess LA function which may be used to predict AF risk	*Ramkumar et. al. Association of the Active and Passive Components of Left Atrial Deformation with Left Ventricular Function. JASE. 2017 Jul;1;30(7):659-66.* DOI: http://dx.doi.org/10.1016/j.echo.2017.03.014	Cross Sectional	Published JASE 2017
7. Determinants of LA dysfunction – identifying patients at early disease stages	*The Importance of Calibration Method in Determining the Association between Central Blood Pressure with Left Ventricular and Left Atrial Strain.*	Cross Sectional	Currently under review by Am J Hypertension
8. Determination of appropriate	*Ramkumar et. al. "Echocardiographic risk assessment to guide screening for atrial fibrillation."* JASE. 2019	Longitudinal	Published JASE 2019

	patients for AF screening	Oct:32(10):1259-1257. *DOI: https://doi.org/10.1016/j.echo.2019.07.003*		
9.	Clinical use of LA/LV strain in AF prediction	*Impact of disease stage on the performance of strain markers in the prediction of atrial fibrillation.*	Cohort	Currently under review by JASE
10.	Other advanced imaging markers of AF risk	*Kawakami H, Ramkumar S et. al. Left atrial mechanical dispersion assessed by strain echocardiography as an independent predictor of new onset atrial fibrillation: A case-control study. JASE. 2019 Oct:32(10):1268-1276. DOI: https://doi.org/10.1016/j.echo.2019.06.002*	Case-control	Published JASE 2019
11.	Selection of candidates for a screening strategy for AF based on opportunistic use of data from previous imaging	*Ramkumar et. al. Cost-effectiveness of Screening for Paroxysmal Atrial Fibrillation in Patients undergoing Echocardiography*	Cost Effectiveness Analysis	Currently under review by JASE
12.	Determining the most appropriate site for AF screening and practical aspects to AF screening	*Atrial Fibrillation Screening – Practical considerations and the impact of recruitment site on detection rates.*	Longitudinal	Currently under review by Eur J Prev Cardiol
13.	Conclusion	*N/A*	-	-

Other publications related to PhD research (not part of thesis)

1. Kawakami, H, Ramkumar S, Pathan F, Wright L, Marwick TH. *"Use of echocardiography to stratify the risk of atrial fibrillation: Comparison of left atrial and ventricular strain."* European Heart Journal – Cardiovascular Imaging 2020 Apr 1;21(4):399-407. DOI: https://doi.org/10.1093/ehjci/jez240

2. Haji K, Wong C, Wright L, Ramkumar S, Marwick TH. *"Left Atrial Strain Performance and its Application in Clinical Practice."* JACC: Cardiovascular Imaging. 2019 Jan 16:2860. DOI: https://doi.org/10.1016/j.jcmg.2018.11.009

3. Potter EL, Ramkumar S, Kawakami H, Yang H, Wright L, Negishi T, Marwick TH. *"Association of asymptomatic diastolic dysfunction assessed by left atrial strain with incident heart failure." In Press.* JACC: Cardiovascular Imaging.

Abstracts/ Presentations at national or international conferences

AHA Scientific Sessions 2019

Oral Presentation - Ramkumar S, Kawakami H, Wong E, Nolan M, Marwick TH. "Cost-effectiveness of screening for paroxysmal atrial fibrillation in patients undergoing echocardiography."

ESC Congress 2019

Moderated Poster Prize - Ramkumar S, Pathan F, Kawakami H, Ochi A, Yang H, Potter EL, Marwick TH. "Impact of disease stage on performance of strain markers for prediction of atrial fibrillation."

Poster Presentation - Potter EL, Ramkumar S, Yang H, Kawakami H, Negishi K, Marwick TH. "Preclinical diastolic dysfunction assessed by left atrial strain and association with incident heart failure."

Oral Presentation - Kawakami H, Ramkumar S, Pathan F, Wright L, Marwick TH. "Incremental benefit of left ventricular global longitudinal strain over clinical and left atrial parameters for predicting new onset atrial fibrillation."

CSANZ Annual Scientific Sessions 2019

Finalist Cardiac Imaging Prize (oral) - Ramkumar S, Pathan F, Kawakami H, Ochi A, Yang H, Potter EL, Marwick TH. "Impact of disease stage on performance of strain markers for prediction of atrial fibrillation."

Mini-Oral Presentation - Kawakami H, Ramkumar S, Pathan F, Wright L, Marwick TH. "Incremental benefit of left ventricular global longitudinal strain over clinical and left atrial parameters for predicting new onset atrial fibrillation."

Poster Presentation - Ball J, Marwick TH, Kalman J, Ramkumar S, Yiallourou S, Carrington M. "Effectiveness of a community-based AF screening program: A pilot study."

AHA Scientific Sessions 2018

Poster Presentation - Ramkumar S, Ochi A, Yang H, Potter EL, D'Elia N, Murray IC, Nattraj N, Negishi T, Negishi K, Marwick TH. *"The role of clinical, social and echocardiographic risk assessment prior to screening for atrial fibrillation."*

Poster Presentation - Kawakami H, Ramkumar S, Wright L, Yang H, Negishi K, Marwick TH. *"Left atrial mechanical dispersion assessed by strain echocardiography as an independent predictor of new onset atrial fibrillation: A case-control study."*

CSANZ Annual Scientific Sessions 2018

Mini-Oral Presentation - Ramkumar S, Yang H, Wang Y, D'Elia N, Ochi A, West H, Nolan M, Negishi K, Marwick TH. *"Association between low socio-economic status and risk of incident atrial fibrillation."*

Poster Presentation - Ramkumar S, Ochi A, Yang H, Potter EL, D'Elia N, Murray IC, Nattraj N, Negishi T, Negishi K, Marwick TH. *"The role of clinical, social and echocardiographic risk assessment prior to screening for atrial fibrillation."*

Poster Presentation - Ramkumar S, Ochi A, Yang H, Potter EL, D'Elia N, Murray IC, Nattraj N, Marwick TH. *"The Association between subclinical left ventricular dysfunction and atrial fibrillation."*

Poster Presentation - Ramkumar S, Ochi A, Potter EL, Yang H, D'Elia N, Murray IC, Nattraj N, Marwick TH. *"Regional variation of unrecognised atrial fibrillation in the community."*

Mini-Oral Presentation - Potter EL, Ramkumar S, Yang H, Marwick TH. *"Left atrial strain and incident heart failure: Validation of left atrium strain defined diastolic dysfunction grade and comparison with current American Society of Echocardiography guidelines."*

AHA Scientific Sessions 2017

Mini-Oral Presentation - Ramkumar S, Yang H, Wang Y, D'Elia N, Ochi A, West H, Nolan M, Negishi K, Marwick TH. *"Association between low socio-economic status and risk of incident atrial fibrillation."*

ESC Congress 2017

Poster Presentation - Ramkumar S, Yang H, Middeldorp M, Sanders P, Marwick TH. *"Use of left atrial strain for risk stratification in atrial fibrillation with low clinical thromboembolic risk."*

Poster Presentation - Ramkumar S, Yang H, Wang Y, Howlett-Jansen Y, Nolan M, Marwick TH, Negishi K. *"Is the calibration method for central blood pressure important in assessing the association between central blood pressure with LV and left atrial strain."*

Poster Presentation - Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Marwick TH. *"Prediction of heart failure and atrial fibrillation using the CHARGE-AF and ARIC risk scores."*

CSANZ Annual Scientific Sessions 2017

Mini-Oral Presentation - Ramkumar S, Yang H, Wang Y, D'Elia N, Ochi A, West H, Nolan M, Negishi K, Marwick TH. *"Left atrial and left ventricular strain in the prediction of atrial fibrillation in a community cohort with risk factors."*

Poster Presentation - Ramkumar S, Yang H, Middeldorp M, Sanders P, Marwick TH. *"Left atrial strain to risk stratify a group of patients with atrial fibrillation with low clinical thromboembolic risk."*

Poster Presentation - Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Marwick TH. *"Prediction of heart failure and atrial fibrillation using the CHARGE-AF and ARIC risk scores."*

Poster Presentation - Ramkumar S, Yang H, Wang Y, Howlett-Jansen Y, Nolan M, Marwick TH, Negishi K. *"Is the calibration method for central blood pressure important in assessing the association between central blood pressure with LV and left atrial strain."*

Poster Presentation - Ramkumar S, Ochi A, D'Elia N, West H, Marwick TH. *"The challenges involved in implementing a community screening program to detect subclinical atrial fibrillation."*

ASE Annual Scientific Meeting 2017

Poster Presentation - Ramkumar S, Yang H, Wang Y, D'Elia N, Ochi A, West H, Nolan M, Negishi K, Marwick TH. *"The role of left atrial and ventricular function in prediction of atrial fibrillation."*

***ACC Scientific Sessions* 2017**

Poster Presentation - Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Marwick TH. *"Left atrial function and role in prediction of heart failure."*

Poster Presentation - Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Marwick TH. *"Independent association of atrial mechanics with risk of incident atrial fibrillation."*

AHA Scientific Sessions 2016

Poster Presentation - Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Marwick TH. *"Comparing the prediction of heart failure symptoms using a clinical score assessing risk of atrial fibrillation (CHARGE-AF) to traditional heart failure risk scores."*

Poster Presentation - Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Marwick TH. "*Reduced functional capacity: An independent risk predictor of atrial fibrillation."*

Poster Presentation - Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Marwick TH. *"Left Ventricular mechanics as an independent risk predictor of atrial fibrillation."*

Poster Presentation - Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Marwick TH. *"Is atrial strain just a mirror image of ventricular strain?"*

CSANZ Annual Scientific Sessions 2016

Oral Presentation - Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Marwick TH. *"Comparing the prediction of heart failure symptoms using a clinical score assessing risk of atrial fibrillation (CHARGE-AF) to traditional heart failure risk scores."*

Mini-Oral Presentation - Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Marwick TH. "*Reduced functional capacity: An independent risk predictor of atrial fibrillation."*

Mini-Oral Presentation - Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Marwick TH. *"Left Ventricular mechanics as an independent risk predictor of atrial fibrillation."*

Structure of Thesis

Section I – AF Detection

Chapter 1 – provides a brief overview of the burden of AF, the benefits of early diagnosis and screening including the current gaps in disease management. There is also a review of AF risk assessment including the use of echocardiography. This section will introduce the concept of LA strain, the advantages and limitations and discuss potential clinical applications.

Chapter 2 – will review the methods of each individual study included in the thesis. This will include an overview of the patient population and the standard 2D echocardiographic assessment performed in the study. The techniques used to assess LA and LV strain using speckle tracking will also be discussed.

Chapter 3 – will investigate the most suitable monitoring method for AF screening. Screening requires a device which is cost-effective, highly sensitive and easy to use for patients. Traditional 12 lead ECG is inadequate for screening, given many patients may have brief episodes of AF, many of whom are asymptomatic. Therefore, single timepoint assessment will lack sensitivity. Implantable devices and pacemakers are invasive and cannot be used for screening. Traditional methods of screening have mainly involved Holter monitors which require electrodes to be in contact with the skin for the entire period of monitoring (usually 24-48 hrs). They are expensive and uncomfortable for patients. The improvement in technology has allowed the development of portable ECG monitoring devices which are able to capture single lead ECG traces for 30-60 seconds using finger contact with electrodes. They are potentially much easier to implement for mass screening and have been shown to be cost-effective. In this chapter we perform a systematic review and meta-analysis of studies which have used these portable ECG devices for AF screening compared with continuous (Holter) monitoring. The aim will be to identify if multiple intermittent monitoring using portable devices can replicate similar detection rates to continuous monitoring. This can then justify the use of portable monitoring devices for AF screening.

Section II – Assessing AF Risk

Chapter 4 – will investigate how to select patients for AF screening. There are several clinical risk factors for AF. However, when combined into a clinical risk score, they have poor discriminative ability. In this chapter the association between AF risk and reduced functional capacity will be studied. By identifying these novel risk factors, these can help identify patients at risk of developing AF, hence identifying those most appropriate for screening.

Chapter 5 – will investigate the rate of subclinical AF in a community cohort with risk factors and explore the association between regional SES and AF risk. Low SES has been associated with other diseases such as metabolic syndrome and coronary artery disease. However, the relation with AF has been not been well established. This link has important implications for AF screening as it can help target screening to individuals from areas at highest risk for AF, hence improving cost-effectiveness.

Section III – LA Strain

Chapter 6 – will investigate the role of LA strain in assessment of AF risk. There are several limitations with left atrial strain related to the currently available software algorithms and lack of consensus guidelines. Much of the criticism has surrounded the lack of incremental value of LA strain. Given the relationship between LA and LV function, it has been felt that LA strain merely reflects underlying LV function, thus does not add incremental clinical value. We investigate the association between the three components of LA strain with LV strain to determine if LA strain provides additional information of LA function, independent to LV function. This is an important finding as it may justify the use of LA strain in clinical practice, both as part of risk assessment and for prognostication.

Chapter 7 – will explore the association between BP and LA dysfunction. Hypertension is a common risk factor for AF and is associated with negative LA remodelling. There are different methods of assessing BP (brachial vs. central) with different calibration methods. Central (aortic) blood pressure (CBP) has been shown to be independently associated with

cardiovascular disease and may be more sensitive than brachial BP. In this chapter we assess the relationship between brachial BP/CBP with LA strain. Identifying the most sensitive non-invasive BP measurement associated with LA/LV dysfunction may be useful in patient selection, to aid in identifying patients at early disease stages on the path to AF.

Chapter 8 – will determine the most appropriate cohort suitable for AF screening based on clinical and echocardiographic risk assessment. Mass AF screening has the potential to be resource intense and feasibility may be affected if a suitable at-risk cohort is not identified for screening. In this chapter, we utilise both clinical and imaging parameters of risk assessment and determine how baseline risk assessment can be utilised to identify a suitable target cohort for mass screening.

Chapter 9 – will investigate the performance of strain parameters in the prediction of AF based on different disease stages. LA and LV strain have the potential to provide quantitative information about LA and LV function and hence can be potentially used in predicting those at risk of developing AF. However, the effectiveness of these parameters may be dependent on the underlying disease stage of patients. In this chapter we compare the association between LA and LV strain with incident AF in two different risk cohorts; cohort one is a healthy community cohort ≥65 years with 1 or more risk factor for AF. The second is a cohort of patients admitted to a tertiary hospital with a new stroke or transient ischaemic event. This chapter will investigate the utility of these parameters in risk assessment for AF and will aim to investigate if the impact of strain parameters varies according to the underlying patient disease stage.

Chapter 10 – will investigate the role of LA mechanical dispersion assessed using strain echocardiography in the prediction of new onset AF. LA fibrosis and remodelling have been associated in the pathogenesis of AF, contributing to LA enlargement. However, AF can occur in the absence of LA enlargement. LV fibrosis is associated with mechanical dispersion; however, this has not been well studied in AF. In this chapter we assess mechanical dispersion

in a group of patients with incident AF compared with an age and sex matched control group who remained in sinus rhythm.

Section IV – Feasibility of AF screening

Chapter 11 – will examine the cost-effectiveness of an echo guided AF screening strategy in comparison to an age-based mass screening approach. The main challenge with AF screening programs is addressing feasibility and cost-effectiveness. Recent evidence using single lead portable ECG devices have demonstrated cost-effectiveness however studies have used different screening populations. In this chapter we compare the cost-effectiveness of two main AF screening strategies. Firstly, a strategy of mass screening using single lead portable ECG devices based on an age-based cut-off of 65 years. The second strategy is targeted AF screening of patients recruited from an echo lab with imaging parameters of LA enlargement with either subclinical LV or LA dysfunction. A decision analytic model will be used to assess cost-effectiveness of both screening strategies.

Chapter 12 – will compare the difference in AF detection between community and GP based recruitment and the impact this may have in deciding on the most appropriate location for screening. We also include a brief qualitative discussion of some of the important practical considerations which must be considered when implementing screening programs including patient compliance, addressing patient anxiety, manual dexterity and cognition.

Section V - Conclusion

Chapter 13 –will be a summary of the main conclusions and discussion of limitations as well as topical areas of interest where future research is required.

Preface

Atrial fibrillation (AF), a common heart rhythm disorder is associated with significant morbidity and mortality (1). It is a leading cause of stroke and heart failure (HF) in the community (2). The incidence and prevalence of the condition is expected to rise in the future due to the rise of associated risk factors such as obesity and diabetes mellitus (3). AF can occur silently and is associated with incident ischaemic stroke (up to 10% of strokes). Currently we do not have an effective method for risk assessment, therefore many patients are diagnosed at later stages in the disease course. Early diagnosis allows for risk factor modification and initiation of anticoagulation which may be associated with a reduction in disease progression and complications. Given there are many patients who may develop "silent AF" and this may be associated with an increased risk of stroke, an effective screening strategy is required to identify these patients to allow for early initiation of medical therapy and risk factor modification to prevent complications as well as delaying progression to more advanced disease stages.

Increased LA size is commonly used as an echocardiographic measure of AF risk and continuous heart rhythm monitoring (Holter monitoring) is typically used to diagnose AF (4, 5). However, LA enlargement is typically observed in later disease stages and those at earlier disease stages of LA dysfunction with normal LA volumes may not be recognised. While a standard electrocardiogram (ECG) will identify chronic AF, it usually does not identify paroxysmal AF. Holter monitoring despite offering continuous monitoring, is often limited to 24-48 hours and has modest sensitivity for paroxysmal AF. AF can be either paroxysmal, persistent or permanent. Whilst it is easier to identify those with persistent/permanent AF, those with paroxysmal AF are harder to diagnose as they may not be in AF at the time of ECG recording. However, these patients have the same risk of stroke. Therefore, a systematic approach in identifying these patients is important so that they are recognised and treated prior to the onset of complications.

The main aim of this thesis is to identify those at risk of developing AF using a variety of clinical and imaging parameters and to investigate the feasibility of a mass screening program. Although AF is common, screening is most effective if it is targeted, so the first step is always risk evaluation. A number

of clinical risks for AF have been defined, and I will investigate the role of SES and physical activity as potential additional markers of AF risk assessment.

Many patients with AF risk factors, have echocardiograms performed for other indications, which may provide important information about future AF risk. I propose that echocardiographic parameters assessing LA function (strain analysis) can provide quantitative information which can be used for AF risk assessment and can be a more sensitive marker than LA volume. Assessment of LA strain using speckle tracking is now easily accessible using offline software programs. I will also seek to investigate the feasibility and utility of portable single lead electrocardiographic monitoring devices in the screening process for AF. The resulting observations will provide an appropriate method for AF risk assessment combining clinical, social and echocardiographic parameters which can be translated to a mass community AF screening program.

Aims

The aims of this thesis are:

1. Identify the most appropriate monitoring technology to use for AF screening
    a. compare the AF detection rates of single lead ECG monitoring devices to Holter monitoring.
2. Identify the most appropriate cohort for AF screening
    a. Determine the association between reduced functional capacity and AF risk.
    b. Determine the association between regional SES and AF.
    c. Examine how AF detection varies based on location of recruitment.
3. Examine the relationship between BP and LA function to identify the most sensitive BP marker associated with LA dysfunction
4. Examine the utility of advanced imaging techniques in AF risk prediction
    a. Determine the relationship between LA and LV strain to assess if LA pump strain provides incremental information.
    b. Determine if AF risk stratification can be performed using a combination of imaging parameters including LA and LV strain.
    c. Determine if LA mechanical dispersion is associated with AF.
    d. Examine how disease stage may influence the performance of strain markers in AF prediction.
5. Determine the feasibility and cost-effectiveness of AF screening
    a. Examine if an echo guided AF screening model is more cost effective than age-based mass screening programs.
6. Examine the practical challenges faced when implementing a mass screening program.

Section 1 – AF Detection

Chapter 1. Introduction

1 Introduction

1.1 Medical and Societal burden of AF

AF is the most common heart rhythm disorder of adults, resulting in significant morbidity and increased risk of mortality (1, 2). The lifetime risk of developing AF is approximately 1:4 and currently AF has prevalence of around 1% in the Australian population, with the risk increasing with age, up to 20% in patients ≥80 years (1, 2, 6, 7). AF is associated with increased risk of stroke, myocardial infarction, HF and is associated with reduced QoL and increased anxiety in patients (1, 2, 8-10).

AF places a tremendous strain on the health care system. In Australia, managing AF and its related complications costs at least $1 billion annually (11). In the US, costs related to AF have been estimated at between $6-25 billion (12). Rates of in-hospital AF diagnoses have increased and there has been a rise in hospitalisations related to AF (3, 13). AF is one of the leading causes of ischemic stroke increasing the risk 5-fold, AF related strokes being associated with increased mortality (6, 14, 15)

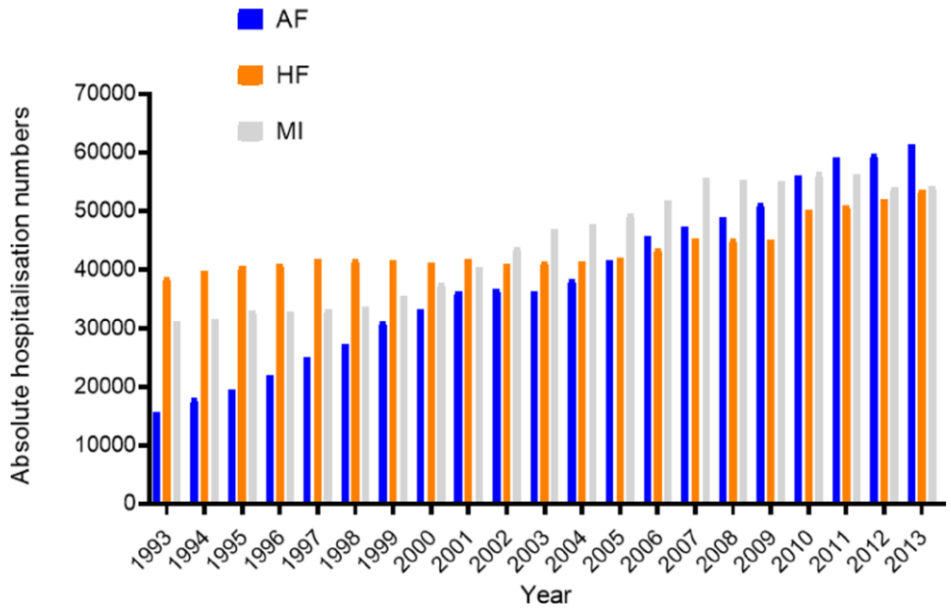


Figure 1.1 - Increasing rates of AF hospitalisations from 1993-2013 in Australia (from Gallagher et. al. 2019) (3).

A consistent rise in hospitalisations related to AF (in blue) is noted over the past 20 years in Australia. The rate of increase in hospitalisations related to AF is higher than for myocardial infarction over a similar time frame.

The AF epidemic continues to grow around the world, driven by an ageing population with increasing rates of associated risk factors such as diabetes and hypertension, accompanied by a sedentary lifestyle

with rising rates of obesity (3, 16-18). A close link with HF has also been established and the rising rates of HF in the community will also contribute to the rising incidence and prevalence (19).

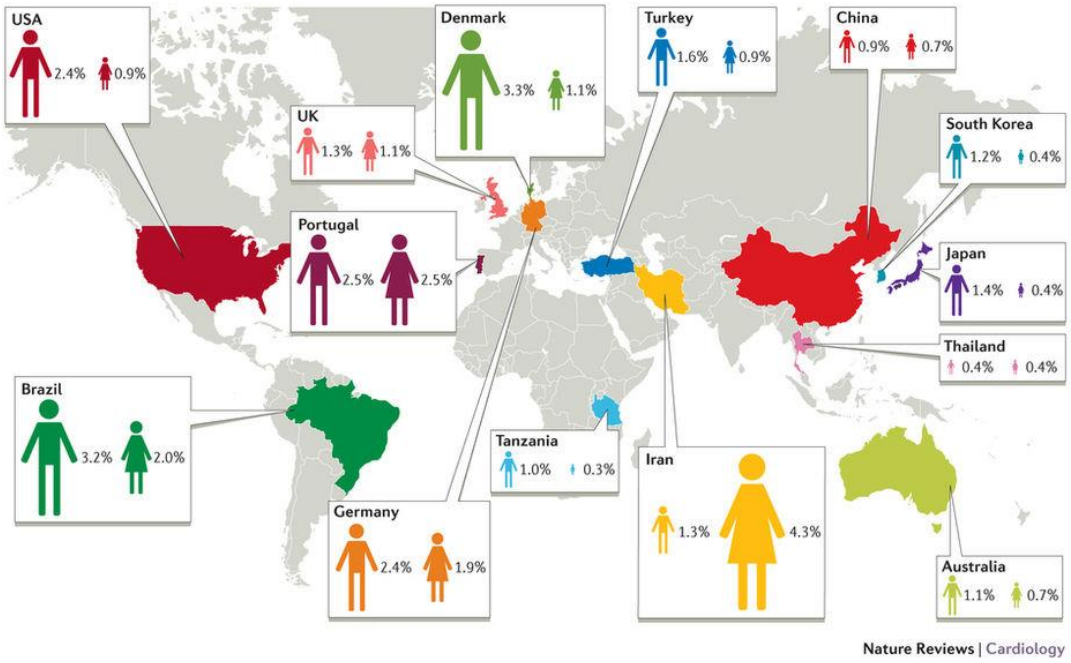


Figure 1.2 - Global AF epidemic (from Ko et. al. 2016) (7).

AF is a multinational disease with similar prevalence seen in developed countries. Lower rates of AF are noted in Africa. There is male predominance in most countries.

1.2 Risk factors for AF

There is overlap between AF and other cardiovascular diseases including HF and coronary artery disease. Typical risk factors associated with AF were originally established from the original Framingham cohort with age, hypertension, HF, coronary artery disease, valvular heart disease and diabetes mellitus all noted to be independent risk factors (20, 21). Other risk factors identified from a meta-analysis include male gender, alcohol consumption, obesity and LVH (20). There appears to be an incremental risk, where the presence of multiple risk factors, increases AF risk cumulatively.

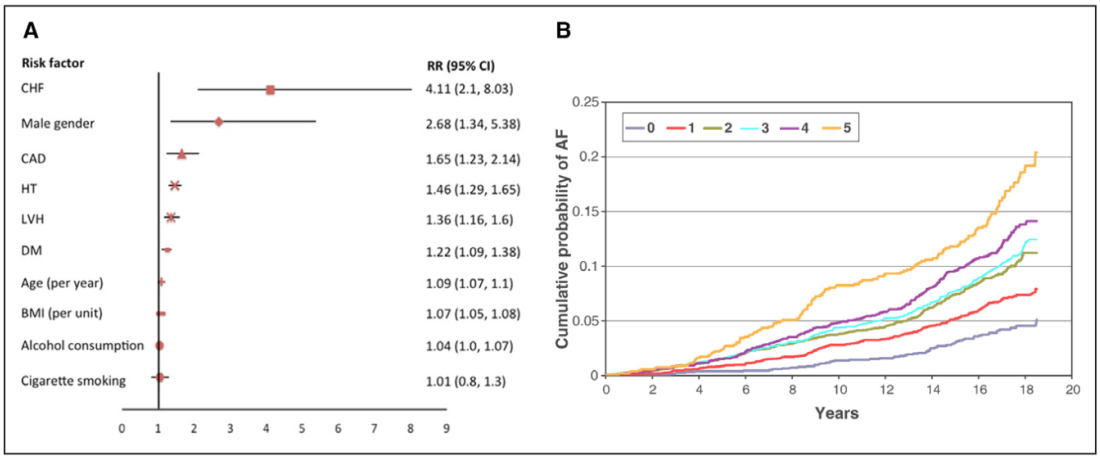


Figure 1.3 - Independent risk factors associated with AF and the cumulative risk associated with the presence of multiple risk factors (from Lau et. al. 2017) (20).

The common risk factors associated with AF include male gender, age, weight, smoking, alcohol consumption as well as co-morbidities such as heart failure, diabetes and hypertension. The risk of AF exponentially increases with the presence of more risk factors,

AF is a complex multisystem disease process and these traditional risk factors do not fully account for this and when combined into risk models, have modest discriminative ability (22). However, these risk factors, many of which are modifiable are critical in the management of AF. Aggressive risk factor management post catheter ablation has been associated with reduced AF recurrence and improved symptoms, whilst there may be a potential role in preventing AF with early risk factor control (23). Novel risk factors have been described, that may also be involved in the pathogenesis of AF. Obstructive sleep apnoea is common in patients with AF and is associated with increased AF risk, independent to obesity (20, 24). There have been associations between physical inactivity and AF and in contrary higher rates of AF have been noted in endurance athletes (20, 25, 26). Genetic predisposition also appears to be important in AF. In the USA, AF is more common in Caucasians than the African-American population (27). In the Framingham study, family history of AF was an independent risk factor and recent advances in genetic sequencing have identified several potential genetic variants which may be involved in ion transport, gap junctions, mediators of inflammation and involvement in the renin-angiotensin-aldosterone and natriuretic peptide pathways (27, 28). Pericardial fat noted on multi-slice computed tomography (CT) is also associated with increased AF risk independent of obesity and may contribute to a pro-inflammatory state which may predispose to AF (27, 29).

Low SES is an independent risk factor for metabolic syndrome and cardiovascular disease (30-32), but the association with AF has had mixed results. A large Swedish study did not find an independent association between SES and hospitalised AF (33), although an association was found in women (33). The ARIC cohort found that low family income was associated with increased risk of AF (34), with lower education levels associated with increased AF risk in women (34).

There has been increasing interest in genetic risk scores as part of AF risk assessment. Although there is a strong association between clinical risk factors with the development of AF, there have been some single nucleotide polymorphisms associated with increased AF risk. Muse et. al. (2018) demonstrated how a genetic risk score could be used to identify patients at higher risk of developing AF, on top of clinical risk (35). Genetic risk scores are still in the early stages of development and with advances in technology and improved accessibility, may be an important adjunct in patient selection for AF screening.

1.3 Cognitive impairment and AF

Given AF is more common in the elderly, there has been increasing research showing a possible association with cognitive impairment. Cognition decreases with age and is associated with vascular risk factors such as hypertension and diabetes (36). There is significant overlap with vascular risk factors and AF risk factors. Possible mechanisms for cognitive impairment have included silent embolic events causing “microinfarcts” as well as cerebral hypoperfusion due to reduced cardiac output (36).

In the Intermountain Heart Collaborative Study, 37,025 patients were followed up over a mean of 5 years for the development of AF and cognitive impairment. AF was independently associated with dementia (OR 1.06-1.73) (36, 37). The Rotterdam prospective study of 6514 patients, noted an association between incident AF and development of dementia (HR 1.33, 95% C.I 1.02-1.73) (38). A recent meta-analysis pooling data from 21 studies with 89,907 patients demonstrated an independent association between AF and cognitive impairment (RR 1.34, 95% C.I 1.13-1.58) and dementia (RR 1.38, 95% C.I 1.22-1.56), independent of stroke (36, 39).

The association between AF and cognition has important implications for screening. Firstly, screening elderly patients may present additional challenges related to cognition and manual dexterity as patient involvement and compliance may be required. Secondly, a potential additional benefit from AF screening may be to reduce the incidence of cognitive impairment in the long-term. AF detection which may lead to initiation of anticoagulation, may result in reduced cerebral embolic events, which may have a positive effect on cognition.

1.4 Pathogenesis of AF

1.4.1 Normal LA physiology

The LA is a thin walled structure which modulates LV filling, from the pulmonary circulation (40). Under normal situations, the LA is a highly elastic, low pressure chamber and has three phases of action. In ventricular systole, it acts as a reservoir for pulmonary venous blood flow (5, 40). In early ventricular diastole and diastasis, it acts as a passive conduit, allowing blood flow from into the LV. In end diastole, there is active LA contraction (contractile function) contributing around 1/3 of LV filling in diastole (5, 40). There is a close relationship between LA and LV function. In the reservoir phase, LA relaxation and compliance are aided by descent of the LV base. In early diastole (part of conduit function), the suction force created by the LA→LV gradient is driven by LV stiffness and relaxation (5). The contractile phase in end-diastole is predominantly modulated by LA contraction, however is influenced by LV end diastolic pressure and compliance (5).

1.4.2 Changes to LA physiology in AF

Several changes occur both at a macro and microscopic level within the LA which contributes to the development of AF. Many of the changes at a cellular level and focal AF mechanisms are still poorly understood with several animal models suggesting changes to actional potential duration, refractoriness and abnormal automaticity (20).

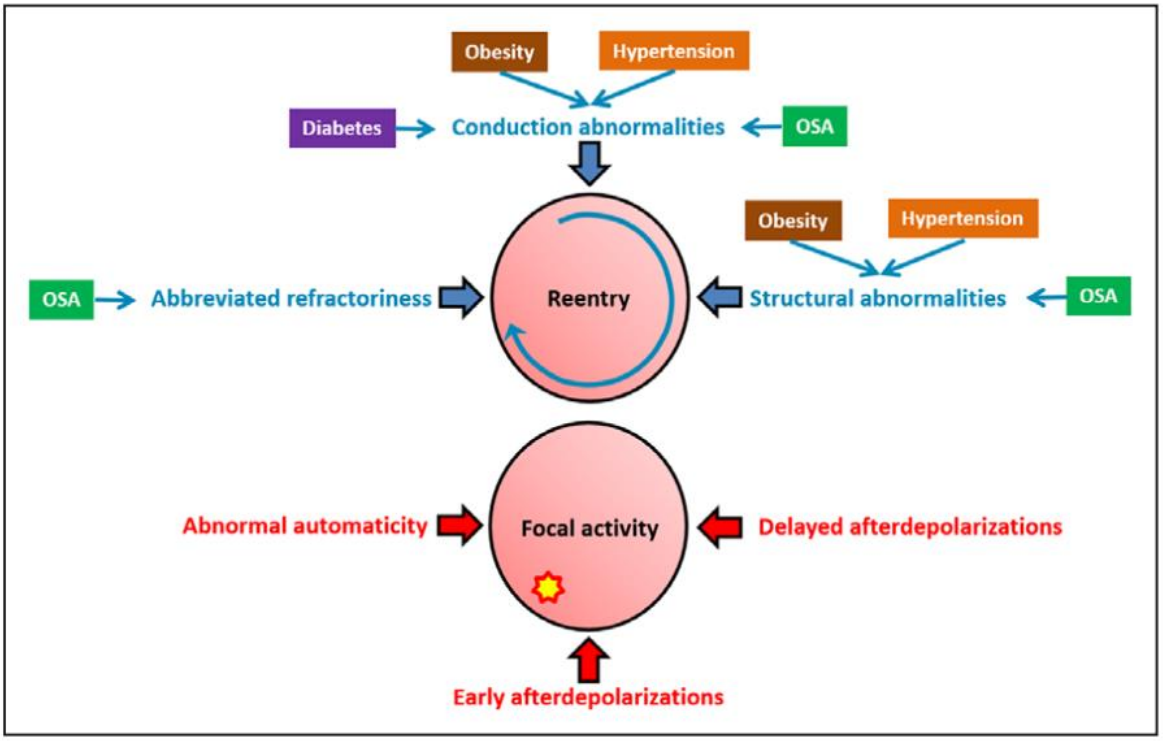


Figure 1.4 - Potential mechanisms for AF (from Lau et. al. 2017) (20).

There are multiple potential mechanisms for the development of AF. Conduction abnormalities can occur with the presence of risk factors such as diabetes and hypertension. Similarly these risk factors can create structural abnormalities within the LA and change electrical signalling pathways, which can contribute to arrhythmogenesis.

There are several changes which occur to LA structure and function, with the presence of long-standing risk factors such as hypertension and T2DM. The LA is a highly elastic and typically a low-pressure chamber. When exposed to these risk factors, there is chronically elevated LA pressure which contributes to LA remodelling, due to mechanical, electrical and metabolic stressors (41, 42). This progressively contributes to LA enlargement, which can readily be assessed on imaging and fibrosis (5, 41). Changes to LA structure may be mediated by fibrotic markers such as tumour necrosis factor-α, platelet-derived growth factor and transforming-growth-factor (41). Pericardial fat may be an important mediator, which may augment pro-inflammatory mediators which perpetuates this chronic inflammatory state. Detecting LA fibrosis non-invasively, is difficult with echocardiography and tissue characterisation may best be evaluated by cardiac magnetic resonance imaging.

Electrical remodelling within the LA also occurs, with "*alterations in ion-channel pumps, gap-junctions and exchangers"* which creates a substrate for either re-entry mechanisms or increased focal

automaticity, the focus of which typically is at the origin at the pulmonary veins, which leads to arrhythmogenesis (41). LA functional remodelling also occurs, which may be earlier than LA structural changes, and may provide a potential avenue in identifying patients at risk of developing AF. With LA and LV remodelling, the LA may become less compliant, with higher resting LV filling pressures, thus impacting on reservoir and conduit function. Given the interdependence of all the phases of LA function, there may be changes to LA contractile function, which may be compensatory at first, until this "atrial kick" is lost with the development of AF (5, 41). These functional changes may be potentially assessed non-invasively with LA strain imaging.

1.4.3 The consequences of "atriopathy"

The structural changes which occur within the LA could be referred to as an "atriopathy." As mentioned previously, clinical risk factors such as hypertension, obesity and diabetes all cause negative LA remodelling. The progressively leads to chamber dilatation, chronic elevation of LA pressure and fibrosis which leads to changes in electrical signalling (as outlined in figure 1.4). This may lead to the development of AF.

However, it is important to recognise the development of "atriopathy" may itself be pathological. AF may purely be an end-organ manifestation of "atriopathy." The development of stroke may not require the presence of AF but may occur in the setting of "atriopathy" which leads to a thrombogenic substrate. Previous studies of embolic strokes of undetermined source, have only identified AF in a small number of cases after a prolonged monitoring period (43). Left atrial enlargement has been shown to be associated with increased stroke risk independent of AF (44-46). This highlights the additional role of echocardiography in AF risk assessment as it provides incremental information about the development of "atriopathy." The ARCADIA study which is currently in the process of recruiting, has used this rationale to assess the efficacy of apixaban in preventing recurrent strokes in patients with embolic source of undetermined source in the absence of AF (46). It also highlights that treatments should also be aimed at targetting the underlying "atriopathy," rather than primary treatment of AF itself.

1.5 AF risk assessment

Prompt recognition of those at risk of AF and early diagnosis is critical to prevent complications and implement risk factor modification and anticoagulation. In a minority of cases, AF risk may be high due to a strong familial link or in endurance athletes. In the vast majority, it is a disease of ageing accelerated by the presence of multiple risk factors (which have been previously discussed).

Clinical AF risk scores aim to make it easier to quantify AF risk at the bedside for clinicians. The Framingham AF risk score was one of the first risk scores, incorporating age, gender, HF, presence of a murmur, SBP, hypertension, BMI and PR interval prolongation to measure a 10 year AF risk score, with moderate discriminative ability (c-statistic 0.78) (47). The ARIC AF risk score was developed in 2011 from the 14,456 participants in the ARIC cohort (48). The ARIC was more racially diverse than the Framingham cohort therefore improving external validity. The ARIC score uses age, sex, smoking status, hypertension, race, height, SBP, diabetes, coronary artery disease and HF in the model, with moderate discriminative ability (c-statistic 0.78) (48).

The CHARGE-AF score was developed using 3 large American cohorts (Framingham, ARIC and Cardiovascular Health Study cohorts) (22, 48, 49). Variables in the model were derived from 18,556 patients (81% Caucasian) in the overall cohort. A 5 year AF risk score was derived using 12 clinical parameters (age, race, height, weight, SBP, DBP, current smoking, use of anti-hypertensives, history of diabetes mellitus/myocardial infarction, history of HF and ECG data (voltage criteria for left ventricular hypertrophy and PR interval) (22). Moderate discriminative ability was demonstrated in the cohort (c-statistic 0.77) (22). A validation study was performed in the AGES (Age, gene and environment – Reykjavik study) European cohort, demonstrating only modest discriminative ability (c-statistic 0.66) (22, 50).

Overall clinical risk scores may aid in identifying those at risk and help patient education and awareness about AF. However, all clinical scores only provide moderate discriminative ability, highlighting their limitations. It suggests that AF is complex and several other risk factors have not been incorporated. Imaging markers of risk are not incorporated into these risk models and may help improve discrimination.

1.6 Role for AF screening

1.6.1 Criteria for an effective screening program

For an effective screening program to be created, it must fulfil several established criteria, which were initially described by Wilson and Junger of the World Health Organisation more than 40 years ago (51).

Box 1. **Wilson and Jungner classic screening criteria**[1]

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Figure 1.5 - Wilson and Junger criteria for an effective screening program (from Andermann et. al. 2008) (51).

AF fulfills most of the criteria established by Wilson and Junger for effective screening programs.

Although limited in some areas such as pathogenesis, our understanding of AF is extensive. The disease is well described, we have effective treatments including stroke prevention and recent advances in technology have made screening more cost-effective and feasible. A case for AF screening can be made, given it satisfies nearly all the Wilson and Junger criteria.

1.6.2 Potential benefits for early AF diagnosis

Four pillars of management of AF have been proposed (20).

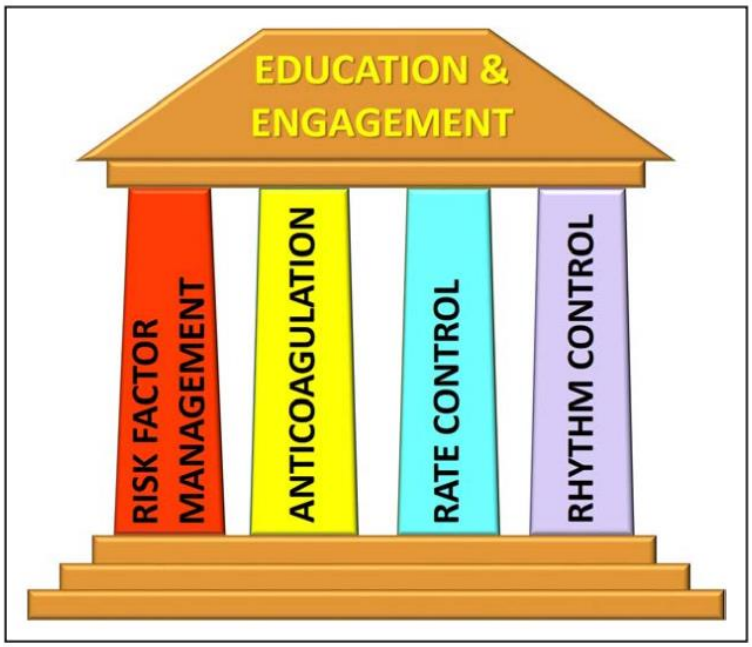


Figure 1.6 - Four pillars of AF management (from Lau et. al. 2017) (20).

Risk factor management is an essential component of AF treatment. Along with anticoagulation, rate and rhythm control, these make up the four pillars of AF management.

With regards to early AF diagnosis at least 2 of these pillars still may have a role. One of the main benefits with screening programs is improved patient education and health awareness. These may translate into improved health outcomes and may allow for patients to be more proactive in decisions regarding their health.

Risk factor management is paramount in the management of AF. It has an established role following catheter ablation, being associated with reduced recurrence and improved symptoms (23, 52). In earlier disease stages, despite the majority of patients being asymptomatic, risk factor management is still important. It may have a role in arresting negative LA remodelling, which may stop disease progression. Risk factor management may also improve other health outcomes such as risk of cardiovascular disease. It may also empower patients to make lifestyle changes.

Anticoagulation has a proven role in stroke prevention in patients with clinically diagnosed AF (53, 54). The role in those with subclinical AF has not been established and requires further clinical trials. However those with subclinical AF do not have a benign disease course (55). Subclinical AF has been associated with increased risk of stroke, myocardial infarction and all-cause mortality (55). Prompt

initiation of anticoagulation in patients with AF, may be associated with reduced thromboembolic complications which may reduce hospitalisations and downstream health care costs (2).

1.6.3 Current recommendations

There is currently a lack of consensus in international clinical practice guidelines with regards to the role of AF screening. In Australia, in the recent AF guidelines published in 2018, opportunistic AF screening is recommended in patients ≥ 65 years with pulse palpation or a rhythm strip (56). This has mirrored recommendations by the European Society of Cardiology who were amongst the first body to advocate for opportunistic AF screening in patients ≥ 65 years (57). However AF screening has not been recommended by recent consensus statements released by the US Preventative Services taskforce and by the National Screening Committee in the UK (58, 59). The Korean guidelines advocate for AF screening, whilst the Canadian guidelines do not explicitly have recommendations on routine AF screening, rather focusing on patients with subclinical device detected AF (60, 61). The AF-Screen collaboration has been established as an AF screening advocacy group and research body which may help in the future to create more uniform recommendations (2).

1.6.4 Monitoring technologies available for AF screening

Several monitoring technologies are available to assist in AF detection (summarised figure 1.7 below). Traditional AF diagnostic methods have involved pulse palpation and 12 lead ECG. The yield from these approaches is <1%, however is age dependent. Lowres et al. (2019) performed a systematic review of 24 AF screening studies and identified that AF detection rate increases with age (from 0.34% in those <60 yrs to 2.73% in those ≥ 85 yrs) (62). Interestingly the choice of screening technology, geographic region or the device used for screening did not influence AF detection rates (62).

Pulse palpation although easy to perform has poor sensitivity and specificity. 12 lead ECG has very high specificity but not practical to perform in a mass screening program. Currently, patients with symptoms such as palpitations or those with a clinical suspicion of AF (such as those with a recent stroke) are referred for Holter monitoring. These provide continuous 24-48 hr heart rhythm monitoring and have automated AF detection algorithms. They currently have an MBS rebate for these indications.

However, there is no indication/rebate for AF screening in asymptomatic patients at risk. They are also not practical for screening purposes as patients find them uncomfortable to wear and it may impact on daily activities. Although providing continuous monitoring, this monitoring period is fixed and may reduce sensitivity. Implantable loop recorders are the gold-standard for long-term AF detection and in the CRYSTAL-AF study, showed a large number of patients with embolic stroke of unknown origin had underlying AF when monitored for long monitoring periods (43). In the primary prevention setting the REVEAL-AF study, ASSERT-2 and the Danish LOOP study all showed a large number of patients with subclinical AF when monitored for a prolonged period (63-65). However, for AF screening in asymptomatic patients, they are invasive, expensive and not feasible.

Newer methods allow for intermittent monitoring for AF outside the clinical setting. Automated BP monitors can assess pulse waveform and offer a limited AF detection tool (66). Photoplethysmography using smartphone apps have been shown to be highly sensitive and may allow for AF detection at different timepoints (67). The most promising have been single lead ECG monitoring devices. A variety of different devices are currently in the marker and use finger contact with electrodes to create a single ECG vector. There are AF detection algorithms, and many have processes in place to alert treating physicians if an abnormal recording is detected. The advantages with these devices are that they are easy to use for patients, have high sensitivity and allow for monitoring at multiple timepoints, thereby improving AF detection rates. These devices have been studied in a variety of cohort studies demonstrating feasibility for AF screening (8, 68-73).

The main limitation of single lead ECG devices is that they are patient dependent. Patients are required to perform monitoring episodes, and this may create potential issues with compliance. Newer technologies may make the screening process more automated with little patient involvement. Recent developments in smartwatches have now made medical grade devices available in a consumer level product, thereby making AF screening now more accessible to large audience. This creates its own issues in creating patient anxiety and increasing diagnoses of benign arrhythmias, however in the Apple Heart Study demonstrated a high positive predictive value of 84% which may make it a useful screening tool (74). The most exciting technology in this field is the use of monitoring patches which provide continuous monitoring without inconvenient electrodes, have automated AF detection algorithms and

require no patient input (74-76). AF screening will continue to evolve in the future, improving feasibility and potentially cost-effectiveness.

Figure 1.7 - Different methods used for AF detection (from Freedman 2016 (77).

The top row shows the MyDiagnostik and Zenicor devices which are single lead ECG monitoring devices available in Europe. In the bottom row from left to right are the Microlife BP monitor, AliveCor single lead ECG monitoring device (available in Australia) and a smartphone with related photoplethysmography apps.

1.6.5 Cost effectiveness for AF screening

Cost-effectiveness for single lead ECG monitoring devices has been demonstrated in multiple studies (8, 78-80). Newer technologies such as smartwatches and monitoring patches, have yet to demonstrate cost-effectiveness, however with increased adoption of these technologies, the costs are likely to reduce. Most studies on cost-effectiveness use stroke prevention as the primary outcome for effectiveness. There are several factors which can influence such analyses. The patient population selected is vital including the presence of vascular co-morbidities, age, SES and access to health care may all influence stroke rates and AF detection. The choice of monitoring device (its associated sensitivity/specificity) and the duration of monitoring will also influence the AF detection rates which will influence the rates of stroke prevention. The prescription of oral anticoagulants and their compliance will also have an impact. These factors must be taken into account prior to widespread adoption of cost analysis data.

Much of these decision made models have focused on the choice of monitoring technology and duration of monitoring in their analysis (8, 78-80). Appropriate patient selection is a key factor in assessing cost-effectiveness, so future studies have to incorporate this into their decision-making models.

1.6.6 Potential issues with AF screening

AF screening as discussed earlier, has several potential benefits. However, several disadvantages and issues have been raised (81):

- There is a concern of false positives related to screening and the potential morbidity this can cause if inappropriate treatments such as anticoagulation are prescribed. Automated AF algorithms have high sensitivity but may lead to false positives.
- With limited financial resources and infrastructure, implementing a community-wide screening program remains a challenge.
- AF screening can potentially lead to increased demands on emergency departments and general practice, due to abnormal ECG recordings and other incidental findings.
- Patient anxiety can be created with screening programs
- There is a potential risk of overdiagnosis. Currently there are no long-term prospective studies clearly showing long-term adverse outcomes in patients with subclinical AF. However, observational studies demonstrate adverse clinical outcomes in these patients (55).
- Appropriate diagnosis of AF is critical, and training of medical personnel may be required. This can be mitigated using automated algorithms.
- Screening requires patient involvement; hence patient compliance is critical.
- Cognitive impairment and manual dexterity are potential issues in an elderly population when using single lead ECG monitoring devices.

1.6.7 Knowledge gaps

There are several areas where there are gaps in the knowledge base regarding AF screening and risk assessment. Some of these will be addressed in the research conducted in subsequent chapters.

1. There is currently insufficient data showing a clear benefit with anticoagulation use in patients with subclinical AF.

2. There is insufficient data showing that patients with subclinical AF have similar adverse outcomes to those with clinically diagnosed AF.
3. Cost-effectiveness has been investigated with AF screening, however assumptions are made regarding treatment effects and prognosis (81).
4. The most appropriate cohort for screening is undefined. Most have proposed population-based screening using age-based cut-offs. However, the use of novel risk factors and imaging may help discern an enriched patient cohort where screening may be more effective.
5. The most appropriate screening technology for AF screening is not well defined.
6. The success rate of risk factor modification in AF prevention in those at early disease stages is unclear.
7. It is unclear if LA remodelling can be reversed if early diagnosis is made and risk factor modification implemented.
8. It is unclear if LA strain provides incremental information to other markers of LV function.
9. The utility of LA strain imaging in AF risk stratification has not been fully investigated.
10. The feasibility of AF screening in Australia has not been extensively studied.
11. The practical challenges of AF screening programs have not been addressed.

1.7 Echocardiography in AF risk assessment

1.7.1 Role of echocardiography in AF

Echocardiography has an important role in patients with a clinical diagnosis of AF. It is non-invasive, reproducible and cost effective. It is used in patients with AF for a variety of reasons including; 1) to assess for underlying structural heart disease which may have led to the development of AF ie. assessment of LV systolic and diastolic function and mitral valve disease; 2) providing a non-invasive assessment of LA pressure which can guide diuretic therapy; 3) assessment of LA size which can be used predict the response of therapy such as catheter ablation and is an important prognostic marker (40).

Echocardiography is not recommended in asymptomatic patients, however can provide important information about AF risk (82). In patients who have had an echocardiogram performed for other

clinical indications, further information can be elicited about future AF risk. Increased LA size is an independent risk predictor for AF and is associated with increased cardiovascular events (5, 40, 83). Increased LA size indicates chronic elevation of LA pressure and likely LA remodelling, which is strongly associated in the pathogenesis of AF. Tissue Doppler imaging can be used to assess LV relaxation, diastolic function and can help to provide non-invasive assessment of LA pressure. These echo indices may also help identify patients at increased risk of stroke and HF independent of AF.

LA phasic function can be assessed by volumetric analysis using 3D echocardiography to obtain LA volumes at different parts of the cardiac cycle which can be used to derive LA ejection fraction and emptying volumes (5). Doppler assessment of pulmonary venous flow can be used as a surrogate for LA reservoir function (5). However, these markers may be time consuming to measure and have not been demonstrated to be predictive of AF. They also may lack sensitivity in identifying patients at earlier disease stages.

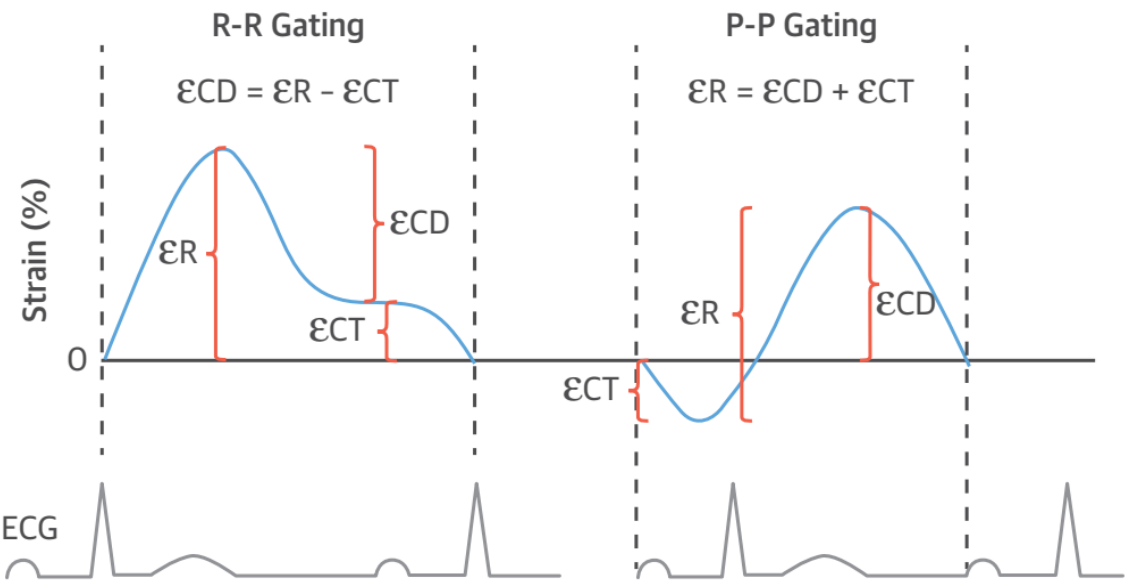
1.7.2 The potential role of LA strain in AF assessment

Assessment of myocardial deformation using speckle tracking allows for quantitative information about segmental, global and phasic LA function. Speckles are acoustic markers that can be used to track myocardial deformation across the cardiac cycle (4). LV GLS is a more sensitive marker than LVEF and has already been shown to have important clinical applications such as identifying patients with subclinical HF, prognostic marker following acute coronary syndrome and assessment of LV dyssynchrony (84-87). There has been an interest in using strain imaging in assessment of LA function. Strain has several potential advantages. It can be used to assess LA phasic function. Secondary it can be used to assess segmental and global function. Changes to LA function may occur much earlier than increased LA size, therefore it may be a more sensitive marker in identifying patients with LA remodelling at earlier disease stages. Compared to tissue Doppler imaging, strain is angle independent, thereby reducing potential for errors.

1.7.3 Measurement of LA strain

LA strain can be measured offline using third-party software programs or may be offered "on-cart" by some vendors to be measured at the time of image acquisition. It requires images with high frame rate (60-80 frames/sec) and typically three consecutive heart cycles are recorded and averaged (4). Apical four and two chamber images are typically used for LA strain measurement. The apical three chamber image is often not used due to potential for error in tracking from the aorta. ECG tracing is used to track the cardiac cycle, with the reference point either the onset of the R wave (R-R gating) or the P wave (P-P gating). The LA endocardial border is manually traced and the software then automatically generates the region of interest which can then be manually adjusted so that tracking quality is maintained (4, 88). The LA is divided into 6 segments. Segments which do not track well, can be excluded from the analysis. The software algorithm then provides longitudinal strain curves of each LA segment as well as a mean.

The LA strain curve varies depending on the ECG gating. During LA reservoir phase, the LA receives pulmonary venous blood flow and stretches, creating a positive peak. Following mitral valve opening, there is passive filling of the LA in early diastole (conduit strain), causing LA relaxation and a downward spike in the LA strain curve than includes diastasis. In end diastole, active atrial contraction "pump function", creates another positive peak which is smaller than the initial reservoir phase peak (4). In AF, the second peak is not present due to loss of the "atrial kick". The three components of LA function are interdependent (the sum of LA pump and LA conduit strain = LARS). The varying strain curve patterns can be used to provide a visual representation of LA remodelling. There have also been recently published "normal reference" values so that strain can be used quantitatively to assess LA function (89).



Components attributable to reservoir, conduit, and contractile strain are labeled. ƐCD = conduit strain; ƐCT = contractile strain; ƐR = reservoir strain; LA = left atrial. Reproduced with permission from Pathan et al. (43).

Figure 1.8 - LA Strain Curve using R-R or P-P gating from Pathan et. al. 2017 (5, 89, 90).

The three components of LA strain (reservoir, conduit and pump) mirror LA function during the cardiac cycle.

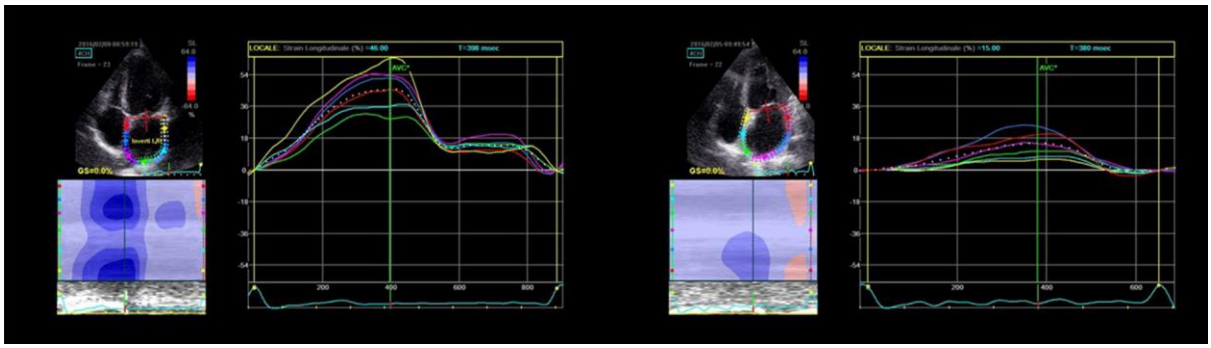


Figure 1.9 - Comparison of LA strain in a healthy subject (left) compared to a patient with AF (right) – from Camelli et. al. 2016 (4).

In AF, there is loss of the second peak due to loss of LA contractile function in end-diastole

1.7.4 Clinical roles for LA strain

LA strain has several potential applications. In patients with AF, LA strain has been shown to be reduced compared to those in sinus rhythm (91). An inverse relationship between LA strain and LA fibrosis assessed on magnetic resonance imaging has been demonstrated (92). LA strain has also been shown to

be useful in predicting response from catheter ablation or direct current cardioversion (93-96). In patients with AF, LA strain can be used to assess thromboembolic risk in addition to clinical risk scores. (97). LA strain may also be an important prognostic marker in HF, acute coronary syndrome and mitral regurgitation (40, 98-100).

1.7.5 Limitations of LA strain

Despite the potential advantages of LA strain, in the assessment of LA function, it has several limitations and disadvantages which need to be addressed prior to widespread clinical applications:

- Multiple software vendors (GE Echopac, Tomtec, Phillips QLAB) exist, each with proprietary strain algorithms which may impact on reproducibility among vendors.
- Dedicated LA strain vendor algorithms should be developed. Currently LA strain utilises a LV strain algorithm, and software programs are "tricked" into treating the LA as the LV in the analysis.
- Recently published consensus guidelines addressing nomenclature, ECG gating and standardisation of image acquisition and measurement of strain has not been widely accepted (101).
- LA strain is time-consuming and requires a learning curve to achieve reproducibility. This may impact on its use in clinical applications.
- LA strain requires third-party software programs which are expensive and may not be widely available in most echo labs.
- Image quality is vital to ensure adequate tracking of each LA segment.
- Frame rates should be optimised by the operator (optimal frame rate ranges often reported by vendors) prior to image acquisition (101).

1.7.6 Definition of risk

In this thesis the term “risk” is used frequently. These are defined as follows:

1. AF risk – The risk of developing AF.
2. AF risk factors – Risk factors associated with the development of AF.
3. HF risk – The risk of developing HF.
4. Cardiovascular risk factors – Risk factors associated with cardiovascular disease such as smoking, hypertension and diabetes mellitus.
5. Stroke risk – Risk of developing stroke associated with atrial fibrillation

Chapter 2. Methods

2 Methods

A summary of the methods for each project is provided in the methods section of each individual chapter. The data from chapters 4,5,6,7,8,8,10, and 12 were from a community-based AF screening study based in Tasmania (Tas-ELF) and Victoria (Vic-ELF). Details of the study are summarised below:

2.1 Study Population

The patients used in the study were recruited as part of the Tas-ELF (Tasmanian study of the Echocardiographic detection of Left ventricular dysFunction) and Vic-ELF (Victorian study of the Echocardiographic detection of Left ventricular dysFunction) studies. The primary aim of this study was for the early detection of stage B HF in the community aided by advanced imaging techniques. Given the significant overlap between AF and HF and similar risk factor profiles, patients in this study were also recruited into the AF sub-study for this research project.

2.2 Recruitment

Participants from the community were recruited into the study by a variety of methods including:

- Radio and newspaper advertising
- Community centres
- Mail out from GP practices
- Community outreach by Lions/Rotary groups
- Word of mouth (from volunteers, participants and researchers)
- Hospital outpatient clinics

2.3 Inclusion Criteria

- Age ≥ 65 years
- 1 or more risk factor for AF/HF, including
    - hypertension (systolic blood pressure > 140mmHg or pre-existing use of anti-hypertensive medications)
    - T2DM (based on self-report of diagnosis or the current use of diabetic medications)

- obesity (defined as a body mass index ≥ 30)

2.4 Exclusion criteria

- Unable to provide written informed consent to participate in this study
- History of previous HF, baseline NYHA >2
- History of coronary artery disease (previous myocardial infarction, myocardial revascularization, coronary stents, positive stress test, or echocardiographic screening of LVEF<40%).
- Known history of more than moderate valvular heart disease
- Systolic BP <110mmHg, pulse <60/minute
- Serious life-threatening disease (anticipated life expectancy <2 years)
- Pre-existing treatment with both investigational drugs (ACE-I/ARB and Beta blocker) classes, or one class at maximum dose
- Contraindications/Intolerance of either beta blockers or ACE-I/ARB,
- Participating in any other clinical research trial
- Any history of AF
- Inability to acquire interpretable images (identified from baseline echo)

Given the study had the primary aim of early detection of HF, some of the exclusion criteria above applied to a HF.

2.5 Clinical Evaluation

Patients were initially recruited for the Tas-ELF study between September 2013 and November 2015 and Vic-ELF from March 2017 to November 2019. Patients were then recruited into the AF substudy during attendance at outpatient clinics for initial clinical assessment or for follow up assessment. Outpatient clinics were conducted in Tasmania and Victoria. Locations in Tasmania included:

- Hobart
- Launceston
- Devonport
- Burnie
- Huonville
- Oatlands
- Deloraine
- Geeveston
- Latrobe
- Longford

In Victoria, all assessment and follow up was performed at Sunshine Hospital or the Baker Heart and Diabetes clinic at Footscray.

Initial clinical evaluation included:

- Clinical history
- Medication list updated
- Physical examination including brachial and CBP measurements
- SEIFA indices used to assess regional SES(102)
- 12 lead ECG
- Six-minute walk test
- Questionnaires to assess QoL
    - Duke Activity Status Index (DASI)(103)
    - Minnesota Living with Heart Failure score (MLHF)(104)
    - Charlson-Index(105)
    - EuroQoL5D Visual-Analog Scale (EQ-VAS)(106)

2.6 Assessment of AF risk

AF risk was assessed using the CHARGE-AF score.(22) This clinical score uses 12 clinical parameters (age, race, height, weight, systolic/diastolic blood pressure, current smoking, use of anti-hypertensives, history of diabetes mellitus/myocardial infarction, history of HF and ECG data (voltage criteria for left ventricular hypertrophy and PR interval) to measure a 5 year risk of developing AF. Where ECG data was not available, the simple model was used (which uses just the clinical variables).

2.7 Echocardiographic Evaluation

All echocardiograms were performed by qualified sonographers using the same equipment (Siemens ACUSON SC2000, Siemens Healthcare, Mountain View, CA) and transducers (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz). Two dimensional, M-mode and Doppler measures were obtained using standard techniques outlined by the American Society of Echocardiography (107).

LV dimensions were calculated in both diastole and systole in parasternal long axis views. LV hypertrophy (LVH) was defined as LVM index >115 g/m^2 in men and >95 g/m^2 in women. LV and LA volumes were indexed to body surface area (LAVi) and calculated by the Simpson biplane method. Abnormal LAVi was defined as ≥34 ml/m^2.

Diastolic function was assessed by calculating mitral inflow peak early and late diastolic velocities (E and A wave respectively), deceleration time and the E/A ratio (ratio <0.8 was used to define impaired relaxation). Mitral annular early diastolic velocity using tissue Doppler imaging (e') was calculated in both septal and lateral and averaged to calculate the E/e' ratio (> 13 was used to define raised LA filling pressures).

2.7.1 Speckle Tracking Echocardiography

The speckle pattern of each segment of the myocardium is unique. Speckles are acoustic markers and can be used to determine myocardial mechanics through speckle tracking. Compared to tissue Doppler imaging, it is angle independent. Strain refers to myocardial deformation and is defined as the change in length normalized to the original length. Given it is a vector quantity, it can be either positive or negative.

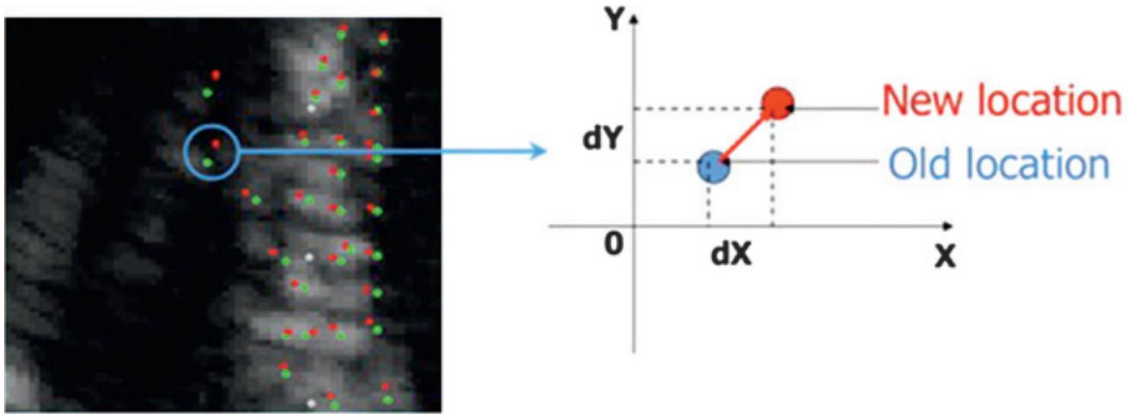


***Figure 2.1 - Speckle tacking (initial position - green dots, final position - red dots) – from Blessberger et. al. Heart 2010* (108).**

Speckles are acoustic markers which can track myocardial deformation throughout the cardiac cycle (the initial position shown by the green dots, and final position shown by the red dots).

Global longitudinal strain (GLS) was calculated in apical 4 chamber views and global circumferential strain (GCS) was calculated in the mid-LV parasternal short axis view. Velocity vector imaging (Syngo VVI, Siemens Medical Solutions) was used to assess LV strain. Manual tracing of the endocardial border of the LV was performed in end-systole and this was tracked during the cardiac cycle.

LA reservoir, conduit and pump strain were assessed using speckle tracking imaging by an external third-party software program (ImageArena, Tomtec, Munich, Germany). Apical four and two chamber images were selected with a frame rate of 60-80 frames/sec. The endocardial border of the LA was manually traced, and strain analysis was performed using the LV strain algorithm, with the average of both the four- and two-chamber values. The reference point for image analysis was taken at the onset of the QRS complex (R-R gating). The LA was divided into 6 segments. If more than 2 segments had poor tracking, LA strain could not be measured in those patients. LA mechanical dispersion was defined as the standard deviation of time to peak positive strain (SD-TPS) from the 12 LA segments. We corrected the SD-TPS by the R-R interval to derive SD-TPS as a percentage of the R-R interval. Patients with poor image quality, where strain analysis could not be performed, were excluded.

2.8 AF Detection and Follow Up

The primary outcome measure in the AF substudy was the AF detection rate during follow up. A minimum median follow up of 12 months was planned for the study. AF detection was planned using a number of methods:

1. Clinically diagnosed AF during the follow up period (patient information collected from hospital electronic records, GP practices and specialist letters at the end of follow up).
2. Inpatient diagnosis of AF (patient information collected from hospital electronic records).
3. Screening for subclinical AF using a single lead ECG monitoring device

2.8.1 Screening for subclinical AF

Screening for subclinical AF was performed using a single lead ECG monitoring device (Remon RM-100, Semacare China). Screening was typically performed within the first month of recruitment. A single lead ECG recording was performed by using the right thumb along with 2 fingers of the left hand placed on the electrodes of the device to create a single ECG vector. Participants were given a device to take home following in person demonstrations at clinics and provision of written instructions. Participants were asked to record 5 x 60 second recordings per day for a 1week period. Devices were then mailed back to the research team for analysis. The ECG recordings were able to be downloaded as PDF files onto a PC using a dedicated app.

All ECG tracings were analysed manually by the candidate. Any ECG tracings with significant motion artefact were excluded from analysis. AF was defined as an irregular rhythm of ≥30 sec with a variable R-R interval and absent P waves. Any ECG recordings suspicious for AF, were then confirmed with a second physician who was blinded from the patient's clinical information.

Patients with a diagnosis of subclinical AF were contacted and made aware of the ECG findings and asked to make an appointment with their local medical officers. The treating GP of the participants was then contacted by mail and copies of relevant ECG tracings provided. Although recommendations were made in the letter to consider anticoagulation, all treatment decisions were left to the participants treating doctor and were not implemented by the research staff.

A pilot sample of 180 participants were given questionnaires to obtain basic qualitative information about some of the practical aspects of screening. The questions addressed issues such as ease of use of the device, patient anxiety and dexterity. In these patients, compliance was assessed by measuring the number of ECG recordings performed (participants were asked to perform 35x 60 second recordings).

Figure 2.2 - Remon RM-100 single lead portable ECG device.

The Remon RM-100 device is a TGA approved single lead ECG device used in this study for AF detection. It requires three points of finger contact to create a single lead ECG tracing for 30-60 seconds which can then be downloaded using a dedicated app for analysis.

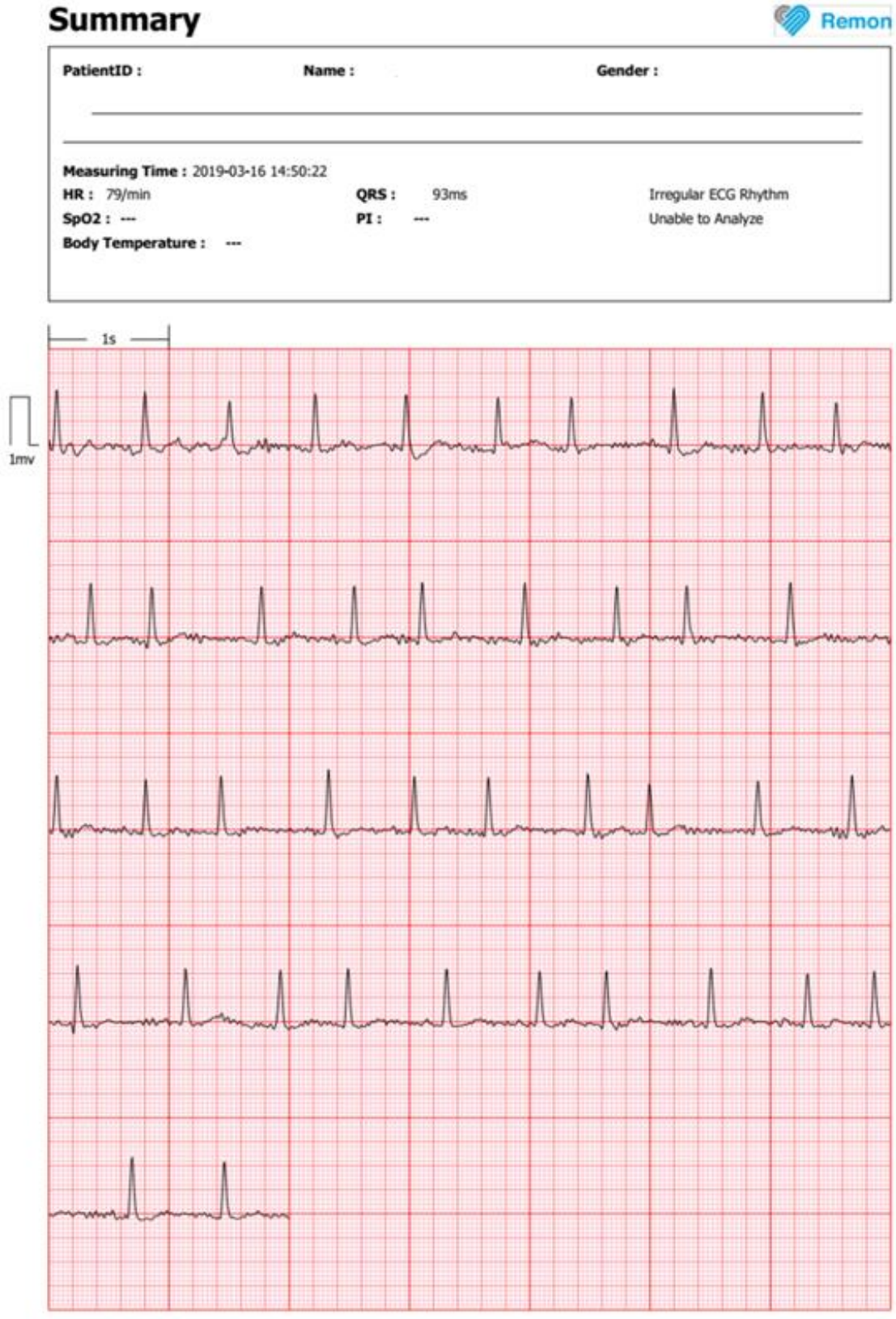


Figure 2.3 - Example of an ECG recording from the Remon RM-100 device demonstrating AF.

An example of an ECG recording from the Remon RM-100 device showing AF.

TASELF ID: ☐☐☐☐

Regarding the Remon ECG device that you used for one week, to what level to you agree/disagree with the following statements about the use of the device:

1. The ECG device was easy to use:

☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

2. The in person instructions explaining how to use the ECG device were clear:

☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

3. The written instructions provided explaining how to use the ECG device were clear:

☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

4. I had difficulty holding the ECG device properly in my hands to take the ECG recording:

☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

5. The alarm on the ECG device was intrusive/annoying:

☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

6. I found myself anxious about the result provided by the ECG device at the end of my recording:

☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

7. I forgot how to use the ECG device:

☐ Strongly Agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly Disagree

8. The ECG device stopped working during the one week period:

☐ Yes ☐ No

9. I contacted the TasELF Study team with an issue about the device during or after the one week period with the ECG device:

☐ Yes ☐ No

Figure 2.4 - Questionnaire sent to patients to collect information about some practical issues with AF screening.

This questionnaire was used to study some of the practical aspects to AF screening (results discussed in Chapter 12).

Chapter 3. Deciding on the most appropriate technology for AF screening

"Atrial Fibrillation Detection using Single Lead Portable Electrocardiographic Monitoring: A Systematic Review and Meta-Analysis."

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Reference: Ramkumar S, Nerlekar N, D'Souza D, Pol DJ, Kalman JM, Marwick TH. Atrial fibrillation detection using single lead portable electrocardiographic monitoring: a systematic review and meta-analysis. BMJ open. 2018 Sep 1;8(9):e024178.

3 Deciding on the most appropriate technology for AF screening.

3.1 Preface

There are multiple methods for heart rhythm monitoring. Recent advances in technology have made AF screening more feasible. In the past the diagnosis of AF was predominantly made by 12 lead ECG in a clinical setting or with Holter monitoring in the community. Although providing continuous monitoring, its utility for AF screening is limited for several reasons. Firstly, it is an expensive screening method. Secondly, for patients it is inconvenient as prolonged periods of monitoring is not feasible given the presence of multiple leads and electrodes which can interfere with activities of daily living. Implantable loop monitors although providing continuous monitoring for extended periods are contraindicated for screening purposes given, they are invasive and expensive.

The diagnosis of AF is fairly easy to make and only requires a single lead for acute diagnosis. Diagnosis relies on the absence of p waves with an irregular R-R interval. Given this, single lead ECG monitoring devices offer a convenient and potentially cost-effective means for screening. The recordings are easy to obtain, are reproducible and some devices have automated detection algorithms which have a high degree of sensitivity. They are much more convenient for patients, are cheaper than Holter monitors and the main advantage is that multiple intermittent periods of monitoring can occur over several days/weeks, thereby increasing the potential diagnostic yield.

In this chapter we compare single lead ECG monitoring devices to Holter monitoring by performing a systematic review of the literature comparing AF detection rates for both methods. By demonstrating comparable AF detection to 24-48 hr Holter monitoring, this can then justify the use of single lead ECG devices for mass AF screening. The following chapter was published in BMJ Open.

3.2 Abstract

Objectives: Recent advances in technology have allowed for heart rhythm monitoring using portable single-lead electrocardiographic (ECG) monitoring devices, which can be used for early diagnosis of atrial fibrillation (AF). We sought to investigate the AF detection rate using portable ECG devices compared with Holter monitoring.

Setting, participants and outcome measures: We searched the Medline, Embase and Scopus databases (search conducted on 8th May 2017) using search terms related to AF and screening and included studies with adults>18 years using portable ECG devices or Holter monitoring for AF detection. We excluded studies using implantable loop recorders and pacemakers. Using a random-effects model we calculated the overall AF detection rate. Meta-regression analysis was performed to explore potential sources for heterogeneity.

Results: Portable ECG monitoring was used in 18 studies (n=117,436) and Holter monitoring was used in 36 studies (n=8498). The AF detection rate using portable ECG monitoring was 1.7% (95% CI 1.4–2.1), with significant heterogeneity between studies (p<0.001). There was a moderate linear relationship between total monitoring time and AF detection rate (r=0.65, p=0.003), and meta-regression identified total monitoring time (p=0.005) and body mass index (p=0.01) as potential contributors to heterogeneity. The detection rate (4.8%, 95% CI 3.6–6.0%) in 8 studies (n=10,199) which performed multiple ECG recordings was comparable to that with 24-hour Holter (4.6%, 95% CI 3.5–5.7%). Intermittent recordings for 19 minutes total produced similar AF detection to 24 hr. Holter monitoring.

Conclusion: Portable ECG devices may offer an efficient screening option for AF compared to 24-hour Holter monitoring.

Study Registration: Prospero database - April 22nd, 2017(CRD42017061021)

3.3 Introduction

Atrial fibrillation (AF) is a leading cause of stroke and HF worldwide, is associated with increased all-cause mortality (109, 110) as well as substantial financial cost (12, 111). The prevalence of AF increases with age, exceeding more than 15% for those aged 85 and older (62, 112). The epidemics of obesity, diabetes mellitus and metabolic syndrome have also been associated with the increasing prevalence of AF (18, 113, 114). Up to 20% of patients with stroke have underlying AF, and detection allows the initiation of anticoagulation which is associated with a significant reduction in stroke recurrence (115). Early diagnosis of AF may have several benefits, including individualized lifestyle intervention (23) and anticoagulation, and may be associated with a reduction in complications and healthcare costs. The importance of early diagnosis has been recognized in recent guidelines from the European Society of Cardiology (ESC) which recommended opportunistic screening using pulse palpation and 12 lead electrocardiogram (ECG) (57). However, screening for AF is challenging for several reasons; many patients are asymptomatic or may have atypical symptoms. There are a variety of monitoring techniques available, all which vary in diagnostic accuracy and sensitivity, and there is no accepted reference standard. Subclinical AF is associated with an increased risk of stroke, cardiovascular disease and all-cause mortality,(8) although there is controversy surrounding the significance of brief paroxysms of AF and the potential benefit of anticoagulant therapy. Implantable devices are expensive, and not cost effective for mass screening, and the use of external devices for long periods of monitoring require electrodes, which may be poorly tolerated by patients.

Recent advances in technology have allowed for the development of single lead portable electrocardiographic monitoring devices. Multiple devices are available, all using multiple points of finger contact to create a single lead ECG trace. The in-built memory of these devices allows for single or multiple time-point screening. Interpretation from a cardiologist or by automated algorithms has achieved high sensitivity and specificity for AF detection (72, 116, 117). Although they have not been incorporated into the latest AF guidelines, the accuracy, ease of use and potential cost-effectiveness of these devices may lead to them having an important role in AF screening. This paper describes a

systematic review of the published literature to investigate the overall AF detection rate using portable ECG devices compared with traditional Holter monitoring.

3.4 Methods.

3.4.1 Search strategy

We conducted our systematic review and meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (PRISMA) (118). We searched the Medline, Scopus and Embase databases using key terms including "atrial fibrillation/AF and screening/monitoring and electrocardiographic/Holter monitoring" which were mapped to subject headings. We also searched the reference lists to identify other potential articles. The search was limited to adult human subjects >18 years and limited to the English language (see search strategy for Medline database in supplementary material). The study was prospectively registered on the Prospero database on April 22nd, 2017(CRD42017061021), and the search was conducted on 8th May 2017.

3.4.2 Search selection

Titles and abstracts of studies identified from the search were reviewed by two independent reviewers (S.R and D.D). Studies which had a primary aim of AF detection in adult participants were included. We included all cohorts including community screening, those with risk factors and recent stroke. The screening methods included portable single lead ECG devices or continuous (Holter) monitoring (up to one week). We included studies which used single lead ECG devices for single episode screening or multiple intermittent screening periods. We included conference abstracts if demographic and outcome data were available. We excluded studies if participants were <18 years or if other forms of monitoring were used (pacemaker, implantable loop recorders, event recorders, monitoring patches and inpatient telemetry). We also excluded studies where AF detection was not the primary aim.

The primary outcome of interest was the detection rate of new AF using either single lead intermittent or continuous monitoring. Our secondary objective was to determine the optimal time of intermittent monitoring which produced equivalent AF detection to continuous monitoring.

3.4.3 Data Collection

Full text manuscripts of studies fitting the inclusion criteria were obtained. Quality of reporting and risk of bias was assessed using the tool developed by Downs and Black (119). A standardized data-extraction form was used by the reviewers which included information about the patient demographics, comorbidities, screening strategy, patients with known AF and overall new AF detection rate. Where data were not reported, we attempted to contact the primary authors of the study. Any disagreements between the two reviewers were resolved by consensus or by consulting a third reviewer (TM).

3.4.4 Statistical Analysis

The cumulative AF detection rate for continuous and intermittent monitoring and the 95% confidence interval was calculated using a random effects model. The results were displayed as a forest plot and heterogeneity amongst the studies was assessed using the I^2 statistic. A subgroup analysis was performed by comparing the cumulative detection rate of single lead ECG studies which performed multiple timepoint recordings with 24-hour Holter monitoring studies. Linear regression analysis was used to determine the association between the total monitoring time and AF detection using single lead ECG devices. This formula was used to determine the monitoring time using single lead ECG devices to approximate the overall AF detection rate using 24-hour continuous monitoring. Univariate meta-regression analysis was performed to assess the influence of various clinical and screening factors with AF detection. Publication bias was assessed using a funnel plot and the Egger test. Statistical analysis was performed using Stata v.13 (StataCorp, College Station, TX) with two-tailed p-values <0.05 used to denote statistical significance.

3.5 Results

3.5.1 Study Characteristics.

The PRISMA flowchart of our included studies is shown in figure 3.1. Our initial search strategy identified 5427 studies, with another 26 identified through other sources. After removing duplicate records, 4122 studies were left. After screening those using the inclusion/exclusion criteria, we identified 111 full text studies for detailed review, which excluded 59 studies, leaving 52 full text studies for inclusion in the meta-analysis (see supplementary table 3-5 for excluded studies). Of the 52 studies

included, 34 used continuous (Holter) monitoring (n=8154), (120-153) 16 (n=117,092) used single lead portable ECG monitoring, (8, 68-70, 72, 73, 78, 79, 117, 154-160) and 2 studies (n=344) used both continuous and intermittent single lead monitoring for AF detection in a head to head comparison (161, 162).

The baseline characteristics of the individual studies is presented in Table 3-1. There was a considerable range in age (54-76 years), and gender (male 29-77%) between studies. As many studies chose healthy volunteers and other studies focused on patients post stroke or those with AF risk factors, there was significant variation in comorbidities such as diabetes, hypertension and obesity. Stroke risk determined by the CHADS or CHA_2DS_2-VASC score was reported in only 14/52 studies (27%). Of the 52 studies, 36 (69%) were conducted in Europe, 8 (15%) were in Asia, 5 (10%) were in North America and 3 (6%) in Australia. Nine studies (17%) were retrospective, the remainder all being prospective cohort or randomized controlled trials.

Of the 18 studies using single lead ECG devices, 10 studies (56%) used a single 10-60 sec recording for AF detection whilst 8 studies (44%) used multiple readings over a 1-52 week period. There were five portable ECG devices used (Table 3-1). Sixteen studies (89%) used healthy participants with risk factors (8, 69, 70, 72, 73, 78, 79, 117, 154-158, 162). Two studies assessed patients following stroke or transient ischemic attack (TIA) (159, 161).

Of the 36 studies using continuous (Holter) monitoring, 27 studies (75%) used 24-hour continuous monitoring, (120-125, 127-130, 135-138, 140, 141, 143-147, 149-152, 161, 162) 4 studies (11%) used 1 week monitoring, (132-134, 153) 2 studies (6%) used 48-hour monitoring, (139, 148) 2 studies (6%) used 72-hour monitoring, (126, 131) and 1 study (3%) used 96-hour monitoring (142).

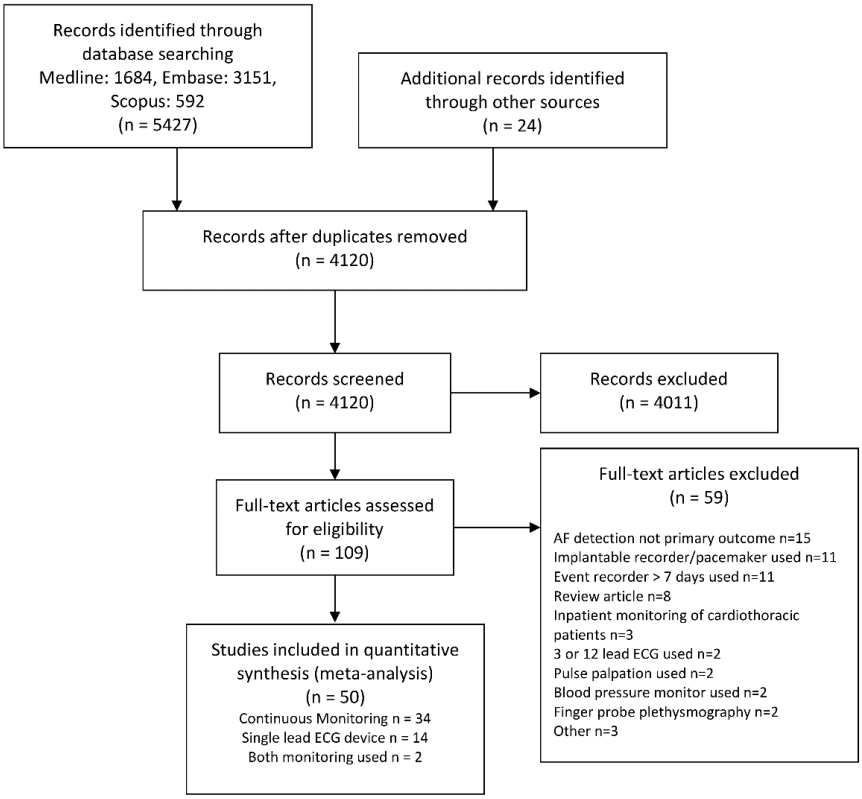

Figure 3.1 - Overview of inclusion and exclusion of studies based on the PRISMA flowchart.

A total of 50 studies were included in the meta-analysis. 34 studies used continuous Holter monitoring, 14 studies used single lead ECG monitoring and 2 studies used both technologies.

Table 3-1 - Summary of included trials investigating AF detection using single lead ECG devices or Holter Monitoring

Study	n	Country	Type of patients used	Device Used	Duration of recording (sec)	Frequency of recording /day	Total monitoring (days)	Mean/ median age (yrs)	Male (%)	BMI (kg/ m2)	HTN (%)	DM (%)	IHD (%)	Previous diagnosis of AF (%)	HF (%)	Previous stroke (%)	Mean/ median CHADS2/ CHADS-VASC	Definition of AF	New AF (n)	New AF rate (%)
Lowres et. al. (2014) (8)	1000	Australia	Community pharmacy screening	Alive Cor	60	1	0	76	44	NR	62	23	16	10.4	3	7	3.3	Cardiologist Interpretation	15	1.5
Svennberg et. al. (2015) (71)	7173	Sweden	Community screening (75-76 yr olds)	Zenicor	30	2	14	75	46	25.9	50	11	9.2	9.2	3.4	9	3.4	30 sec irregular rhythm without p waves or 2x episodes between 10-29 sec	218	3
Proietti et. al. (2016) (69)	65747	Belgium	Belgian Heart Week screening	Omron Heartscan HCG-801	30	1	0	58	41	NR	36	21	23	0.5	20	20	2	irregular R-R interval, no distinct p waves, variable atrial cycle length	603	1.1
Kaasenbrood et. al. (2016) (68)	3269	Holland	Influenza vaccination - opportunistic screening	MyDiagnostik	60	1	0	64.1	49	NR	NR	NR	NR	2.6	NR	NR	NR	Cardiologist Interpretation x 2	37	1.1
Engdahl et. al. (2013) (154)	848	Sweden	Community screening (75-76 yr olds) in Halmstad, Sweden	Zenicor	30	2	14	75	43	NR	53	11	NR	9.6	4	10	1.9	30 sec duration of irregular rhythm or >= 2 episodes of 10 or more sec	40	4.7
Hendrikx et. al. (2013) (155)	928	Sweden	GP practices	Zenicor	10	2	28	69.8	50	NR	90.3	31.6	19.8	0	3.7	8.6	2	10 sec irregular rhythm without p waves	35	3.8
Hendrikx et. al. (2014) (162)	95	Sweden	Referred for presyncope/palpitations	Zenicor	30	2	28	54.1	44	NR	28.4	1.1	8.4	0	0	6.3	1	30 sec irregular rhythm without p waves	9	9.5
Chan et al. (2016) (67)	1013	Hong Kong	Patients ≥ 65 yrs with hypertension or diabetes	Alive Cor	60	1	0	68.4	47	NR	90.4	36.6	16.2	2.2	4.4	10.5	3	Cardiologist Interpretation	5	0.5
Sobocinski et. al. (2012) (161)	249	Sweden	Patients post TIA/stroke	Zenicor	10	2	30	72	57	NR	65	16	20	0	4	25	3	irregular rhythm of minimum 10 sec without visible p waves	15	6
Doliwa et. al. (2009) (72)	606	Sweden	Community event	Zenicor	10	1	0	NR	64	NR	NR	NR	NR	NR	NR	NR	NR	irregular rhythm without visible p waves	6	1
Ramkumar et. al. (2017) (157)	204	Australia	Community - ≥ 65 yrs with 1 or more risk factor for heart failure	Remon RM-100	60	5	7	70.1	51	29.1	72.1	56.4	5.9	0	0	NR	3	30 sec duration of irregular rhythm with absent p waves	20	9.8
Hendrikx et. al. (2017) (156)	201	Sweden	Patients referred to respiratory clinics with suspicion of obstructive sleep apnoea	Zenicor	30	2	14	56	69	30	51	10	9.2	0	4.6	3.1	NR	Irregular supraventricular extra systoles in series for 30 sec	13	6.5
Claes et. al. (2011) (158)	10758	Belgium	Community heart rhythm screening program through medical centres	Omron Heartscan 'HCG-801	30	1	0	59	38	NR	30.6	8.6	12.2	7.2	7.2	5.4	1	Irregular RR intervals, absence of p waves and variable atrial cycle length (when visible)	167	1.6
Samol et. al. (2013) (159)	132	Germany	Large proportion post stroke/TIA. Also recruited from diabetes, hypertension and dyslipidemia clinics	Omron Heartscan HCG-801	30	1	0	64	58	NR	67	27	NR	0	3	49	NR	Cardiologist Interpretation x 2	7	5.3
Battipaglia et. al. (2016) (73)	855	UK	Community shopping centre screening	MyDiagnostik	15	1	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	7	0.8
Chan et al. (2016) (117)	13122	Hong Kong	Nationwide community screening program	Alive Cor	30	1	0	64.7	29	23.7	38.2	14.8	2.2	0	0.7	2.8	NR	Software algorithm definition with minimum of 30 sec	101	0.8
Chan et al. (2017) (160)	10735	Hong Kong	Nationwide community screening program	Alive Cor	30	1	0	NR	NR	NR	NR	NR	NR	1.2	NR	NR	NR	Cardiologist interpretation (≥ 30 sec)	74	0.7

Halcox et. al. (2017) (70)	501	UK	Community based with individuals > 65 yrs with CHADS-VASC score ≥ 2	Alive Cor	30	2x per week	365	72.6	48	NR	54	26	14	0	1.0	7.0	3.0	30 second duration of an irregular rhythm without P waves	19	3.8
Gladstone et. al. (2014) (120)	277	Canada	Patients admitted with cryptogenic stroke	Holter	continuous	continuous	1	73.2	56	NR	67	19.3	14.7	0	7	12.6	NR	30 second or longer duration of irregular rhythm	9	3.2
Barthelemy et. al. (2003) (121)	60	France	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	64.4	55	NR	50	17	NR	0	NR	27	NR	fibrillatory waves associated with irregular ventricular response ratio at least 30 sec duration	8	13.3
Jabaudon et al. (2004) (122)	149	Switzerland	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	66.9	68	NR	58	16.7	16.8	4.7	NR	16.8	NR	NR	7	4.7
Koudstaal et. al. (1986) (123)	100	Holland	Retrospective study of 100 patients admitted with stroke/TIA	Holter	continuous	continuous	1	60.9	74	NR	NR	NR	41	NR	NR	NR	NR	NR	5	5
Hornig et. al. (1996) (124)	268	Germany	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	59.1	61	NR	43.7	34	NR	NR	14.9	45	NR	NR	10	3.3
Rizos et. al. (2012) (125)	496	Germany	Patients admitted with stroke/TIA	Holter	continuous	continuous	1	69	62	NR	78.8	24.6	NR	NR	NR	22.2	3	Cardiologist interpretation (≥ 30 sec)	14	2.8
Schuchert et. al. (1999) (126)	82	Germany	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	3	59.7	57	NR	36.5	NR	17.1	NR	NR	NR	NR	Small irregular baseline undulations of variable amplitudes and morphology at a rate >350/min with an irregular ventricular response for at least 1 min.	5	6
Schaer et. al. (2009) (127)	241	Switzerland	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	68.7	59	NR	76	25	41	7	NR	4.6	NR	NR	0	0
Schaer et. al. (2004) (128)	425	Switzerland	Retrospective review of patients post stroke/TIA with Holter monitoring	Holter	continuous	continuous	1	67.4	61	NR	NR	NR	NR	NR	NR	1.2	NR	Self-terminating sequence of >30 seconds of irregular RR intervals and the presence of fibrillatory P waves.	9	2.1
Shafqat et. al. (2004) (129)	465	Pakistan	Retrospective review of consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	66.8	56	NR	NR	NR	NR	NR	NR	NR	NR	NR	5	2.4
Lazzaro et. al. (2012) (130)	133	USA	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	63.1	50	NR	70	29.3	18.8	0	NR	2.3	NR	Supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with fibrillatory waves varying in amplitude, shape, and timing, replacing consistent P waves and with a duration >30 sec	8	6
Grond et. al. (2013) (131)	1135	Germany	Patients admitted in 7 German centres with stroke/TIA	Holter	continuous	continuous	3	67	55	27.4		20.4	7.3	0	5.8	17.4	NR	≥ 1 period of >30 sec duration of an absolute arrhythmia without detectable P waves and without a pattern more consistent with an alternate diagnosis	49	4.3
Stahrenberg et. al. (2010) (132)	224	Germany	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	7	68	58	27.6	72.9	22.3	14.8	0	5.2	16.2	NR	2 x Cardiologist interpretation of software algorithm detection of events	28	12.5
Ritter et. al. (2013) (133)	60	Germany	Patients admitted with cryptogenic stroke	Holter	continuous	continuous	7	61.8	57	NR	70	11.7	13.3	NR	0	NR	4	Cardiologist interpretation (> 30 sec)	1	1.7
Higgins et. al. (2013) (134)	50	Scotland	Patients admitted with stroke/TIA	Holter	continuous	continuous	7	67.1	48	NR	56	8	16	0	NR	NR	NR	Cardiologist interpretation (> 30 sec)	4	8

Hendrikx et. al. (2014) (162)	95	Sweden	Patients investigated for palpitations and presyncope	Holter	continuous	continuous	1	54.1	42	NR	28.4	1.1	8.4	0	0	6.3	1	30 sec irregular rhythm without p waves	2	2.1
Thakkar et. al. (2014) (135)	52	India	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	59.5	77	NR	51.9	23.1	15.4	0	1.7	7.7	NR	30 sec irregular rhythm without p waves	3	5.8
Wachter et. al. (2017) (136)	198	Germany	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	73.2	62	NR	80.7	26.4	9.1	0	4.6	21.7	4.8	>30 seconds rhythm with irregular RR intervals and the presence of fibrillatory P waves.	9	5
Gumbinger et. al. (2012) (137)	192	Germany	Patients admitted with stroke/TIA	Holter	continuous	continuous	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2	1
Alhadramy et. al. (2010) (138)	426	Canada	Retrospective review of patients post stroke/TIA with Holter monitoring	Holter	continuous	continuous	1	64.9	48	NR	58.2	14.1	14.1	0	1.6	6.3	NR	Irregular ventricular response in the absence of p-waves or with fibrillatory waves	11	2.5
Sobocinski et. al. (2012) (161)	249	Sweden	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	72	57	NR	65	16	20	0	4	25	3	irregular rhythm of minimum 10 sec without visible p waves	5	2
Dangayach et. al. (2011) (139)	51	USA	Retrospective audit of patients admitted with cryptogenic stroke	Holter	continuous	continuous	2	58.2	43	NR	35.3	16	15.7	7.4	NR	NR	NR	NR	15	29.4
Gunalp et. al. (2006) (140)	26	Turkey	Patients admitted with ischaemic stroke	Holter	continuous	continuous	1	66	69	NR	61	26	31	NR	NR	NR	NR	NR	11	42.3
Fonseca et. al. (2013) (141)	80	Portugal	Patients admitted with cryptogenic stroke	Holter	continuous	continuous	1	69.3	53	NR	71.3	28.8	11.3	NR	NR	22.5	NR	NR	17	21
Manina et. al. (2014) (142)	114	Italy	Patients admitted with cryptogenic stroke	Holter	continuous	continuous	4	63.1	NR	NR	52.6	9.6	NR	NR	NR	NR	NR	Irregular ventricular response in the absence of p waves or with fibrillatory waves	29	25.4
Tagawa et. al. (2007) (143)	308	Japan	Consecutive patients admitted with ischaemic stroke	Holter	continuous	continuous	1	72.6	60	NR	70.1	25.3	NR	20.4	NR	NR	NR	small irregular baseline undulations of variable amplitude and morphology at a rate of 300-350/min associated with irregular ventricular response	26	8.4
Shibazaki et. al. (2012) (144)	536	Japan	Consecutive patients admitted with ischaemic stroke	Holter	continuous	continuous	1	72.4	64	NR	65.9	25.7	9.8	NR	0.3	NR	NR	NR	12	2.2
Vandebroucke et. al. (2004) (145)	136	Belgium	Retrospective audit of patients admitted with ischaemic stroke	Holter	continuous	continuous	1	68	52	NR	NR	NR	NR	NR	NR	NR	NR	NR	7	5.1
Yodogawa et. al. (2013) (146)	68	Japan	Consecutive patients admitted with ischaemic stroke	Holter	continuous	continuous	1	69.9	54	NR	66.2	14.7	NR	NR	NR	NR	NR	irregular and uncoordinated atrial electrical activity on surface ECG lasting > 30 sec	17	25
Atmuri et. al. (2012) (147)	140	Australia	Retrospective audit of patients admitted with ischaemic stroke/TIA	Holter	continuous	continuous	1	NR	NR	NR	65	20	37.1	18.6	NR	NR	NR	NR	12	8.6
Salvatori et. al. (2015) (148)	274	Italy	Cohort study of patients ≥ 65 yrs with hypertension in multiple GP clinics	Holter	continuous	continuous	2	70	54	NR	100	15	9	7	4	2.2	NR	Cardiologist interpretation	4	1.5
Beaulieu-Boire et. al. (2013) (149)	284	Canada	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	70.6	52	NR	68.7	26.7	27.4	NR	2.2	22.3	NR	Cardiologist interpretation	18	6.3
Dogan et. al. (2011) (150)	400	Turkey	Retrospective review of patients admitted post stroke	Holter	continuous	continuous	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	40	10

Douen et. al. (2008) (151)	126	Canada	Retrospective review of patients admitted post stroke	Holter	continuous	continuous	1	NR	NR	NR	NR	NR	NR	7	NR	NR	NR	NR	9	7.1
Suissa et. al. (2012) (152)	354	France	Consecutive patients admitted with ischaemic stroke	Holter	continuous	continuous	1	62.4	57	NR	51.1	18.6	NR	0	NR	NR	NR	Cardiologist interpretation	2	0.6
Wohlhahrt et. al. (2013) (153)	224	Germany	Patients admitted with ischaemic stroke	Holter	continuous	continuous	7	68.5	59	NR	73.2	22.3	15.2	NR	5.4	24.1	NR	>30 second irregular rhythm	29	12.9

AF – Atrial Fibrillation BMI – Body Mass Index (kg/m^2) DM – Diabetes Mellitus HF – Heart Failure HTN - Hypertension IHD – Ischaemic Heart Disease

3.5.2 Overall AF detection.

The combined AF detection rate using single lead ECG monitoring (n=117,436 from 18 studies) was 1.7% (95% CI 1.4% – 2.1%). The cumulative AF detection rate using continuous (Holter) monitoring (n=8498 from 36 studies) was 5.5% (95% CI 4.4% – 6.6%). There was significant heterogeneity between studies (I^2 = 94% for single lead ECG monitoring, 87% for Holter monitoring). The overall new AF detection rate is presented in figure 3.2 (below).

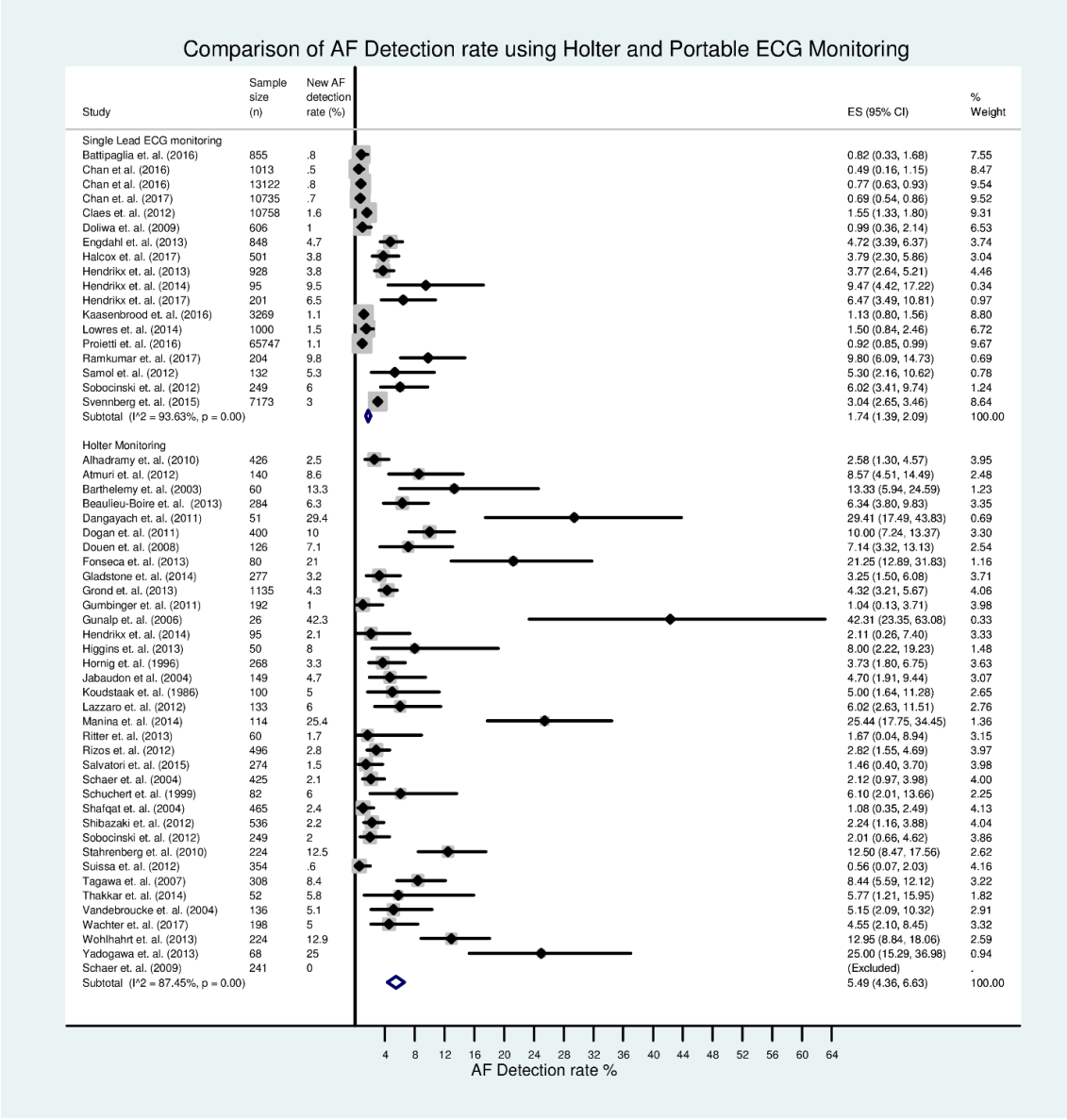

Figure 3.2 - Forest Plot showing the overall AF detection rate between single lead ECG devices and Holter monitoring.

The overall mean AF detection rate was 1.7% with single lead ECG monitoring and 5.5% with continuous Holter monitoring.

3.5.3 Comparison of multiple intermittent monitoring to 24-hour Holter.

There was significant variation in the monitoring time using both single lead and Holter monitoring which contributed to the difference in the cumulative detection rate seen in figure 3.2. Figure 3.3 compares the detection rate of multiple intermittent single lead recordings to 24-hour continuous monitoring, which is used routinely in clinical practice. There were 8 studies (n=10,199, mean weighted age 68.8±8.4 years from 6 studies, 47% male from 8 studies) that performed multiple intermittent single lead ECG recordings and 27 studies (n=6284, mean weighted age 67.8±5.1 years from 23 studies, 58% male from 23 studies) that used 24-hour Holter monitoring. From the data available, the multiple intermittent ECG group had a lower AF risk to the 24-hour Holter group (hypertension – 55% (n=8 studies) vs 65% (n=20 studies), diabetes mellitus – 15% (n=8 studies) vs 22% (n=20 studies), HF – 3.3% (n=8 studies) vs 3.9% (n=11 studies), ischemic heart disease – 11% (n=6 studies) vs 19% (n=15 studies) and previous stroke/TIA – 9% (n=7 studies) vs 16% (n=15 studies)) respectively. The combined AF detection rate was 4.8% (95% CI 3.6–6.0%) using multiple intermittent ECG recordings. The cumulative AF detection rate using 24-hour Holter monitoring was 4.6% (95% CI 3.5–5.7%).

3.5.4 Association between monitoring time and AF detection.

Using single lead ECG devices, we found a moderate linear relationship between the total monitoring time and AF detection rate (β=0.13, R^2 = 0.42). Using this formula, we noted that approximately 19 minutes of total intermittent monitoring produced similar AF detection to 24-hour continuous monitoring (figure 3.4). The study by Halcox et. al. was an outlier, with a much lower AF detection rate than other studies (3.8% from 52 minutes of total monitoring) and this reduced the linear correlation between total monitoring time and AF detection rate (70). Exclusion of these data led to a stronger linear relationship (β=0.26, R^2 = 0.80) and a much lower total intermittent monitoring time required (12 min) to produce a similar AF detection rate to 24-hour Holter monitoring.

3.5.5 Meta-regression.

Sources of heterogeneity in the 18 studies using single lead ECG monitoring were investigated using meta-regression (Table 3-2). Monitoring time per participant (β=0.11, 95% CI 0.04-0.18, p=0.005) and body mass index (β=1.1, 95% CI 0.58-1.5, p=0.01) were associated with AF detection.

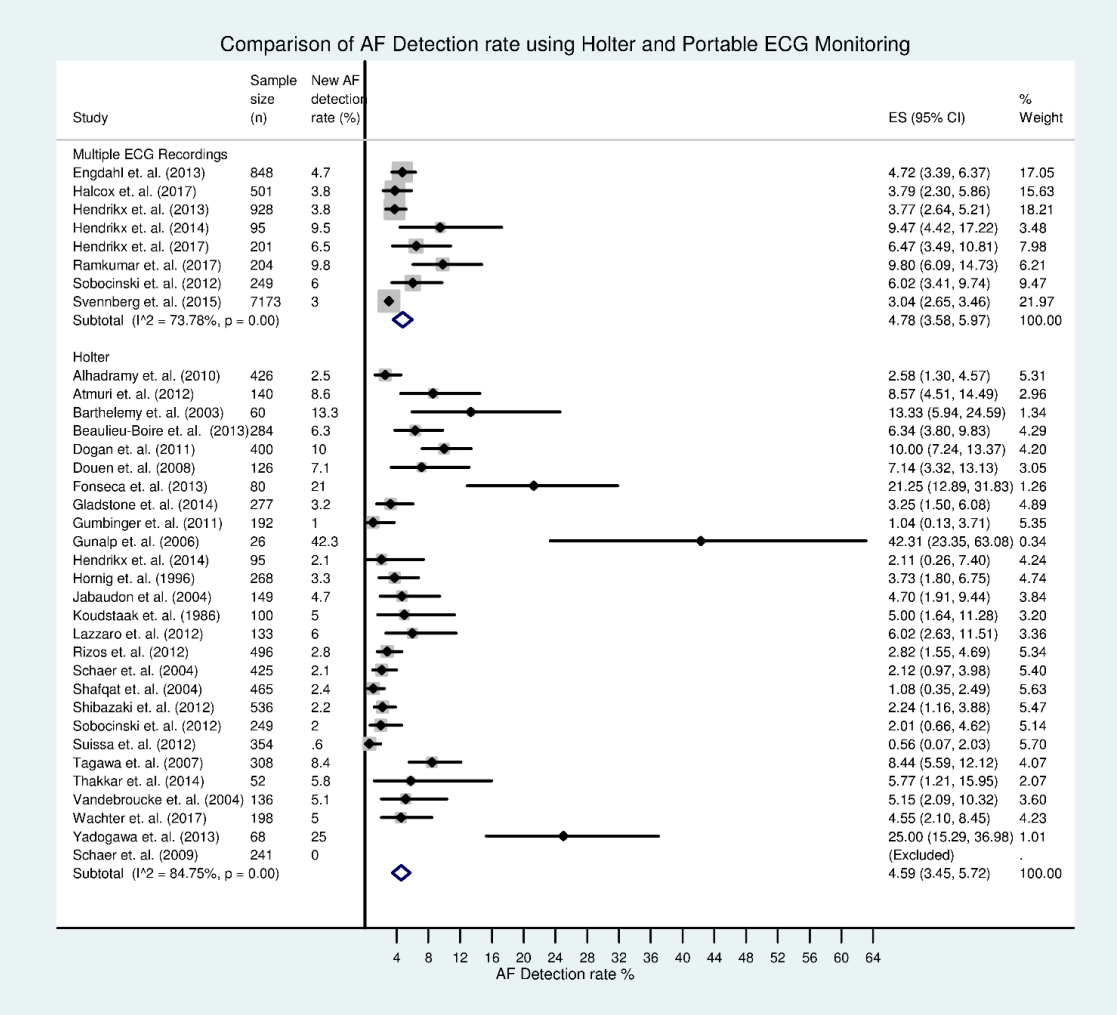

Figure 3.3 - Forest Plot comparing the AF detection rate between 24 hour Holter monitoring and performing multiple intermittent single lead ECG recordings.

The AF detection rate between studies that performed multiple intermittent single lead ECG recordings and 24-hour Holter monitoring were similar (4.8% vs 4.6%).

Table 3-2 - Meta Regression Analysis for AF detection (Single lead ECG studies).

Variable	Number of studies	β (95% C.I)	P value
Age (years)	15	0.00 (-0.22 – 0.24)	0.95
Monitoring time per participant (min)	18	0.11 (0.04 – 0.18)	0.005
Body Mass Index (kg/m^2)	4	1.1 (0.58 – 1.5)	0.01
CHADS Score (%)	11	-0.13 (-2.6 – 2.4)	0.91
Hypertension (%)	14	0.01 (-0.08 – 0.10)	0.75
Previous diagnosis of AF (%)	16	-0.13 (-0.50 – 0.24)	0.46
Ischaemic Heart Disease (%)	12	-0.10 (-0.42 – 0.21)	0.48
Previous stroke (%)	13	0.06 (-0.09 – 0.19)	0.45
Male gender	16	0.10 (-0.04 – 0.24)	0.16

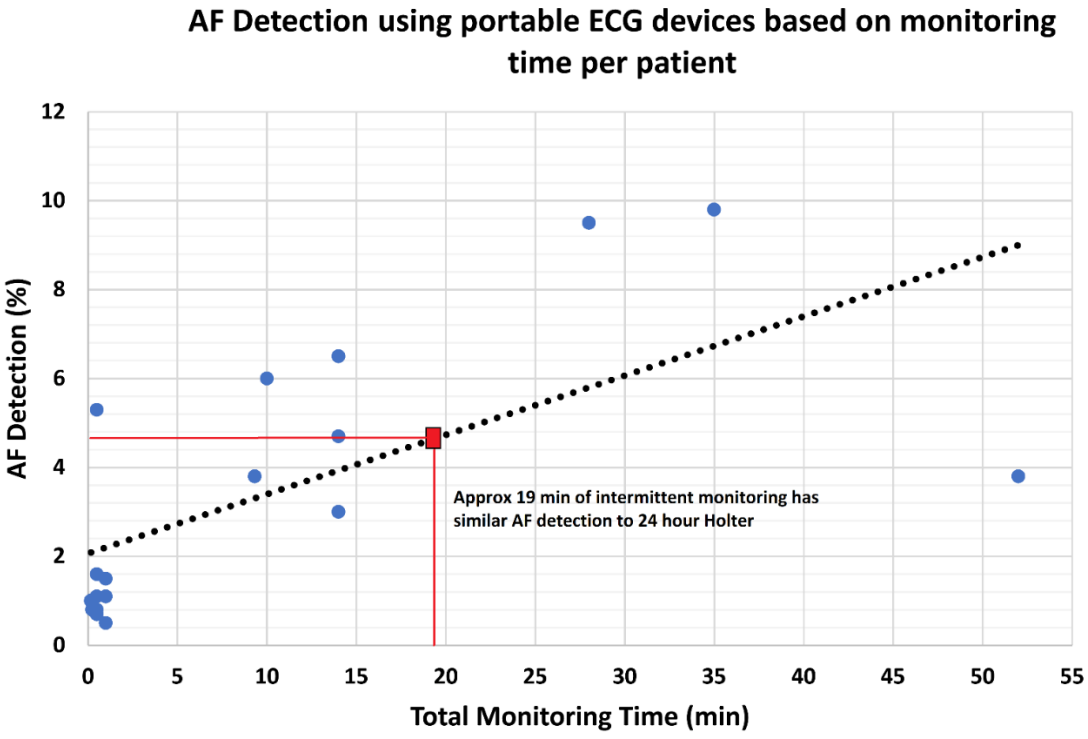

Figure 3.4 - Graph showing the linear relationship between total monitoring time and AF detection rate in single lead ECG devices.

AF detection was higher with increased monitoring time. Approximately 19 minutes of intermittent single lead ECG recording produced equivalent AF detection to 24-hour Holter monitoring.

3.5.6 Sensitivity Analysis.

A number of outlier studies were observed in the meta-analysis that could influence the cumulative AF detection rate (139-142, 146). Removal of these outlier studies resulted in a reduction in the overall AF detection rate in all Holter studies (table 3-3) and for 24 hour Holter studies (table 3-4). When these outlier studies were removed the overall AF detection rate for 24 hour Holter was 3.86% (95% C.I 2.88% – 4.83%), much lower than the detection rate by multiple intermittent ECG recordings using portable single lead devices (4.78%, 95% C.I 3.58% – 5.97%). A cumulative meta-analysis (figure 3.5) did not show any significant variation in the AF detection rate over time using either Holter or single lead ECG monitoring.

Table 3-3 - Outlier studies omitted (all Holter studies) to assess the change to the overall AF detection rate.

Study Omitted	Overall AF detection rate (%)	95% C.I (%)
Dangayach et. al. (2011)	5.27	4.17 – 6.38
Fonseca et. al. (2013)	5.26	4.15 – 6.36
Gunalp et. al. (2006)	5.32	4.21 – 6.42
Manina et. al. (2014)	5.11	4.03 – 6.20
Yadogawa et. al. (2013)	5.25	4.14 – 6.35
All studies excluded	4.31	3.36 – 5.26

Table 3-4 - Outlier studies omitted (24 hour Holter) to assess the change to the overall AF detection rate.

Study Omitted	Overall AF detection rate (%)	95% C.I (%)
Fonseca et. al. (2013)	4.30	3.21 – 5.39
Gunalp et. al. (2006)	4.39	3.30 – 5.47
Yadogawa et. al. (2013)	4.30	3.22 – 5.38
All studies excluded	3.86	2.88 – 4.83

3.5.7 Publication bias.

Publication bias was explored using a funnel plot of all included studies (supplementary figure 3.6). There was significant publication bias in both single lead ECG device and Holter monitoring studies (Egger test, $p=0.003$ and $p<0.001$ respectively).

3.5.8 Quality of studies.

A summary of the quality analysis (Supplemental Table 3-6) showed that overall quality of reporting was moderate. All studies described the primary objective of the trial and included a summary of the main findings. Detailed comorbidities of the study participants were only adequately reported in 28/52 (54%), and limitations were discussed in 35/52 (67%) of studies. Most had a very selective patient population, 31/52 (60%) were post stroke/TIA cohorts.

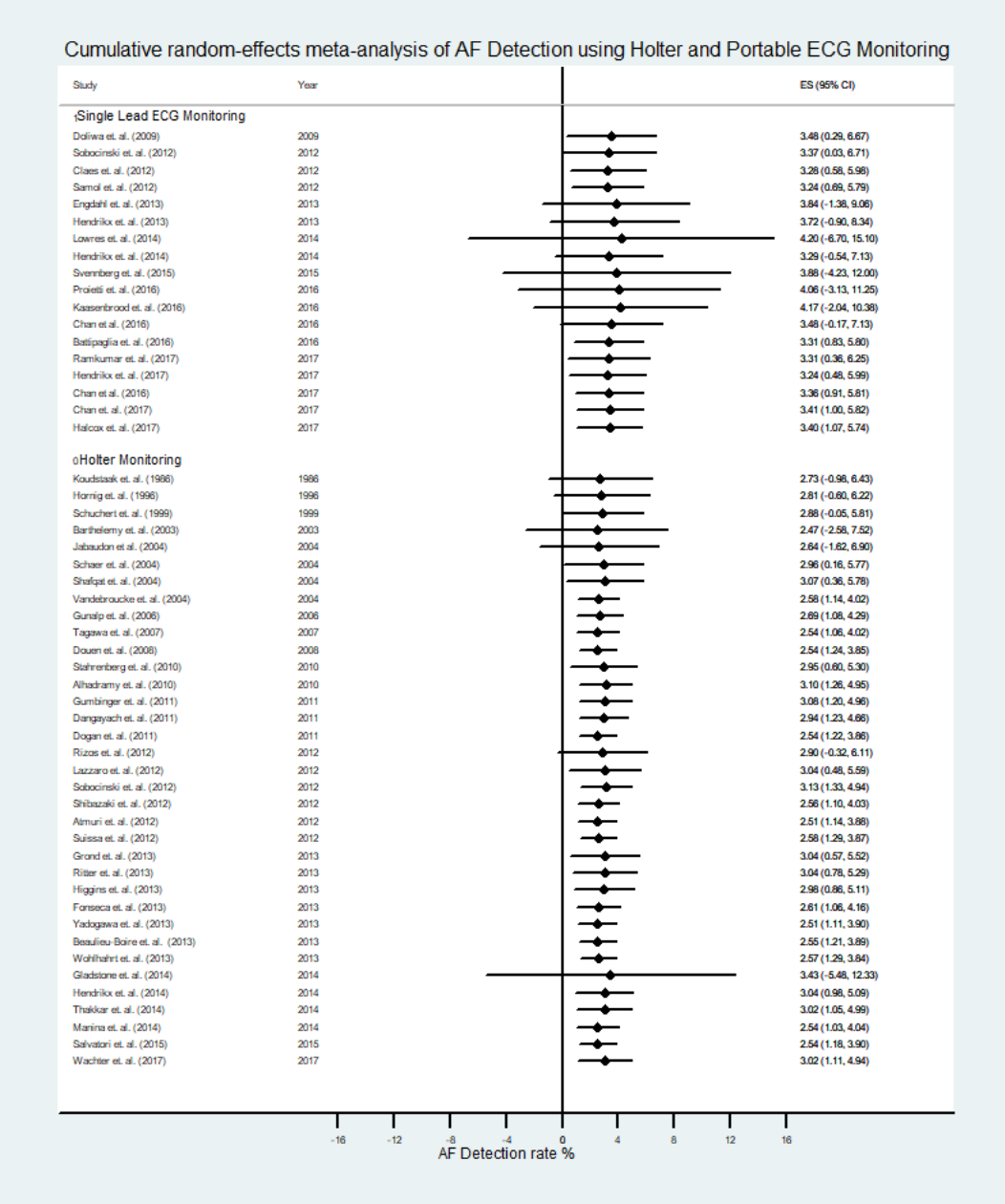

Figure 3.5 - Cumulative Meta-analysis showing minimal variation in AF detection over time using Holter and single lead ECG devices.

Studies sorted based on chronological order – there was minimal variation in AF detection over time.

3.6 Discussion

Our study is the only systematic review that we are aware of that has studied the overall AF detection rate of single lead portable ECG devices. The results of our systematic review suggest a linear relationship between monitoring time per patient and AF detection rate. Single timepoint screening has an approximate 1% AF detection rate which can be increased to around 5% when multiple recordings

are performed. We noted that approximately 19 minutes of intermittent monitoring produced similar detection rates to conventional 24 hours continuous Holter monitoring.

3.6.1 Early diagnosis of AF

AF creates a significant burden on both patients as well as the health care system. AF will continue to rise in incidence and the costs to the health care system will continue to increase, due to aging, sedentariness, and the prevalence of obesity and the metabolic syndrome (12, 16). Early diagnosis offers the possibility for early initiation of treatment which may reduce the occurrence of the complications which may lead to reduced hospital admissions and associated health care costs. Early treatment for AF can be achieved in different ways. Patients with subclinical AF have an increased risk of stroke and cardiovascular events, like those with established AF (8, 163). Anticoagulation may help reduce the incidence of stroke in this cohort.

The close relationship between metabolic syndrome and AF has encouraged research into the benefits of lifestyle intervention. Aggressive lifestyle intervention in patients with AF undergoing catheter ablation has been reported to lead to a reduction in symptom burden, improved quality of life and the need for repeat ablation procedures (23). It remains to be tested whether initiation of lifestyle intervention and aggressive risk factor modification following the early diagnosis of AF may be associated with positive LA remodeling and reduction of disease progression. Such a process may lead to additional health benefits, including reduction in cardiovascular risk and improvement in exercise capacity.

3.6.2 AF screening and feasibility.

AF is a leading cause of stroke and HF in the community. As well as an association with increased all-cause mortality, it is associated with reduced quality of life. The availability of preventive therapies, including anticoagulation, has led to increasing recognition of the importance of AF screening for early diagnosis. However, AF screening shares the limitations of screening with other diagnostic tests. The screening tool must have high sensitivity and needs to be inexpensive and cost effective. We also need to minimize and have a method of addressing false positives. Current guidelines recommend opportunistic screening using pulse palpation and 12 lead ECG (57). In a previous systematic review

this was associated with a new AF detection rate of approximately 1% (62, 112). Pulse palpation may be non-specific in patients with other irregular rhythms such as ventricular ectopy, and 12 lead ECG is only able to capture a single timepoint for screening. There are multiple other methods for AF detection. Continuous Holter monitoring is probably the most commonly used in clinical practice, especially in stroke cohorts. It has the potential advantage of assessing heart rhythm throughout the day and may be useful in detecting nocturnal subclinical AF. However, the disadvantages include the cost of Holter monitoring (especially for mass screening), the inconvenience of leads and electrodes (which may affect compliance), and typical limitation to 1-2 days of capture (as extended periods are more cumbersome and less cost-effective. Other event recorders are again expensive and limited to symptomatic patients. Extended period monitoring using implantable devices have shown promise in the cryptogenic stroke population (where many have been diagnosed with paroxysmal AF), (43) but they are invasive and not feasible for mass screening.

Portable single lead ECG devices permit multiple 30-60 second recordings to be captured and downloaded to a computer. These devices have several potential advantages over Holter monitoring. They are leadless and require finger contact (and are hence easy to use and acceptable to patients). They have a high degree of sensitivity for identifying AF (1, 164, 165). Most interface with a web-based cloud system where ECG rhythms can be wirelessly transferred to clinicians, allowing rapid analysis and diagnosis. The development of automated algorithms to detect AF is helpful for mass screening. In two small studies they have demonstrated superior AF detection compared with 24 hour Holter monitoring (161, 162). Although screening using these portable devices are currently not in the latest AF guidelines, they may offer a feasible option for mass screening. Screening using these devices has been demonstrated to be cost effective (78).

We noted a moderate linear association between monitoring time and AF detection rate. Single timepoint screening for 30-60 sec achieved an overall detection rate of approximately 1%. This is no better than what has been reported using pulse palpation or 12 lead ECG, hence does not add any incremental benefit in screening programs (79, 112). Multiple intermittent recordings improve AF detection; we found that at least 19 minutes of total monitoring should be performed to achieve detection rates similar to 24 Holter monitoring.

The linear relationship between monitoring time and AF detection rate (R^2=0.80) and the reproduction of AF detection rates of 24 hour Holter monitoring with only 12 minutes of intermittent monitoring was possible in our study only after exclusion of an outlier (70). Despite the inclusion of elderly participants with at least one risk factor for AF, the use of a validated single lead ECG device and a prolonged monitoring period, that study had a lower AF detection rate (3.8%) than the remaining studies, even using a shorter monitoring period (78, 154, 155). Relatively low rates of adherence (only approximately 25% completed 2 x 30 second ECG recordings every week for the full year of monitoring) may be a potential explanation for the lower AF detection rate noted (70).

3.6.3 Limitations.

There are several challenges inherent in this meta-analysis of studies investigating AF detection. The most important is the target screening population. Most studies did not report the CHADS or CHA_2DS_2-VASC score, a history of previous stroke, or other co-morbidities. Consequently, it was difficult to ascertain if the risk profiles of patients in these studies were equivalent. Most Holter monitoring studies were performed in the stroke population – which is likely a population with higher AF risk than many studies using portable ECG devices, which recruited mainly healthy participants or those with AF risk factors from the community. The significant heterogeneity amongst both Holter and portable ECG device studies make it difficult to perform direct comparisons between both groups. The type/duration of monitoring and type of device used will also influence the overall AF detection rate and varied significantly between studies. There are several possible confounders which may not have been taken into account. The validity of the linear regression analysis comparing detection time and rate may be limited due to the significant differences in study population, study design and AF definitions. However, despite these limitations, the analysis may provide some important inferences into AF screening. Multiple intermittent ECG recordings achieved a similar AF detection rate to 24-hour Holter monitoring. This may suggest that in a similar cohort of patients with the same comorbidities, single lead intermittent monitoring may be superior for AF detection.

Compared to 24-hour continuous monitoring, single lead portable ECG monitoring is more patient dependent. Good patient compliance is essential to obtain multiple readings across different timepoints

which improves sensitivity. The analysis performed does not take into account patient compliance as this is difficult to assess and poorly reported across the individual studies. Most single lead device manufacturers have proprietary automated AF detection algorithms which were used for diagnosis. Not all of these algorithms have had rigorous testing and comparison to a reference standard. It is also difficult to distinguish AF from other supraventricular tachycardias using single lead ECG devices as the P wave is often not readily discernible. The use of different automated algorithms makes AF definitions non-standardized and can potentially create issues with both over and underdiagnoses.

There are other limitations in this analysis. The efficacy of intermittent monitoring is critically dependent on AF burden and density. All studies varied in their monitoring period and strategy. The linear regression model used was able to determine a total intermittent monitoring time which produced similar AF detection rates to 24-hour continuous monitoring. However, it is difficult to translate the total monitoring time into an effective monitoring strategy. For example, we are unable to determine from our analysis if 12 x 60 second recordings over 12 consecutive days is different to 2 x 60 second recordings daily for 6 consecutive days. The definitions of AF also vary between studies. Many are based on individual physician interpretation and criteria for diagnosis were not explicitly specified. The duration of AF varied from 10-30 seconds between studies, although a cut-off of 30 seconds, was the most widely adopted practice.

3.7 Conclusion.

Single lead portable ECG devices may offer an efficient screening option for AF compared to 24 hr. Holter monitoring. Total monitoring time is related with AF detection and a total of 19 minutes may achieve a similar detection rate to 24-hour Holter monitoring.

3.8 Appendix

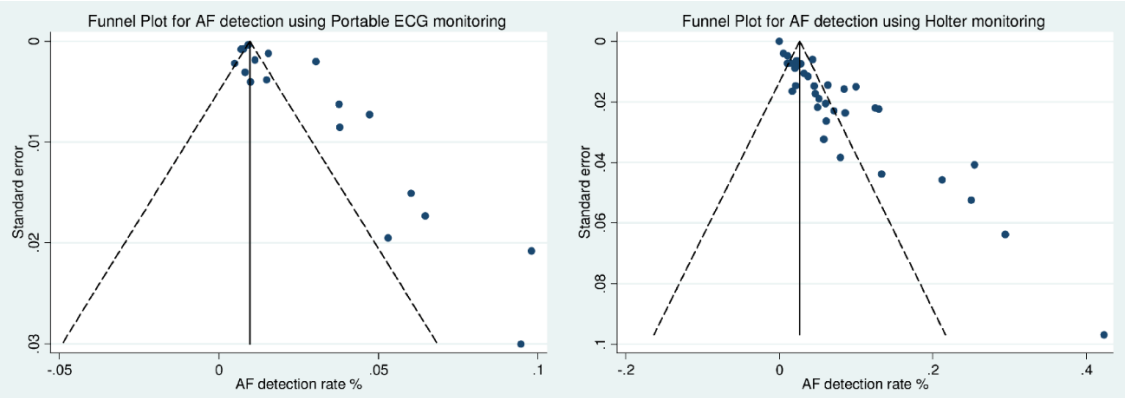

Figure 3.6 (Supplementary figure) - Funnel Plots for Holter monitoring and single lead ECG device studies.

There was significant publication bias in both single lead ECG monitoring and Holter monitoring studies

Table 3-5 (Supplementary Table) - Summary of excluded studies in the meta-analysis.

Author	Year	Reason for exclusion
Barrett et. al.	2014	Primary outcome not AF detection
Bhatt et. al.	2011	28-day event recorder used for AF detection
Kamel et. al.	2013	21-day mobile cardiac outpatient telemetry unit used for AF detection
Miller et. al.	2013	30-day mobile cardiac outpatient telemetry unit used for AF detection
Rabenstein et. al.	2013	21-day mobile cardiac outpatient telemetry unit used for AF detection
Tayal et. al.	2008	21-day mobile cardiac outpatient telemetry unit used for AF detection
Flint et. al.	2012	30-day event recorder used for AF detection
Christensen et. al.	2014	Implantable loop recorder used for AF detection
Cotter et. al.	2013	Implantable loop recorder used for AF detection
Dion et. al.	2010	Implantable loop recorder used for AF detection
Sanna et. al.	2014	Implantable cardiac monitor used for AF detection
Merce et. al.	2013	Implantable loop recorder used for AF detection
Elijovich et. al.	2009	30-day event recorder used for AF detection
Wallmann et. al.	2007	Serial 7-day event recorders used for AF detection
Kral et. al.	2015	Substudy (poster) only investigating patients <40 yrs
Lip et. al.	2016	AF detection not primary objective
Anczykowski et. al.	2016	Trans-telephonic event recorder used for arrhythmia detection
Baturova et. al.	2016	AF detection not primary objective
Yu et. al.	2009	Retrospective review with missing demographic data and AF detection not primary objective
Destaghe et. al.	2016	Primary purpose was assessing test performance of 2 different ECG devices
Lowres et. al.	2016	Post cardiothoracic surgery patients with known episode of AF post-op
Benito et. al.	2015	12 lead ECG used for screening
Bury et. al.	2012	3 lead ECG used for screening
Turakhia et. al.	2015	Wearable patch used for ambulatory monitoring
Tieleman et. al.	2014	AF screening not primary objective
Rabenstein et. al.	2015	Review article
Sposato et. al.	2015	Review article
Schnabel et. al.	2009	Main aim was to develop an AF risk score
Chamberlain et. al.	2011	Main aim was to develop an AF risk score
Lowres et. al.	2013	Review article
de Vito et. al.	2014	AF in post orthopaedic surgery patients with inpatient monitoring
Magee et. al.	2007	Post cardiothoracic surgery patients with inpatient monitoring
Her et. al.	2013	Post cardiothoracic surgery patients with inpatient monitoring
Freedman et. al.	2016	Editorial article
Turakhia et. al.	2016	Review article

Levin et. al.	2015	Cost analysis primary objective
Fitzmaurice et. al.	2007	Pulse palpation used for AF detection
Rhys et. al.	2013	Pulse palpation used for AF detection
Ziegler et. al.	2010	Used implantable devices for AF detection
Akiyama et. al.	2017	Wearable patch used for AF detection
Thom et. al.	2016	Review article
Engdahl et. al.	2017	Trial design paper
Rojo-Martinez et. al.	2013	Implantable cardiac monitor used for AF detection
Poisson et. al.	2011	Review article
Etgen et. al.	2013	Implantable cardiac monitor used for AF detection
Marazzi et. al.	2012	Blood Pressure monitor used for AF detection
Wiesel et. al.	2014	Blood Pressure monitor used for AF detection
Lewis et. al.	2011	Finger probe plethysmography used for AF detection
McManus et. al.	2016	Iphone based plethysmography used for AF detection
Shanmugam et. al.	2012	Heart failure patients with cardiac resynchronization therapy
Keach et. al.	2015	Review article
Borian et, al.	2014	Implantable devices used for AF detection
Alonso et. al.	2013	Primary aim was to determine clinical score to assess AF risk
Steven et. al.	2016	Trial design paper - wearable sensors for AF detection
Lau et. al.	2013	Primary aim was to determine accuracy of AF algorithm
Gaillard et al.	2010	Transtelephonic monitoring used for AF detection
Orlov et. al.	2007	AF detection based on patients with permanent pacemakers
Martinez et. al.	2014	Primary aim was to determine prognosis of patients with subclinical AF
Wang et al.	2017	Trial design paper

Table 3-6 (Supplementary Table) - Summary of quality analysis of included studies.

Study	Objective and outcome described	Appropriate reporting of comorbidities	Inclusion criteria specified	Incomplete Outcome Data	Efforts to reduce bias	Limitations discussed	External validity of study discussed
Lowres et. al. (2014)	Yes	Yes	Yes	No	No	No	Yes
Svennberg et. al. (2015)	Yes	Yes	Yes	No	No	Yes	Yes
Proietti et. al. (2016)	Yes	Yes	Yes	No	No	Yes	Yes
Kaasenbrood et. al. (2016)	Yes	No	Yes	Yes	No	Yes	No
Engdahl et. al. (2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hendrikx et. al. (2013)	Yes	Yes	Yes	No	No	Yes	Yes
Hendrikx et. al. (2014)	Yes	Yes	Yes	No	No	Yes	Yes
Chan et al. (2016)	Yes	Yes	Yes	Yes	No	No	Yes
Sobocinski et. al. (2012)	Yes	Yes	Yes	No	No	Yes	Yes
Doliwa et. al. (2009)	Yes	No	Yes	No	No	Yes	Yes
Ramkumar et. al. (2017)	Yes	Yes	Yes	No	No	Yes	Yes
Hendrikx et. al. (2017)	Yes	Yes	Yes	No	No	Yes	Yes
Claes et. al. (2011)	Yes	Yes	Yes	Yes	No	Yes	Yes
Samol et. al. (2012)	Yes	Yes	Yes	No	No	Yes	Yes
Battipaglia et. al. (2016)	Yes	No	No	No	Yes	Yes	Yes
Chan et al. (2016)	Yes	Yes	Yes	No	Yes	Yes	Yes
Chan et al. (2017)	Yes	No	Yes	No	No	Yes	Yes
Halcox et. al. (2017)	Yes	Yes	Yes	No	No	Yes	Yes
Gladstone et. al. (2014)	Yes	Yes	Yes	No	Yes	Yes	Yes
Barthelemy et. al. (2003)	Yes	Yes	Yes	No	Yes	No	No
Jabaudon et al. (2004)	Yes	Yes	Yes	No	No	No	Yes
Koudstaal et. al. (1986)	Yes	No	Yes	No	No	No	No
Hornig et. al. (1996)	Yes	No	Yes	No	Yes	No	Yes
Rizos et. al. (2012)	Yes	Yes	Yes	No	Yes	Yes	Yes
Schuchert et. al. (1999)	Yes	No	Yes	No	No	No	No
Schaer et. al. (2009)	Yes	Yes	Yes	No	No	Yes	Yes
Schaer et. al. (2004)	Yes	No	Yes	No	No	Yes	Yes
Shafqat et. al. (2004)	Yes	No	Yes	No	No	No	Yes
Lazzaro et. al. (2012)	Yes	Yes	Yes	No	No	Yes	Yes
Grond et. al. (2013)	Yes	Yes	Yes	Yes	Yes	No	Yes
Stahrenberg et. al. (2010)	Yes	Yes	Yes	Yes	Yes	No	Yes
Ritter et. al. (2013)	Yes	Yes	Yes	No	No	No	Yes
Higgins et. al. (2013)	Yes	No	Yes	No	Yes	Yes	Yes
Thakkar et. al. (2014)	Yes	Yes	Yes	No	Yes	Yes	Yes
Wachter et. al. (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gumbinger et. al. (2012)	Yes	No	Yes	No	Yes	No	Yes
Alhadramy et. al. (2010)	Yes	Yes	Yes	No	Yes	Yes	Yes

Dangayach et. al. (2011)	Yes	Yes	Yes	No	Yes	No	Yes
Gunalp et. al. (2006)	Yes	No	Yes	No	Yes	No	No
Fonseca et. al. (2013)	Yes	Yes	Yes	No	Yes	Yes	Yes
Manina et. al. (2014)	Yes	No	Yes	No	Yes	No	Yes
Tagawa et. al. (2007)	Yes	No	Yes	No	Yes	Yes	Yes
Shibazaki et. al. (2012)	Yes	Yes	Yes	No	Yes	Yes	Yes
Vandebroucke et. al. (2004)	Yes	No	Yes	No	No	Yes	Yes
Yodogawa et. al. (2013)	Yes	No	Yes	No	Yes	Yes	Yes
Atmuri et. al. (2012)	Yes	No	Yes	No	No	Yes	Yes
Salvatori et. al. (2015)	Yes	Yes	Yes	No	Yes	No	Yes
Beaulieu-Boire et. al. (2013)	Yes	Yes	Yes	No	Yes	Yes	Yes
Dogan et. al. (2011)	Yes	No	Yes	No	No	Yes	No
Douen et. al. (2008)	Yes	No	Yes	No	Yes	No	No
Suissa et. al. (2012)	Yes	No	Yes	No	Yes	Yes	Yes
Wohlhahrt et. al. (2013)	Yes	Yes	Yes	No	Yes	Yes	Yes

3.9 Postscript

The choice of monitoring technology is critical to an effective screening program for AF. Single lead ECG monitoring devices are an attractive technology for AF screening given the ease of use for patients, the potential for an automated AF detection algorithm and high sensitivity. The findings from this chapter support the use of this technology in AF screening programs. Performing multiple intermittent recordings may improve the AF detection rate, and the results from our analysis suggests that around 20 recordings (each 60 second) can reproduce the detection rates of Holter monitors. However, limitations must be addressed. The impact of age was not explored in the analysis, and comparison of single lead ECG and Holter monitoring may not take into account important confounders and patient selection. This may have influenced the results of our study.

Since this study was published, there have been other important screening technologies which have been investigated. The mSTOPS study investigated the role of a monitoring patch for AF detection (166). The Apple Heart study recently demonstrated that smartwatch technology could be adopted for AF screening (167). There have also been recent trials showing the utility of implantable loop recorders for AF detection (64, 65).

The challenges that we encountered using these devices are discussed in chapter 12. Although we take technology for granted, for an elderly cohort, they may be difficult to use and manual dexterity may be required. The main strength and indeed its major weakness with this technology is that patient involvement is required. It empowers patients to take an active role in screening which is clearly an advantage. However, in patients with poor compliance or mild cognitive impairment, getting a diagnostic screening sample may be difficult.

Having decided on the screening technology, the next most important question is deciding on which cohort of patients to screen for AF and how to identify those at risk of developing AF. In the next two chapters, we investigate novel risk factors for AF (functional capacity and regional SES).

Section II – Assessing AF risk.

Chapter 4.
Selection of patients for AF screening

"Relation of Functional Status to Risk of Development of Atrial Fibrillation "

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Reference

Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Sanders P, Marwick TH. Relation of Functional Status to Risk of Development of Atrial Fibrillation. American Journal of Cardiology. 2017 Feb 15;119(4):572-8.

4 Selection of Patients for AF screening

4.1 Preface

AF is associated with reduced exercise capacity and quality of life. However, it is difficult to identify patients at risk of developing AF. Traditional clinical risk scores have poor discriminative ability. Thus, we need to identify more novel risk factors which can be incorporated in our risk assessment models.

Patients with AF who have had catheter ablation have reduced symptom burden and recurrence rates with the implantation of aggressive risk factor modification programs which includes increased physical activity (23). The traditional viewpoint has been that those with reduced exercise capacity are more likely to have associated co-morbidities such as hypertension, obesity and diabetes mellitus which are strongly associated with AF risk. However, it has not been established if reduced exercise capacity itself contributes to increased AF risk. There may be multiple potential mechanisms such as increased risk of comorbidities such as obesity and diabetes, negative LA remodelling related to inactivity and other neurohormonal pathways that are not fully understood.

In this chapter, we explore the potential association between functional capacity and AF risk in a cross-sectional analysis of patients recruited for AF screening. The following chapter was published in the American Journal of Cardiology.

4.2 Abstract

Background: Identifying patients at risk is now important as there are demonstrable ways to alter disease progression which could potentially prevent atrial fibrillation (AF) and its complications. We sought whether impaired functional capacity was associated with risk of AF, independent of myocardial dysfunction.

Methods: In this community-based study, asymptomatic participants ≥ 65 years were recruited if they had ≥1 risk factor (e.g. hypertension, diabetes mellitus and obesity). Participants underwent baseline echocardiography (including measurement of myocardial mechanics) and six-minute walk test (SMWT). The CHARGE-AF score was used to calculate 5-year risk of developing AF. Receiver operator characteristics (ROC) curves were used to assess for independent risk factors for AF.

Results: A total of 607 patients (age 71±5 years, male 47%) were studied at baseline and followed for at least 6 months. Patients in the higher AF risk groups were older and had increased rates of hypertension, diabetes mellitus and ischemic heart disease ($p<0.05$). Higher AF risk was associated with lower exercise capacity, independent of lower mean global longitudinal strain (GLS), global circumferential strain (GCS), higher mean E/e' ratio, indexed left atrial (LA) volume and LV mass. Multivariable linear regression confirmed association of LV and functional capacity parameters with AF risk. Although functional capacity is impaired in AF, this association precedes the onset of AF.

Conclusion: Poor functional status is associated with AF risk, independent of LV function.

4.3 Introduction

Atrial fibrillation (AF) is associated with significant morbidity and mortality, (17, 168) including stroke, HF with impaired and preserved ejection fraction, (169) functional impairment, (170) and poor prognosis (171). Although the prevalence of atrial fibrillation (AF) continues to increase in the aging population, there is currently not a proactive management approach in which patients at risk of AF are identified and treated before the onset of symptoms or complications. Earlier diagnosis of AF might have several benefits. The risk of AF increases following episodes of AF (172) and this likely contributes to atrial remodelling and altered mechanics (173). Early diagnosis may allow prevention of complications such as stroke and HF, and prevention may avoid the symptoms, impaired quality of life and overall burden on the health care system associated with AF (17, 168). When implemented early, lifestyle interventions (e.g. weight loss) have been associated with a reduction in symptom burden as well as improved cardiac remodelling (116). Such an approach to prevention may be analogous to stage B HF, (174) the diagnosis of which in patients with risk factors permits the early implementation of pharmacological therapy and risk factor management to prevent or delay the onset of symptomatic HF. The risk factors for AF (hypertension, obesity and the metabolic syndrome) are common and not specific. We sought whether the detection of impaired functional capacity could better characterize risk of AF.

4.4 Methods.

4.4.1 Study Population

This observational cohort study recruited patients from a large community based in Tasmania, which had the primary objective of early detection of HF. Asymptomatic participants ≥65 years were recruited if they had 1 or more risk factors, including hypertension (systolic blood pressure > 140mmHg or pre-existing use of anti-hypertensive medications), T2DM (based on self-report of diagnosis or the current use of diabetic medications), obesity (defined as a body mass index ≥ 30), previous chemotherapy, previous history of coronary artery disease or family history of HF. Exclusion criteria included: (1) Inability to provide written consent to participate in the study, (2) history of moderate or greater valvular

disease, (3) known history of HF, (4) reduced left ventricular (LV) systolic function on baseline echocardiogram (LV ejection fraction <40%), (5) contraindications to beta blockers and angiotensin converting enzyme inhibitors, (6) expected life expectancy of less than one year or (7) inability to acquire interpretable images from baseline echocardiogram. All patients with a known history of AF or documented AF on baseline electrocardiography (ECG) were excluded from the study. All patients were provided written informed consent and ethics approval was obtained from the institution's Human Research Ethics Committee.

4.4.2 Clinical data collection

All participants undertook a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, medical history, medication history as well as baseline examination data (height, weight, body mass index and blood pressure was recorded for all participants. Baseline ECG and echocardiography was conducted in all participants.

The CHARGE-AF score(22) uses 12 clinical parameters (age, race, height, weight, systolic/diastolic blood pressure, current smoking, use of anti-hypertensives, history of diabetes mellitus/myocardial infarction, history of HF and ECG data (voltage criteria for left ventricular hypertrophy and PR interval) to assess 5 year risk of AF. Cardiovascular fitness was assessed using the six-minute walk test (SMWT). This was conducted in marked corridors adjacent to the clinic where the total distance covered over six minutes was calculated to the nearest meter. All patients answered questionnaires to assess overall quality of life and function. These included the Duke Activity Status Index (DASI)(103), Minnesota Living with Heart Failure score (MLHF)(104), Charlson Index(105) and EuroQoL5D Visual Analog Scale (EQ-VAS).(106)

4.4.3 Echocardiography

Echocardiograms were performed by qualified sonographers using the same equipment (Siemens ACUSON SC2000, Siemens Healthcare, CA) and transducer (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz). Two-dimensional, M-Mode and Doppler measures were obtained using techniques outlined by the American Society of Echocardiography. LV dimensions were calculated in both diastole and systole

in parasternal long axis views. LV hypertrophy was defined as LV mass index >115 g/m^2 in men and >95 g/m^2 in women. LV and left atrial (LA) volumes were indexed to body surface area and calculated by the Simpson biplane method. Abnormal LA volume index was defined as ≥34 ml/m^2.

Diastolic function was assessed by calculating mitral inflow peak early and late diastolic velocities (E and A wave), deceleration time and the E/A ratio (ratio <0.8 was used to define for impaired relaxation). The average of septal and lateral mitral annular early diastolic velocity (e') was used to calculate the E/e' ratio (> 13 was used to define raised LA filling pressures).

Global longitudinal strain (GLS) was calculated in apical 4 chamber views and global circumferential strain (GCS) was calculated in the mid-LV parasternal short axis view. Velocity vector imaging was used to assess ventricular strain. Manual tracing of the endocardial border of the LV was performed in end-systole and this was tracked during the cardiac cycle.

4.4.4 Statistical Analysis

Patients were split into four groups based on AF risk (low 0-5%, medium 5-10%, high 10-15% and very high >15%). The primary outcome was to assess whether poor functional capacity was an independent risk factor for AF. All categorical variables are presented as frequencies/percentages and continuous variables presented as means/standard deviation (if normally distributed) or medians/IQR (if non-parametric). Statistical significance was performed using the chi square test for categorical data. Analysis of variance (ANOVA) was used to assess the interaction between groups. Associations between variables were assessed using linear regression. All variables with $p<0.1$ in univariable analyses were considered in multivariate models. ROC curves were generated to determine optimal cut-off values of continuous variables. Analyses were considered to be statistically significant if 2 tailed p values were <0.05. Statistical analysis was performed using SPSS v.22 (IBM, Chicago, Illinois).

4.5 Results

4.5.1 Patient Characteristics

A total of 607 patients were included (mean±SD age 70.9±4.8 years, male 47%). The majority of patients had risk factors for HF and AF including T2DM (51%), obesity (43%), hypercholesterolemia (51%) and hypertension (79%). The median AF risk (CHARGE-AF) was 7.0% (IQR 3.5–10.5%). Baseline patient characteristics are summarized in Table 4-1.

Table 4-1 - Baseline characteristics of cohort.

Baseline Characteristic	**Total Cohort (n = 607)**
Age - years (SD)	70.9 (4.8)
Male n/total n (%)	282 (47)
Systolic BP (mmHg) (SD)	140.0 (16.8)
Diastolic BP (mmHg) (SD)	81.8 (10.4)
BMI (kg/m^2) (SD)	29.4 (5.3)
Current Smoking n/total n (%)	14 (2)
Diabetes Mellitus n/total n (%)	311 (51)
Obesity n/total n (%)	263 (43)
Hypercholesterolemia n/total n (%)	307 (51)
Hypertension n/total n (%)	481 (79)
Previous history of IHD n/total n (%)	47 (8)
Previous chemotherapy n/total n (%)	74 (12)
Baseline Medications	
Beta blockers n/total (%)	40 (7)
ACE-I/ARB n/total (%)	405 (67)
Calcium blockers n/total (%)	129 (21)
Lipid Lowering drugs n/total n (%)	306 (50)
Anti-platelet agents n/total n (%)	209 (34)

4.5.2 Patient characteristics based on AF risk

Participants were split into 4 groups based on AF risk (low 0-5%, medium 5-10%, high 10-15% and very high risk >15%) (Table 4-2). Patients with higher AF risk were older, more likely to be male with higher systolic blood pressure and rates of diabetes mellitus, hypercholesterolemia and ischemic heart disease ($p<0.05$). Patients with low AF risk had a higher proportion who had previous chemotherapy. There was no statistically significant difference in smoking rates and body mass index between groups.

Table 4-2 - Clinical characteristics of participants in relation to AF risk.

There are significant differences in relation to age, sex, blood pressure, diabetes, hypertension, ischemic heart disease, past chemotherapy and current medical therapy.

	Low Risk (0-5%) n = 185	**Moderate Risk (5-10%) n = 228**	**High Risk (10-15%) n = 103**	**Very High Risk (> 15%) n = 91**	**P Value**
Age - years (SD)	68.1 (2.9)	68.9 (3.5)	72.7 (4.0)	76.9 (5.0)	<0.001
Male n/total n (%)	44/185 (24)	118/228 (52)	66/103 (64)	54/91 (59)	<0.001
Systolic BP (mmHg) (SD)	136.0 (15.1)	138.8 (14.6)	140.7 (16.4)	150.5 (21.1)	<0.001
Diastolic BP (mmHg) (SD)	81.0 (10.4)	81.5 (9.8)	82.7 (10.3)	83.2 (12.0)	0.324
BMI (kg/m^2) (SD)	28.9 (4.9)	29.4 (5.4)	30.7 (6.1)	29.3 (4.9)	0.064
Current Smoking n/total n (%)	1/185 (0.5)	5/228 (0.2)	3/103 (3)	5/91 (5.4)	0.077
Diabetes Mellitus n/total n (%)	68/185 (37)	118/228 (52)	69/103 (67)	56/91 (62)	<0.001
Obesity n/total n (%)	75/185 (41)	96/228 (42)	51/103 (49.5)	41/91 (45)	0.486
Hypercholesterolemia n/total n (%)	83/183 (45)	115/209 (55)	58/96 (60)	51/85 (60)	0.039
Hypertension n/total n (%)	126/185 (68)	181/228 (79)	88/103 (85)	86/91 (95)	<0.001
Previous history of IHD n/total n (%)	3/185 (2)	15/228 (7)	14/103 (14)	15/91 (16)	<0.001
Previous chemotherapy n/total n (%)	32/185 (17)	26/228 (11)	12/103 (12)	4/91 (4)	0.020
Baseline Medications					
Beta blockers n/total (%)	8/185 (4)	15/228 (7)	9/103 (9)	8/91 (9)	0.387
ACE-I/ARB n/total (%)	111/185 (60)	157/228 (69)	74/103 (72)	63/91 (69)	0.127
Calcium blockers n/total (%)	25/182 (14)	49/199 (25)	27/95 (28)	28/79 (35)	0.001
Lipid Lowering drugs n/total n (%)	85/182 (47)	111/202 (55)	59/95 (62)	51/79 (65)	0.019
Anti-platelet agents n/total n (%)	49/182 (27)	78/200 (39)	41/93 (44)	41/79 (52)	0.001

4.5.3 Association with AF risk

AF risk was associated with reduced functional capacity (Table 4-4). SMWT was lower in higher AF risk groups (496m in low risk vs. 432m in very high risk, p<0.001), and patients with higher AF risk had lower DASI scores (p<0.001) and had more medical co-morbidities (p=0.04).

Univariable regression showed clinical AF risk was associated with impaired functional capacity (assessed by SMWT and DASI), as well as quality of life (EQ-VAS), Charlson Index and male gender. In a multivariable linear regression model, SMWT (β = -0.188, p<0.001) was independently associated with clinical AF risk. Using ROC curves, the optimal cutoff for SMWT was 500m (AUC 0.60, 95% C.I 0.56 to 0.65, p<0.001), for DASI was 42.7 (AUC 0.64, 95% C.I 0.59 to 0.69, p<0.001) and for MLHF was 24 (AUC 0.59, 95% C.I 0.51 to 0.68, p=0.02) (see figure 4.1).

The association between AF risk and atrial and LV parameters is shown in Table 4-3. Higher clinical AF risk was associated with lower ejection fraction (60±5.9 vs. 62±4.8% in lowest risk, p=0.001), worse GLS (-17.6±2.6% vs -19.1±2.4% in lowest risk, p<0.001) and GCS (-29.7±4.9 vs -31.0±5.7%, p=0.002). Indexed LV mass was noted to be higher in patients with higher AF risk (99.4±24.8 g/m^2 vs 84.5±21.4 g/m^2, p<0.001). AF risk was associated with GLS (β = 0.19, p< 0.001), E/e' (β = 0.16, p<0.001) and male gender (β = 0.26, p< 0.001). Using ROC curves, the optimal cutoff for GLS was -18% (AUC 0.598, 95% C.I 0.552 to 0.643, p<0.001), and that for indexed LA volume was 35 ml/m^2 (AUC 0.586, 95% C.I 0.537 to 0.635, p = 0.001).

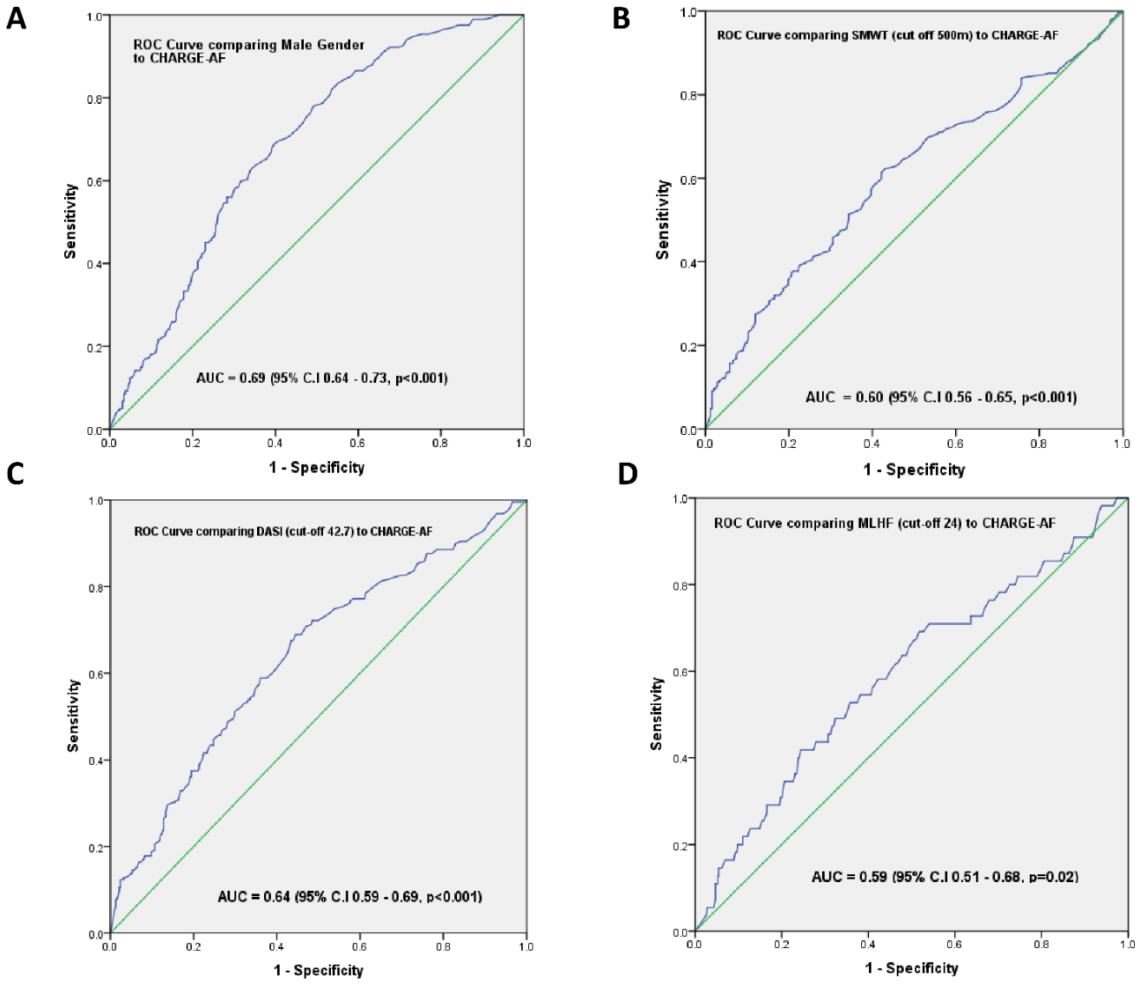

Figure 4.1 - Receiver Operator Characteristic (ROC) Curves comparing functional capacity parameters to AF risk.

Abbreviations: DASI – Duke Activity Status Index, MLHF – Minnesota Living with Heart Failure Score, SMWT – Six-minute walk test. A) ROC curve comparing male gender to CHARGE-AF. B) ROC curve comparing six-minute walk test cutoff 500m to CHARGE-AF. C) ROC curve comparing Duke Activity Status Index cutoff 42.7 to CHARGE-AF. D) ROC curve comparing Minnesota Living with Heart failure Score cutoff 24 to CHARGE-AF.

Table 4-3 - Association between AF risk with atrial and left ventricular dysfunction.

	Clinical AF risk (CHARGE-AF)						Simple Linear Regression		Multivariate Regression Model		ROC
Independent Variables	**Low Risk (0-5%) Mean (SD)**	**Medium Risk (5-10%) Mean (SD)**	**High Risk (10-15%) Mean (SD)**	**Very High Risk (> 15%) Mean (SD)**	**P value**	**R^2**	**Standardized Coefficient (β)**	**ANOVA F statistic (P value)**	**β**	**P Value**	**AUC (95% CI, p value)**
Male	44/185 (24)	118/228 (52)	66/103 (64)	54/91 (59)	< 0.001	0.068	0.260	F(1, 605) = 44.0 (< 0.001)	0.263	<0.001	0.685 (0.643 – 0.727, <0.001) (male)
Ejection Fraction (%)	62.2 (4.8)	60.7 (5.6)	60.2 (6.0)	59.6 (5.9)	0.001	0.018	-0.134	F(1, 599) = 11.0 (0.001)			
Global Longitudinal Strain (%)	-19.1 (2.4)	-18.4 (2.6)	-18.4 (2.5)	-17.6 (2.6)	< 0.001	0.035	0.186	F(1, 605) = 21.6 (< 0.001)	0.125	0.002	0.598 (0.552 – 0.643, <0.001) (cut-off -18%)
Global Longitudinal Strain Rate (s^{-1})	-1.38 (0.24)	-1.33 (0.18)	-1.35 (0.18)	-1.31 (0.20)	0.21	0.009	0.094	F(1, 604) = 5.4 (0.02)			
Global Circumferential Strain (%)	-31.0 (5.7)	-29.5 (5.4)	-28.6 (6.0)	-29.7 (4.9)	0.002	0.004	0.066	F(1, 603) = 2.6 (0.11)			0.607 (0.533 – 0.682, 0.016) (cut off -22%)
Global Circumferential Strain Rate (s^{-1})	-2.7 (0.71)	-2.5 (0.62)	-2.5 (0.65)	-2.6 (0.56)	0.263	0.001	0.028	F(1, 603) = 0.47 (0.50)			
$E^{'}$ Average (m/s)	0.076 (0.02)	0.078 (0.02)	0.076 (0.02)	0.070 (0.02)	0.003	0.017	-0.131	F(1, 605) = 10.6 (0.001)			
E/e' (Average septal and lateral)	8.71 (2.4)	8.60 (2.4)	8.98 (2.5)	10.0 (3.1)	< 0.001	0.026	0.162	F(1, 605) = 16.3 (< 0.001)	0.202	<0.001	0.635 (0.493 – 0.777, 0.051) (cut off 15)
Left atrial volume (ml/m^2) - indexed	30.1 (9.2)	31.4 (10.0)	32.6 (7.6)	34.7 (10.5)	0.001	0.029	0.170	F(1, 604) = 18.1 (<0.001)			0.586 (0.537 – 0.635, 0.001) (cut off 35 ml/m^2)
Left Ventricular mass (g/m^2) – indexed	84.5 (21.4)	92.1 (21.2)	96.1 (23.1)	99.4 (24.8)	< 0.001	0.053	0.230	F(1, 604) = 33.6 (<0.001)			
Multivariate Regression Model						0.124				F (3,603) = 28.5 (<0.001)	

Table 4-4 - Association between AF and functional capacity.

	Clinical AF risk (CHARGE-AF)					Simple Linear Regression					ROC
Independent Variables	**Low Risk (0-5%) Mean (SD) n= 185**	**Medium Risk (5-10%) Mean (SD) n = 228**	**High Risk (10-15%) Mean (SD n = 103**	**Very High Risk (> 15%) Mean (SD) n = 91**	**P value**	**R^2**	**Standardized Coefficient (β)**	**ANOVA F statistic (P value)**	**β**	**P Value**	**AUC (95% CI, p value)**
Age	68.1 (2.9)	68.9 (3.5)	72.7 (4.0)	76.9 (5.0)	< 0.001						
Male	44/185 (24)	118/228 (52)	66/103 (64)	54/91 (59)	< 0.001	0.068	0.260	F(1, 605) = 44.0 (< 0.001)	0.306	<0.001	0.685 (0.643 – 0.727, <0.001) (male)
Six Minute Walk Test (m)	495.8 (89.4)	484.9 (93.7)	438.9 (110.6)	431.8 (117.2)	< 0.001	0.064	-0.253	F(1, 571) = 39.1 (<0.001)	-0.188	< 0.001	0.603 (0.557 – 0.649, <0.001) (cut-off 500m)
DASI	46.8 (10.5)	44.2 (11.6)	40.2 (13.3)	38.6 (13.5)	< 0.001	0.078	-0.279	F(1, 592) = 50.0 (< 0.001)	-0.167	0.001	0.640 (0.593 – 0.686, <0.001) (cut-off 42.7)
MLHF	4.7 (10.4)	6.0 (12.1)	9.7 (12.9)	10.8 (16.2)	< 0.001	0.040	0.199	F(1, 590) = 24.3 (<0.001)	0.066	0.143	0.594 (0.511 = 0.676, 0.022) (cut-off 24)
EuroQoL EQ-5D VAS	82.2 (13.8)	80.5 (15.4)	79.8 (15.2)	78.9 (14.8)	0.308	0.007	-0.084	F(1, 590) = 4.21 (0.041)	0.042	0.323	0.607 (0.533 – 0.682, 0.016) (cut off -22%)
Charlson Index	1.8 (2.4)	1.6 (2.0)	2.3 (2.8)	2.2 (2.6)	0.043	0.008	0.087	F(1, 605) = 4.59 (0.033)	0.005	0.892	
Multivariate Regression Model						0.184				F (6, 562) = 21.2 (<0.001)	

4.6 Discussion

This study suggests that AF risk is associated with impaired functional capacity as assessed with the SMWT and less activity (assessed by the DASI), independent of LV function and LV mass. SMWT <500m as well as DASI <42.7 and MLHF >24 were associated with AF risk.

4.6.1 Assessment of AF risk

A number of clinical features are associated with AF, including the metabolic syndrome, hypertension and T2DM. The CHARGE-AF score was developed from a total of 18,556 patients with a wide age range (46–94 years) and ethnic diversity (19% African-Americans) based on pooled data from the Framingham Heart Study(47), the ARIC(48) and the Cardiovascular Health Study (CHS) (49). The bedside clinical score gives a 5 year risk of developing AF using clinical variables including age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive therapy, history of diabetes mellitus/myocardial infarction and heart failure with overall good model discrimination (C-statistic 0.765, 95% C.I 0.748 – 0.781). The CHARGE-AF score has been validated in multiple cohorts, is easy to implement in clinical practice, and can be calculated in the absence of ECG data (22).

4.6.2 Role of imaging in AF risk assessment

A deficiency in clinical risk scores is that they do not incorporate atrial or LV mechanics or LA size, all of which are implicated in the pathogenesis of AF (22, 173, 175, 176). AF risk is associated with reduced atrial reservoir, conduit and pump strain (177) which is likely a marker of progressive atrial fibrosis and can be used to predict recurrence following catheter ablation (96) or cardioversion (178). The use of LV strain analysis to predict AF risk is poorly understood. LV regional deformation allows for objective assessment of systolic function (179). LV strain analysis has important applications for the assessment for cardiomyopathy, myocardial ischemia (179, 180) and assessment for LV dyssynchrony post cardiac resynchronization therapy (179). Changes to atrial size and fibrosis in the absence of mitral valve disease is often due to progressive changes to the LV including increase in LV mass, higher filling pressures and concentric remodelling which are commonly associated with age and hypertension and give rise to poor exercise capacity (181).

We have found in this study that altered myocardial mechanics are independently associated with AF risk. This has several implications for clinical practice. Echocardiography and deformation analysis are non-invasive, easily accessible and cost effective and can be utilised in screening programs. This can potentially lead to early diagnosis of AF prior to the onset of complications such as stroke. The relationship between AF and LV mechanics also raises the possibility of AF risk in patients with underling structural heart disease or a known history of HF. AF in these patients is associated with a poorer prognosis, thus early diagnosis would impact prognosis (171).

4.6.3 Association of AF with functional capacity

AF is associated with impaired quality of life and poor functional capacity (168) Restoration of sinus rhythm following pharmacological therapy or catheter ablation is associated with improvement in New York Heart Association functional class, improvement in quality of life and modest improvement in exercise capacity (182). Whilst the link between AF and quality of life is well understood, it is unclear if poor functional capacity can contribute to AF risk. Common risk factors for AF such as obesity, hypertension and T2DM are associated with impaired quality of life and reduced exercise capacity (24, 116). Poor exercise capacity could offer a surrogate risk assessment tool in clinical practice to identify patients at risk of AF.

While the link between AF and quality of life is well understood, previous work has not shown whether poor functional capacity can contribute to AF risk. The results of our study suggest that poor exercise capacity is an independent risk factor for AF. Exercise and weight loss programs have recently been shown to improve AF symptom burden and atrial remodelling (23). The reasons why poor exercise capacity contributes to AF risk is unclear. Improvement in cardiovascular fitness may have a protective role in AF possibly by preventing atrial remodelling. The strong association between immobility and obesity may lead to altered atrial mechanics and increased atrial size which can create a substrate for arrhythmia. Patients with poor functional capacity are more likely to have associated co-morbidities such as hypertension and diabetes mellitus which are known risk factors for AF. Poor exercise capacity could offer a surrogate risk assessment tool in clinical practice to identify patients at risk of AF.

4.6.4 Limitations

The limitations of our study include potential for population selection bias as patients were recruited with newspaper and radio advertising. Our study is an observational study and our primary outcome measure was to assess AF risk using a validated risk score. A potential weakness is that we did not follow up patients to assess the true incidence of AF in the cohort. Hence although we are able to attribute higher AF risk, we are unable to demonstrate a higher incidence of AF in patients with reduced functional capacity.

4.7 Conclusion

AF places a huge burden on the health care system and screening programs to identify patients at risk of AF will be important in the future, as there are demonstrable ways to alter disease progression which could potentially prevent AF and its complications. Mass screening has the potential to be expensive so assessment should begin with a clinical risk assessment tool.

The association of reduced exercise capacity and functional status with AF risk has two implications. It may be a marker of treatable risk, similar to obesity, as well as identifying a patient subgroup appropriate for close monitoring for AF.

4.8 Postscript

Risk assessment for AF is vital to aid in targeted screening of individuals. Current clinical and echocardiographic risk assessment tools have several deficiencies. The use of other markers of risk will aid clinicians in identifying those patients who may benefit from AF screening. Reduced functional capacity is easy to assess and may highlight increased risk of developing AF which may prompt screening or close surveillance.

The mechanism by which exercise capacity increases risk is not well understood. It is evident that many of these patients have associated co-morbidities such as obesity and hypertension which may contribute to negative LA remodelling. However, exercise itself may offer a protective role in preventing AF. Hence reduced exercise capacity may impact on this and exacerbate the remodelling process. It is important to identify this for two reasons. Firstly, it can be used as a tool to identify patients at risk. Secondly it is a potential modifiable risk factor thereby offering an opportunity for early intervention. The role of exercise and AF has been investigated in other studies. The Cardiovascular Health study showed reduced AF incidence in those who performed light-moderate exercise (183). The Women's Health Initiative study demonstrated a similar reduction in AF incidence in those who were physically active (184). In the CARDIO-FIT study, patients who underwent an exercise program had improved symptoms and reduced AF burden (185, 186). Although there has been an increase in AF in endurance athletes, there is evidence to suggest a beneficial role of light-moderate exercise in reducing AF incidence (186).

The limitations of this study should be acknowledged. The association between functional capacity was with CHARGE-AF (a clinical AF risk score), and not with incident AF, therefore causality cannot be implied. The associations although statistically significant, had a poor discrimination (low c-statistic). This suggests that functional capacity alone is not sufficient for patient selection and should be incorporated into other clinical and imaging markers.

The assessment of risk is not just individual when setting up a screening program. We need to account for regional risk. In the next chapter we further define appropriate patient selection for AF screening by exploring the association between regional SES and AF risk.

Chapter 5

Selecting Patients to Undergo AF Screening – Importance of Regional SES

"Association between Socio-Economic Status and Atrial Fibrillation"

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5 Selection of patients for AF screening – importance of regional SES

5.1 Preface

Low SES is associated with reduced cardiovascular health. There are multiple potential mechanisms for this, including poor access to health care, reduced health literacy, poor compliance and higher rates of comorbidities and reduced physical activity. The link between SES and AF is not as well established compared with coronary artery disease. However, the same potential mechanisms may be involved in higher AF risk. Individual assessment of SES can be performed with multiple indices including income, employment, housing and education levels. When translating this to a population level, an assessment of regional SES may be important in determining the most appropriate cohort for AF screening.

In Australia, the socioeconomic indices for areas (SEIFA) have been established which allows different regions of the country to be compared using multiple parameters such as finances, employment, education and housing. Understanding the link between AF and regional SES has important implications for screening programs. These areas often have poor access to health care and poor health literacy. Therefore, individuals in these areas are often the most vulnerable and at risk for complications. AF rates may also be higher in these areas given the factors discussed above, thereby potentially improving the yield of screening. The following chapter was published in the Internal Medicine Journal.

5.2 Abstract

Background and Objective: Low socio-economic status is associated with cardiovascular diseases, and an association with atrial fibrillation (AF) could guide screening. We investigated if indices of disadvantage (IAD), education/occupation (IEO) and economic resources (IER) were associated with incident AF, independent of risk factors and cardiac function.

Methods: We studied community-based participants aged ≥65 years with AF risk factors (n=379, age 70±4 years, 45% men). All underwent clinical AF risk assessment using the CHARGE-AF score and baseline echocardiography. IAD, IEO and IER were obtained from the 2011 Socio-Economic Indexes for Areas (SEIFA) score, in which higher decile ranks indicate more advantaged areas. Patients were followed up for incident AF (median 21 (range 5-31) months), with AF diagnosed by clinical review including 12 lead ECG, as well as single lead portable ECG monitoring used to record 60 second ECG tracings five times/day for one week. Cox proportional hazards models were used to assess the association between socio-economic status and incident AF.

Results: Subjects with AF (n=50, 13%) were more likely to be male (64% vs.42%, p=0.003) and had higher CHARGE-AF score (median 7.1%(5.2-12.8%) vs. 5.3%(3.3-8.6%), p<0.001). Areas with lower socio-economic status (IAD and IEO) had a higher risk of incident AF independent of LV function and CHARGE-AF score (HR for IAD 1.16, 95% C.I 1.05-1.29, p=0.005 and HR for IEO 1.18, 95% C.I 1.07-1.30, p=0.001).

Conclusion: Regional socio-economic status is associated with risk of incident AF, independent of LV function and clinical risk. This association might permit better regional targeting of prevention.

5.3 Introduction

Atrial fibrillation (AF) is associated with stroke, HF, increased all-cause mortality, (109, 110) and substantial financial cost (12, 111). The epidemics of obesity, diabetes mellitus and metabolic syndrome have been associated with the increasing prevalence of AF, which has become a significant population health problem (18, 113, 114). The early diagnosis of AF may lead to individualized lifestyle intervention (23) and anticoagulation, and these steps may be associated with a reduction in complications and health care costs. The development of hand-held electrocardiogram (ECG) screening devices (8, 69, 70, 78, 79, 117, 154), has increased the feasibility of AF screening. Appropriate selection of patients for screening is of critical importance; the development of a risk assessment score, (22, 187) based upon the link between AF and clinical risk factors, is an important component of identifying individual patients at risk. The introduction of a screening program should also involve consideration of which communities are at risk.

Socio-economic deprivation is strongly associated with increased risk of metabolic syndrome and coronary artery disease, (30-32) beyond its association with reduced health care access. Low household income influences dietary choices, psychological well-being and is associated with a sedentary lifestyle (188). Poor literacy and education levels may affect treatment adherence and risk awareness. There may also be higher rates of substance and alcohol abuse in deprived areas (189). However, the association between socioeconomic deprivation and AF risk is controversial, with reports of an association of lower household income with increased AF risk, (34) balanced by other evidence that neighborhood deprivation and socioeconomic disparities were not independently associated with AF (33). The purpose of this study was to assess the association of regions of socioeconomic deprivation with risk of incident AF.

5.4 Methods.

5.4.1 Study population.

This prospective observational cohort study recruited participants from both urban and rural settings in Tasmania (an island located south of the Australian mainland) and Victoria (a larger State in the south of mainland Australia). Apart from the major cities (Hobart and Launceston), much of Tasmania is geographically isolated, with limited access to health care (102). Participants from the community ≥65 years were recruited if they had 1 or more AF/heart failure (HF) risk factors, including hypertension (systolic BP >140mmHg or pre-existing use of anti-hypertensive medications), T2DM, based on self-report of diagnosis or the current use of diabetic medications), and obesity (body mass index ≥30). Subjects were excluded if they were unable to provide written consent, had known HF or left ventricular (LV) systolic dysfunction, moderate/severe valvular disease or life expectancy <1 year. All patients were provided written informed consent and approval was obtained from the Tasmanian Human Research Ethics Committee (HREC project number H0013333).

5.4.2 Clinical findings.

Participants provided a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, past medical history, medication history as well as baseline examination data (height, weight, body mass index [BMI], blood pressure [BP]) was recorded for all participants. Baseline 12 lead ECG and echocardiography were conducted in all participants, and patients with previously unrecognized HF were excluded. Assessment of AF risk was performed using the CHARGE-AF score (22). Exercise capacity was assessed using the six-minute walk test.

5.4.3 Assessment of SES

All participants had information collected on education level. The Socio-Economic Indexes for Areas (SEIFA) score is derived from several domains of national census data (including education, housing, household income, employment and occupation) to provide a multidimensional assessment of SES based on postcode. This was used to describe the regional variations of participants' overall SES (102).

The SEIFA score has three main indices; an index of advantage/disadvantage (IAD, based on income, occupation and housing), an index of education/occupation (IEO, based on education and occupation) and an index of economic resources (IER, based on individual income, mortgage repayments, rental return and family income). These indices are expressed to deciles, with the lowest scoring 10% of areas given a decile number of 1 and the highest 10% of areas are given a decile number of 10. Hence, higher scores reflect more advantaged areas (102).

5.4.4 AF follow-up.

AF was diagnosed using multiple detection methods. All participants had baseline and follow-up assessment including a 12-lead ECG and echocardiogram. In the interim, any patients diagnosed with AF by local physicians were documented. Screening for subclinical AF was performed using a single lead ECG device (Remon RM-100, Semacare, China). The single lead device was used to record 60 second single lead ECG tracings using three points of finger contact with electrodes, five times per day for a one week (i.e. 35 recordings). ECG recordings were then exported as PDF files for interpretation, and all were assessed by a physician. The presence of AF (an irregular rhythm of ≥30 sec with a variable R-R interval and absent P waves) was confirmed by two independent physicians who were blinded to the patient's clinical details. The patient was advised of the recognition of subclinical AF, and further management and investigation was provided by their usual medical practitioner.

5.4.5 Outcome measures.

Our primary outcome measure was the overall proportion of the cohort with new onset AF during the follow-up period.

5.4.6 Statistical analysis

All categorical variables are presented as frequencies/percentages and continuous variables presented as means/standard deviation (if normally distributed) or medians/inter-quartile range (if non-parametric). Patients with incident AF were compared to those remaining in sinus rhythm. Groups were compared using the chi square test for categorical data and the independent two sample t-test for continuous data. Patients were grouped according to the SEIFA rank (<5 vs. ≥5) and Nelson-Aalen cumulative hazard estimate plots were constructed, and the log-rank test used to assess the differences

between curves. A Cox proportional hazards regression analysis was used to calculate the adjusted hazard ratios (HR) and 95% confidence intervals for the association between each socioeconomic index and incident AF. Clinically relevant model covariates included CHARGE-AF score, global longitudinal strain, gender and indexed left atrial volume. The follow up time was the time from the initial baseline clinical assessment to the completion of portable device screening or the date of diagnosis of AF (whichever came first). Analyses were considered to be statistically significant if two-tailed p values were <0.05. Statistical analysis was performed using SPSS v.22 (SPSS, Chicago, IL) and Stata v.13 (StataCorp, College Station, TX).

5.5 Results

5.5.1 Patient characteristics.

Baseline characteristics of the 379 subjects included in the study (mean age 70±4 years, 45% male) are summarized in Table 5-1. Thirteen participants (3%) had a previous diagnosis of paroxysmal AF. Cardiovascular risk factors (including T2DM, obesity, hypercholesterolemia and hypertension) were highly prevalent. There was a large proportion of participants with low education levels (43% had not completed high school and approximately 3 in 4 had not completed university education). Most participants were recruited from areas with socioeconomic deprivation (median IAD 5±6, median IEO 5±6 and median IER 4±5).

Table 5-1 - Baseline Characteristics of the overall cohort.

Demographics	**n = 379**
Age - years (SD)	70.3 (4.2)
Male n (%)	169 (45)
Systolic BP mmHg (SD)	140.6 (15.9)
Diastolic BP mmHg (SD)	82.5 (9.9)
Heart Rate /min (SD)	68.7 (10.8)
BMI (kg/m^2) (SD)	29.8 (5.2)
Current Smoking n (%)	8 (2)
Diabetes Mellitus n (%)	176 (46)
Obesity n (%)	176 (46)
Hypercholesterolemia n (%)	205 (54)
Hypertension n (%)	293 (77)
Previous history of IHD n (%)	16 (4)
Previous history of AF n (%)	13 (3)
Previous chemotherapy n (%)	36 (10)
Median Six-minute walk test m (IQR)	504 (96)
Median CHARGE-AF % (IQR)	6.8 (6.6)
Median CHA_2DS_2-VASC % (IQR)	3.0 (2.0)
Echocardiographic Parameters	**Mean (SD)**
Ejection Fraction % (SD)	62.8 (6.2)
Global Longitudinal Strain % (SD)	-18.8 (2.5)
E/e' (Average of lateral and septal) (SD)	8.7 (2.5)
Left atrial volume - indexed ml/m^2 (SD)	31.5 (9.1)
Left Ventricular mass – indexed g/m^2 (SD)	88.8 (21.7)
Social Factors	
Median SEIFA Index of Advantage/Disadvantage (IQR)	5 (6.0)
Median SEIFA Index of Education/Occupation (IQR)	5 (6.0)
Median SEIFA Index of Economic Resources (IQR)	4 (5.0)
Completed High School n(%)	214/375 (57)
Completed University n(%)	88/376 (23)

5.5.2 AF during follow up.

Over a median follow-up of 21 months (range 5-31 months), 50 patients (13%) were diagnosed with AF. Of these 37 patients (9.8%) were diagnosed with incident AF, 23 of whom (6%) were diagnosed with portable ECG monitoring while 14 (4%) were diagnosed by local physicians during the follow up

period or had AF during hospitalizations. Table 5-2 compares the characteristics of those with AF and sinus rhythm; new onset AF was more likely in men, and in those with a higher CHARGE-AF score and those from socioeconomically deprived areas ($p<0.05$).

Table 5-2 - Comparison of baseline characteristics between patients with AF and sinus rhythm.

Demographics	**AF n = 50**	**Sinus Rhythm n = 329**	**P Value**
Age - years (SD)	71.3 (5.0)	70.1 (4.0)	0.12
Male n (%)	32 (64)	137 (42)	0.003
Systolic BP mmHg (SD)	135.5 (18.3)	141.4 (15.3)	0.01
Diastolic BP mmHg (SD)	82.6 (11.2)	82.5 (9.7)	0.99
BMI (kg/m^2) (SD)	29.3 (4.7)	29.9 (5.3)	0.39
Current Smoking n (%)	3 (6)	5 (2)	0.04
Diabetes Mellitus n (%)	27 (54)	149 (45)	0.25
Obesity n (%)	19 (38)	157 (48)	0.419
Hypercholesterolemia n (%)	25/47 (53)	180/321 (56)	0.71
Hypertension n (%)	38 (76)	255 (78)	0.81
Previous history of IHD n (%)	5 (10)	11 (3.3)	0.03
Median CHARGE-AF % (IQR)	7.1 (7.6)	5.3 (5.3)	<0.001
Median CHA_2DS_2-VASC (IQR)	3.0 (2.0)	3.0 (2.0)	0.93
Functional Capacity			
Six Minute Walk Test m (SD)	498 (102)	508 (98)	0.50
Social Factors			
Median SEIFA Index of Advantage/Disadvantage (IQR)	4 (4.0)	5.0 (5.0)	0.005
Median SEIFA Index of Education/Occupation (IQR)	3.5 (5.0)	6.5 (6.0)	0.02
Median SEIFA Index of Economic Resources (IQR)	4.0 (3.0)	5.0 (5.0)	0.002
Completed High School n(%)	28 (56)	186/325 (57)	0.87
Completed University n(%)	8 (16)	80/326 (25)	0.18
Echocardiographic Parameters			
Ejection Fraction % (SD)	60.7 (7.2)	63.2 (5.9)	0.01
Global Longitudinal Strain % (SD)	-17.7 (3.3)	-19.0 (2.3)	0.01
E/e' (Average of lateral and septal) (SD)	8.6 (2.7)	8.8 (2.5)	0.67
Left atrial volume - indexed ml/m^2 (SD)	34.0 (10.3)	31.1 (8.9)	0.03
Left Ventricular mass – indexed g/m^2 (SD)	93.6 (23.3)	87.8 (21.3)	0.10

BMI – Body Mass Index BP – Blood Pressure IHD – Ischaemic Heart Disease

5.5.3 Association between SES and AF risk.

SEIFA data was available in 370/379 participants (with 48 AF outcomes). Table 5-3 summarizes the features associated with AF risk - including increased age, male gender, reduced global longitudinal strain, increased left atrial volume, as well as socioeconomic deprivation. Those who developed AF had lower median SEIFA indices compared to those in sinus rhythm (IAD (4.0 (range 2-6) vs. 5.0 (range 3-8), p=0.005), IER (4.0 (range 2-5) vs. 5.0 (range 3-8), p=0.002) and IEO (3.5 (range 2-7) vs. 6.5 (range 2-8), p=0.02)). There were no differences in AF rates noted in participants with high school or tertiary level education. In a multivariable model, adjusted for gender, clinical risk factors, LV function and left atrial volume, increased incident AF risk was associated with disadvantaged areas (HR for IAD = 1.16, 95% C.I 1.05-1.29, p=0.005) and areas with lower education/occupation levels (HR for IEO = 1.18, 95% C.I 1.07-1.30, p=0.001) (figure 5.1, 5-3 and Table 5-3). Areas with lower economic resources were not independently associated with increased incident AF risk (HR for IER = 1.11, 95% C.I 0.99-1.24, p=0.08) (figure 5.2).

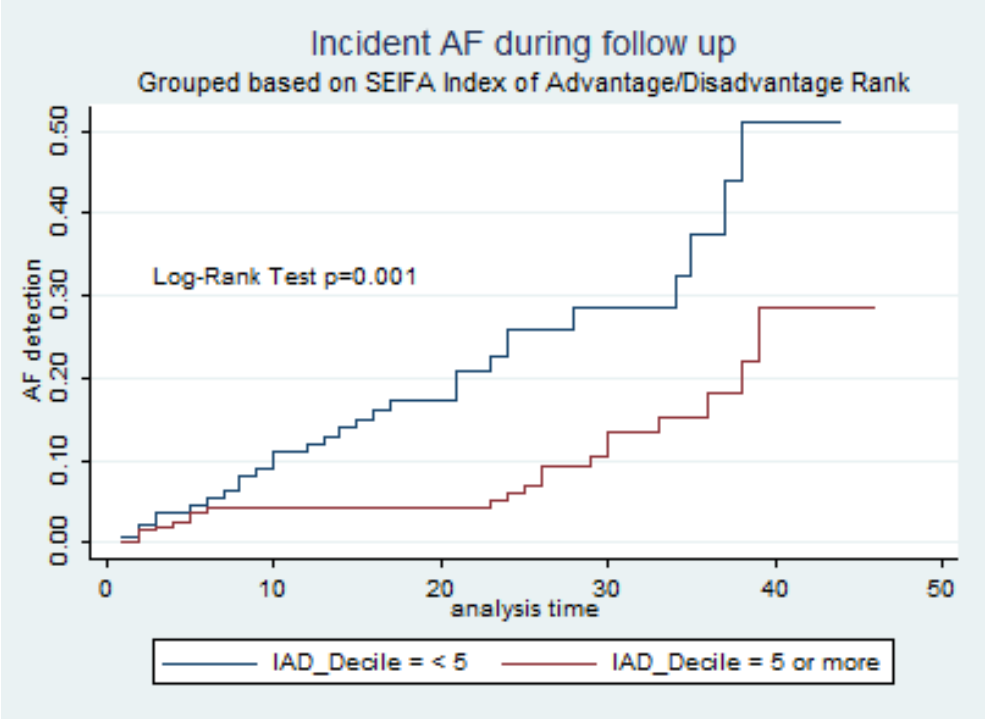

Figure 5.1 - Nelson-Aalen Curve showing incident AF diagnosis based on IAD decile rank.

Areas with low SEIFA index of advantage/disadvantage had higher AF detection.

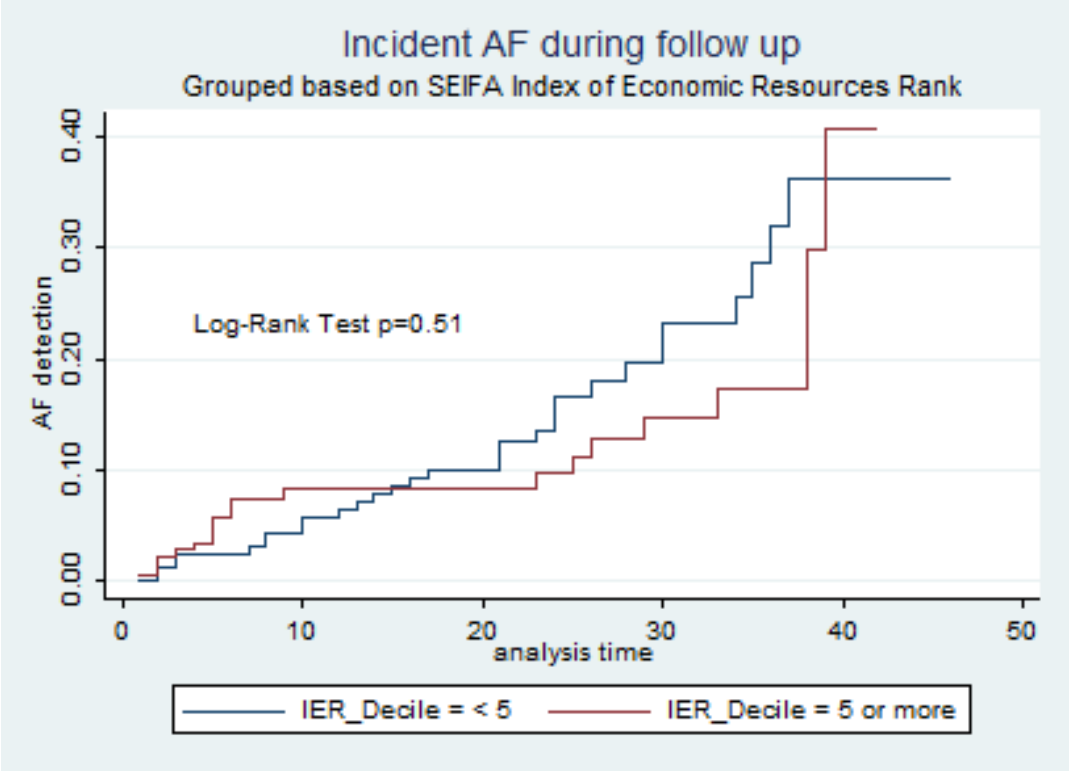

Figure 5.2 - Nelson-Aalen Curve showing incident AF diagnosis based on IER decile rank.

Areas with low SEIFA index of economic resources did not demonstrate a significantly higher AF detection.

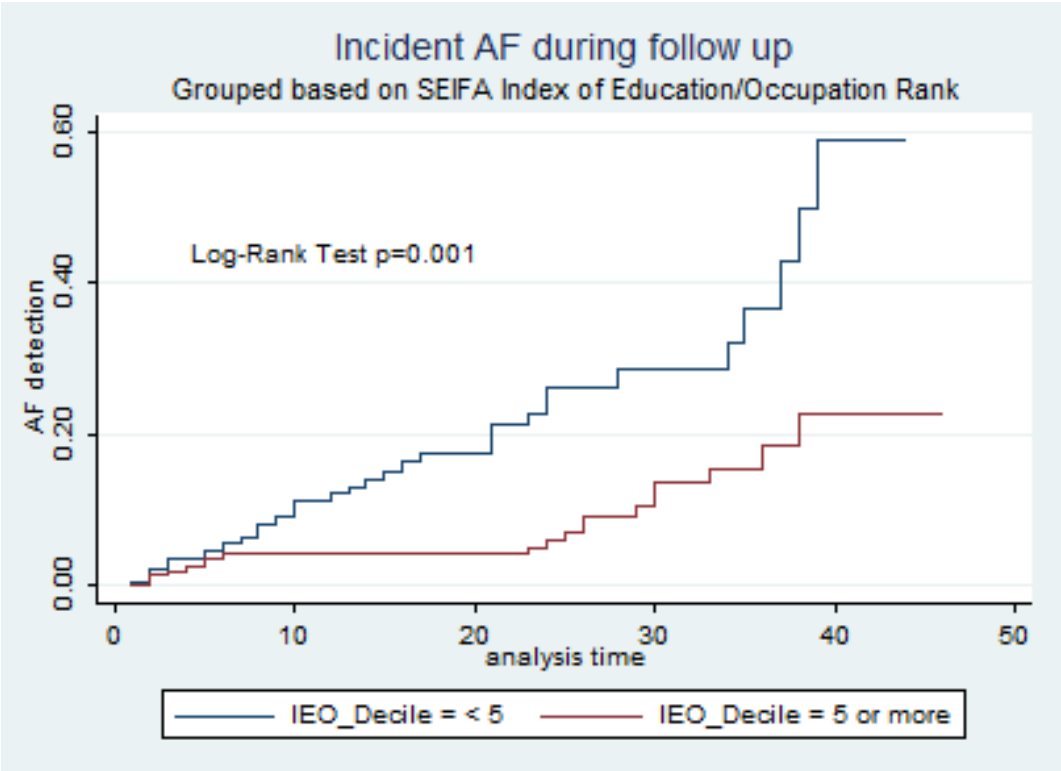

Figure 5.3 - Nelson-Aalen Curve showing incident AF diagnosis based on IEO decile rank.

Areas with low SEIFA index of education/occupation had higher AF detection.

Table 5-3 - Cox regression analysis showing association between SES and AF. Multivariable model adjusted for gender, CHARGE-AF score, Left atrial volume and Global Longitudinal strain.

Independent Variables	Unadjusted Hazard Ratio (95% C.I)	P value	Adjusted Hazard Ratio (95% C.I)	P value
Age (years)	1.06 (1.00 – 1.12)	0.048		
Male Gender	2.44 (1.37 – 4.36)	0.003	1.78 (0.96–3.31)	0.07
Body Mass Index (kg/m^2)	1.01 (0.95 – 1.06)	0.83		
Systolic Blood Pressure (mmHg)	0.98 (0.96 – 0.99)	0.02		
Diastolic Blood Pressure (mmHg)	1.01 (0.98 – 1.04)	0.51		
T2DM	1.33 (0.75 – 2.34)	0.32		
Obesity	0.90 (0.51 – 1.59)	0.71		
Hypertension	0.99 (0.52 – 1.91)	0.99		
Ejection Fraction (%)	0.93 (0.90 – 0.97)	0.001		
Global Longitudinal Strain (%)	1.21 (1.09 – 1.36)	0.001	1.22 (1.08–1.38)	0.002
Left atrial volume - indexed (ml/m^2)	1.05 (1.02 – 1.08)	0.002	1.04 (1.01–1.07)	0.01
Left Ventricular mass – indexed (g/m^2)	1.01 (0.99 – 1.02)	0.02		
Six Minute Walk Test (m)	1.00 (0.99 – 1.00)	0.87		
CHARGE-AF Score (%)	1.04 (0.99 – 1.09)	0.10	0.98 (0.92–1.03)	0.37
CHA_2DS_2-VASC Score	0.98 (0.71 – 1.34)	0.89		
SEIFA Index of Advantage/Disadvantage	1.15 (1.04 – 1.27)	0.007	1.16 (1.05–1.29)	0.005
SEIFA Index of Education/Occupation	1.17 (1.06 – 1.28)	0.001	1.18 (1.07–1.30)	0.001
SEIFA Index of Economic Resources	1.11 (0.99 – 1.25)	0.07	1.11 (0.99–1.24)	0.08
Completed High School	0.67 (0.39 – 1.18)	0.17		
Completed University	0.55 (0.26 – 1.16)	0.12		

5.6 Discussion

The results of our study suggest that a significant number of elderly people in the community with risk factors have subclinical AF. Socioeconomic deprivation is a risk factor for AF independent of other clinical risk factors and cardiac function. Areas with higher household income, higher rates of education and employment had lower risk of incident AF.

5.6.1 SES and AF.

Socioeconomic deprivation is well established as a risk factor for metabolic syndrome and cardiovascular disease, (30-32) but the association between SES and AF is less clear. A large Swedish study did not find an independent association between SES and hospitalised AF, (33) although an association was found in women (33). The ARIC cohort found that low family income was associated with increased risk of AF, (34) with lower education levels associated with increased AF risk in women (34). After adjusting for confounders, we found that regional indices of low income/education were associated with AF in both sexes. The use of regional indices of SES provide a basis of using geographic location in planning screening, in a way that using individual income or educational data would be inaccessible.

There may be several mechanisms by which SES can affect AF risk and management. AF has been strongly associated with metabolic syndrome and obesity, (113, 114) both of which are strongly influenced by SES. Household income and education levels influence dietary habits and physical activity levels. Children born to parents of low SES have higher risk of low birth weight which has been shown to be associated with AF risk (190). The higher rates of alcohol and substance abuse in areas of socioeconomic deprivation are both associated with AF risk (189). There may be added challenges such as poor health awareness in this cohort and issues relating to poor adherence, as limited household income may influence decisions made on anticoagulation and other pharmacological therapy (191). Irrespective of the mechanisms involved, SES appears to be associated with AF and in our study, it was as important a risk factor as left atrial volume and left ventricular function.

5.6.2 Early diagnosis of AF and community screening.

AF creates a significant burden on both patients and the health care system. For patients, it is associated with increased risk of stroke and heart failure as well as causing symptoms and impaired quality of life. AF seems likely to continue to increase in incidence and the costs to the health care system will continue to increase (12, 18, 109). Early diagnosis might be achieved by community screening programs, but successful AF screening requires both an appropriate diagnostic tool as well as careful selection of the at-risk population.

The incident AF rate of 9.8% in this study - higher than previously reported in the literature (8, 78, 117) – is attributable to not only age and clinical risk factors for AF, but also social vulnerability. Elderly, socially isolated patients with poor access to affordable health care, limited household income and poor education levels are often encountered in hospital following the complications of AF. Early diagnosis offers the possibility for early initiation of treatment which may offset some of the complications which may lead to reduced hospitalizations and associated health care costs. Patients with subclinical AF and atrial tachyarrhythmias have an increased risk of stroke and cardiovascular events similar to those with established AF, (8, 163) and anticoagulation may help reduce the incidence of stroke in this cohort. Active lifestyle intervention may lead to a reduction in symptom burden and in the need for repeat ablation procedures and an improvement in quality of life (23). Initiation of lifestyle intervention and risk factor modification following early diagnosis of AF may be associated with positive LA remodelling, may reduce disease progression, and may produce additional health benefits including reduction in cardiovascular risk and improvement in exercise capacity.

5.6.3 Clinical Implications.

The results of our study have several important clinical implications. We have demonstrated a significant burden of subclinical AF in elderly people with risk factors. We have also demonstrated that AF screening using portable ECG monitoring is feasible. The finding that low regional SES is associated with increased AF risk has important implications for mass screening. Screening programs conducted in these areas will likely yield higher detection rates, improving cost-effectiveness and providing access to early intervention programs to those at the highest risk of complications and hospitalisations.

5.6.4 Limitations

There are several limitations of our study. There is a potential for population selection bias as participants were recruited with newspaper and radio advertising. Our patient sample was small, and we had a limited number of AF outcomes. Our patient population was predominantly white Australian, and our results are not generalizable to the indigenous population or other ethnicities. Our screening for subclinical AF was done for a one-week period of intermittent ECG monitoring, and it is possible that

resulted in some AF outcomes to be potentially missed. Our study focused on the assessment of regional SES as we investigated the implications to a community AF screening program. Hence, the results of our study cannot be used for individual risk assessment.

5.7 Conclusion

Elderly patients with risk factors have a high prevalence of subclinical AF, especially in regions of socioeconomic deprivation. The finding that socioeconomic deprivation is independently associated with incident AF suggests that additional resources and access to health care in selected communities to improve health outcomes.

5.8 Postscript

This chapter highlights the strong association between regional SES and AF. SES was not assessed at the individual level in the study, but this is not pertinent to planning the location of a new screening service. Individual risk assessment is a vital component on AF screening as it should be tailored to high risk patients. However, selection at a cohort/population level is also important. The finding that low regional SES was associated with AF has not been widely reported in the literature. However, the finding might be anticipated, given these cohorts typically have poor access to health care and have higher prevalence of comorbidities. We tried to the best of our ability to exclude patients with a history of AF in the past by reviewing GP medical records and doing a baseline echocardiogram and ECG. It is possible that some patients may have had AF diagnosed in the past that we were unaware of (and which was not recorded in the GP medical record). This may artificially have created higher AF detection rates in the study and should be acknowledged as a limitation.

From a health policy level, the findings of this study are potentially important. We have limited resources and we must target programs such as AF screening to those at highest risk of developing the disease and its associated complications. Given the SEIFA is freely available and covers most areas in the country, it can provide a simple framework to target initial pilot screening programs. This may provide an "enriched" patient cohort where screening is likely to be effective. Following on from this initial population level selection, individual patient selection can be performed utilizing clinical risk stratification supplemented by information from imaging. This will improve cost-effectiveness and overall feasibility.

Having investigated the use of screening technologies and appropriate selection, I will investigate another widely available risk predictor that is underused in AF risk prediction – coincidental cardiac imaging, especially with echocardiography. In Australia about a million outpatient echocardiograms are performed each year, and many of these are done in patients with AF risk factors. By applying advanced imaging techniques to these studies, information could be gathered to assist in the risk-stratification of these patients. In the next chapter the association between LA and LV strain is assessed in a cross-sectional study. Sceptics of LA strain have argued that it does not provide incremental

information to LV strain. In the next chapter I will investigate if some of the phasic components of LA function act independent to LV function.

Section III – LA Strain

Chapter 6

Using Imaging to assess LA function which may be used to predict AF risk

"Left Atrial Strain: Association with AF risk and LV strain"

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Reference: Ramkumar S, Yang H, Wang Y, Nolan M, Negishi T, Negishi K, Marwick TH. Association of the Active and Passive Components of Left Atrial Deformation with Left Ventricular Function. Journal of the American Society of Echocardiography. 2017 Jul 1;30(7):659-66.

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6 Using Imaging to assess LA function which can be used to predict AF risk

6.1 Preface

LA enlargement is a strong risk factor for AF and occurs in the setting of remodeling and increased LA pressure. However, this can often occur late in the disease course, thus patients at risk of developing AF may not be identified early. Assessment of myocardial deformation using speckle tracking allows for quantitative assessment of phasic LA function. It has the advantage of being a more sensitive marker of "atriopathy" at earlier disease stages than LA volume and also allows for segmental function to be assessed.

LA strain does however have disadvantages. It is time consuming and requires a learning curve to ensure reproducibility and accuracy. Despite recent advances in standardization of acquisition protocols and ECG gating, it is vendor dependent and uses a LV strain algorithm. Realistically for it to be adopted in routine clinical practice for AF risk stratification, it has to provide incremental information to LA volume and LV strain. Otherwise, it will remain purely as a research tool with limited clinical utility.

In this chapter we investigate the association between LA and LV strain. If some component of LA function (pump) acts independently to LV function, it provides a rationale for the use of LA strain. This leads on to chapters 8 and 9 where the clinical utility of LA strain is investigated with regards to AF risk stratification. The following chapter was published in the Journal of the American Society of Echocardiography.

6.2 Abstract

Background: Left atrial (LA) strain imaging allows for quantitative assessment of LA function. The clinical relevance of these measurements is dependent on the provision of information incremental to the LV evaluation. We hypothesized that LA pump function but not reservoir function was independent of measurement of left ventricular (LV) mechanics.

Methods: Echocardiograms were undertaken in a community-based study of 576 participants ≥65 years with ≥1 risk factor (e.g. hypertension, diabetes mellitus, obesity). Strain analysis was conducted using a dedicated software package, using R-R gating. LV function was classified as normal in the presence of global longitudinal strain (GLS) (≤-18%) or global circumferential strain (GCS) (≤-22%). The associations between GLS or GCS and LA reservoir, conduit and pump strain were assessed using univariable and multivariable linear regression.

Results: Patients (age 71±5 years, 54% female), with reduced GLS had higher blood pressure and rates of diabetes and obesity ($p<0.05$). LARS and conduit strain were lower in the impaired GLS group (38.2±7.3 vs. 39.9±6.4% $p=0.004$) and (18.7±5.7 vs. 20.5±5.1, $p<0.001$) however there was no difference in LA pump strain (19.5±5.5 vs. 19.3±4.6, $p=0.72$). GLS was independently associated with LA reservoir and conduit strain ($p<0.05$), but not independently associated with LA pump strain ($p=0.91$). Reduced GCS was associated with a larger body mass index, male sex and diabetes ($p<0.05$). There were no differences in LA reservoir, conduit and pump strain in patients with normal and abnormal GCS ($p>0.05$).

Conclusion: The application of LA strain is specific to the component measured. LA pump strain is independent of LV mechanics.

6.3 Introduction

There is increasing recognition of the importance of altered LA function, incremental to LA dilatation, and the feasibility of its assessment has increased with the application of strain imaging to LA function (192, 193). Although there are currently no standardized guidelines with regards to ECG gating, image acquisition or analysis techniques (193, 194), this parameter is reliable and reproducible (192, 193), and is able to quantify the contributions of reservoir, conduit and active pump function (192).

LA strain imaging can be used as part of the assessment of LV diastolic function (92, 97, 195), but it is unclear as to whether it provides incremental information to other echocardiographic measures of diastolic function such as mitral inflow or mitral annular velocities. As LA reservoir and conduit function reflect underlying LV function, there has been some skepticism about the utility of LA strain when compared to other markers of LV strain such as GLS (88, 192, 196) – indeed, atrial and ventricular volumes reciprocate at different phases in the cardiac cycle. In contrast, LA contractile strain is a measure of LA systolic function relative to the LA load as it fills the LV and pulmonary veins. Hence, although LA pump function contributes approximately 30% to LV filling during end diastole (and even more in older patients), it is less dependent on LV function (40, 193). The loss of the LA "kick" is also felt to contribute to symptoms of HF in patients with AF (197, 198). Given the important physiological role of the LA pump, we hypothesized that atrial pump strain was independent of LV strain.

6.4 Methods.

6.4.1 Study population.

This prospective observational cohort study recruited patients from a large community-based study in Australia, which had the primary objective of early detection of HF in the community. Asymptomatic participants ≥65 years were recruited if they had 1 or more risk factors, including hypertension (systolic BP > 140mmHg or pre-existing use of anti-hypertensive medications), T2DM, based on self-report of diagnosis or the current use of diabetic medications), and obesity (defined as a body mass index ≥ 30). Exclusion criteria included: (1) inability to provide written consent to participate in the study, (2) history of moderate or greater valvular disease, (3) known history of HF, (4) reduced LV systolic function on

baseline echocardiogram (LVEF <40%), (5) contraindications to beta blockers and angiotensin converting enzyme inhibitors (ACE-I), (6) expected life expectancy of less than one year or (7) inability to perform strain analysis or acquire interpretable images from baseline echocardiogram. All patients with a known history of AF or documented AF on baseline ECG were excluded from the study. All patients were provided written informed consent and approval was obtained from the institution's Human Research Ethics Committee.

6.4.2 Clinical findings.

All participants undertook a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, past medical history, medication history as well as baseline examination data (height, weight, body mass index (BMI), blood pressure (BP) was recorded for all participants. Baseline electrocardiography (ECG) and echocardiography was conducted in all participants.

6.4.3 Echocardiography

All echocardiograms were performed by qualified sonographers using the same equipment (Siemens ACUSON SC2000, Siemens Healthcare, Mountain View, CA) and transducers (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz). Two-dimensional, M-mode and Doppler measures were obtained using standard techniques outlined by the American Society of Echocardiography. LV dimensions were calculated in both diastole and systole in parasternal long axis views. LV hypertrophy (LVH) was defined as LVM index >115 g/m^2 in men and >95 g/m^2 in women. LV and LA volumes were indexed to body surface area (LAVi) and calculated by the Simpson biplane method. Abnormal LAVi was defined as ≥34 ml/m^2. Diastolic function was assessed by calculating mitral inflow peak early and late diastolic velocities (E and A wave respectively), deceleration time and the E/A ratio (ratio <0.8 was used to define impaired relaxation). Mitral annular early diastolic velocity using tissue Doppler imaging (e') was calculated in both septal and lateral and averaged to calculate the E/e' ratio (> 13 was used to define raised LA filling pressures).

Global longitudinal strain (GLS) was calculated in apical 4 chamber views and global circumferential strain (GCS) was calculated in the mid-LV parasternal short axis view. Velocity vector imaging was used to assess ventricular strain. Manual tracing of the endocardial border of the LV was performed in end-systole and this was tracked during the cardiac cycle. LA reservoir, conduit and pump strain were assessed using speckle tracking imaging by an external third-party software program (ImageArena, Tomtec, Munich, Germany). Apical four and two chamber images were selected with a frame rate of 60-80 frames/sec. The endocardial border of the LA was manually traced, and strain analysis was performed using the LV strain algorithm, with the average of both the four- and two-chamber values. The reference point for image analysis was taken at the onset of the QRS complex (R-R gating). Patients with poor image quality, where strain analysis could not be performed, were excluded. All strain measurements were performed by two investigators. Reproducibility was assessed using a random sample of 20 patients and mean percentage difference was calculated.

6.4.4 HF follow up.

All participants were followed up using questionnaires, phone calls and follow up clinical visits at a median time of 12 months (IQR 6 months). HF symptoms were assessed using the Framingham criteria. We included patents with both HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) as per criteria outlined by the European Society of Cardiology (199, 200). All patients were reviewed by a cardiologist in the clinics and information was collected regarding symptoms and examination findings. Patients underwent echocardiography to confirm the presence of HF.

6.4.5 Statistical analysis.

Patients were split into two groups based on GLS (cut-off -18%) and GCS (cut-off -22%). All categorical variables are presented as frequencies/percentages and continuous variables presented as means/standard deviation (if normally distributed) or medians/IQR (if non-parametric). Statistical significance was performed using the chi square test for categorical data and independent sample t test for continuous data. Simple linear regression was used to identify association between LV function and clinical parameters with LA reservoir/conduit and pump strain. All variables with $p<0.1$ in univariate

analyses were considered in multivariate regression models. Cox proportional hazard models were used to assess for the association between LA strain and incident HF. Analyses were considered to be statistically significant if 2 tailed p values were <0.05. Statistical analysis was performed using SPSS v.22 (SPSS, Chicago, IL).

6.5 Results

6.5.1 Baseline characteristics.

A total of 576 patients were included in the study (age 70.7±4.7 years, male 46%). The majority of patients had T2DM (52%), obesity (43%), hypercholesterolemia (54%) and hypertension (79%). The LA reservoir, conduit and pump strain were 39.3%±6.8, 19.8%±5.4 and 19.4%±5.0 respectively. A summary of baseline patient characteristics is shown in Table 6-1.

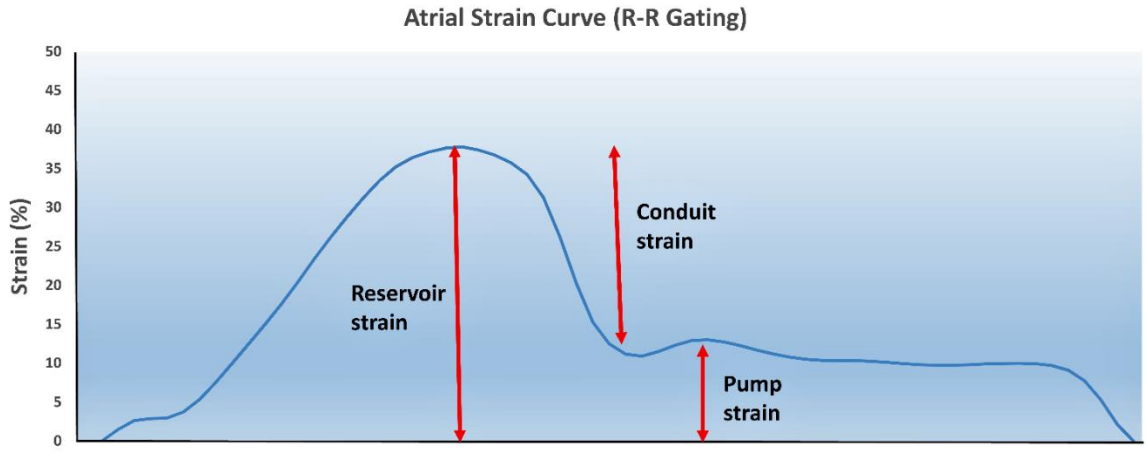

Figure 6.1 - Components of LA strain.

There are 3 components of LA strain – Reservoir strain, conduit strain and pump strain which mirror the different phasic functions of the LA.

Table 6-1 - Baseline demographics and echocardiographic parameters.

Baseline Patient Characteristics	**n = 576**
Demographics	
Age - years (SD)	70.7 (4.7)
Male n/total n (%)	264/576 (46)
Systolic BP mmHg (SD)	140.0 (16.8)
Diastolic BP mmHg (SD)	81.8 (10.4)
Heart Rate /min (SD)	66.8 (10.5)
BMI (kg/m^2) (SD)	29.4 (5.2)
Current Smoking n/total n (%)	13/576 (2)
Diabetes Mellitus n/total n (%)	297/576 (52)
Obesity n/total n (%)	249/576 (43)
Hypercholesterolemia n/total n (%)	293/545 (54)
Hypertension n/total n (%)	457/576 (79)
Previous history of IHD n/total n (%)	42/576 (7)
Previous chemotherapy n/total n (%)	70/576 (12)
Medications	**n/total n (%)**
Beta blockers	40/576 (7)
ACE Inhibitor/Angiotensin Receptor Blocker	385/576 (67)
Calcium Blocker	123/526 (23)
Lipid lowering agents	291/529 (55)
Anti-platelet agents	196/525 (37)
Echocardiographic Parameters	**Mean (SD)**
Ejection Fraction % (SD)	63.6 (5.9)
Global Longitudinal Strain % (SD)	-18.5 (2.5)
Global Circumferential Strain % (SD)	-29.8 (5.5)
E/e' (Average of lateral and septal) (SD)	8.9 (2.6)
Left Atrial volume - indexed ml/m^2 (SD)	31.8 (9.4)
Left Ventricular mass – indexed g/m^2 (SD)	91.7 (22.9)
LARS % (SD)	39.3 (6.8)
Left Atrial Conduit Strain % (SD)	19.8 (5.4)
Left Atrial Pump Strain % (SD)	19.4 (5.0)

6.5.2 Association of impaired LV strain.

Participants were split into 2 groups based on GLS (normal ≤ -18%, n=352). Table 6-2 shows that patients with abnormal GLS were older, more likely to be male, hypertensive, obese and suffering from diabetes mellitus. LA reservoir and conduit strain were reduced in the abnormal GLS group (38.2±7.3% vs. 39.9+6.4%, p=0.004 for reservoir strain) and (18.7±5.7% vs. 20.5±5.1%, p<0.001 for conduit strain). There were no significant differences with regards to LA pump strain (19.5±5.5% vs. 19.3±4.7%, p=0.72).

Participants were also split into 2 groups based on GCS (normal ≤ -22%, n=533 and abnormal > -22%, n=43) (Table 6-3). Patients with abnormal GCS were more likely to be male with higher body mass index (BMI) and rates of diabetes mellitus and ischemic heart disease (p<0.05). Groups were not different in relation to LA reservoir (39.3±6.8% vs. 39.0+7.3%, p=0.83), conduit (19.9±5.3% vs. 19.0±6.5%, p=0.30) and pump strain (19.4±5.0% vs. 20.0±5.3%, p=0.38).

6.5.3 Associations of LA and ventricular function.

LARS was independently associated with GLS (r=0.16, β =-0.13, p=0.001). GCS was not associated with reservoir strain. LARS was associated with E/e' (r=0.16, β =-0.12, p=0.004) and LV mass (r=0.14, β =-0.09, p=0.03) independent of age (r=0.26, β =-0.21, p<0.001). It was not associated with A wave or deceleration time (p>0.05) (Table 6-3).

LA conduit strain was independently associated with GLS (r=0.21, β =-0.14, p=0.01). GCS was not independently associated with conduit strain. LA conduit strain was associated with E wave (r=0.14, β =0.21, p<0.001) and A wave (r=0.11, β =-0.19, p<0.001), independent of age (r=0.23, β=-0.18, p<0.001), It was not associated with deceleration time or LV mass (p>0.05) (Table 6-4).

LA pump strain was associated with E wave (r=0.10, β =-0.23, p<0.001) and A wave (r=0.12, β =0.24, p<0.001) independent of age (r=0.10, β =-0.13, p=0.002). There was no association noted between LA pump strain and ventricular strain (GLS (r=0.005, p=0.91), GCS (r=0.0, p=0.99)). LA pump strain was not independently associated with deceleration time or LV mass (p>0.05) (Table 6-5).

6.5.4 Association between LA function and incident HF.

Among 478 out of 576 patients with follow-up data available for analysis (median follow up 12±6 months), 54 (11%) developed new incident HF. LA function was not independently associated with new incident HF (reservoir strain p=0.28, conduit strain p=0.38, pump strain p=0.66).

Table 6-2 - Baseline characteristics for groups with normal and reduced GLS (cut-off -18%) and GCS (cut-off -22%).

Note – GLS ≥ -18 refers to values less negative than -18% and GCS ≥ -22 refers to values less negative than -22%

	GLS > -18% n = 224	**GLS ≤ -18% n = 352**	**P Value**	**GCS > -22% n = 43**	**GCS ≤ -22% n = 533**	**P Value**
Age - years (SD)	71.2 (4.4)	70.4 (4.7)	0.007	70.4 (4.0)	70.8 (4.7)	0.65
Male n/total n (%)	127/224 (57)	137/352 (39)	<0.001	30/43 (70)	234/533 (44)	0.001
Systolic BP (mmHg) (SD)	142.3 (19.6)	138.7 (14.6)	0.02	138.1 (17.8)	140.2 (16.7)	0.43
Diastolic BP (mmHg) (SD)	84.2 (10.4)	80.3 (10.1)	<0.001	83.3 (10.6)	81.7 (10.4)	0.31
Heart Rate /min (SD)	69.2 (11.2)	65.3 (9.8)	<0.001	72.6 (11.6)	66.4 (10.3)	<0.001
BMI (kg/m^2) (SD)	29.9 (5.5)	29.1 (5.0)	0.08	31.7 (6.1)	29.2 (5.1)	0.003
Current Smoking n/total n (%)	9/224 (4)	4/352 (1)	0.02	1/43 (2)	12/533 (2)	0.97
Diabetes Mellitus n/total n (%)	151/224 (67)	146/352 (42)	<0.001	31/43 (72)	266/533 (50)	0.005
Obesity n/total n (%)	111/224 (49)	138/352 (39)	0.02	23/43 (54)	226/533 (42)	0.16
Hypercholesterolemia n/total n (%)	121/210 (58)	172/335 (51)	0.15	20/37 (54)	273/508 (54)	0.97
Hypertension n/total n (%)	178/224 (80)	279/352 (79)	0.95	35/43 (81)	422/533 (79)	0.73
Previous history of IHD n/total n (%)	21/224 (9)	21/352 (6)	0.13	7/43 (16)	35/533 (7)	0.02
Previous chemotherapy n/total n (%)	28/224 (13)	42/352 (12)	0.84	6/43 (14)	64/533 (12)	0.71
Ejection Fraction % (SD)	61.8 (6.8)	64.8 (4.9)	<0.001	58.8 (8.1)	64.0 (5.5)	<0.001
Global Longitudinal Strain % (SD)	-16.1 (1.6)	-20.1 (1.5)	<0.001	-16.7 (2.4)	-18.7 (2.5)	<0.001
Global Circumferential Strain % (SD)	-28.7 (6.0)	-30.4 (5.0)	<0.001	-20.0 (1.7)	-30.6 (4.9)	<0.001
E/e' (Average septal and lateral) (SD)	9.0 (2.8)	8.8 (2.5)	0.40	8.7 (2.7)	8.9 (2.6)	0.53
Left atrial volume - indexed ml/m^2 (SD)	32.6 (9.9)	31.2 (9.0)	0.10	30.1 (7.6)	31.9 (9.5)	0.23
Left Ventricular mass – indexed g/m^2 (SD)	95.9 (24.9)	89.0 (21.1)	0.001	96.5 (23.4)	91.3 (22.8)	0.15
Atrial Reservoir Strain % (SD)	38.2 (7.3)	39.9 (6.4)	0.004	39.0 (7.3)	39.3 (6.8)	0.83
Atrial Conduit Strain % (SD)	18.7 (5.7)	20.5 (5.1)	<0.001	19.0 (6.5)	19.9 (5.3)	0.30
Atrial Pump Strain % (SD)	19.5(5.5)	19.3 (4.7)	0.72	20.0 (5.3)	19.4 (5.0)	0.38

Table 6-3 - Associations of atrial reservoir strain and LV mechanics and diastolic function. Multivariable adjusted R^2 = 0.10; p<0.001

	Univariable			Multivariable		
Variables	**Unstandardized co-efficient (95% C.I)**	**Standardized β**	**p**	**Unstandardized co-efficient (95% C.I)**	**Standardized β**	**p**
Age (years)	-0.38 (-0.49, -0.26)	-0.26	<0.001	-0.31 (-0.43, -0.19)	-0.21	<0.001
GLS (%)	-0.44 (-0.66, -0.22)	-0.16	<0.001	-0.36 (-0.57, -0.14)	-0.13	0.001
GCS (%)	-0.08 (-0.18, 0.02)	-0.07	0.12			
E/e' ratio	-0.43 (-0.64, -0.21)	-0.16	<0.001	-0.31 (-0.52, -0.10)	-0.12	0.004
E wave (m/s)	1.51 (-2.0, 5.0)	0.04	0.40			
A wave (m/s)	-0.12 (-3.1, 2.8)	-0.003	0.94			
Decel.time (msec)	0.0 (-0.01, 0.01)	0.0	0.99			
LV mass (g/m^2)	-0.04 (-0.07, -0.02)	-0.14	0.001	-0.03 (-0.05, -0.003)	-0.09	0.03

Table 6-4 - Association between atrial conduit strain and LV mechanics and diastolic dysfunction. Multivariable adjusted R^2 = 0.12; p<0.001

	Univariable			Multivariable		
Variables	**Unstandardized co-efficient (95% C.I)**	**Standardized β**	**p**	**Unstandardized co-efficient (95% C.I)**	**Standardized β**	**p**
Age (years)	-0.27 (-0.36, -0.17)	-0.23	<0.001	-0.21 (-0.30, -0.11)	-0.18	<0.001
GLS (%)	-0.44 (-0.62, -0.27)	-0.21	<0.001	-0.31 (-0.48, -0.13)	-0.14	0.001
GCS (%)	-0.08 (-0.16, 0.002)	-0.08	0.06	-0.02 (-0.10, 0.06)	-0.02	0.57
E/e' ratio	-0.28 (-0.45, -0.11)	-0.13	0.001	-0.31 (-0.52, -0.10)		
E wave (m/s)	4.9 (2.1, 7.7)	0.14	0.001	7.1 (4.0, 10.2)	0.21	<0.001
A wave (m/s)	-3.3 (-5.6, -0.92)	-0.11	0.007	-5.5 (-8.1, -3.0)	-0.19	<0.001
Decel.time (msec)	-0.01 (-0.02, 0.002)	-0.06	0.15			
LV mass (g/m^2)	-0.02 (-0.04, 0.0)	-0.08	0.05	-0.01 (-0.03, 0.01)	-0.04	0.36

Table 6-5 - Association between atrial pump strain and LV mechanics and diastolic dysfunction. Multivariable adjusted R^2 = 0.07; p<0.001

	Univariable			Multivariable		
Variables	**Unstandardized co-efficient (95% C.I)**	**Standardized β**	**p**	**Unstandardized co-efficient (95% C.I)**	**Standardized β**	**p**
Age (years)	-0.11 (-0.20, -0.02)	-0.10	0.01	-0.14 (-0.23, -0.05)	-0.13	0.002
GLS (%)	0.01 (-0.15, -0.17)	0.005	0.91			
GCS (%)	0.0 (-0.08, 0.08)	0.0	0.99			
E/e' ratio	-0.14 (-0.30, 0.02)	-0.07	0.08			
E wave (m/s)	-3.3 (-5.9, -0.69)	-0.10	0.01	-7.2 (-10.1, -4.3)	-0.23	<0.001
A wave (m/s)	3.1 (0.94, 5.3)	0.12	0.005	6.3 (3.8, 8.7)	0.24	<0.001
Decel.time (msec)	0.01 (-0.002, 0.02)	0.06	0.15			
LV mass (g/m^2)	-0.02 (-0.04, -0.003)	-0.10	0.02	-0.02 (-0.03, 0.001)	-0.07	0.07

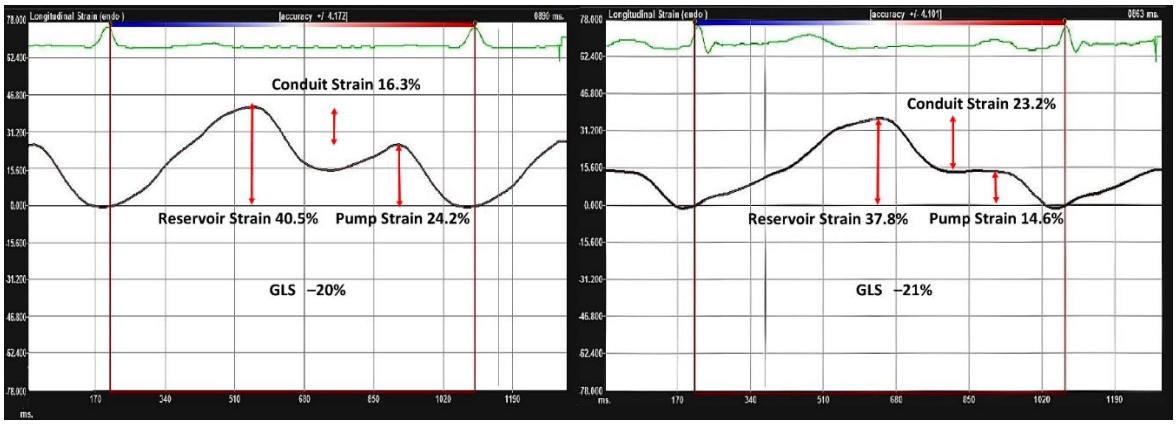

Figure 6.2 - Variability of LA pump strain in two patients with similar GLS and LARS.

In both LA strain curves we see significantly different LA pump strain (much higher in the left panel and lower in the right panel), despite similar GLS and LARS. This highlights that changes to pump function may occur independently of LV function.

6.5.5 Reproducibility.

Reproducibility was assessed by blinded strain measurements in a random sample of 20 patients. All measurements were done by the same two investigators (SR and TN) and the mean of the absolute value

of differences between measurements was calculated. For GLS and GCS the mean±SD difference between was 0.7±0.7% and 4.0±3.9% respectively. For LA strain the mean difference was 8.0±7.0% for reservoir strain, 5.4±4.1% for conduit strain and 5.6±4.6% for pump strain. Intra-observer variability was assessed by one investigator (SR) who repeated LA strain measurements in the same 20 patients at a different timepoint. The mean difference for LA strain was 3.8±2.9% for reservoir strain, 2.7±1.4% for conduit strain and 2.7±1.4% for pump strain.

6.6 Discussion

The results of our study suggest that GLS was independently associated with LA reservoir and conduit strain but was not independently associated with LA pump strain. GCS was not found to be associated with LA strain. LA strain was associated with diastolic function yet not independently associated with incident HF.

6.6.1 LA physiology.

The LA is thin-walled, with a high degree of compliance which allows it to stretch during the reservoir phase (40). Therefore, in ventricular systole, the LA acts as a reservoir for blood flow from the pulmonary circulation. The elasticity of the LA allows it to return to normal size during the conduit and pump phases (193). The independent association of LV-GLS with reservoir function is a reflection of how LV pathology is associated with higher LV filling pressures, increased LA pressure and tension and impaired LA compliance (201). The maladaptive compensatory changes of the thin walled LA in response to high pressures (202-204) leads to progressive pathological changes, including fibrosis as a response to inflammatory mediators (92, 205, 206), resulting in reduced reservoir function.

One of the main functions of the LA is acting as a passive conduit during early diastole, which contributes up to 35% of ventricular filling (207). An essential aspect to normal conduit function is a pressure gradient across the mitral valve which occurs during LV relaxation (40). The association of impaired GLS with reduced conduit strain in our study is a reflection of the contribution of a stiff LV to a lower LA-LV gradient (201).

LA contraction at the end of diastole is influenced by age, LV relaxation, atrial preload and LV end diastolic pressure (afterload). The LA pump contributes approximately 30% of ventricular filling and can be higher in older patients (40, 95). The LA pump has an important role in ventricular filling where conduit function is reduced. In the early stages of diastolic dysfunction, the LA is able to compensate for reduced conduit function by an increased "atrial kick" at end diastole (40). Although patients can remain asymptomatic during this phase, they have less functional reserve. Reduced LA strain has been shown to be associated with reduced exercise capacity (178, 208, 209). Patients who lose the "atrial kick" such as those who develop AF or patients who develop tachycardia (associated with reduced diastolic filling time) can manifest symptoms of HF and decompensate acutely (40, 192).

6.6.2 Measurement of LA strain.

Several concerns are relevant to LA strain measurement. There are limited guidelines or consensus on image acquisition, ECG gating and what parameters to measure (95, 192). LA strain measurement may be operator-dependent and time-consuming, as the thin endocardial border is difficult to track (95). The calculation of LA strain has to be done using a LV strain algorithm as software vendors have yet to develop a dedicated algorithm (192). In contrast, GLS is more robust, has been validated in different populations to assess for subclinical LV dysfunction and can be used to assess prognosis in patients admitted with myocardial infarction and HF (179, 180).

6.6.3 What factors influence LA pump function?

In our study we have attempted to highlight the importance of the atrial pump, as most studies have focused on LARS. We have shown that in comparison to reservoir or conduit function, the atrial pump is less associated with LV function. This suggests that there may be other mechanisms which can influence atrial pump function.

LA function is mainly influenced by LV systole and relaxation – as reservoir and conduit function are reflections of changes to the LV, the independent value of LA contractile strain might be expected but has not been proven (88, 192, 196). The LA pump involves the interplay of multiple factors (83, 193). In our study, we have emphasized that LA pump function is independent of LV function.

The first component influencing pump function is atrial preload. Pulmonary venous flow is a determinant of LA volume, and therefore atrial ejection. Second, there is a co-dependence between the three components of LA strain. LA reservoir function is influenced by LV compliance and descent of the LV base during diastole, but also by LA systole. In elderly patients, changes to LV compliance and impaired relaxation reduces conduit strain, and the LA may compensate by ejecting a larger volume during end diastole, until the eventual loss of LA reserve may lead to symptoms of HF. This interdependence between the three components of LA function demonstrates an indirect influence of LV function on pump function. Third, the LA pump is influenced by the LV end-diastolic pressure (afterload) as the LA must pump blood across a higher-pressure gradient.

In our study, we have attempted to highlight the importance of the LA pump. Despite the indirect involvement of the LV on LA function, outlined by the mechanisms above, our results demonstrate that LA pump function is not directly dependent on LV function. To further understand the physiology of the LA pump and the various influencing factors, further research combining LA strain with invasive hemodynamic data will allow us to better understand this relationship.

6.6.4 LA strain and association with diastolic function.

Current echocardiographic assessment of diastolic function is primarily based on assessment of mitral inflow velocities, early diastolic mitral annular velocity and assessment of LA volume (210). The novel role of LA strain in assessment of diastolic function is mentioned in the latest ASE guidelines, however there is acknowledgement of current limitations (210). In our study, we have demonstrated a close relationship between diastolic function and LA strain. The LA acts as a reservoir during ventricular systole and we noted that reservoir function was associated with E/e'. This suggests that the ability of the LA to stretch and act as a reservoir is directly influenced by the pressure within the LA as well as the LV-LA gradient. Conduit function was associated with both the E and A wave suggesting a close relationship with LV relaxation and filling pressures rather than LA size. LA pump function was not associated with LV mass or LV strain and was closely associated with the E and A wave. This suggests that pump function is not influenced primarily by LV function and is influenced by other external factors that directly influence LA function.

6.6.5 Usefulness of LA strain compared to other echocardiographic markers of diastolic function.

The use of transmitral Doppler and annular tissue Doppler imaging in the echocardiographic evaluation of diastolic function are constrained by a number of situations where the measurements confounded by other disease processes – for example, mitral annular calcification or mitral regurgitation. LA strain has a few advantages over tissue Doppler imaging - it is angle independent (194), and it provides quantitative assessment of the various active and passive components of LA function – potentially including regional function (192, 194). As discussed previously, the main disadvantages are the lack of consensus guidelines on image acquisition, ECG gating and variable software vendor algorithms (193, 194). We have noted in our study the close correlation between some LA strain parameters and other markers of diastolic function. Interestingly, however, there was no significant difference in E/e' or LA volume between both normal and abnormal LV strain groups, despite differences in LA reservoir and conduit strain. It is possible that LA strain analysis has greater sensitivity in detecting early pathological changes in LA function. This may be analogous to the greater sensitivity of LV strain compared to standard systolic markers of LV dysfunction (179).

There are also certain clinical situations in which assessment of LA strain may offer incremental information. Fibrosis is the hallmark of LA remodeling. LA strain has also been correlated with LA stiffness and fibrosis (92, 149), thus allowing for non-invasive assessment. In HF patients, LARS is associated with exercise capacity (178) and has higher sensitivity than E/e' in predicting LV filling pressures (211). LA strain may be useful in predicting AF recurrence following cardioversion (93). Compared to traditional markers of diastolic function, LARS provides additional prognostic information in AF, myocardial infarction and mitral valve disease (40, 96, 100, 212-214).

6.6.6 Clinical implications.

LARS is an important prognostic marker in predicting both mortality and HF endpoints in both HFpEF (213) and HFrEF (214), and LA strain is also associated with reduced exercise capacity in HFrEF (178). However, in this study, LA function was not associated with new onset HF. It is possible that patients with LA dysfunction without significant LV dysfunction can compensate and hence do not manifest symptoms.

As discussed above, LARS is an alternative marker of LV diastolic function that may be of value in patients with symptoms of HF who have indeterminate diastolic function from tissue Doppler imaging. In patients with HF, LARS can be used for prognostication and prediction of exercise capacity (178, 213).

The results from our study suggests that LA contractile function is independent of LV function. In patients with new onset AF with a normal LA volume, measurement of contractile strain may help delineate underlying abnormal LA function. LA strain may also be useful to predict recurrence of AF after cardioversion or catheter ablation (93, 215).

There are several sources of variability of LA strain that should be resolved. The utility and feasibility of LA strain in routine clinical practice are still undefined. Standardized guidelines on ECG gating and image acquisition techniques may help provide more uniform measurements and reduce variability. Nomenclature for LA strain should be standardized so that results across studies can be compared. Development of a dedicated LA strain algorithm by external software vendors may help improve accuracy, reduce measurement time and reduce error. We also need consensus definition of normal LA strain values across age groups to make it easier to identify patients with abnormal measurements.

The results of our study also highlight several areas which may be of interest for future research. Linking LA strain to LA remodeling and fibrosis may offer further insight into the "atriopathy" that develops in conditions such as hypertension and obesity. LA strain appears to be of value in prediction of AF, but a prospective study could better establish this parameter in decision-making. A comparison of LA strain with LA voltage mapping could help identify whether strain may offer a non-invasive method of identifying LA negative/positive remodeling. There is a potential role for LA strain in predicting stroke risk in patients with AF, incremental to clinical risk scores.

6.6.7 Limitations.

The limitations of our study include potential for population selection bias as patients were recruited with newspaper and radio advertising. Ventricular and atrial strain were both measured using speckle tracking but using software from different manufacturers (albeit very similar). The primary reason for this was to allow rapid assessment for subclinical LV dysfunction using the on-cart software for clinical

assessment. Although the use of different strain analysis techniques from different vendors has been previously shown to create inconsistencies and errors, this problem has been substantially ameliorated by recent efforts to improve concordance (42). This we do not think that this difference in software has influences our assessment of the associations between LV and LA function.

LA strain imaging, like other imaging techniques, is operator dependent. In our study there was approximately 8% difference in LARS and approximately 5-6% difference in conduit and pump measurements during our validation study.

6.7 Conclusion.

LA strain is not a single entity. The ASE/EAE Recommendations for the evaluation of LV diastolic function (30) describe an association between LV systolic and diastolic strain, LA strain and LV diastolic function. However, LA strain is not merely duplicative of LV diastolic function – the results of this study emphasize that LA pump strain is independent of LV function. Changes to atrial pump function is not primarily dependent on changes to the LV and may be due to the development of an underlying “atriopathy.”

6.8 Postscript

The results of this study demonstrate that LA contractile function is independent of LV function. LA reservoir and conduit function are closely correlated to LV function. Measurement of LA strain allows for quantitative assessment of all three components of LA function. This study has helped dispel the theory that LA strain is purely just a "mirror image" of LV function therefore has no incremental value. Given one of the three components of LA function was shown to be independent, it provides a rationale to further investigate the association of LA strain with AF. These imaging parameters may also be useful as a non-invasive marker of stroke risk as they provide information about the underlying "atriopathy" which has developed.

In the next chapter we investigate the potential confounding effect of hypertension on LA function. BP is typically measured at the brachial artery to estimate the SBP and DBP. However, there is evidence to suggest that CBP (measured at the aorta) is more closely associated with clinical outcomes. It can be assessed using different algorithms from the brachial artery (either SBP/DBP or MAP/DBP). In the next chapter we investigate the calibration between the different CBP measurements to determine which is more accurate and we investigate the relationship between the BP and LA strain.

Chapter 7

Determinants of LA Dysfunction – Identifying patients at early disease stages.

"The Importance of Calibration Method in Determining the Association between Central Blood Pressure with Left Ventricular and Left Atrial Strain."

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7 Determinants of LA dysfunction – Identifying patients at early disease stages.

7.1 Preface

Afterload is an important determinant of LV and LA function. Hypertension is a known independent risk factor for AF and cardiovascular disease. It can contribute to LA negative remodeling which creates a substrate for arrhythmogenesis. There are different noninvasive methods of measuring BP. Typically brachial SBP and DBP is commonly utilized in clinical practice. However, CBP (aortic pressure) may be more closely associated with cardiovascular outcomes. There are different non-invasive methods of estimating CBP.

Hypertension has a direct relationship with LA function. LA strain which is used as a non-invasive marker of LA function is influenced by BP. Identifying patients with abnormal LA/LV strain may be important clinically to determine patients at risk of developing AF or HF. BP may be an important marker in identifying patients with an underlying “atriopathy”. CBP may be a more sensitive marker compared with brachial BP, which may assist in identifying patients at earlier disease stages at risk of developing AF.

In this chapter we investigate the association between BP and LA/LV function. We compare different calibration methods for CBP to determine the most sensitive BP marker associated with abnormal LA and LV strain. The preliminary results of this chapter were presented at the European Society of Cardiology Congress in 2017.

7.2 Abstract

Background: Afterload is an important determinant of left ventricular (LV) and atrial (LA) function, including myocardial strain. Central blood pressure (CBP) is the major component of cardiac afterload and independently associated with cardiovascular risk. However, the optimal means of calibrating CBP is unclear - standard CBP assessment uses systolic (SBP) and diastolic blood pressure (DBP) from brachial waveforms, but calibration with mean pressure (MAP) and DBP purports to be more accurate. Therefore, we sought which CBP is best associated with LA and LV strain.

Methods: CBP was measured using both standard and MAP based calibration methods in 546 participants (age 70.7±4.7 years, 45% male) with risk factors for HF. Echocardiography was performed in all patients and strain analysis conducted to assess LA/LV function. The associations between CBP with LA and LV strain were assessed using linear regression.

Results: MAP-derived CSBP (150±20mmHg) was higher than standard CSBP (128±15mmHg) and brachial SBP (140±17mmHg, $p<0.001$), whereas DBPs were similar (84±10, 83±10, and 82±10 mmHg). MAP-derived CSBP was not independently associated with LV strain ($p>0.05$), however was independently associated with LA reservoir strain ($p<0.05$). Brachial and central DBP were more strongly associated with LA reservoir/conduit and LV strain than brachial and central SBP. LA pump strain was not independently associated with any SBP or DBP parameter ($p>0.05$). MAP-derived CBP was more accurate in identifying patients with abnormal LA and LV strain than brachial SBP and standard CBP calibration.

Conclusion: CBP calibrated using MAP and DBP may be more accurate in identifying patients with abnormal LA and LV function than standard brachial calibration methods.

7.3 Introduction

Hypertension is a leading cause of morbidity and mortality (216, 217). Recent changes in clinical practice guidelines have advocated for an aggressive approach in the diagnosis and treatment of hypertension (216). However, there remains contention regarding the use of the most appropriate blood pressure (BP) marker (218), which is easily measurable, reproducible and correlates with clinical outcomes. Among some studies, central blood pressure (CBP) is more closely associated with cardiovascular outcomes compared with peripheral brachial BP (219-222). There are multiple non-invasive methods of calculating central (aortic) pressure (223). Most commonly, a waveform calibration method is to use brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP). This method may be associated with inaccuracy leading to underestimation of the systolic CBP and overestimation of diastolic CBP (224). The use of mean arterial pressure (MAP) along with DBP may be a more accurate calibration method of CBP (223). We previously reported better associations between MAP-derived CBP and cardiac anatomy as a marker of end-organ damage (225) but little is known about relationships against cardiac functions. Identifying the BP parameter most closely associated with altered cardiac function is important as it may indicate those with early signs of end-organ damage related to hypertension.

Strain analysis using speckle tracking allows for quantitative assessment of LA and LV function. Hypertension has a direct impact on both LV and LA function – the latter through LV stiffness contributing to increased LA pressure leading to LA dilatation and fibrosis (226). CBP (assessment of aortic pressure) may be a more accurate marker for the assessment of LA and LV dysfunction, compared with brachial BP however, this has not been validated. In this study, we aimed to elucidate the associations between the BPs and myocardial deformation parameters with the aim of validating the use of MAP-derived central SBP in identifying patients with LA and LV dysfunction.

7.4 Methods.

7.4.1 Study population.

This is a cross-sectional study using baseline data from a large community-based study of stage A HF, with the primary objective of early detection of left ventricular dysfunction using strain imaging (Tas-ELF study, ACTRN12614000080628**).** Asymptomatic participants ≥65 years were recruited if they had 1 or more risk factors, including hypertension (systolic BP ≥ 140mmHg, DBP ≥ 90mmHg or pre-existing use of anti-hypertensive medications), T2DM, based on self-report of diagnosis or the current use of diabetic medications), or obesity (defined as a body mass index ≥ 30 kg/m^2). Exclusion criteria included: (1) inability to provide written consent to participate in the study, (2) history of moderate or greater valvular disease, (3) known history of HF, (4) reduced LV systolic function on baseline echocardiogram (LVEF <40%), (5) contraindications to beta blockers or angiotensin converting enzyme inhibitors (ACE-I), (6) expected life expectancy of less than one year or (7) inability to perform strain analysis or acquire interpretable images from baseline echocardiogram. All patients with a known history of AF or documented AF on baseline ECG were excluded from the study. All patients were provided written informed consent and approval was obtained from the institution's Human Research Ethics Committee (University of Tasmania HREC project number H0013333)

7.4.2 Baseline data collection.

All participants undertook a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, past medical history, medication history as well as baseline examination data (height, weight, BMI) was recorded for all participants. Baseline ECG and echocardiography was conducted in all participants.

7.4.3 BP measurement.

Peripheral BP (3x measurements) was measured in the supine position following a minimum of 10 minutes in a quiet room without auditory stimuli. A validated oscillometric device (Mobil-O-Graph, IEM, Stolberg, Germany) was used for all measurements. CBP was measured using two calibration methods. Standard CBP was measured from calibration of the brachial BP waveforms using oscillometric SBP and DBP. Using an automated batch method, each brachial BP waveform was then

recalibrated to derive MAP based CBP using oscillometric MAP and DBP measurements. Cut-offs for hypertension using CBP was determined as BP ≥ 130/80 mmHg whilst brachial BP cut-off was set at ≥ 140/90 mmHg.

7.4.4 Echocardiography.

All echocardiograms were performed by qualified sonographers who were blinded to clinical information using the same equipment (Siemens ACUSON SC2000, Siemens Healthcare, Mountain View, CA) and transducers (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz). Two-dimensional, M-mode, and Doppler measures were obtained using standard techniques outlined by the American Society of Echocardiography. LV dimensions were calculated in both diastole and systole in parasternal long axis views. LV hypertrophy (LVH) was defined as LVM index >115 g/m^2 in men and >95 g/m^2 in women. LV and LA volumes were indexed to body surface area (LAVi) and calculated by the Simpson biplane method. Abnormal LAVi was defined as ≥34 ml/m^2.

Global longitudinal strain (GLS) was calculated in apical views using speckle tracking imaging. Manual tracing of the endocardial border of the LV was performed in end-systole and this was tracked during the cardiac cycle. Abnormal GLS was defined as >-16%(227). LA reservoir, conduit and pump strain were assessed using speckle tracking imaging by an external third-party software program (ImageArena, Tomtec, Munich, Germany). Apical four and two chamber images were selected with a frame rate of 60-80 frames/sec. The endocardial border of the LA was manually traced, and strain analysis was performed using the LV strain algorithm, utilizing the average of both the four- and two-chamber values. The reference point for image analysis was taken at the onset of the QRS complex (R-R gating). Abnormal LA strain was defined as LARS <38%, LA conduit < 21% and LA pump strain < 16%. Patients with poor image quality, where strain analysis could not be performed, were excluded. All strain measurements were performed by two investigators. Reproducibility was assessed using a random sample of 20 patients and mean percentage difference was calculated.

7.4.5 Statistical analysis.

All categorical variables are presented as frequencies/percentages and continuous variables presented as means/standard deviation (if normally distributed) or medians/IQR (if non-parametric). Clinical and

echocardiographic characteristics were compared in participants with normal/abnormal GLS. Baseline characteristics were compared using the chi-square test for categorical data, and Student t-test for continuous data or the Mann-Whitney U test as appropriate. The correlation between standard and MAP-derived CBP was assessed using scatterplots and Pearson's r. Scatterplots were also used to compare both standard and MAP-derived CBP based on the presence of reduced GLS/LA strain. Multivariable linear regression analysis was used to assess the independent association between BP parameters and strains by adjusting for BMI, T2DM, family history of HF, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta blockers, calcium channel blockers and diuretics. Correlation co-efficients between standard and MAP-derived CBP were compared using Steiger's Z test. Analyses were considered statistically significant if 2-tailed p-values were <0.05. Statistical analysis was performed using SPSS v.22 (SPSS, Chicago, IL), R version 3.5.0 [https://www.r-project.org]) and Stata v.13 (StataCorp, College Station, Texas).

7.5 Results

7.5.1 Baseline characteristics.

A summary of baseline patient characteristics is shown in Table 7-1. A total of 546 patients were included in the study (age 70.7±4.7 years, male 45%). The majority of patients had T2DM (52%), obesity (43%), hypercholesterolemia (54%) and hypertension (79%). The mean GLS, LA reservoir, conduit and pump strain of the overall cohort was -18.6±2.5%, 39.3±6.8%, 19.9±5.4%, and 19.4±5.0%, respectively.

87 participants (16%) of the cohort had abnormal GLS (GLS -14.6%±1.3% vs. -19.3%±1.9% in those with normal GLS, p<0.001). Those with abnormal GLS had higher BMI, were more likely to have a diagnosis of diabetes mellitus and had reduced exercise capacity based on the six-minute walk test (p<0.05). SBP was not significantly different in those with normal and abnormal GLS (p>0.05), however, those with abnormal GLS had higher DBP compared with those with normal GLS (85.2±10.3 vs. 81.1±10.2 mmHg for brachial DBP, 86.7±10.4 vs. 82.1±9.9 mmHg for standard central DBP and 87.7±10.9 vs. 83.0±10.0 mmHg for MAP-derived central DBP, p<0.001). LA strain was lower in those

with abnormal GLS (36.7%±7.9% vs. 39.7%±6.5%, p=0.001 for LARS; and 18.1%±5.9% vs. 20.2%±5.2%, p=0.002 for LA conduit strain). LA pump strain was similar among the groups (p>0.05).

Table 7-1 - Baseline characteristics of the overall cohort and participants grouped by the presence of LVH.

Baseline Patient Characteristics	**Entire cohort**	**Subjects with normal GLS (≤-16%)**	**Subjects with abnormal GLS (>-16%)**	**P value**
Demographics	**n=546**	**n=459**	**n=87**	
Age - years (SD)	70.7 (4.7)	70.6 (4.7)	71.3 (4.6)	0.20
Male n(%)	247 (45)	194 (42)	53 (61)	0.001
BMI (kg/m^2) (SD)	29.4 (5.2)	29.2 (5.1)	30.5 (6.1)	0.03
Current Smoking n(%)	12 (2)	11 (2)	1 (1)	0.47
Diabetes Mellitus n(%)	284 (52)	224 (49)	60 (69)	0.001
Obesity n(%)	234 (43)	192 (42)	42 (48)	0.27
Hypercholesterolemia n(%)	281/533 (54)	234/442 (53)	47/80 (59)	0.34
Hypertension n(%)	429 (79)	360 (78)	69 (79)	0.86
Previous history of IHD n(%)	38 (7)	29 (6)	9 (10)	0.18
Median Six Minute Walk Test m(IQR)	485 (115.5)	490 (111.8)	469 (129.0)	0.02
Medications				
Beta blockers n(%)	34 (6)	24 (5)	10 (12)	0.03
ACE-I/ARB n(%)	363 (67)	309 (67)	54 (62)	0.34
Calcium Channel Blocker n(%)	117/503 (23)	91/425 (21)	26/78 (33)	0.02
Lipid lowering agents n(%)	278/505 (55)	231/427 (54)	47/78 (60)	0.32
Anti-platelet agents n(%)	189/502 (38)	159/426 (37)	30/76 (40)	0.72
Blood Pressure				
Brachial SBP mmHg (SD)	140.0 (16.6)	139.7 (15.7)	141.8 (20.6)	0.38
Brachial DBP mmHg (SD)	81.7 (10.3)	81.1 (10.2)	85.2 (10.3)	0.001
Standard Systolic CBP mmHg (SD)	128.2 (15.2)	127.9 (14.6)	130.0 (18.0)	0.30
Standard Diastolic CBP mmHg (SD)	82.8 (10.2)	82.1 (9.9)	86.7 (10.4)	<0.001
MAP-derived Systolic CBP mmHg (SD)	150.3 (20.2)	150.0 (18.7)	151.7 (26.5)	0.59
MAP-derived Diastolic CBP mmHg (SD)	83.7 (10.3)	83.0 (10.0)	87.7 (10.9)	<0.001
Echocardiographic Parameters	**Mean (SD)**			

Ejection Fraction % (SD)	63.7 (5.9)	64.4 (5.2)	60.0 (7.6)	<0.001
Global Longitudinal Strain % (SD)	-18.6 (2.5)	-19.3 (1.9)	-14.6 (1.3)	<0.001
E/e' (Average of lateral and septal) (SD)	8.9 (2.6)	8.9 (2.6)	8.8 (2.8)	0.66
Left atrial volume - indexed ml/m^2 (SD)	31.6 (9.2)	31.5 (9.1)	32.4 (9.9)	0.38
LV mass index g/m^2 (SD)	91.5 (22.7)	90.0 (21.6)	99.2 (26.8)	0.003
LARS % (SD)	39.3 (6.8)	39.7 (6.5)	36.7 (7.9)	0.001
LA Conduit Strain % (SD)	19.9 (5.4)	20.2 (5.2)	18.1 (5.9)	0.002
LA Pump Strain % (SD)	19.4 (5.0)	19.5 (4.9)	18.6 (5.5)	0.14

ACE-I – Angiotensin converting enzyme inhibitor ARB – Angiotensin receptor blocker

7.5.2 Correlation between different CBP calibration methods.

Figure 7.1 illustrates a scatterplot showing the correlation among the three BP methods. MAP-derived central SBP was higher than standard systolic CBP and brachial SBP (150±20 mmHg vs. 128±15 mmHg vs. 140±17mmHg, both $p<0.001$). Whereas MAP-derived central DBP was similar to standard central DBP and brachial DBP (84±10 mmHg vs. 83±10 mmHg vs. 82±10 mmHg, $p>0.05$). There was a modest correlation between MAP-derived central SBP and standard central SBP (Pearson's $r = 0.74$, $p<0.001$). There was a stronger correlation between standard central SBP with brachial SBP (Pearson's $r = 0.87$, $p<0.001$), compared with between MAP-derived central SBP and brachial SBP (Pearson's $r = 0.82$, $p<0.001$). There was strong correlation between brachial DBP, MAP-derived central DBP and standard central DBP (Pearson's r between 0.93-0.98, all $p<0.001$).

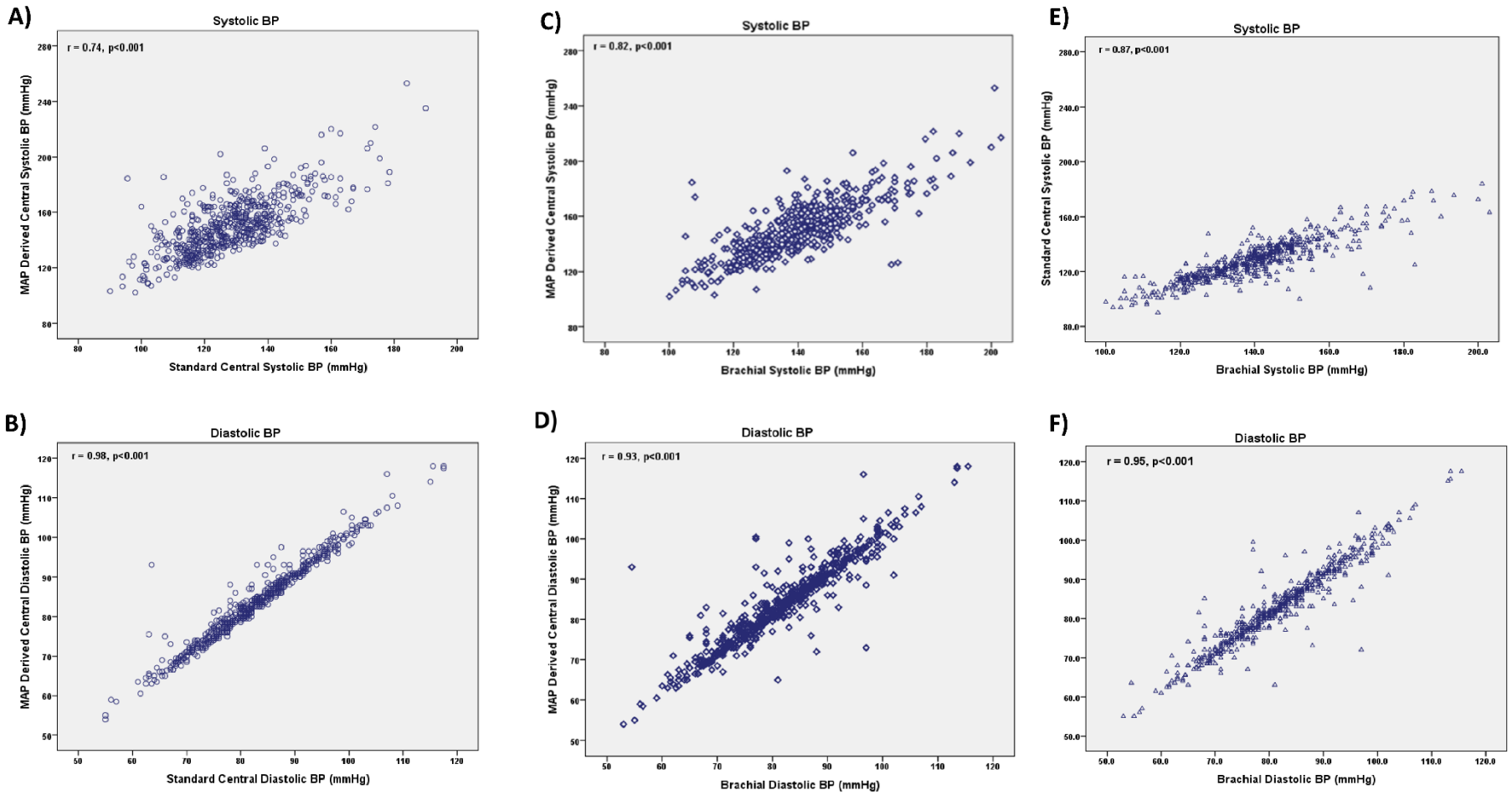

Figure 7.1 - Scatterplot comparing correlation between brachial, standard and MAP-derived CBP measurements.

Figures B, D and F demonstrate the strong linear relationship between DBP's whilst only a moderate linear relationship between SBP's (figures A, C and E). Standard central SBP had a stronger correlation with brachial SBP (figure E – r=0.87, p<0.001) compared with MAP-derived central SBP (figure C – r=0.82, p<0.001).

7.5.3 Association between BP and LA/LV strain.

Table 7-2 summarizes the associations between BPs and strains. DBP (both brachial and central) were independently associated with GLS, LA reservoir and LA conduit strain ($p<0.05$) but not with LA pump strain ($p>0.05$). Brachial and standard central SBPs were independently associated with GLS ($\beta=-0.09$, $p=0.04$ for brachial SBP and $\beta=-0.15$, $p=0.001$ for standard central SBP). MAP-derived central SBP was independently associated with LARS ($\beta=-0.12$, $p=0.01$) but not with GLS or LA conduit strain ($p>0.05$). No BP parameter was independently associated with LA pump strain ($p>0.05$).

Table 7-2 - Association between brachial/CBP and LV/LA strain.

		LV Strain		LA Strain					
		GLS		Reservoir		Conduit		Pump	
Variables		β	P value	β	P value	β	P value	β	P value
SBP	**Brachial**	**-0.09**	**0.04**	**-0.09**	**0.04**	**-0.13**	**0.004**	0.01	0.78
	Standard Central	**-0.15**	**0.001**	-0.06	0.21	**-0.12**	**0.006**	0.06	0.23
	MAP-Derived Central	-0.05	0.23	**-0.12**	**0.01**	-0.07	0.12	-0.08	0.09
DBP	**Brachial**	**-0.20**	**<0.001**	**-0.14**	**0.002**	**-0.20**	**<0.001**	0.02	0.70
	Standard Central	**-0.22**	**<0.001**	**-0.12**	**0.01**	**-0.19**	**<0.001**	0.04	0.36
	MAP-Derived Central	**-0.20**	**<0.001**	**-0.14**	**0.002**	**-0.19**	**<0.001**	0.01	0.87

Multivariable model adjusted for body mass index, T2DM, family history, angiotensin-converting enzyme/angiotensin receptor blocker, beta blocker, calcium channel blocker and diuretics.

The above table shows than DBP is more closely associated with LA and LV function than SBP. Standard CBP and brachial SBP was more closely associated with LV function than MAP-derived CBP calibration. Steiger's Z test (comparing correlation co-efficient of MAP central SBP and Standard central SBP): (LA Reservoir - Z score = 0.96, p=0.36, GLS – Z score = -1.1, p=0.27)

7.5.4 Discrimination of abnormal LA and LV function.

Figures 7.2 and 7.3 demonstrate scatterplots among brachial BP, MAP-derived or standard central SBP with abnormal GLS and LARS being color-coded (cut-offs reported in methods section). These plots were divided into 4 subsections based on cutoffs for SBP (130 mmHg for central SBP and 140mmHg for brachial SBP). Based on these cut-off values for central BPs, MAP-derived central SBP identified an additional 28 (32%) patients with abnormal GLS (total n=87 for abnormal GLS) who were classified as normotensive based on standard central SBP criteria (Figure 7.2A). For LA strain, MAP-derived central SBP identified an additional 87 (41%) patients with abnormal LARS (total n=213) (Figure 7.2C), 133 (41%) patients with abnormal LA conduit strain (total n=321) (Figure 7.3A); and 57 (44%) patients with abnormal LA pump strain (total n=130) who were classified as normotensive based on standard central SBP (Figure 7.3C).

Compared with brachial SBP, MAP-derived central SBP identified an additional 27 (31%) patients with abnormal GLS (Figure 7.2B), 68 (32%) patients with abnormal LARS (Figure 7.2D), 108 (34%) patients with abnormal LA conduit strain (Figure 7.3B), and 49 (38%) patients with abnormal LA pump strain who were classified as normotensive based on brachial SBP criteria (Figure 7.3D). On the contrary, brachial SBP identified an additional 2 patients with abnormal GLS and 1 patient with abnormal LA reservoir/conduit/pump strain who were classified as normotensive based on MAP-derived central SBP. Collectively, net increments of patients with abnormal GLS, LA reservoir, conduit, and pump strain were 25 (29%), 67 (31%), 107(33%), and 48(37%), respectively.

7.5.5 Reproducibility.

Reproducibility was assessed by blinded strain measurements in a random sample of 20 patients. All measurements were done by the same two investigators (SR and TN) and the mean of the absolute value of differences between measurements was calculated. For GLS the mean±SD difference was 0.7±0.7%. For LA strain the mean difference was 8.0±7.0% for reservoir strain, 5.4±4.1% for conduit strain and 5.6±4.6% for pump strain. Intra-observer variability was assessed by one investigator (SR) who repeated LA strain measurements in the same 20 patients at a different timepoint. The mean difference

for LA strain was 3.8±2.9% for reservoir strain, 2.7±1.4% for conduit strain and 2.7±1.4% for pump strain.

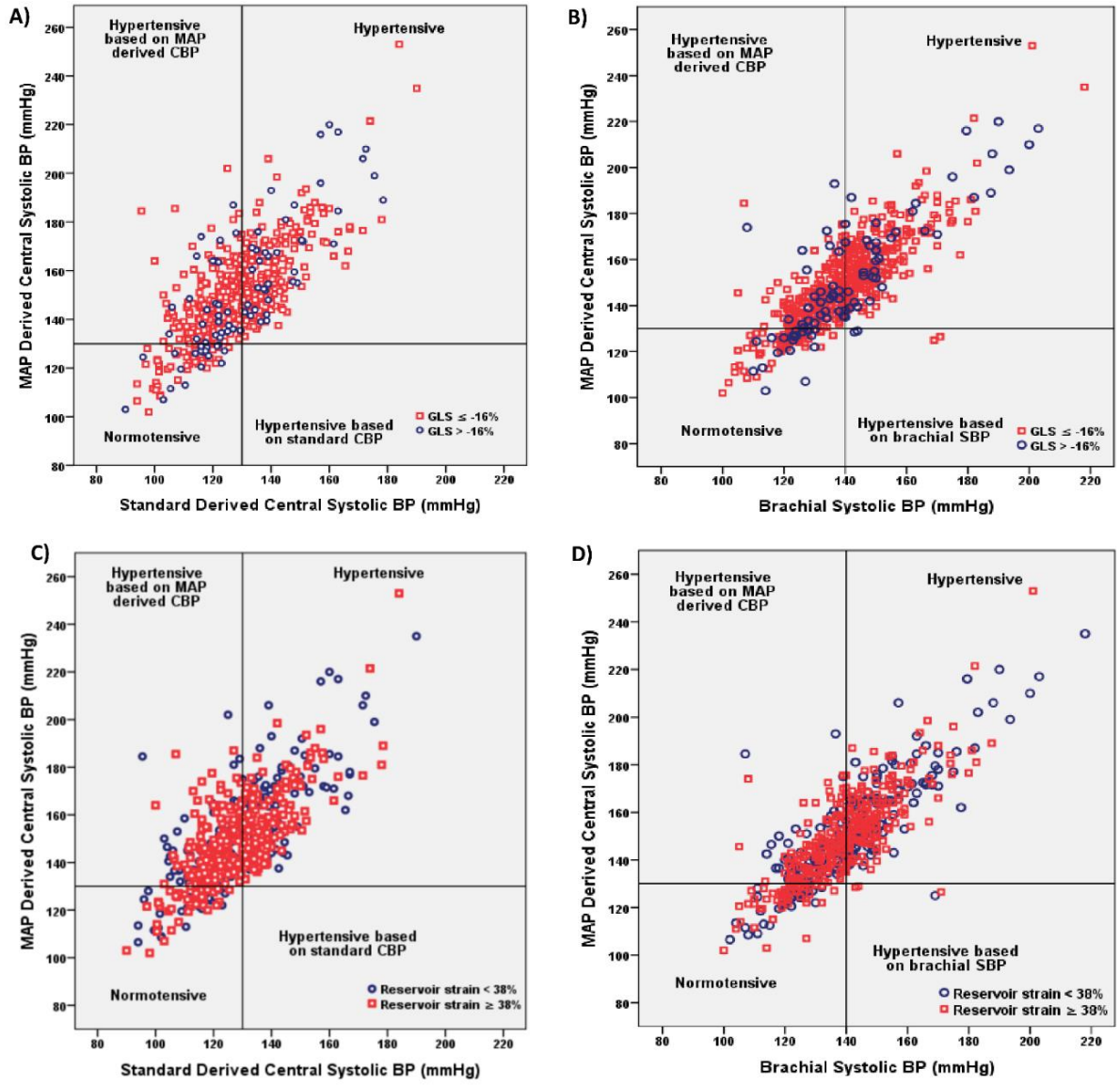

Figure 7.2 - Scatterplots comparing MAP-derived central SBP with standard central SBP and brachial SBP based on presence of reduced GLS and LARS (cut-off LA reservoir 38%, GLS -16%).

Overall MAP-derived central SBP was more sensitive than brachial and standard central SBP in identifying patients with reduced GLS and LARS.

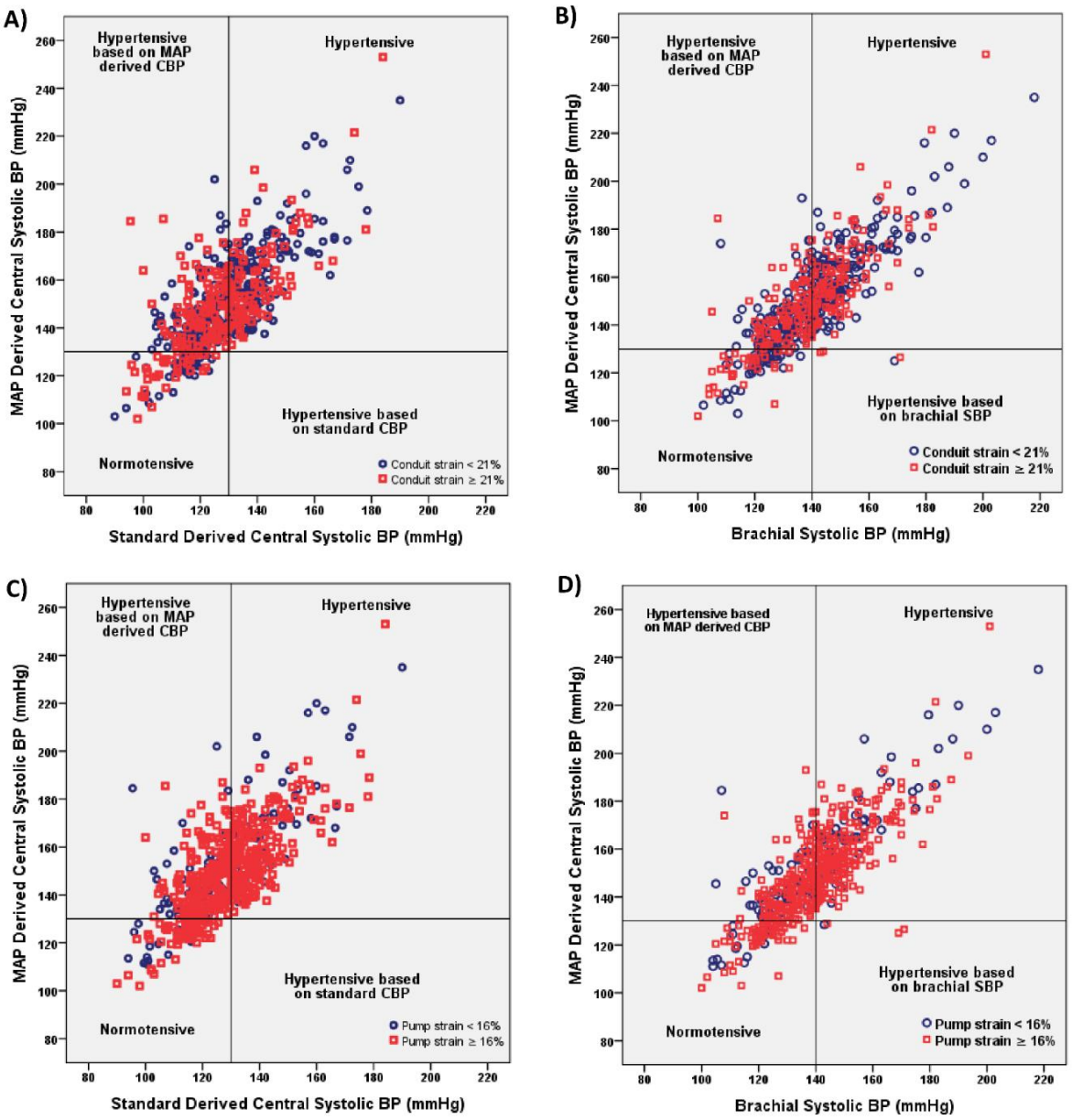

Figure 7.3 - Scatterplots comparing MAP-derived central SBP with standard central SBP and brachial SBP based on presence of reduced LA conduit and pump strain (cut-off LA conduit 21%, LA pump 16%).

Overall MAP-derived central SBP was more sensitive than brachial and standard central SBP in identifying patients with reduced LA conduit and pump strain.

7.6 Discussion

This study demonstrated that MAP-derived central SBP identified more patients with abnormal LA and LV strain (i.e. those with subclinical LV/LA dysfunction) compared with standard central SBP. Strong correlations among DBP (both brachial and central) measurements were observed whilst only moderate correlations in SBP measurements were observed. MAP-derived central SBP was higher than standard central SBP. CBP calibrated using MAP and DBP was more closely associated with LA reservoir strain compared with standard CBP, which is based on SBP and DBP. Compared with SBP, DBP was more strongly associated with LA reservoir/conduit strain and GLS.

7.6.1 Clinical Relevance of CBP.

Clinical assessment of BP is an essential component of patient assessment. Use of peripheral (brachial) BP is convenient, easily reproducible and non-invasive. Clinical practice guidelines and cardiovascular risk assessment currently depend on brachial BP recordings (216). However brachial BP only provides an estimate of central (aortic) pressure (223). Previously CBP was only able to be measured invasively, having a limited clinical role. Newer methods of measuring CBP non-invasively using waveform analysis have several advantages. There has been evidence to suggest that CBP maybe more closely representative of invasive aortic pressure than brachial BP (223, 224, 228), and may have a useful role in assessment of cardiovascular outcomes (219-222), having a prognostic role (222) and potentially associated with improved hypertension management (229).

7.6.2 Association of BP with LA/LV strain.

Strain analysis using speckle tracking provides quantitative information of LA and LV function. BP has a strong impact on LA and LV function. Elevated BP leads to LV hypertrophy, reduced compliance and increased stiffness. The increase in LA pressure contributes to LA dilatation and may lead to fibrosis (226, 230). There is interdependence on the three components of LA strain and LV function has a direct influence on LA reservoir and conduit function (231). LA pump function in much less dependent on

LV function (231).This is important in the pathogenesis in conditions such as HF with preserved ejection fraction as well as AF.

We noted in our study that overall DBP was more strongly associated with GLS and LA strain compared with SBP. This is an interesting finding as some studies have not demonstrated a strong association between DBP and cardiovascular outcomes compared with SBP (216, 232). SBP is also more commonly used in clinical practice to guide diagnosis. This finding may have important clinical implications and highlights the potential importance in monitoring DBP in patients with hypertension and the use of DBP in identifying those with subclinical LA/LV dysfunction. There was a strong correlation noted between all three methods of DBP, with little difference in measured values. Thus, there may not be additional utility in measurement of central DBP compared with brachial DBP.

In our study we noted that mean MAP-derived central SBP was higher compared with brachial SBP and standard central SBP. There was also a weaker correlation between MAP-derived central SBP with brachial SBP compared with standard central SBP. MAP-derived central SBP identified more patients with abnormal LV and LA strain compared with standard central SBP/brachial SBP. These observations have important clinical implications. Firstly, it highlights the differences between peripheral and CBP measurements and the different calibration methods. Therefore, it cannot be assumed that all non-invasive assessments of BP are the same. MAP-derived CBP may provide a more sensitive marker in the diagnosis of hypertension, however, more importantly may help identify those with end organ damage. Those with subclinical LV and LA dysfunction may be at risk of developing HF or AF. Therefore, MAP-derived CSBP can be utilized as a gate keeper to rule-out low risk patients and identify those who would have benefit from further advanced echocardiographic assessment. This finding is also consistent with our previous findings showing that MAP-derived central SBP had increased discriminatory power compared with other SBP markers in detecting those with LVH and LA enlargement in patients with stage A HF (225).

7.6.3 Use of CBP in hypertension management.

CBP may be a more appropriate BP marker to use in the diagnosis of hypertension. MAP-derived central SBP was noted in our study to be higher than brachial SBP, which has been observed in other studies.

(225, 233). This suggests an underestimate of central SBP using brachial SBP calibration. Given recent guidelines have advocated for earlier recognition of patients with hypertension and more aggressive treatment of BP, the use of a more sensitive marker will aid diagnosis and monitoring With improved accuracy, it will reduce overdiagnosis, limiting treatment to those at truly high risk. Anti-hypertensive drugs may have different effects on CBP compared with peripheral BP hence the use of CBP may result in improved drug titration and may represent a more accurate reflection on treatment response (223, 234-236).

7.6.4 Comparison of MAP-derived and standard CBP calibration methods.

There are multiple different calibration methods used to calculate CBP non-invasively (223). Previously there were no standardized guidelines and different algorithms and calibrations were utilized leading to discrepancy in the accuracy of CBP measurements. A recent taskforce has been established to help create more uniform standards (223). The use of different calibration standards has potentially a large impact on clinical outcomes. We noted a large discrepancy in SBP recordings using the two most common CBP calibration methods and brachial BP. DBPs were much more strongly correlated with each other. Future research is required in determining the most appropriate calibration method which should be used in measuring CBP. Currently brachial BP offers a simple, effective and reproducible assessment of BP in clinical practice. However, with further improvements in determining CBP accurately using non-invasive, cost effective methods, may translate into a more feasible assessment tool for clinical practice.

7.6.5 Limitations.

This was a cross sectional study, so causality is unable to be established. CBP was not assessed invasively and we used a single CBP device for all measurements. Although this device has been validated (233), it will be important to replicate these results across other device vendors to ensure no variability exists. LA and LV strain were both measured using speckle tracking. This was performed offline using an LV algorithm. There are currently differences in the algorithm used amongst software vendors as well as differences in nomenclature and ECG gating. Despite recent attempts at creating

normal reference values for LA strain (89) and standard consensus guidelines(101), further studies are warranted to assess the generatability of our results.

7.7 Conclusion.

CBP calibrated using MAP and DBP may be more closely associated with LA and LV function than standard brachial calibration methods. MAP-derived CBPs can be used as a sensitive tool to detect functional target organ damages from hypertension.

7.8 Postscript

The results of this chapter suggest that CBP calibrated using MAP and DBP may more accurately identify patients with an underlying "atriopathy" where future AF risk may be high. This may have an important role in AF risk stratification as it may identify more individuals with hypertension, in which AF risk is higher, therefore AF screening may be of benefit. However, this analysis was limited in that it was cross sectional. Confirmation of these results in a prospective cohort study is required to translate this association to clinical outcomes such as AF and HF.

Hypertension is strongly associated with AF and HF. It also leads to negative LA remodelling contributing to increase LA pressure and fibrosis. Accurate methods in measuring hypertension are important for two reasons. Firstly, they can help identify patients at earlier disease stages who may benefit from AF screening. Secondly a more sensitive BP marker can also help exclude some patients at low risk of developing AF from screening, thereby improving patient selection. In this chapter we have identified that CBP may have an important role in hypertension diagnosis and management. Given CBP can now be assessed non-invasively, it is more practical and feasible to be incorporated into clinical practice. The results of this chapter are important for AF screening as it outlines a more sensitive BP maker which can be used to assist in patient selection.

In the following chapters we investigate the role of imaging parameters in the prediction of AF. The aims will be to see which echocardiographic parameters can be combined with clinical and socioeconomic parameters to create an AF risk stratification algorithm.

Chapter 8

Determination of Appropriate Patients for AF screening

"Echocardiographic Risk Assessment to Guide Screening for Atrial Fibrillation."

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8 Determination of appropriate patients for AF screening

8.1 Preface

Echocardiography is an important imaging modality in AF risk assessment. It is non-invasive, reproducible and relatively inexpensive and provides qualitative and quantitative information about LV and LA structure and function. In current clinical practice, patients are typically referred for a TTE following a diagnosis of AF to look for causes such as HF, mitral valve disease. LA size can also be an important risk predictor and can be used to help predict the success of therapies such as catheter ablation.

Echocardiography can also be very useful to guide AF screening. Routine TTE in patients for the purposes of AF risk stratification is not cost-effective and is not an indication in current appropriate use criteria (82). However, many patients have TTE performed for a variety of indications arranged by local general practitioners, specialists and during inpatient admissions. Although commentary about AF risk is routinely not included on most echocardiography reports, identification of additional AF risk based on imaging parameters could be clinically very useful as it can alert treating physicians prompting AF screening or close surveillance.

In this chapter we investigate the use of echocardiography including strain imaging for AF risk stratification in a community cohort of individuals ≥ 65 yrs with additional risk factors for AF. The results of this chapter can be incorporated into an AF screening algorithm. The following chapter was published in the Journal of the American Society of Echocardiography.

8.2 Abstract

Background: Although atrial fibrillation (AF) is a significant population health burden, and an avoidable cause of stroke, AF screening remains controversial. We investigated whether coincidental echocardiography could provide information about patients at risk of AF.

Methods: Asymptomatic participants of ≥65 years with >1 AF risk factor (n=445) undergoing echocardiography for risk evaluation were followed over a median of 15 months for incident AF. Left atrial volume (LAVi), left ventricular global longitudinal strain (LV-GLS) (absolute value), left atrial (LA) strain and LV mass were measured. During the follow-up period, AF was diagnosed clinically by primary care physicians or by using a single lead portable ECG monitoring device (5x60 second recordings performed by participants over 1 week).

Results: AF was diagnosed in 45 patients (10%; mean age 70.5±4.2years, 55% female). AF detection was higher in those with LV hypertrophy, GLS < 16%, LAVi>34ml/m^2 and LARS <34%. GLS, LAVi and LARS were independently associated with AF ($p<0.05$). Those with AF had reduced GLS, higher LAVi and higher LV mass ($p<0.05$), but LA strain was similar in both groups ($p>0.05$). GLS and LAVi were the strongest predictors and cut-points of 14.3% for GLS and 39 ml/m^2 were associated with increased risk of developing AF. Those with all 4 risk parameters (LV hypertrophy, GLS <16%, LARS<34% and LAVi >34ml/m^2 had a 60% AF detection rate, compared with 7% without these features ($p=0.004$).

Conclusion: Echocardiography is widely used in patients at risk of AF, and simple LV and LA measurements may be used to enrich the process of AF screening.

8.3 Introduction

The magnitude of atrial fibrillation (AF) as a population health problem is increasing, driven by the aging population and the rise of AF risk factors including obesity, physical inactivity and diabetes mellitus (18, 237). The consequences of AF include debilitating symptoms and reduced quality of life. Complications such as stroke, heart failure (HF) and cognitive impairment are associated with increased all-cause mortality (110, 238), and place a substantial cost burden on the health care system (12). The early diagnosis of AF allows for individualized lifestyle intervention, which has been shown to reduce AF burden (23). The initiation of anticoagulation may be associated with reduced complications and hospitalizations.

Several screening technologies for AF offer an opportunity for early diagnosis, but they need to be accurate, reproducible and cost-effective. Standard ECG monitoring has limited value for detection of new AF (16, 239), and longer term monitoring is limited by poor adherence. Invasive options such as loop recorders are expensive and unsuitable for screening. Single lead portable ECG devices are unobtrusive (and consequently acceptable for patients) and sensitive for identifying AF (1, 164, 165). The development of automated algorithms to detect AF with these devices may allow for mass screening. In two small studies they have demonstrated superior AF detection compared with 24 hour Holter monitoring (161, 162) and a systematic review demonstrated similar AF detection rates to 24 hour Holter monitoring (240). The use of these devices in screening studies has provided AF detection rates of 1-5% (8, 69-71, 241), and has been demonstrated to be cost effective (8, 78).

Although opportunistic screening for AF is recommended on current European guidelines using both pulse palpation and assessment of a rhythm strip (57), routine AF screening is not recommended in the United Kingdom (242) or the United States (58) . This is because while AF screening satisfies most of the criteria for mass screening (2, 243), concerns persist about both false positive and false negative results (244). The appropriate selection of patients could reduce the number of false positive tests by avoiding low risk patients. Clinical risk scores for AF aid in this process, but imaging parameters provide important clues in risk assessment (22). As echocardiography is widely performed for other

reasons in patients at risk of AF (19), we sought whether this information could provide an opportunity to assess AF risk and thereby guide AF screening.

8.4 Methods.

8.4.1 Study population.

Participants in this prospective observational cohort study were healthy, asymptomatic subjects recruited into a community HF screening study in the Victorian and Tasmanian communities. Recruitment was by several methods including from community centers, local medical clinics and through radio and newspaper advertising. Asymptomatic participants ≥65 years were recruited if they had ≥1 or more risk factors for AF, including hypertension (systolic BP >140 mmHg or pre-existing use of anti-hypertensive medications), T2DM, based on self-report of diagnosis or the current use of diabetic medications), and obesity (defined as a body mass index (BMI) ≥30). Exclusion criteria included: (1) inability to provide written consent to participate in the study, (2) history of moderate or greater valvular disease, (3) known history of HF based on the 2013 AHA/ACC guidelines(245), (4) reduced LV systolic function on baseline echocardiogram (LVEF ≤40%), (5) contraindications to beta blockers and angiotensin converting enzyme inhibitors (ACE-I), (6) expected life expectancy of less than one year or (7) inability to acquire interpretable images for performance of strain analysis from the baseline echocardiogram. All patients with documented AF on a baseline 12 lead ECG or a history of AF were excluded from the study. Patients were recruited from both urban and rural environments. All patients were provided written informed consent and approval was obtained from the institution's Human Research Ethics Committee (University of Tasmania HREC project number H0013333 and Bellberry HREC project number 2016-10-727-A-7).

8.4.2 Clinical Assessment.

Participants undertook a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, past medical history, medication history, baseline examination data (height, weight, BMI and blood pressure (BP) were recorded for all participants. Baseline 12 lead ECG and echocardiography were conducted in all participants. Clinical AF risk assessment was performed using a validated AF risk score (the CHARGE-AF score) that

includes 12 clinical parameters (age, race, height, weight, systolic/diastolic blood pressure, current smoking, use of anti-hypertensives, history of diabetes mellitus/myocardial infarction, history of HF and ECG data (voltage criteria for left ventricular hypertrophy (LVH) and PR interval)) to assess 5 year risk of AF (22).

8.4.3 Assessment of risk based on imaging.

All echocardiograms were performed by qualified sonographers using the same equipment (Siemens ACUSON SC2000, Siemens Healthcare, Mountain View, CA) and transducers (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz). Two-dimensional, M-mode and Doppler measures were obtained using standard techniques outlined by the American Society of Echocardiography. LV dimensions were calculated in both diastole and systole in parasternal long axis views. LV hypertrophy (LVH) was defined as LV mass index >115 g/m^2 in men and >95 g/m^2 in women. LA volume was indexed to body surface area (LAVi) and calculated by the Simpson biplane method. Abnormal LAVi was defined as ≥34 ml/m^2.

Global longitudinal strain (GLS) measurements were obtained from apical four-chamber, two-chamber and long-axis views. GLS was analyzed using velocity vector imaging (Syngo VVI, Siemens Medical Solutions, Mountain View, CA). All measurements were performed online by averaging strain measurements from the three views. Manual tracing of the endocardial LV border was performed in end-systole and this was tracked during the cardiac cycle. Abnormal GLS was defined as <16% (absolute values were used throughout the study). Patients with poor image quality, where GLS could not be performed, were excluded.

LA reservoir, conduit and pump strain were assessed offline using speckle tracking imaging by an external third-party software program (ImageArena, Tomtec, Munich, Germany). Apical four and two chamber images were selected with a frame rate of 60-80 frames/sec. The endocardial border of the LA was manually traced, and strain analysis was performed using the LV strain algorithm, using the average of the four- and two-chamber values. The reference point for image analysis was taken at the onset of the QRS complex (R-R gating). All strain measurements were performed by two investigators. If more than 1 segment of the 6 LA segments could not be tracked, the sample was excluded. We used a cut-point of 34% for LARS to determine high risk of AF.

Inter-observer reliability was assessed by a second operator who performed strain measurement in a random sample of 20 participants and was blinded to all clinical and imaging data. Intra-observer reliability was performed by the primary author (SR) who performed repeated strain measurements in a random sample of 20 patients at a different time point. The mean percentage difference was calculated.

8.4.4 Outcomes.

Participants were followed for a median of 15 months for incident AF, which was the primary outcome measure. AF was diagnosed using multiple detection methods. Patients with a clinical diagnosis of AF during the follow-up period by primary care physicians (confirmed on 12 lead ECG or Holter monitoring) was documented. Screening for subclinical AF was performed using a single lead ECG device (Remon RM-100, Semacare, China). Screening was performed within the first month of recruitment into the study. The single lead device was used to record 60 second single-lead ECG tracings using three points of finger contact with electrodes, five times per day for one week (i.e. 35 recordings). ECG recordings were then exported as PDF files for interpretation, and all were assessed by a physician. The presence of AF (an irregular rhythm of ≥30 sec with a variable R-R interval and absent P waves) was confirmed by two independent physicians who were blinded to the patient's clinical details. The patient was advised of the recognition of subclinical AF, and further management and investigation was provided by their usual medical practitioner.

8.4.5 Statistical analysis.

All categorical variables are presented as frequencies/percentages and continuous variables presented as means/standard deviation (if normally distributed) or medians/inter-quartile range (if non-parametric). Patients with incident AF were compared to those in sinus rhythm. Groups were compared using the chi square test for categorical data and the independent two sample t-test for continuous data. Patients were then grouped based on four imaging parameters of AF risk (LAVi, presence of LVH, GLS and LARS) based on the cut-offs defined above. Nelson-Aalen cumulative hazard estimate plots were constructed for groups based on the baseline risk parameters, and the log-rank test used to assess the differences between curves. The AF rate was compared between those at the highest risk to those with the lowest risk using the chi-square test. Cox proportional hazards regression analysis was used to

calculate the hazard ratios (HR) and 95% confidence intervals for the association between each risk parameter and incident AF. The follow-up time was the time from the initial baseline clinical assessment to the completion of portable device screening or the date of diagnosis of AF (whichever came first). Classification and regression tree (CART) analysis was performed to identify appropriate discriminatory cut-points to identify those at risk of developing AF. Analyses were considered to be statistically significant if two-tailed p values were <0.05. Statistical analysis was performed using SPSS v.22 (SPSS, Chicago, IL), SPSS Modeler v18.1 (SPSS, Chicago, IL) and Stata v.13 (StataCorp, College Station, Texas).

8.5 Results

8.5.1 Patient characteristics.

The baseline characteristics of the 445 subjects included in the study (mean age 70.5±4.2 years, 45% male) are summarized in Table 8-1. Cardiovascular risk factors (including T2DM, obesity, hypercholesterolemia and hypertension) were highly prevalent. There was a large proportion of participants with low education levels (43% had not completed high school and approximately 3 in 4 had not completed tertiary level of education). LA strain was able to be measured in 417/445 patients (94%).

Table 8-1 - Baseline Characteristics of the overall cohort.

Demographics	**n = 445**
Age - years (SD)	70.5 (4.2)
Male n (%)	198 (45)
Systolic BP mmHg (SD)	141 (15.7)
Diastolic BP mmHg (SD)	83 (10.1)
Heart Rate /min (SD)	69 (10.7)
BMI (kg/m^2) (SD)	30.3 (5.3)
Current Smoking n (%)	12 (3)
Diabetes Mellitus n (%)	190 (43)
Obesity n (%)	226 (51)
Hypercholesterolemia n (%)	244/434 (55)
Hypertension n (%)	353 (79)
Previous history of IHD n (%)	16 (4)
Previous history of stroke/TIA n (%)	26 (6)
Median Six-minute walk test m (IQR)	474 (98)
Median CHARGE-AF % (IQR)	5.1 (5.1)
Median CHA_2DS_2-VASC % (IQR)	3.0 (2.0)
Echocardiographic Parameters	
Ejection Fraction % (SD)	62.6 (6.3)
Global Longitudinal Strain % (SD)	18.8 (2.5)
E/e' (Average of lateral and septal) (SD)	8.8 (2.4)
Left atrial volume - indexed ml/m^2 (SD)	32.2 (9.1)
Left Ventricular mass – indexed g/m^2 (SD)	81.8 (22.4)

8.5.2 AF during follow up.

An overview of patient recruitment and AF detection is summarized in figure 8.1. Over a median follow-up of 15 months (range 5-27 months), 45 patients (10%) were diagnosed with AF; 28 (6%) with portable ECG monitoring and 17 (4%) by local physicians during the follow-up period. Among the 417 patients with measurable LA strain, there were 42 AF outcomes. Table 8-2 compares the characteristics of those with AF and sinus rhythm; new onset AF was more likely in men, and in those with a higher CHARGE-AF score, reduced GLS and increased LAVi and LV mass ($p<0.05$). There were no significant differences in LA strain between both groups ($p>0.05$).

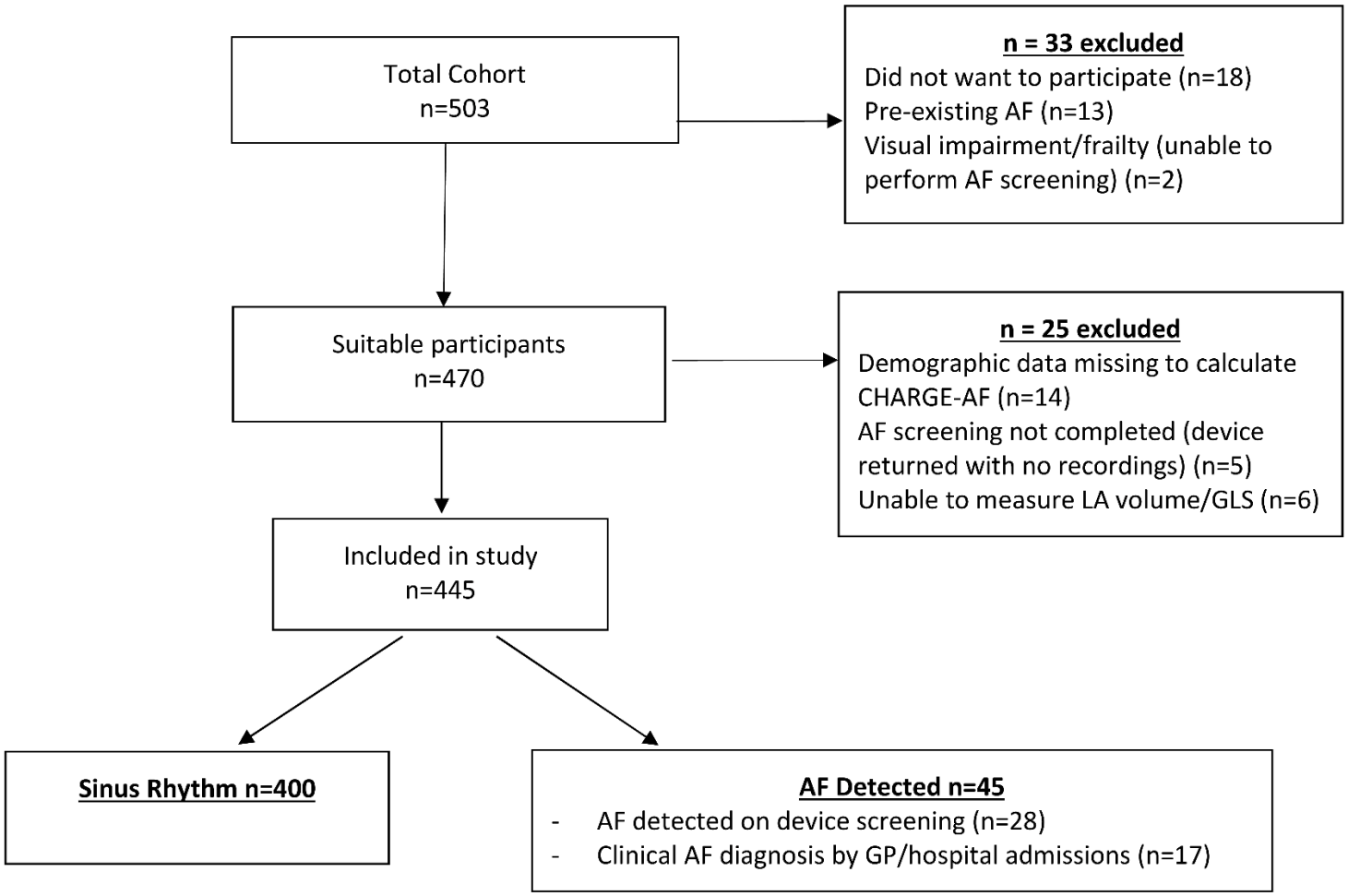

Figure 8.1 - Flowchart showing patient recruitment in the study

From the initial cohort of 503 patients, 445 patients were recruited in the study. 45 patients (10%) had AF diagnosed during the follow up period.

Table 8-2 - Comparison of baseline characteristics between patients with AF and sinus rhythm.

Demographics	**AF n = 45**	**Sinus Rhythm n = 400**	**P Value**
Age - years (SD)	71.7 (5.3)	70.3 (4.1)	0.11
Male n (%)	27 (60)	171 (43)	0.03
Systolic BP mmHg (SD)	134 (15.6)	142 (15.5)	0.002
Diastolic BP mmHg (SD)	82 (11.0)	83 (10.0)	0.38
BMI (kg/m^2) (SD)	29.6 (5.2)	30.3 (5.3)	0.34
Current Smoking n (%)	2 (4)	10 (3)	0.45
Diabetes Mellitus n (%)	21 (47)	169 (42)	0.57
Obesity n (%)	18 (40)	208 (52)	0.12
Hypercholesterolemia n (%)	24/43 (56)	220/391 (56)	0.96
Hypertension n (%)	36 (80)	317 (79)	0.91
Previous history of IHD n (%)	5 (11)	11 (3)	0.004
Previous history of TIA/stroke n(%)	2 (4)	24 (6)	0.63
Median CHARGE-AF % (IQR)	6.6 (8.2)	4.8 (4.7)	0.001
Median CHA_2DS_2-VASC (IQR)	3.0 (2.0)	3.0 (2.0)	0.52
Functional Capacity			
Median Six Minute Walk Test m (IQR)	488 (110.8)	473 (98)	0.22
Echocardiographic Parameters			
Ejection Fraction % (SD)	60.9 (7.3)	62.7 (6.1)	0.06
Global Longitudinal Strain % (SD)	18.0 (3.4)	18.8 (2.4)	0.04
E/e' (Average of lateral and septal) (SD)	8.5 (2.5)	8.8 (2.4)	0.52
Left atrial volume - indexed ml/m^2 (SD)	34.8 (10.4)	31.9 (8.9)	0.04
Left Ventricular mass – indexed g/m^2 (SD)	93.3 (25.2)	80.5 (21.7)	0.002
Left Atrial Strain	**AF n=42**	**Sinus rhythm n=375**	
LARS % (SD)	36.5 (8.0)	37.7 (6.9)	0.33
Left atrial conduit strain % (SD)	17.6 (5.3)	18.3 (5.6)	0.49
Left atrial pump strain % (SD)	18.9 (6.9)	19.4 (4.9)	0.68

BMI – Body Mass Index BP – Blood Pressure IHD – Ischaemic Heart Disease TIA – Transient Ischaemic Attack

8.5.3 AF detection based on risk parameters.

Participants were grouped based on the four risk parameters highlighted earlier (LAVi, presence of LVH, GLS and LARS). Grouping participants based on these risk parameters resulted in a range of AF detection rates (range 0-60%) with the presence of more positive risk parameters associated with higher AF detection rates (Table 8-3 and figure 8.2).

Table 8-4 and figures 8.3 and 8.4 summarize the association between the risk parameters and AF. When patients were grouped based on abnormal LAVi (cut-off 34 ml/m^2), GLS (cut-off 16%) and LARS (cut-off 34%), there was higher AF detection noted in the abnormal groups (figure 8.3, all $p<0.05$). Participants were then grouped based on the total number of baseline risk parameters (LAVi, LARS, LVH and GLS) (figure 8.4). AF detection was higher with the presence of more baseline risk parameters ($p=0.004$). Participants with all four risk parameters had a higher AF detection rate compared to those without any risk parameters (60% [3/5] vs. 7% [11/160], $p=0.004$).

On univariable analysis, abnormal LAVi, LARS and GLS were all associated with AF ($p<0.05$), but LA pump strain was not associated with AF ($p=0.86$). LARS along with LA pump strain were included in the multivariable model (LA conduit strain was not included given the possibility of collinearity when included with GLS). In a multivariable model abnormal LAVi, GLS and LARS were independently associated with AF (abnormal LAVi HR 2.01 [1.06–3.81], $p=0.03$, abnormal GLS HR 2.46 [1.21–5.00], $p=0.01$ and abnormal LARS HR 2.14 [1.04–4.38], $p=0.04$). LA pump strain and presence of LVH were not independently associated with AF ($p>0.05$).

Table 8-3 - Summary of AF detection based on risk groups.

Patients were divided into high and low risk for LVH, LAVi, GLS and LARS. Cut-offs used were (LVH - 115 g/m^2 for men and 95 g/m^2 for women, LAVi of 34 ml/m^2, GLS of 16% and LARS of 34%).

LVH	LAVi	GLS	LARS	n (total n=417)	AF Detected n(%) (total n=42)
No	Normal (<34 ml/m^2)	Normal (≥16%)	Normal (≥34%)	160	11 (7)
			Low (<34%)	44	1 (2)
		Low (<16%)	Normal (≥34%)	22	4 (18)
			Low (<34%)	11	2 (18)
	Increased (≥34 ml/m^2)	Normal (≥16%)	Normal (≥34%)	65	6 (9)
			Low (<34%)	38	4 (11)
		Low (<16%)	Normal (≥34%)	5	0 (0)
			Low (<34%)	8	1 (13)
Yes	Normal (<34 ml/m^2)	Normal (≥16%)	Normal (≥34%)	18	3 (17)
			Low (<34%)	5	0 (0)
		Low (<16%)	Normal (≥34%)	2	0 (0)
			Low (<34%)	1	0 (0)
	Increased (≥34 ml/m^2)	Normal (≥16%)	Normal (≥34)	19	2 (11)
			Low (<34%)	11	4 (36)
		Low (<16%)	Normal (≥34%)	3	1 (33)
			Low (<34%)	5	3 (60)

Table 8-4 - Cox regression analysis showing association between risk parameters and AF.

Multivariable model contained abnormal LAVi (cut-off 34 ml/m^2), abnormal GLS (cut-off 16%), abnormal LARS (cut-off 34%), presence of LVH and LA pump strain (n=417, AF outcomes n=42).

Independent Variables	Unadjusted Hazard Ratio (95% C.I)	P value	Adjusted Hazard Ratio (95% C.I)	P value
Abnormal GLS	2.79 (1.40 – 5.56)	0.003	2.46 (1.21 – 5.00)	0.01
Abnormal LAVi	2.17 (1.18 – 3.98)	0.01	2.01 (1.06 – 3.81)	0.03
Abnormal LARS	2.13 (1.13 – 4.03)	0.02	2.14 (1.04 – 4.38)	0.04
Presence of LVH	1.59 (0.82 – 3.09)	0.17	1.22 (0.60 – 2.49)	0.58
LA Pump strain (%)	0.99 (0.93 – 1.06)	0.86	1.04 (0.97 – 1.11)	0.25

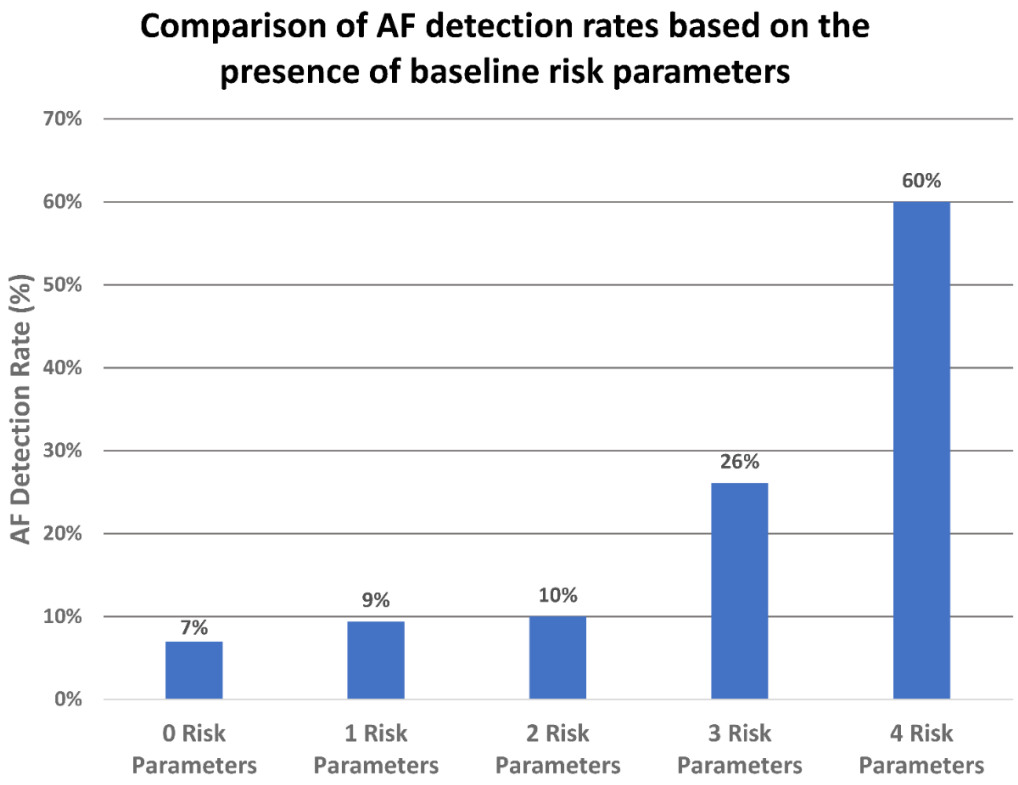

Figure 8.2 - Comparison of AF detection based on the presence of baseline risk parameters - risk parameters defined based on cut-off for LVH – LV indexed mass ≥ 115g/m2 for men and ≥95g/m2 for women, LAVi ≥ 34ml/m2, GLS < 16% and LARS <34%.

AF detection increased with the presence of more baseline imaging risk parameters.

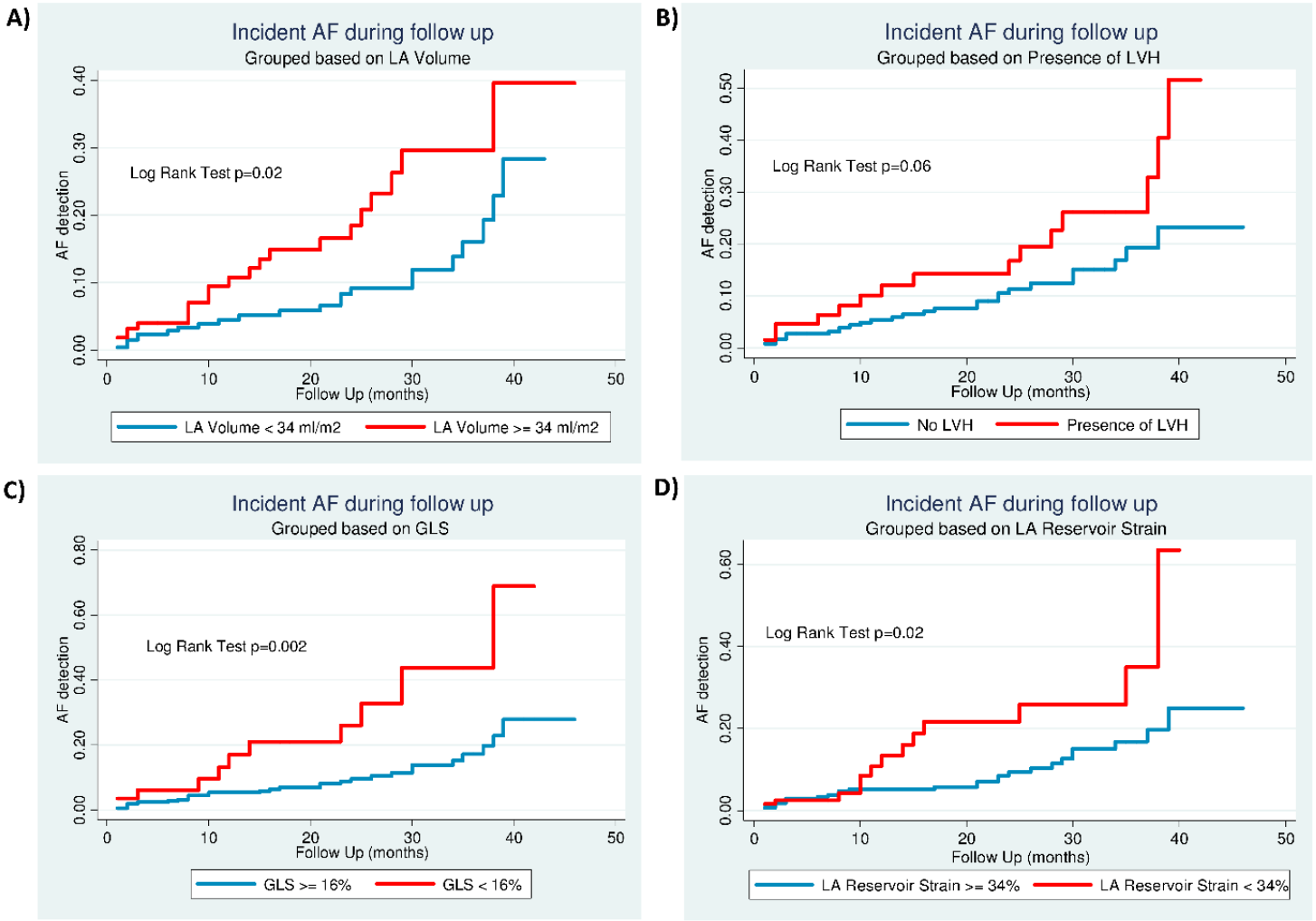

Figure 8.3 - Nelson-Aalen Curves showing AF detection based on baseline risk parameters - risk parameters defined based on cut-off for LAVi ≥ 34ml/m2, GLS < 16%, LVH – LV indexed mass ≥ 115g/m2 for men and ≥95g/m2 for women and LARS < 34%.

Patients with reduced GLS, LARS and increased LAVi had significantly higher AF detection ($p<0.05$)

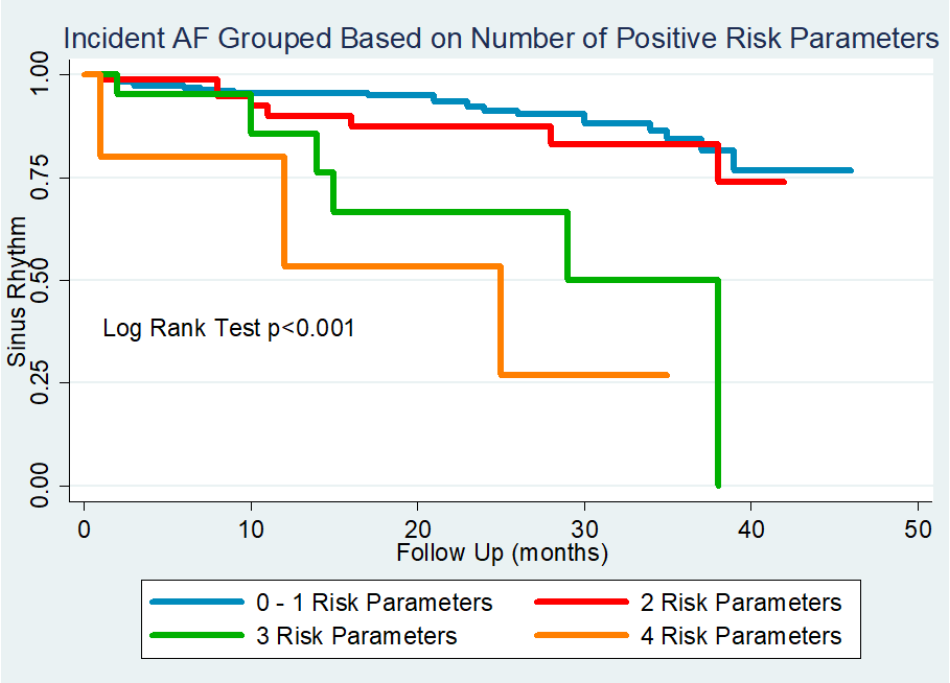

Figure 8.4 - Kaplan-Meier curve showing AF detection based on the number of positive baseline risk parameters - risk parameters defined based on cut-off for LAVi ≥ 34ml/m2, GLS < 16%, LVH – LV indexed mass ≥ 115g/m2 for men and ≥95g/m2 for women and LARS < 34%.

This Kaplan-Meier curve demonstrates that cumulative AF risk was higher in those with more baseline imaging risk parameters.

The CART analysis identified 3 discriminatory nodes as predictors of AF. A GLS cut-point of 14.3% was identified (p=0.02). In those with a GLS ≤14.3%, a second discriminatory node using LAVi (cut-point of 39 ml/m^2) was identified (p=0.01). The intermediate group with a LAVi ≤ 39ml/m^2 could then be discriminated using a third node - LARS with a cut-point of 33.9%, p=0.01). This correctly identified 91% of participants.

The results of the CART analysis can potentially be incorporated into an AF risk stratification algorithm. Participants with a GLS >14.3% can be categorized as "low risk" where AF screening has low detection rates and may not be required. In those with GLS ≤14.3, LAVi >39 ml/m^2 can be used to classify the "high-risk" group where AF screening may have high detection rates. In the intermediate group (GLS < 14.3% and LAVi ≤39ml/m^2), LARS can be used with a cut-point of 34% to reclassify patients as "moderate-high" (LARS <34%) vs "low-moderate" (LARS >34%) risk. Screening should be considered in the moderate-high risk group.

8.5.4 Reproducibility.

Inter-observer variability was assessed by blinded strain measurements in a random sample of 20 patients. All measurements were done by the same two investigators (SR and TN) and the mean of the absolute value of differences between measurements was calculated. For GLS the mean±SD difference between was 0.7±0.7%. For LA strain the mean difference was 8.0±7.0% for LARS, 5.4±4.1% for LA conduit strain and 5.6±4.6% for LA pump strain. Intra-observer variability was assessed by the primary investigator (SR) who repeated GLS measurements in a random sample of 20 patients at a different timepoint. The mean difference for GLS was 0.8±0.6%. The mean difference for LA strain was 3.8±2.9% for LARS, 2.7±1.4% for LA conduit strain and 2.7±1.4% for LA pump strain.

8.6 Discussion

Many at risk individuals have echocardiography performed for other reasons, therefore the incidental finding of these risk parameters can be used to alert referring physicians to future AF risk. The results of our study suggest that individuals with more imaging risk parameters have a higher likelihood of AF. In our study we found that reduced LARS, reduced GLS and increased LAVi were independently associated with AF. Targeted screening using portable single lead ECG devices can capture a significant proportion of patients with subclinical AF (70, 71).

8.6.1 Early diagnosis of AF.

AF is a leading cause of stroke and HF, placing a tremendous burden on the health care system with rising costs and hospitalizations (12, 109, 111). Patients with asymptomatic (or subclinical) AF have been shown to have increased all-cause mortality and increased stroke risk in a large cohort study (55). Early diagnosis has several potential benefits. Even in the early stages, AF is not a benign condition and is associated with long term morbidity and mortality (55). The early diagnosis of AF serves as an important warning to both the patient and the treating physician, and may prompt important discussions about risk factor modification, improve treatment adherence and allow for closer monitoring of “high risk” patients. Aggressive risk factor modification and weight loss has been shown to be equivalent to an anti-arrhythmic drug in patients with established AF (23, 52), although incident AF was not reduced

with an intensive weight loss in a large randomized trial. Early diagnosis might prompt improvement in physical activity and reduction in blood pressure, cholesterol and blood glucose levels – all of which have cardiovascular benefits (246). Anticoagulation may have a role in stroke and systemic embolism prevention in this cohort of patients, but this has not been assessed in a large randomized trial.

8.6.2 Improving the AF detection in screening programs.

For mass screening to be viable, we need to have an efficient screening process with a high AF detection rate. The main focus of screening has looked at three main factors; device technology, patient age and clinical risk factors. Age is the biggest risk factor for AF so many screening studies have used population based screening methods based on age cut-offs of 65 or 75 years (70, 71). Lowres et al. showed an increase in AF detection rates from approximately 1% in the 65-69 year old cohort to >3% in patients >85 years after combining four large AF screening cohorts (247). Clinical risk factors associated with AF and stroke risk can also increase the detection rate. Use of an age-based population screening strategy may improve sensitivity by screening a larger cohort but reduces efficiency as many will have normal investigations. The use of clinical risk scores such as CHARGE-AF can help identify those who benefit the most from screening (22). This is a simple bedside scoring system utilizing several risk parameters providing a 5 year AF risk assessment which has been validated in several large multi-ethnic cohorts (22). Combining an age-based cut-off with clinical risk factors results in increased AF rates and more importantly translates into implementation of pharmacological treatments as all participants will qualify for anticoagulation (i.e. CHA_2DS_2-VASC score $\geq$ 2). Single timepoint screening has a new AF detection rate of approximately 1% which can be increased with multiple-timepoint screening over a 1-2 week period (8, 71). We have previously investigated the role of other AF risk factors such as physical activity and socioeconomic deprivation (237, 248).

8.6.3 The use of echocardiography in risk assessment.

In this study, those with increased LAVi and reduced GLS and LARS were at higher risk of developing AF. We noted a higher AF detection rate in those with a LARS < 34%, despite mean LARS being similar in both the AF and sinus rhythm groups. This was a surprising finding as we expected a difference in both groups. It can potentially be explained by the small sample of patients with AF,

therefore there was inadequate power in our study to show a difference in both groups. There were a wide range of LARS values noted. There has not been accepted consensus on the "normal" range for LARS. A few patients were noted to have AF despite high LARS values which could have offset those with reduced LARS, thus making both means similar.

Although the traditional use of echocardiography in AF follows a confirmed clinical diagnosis of AF (to determine the etiology of AF, guide management and provide important prognostic information) (82), many individuals at risk of AF have an echocardiogram for other reasons, such as investigation of hypertension, cardiac murmur, or peri-operative risk. However, there is no systematic method in traditional echocardiogram reporting to alert referring physicians to AF risk. Targeting a group with echocardiographic risk features with portable ECG monitoring may be associated with high AF detection rates. Nonetheless, AF risk assessment is complex therefore the next step would be to create a multi parameter risk assessment strategy incorporating clinical, imaging and socioeconomic markers of risk.

8.6.4 Limitations.

The limitations of our study include the potential for population selection bias as patients were recruited with newspaper and radio advertising. Our cohort was relatively small, resulting in a small number of AF outcomes, with a very selective patient population; hence adaption of these findings to a large screening population would need to assume external validity. The small number of AF outcomes also limited the number of covariates in our multivariable model, so it is possible that other potential confounders were not accounted for. AF detection was based on the use of a single lead portable ECG device for a one-week period. It is possible that we missed subclinical AF in some patients and extended monitoring may increase the AF detection rate. Detailed cost analysis was not performed in our study. Cut-off values for GLS and LA strain used in this study were arbitrary. We did not collect data from local practitioners on anticoagulation prescription following a diagnosis of AF hence were unable to assess the impact of early diagnosis. We did not perform long term follow up to assess if those with subclinical AF had similar clinical outcomes to those with clinically diagnosed AF.

8.7 Conclusion

Elderly patients with risk factors have a high prevalence of subclinical AF. Baseline risk assessment using echocardiographic parameters of LV and LA function can be used to improve AF detection rates and could be relevant to the implementation of population screening programs.

8.8 Postscript

In this chapter we have demonstrated that previous echo results (done for other reasons) can be useful in AF risk stratification and both LV and LA strain are associated with AF independent of LA volume. Changes to LA strain may occur earlier than changes to LA size, therefore this may be more useful in earlier disease stages, in which screening is most useful. Commentary about AF risk is not routinely reported in most TTE reports but may be important to alert referring physicians as many may not be fully aware of the nuances of echocardiography. Strain imaging despite being useful in this setting still has limitations to overcome. Current software algorithms vary between vendors, strain measurement can be time consuming and requires offline analysis with expensive software packages which limits access to most echo labs. These shortcomings are being addressed and will facilitate widespread adoption of strain in clinical practice.

It was interesting that LA pump strain was not independently associated with AF compared with LARS. We demonstrated in chapter 6 that LA pump strain was independent of LV function whereas LARS was closely related to LV function. It is possible that in earlier disease stages, LA pump strain is less predictive, and LARS is more useful. However, in more advanced stages of "atriopathy" pump function may become more adversely effected, therefore being a stronger predictor of AF and thromboembolic risk.

AF like most diseases has different stages. In this chapter we assessed patients at earlier disease stages (i.e. patients with risk factors). Imaging signals (including strain) should also be investigated in different patient populations to assess if the association with AF changes depending on the disease stage. In the

next chapter we compare the association of LV and LA strain with AF in cohorts at different disease stages.

Chapter 9

Clinical use of LA and LV Strain in AF prediction.

"Impact of Disease Stage on Performance of Strain Markers for Prediction of Atrial Fibrillation."

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9 Clinical use of LA and LV strain in AF prediction

9.1 Preface

In the previous chapter we demonstrated that imaging parameters could be used for AF risk stratification. There was an association between both LARS and GLS with AF and this was independent of LA volume. There are different disease stages in AF and the ability of strain to predict AF has not been demonstrated in different stages. In the previous chapter, the cohort were healthy individuals from the community with risk factors. It is likely that these individuals are in an early phase of "atriopathy". AF is a common cause of stroke. Patients admitted with a stroke typically have investigations for underlying AF (mainly a TTE and Holter monitor). A previous study had demonstrated that LA strain was useful in predicting AF in patients following cryptogenic stroke (90). It is likely that these patients were at an advanced disease stage of "atriopathy" with higher risk of AF (along with a higher rate of thromboembolism).

In this chapter we compare the association between strain and AF in both cohorts to determine if 1) strain can be equally predictive in both cohorts and 2) if the strength of association changes as the disease stage is more advanced. The preliminary results of this chapter were presented at the European Society of Cardiology Congress in 2019 and have been submitted for publication at the Journal of the American Society of Echocardiography.

9.2 Abstract

Background: Assessing atrial fibrillation (AF) risk may be useful in primary prevention (PP; people with risk factors) and secondary prevention (SP; eg. embolic stroke of unknown source). We sought whether disease stage influenced the prediction of AF by echocardiography.

Methods: We compared a PP cohort (351 community-based participants ≥65 years with ≥1 risk factor for AF) and a SP cohort (453 patients after transient ischemic attack or stroke). LV global longitudinal strain (GLS) and left atrial reservoir strain (LARS) were measured from DICOM images. AF was diagnosed by 12 lead ECG, Holter or by single lead monitor over median follow-up of 22 months (PP) and 35 months (SP). The clinical and echocardiographic characteristics of those with AF were compared to those in sinus rhythm. Nested Cox-regression models assessed for independent and incremental predictive value of LARS and GLS in both cohorts.

Results: AF developed in 42 PP (12%) and 60 SP (13%), and was associated with age, higher CHARGE-AF score, increased LA volume and LV mass ($p<0.05$). Patients developing AF had reduced GLS (17±3.5% vs. 20±3%, $p<0.001$) and LARS (28±11% vs. 35±8%, $p<0.001$). However, the predictive value of both GLS (area under the ROC curve 0.83 vs 0.56, $p<0.001$) and LARS (0.83 vs 0.57, $p<0.001$) was greater in SP than PP. LARS was independently associated with AF in both cohorts ($p<0.05$), but GLS was only independently associated in the SP cohort.

Conclusion: AF risk assessment with LARS is suitable for different risk cohorts, but GLS is more useful in SP.

9.3 Introduction.

Atrial fibrillation (AF) has developed into a significant population health problem, being driven by an ageing population with reduced physical activity and increasing prevalence of risk factors such as obesity, T2DM and hypertension (109, 249). Rising AF rates will lead to increased hospitalizations, health care costs and complications such as stroke and HF which may be associated with significant morbidity and mortality as well as impact on quality of life (18, 110). There was been emerging advocacy for the role of mass AF screening lead by the AF-Screen Collaboration, with recent cohort studies demonstrating high rates of subclinical AF and cost analysis studies demonstrating cost effectiveness (2, 8, 71, 78, 240, 248).

Transthoracic echocardiography provides a reliable, non-invasive and inexpensive modality to assess left ventricular (LV) and left atrial (LV) function and size. Many patients who will develop AF in the future may have had echocardiograms performed in the outpatient setting, arranged by local general practitioners or specialists. The results of these investigations may aid in identifying those at risk of developing AF. LA volume is a strong predictor of AF (250). Myocardial deformation assessment by strain imaging allows for quantitative information of LV function and phasic LA function (5). Efforts to standardize LA strain measurement protocols will aid in improving feasibility and clinical applicability (101).

We currently do not have a systematic method in alerting referring clinicians about an individuals' future AF risk based on the results of echocardiograms. Combining imaging risk parameters with clinical risk factors may provide an enriched cohort for AF screening which may improve feasibility and cost-effectiveness. We have previously published a risk assessment algorithm combing clinical and imaging parameters which may help in improving the diagnostic yield of AF screening programs (251). However, it is not clear which imaging parameter is most predictive of AF. It is also unclear if the association of LA and LV strain with AF is the same in patients with different risk factor profiles. This is important to establish prior to widespread adoption of strain in AF risk assessment. In this study, we sought to investigate the performance of LA and LV strain markers in different patient risk cohorts in the prediction of AF.

9.4 Methods.

9.4.1 Study population.

In this observational cohort study, AF prediction was assessed using two unique patient cohorts to represent different disease stages (figure 9.1).

1. Primary prevention (PP) cohort - Participants in this cohort were healthy, asymptomatic subjects ≥65 years with one or more risk factor for AF including hypertension (systolic BP >140 mmHg or pre-existing use of anti-hypertensive medications), T2DM, based on self-report of diagnosis or the current use of diabetic medications), and obesity (defined as a body mass index (BMI) ≥30). Participants were recruited from both urban and rural communities from two Australian states (Victoria and Tasmania). Recruitment was by several methods including from community centers, local medical clinics and through radio and newspaper advertising. Exclusion criteria included: (1) inability to provide written consent to participate in the study, (2) known history of AF, (3) history of moderate or greater severity valvular heart disease, (4) known history of HF based on the 2013 AHA/ACC guidelines(245), (5) reduced LV systolic function on baseline echocardiogram (LVEF ≤40%), (6) expected life expectancy of less than one year or cognitive impairment/frailty which would not allow for AF screening to be undertaken and (7) inability to acquire interpretable images for performance of strain analysis from the baseline echocardiogram.
2. Secondary Prevention (SP) cohort – consecutive patients ≥ 50 years admitted with an ischemic stroke/transient ischemic attack from 2010-2014 to a large tertiary stroke unit (Royal Hobart Hospital, Tasmania, Australia) and who had an echocardiogram at the institution were recruited. All neurological events were confirmed by a consultant neurologist using either computed tomography or magnetic resonance imaging. Cytogenic strokes were defined as per the TOAST (Trial of Acute Stroke Treatment) guidelines (252). Exclusion criteria included: (1) inability to provide written consent to participate in the study, (2) a known history of AF or AF diagnosed during hospital admission prior to the echocardiogram being performed, (3) an alternate cause of stroke identified such as left sided endocarditis, LV/LA thrombus, intra-

cardiac mass, patent foramen ovale or ipsilateral carotid artery stenosis ≥70%, (4) only transesophageal echocardiogram performed and (5) inability to acquire interpretable images for performance of strain analysis from the baseline echocardiogram.

All patients were provided written informed consent and approval was obtained from the institution's Human Research Ethics Committee (University of Tasmania HREC project number H0013333/H0015502 and Bellberry HREC project number 2016-10-727-A-7).

9.4.2 Clinical Assessment.

Participants undertook a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, past medical history, medication history, baseline examination data (height, weight, BMI and blood pressure (BP) were recorded for all participants. Baseline 12 lead ECG and echocardiography were conducted in all participants. Clinical AF risk assessment was performed using a validated AF risk score (the CHARGE-AF score) that includes 12 clinical parameters (age, race, height, weight, systolic/diastolic blood pressure, current smoking, use of anti-hypertensives, history of diabetes mellitus/myocardial infarction, history of HF and ECG data (voltage criteria for left ventricular hypertrophy (LVH) and PR interval) to assess 5 year risk of AF (22).

9.4.3 Echocardiographic assessment.

All echocardiograms were performed by qualified sonographers. Two-dimensional, M-mode and Doppler measures were obtained using standard techniques outlined by the American Society of Echocardiography (253). LV dimensions were calculated in both diastole and systole in parasternal long axis views. LVH was defined as LV mass index >115 g/m^2 in men and >95 g/m^2 in women. LA volume was indexed to body surface area (LAVi) and calculated by the Simpson biplane method.

Global longitudinal strain (GLS) measurements were obtained by manually tracing the LV endocardial border in end systole in the apical four-chamber, two-chamber and long-axis views. This was then tracked throughout the cardiac cycle. GLS was analyzed using speckle tracking imaging by an external third-party software program (ImageArena, Tomtec, Munich, Germany). All measurements were

performed by averaging strain measurements from the three views. Abnormal GLS was defined as <18% (absolute value). Patients with poor image quality, where GLS could not be performed, were excluded.

The three phasic functions of LA function (reservoir, conduit and pump function) were assessed using strain imaging. Apical four and two chamber images were selected with a high frame rate of 60-80 frames/second. Offline speckle tracking analysis was performed using an external third-party software program (ImageArena, Tomtec, Munich, Germany). The endocardial border of the LA was manually traced, and strain analysis was performed using the LV strain algorithm. The average of the four- and two-chamber values were used to measure each strain component. The reference point for image analysis was taken at the onset of the QRS complex (R-R gating) in accordance with recent consensus guidelines (101). If more than 1 segment of the 6 LA segments could not be tracked, the sample was excluded. We used an arbitrary cut-point of 34% for LARS to determine high risk of AF. An example of a typical LA strain curve is shown in figure 9.2.

Inter-observer reliability was assessed by a second operator who performed strain measurement in a random sample of 20 participants and was blinded to all clinical and imaging data. Intra-observer reliability was performed by the primary author (SR) who performed repeated strain measurements in a random sample of 20 patients at a different time point. The mean percentage difference was calculated.

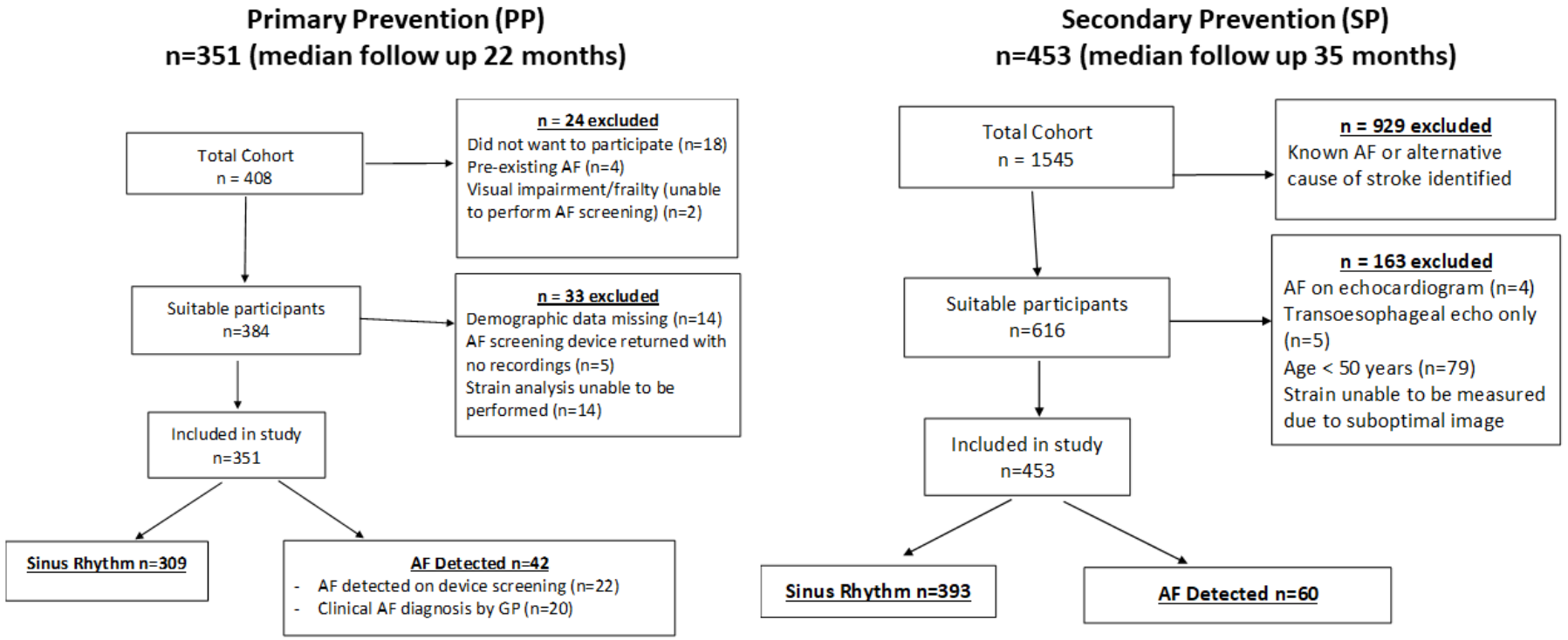


Figure 9.1 - Flowchart showing patient recruitment in the study.

The PP cohort had 351 participants recruited with a median follow up of 22 months. The SP cohort had 453 participants recruited with a median follow up of 35 months.

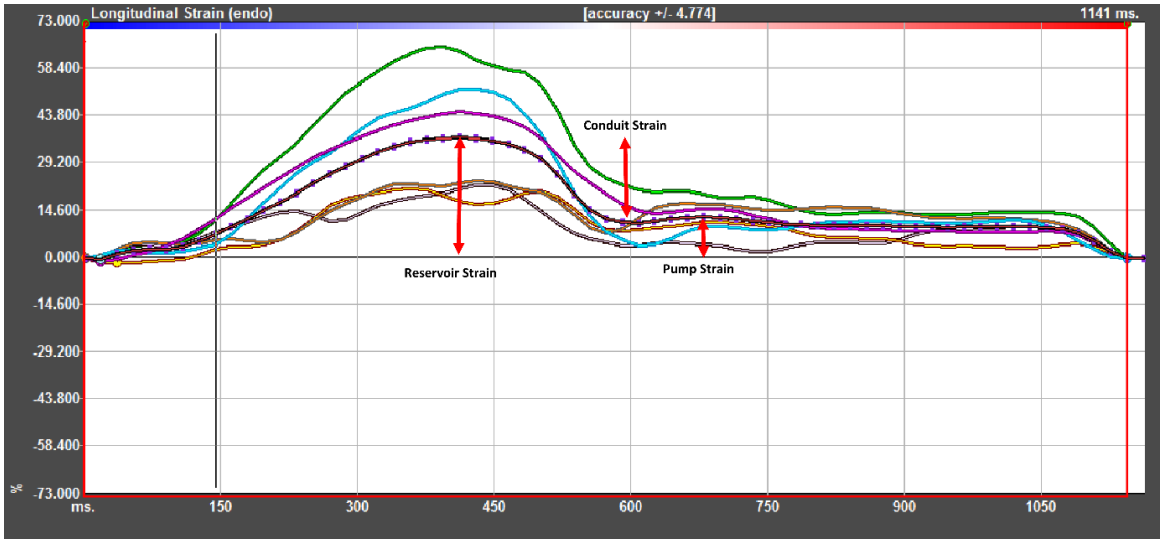


Figure 9.2 - LA strain curve showing the 3 components of LA strain (reservoir, conduit and pump strain).

The LA strain curve mirrors the phasic functions of the LA (reservoir, conduit and pump function).

9.4.4 Outcomes.

Participants were followed for incident AF (median 22 months in PP cohort, median 35 months in SP cohort), which was the primary outcome measure. AF was diagnosed using multiple detection methods. In the PP cohort, we contacted local general practitioners and viewed electronic hospital records to investigate those with clinically diagnosed AF during the follow-up period (confirmed on 12 lead ECG or Holter monitoring). Screening for subclinical AF was performed using a single lead ECG device (Remon RM-100, Semacare, China), within the first month of recruitment into the study. The single lead device was used to record 60 second single-lead ECG tracings using three points of finger contact with electrodes, five times per day for one week (i.e. 35 recordings). ECG recordings were then exported as PDF files for interpretation, and all were assessed by a physician. The presence of AF (an irregular rhythm of ≥30 sec with a variable R-R interval and absent P waves) was confirmed by two independent physicians who were blinded to the patient's clinical details. The patient was advised of the recognition of subclinical AF, and further management and investigation was provided by their usual medical practitioner.

In the SP cohort, AF was diagnosed in multiple ways. We reviewed electronic hospital records to find patients with AF identified using inpatient telemetry and Holter monitoring. We also reviewed results

of outpatient investigations such as Holter monitoring and interrogation of implantable loop recorders/permanent pacemakers to identify those with AF following hospital discharge.

9.4.5 Statistical analysis.

All categorical variables are presented as frequencies/percentages and continuous variables presented as means/standard deviation (if normally distributed) or medians/inter-quartile range (if non-parametric). Patients with incident AF were compared to those in sinus rhythm. Groups were compared using the chi-square test for categorical data and the independent two sample t-test for continuous data. Nested Cox-proportional hazards regression analysis was used to assess the incremental predictive value of both GLS and LARS. This was performed in both the PP and SP cohorts. We calculated the hazard ratios (HR) and 95% confidence intervals for the association between each strain marker and incident AF. The follow-up time was the time from the initial baseline clinical assessment to the completion of the study or the date of diagnosis of AF (whichever came first). Other parameters in the model included the CHARGE-AF score, LAVi and E/e'.

Nelson-Aalen cumulative hazard estimate plots were constructed to assess AF diagnoses between low and high-risk groups based on arbitrary cut-offs for LARS (34%) and GLS (18%). The log-rank test used to assess the differences between curves. Receiver operator characteristic (ROC) curves were constructed for both GLS and LARS for both PP and SP cohorts to determine the discriminative ability of both strain markers in different disease stages. The area under the curves (AUC) of both cohorts were compared by the Hanley and McNeil method (254). Analyses were considered to be statistically significant if two-tailed p values were <0.05. Statistical analysis was performed using SPSS v.22 (SPSS, Chicago, IL) and Stata v.13 (StataCorp, College Station, Texas).

9.5 Results

9.5.1 Patient characteristics.

In the PP cohort, 351 participants (mean age 70 yrs ± 4.1 yrs, 43% male) were included, and in the SP cohort, 453 participants (mean age 70 yrs ± 11.0 yrs, 57% male) were included. Both cohorts were heterogenous and demonstrated variability in baseline clinical and echocardiographic characteristics.

Table 9-1 - Baseline Characteristics of the overall cohort.

Demographics	Primary Prevention (PP) cohort (n=351)	Secondary Prevention (SP) cohort (n=453)	P Value
Age - years (SD)	70.3 (4.1)	70.1 (11.1)	0.77
Male n (%)	152 (43)	258 (57)	<0.001
Systolic BP mmHg (SD)	141 (15.7)	134 (13.9)	<0.001
Diastolic BP mmHg (SD)	82 (9.8)	74 (8.7)	<0.001
Heart Rate /min (SD)	68 (10.4)	69 (12.6)	0.40
BMI (kg/m^2) (SD)	29.9 (5.2)	27.6 (4.9)	<0.001
Current Smoking n (%)	7 (2)	121 (27)	<0.001
Diabetes Mellitus n (%)	167 (48)	89 (20)	<0.001
Obesity n (%)	165 (47)	106 (23)	<0.001
Hypertension n (%)	272 (78)	302 (67)	0.001
Previous history of IHD n (%)	14 (4)	61 (14)	<0.001
Previous history of HF n (%)	0 (0)	14 (3.1)	0.001
Median CHARGE-AF % (IQR)	5.6 (5.5)	6.3 (12.7)	0.12
Median CHA_2DS_2-VASC % (IQR)	3.0 (2.0)	5.0 (2.0)	<0.001
AF during follow up (%)	42 (12)	60 (13)	0.60
Echocardiographic Parameters			
Ejection Fraction % (SD)	63 (6.1)	60 (10.5)	<0.001
Global Longitudinal Strain % (SD)	18.9 (2.4)	19.9 (3.6)	<0.001
E/A (SD)	0.83 (0.25)	0.93 (0.39)	<0.001
E/e' (Average of lateral and septal) (SD)	8.7 (2.5)	11.2 (4.9)	<0.001
Left atrial volume - indexed ml/m^2 (SD)	31.6 (8.9)	35.3 (12.1)	<0.001
Left Ventricular mass – indexed g/m^2 (SD)	83.8 (22.0)	97.9 (29.9)	<0.001
LARS % (SD)	38.4 (6.6)	30.3 (8.5)	<0.001
Left Atrial Conduit strain % (SD)	19.2 (5.3)	15.7 (6.2)	<0.001
Left Atrial Pump strain % (SD)	19.2 (5.3)	14.6 (4.8)	<0.001

BMI – Body Mass Index BP – Blood Pressure IHD – Ischaemic Heart Disease

9.5.2 AF during follow up.

Over a median follow-up of 22 months, 42 patients in the PP cohort (12%) were diagnosed with AF - 22 patients with subclinical AF diagnosed with portable ECG monitoring and 20 patients with AF diagnosed at clinical review. Over a median follow up of 35 months, 60 patients in the SP cohort (13%) were diagnosed with AF. Table 9-2 compares the characteristics of those with AF and sinus rhythm; those diagnosed with AF were older and had higher baseline CHARGE-AF and CHA_2DS_2-VASC

scores (p<0.001). Compared to those in sinus rhythm, patients with AF had reduced GLS (17.0±3.5% vs 19.8±3.0%, p<0.001), reduced LARS (27.8±10.6% vs 34.7±8.0%, p<0.001) and increased LAVi and LV mass (both p<0.001).

9.5.3 Incremental value of strain markers.

A summary of the nested cox regression analysis is summarized in figures 9.4 and 9.5. The sequential models included CHARGE-AF, LAVi, E/e', GLS and LARS (in order). In the PP cohort, LARS and LAVi provided independent and incremental predictive value (p<0.05). GLS provided incremental predictive value although this was not independent of the other covariates in the final model (HR 1.13, 95% C.I 1.00-1.28, p=0.06). In the SP cohort, both GLS and LARS provided independent and incremental predictive value (GLS - HR 1.12, 95% C.I 1.03-1.22, p=0.007 and LARS – HR 0.92, 95% C.I 0.88-0.97, p=0.001).

9.5.4 AF prediction from strain values.

The results of the ROC analysis are shown in figure 9.6. For both GLS and LARS, a larger AUC was noted in the SP cohort compared with the PP cohort (AUC 0.83 vs 0.58, p<0.001 for GLS and AUC 0.83 vs. 0.57, p<0.001 for LARS).

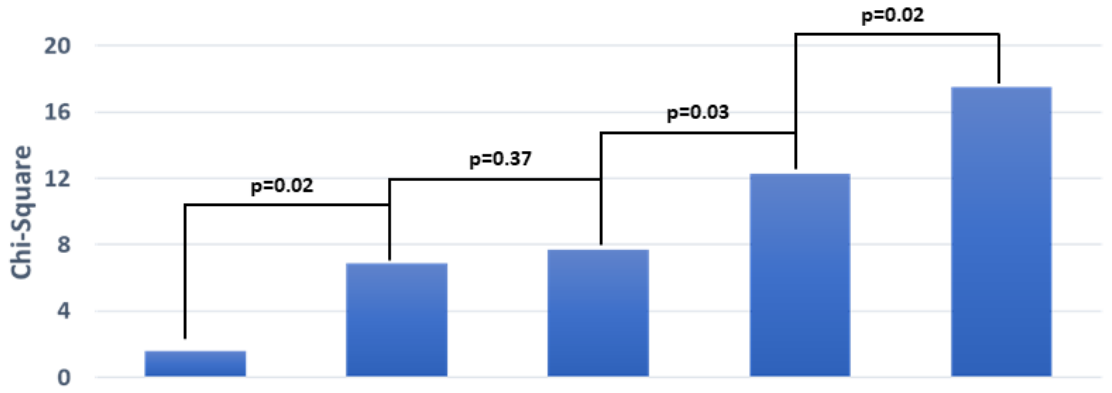
Nelson-Aalen curves showing AF detection based on cut-offs for LARS (cut-point 34%) and GLS (cut-point 18%) are shown in figure 9.7. For LARS, higher AF detection was noted in patients with reduced LA strain <34% in both PP and SP cohorts (p<0.05). For GLS higher AF detection was noted in patients with GLS <18% only in the SP cohort (p<0.001) (p=0.14 for PP cohort).

Table 9-2 - Comparison of baseline characteristics between patients with AF and sinus rhythm.

Demographics	**Sinus Rhythm (n=702)**	**AF (n=102)**	**P Value**
Age - years (SD)	69.4 (8.6)	75.4 (7.6)	<0.001
Male n (%)	357 (51)	53 (52)	0.84
Systolic BP mmHg (SD)	138 (11.5)	134 (15.3)	0.02
Diastolic BP mmHg (SD)	78 (10.0)	75 (11.0)	0.03
Heart Rate /min (SD)	68 (11.5)	69 (12.7)	0.73
BMI (kg/m^2) (SD)	28.7 (5.1)	27.8 (5.4)	0.11
Current Smoking n (%)	110 (16)	18 (18)	0.61
Diabetes Mellitus n (%)	223 (32)	33 (32)	0.91
Obesity n (%)	242 (35)	29 (28)	0.22
Hypertension n (%)	492 (70)	82 (80)	0.03
Previous history of IHD n (%)	61 (9)	14 (14)	0.10
Previous history of HF n (%)	7 (1)	7 (7)	<0.001
Median CHARGE-AF % (IQR)	5.3 (7.8)	11.7 (12.0)	<0.001
Median CHA_2DS_2-VASC % (IQR)	4.0 (2.0)	5.0 (3.0)	<0.001
Echocardiographic Parameters			
Ejection Fraction % (SD)	62 (8.8)	59 (10.0)	0.006
Global Longitudinal Strain % (SD)	19.8 (3.0)	17.0 (3.5)	<0.001
E/A (SD)	0.88 (0.31)	0.94 (0.47)	0.22
E/e' (Average of lateral and septal) (SD)	9.9 (3.8)	11.5 (5.8)	0.01
Left atrial volume - indexed ml/m^2 (SD)	33.1 (10.5)	37.6 (13.3)	0.001
Left Ventricular mass – indexed g/m^2 (SD)	90.9 (26.6)	97.5 (29.3)	0.02
LARS % (SD)	34.7 (8.0)	27.8 (10.6)	<0.001
Left Atrial Conduit strain % (SD)	17.6 (6.0)	14.5 (5.8)	<0.001
Left Atrial Pump strain % (SD)	17.1 (5.0)	13.3 (7.1)	<0.001

9.5.5 Reproducibility.

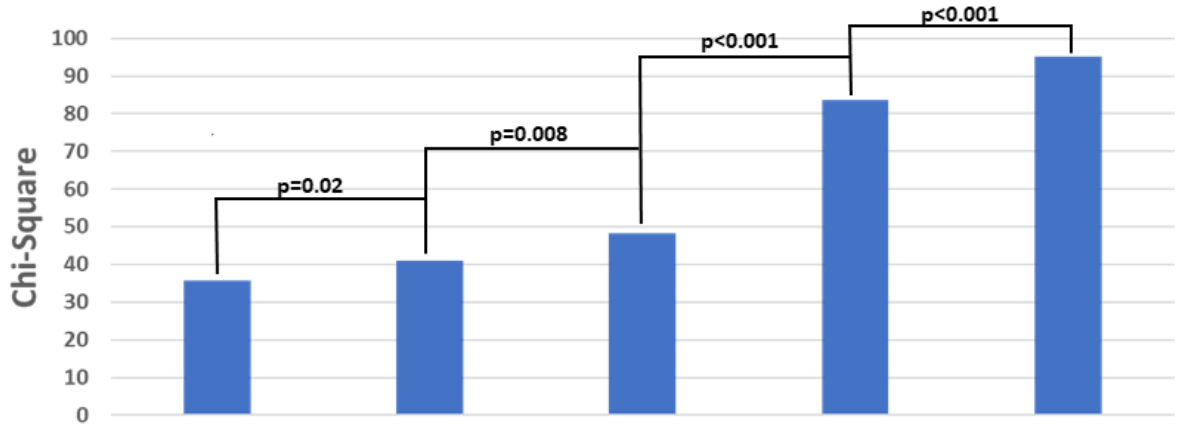
Inter-observer variability was assessed by blinded strain measurements in a random sample of 20 patients. All measurements were done by the same investigators and the mean of the absolute value of differences between measurements was calculated. The mean±SD difference for GLS was 0.7±0.7%, and for LARS it was 3.8±3.1%. Intra-observer variability was assessed by the primary investigator (SR) who repeated GLS measurements in a random sample of 20 patients at a different timepoint. The mean difference for GLS was 0.8±0.6%, and for LARS was 3.8±2.9%.



	MODEL 1 Chi-Square = 1.6 HR (95% C.I), p	MODEL 2 Chi-Square = 6.9 HR (95% C.I), p	MODEL 3 Chi-Square = 7.7 HR (95% C.I), p	MODEL 4 Chi-Square = 12.3 HR (95% C.I), p	MODEL 5 Chi-Square = 17.5 HR (95% C.I), p
CHARGE-AF (per 1% rise)	1.04 (0.98-1.09) p=0.19	1.02 (0.97-1.08) p=0.40	1.03 (0.97-1.08) p=0.34	1.01 (0.95-1.07) p=0.75	1.01 (0.95-1.07) p=0.82
LA Volume (per 1ml/m² rise)		**1.05 (1.01-1.08) p=0.02**	**1.04 (1.01-1.08) p=0.01**	**1.04 (1.01-1.07) p=0.01**	**1.04 (1.01-1.07) p=0.02**
E/e' (per 1 point rise)			0.94 (0.83-1.08) p=0.38	0.96 (0.84-1.09) p=0.54	0.94 (0.82-1.07) p=0.32
GLS (per 1% drop)				**1.15 (1.01-1.31) p=0.03**	1.13 (1.00-1.28) p=0.06
LA Reservoir Strain (per 1% rise)					**0.95 (0.90-0.99) p=0.02**

Figure 9.3 - Nested Cox Regression model showing incremental predictive value of LARS in PP cohort. GLS was not independently associated with AF.

Compared with GLS, LARS was independently associated with AF in the PP cohort.



	MODEL 1 Chi-Square = 35.7 HR (95% C.I), p	MODEL 2 Chi-Square = 41.1 HR (95% C.I), p	MODEL 3 Chi-Square = 48.2 HR (95% C.I), p	MODEL 4 Chi-Square = 83.6 HR (95% C.I), p	MODEL 5 Chi-Square = 95.2 HR (95% C.I), p
CHARGE-AF (per 1% rise)	**1.09 (1.06-1.12) p<0.001**	**1.08 (1.04-1.11) p<0.001**	**1.07 (1.04-1.11) p<0.001**	**1.05 (1.02-1.09) p=0.002**	**1.05 (1.01-1.08) p=0.009**
LA Volume (per 1ml/m^2 rise)		**1.04 (1.01-1.06) p=0.001**	**1.03 (1.00-1.05) p=0.02**	1.02 (1.00-1.05) p=0.06	1.01 (0.99-1.03) p=0.40
E/e' (per 1 point rise)			**1.07 (1.02-1.12) p=0.005**	**1.06 (1.01-1.11) p=0.03**	1.04 (0.99-1.10) p=0.10
GLS (per 1% drop)				**1.22 (1.15-1.30) p<0.001**	**1.12 (1.03-1.22) p=0.007**
LA Reservoir Strain (per 1% rise)					**0.92 (0.88-0.97) p=0.001**

Figure 9.4 - Nested Cox Regression model showing incremental predictive value of LARS and GLS in SP cohort.

Both GLS and LARS were independently associated with AF in the SP cohort

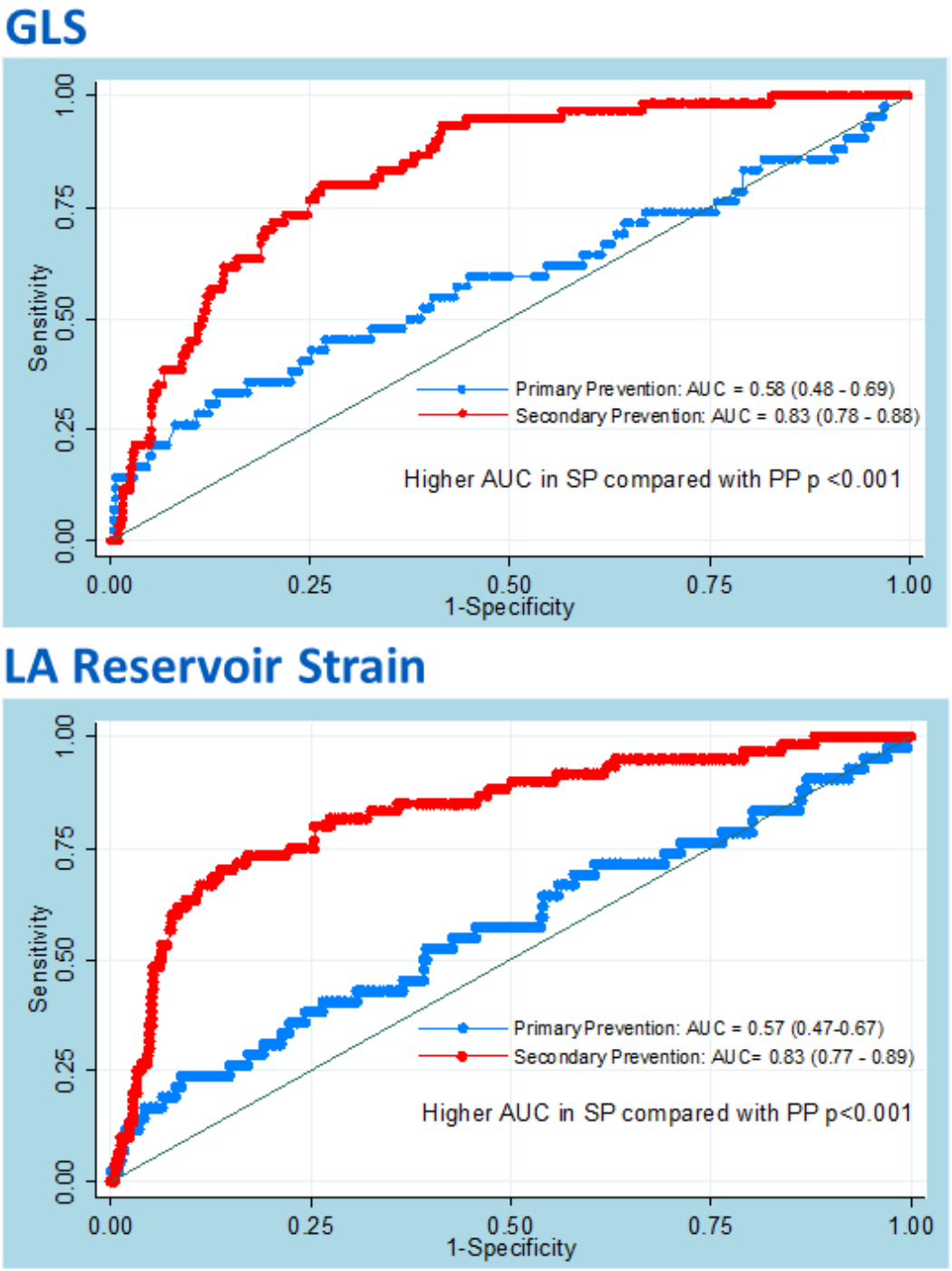


Figure 9.5 - Receiver operator characteristic (ROC) analysis showing the discriminative ability of both strain markers in both patient cohorts. The AUC is much larger in the SP cohort for both strain parameters (p<0.001).

The ROC curves show much higher discrimination of both strain parameters in the SP cohort compared with the PP cohort. This suggests that the usefulness of strain parameters in AF prediction improves in more advanced disease stages.

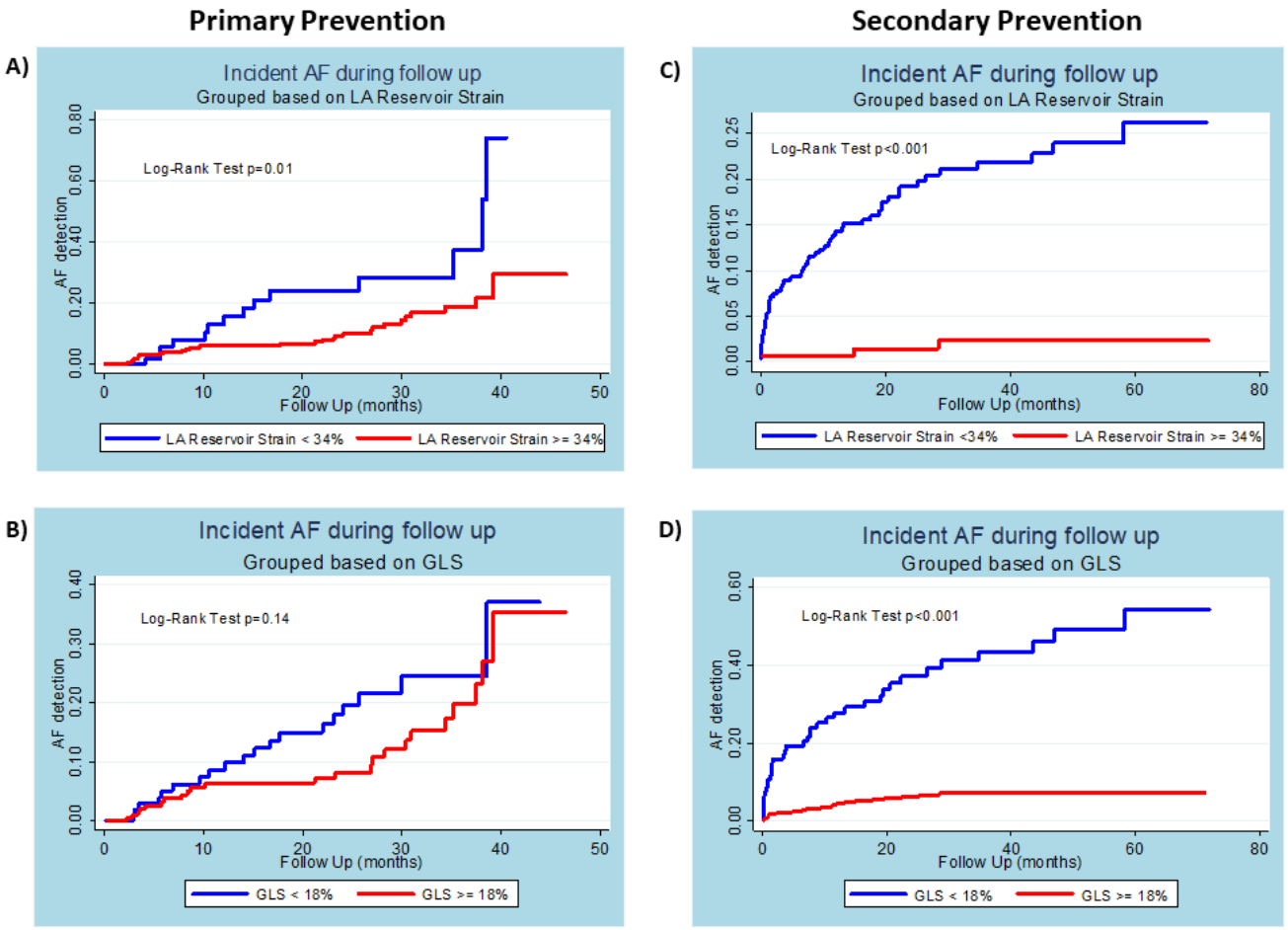


Figure 9.6 - Nelson-Aalen Curves showing AF detection based on arbitrary cut-offs for strain (LARS < 34% and GLS > 18%).

In panel A patients with LARS <34% had higher AF detection rates compared with those with LARS ≥ 34% (p=0.01). In panel B, there was not a statistically significant difference in AF detection rates between patients with GLS <18% compared to those with GLS ≥18% (p=0.14). Panels C and D show statistically significant difference in AF detection rates for both LARS and GLS in the SP cohort (p<0.001, with higher AF detection rates in those with LARS <34% and GLS <18%).

9.6 Discussion

The results of our study suggest that the association of strain markers with AF improves in higher risk cohorts. LARS was independently associated with AF with incremental predictive value over clinical parameters and LA volume. GLS was independently associated with AF only in a high-risk stroke cohort.

9.6.1 The use of strain in AF risk assessment.

LA strain has emerged as a novel parameter for the phasic assessment of LA function (5). The three components of LA function (reservoir, conduit and pump) can be assessed and there have been important clinical applications of LA strain such as a prognostic marker in HF and as a risk marker of thromboembolic complications in AF (88, 97, 213, 255). We have previously demonstrated the association of LA strain with AF (251). Unlike other robust strain parameters such as GLS, there have been some challenges which have limited the widespread adoption of LA strain into clinical practice (231). Currently LA strain is measured using a LV strain algorithm which are vendor specific with variations in ECG gating, nomenclature and image acquisition techniques (5, 101). The normal values of LA strain are also variable among vendors, with a recent meta-analysis providing a reference range (89). There have been recent published consensus guidelines aiming to address some of these limitations which will help standardize reporting and improve feasibility (101).

Despite its limitations, LA strain has an important role in AF assessment (4, 92, 97). LA strain provides quantitative information about LA phasic function which may be a more sensitive marker that LA volume - which is the current standard echocardiographic risk marker for AF (250). Much like GLS has been used to identify those with subclinical LV dysfunction, LA strain may allow us to identify patients with an underlying “atriopathy”, thereby helping to identify those at increased risk of developing AF. Our study confirms that LARS is independently associated with AF and provides incremental predictive value to LA volume and clinical parameters. Importantly in our study we found that LA strain was both feasible and reproducible. In patients with stroke and AF related complications, GLS may be an important predictive marker.

9.6.2 Early diagnosis of AF.

AF is a leading cause of stroke and HF (1, 2), the rising incidence and prevalence of which is associated with increasing health care costs and hospitalizations (12, 109, 111). Patients with asymptomatic (subclinical) AF do not have a benign prognosis and may have similar rates of stroke than those with symptomatic AF (55, 256). Screening for AF has been a topical issue and with improvements in monitoring technology, has been shown to be cost-effective and feasible (8, 78, 257). Screening is recommended by the European Society of Cardiology (57) and by the AF-Screen Collaboration (2), however due to concerns of false positives/negatives as well as the risk of overdiagnosis and feasibility, is currently not recommended in United Kingdom or United States guidelines (58, 59).

Despite the controversy of screening, early diagnosis of AF has several potential benefits. It allows for aggressive risk factor modification and screening for comorbid conditions such as sleep apnoea which has been shown to be of significant benefit post catheter ablation in those with symptomatic AF (23). Although initiation of anticoagulation in this setting has not been studied in a randomized clinical trial in the subclinical AF cohort, this may translate to reduced hospitalizations and health care costs.

9.6.3 Improving the efficiency of AF screening.

The efficiency of screening programs is dependent on the underlying AF risk of patients. Risk assessment for AF is challenging and no single parameter has been demonstrated to have a high predictive value. Although validated clinical bedside scores such as the CHARGE-AF are easy to calculate and useful for clinical assessment, they only have moderate discriminative ability and in a recent retrospective study, was not a strong predictor of AF in hospitalized patients (22, 258).

Most screening programs have adopted opportunistic screening of patients based on arbitrary age cut-offs and this is currently recommended by the AF-Screen Collaboration (2). Much of the focus has also been on the monitoring technology and the duration of monitoring. While these are important considerations, there have been few studies investigating strategies to refine the screening population to improve efficiency. Although we would not propose routine echocardiograms purely for AF risk assessment, we often find that patients at risk of AF have had echocardiograms performed for a variety of indications(82). In this situation, the results of echocardiography could provide a powerful, relatively

inexpensive and reproducible method of refining the “at risk” cohort. We have previously proposed a systematic method of reporting an individual’s AF risk based on the presence of imaging risk factors such as LA enlargement or LVH. LA strain can also be a useful marker in these patients to identify those with an underlying "atriopathy”. The results of our study suggest that by combining clinical risk parameters with imaging risk parameters may help enrich the screening cohort, thereby making AF screening more efficient, further improving cost-effectiveness.

9.6.4 Limitations.

The limitations of our study include the comparison of heterogenous patient cohorts which may have translated into some important confounders not being included in the analysis. Nonetheless, although from different geographical locations, the health system of both locations is the same and demographics were similar.

We had a small number of AF outcomes and some outcomes may have been missed due to the limited AF monitoring period. AF was diagnosed using a variety of methods, which were not the same in both groups, although the overall AF detection rate was similar in both groups. Moreover, other cohort studies have shown equivalence in the frequency of detection of subclinical AF using intermittent device tracings over multiple days and continuous recording over a single day (55, 240, 256).

We did not collect data from local practitioners on anticoagulation prescription following a diagnosis of AF hence were unable to assess the impact of early diagnosis. Likewise, we did not perform long term follow-up to assess if those with subclinical AF had similar clinical outcomes to those with clinically diagnosed AF.

9.7 Conclusion.

The performance of strain markers improves in higher risk patient cohorts. LARS is independently associated with AF in different risk cohorts and its effect is incremental to clinical parameters and LA volume. GLS may be more useful in AF risk assessment in those with AF related complications.

9.8 Postscript

In this chapter we have demonstrated that the performance of LA and LV strain in prediction of AF varies according to disease stage. LA strain may be a useful marker in detecting early signs of adverse LA remodeling and may help predict those that develop AF. However, in very low risk patients, it may not be as predictive. In contrast, those patients at high risk with multiple risk factors, strain (both LA and LV strain) may be a more powerful imaging marker to predict future AF risk.

For this study we assumed that the primary prevention cohort were at earlier disease stages than those from the secondary prevention cohort. Whilst the development of stroke suggests that these patients may have a more advanced "atriopathy," it is possible that those from the community with risk factors may also have a more advanced "atriopathy" given the presence of multiple risk factors such as hypertension and diabetes. This should be acknowledged as a limitation in our study. It is difficult to accurately group or classify the degree of "atriopathy" or stroke risk. However, what we can learn from this study is that LA strain can be used in different patient groups to assess AF risk. It is also evident that the strength of association varies according to different groups. These imaging parameters may also provide a non-invasive marker of LA remodeling and "atriopathy" which indirectly may represent a marker of stroke (independent of the development of AF).

As we demonstrated in chapter 8, AF modelling and risk assessment is complex, and no single imaging or clinical parameter is predictive. However, we require a multi-faceted risk assessment strategy combining clinical, socioeconomic and multiple imaging parameters. In the next chapter, we investigate other novel imaging markers of AF risk - LA mechanical dispersion.

Chapter 10

Other Advanced Imaging Markers of AF Risk

"Left Atrial Mechanical Dispersion Assessed by Strain Echocardiography as an Independent Predictor of New-onset Atrial Fibrillation: A Case-Control Study."

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10 Other Advanced Imaging Markers of AF risk

10.1 Preface

In previous chapters we investigated the association between AF and LA strain. Myocardial strain also allows assessment of the timing of segmental contraction of different myocardial segments. With progressive LA remodeling and enlargement, fibrosis can occur which leads to delayed contraction. This mechanical delay in contraction between different LA segments which can be assessed using strain, can be a potential surrogate non-invasive marker for LA fibrosis. Therefore, it may have a role in AF risk stratification.

In this chapter we investigate the role of LA mechanical dispersion and determine its association with AF.

10.2 Abstract

Background: Left atrial (LA) enlargement is associated with atrial fibrillation (AF), but new-onset AF often occurs in the absence of LA enlargement. AF may be related to myocardial fibrosis, and even though left ventricular fibrosis is associated with mechanical dispersion, this phenomenon is not well studied in AF. We hypothesized that detection of LA dysfunction and mechanical dispersion using strain echocardiography is useful for predicting new-onset AF.

Methods: Baseline echocardiography was performed at entry in 576 community-based participants at risk of HF or AF. In this case-control study, we compared 35 individuals with new-onset AF (age 70±4 years; 57% men) over 2 years follow-up with 35 age and sex matched individuals who did not develop AF from same cohort. Using speckle-tracking echocardiography, we measured the LA strain in each of 12 segments in two- and four-chamber views. LA mechanical dispersion was defined as the standard deviation of time to peak positive strain corrected by the R-R interval (SD-TPS, %).

Results: There was no significant difference in LA volume index (32.5±9.2 ml/m^2 vs. 29.5±8.3 ml/m^2, p=0.16), patients with new-onset AF had significantly worse LA pump strain (16.6±4.3% vs. 20.6±4.3%, p<0.01) and reservoir strain (31.4±7.7% vs. 38.0±7.3%, p<0.01) than those without AF. SD-TPS was significantly higher in patients with AF than in those without it (6.3%±2.3% vs. 3.9%±1.6%, p<0.01). SD-TPS was independently associated with new-onset AF after adjustment for patient characteristics, LA volume and strain (hazard ratio, 1.26; 95% confidence interval, 1.10–1.45; p<0.01). In the nested Cox models, the model based on the LA volume and strain for predicting new onset AF was significantly improved by adding SD-TPS (p<0.01).

Conclusion: LA dispersion obtained from strain echocardiography provides incremental information to LA volume and function in the prediction of new-onset AF.

10.3 Introduction

Atrial fibrillation (AF) is the most common serious arrhythmia, and its increasing incidence reflects the aging population (259, 260). Risk stratification for the development of this arrhythmia has a potential public health impact, because the recognition of AF is often delayed and the major complication of AF (stroke) is potentially preventable with anticoagulation. Transthoracic echocardiography has played an important role in assessing this remodeling because it is non-invasive, highly accessible and portable.

AF is a progressive disease that facilitates its own persistence through the process of atrial remodeling (261); both left atrium (LA) structural and functional remodeling are associated with AF (40, 262). LA enlargement is a well-known predictor for new-onset AF (175, 263, 264), but AF is often observed in patients without LA enlargement because functional impairment precedes morphological changes (265, 266). Strain echocardiography can accurately assess regional myocardial function, and impaired LA strain is a marker of AF risk (267, 268). Myocardial strain may also be used to measure the timing of contraction, and several studies have revealed an association between LV mechanical dispersion and ventricular arrhythmias (92, 269-271). Disturbances in the timing of LA contraction reflect the presence of atrial fibrosis and electrophysiological disorders (272, 273). A most recent study reported that intra-atrial dyssynchrony during sinus rhythm was an independent predictor of recurrence after the first AF ablation (273). Accordingly, we hypothesized that measurement of LA mechanical dispersion can be a useful biomarker to stratify the risk for new-onset AF. The purpose of this study was to quantify the association and impact of LA dispersion on the incidence of new-onset AF, and to assess whether LA dispersion provided additional predictive information toward new-onset AF over LA enlargement and dysfunction.

10.4 Methods

10.4.1 Study population.

In this prospective, observational case control study, we selected participants from a community-based study in Australia, which had the primary objective of early detection of HF and AF. This community-based cohort included asymptomatic individuals older than 65 years with more than one risk including

hypertension (systolic blood pressure >140 mm Hg or pre-existing use of antihypertensive medications), T2DM (based on self-reports of diagnosis or the current use of diabetic medications), obesity (body mass index ≥ 30), previous chemotherapy, and family history of HF. Exclusion criteria were (1) inability to provide written consent to participate in the study, (2) history of moderate or greater valvular disease, (3) known history of HF, (4) reduced left ventricle (LV) systolic function on baseline echocardiography (LV ejection fraction < 40%), (5) contraindications to beta-blockers and angiotensin-converting enzyme inhibitors, (6) life expectancy < 1 year, and (7) inability to perform strain analysis or acquire interpretable images from baseline echocardiography. All patients were provided written informed consent, and approval was obtained from the institution's human research ethics committee. From this initial cohort, we excluded all patients with known histories of AF or with documented AF on baseline electrocardiography, leaving 576 eligible individuals for inclusion into our study.

10.4.2 Clinical data.

We obtained clinical histories from all participants and they answered questionnaires to assess their overall health status at the start of the study. Clinical parameters (sociodemographic variables, medical history, medication history, and baseline examination data) were comprehensively assessed. Using these data, we computed the CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology Atrial Fibrillation)(22) and CHA_2DS_2-VASc scores. We also performed baseline electrocardiography and echocardiography in all participants at entry.

10.4.3 Recognition of AF.

Incident AF was identified over a median follow-up of 15 months. All patients were followed clinically, and a clinical diagnosis of AF was sought on the basis of history and confirmed by 12-lead ECG. In addition, a single lead ECG device using three points of finger contact (Remon RM-100, Semacare, China) was used to record 60 second single-lead ECG tracings, five times per day for one week. AF was identified as an irregular rhythm of ≥30 sec with a variable R-R interval and absent P waves, confirmed by two independent physicians who were blinded to the patient's clinical details. The patient

was advised of the recognition of subclinical AF, and further management and investigation was provided by their usual medical practitioner.

10.4.4 Conventional echocardiography.

All echocardiographic examinations were performed by qualified sonographers using the same equipment (Siemens Acuson SC2000, Siemens Medical Solutions, Mountain View, CA) and transducers (4V1c [1.25–4.5 MHz] and 4Z1c [1.5–3.5 MHz]) during sinus rhythm. Conventional echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography (107, 210). Early and late diastolic mitral annular tissue velocity (e' and a') were measured in the apical four-chamber view, with the sample volume positioned at both the septal and lateral mitral annuli and being the average of these two values. LA volume was calculated using the biplane method of disks (Simpson's modified rule) and indexed to body surface area (left atrial volume index [LAVI]).

10.4.5 Strain analysis.

All strain parameters were assessed by speckle-tracking imaging using an external third-party software program (Research Arena; TomTec Imaging Systems, Munich, Germany). After manual tracing of the LA and LV endocardial border, the dedicated software automatically tracked the myocardium throughout the cardiac cycle. All tracking was reviewed to ensure that it was appropriate and a true representation of LA and LV motion. Left ventricular global longitudinal strain and global circumferential strain were measured using standard methodologies (227). The strain curves of the global and regional LA wall were generated by the software automatically, and the reference point for image analysis was taken at the onset of the QRS complex (R-R gating) as has been previously described (89). Apical four- and two-chamber images were selected with a frame rate of 60 to 80 frames/sec, and strain results were obtained by averaging the two views. The resulting atrial strain curve provided 2 peaks consistent with reservoir and contractile strain, and the difference between these was conduit strain (figure 10.1a). LA mechanical dispersion was defined as the standard deviation of time to peak positive strain (SD-TPS) from the 12 LA segments (figure 10.1b). We corrected the SD-TPS by the R-

R interval to derive SD-TPS as a percentage of the R-R interval. Higher values of SD-TPS are thought to suggest greater degree of LA dispersion. Patients without interpretable images, such as those with incomplete strain measurements, were excluded from this study. All echocardiographic analysis was performed by one investigator experienced with strain imaging who was blinded to the patient characteristics and the outcome.

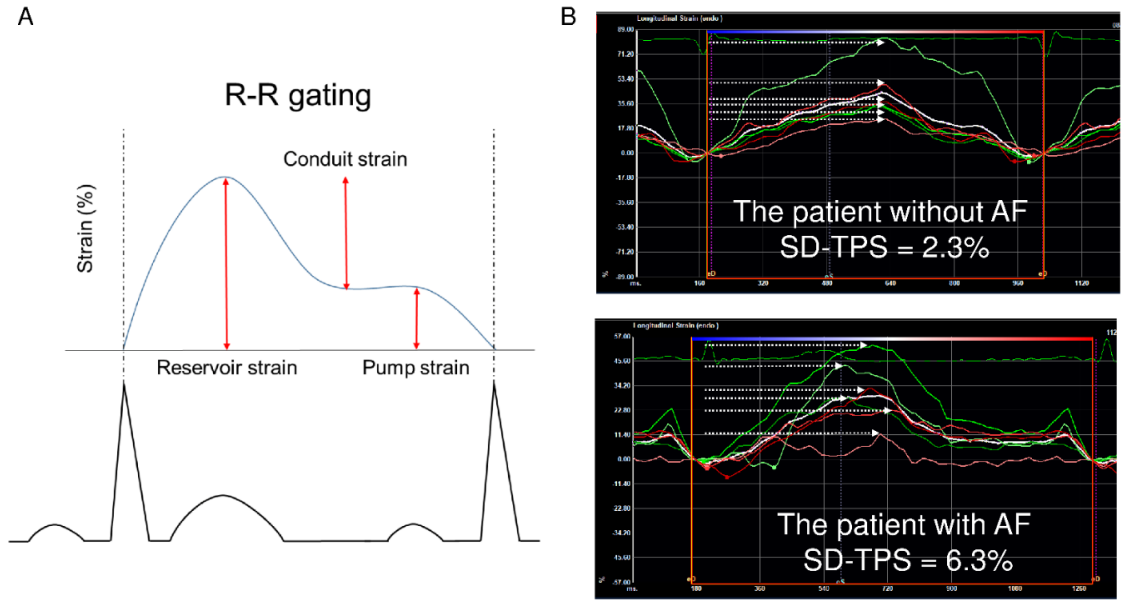


Figure 10.1 - Measurements of LA strain.

The left panel shows the LA strain components (A). The right panel shows the measurements of LA dispersion and representative cases in patients with and without AF (B). White arrows indicate contraction durations defined as the time from the end-diastole (the R wave on the electrocardiogram) to the maximal time of positive deformation in each LA segment. SD-TPS was calculated as the standard deviation of time to peak and expressed as a percentage of the R-R interval. The patients with new-onset AF showed higher SD-TPS. AF = atrial fibrillation; LA = left atrium; SD-TPS = standard deviation of the time to peak strain.

10.4.6 Statistical analysis.

Continuous variables are expressed as mean ± standard deviation or median (interquartile range), and categorical variables are shown in percentages. The significance of differences between the groups was assessed using Student's t test for data with normal distribution, and the Mann-Whitney U test was used for data that were not normally distributed. For categorical variables, the χ^2 test or Fisher's exact test was used, as appropriate. Univariable and multivariable linear regression analysis were used to evaluate the associations between SD-TPS and other echocardiographic parameters. Univariable and multivariable Cox regression analysis was used to assess independent predictors for new-onset AF. The

independence and robustness of SD-TPS were examined using several models. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated for each echocardiographic variable, and the value closest to the corner of the ROC curve determined the optimal cutoff for the ability of the variables to discriminate between patients with and without new-onset AF. Kaplan-Meier survival analyses with follow-up censored at 40 months were performed for participants with SD-TPS above and below an optimal cut-off in a previous study (274).

The incremental value of SD-TPS in the overall group was assessed in three modeling steps using nested models. Covariate selection for model entry was based on clinical experience and identification of known correlates. The first step consisted of fitting a multivariable model based on CHARGE-AF score and LAVI. LARS was then included in the second step and SD-TPS in the third step. The incremental value of SD-TPS over baseline clinical characteristics and conventional LA factors for predicting new-onset AF was determined by calculating the improvement in the global χ^2 statistic. Reclassification was evaluated to assess the incremental benefit of adding SD-TPS to the model on the basis of LA volume and function with net reclassification improvement. Inter- and intra-observer variability for LARS and SD-TPS were studied a random sample of 10 patients, and the mean of the absolute value of differences between measurements was calculated. In addition, the mean differences and limits of agreement between measurements were assessed using Bland-Altman plots.

All statistical analyses were performed using a standard statistical software package (SPSS version 21 [SPSS, Chicago, IL, USA] and R version 3.5.0 [https://www.r-project.org]). All p values reported are from two-sided tests and values <0.05 were considered statistically significant.

10.5 Results

10.5.1 Patient characteristics.

Among 576 patients, new-onset AF developed in 35 participants (mean age, 70±4 years; 57% men, 49% paroxysmal AF and 51% non-paroxysmal AF) over 2 years follow-up, and we selected as controls 35 age and sex matched individuals who did not develop AF from same cohort. Thus, we performed our final analyses with data from a total of 70 participants (Table 10-1). The majority of the patients had T2DM (54%), obesity (44%), hypercholesterolemia (48%), and hypertension (76%), but the average values for LAVI, LA, and LV function were in the normal range. Table 10-1 also shows a comparison of baseline characteristics and echocardiographic parameters between the patients with and without new-onset AF. Although there was no significant difference in LAVI (32.5±9.2 vs. 29.5±8.3 ml/m^2, p=0.16), the patients with new-onset AF had significantly worse LA pump strain (16.6±4.3% vs. 20.6±4.3%, p<0.01) and reservoir strain (31.4±7.7% vs. 38.0%±7.3%, p<0.01) than those without AF. SD-TPS was significantly higher in the patients with AF than in those without it (6.3±2.3% vs. 3.9±1.6%, p<0.01). Figure 10.1B shows representative cases of LA strain curves and SD-TPS in four-chamber view for patients with and without new-onset AF.

Table 10-1 - Baseline characteristics.

	All patients n = 70	AF n = 35	No AF n = 35	P
Demographics				
Age (years)	70 ± 4	70 ± 4	70 ± 4	
Male	40 (57)	20 (57)	20 (57)	
BSA (m^2)	1.9 ± 0.2	2.0 ± 0.2	1.9 ± 0.2	0.82
BMI (kg/m^2)	29.5 ± 4.6	29.7 ± 5.0	29.4 ± 4.3	0.79
Heart rate (beats/min)	67.3 ± 12.0	69.1 ± 13.5	65.5 ± 10.2	0.21
T2DM	38 (54)	19 (54)	19 (54)	1.00
Obesity	31 (44)	14 (40)	17 (49)	0.47
Hypercholesterolemia	32 (48)	15 (45)	17 (50)	0.71
Hypertension	53 (76)	27 (77)	26 (74)	0.78
CHA_2DS_2Vasc score	3.0 ± 1.0	3.1 ± 0.9	3.0 ± 1.0	0.71
CHARGE-AF score	8.3 (5.0-12.7)	6.9 (5.1-12.2)	8.7 (4.8-14)	0.49
Medication				
ACE inhibitors or ARBs	44 (63)	20 (57)	24 (69)	0.32
β-blockers	7 (10)	5 (14)	2 (6)	0.43
Calcium blocker	16 (26)	5 (16)	11 (37)	0.06
Lipid Lowering drugs	33 (53)	15 (47)	18 (60)	0.30
Antiplatelet agents	19 (31)	9 (28)	10 (33)	0.66
Echocardiographic parameters				
LVEF (%)	62.7 ± 6.2	61.3 ± 6.3	64.1 ± 5.8	0.058
GLS (%)	-18.5 ± 2.7	-18.1 ± 3.3	-18.8 ± 1.9	0.46
GCS (%)	-29.9 ± 5.4	-29.9 ± 5.8	-30.0 ± 5.0	0.94
E/e’	8.9 ± 2.7	8.6 ± 2.6	9.1 ± 2.8	0.44
LV mass index	81.8 ± 17.0	81.7 ± 18.2	82.0 ± 16.0	0.94
LAVI (ml/m^2)	31.0 ± 8.8	32.5 ± 9.2	29.5 ± 8.3	0.16
LA pump strain (%)	18.6 ± 4.7	16.6 ± 4.3	20.6 ± 4.3	< 0.01
LA conduit strain (%)	16.0 ± 5.2	14.8 ± 4.9	17.1 ± 5.4	0.06
LARS (%)	34.7 ± 8.1	31.4 ± 7.7	38.0 ± 7.3	< 0.01
SD-TPS (%)	5.1 ± 2.3	6.3 ± 2.3	3.9 ± 1.6	< 0.01

Data are expressed as mean ± SD, number (percentage), or median (interquartile range).
**P value compared with patients ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; BSA = body surface area; GCS = global circumferential strain; GLS = global longitudinal strain; LA = left atrium; LAVI = left atrial*

volume index; LV = left ventricle; LVEF = left ventricular ejection fraction; SD-TPS = standard deviation of the time to peak strain. SD-TPS was corrected by the R-R interval to derive SD-TPS as a percentage of the R-R interval.

10.5.2 Association between SD-TPS and other echocardiographic parameters.

The association between SD-TPS and other echocardiographic parameters was evaluated using univariable and multivariable linear regression analyses (Table 10-2 and Supplementary Table 10-8). In the multivariable analysis, SD-TPS was significantly associated with LV ejection fraction (r=-0.38, $\beta = -0.27$; p=0.03) and LARS (r=-0.39, $\beta = -0.27$; p=0.04). LA pump and conduit strain were excluded from the multivariable models because of collinearity.

10.5.3 Predictors of new-onset AF.

In the univariable Cox regression analysis, new-onset AF was associated with LAVI, LARS, and SD-TPS (Table 10-3). The independent association of SD-TPS with new-onset AF was examined using three different models. SD-TPS had a consistently significant association with new-onset AF in every model and the hazard ratios (HRs) were similar (1.28-1.37). In addition, SD-TPS was independently associated with new-onset AF after adjusting for CHARGE-AF score, LAVI, and LARS (HR, 1.26; 95% confidence interval, 1.10–1.45; p<0.01) (figure 10.2). We also confirmed the independent association of LARS with new-onset AF using the same models (Supplementary Table 10-9 and figure 10.2).

Table 10-4 summarizes the ROC curve analysis results. SD-TPS and LARS were identified as echocardiographic predictors with high AUC (0.80 for SD-TPS and 0.75 for LARS), with the AUC for SD-TPS being the highest. Using the previously-defined SD-TPS cutoff of 5.3% (274), patients with new-onset AF were identified with a sensitivity of 65.7% and specificity of 85.7%. The AF-free survival was significantly better in those with SD-TPS <5.3% than those with SD-TPS ≥5.3% (log-rank p<0.01) (figure 10.3A).

10.5.4 Incremental value of SD-TPS.

Figure 10.2 and supplementary figure 10.4 show the incremental benefit of using sequential Cox models for the prediction of new-onset AF. In figure 10.2, a model based on clinical and conventional echocardiographic variables including CHARGE-AF scores and LAVI (Chi-square, 5.3) was significantly improved by addition of LARS (Chi-square, 17.8; $p<0.01$) and further improved by adding SD-TPS (Chi-square, 27.5; $p<0.01$).

The addition of SD-TPS to a risk classification model based on LAVI or LARS alone resulted in the correct reclassification of patients without new-onset AF to the low-risk category (net reclassification improvement, 0.26 and 0.17, respectively; both $p<0.05$) (Table 10-5 and 10-6). Moreover, adding SD-TPS to combined LAVI and LARS model resulted in a significantly improved reclassification (net reclassification improvement, 0.14; $p=0.04$) (Table 10-7).

10.5.5 Reproducibility

Reproducibility was assessed by blinded strain measurements in a random sample of 10 patients. Inter-observer variability was assessed by two investigators, and the mean of the absolute value of differences between measurements was calculated (supplementary figure 10.5). For LARS and SD-TPS, the mean differences were 3.8±3.1% and 0.5±0.3%, respectively. Intra-observer variability was assessed by one investigator, who repeated LA strain at a different time point. For LARS and SD-TPS, the mean differences were 2.3±1.5%, 0.6±0.4%, respectively.

Table 10-2 - Associations of SD-TPS and other echocardiographic parameters.

	Univariable		Multivariable Clinical Model		Medical Model		Echo Model	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
BMI (per 1 kg/m^2 increase)	1.00 (0.94-1.07)	0.94	0.96 (0.89-1.04)	0.30				
CHA2DS2Vasc score (per 1-point increase)	1.05 (0.76-1.45)	0.79	0.97 (0.65-1.44)	0.87				
CHARGE-AF score (per 1-point increase)	0.97 (0.90-1.04)	0.41	0.96 (0.88-1.05)	0.35				
ACE inhibitors or ARBs	1.58 (0.81-3.10)	0.18			1.89 (0.85-4.21)	0.12		
β-blockers	0.57 (0.22-1.50)	0.26			0.52 (0.16-1.66)	0.27		
Calcium blocker	1.58 (0.61-4.09)	0.35			1.80 (0.67-4.86)	0.25		
LVEF (per 1 % increase)	0.96 (0.91-1.01)	0.08					1.02 (0.96-1.08)	0.59
LAVI (per 1 ml/m^2 increase)	1.04 (1.00-1.07)	0.04					1.00 (0.95-1.08)	0.88
LARS (per 1 % increase)	0.92 (0.88-0.96)	< 0.01					0.93 (0.86-0.99)	0.02
SD-TPS (per 1 % increase)	1.32 (1.17-1.50)	< 0.01	1.37 (1.20-1.59)	< 0.01	1.37 (1.21-1.56)	< 0.01	1.28 (1.08-1.51)	< 0.01

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; CI = confidence interval; GLS = global longitudinal strain; HR =hazard ratio; LA = left atrium; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; SD-TPS = standard deviation of the time to peak strain.

Table 10-3 - Univariable and multivariable Cox regression analysis for new-onset AF.

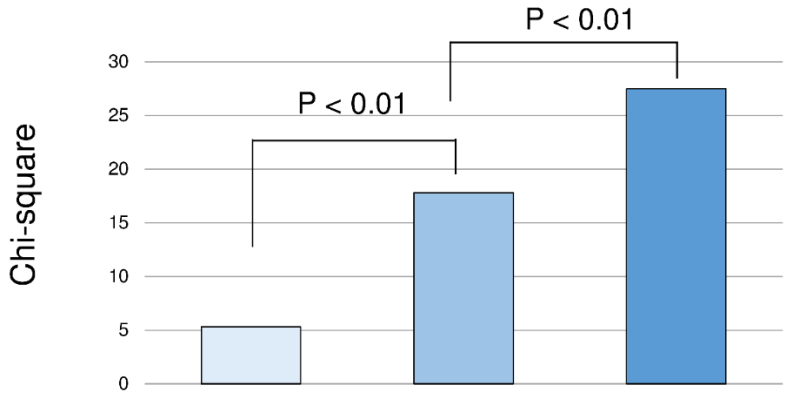
	Univariable			Multivariable		
	Unstandardized β (95%CI)	Standardized β	P	Unstandardized β (95%CI)	Standardized β	P
LVEF	-0.144 (-0.227 to -0.060)	-0.384	< 0.01	-0.101 (-0.190 to -0.013)	-0.271	0.03
GCS	0.036 (-0.068 to 0.140)	0.083	0.49			
GLS	0.292 (0.098 to 0.486)	0.342	<0.01	0.118 (-0.095 to 0.330)	0.138	0.27
E/e’	0.187 (-0.015 to 0.388)	0.219	0.07			
LAVI	0.051 (-0.011 to 0.114)	0.196	0.10	0.012 (-0.050 to 0.075)	0.047	0.69
LA pump strain	-0.123 (-0.238 to -0.007)	-0.249	0.04			
LARS	-0.109 (-0.173 to -0.046)	-0.385	< 0.01	-0.076 (-0.147 to -0.004)	-0.266	0.04

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; CI = confidence interval; GLS = global longitudinal strain; HR =hazard ratio; LA = left atrium; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; SD-TPS = standard deviation of the time to peak strain. SD-TPS was corrected by the R-R interval to derive SD-TPS as a percentage of the R-R interval.

Table 10-4 - AUC for ROC analysis of echocardiographic variables.

	AUC	95%CI	P value	Optimal cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SD-TPS (%)	0.80	0.69-0.90	< 0.01	5.3	65.7	85.7	82.1	71.4
LARS (%)	0.75	0.63-0.87	< 0.01	36.8	82.9	65.7	70.7	79.3
LVEF (%)	0.62	0.49-0.76	0.08	63.6	71.4	54.3	61.0	65.5
LAVI (ml/m^2)	0.59	0.46-0.73	0.18	28.9	62.9	51.4	56.4	58.1
GLS (%)	0.55	0.41-0.69	0.46	-17.6	45.7	71.4	61.5	56.8

AUC = area under the receiver-operating characteristic curve; CI = confidence interval; GLS = global longitudinal strain; LA = left atrium; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; NPV = negative predictive value; PPV = positive predictive value; ROC = receiver-operating characteristic; SD-TPS = standard deviation of the time to peak strain.



Variable	Model 1 Chi-square = 5.3 HR (95%CI), P value	Model 2 Chi-square = 17.8 HR (95%CI), P value	Model 3 Chi-square = 27.5 HR (95%CI), P value
CHARGE-AF score (per 1 point increase)	0.96 (0.90-1.04), P = 0.33	0.93 (0.86-1.01), P = 0.07	0.93 (0.85-1.00), P = 0.06
LAVI (per 1 ml/m² increase)	**1.04 (1.00-1.07), P = 0.03**	1.00 (0.96-1.04), P = 0.81	1.00 (0.96-1.05), P = 0.99
LA reservoir strain (per 1 % increase)		**0.90 (0.85-0.95), P < 0.01**	**0.92 (0.86-0.98), P < 0.01**
SD-TPS (per 1% increase)			**1.26 (1.10-1.45), P < 0.01**

Figure 10.2 - Incremental value of SD-TPS over existing indices.

A comparison is made with CHARGE-AF score, LAVI, and LARS in risk stratification for new-onset AF. AF = atrial fibrillation; LA = left atrium; LAVI = left atrial volume index; SD-TPS = standard deviation of the time to peak strain. SD-TPS was corrected by the R-R interval to derive SD-TPS as a percentage of the R-R interval.

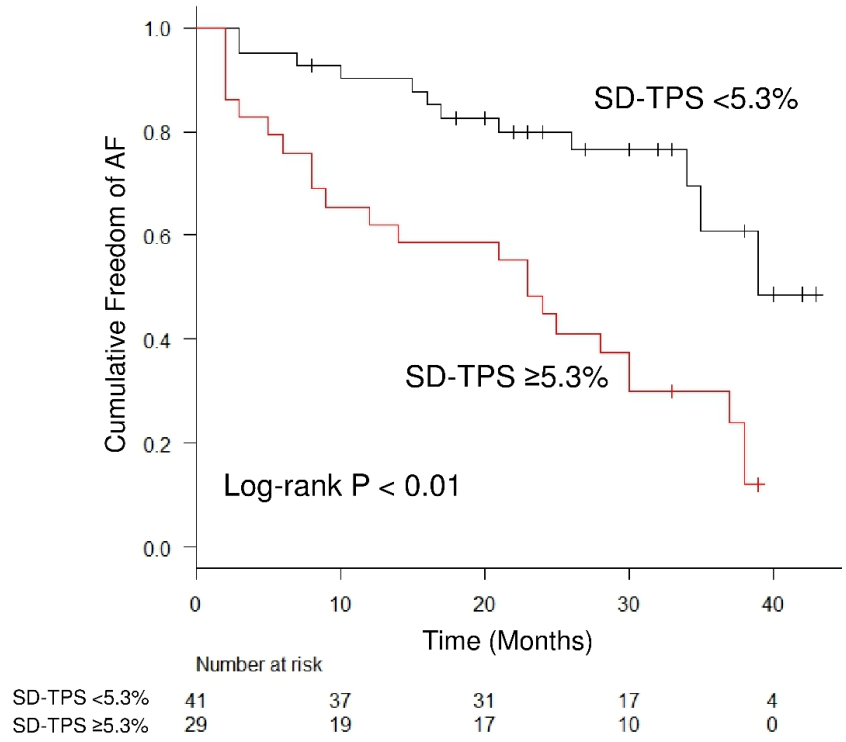


Figure 10.3 - Kaplan-Meier curves showing freedom from new-onset AF.

Patients with SD-TPS ≥5.3% had more AF events than patients with SD-TPS <5.3% (p<0.01). AF = atrial fibrillation; SD-TPS = standard deviation of the time to peak strain. SD-TPS was corrected by the R-R interval to derive SD-TPS as a percentage of the R-R interval.

Table 10-5 - Net reclassification table. The addition of SD-TPS to the model based on LAVI.

No new-onset AF (n = 35)	**LAVI + SD-TPS**		**Reclassified**		**Net correctly reclassified** (%)
	Low risk	High risk	Increased risk*	Decreased risk*	
LAVI					
Low risk	0	0	0	11	31.4
High risk	11	24			
New-onset AF (n = 35)	**LAVI + SD-TPS**		**Reclassified**		**Net correctly reclassified** (%)
	Low risk	High risk	Increased risk*	Decreased risk*	
LAVI					
Low risk	0	0	0	2	-5.7
High risk	2	33			
					Net reclassification improvement = 0.26 (P < 0.01)

AF = atrial fibrillation; LAVI = left atrial volume index; SD-TPS = standard deviation of the time to peak strain.

The risk for new-onset AF was stratified into low (0% to < 20%) and high risk (≥ 20%).

*The number of individuals who were reclassified upward and downward, respectively.

The net reclassification improvement is the sum of correctly reclassified individuals with and without new-onset AF.

Table 10-6 - Net reclassification table. The addition of SD-TPS to the model based on LARS.

	LARS + SD-TPS		Reclassified		
No new-onset AF (n = 35)	Low risk	High risk	Increased risk*	Decreased risk*	**Net correctly reclassified** (%)
LARS					
Low risk	5	0	0	7	20.0
High risk	7	23			
	LARS + SD-TPS		**Reclassified**		
New-onset AF (n = 35)	Low risk	High risk	Increased risk*	Decreased risk*	**Net correctly reclassified** (%)
LARS					
Low risk	1	0	0	1	-2.9
High risk	1	33			
					Net reclassification improvement = 0.17 (P = 0.02)

AF = atrial fibrillation; LA = left atrium; SD-TPS = standard deviation of the time to peak strain.

The risk for new-onset AF was stratified into low (0% to < 20%) and high risk (≥ 20%).

*The number of individuals who were reclassified upward and downward, respectively.

The net reclassification improvement is the sum of correctly reclassified individuals with and without new-onset AF.

Table 10-7 - Net reclassification table. The addition of SD-TPS to the model based on LAVI and LARS.

	LAVI + LARS + SD-TPS		**Reclassified**		
No new-onset AF (n = 35)	Low risk	High risk	Increased risk*	Decreased risk*	**Net correctly reclassified** (%)
LAVI + LARS					
Low risk	5	0	0	6	17.1
High risk	6	24			
	LAVI + LARS + SD-TPS		**Reclassified**		
New-onset AF (n = 35)	Low risk	High risk	Increased risk*	Decreased risk*	**Net correctly reclassified** (%)
LAVI + LARS					
Low risk	1	0	0	1	-2.9
High risk	1	33			
					Net reclassification improvement = 0.14 (P = 0.04)

AF = atrial fibrillation; LA = left atrium; LAVI = left atrial volume index; SD-TPS = standard deviation of the time to peak strain.

The risk for new-onset AF was stratified into low (0% to < 20%) and high risk (≥ 20%).

*The number of individuals who were reclassified upward and downward, respectively.

The net reclassification improvement is the sum of correctly reclassified individuals with and without new-onset AF.

10.6 Discussion

The principal finding of this study was that LA mechanical dispersion assessed by speckle tracking echocardiography is a useful predictor of new-onset AF, superior and incremental to and independent of clinical risk factors and conventional echocardiographic predictors including LA enlargement and dysfunction.

10.6.1 LA dispersion as a predictor of new-onset AF.

During the past 10 years, myocardial mechanical dispersion assessed by strain echocardiography has emerged as a useful tool to evaluate supraventricular and ventricular arrhythmias. Haugaa et al. have demonstrated that mechanical dispersion assessed in the LV was an independent and powerful predictor for ventricular arrhythmias in a variety of cardiovascular diseases (269-271). Similarly, LA dispersion is greater in patients with AF than in healthy individuals (274-277), and increases in proportion to the duration of AF (275). LA dispersion predicts progression from paroxysmal to persistent AF (278), and may predict recurrent AF after catheter ablation (276, 279). Importantly, LA dispersion can also detect LA functional impairment and asynchrony in patients without LA enlargement (274, 276, 279, 280) - indeed, in the present study, the average LAVI in the patients with new-onset AF was within the normal range. However, despite studies showing the association between LA dispersion and AF (274-280), only one previous study has linked LA dispersion to incident AF – but this used tissue Doppler imaging, and was limited to patients with HF (280). To our knowledge, this is the first study demonstrating that LA dispersion assessed by speckle-tracking echocardiography predicts the future development of new AF in a community-based cohort.

LA strain is inversely associated with LA fibrosis detected by cardiac magnetic resonance (CMR) (92, 273), and these imaging markers are related to AF burden (92). Furthermore, LA dispersion was a more specific marker of LA scarring evaluated by CMR than LA volume and global function in the patients undergoing AF ablation (273). In a study of electro-anatomical mapping and LA strain in patients undergoing AF ablation, LA dispersion was significantly increased in patients with low-voltage zones and the severity of LA dispersion was related to the LA conduction delay (272).

10.6.2 Clinical implications.

The findings in this study suggest that LA dispersion assessed by speckle tracking echocardiography may be a useful biomarker to estimate LA structural and electrical remodeling regardless of LA enlargement. In addition, recent studies demonstrated that LA dispersion has an incremental value over CHA_2DS_2-VASc score for predicting risk of thrombus formation in patients with AF (281). Based on these findings, the mean age (70 years) and CHA_2DS_2-VASc score (3.0) of the current cohort would suggest a significant risk of stroke if the individuals had AF, and better risk stratification may facilitate decision-making about AF prevention, and follow-up for early diagnosis. LA dispersion might the potential to contribute to the risk stratification for incident AF and for thrombus formation.

10.6.3 Limitations.

There are several limitations in the present study. First, the biggest limitation in the present study is that this is a case-control study of a small selected group. In addition, the number of AF cases in the cohort may have been underestimated because some AF events are asymptomatic. Although the association of LV abnormalities such as LV hypertrophy and dysfunction with incidence of AF are well-established (282, 283), there were no significant association between AF and LV mass index and GLS in this study. These discrepancy of results between the present and previous studies might be affected by the methods of patient selection. Further prospective multicenter studies are needed to confirm the external validity of our findings and translate LA dispersion into risk stratification for AF. Moreover, we did not compare of LA strain and dispersion with electrocardiographic parameters such as P wave duration and PR intervals, which are also established predictors of AF (284, 285). Further comparison of echocardiographic parameters to electrocardiogram's findings might be useful for better understanding the mechanics of arrhythmogenic substrate of AF. Second, it was difficult to select the optimal LA dispersion cutoff for predicting new-onset AF - the normal LA dispersion range is unknown and we applied a cutoff from a previous cross-sectional study (274). Although our cut-off value of SD-TPS completely consisted with the result of this previous study (274), ROC analysis in this study was used to derive optimal cutoff values and report those values in the same derivation cohort, rather than in an independent group of patients. This cut-off should be verified in other cohorts. Third, a specific software

for evaluating LA strain by speckle-tracking is not yet available; therefore, we analyzed LA strain using software for evaluating the LV. Vender differences may affect the cut-off of LA strain and SD-TPS. In addition, the difference between tracking technologies, edge-tracking and speckle-tracking should be considered in strain assessment. However, we thought the effect different of both was limited because the wall thickness in LA was very thin (286). Finally, strain imaging, like other imaging techniques, is operator dependent. However, there was no evidence of large difference during our validation study (supplementary figure 10.4).

10.7 Conclusions

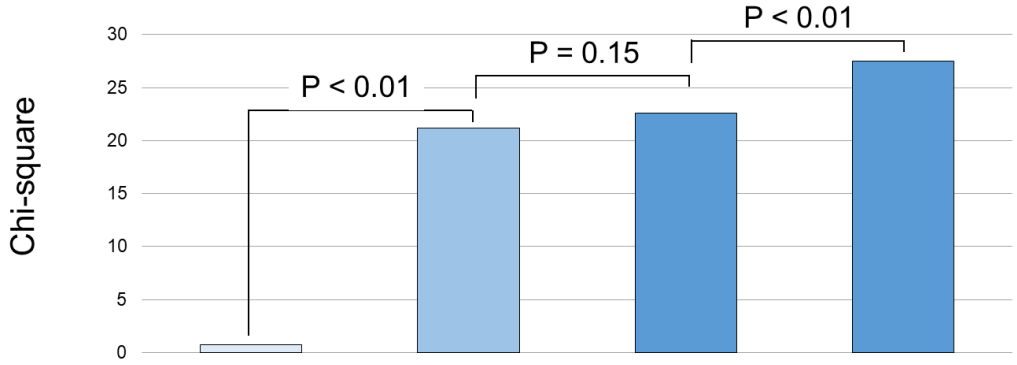
LA dispersion assessed by speckle tracking echocardiography is a predictor of new-onset AF, superior and incremental to and independent of clinical risk factors and conventional echocardiographic predictors including LA enlargement and dysfunction.

10.8 Appendix

Table 10-8 (Supplementary Table) - The results of linear regression analysis.

The strength of the relation between SD-TPS and other echocardiographic parameters was expressed using r value.

Variable	r	P
LVEF	-0.384	< 0.01
GCS	0.083	0.49
GLS	0.342	< 0.01
E/e’	0.219	0.07
LAVI	0.196	0.10
LA pump strain	-0.249	0.04
LARS	-0.385	< 0.01



Variable	Model 1 Chi-square = 0.7 HR (95%CI), P value	Model 2 Chi-square = 21.2 HR (95%CI), P value	Model 3 Chi-square = 22.6 HR (95%CI), P value	Model 4 Chi-square = 27.5 HR (95%CI), P value
CHARGE-AF score (per 1 point increase)	0.97 (0.91-1.04), P = 0.41	0.96 (0.89-1.03), P = 0.23	0.95 (0.88-1.02), P = 0.15	0.93 (0.85-1.00), P = 0.06
SD-TPS (per 1% increase)		**1.34 (1.18-1.53), P < 0.01**	**1.32 (1.16-1.51), P < 0.01**	**1.26 (1.10-1.45), P < 0.01**
LAVI (per 1 ml/m^2 increase)			1.03 (0.99-1.07), P = 0.13	1.00 (0.96-1.05), P = 0.99
LA reservoir strain (per 1 % increase)				**0.92 (0.86-0.98), P < 0.01**

Figure 10.4 (Supplemental) - Incremental value of SD-TPS over existing indices.

A comparison is made with CHARGE-AF score, LAVI, and LARS in risk stratification for new-onset AF

Table 10-9 (Supplementary Table) - Univariable and multivariable Cox regression analysis for new-onset AF.

	Univariable		Multivariable					
			Clinical Model		Medical Model		Echo Model	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
BMI	1.00 (0.94-1.07)	0.94	0.98 (0.91-1.06)	0.65				
CHA2DS2Vasc score	1.05 (0.76-1.45)	0.79	0.86 (0.57-1.30)	0.47				
CHARGE-AF score	0.97 (0.90-1.04)	0.41	0.94 (0.86-1.03)	0.16				
ACE inhibitors or ARBs	1.58 (0.81-3.10)	0.18			1.64 (0.79-4.03)	0.16		
β-blockers	0.57 (0.22-1.50)	0.26			1.37 (0.40-4.69)	0.61		
Calcium blocker	1.58 (0.61-4.09)	0.35			1.50 (0.56-4.05)	0.42		
LVEF	0.96 (0.91-1.01)	0.08					1.02 (0.96-1.08)	0.59
LAVI	1.04 (1.00-1.07)	0.04					1.00 (0.95-1.08)	0.88
LARS	0.92 (0.88-0.96)	< 0.01	0.90 (0.85-0.94)	< 0.01	0.91 (0.87-0.96)	< 0.01	0.93 (0.86-0.99)	0.02
SD-TPS	1.32 (1.17-1.50)	< 0.01					1.28 (1.08-1.51)	< 0.01

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; CI = confidence interval; GLS = global longitudinal strain; HR =hazard ratio; LA = left atrium; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; SD-TPS = standard deviation of the time to peak strain.

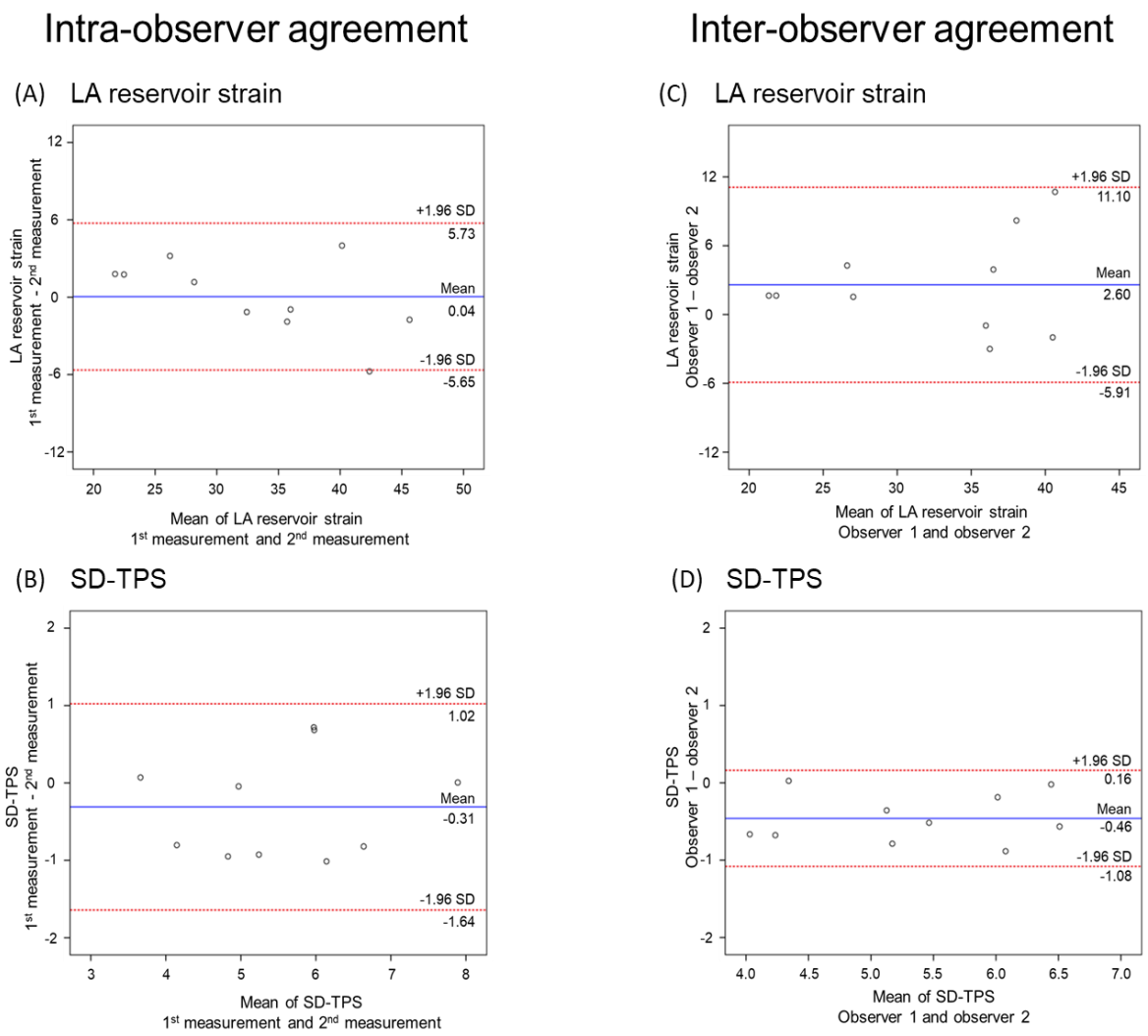


Figure 10.5 (Supplemental) - The Bland-Altman plots.

10.9 Postscript

This chapter demonstrated a potential role for LA mechanical dispersion in AF prediction, independent of LA volume and strain. These three components may provide a sensitive assessment of LA remodelling which may have a useful role in AF prediction. LA volume may a good marker of chronicity. LA strain provides quantitative assessment of phasic LA function, whilst LA mechanical dispersion may provide a non-invasive assessment of LA fibrosis. Given the small numbers, this was a proof of concept study and requires investigation in a larger cohort study to determine its clinical significance.

Having investigated screening technologies, patient selection and novel imaging techniques for AF risk assessment, in the next two chapters we will investigate the feasibility of AF screening. In the next chapter we perform a decision model analysis to determine cost-effectiveness of an imaging guided AF screening strategy compared with an age-based screening model.

Section IV – Feasibility of AF screening

Chapter 11

Selection of Candidates for a Screening Strategy for AF based on opportunistic use of data from previous imaging.

"Cost-effectiveness of Screening for Paroxysmal Atrial Fibrillation in Patients undergoing Echocardiography."

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11 Selection of candidates for a screening strategy for AF based on opportunistic use of data from previous imaging.

11.1 Preface

The cost-effectiveness of AF screening programs has been demonstrated in previous studies (8, 78, 79). Most studies have adopted an age-based cut-off (usually 65 or 75 years). Single lead ECG monitoring devices have typically been used in recent screening studies. We have demonstrated in previous chapters that imaging can be used for AF risk stratification. Doing echocardiograms in asymptomatic patients for AF screening is not realistic. However, echocardiograms are currently done in patients with risk factors for AF. Most echo labs have databases of patients that have imaging parameters associated with increased AF risk. Combining this with clinical risk factors can potentially improve cost-effectiveness further and have improved AF yields with screening.

In this chapter we explore the cost-effectiveness of an imaging guided AF screening strategy compared with an age-based screening model. The results from this chapter were presented at the American Heart Association Annual Scientific Sessions in 2019.

11.2 Abstract

Background. Many patients at risk of atrial fibrillation (AF) have echocardiograms for other reasons, and this test can quantify their risk of AF. We compared the cost-effectiveness of echocardiographic guidance with unselected screening with portable electrocardiographic (ECG) monitoring devices.

Methods. In the base case of a 65-year-old man (CHA_2DS_2-VASC score 3) at risk of AF, based on hypertension and diabetes mellitus, two strategies of portable ECG screening for AF were compared in asymptomatic patients ≥65 years with a previous echocardiogram but without a cause for AF (e.g. mitral valve disease, LV dysfunction). With age-based screening (AgeScreen), all patients underwent ECG, and we expected a 3% AF detection rate. With imaging-guided screening (ImagingScreen; 5% detection rate), only patients with left atrial volume (LA) ≥34ml/m^2 and LARS <34% or LV global longitudinal strain (GLS)>-18% underwent portable ECG screening. A Markov decision-analysis model was constructed using data from published literature on the costs/quality-adjusted life years (QALY). Costs, effects and incremental cost-effectiveness ratio (ICER) were assessed for each screening strategy over a 20-year period. The willingness-to-pay threshold was $53,000/QALY gained.

Results: In the reference case an ImagingScreen approach (11.56 QALY, $54,823 cost over 20 years) was more cost-effective than AgeScreen (11.52 QALY, $57,842 over 20 years). Monte Carlo simulation demonstrated that 61% of observations were more efficacious with ImagingScreen, with cost below willingness-to-pay. The main cost determinants were annual costs of stroke or HF and AF detection rates. ImagingScreen was more cost-effective across a range of annual stroke ($24,000-$102,000) and HF ($4,000-$12,000) costs. ImagingScreen was more cost-effective for AF detection rates up to 14%, after which AgeScreen became more cost-effective.

Conclusion: In patients with a previous echocardiogram, targeting AF screening to those with baseline clinical and imaging risk parameters is more cost-effective than age-based screening programs.

11.3 Introduction

Current European guidelines recommend routine atrial fibrillation (AF) screening for patients ≥ 65 years using a rhythm strip or pulse palpation (57), supported by recent trials demonstrating feasibility and cost-effectiveness (2, 70, 71, 80) of screening technologies such as smartwatches or portable ECG monitoring devices. Early AF diagnosis through active screening programs may encourage enrolment in lifestyle modification programs, which have been shown to benefit patients following catheter ablation (52), and anticoagulation is expected to reduce thromboembolic complications. AF fulfills most of the criteria for mass screening outlined by Wilson and Junger (287), but these recommendations for screening have not been endorsed in the United States or United Kingdom (58). A major reservation has pertained to defining the most appropriate cohort for screening, as the possibility of misdiagnosis is greatest in low risk patients. Most studies have either adopted arbitrary age based cut-offs (usually 65-75 years) (70, 71) while other studies have performed screening on consecutive patient irrespective of age or baseline AF risk (69). Targeted screening to those at highest risk will likely improve AF yield, potentially improving cost-effectiveness.

AF most commonly occurs in the setting of abnormal atrial structure and function, which can readily be detected by transthoracic echocardiography (TTE). Although many indications for TTE are associated with AF (e.g. symptomatic HF or valvular disease), many TTE are performed for the investigation of nonspecific symptoms, and >40% are normal (8, 288). Incidental findings of LA enlargement, LV hypertrophy or subclinical LV dysfunction are common, and we have proposed that echocardiography reports should provide commentary about AF risk (251). Many echo labs have large databases of patients with both clinical and imaging risk factors for AF. Therefore, targeted selection of this enriched cohort of patients for AF screening may improve detection rates, thereby improving cost effectiveness. In this study, we hypothesized that patients >65 years old with echocardiographic features of risk may be an appropriate cohort for AF screening, and we sought the cost-effectiveness of this approach.

11.4 Methods.

11.4.1 Screening strategies.

We developed a decision analytic model accounting for mortality, cardiovascular complications and medication complications following a screening strategy based on portable ECG monitoring devices with multiple intermittent recordings (usually 4/day) over a 2-week period. The model was restricted to patients without pre-existing AF or a known cause of AF (such as mitral valve disease or LV dysfunction) aged ≥65 years, who had undergone a previous TTE (for any indication). Two selection strategies were compared:

1) AgeScreen – All patients screened in a community/pharmacy or general practitioner setting. Based on a large population based study (which used 75-76 year old participants), the average new AF detection rate was estimated at ~3% (71).
2) ImagingScreen – In this echo-based model, AF screening was restricted to patients who had incidental LA enlargement (≥34 ml/m^2) with either subclinical LV (global longitudinal strain (GLS) >-18%) or LA dysfunction (LARS <34%). We estimated that the AF detection rate was at least 5% based on our previously published AF screening studies (248, 251).

11.4.2 Decision Tree.

The base case was a 65-year-old man (the age cut-off where routine AF screening is recommended) with a history of diabetes mellitus and hypertension (i.e. CHA_2DS_2-VASC score of 3). At the start of the decision tree, the base case was assigned one of the two screening strategies. The potential transition states of the Markov model are shown in figure 11.1. Patients diagnosed with AF were treated with anticoagulation (using a direct oral anticoagulant, DOAC). The rate of anticoagulant prescription and discontinuation rate was obtained from published real-world registry studies (289, 290). Modelling was performed for 20 years; the cycle length was assumed to be one year.

11.4.3 Health Transitions.

The main clinical outcomes included death, stroke, HF, myocardial infarction and major bleeding including intracerebral hemorrhage. Transitions between health states (annualized probabilities) were

obtained from the medical literature and shown in Table 11-1. Definitions of stroke and major bleeding/intracerebral hemorrhage were adapted from previous DOAC trials for non-valvular AF (53, 54). HF was defined by guideline diagnostic criteria (291). If data was unavailable, we made assumptions based on available evidence and expert consensus.

11.4.4 Cost and utilities.

Costs and health utility data (Tables 11-2 and 11-3), obtained from the medical literature, were attributed as patients progressed through various health states. Health utility data ranged from 0 (dead) to 1 (healthy). Costs were calculated and expressed in US dollars (USD), and cost analysis was based on the perspective of the government/healthcare payer. Costs and benefits (based on quality adjusted life years - QALY) were measured over the 20-year lifecycle; the discount rate for all future costs and benefits was assumed at 3% per annum. A willingness to pay (WTP) threshold of $53,000 per QALY was applied to the analysis, based on the per capita gross domestic product in many Western countries (292).

11.4.5 Sensitivity analysis.

Sensitivity analysis was performed to explore the impact of variation in major health transition probabilities, costs and utilities. Standard errors and ranges were based on previously published literature. One-way sensitivity analysis was performed and represented as a tornado diagram to show the impact of these variations on overall cost analysis. One-way sensitivity analysis evaluating net monetary benefits (NMB) was performed across a range of AF detection rates for echo-based AF screening (ImagingScreen) using a WTP of $53,000 to determine which screening strategy was superior. One-way sensitivity analysis was also performed across a wide range of annual stroke follow-up costs to assess the effect on cost analysis.

11.4.6 Monte-Carlo simulation.

Monte Carlo simulation was performed using TreeAge Pro 2019 (TreeAge Software Inc. Williamtown, MA) to assess changes to clinical outcomes and costs based on both screening strategies using a

hypothetical cohort of 10,000 patients using probabilistic sensitivity analysis. Annual probabilities of events/clinical outcomes along with utilities were assigned beta distributions whilst costs of investigations and clinical outcomes were assigned gamma distributions. Cost-effectiveness acceptability curves were used to assess both screening strategies to determine the most cost-effective option based on the probability that the incremental cost-effectiveness ratio (ICER) was below the WTP threshold. An ICER scatterplot generated from probabilistic sensitivity analysis was created to compare both screening strategies. This study was conducted in accordance with the Consolidated Health Evaluation Reporting Standards (CHEERS) guidelines (293).

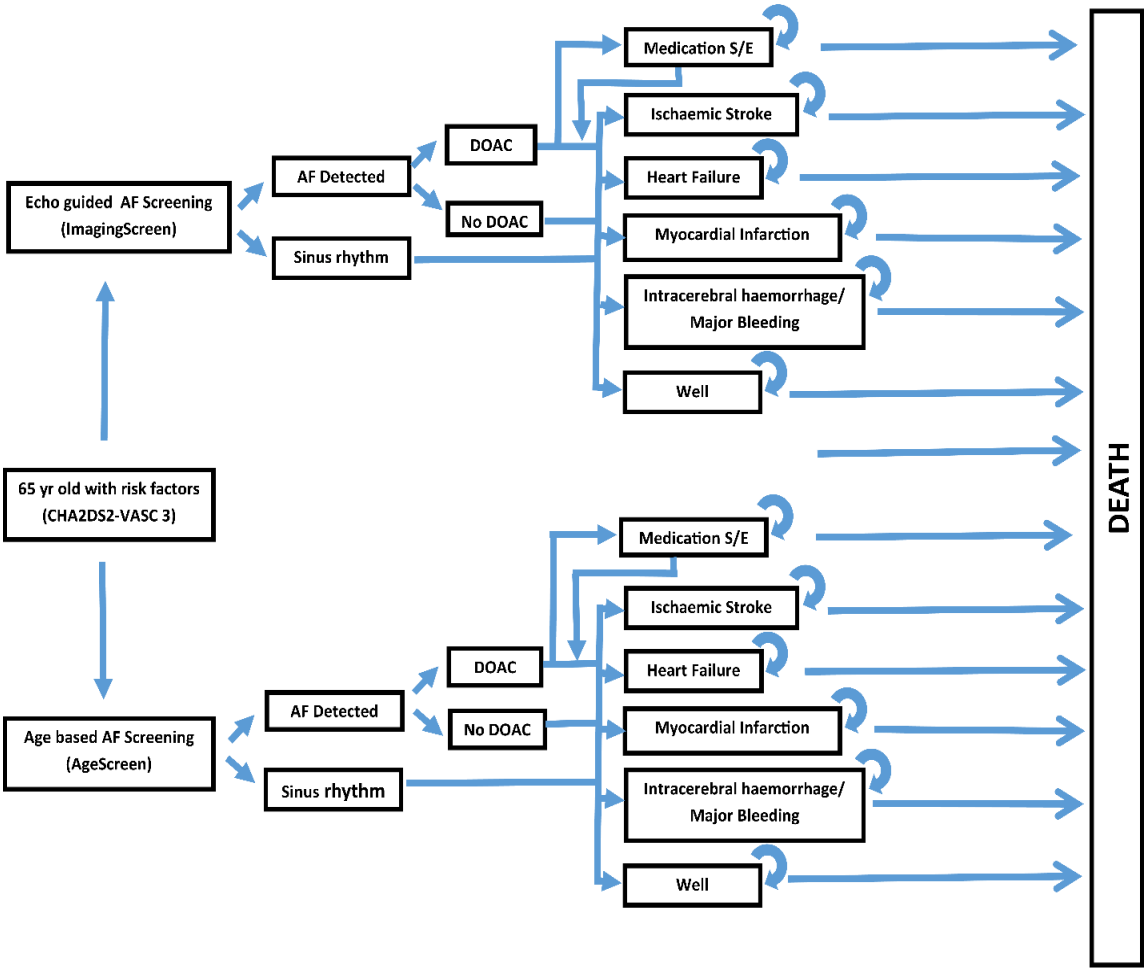

Figure 11.1 - Bubble diagram representing the transition states and clinical outcomes in both screening strategies.

The main outcomes of interest were death, ischaemic stroke, myocardial infarction, HF and major bleeding including intra-cerebral hemorrhage.

Table 11-1 - Values for annual transition probabilities.

Variable (annual probabilities)	Base value	Range		Source
		Minimum	Maximum	
AF Detection				
Age based screening ≥ 65 yrs	0.031	0.03	0.038	(70, 71)
Targeted risk-based screening	0.05	0.03	0.20	(248, 251)
DOAC Use				
DOAC prescribed for AF	0.88	0.85	0.95	(289)
DOAC refused/not prescribed	0.12	0.10	0.14	(289)
DOAC Discontinued	0.17	0.12	0.23	(53, 290)
Outcomes in AF patients on DOAC therapy				
Ischaemic Stroke	0.0088	0.008	0.010	(54, 294)
Mild/non-disabling Stroke	0.506	0.428	0.594	(53, 295, 296)
Disabling stroke	0.392	0.343	0.441	(295, 296)
Fatal stroke	0.102	0.075	0.129	(53, 295, 296)
Major Bleeding	0.026	0.021	0.031	(53, 54)
Fatal hemorrhage	0.069	0.048	0.097	(53, 54)
Discontinue DOAC following major bleed	0.50	0.40	0.80	a
Intracerebral Hemorrhage	0.0053	0.002	0.011	(53, 295)
Fatal intracerebral hemorrhage	0.42	0.35	0.60	(296, 297)
Disabling stroke	0.58	0.40	0.70	(296, 297)
Myocardial infarction	0.007	0.004	0.009	(53, 54, 294, 298)
Fatal myocardial infarction	0.078	0.05	0.10	(294, 299)
Progression to HF	0.20	0.10	0.30	a
HF	0.012	0.012	0.029	(300)
Fatal HF	0.2746	0.25	0.69	(300)
Refractory HF	0.20	0.10	0.30	a
Non cardiac Death	0.012	0.012	0.015	(300)
Outcomes in AF patients not on DOAC therapy				
Ischaemic Stroke	0.037	0.025	0.055	(79, 301)
Mild Stroke	0.405	0.40	0.42	(79, 301)
Disabling stroke	0.378	0.36	0.382	(79, 301)
Fatal stroke	0.216	0.21	0.24	(79, 301)
Major Bleeding	0.0056	0.0009	0.034	(79, 301)
Fatal hemorrhage	0.178	0.059	0.556	(79, 301)
Intracerebral hemorrhage	0.0025	0.0012	0.0037	(79, 301)
Fatal intracerebral hemorrhage	0.42	0.35	0.60	(296, 297)
Disabling stroke	0.58	0.40	0.70	(296, 297)
Myocardial infarction	0.029	0.012	0.073	(79, 301)
Fatal myocardial infarction	0.10	0.05	0.15	a
Progression to HF	0.20	0.10	0.30	a
HF	0.012	0.012	0.029	(300)
Fatal HF	0.2746	0.25	0.69	(300)
Refractory HF	0.20	0.10	0.30	a
Non cardiac Death	0.012	0.012	0.015	(300)
Outcomes in patients with sinus rhythm				
Ischaemic Stroke (ImagingScreen)	0.0152	0.012	0.02	a
Ischaemic stroke (AgeScreen)	0.0168	0.015	0.02	a
Mild Stroke	0.506	0.428	0.594	a

Disabling stroke	0.392	0.343	0.441	a
Fatal stroke	0.102	0.075	0.129	a
Major Bleeding	0.0056	0.0009	0.034	a
Fatal hemorrhage	0.178	0.059	0.556	a
Intracerebral hemorrhage	0.0025	0.0012	0.0037	(79, 301)
Fatal intracerebral hemorrhage	0.42	0.35	0.60	(296, 297)
Disabling stroke	0.58	0.40	0.70	(296, 297)
Myocardial infarction	0.019	0.015	0.023	(302)
Fatal myocardial infarction	0.10	0.05	0.15	a
Progression to HF	0.20	0.10	0.30	a
HF	0.01	0.005	0.015	(303, 304)
Fatal HF	0.20	0.10	0.30	a
Refractory HF	0.20	0.10	0.30	a
Non cardiac Death	0.012	0.012	0.015	a

DOAC – Direct oral anticoagulant

Table 11-2 - Values for utilities.

Variable (annual probabilities)	Base value	Range		Source
		Minimum	Maximum	
Well – sinus rhythm	0.998	0.994	1.0	(305)
Well – AF	0.994	0.975	1.0	(305)
Mild stroke	0.75	0.60	0.81	(79, 306)
Disabling stroke	0.45	0.36	0.47	(79, 306)
HF	0.83	0.82	0.83	(307)
Refractory HF	0.60	0.52	0.74	(292, 308)
Myocardial infarction	0.84	0.0	1.0	(294, 309)
Major hemorrhage	0.80	0.50	0.99	(305)
Side effects of medications	0.95	0.92	0.98	a
Death	0.0	0.0	0.0	

Table 11-3 - Values for annual costs (USD).

Variable (annual probabilities)	Base value (USD)	Range		Source
		Minimum	Maximum	
Investigations				
Single lead ECG monitoring	100	50	300	a
Transthoracic Echocardiogram	250	100	400	(310)
One Time costs				
Ischaemic stroke (mild)	9400	4000	16000	(296, 311)
Ischaemic stroke (disabling)	13900	10000	25000	(296, 311)
Fatal stroke	11171	5000	15000	(312)
Myocardial Infarction	19100	15000	25000	(296, 313)
Fatal myocardial infarction	5829	4000	8000	(312)
HF/Fatal HF	18158	12148	26595	(307)
Major hemorrhage	5600	2000	8000	(296)
Fatal Major hemorrhage	10425	8000	15000	(296)
Intracerebral hemorrhage	39100	15000	65000	(296, 311)
Non-cardiac death	10000	1000	20000	(296, 314)
Medication side effects	500	200	1000	a
Yearly costs				
Ischaemic stroke (mild)	20880.24	12000	48000	(294)
Ischaemic stroke (disabling)	64629.36	24000	102000	(294)
Myocardial Infarction	3638.40	1568.28	7267.68	(294, 305)
HF	7000	4000	12000	(292, 315)
DOAC	3920	1825	5475	(294)
Discount Rate (%)	3.0	0.0	5.0	(316)

11.5 Results

11.5.1 Health outcomes and costs.

Results of cost-effectiveness analysis are summarized in Table 11-4. Based on the reference case (65-year-old man without a history of AF with risk factors of hypertension and diabetes mellitus), ImagingScreen ($54,823, 11.56 QALY over 20-year cycle) was superior to AgeScreen ($57,842, 11.52 QALY over a 20-year cycle).

Table 11-4 - Deterministic cost-effectiveness results in both strategies.

Strategy	Total costs (USD)	Total QALYs	ICER (USD/QALY) vs echo-based screening
ImagingScreen	54,823	11.56	
AgeScreen	57,842	11.52	-75,540

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year.

11.5.2 Sensitivity analysis.

Figure 11.2 shows the impact of variations in the assumptions on the overall cost-effectiveness analysis. Stroke outcomes and costs had the greatest impact on cost analysis. The variables which had the greatest impact on cost-effectiveness included annual follow-up costs for stroke and HF, AF detection rate and the rate of disabling stroke. The impact of the AF detection rate in ImagingScreen was explored using one-way sensitivity analysis (figure 11.3). ImagingScreen dominated AgeScreen for AF detection rates <14%, above which, AgeScreen was more cost-effective.

The variation in annual follow-up costs for disabling stroke cost was explored in a one-way sensitivity analysis (figure 11.4). ImagingScreen dominated AgeScreen for all possible costs for annual stroke follow-up. The same findings pertained to annual follow-up costs for HF and myocardial infarction.

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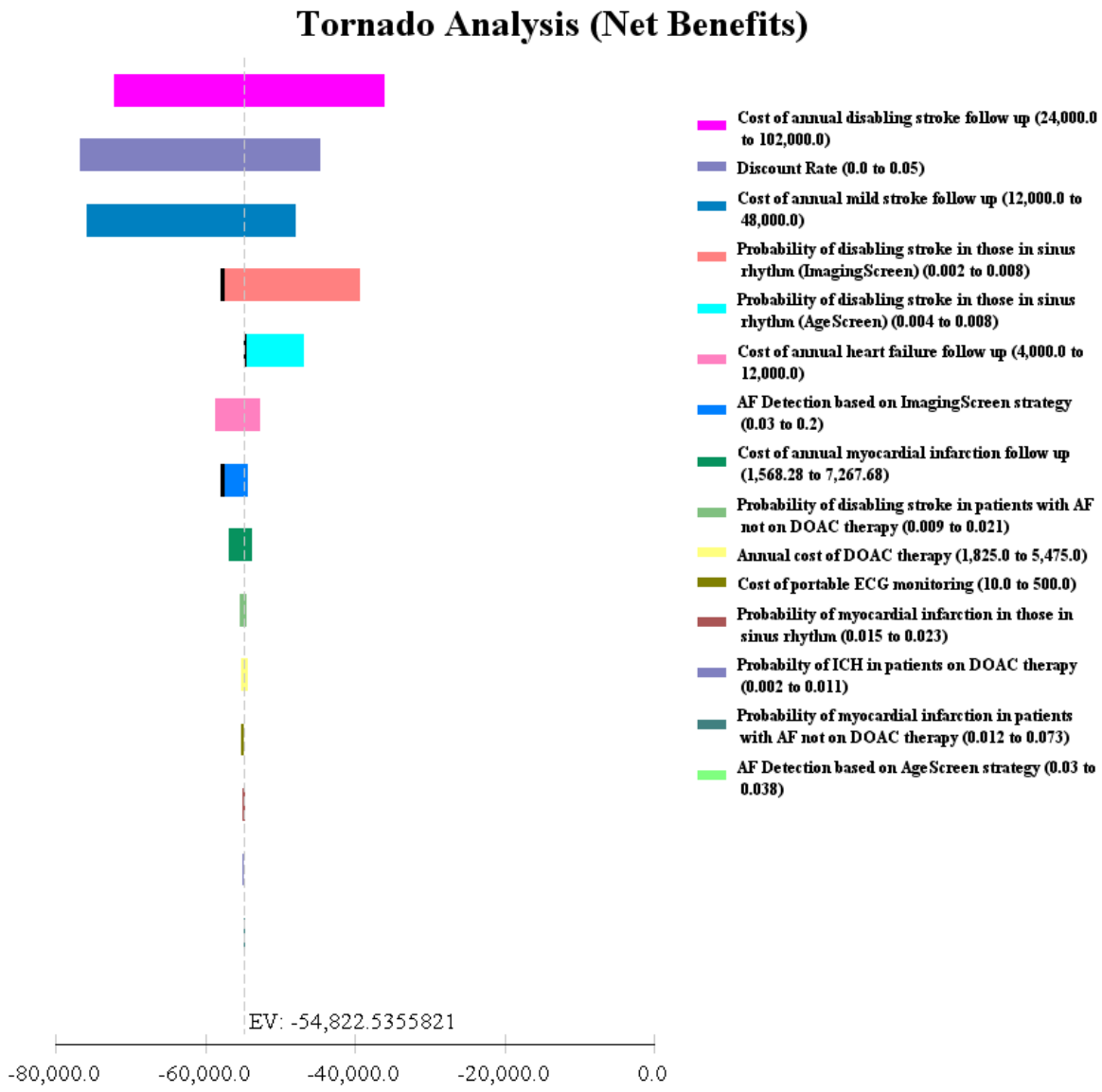

Figure 11.2 - Tornado diagram demonstrating influence of costs and utilities.

The main determinants of costs include annual stroke and HF costs, AF detection rate for ImagingScreen approach and stroke rate in those in sinus rhythm in both screening strategies.

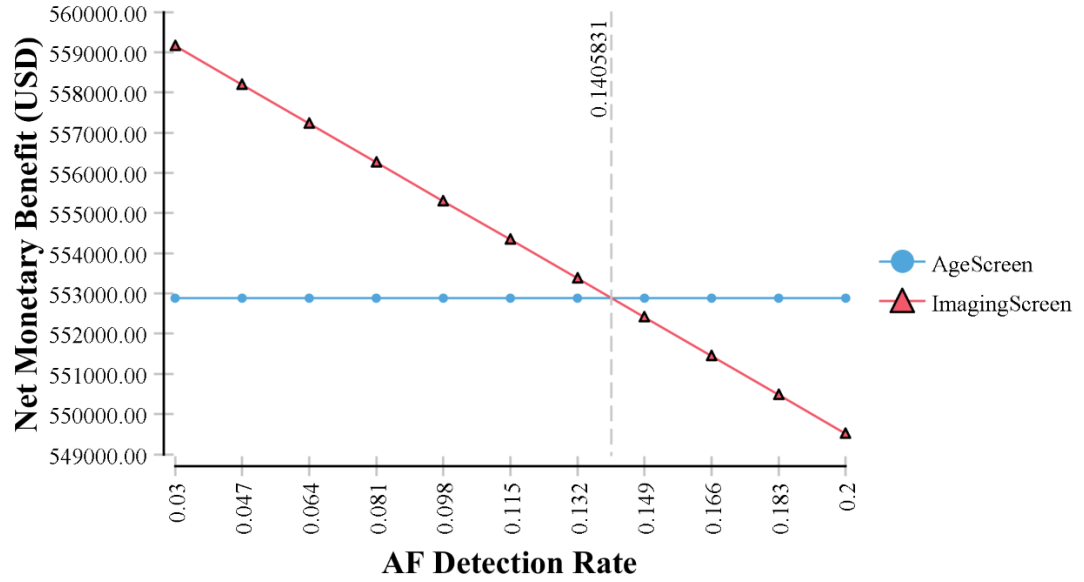

Figure 11.3 - One-way sensitivity analysis showing the NMB across a range of AF detection rates for ImagingScreen (assuming WTP $53,000/QALY).

AgeScreen yielded higher NMB than ImagingScreen once the AF detection rate was >14%.

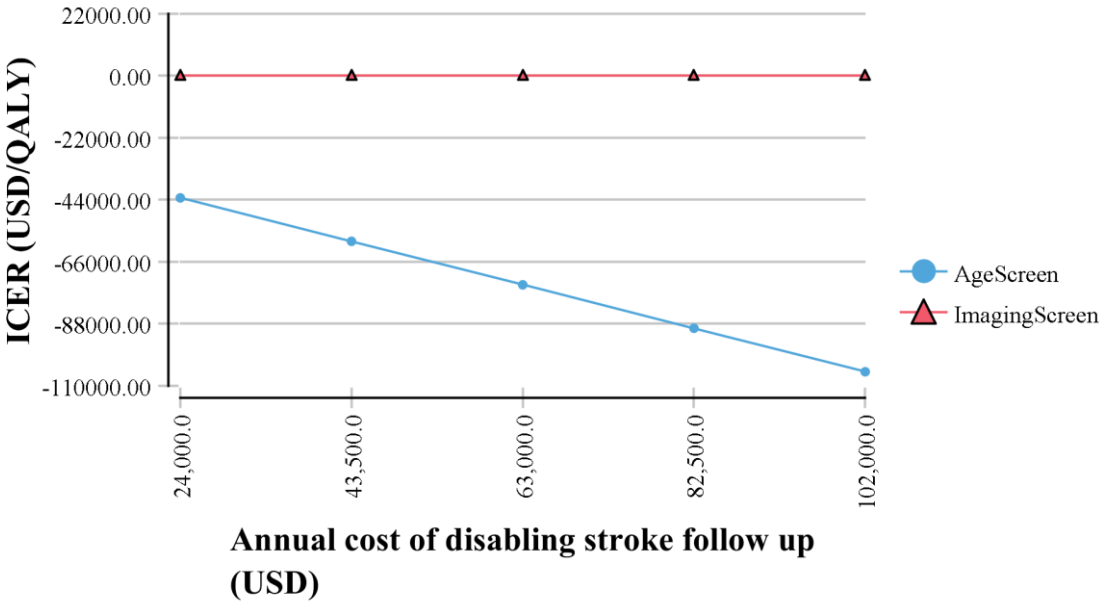

Figure 11.4 - One-way sensitivity analysis showing the incremental cost-effectiveness ratio (ICER) across a range of annual disabling stroke follow up costs.

Imaging Screen more cost-effective than AgeScreen for all possible annual disabling stroke follow up costs.

11.5.3 Monte Carlo simulation.

Monte Carlo simulation (10,000 simulations) was used to explore the effect of uncertainty in transition probabilities, utilities and costs to the overall cost-analysis model. A cost-effectiveness acceptability curve (figure 11.5) demonstrated that ImagingScreen was consistently more cost-effective than AgeScreen across a range of possible WTP (from $0 to $100,00 per annum). An ICER scatterplot (figure 11.6) demonstrated with a moderate level of confidence that ImagingScreen was more cost-effective compared to AgeScreen, with 61% of observations more efficacious with cost below WTP.

We also compared ImagingScreen to a single time point screening of all patients ≥65 yrs (either by pulse palpation or rhythm strip). We assumed that 20% of patients ≥65 yrs would have had a TTE performed. ImagingScreen was more cost-effective with 71% of observations more efficacious with cost below WTP (figure 11.7).

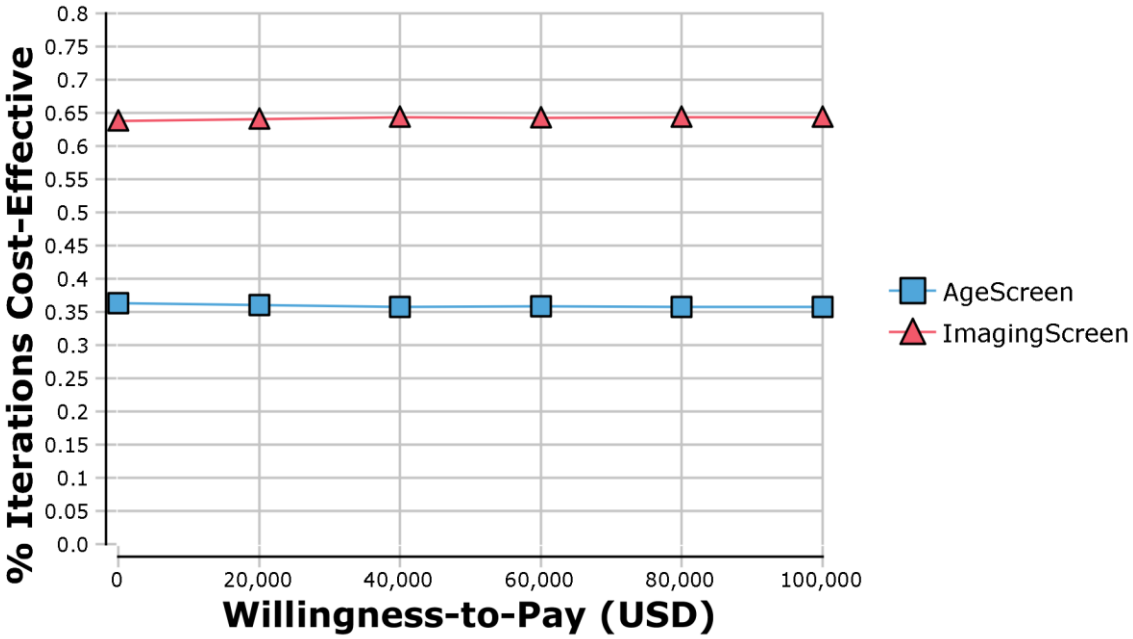

Figure 11.5 - Cost-effectiveness acceptability curve based on 10,000 Monte Carlo simulations based on input transition probabilities and utilities/costs.

ImagingScreen was consistently the more cost-effective screening strategy across a range of WTP figures.

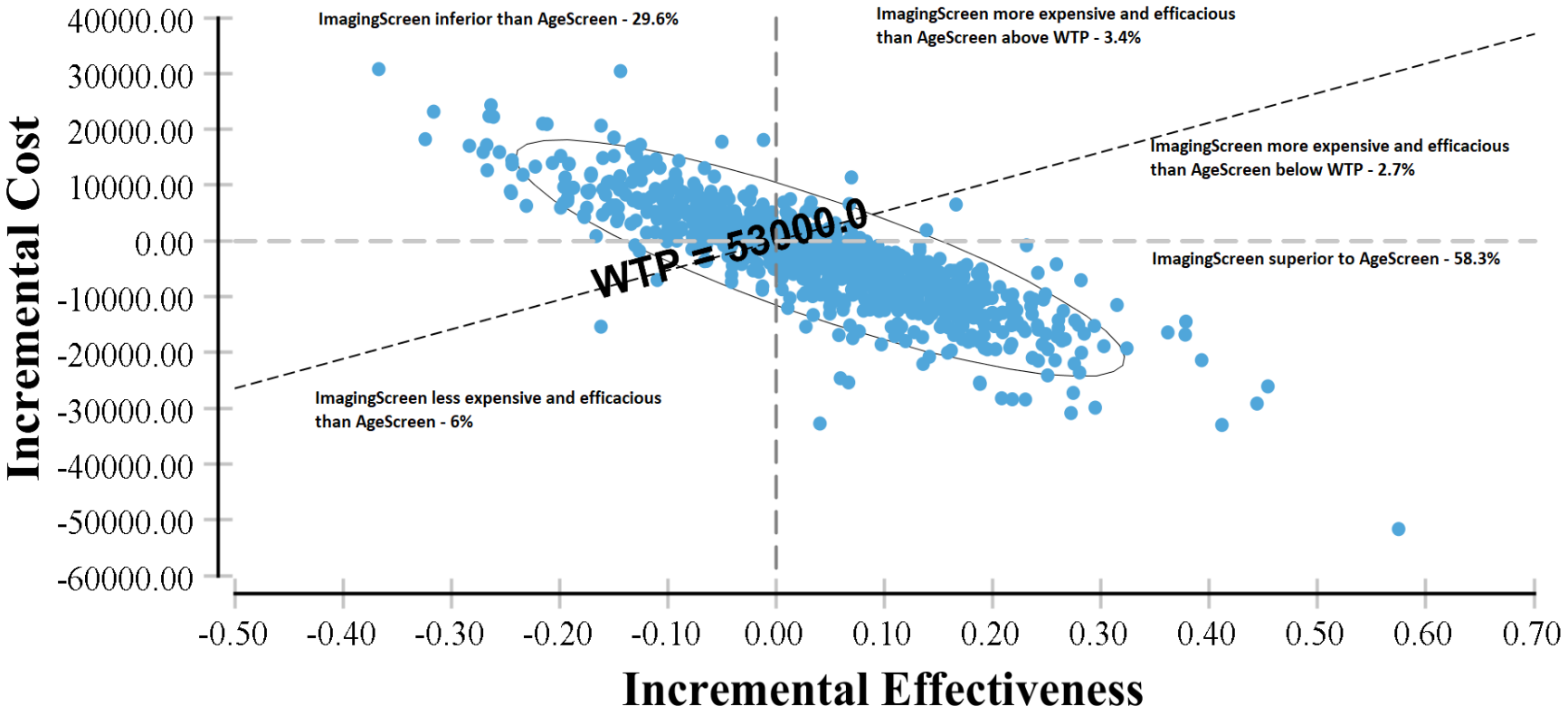

Figure 11.6 - Incremental Cost-Effectiveness Scatterplot generated from probabilistic sensitivity analysis comparing ImagingScreen and AgeScreen

61% of ImagingScreen observations were more efficacious than AgeScreen with costs below WTP.

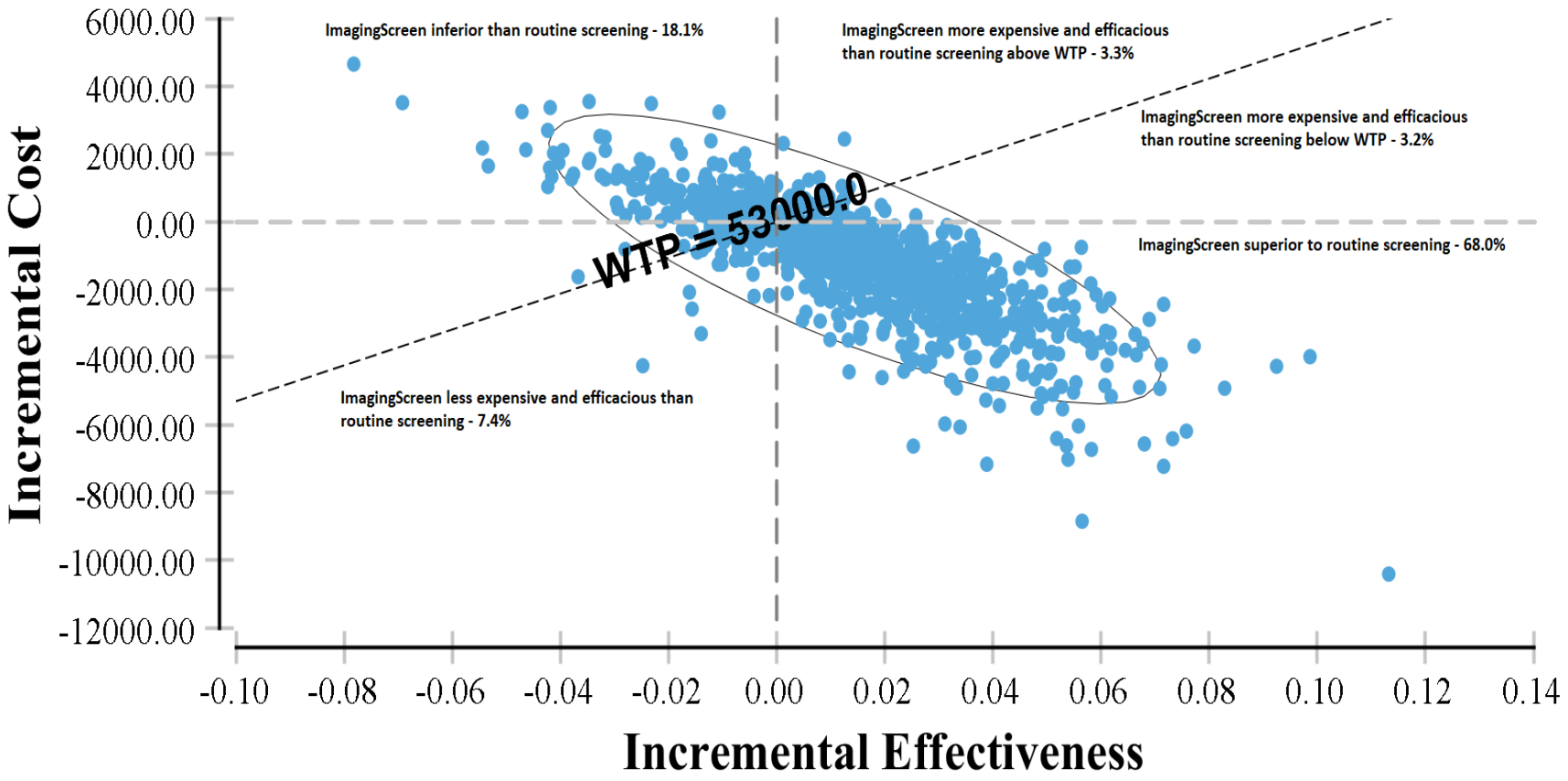

Figure 11.7 - Incremental Cost-Effectiveness Scatterplot generated from probabilistic sensitivity analysis comparing ImagingScreen with single time-point screening of all patients ≥ 65 yrs (either by pulse palpation or rhythm strip - assuming 1% AF detection)

71% ImagingScreen observations were more efficacious than AgeScreen with costs below WTP.

11.6 Discussion

In this study for our base case, we found that an echo guided AF screening strategy (ImagingScreen) dominated an age-based (AgeScreen) screening approach with small savings in QALY and costs. The main driver in cost-effectiveness was a reduction in disabling stroke and stroke mortality with the use of anticoagulants. On Monte Carlo simulation, ImagingScreen was more often the optimal strategy compared with AgeScreen. Sensitivity analysis demonstrated that the main parameters which effected cost analysis were annual stroke follow-up costs, AF detection rates and the rate of disabling stroke.

11.6.1 The role for AF screening.

AF is a leading cause of stroke and HF, placing a tremendous burden on the health care system, with rising costs and hospitalizations (12). Despite not having randomized control trial evidence of a role for anticoagulation in subclinical AF, there is interest in screening and treatment because these patients do not have a benign course and may have increased mortality and stroke risk (55). Early diagnosis allows for aggressive risk factor modification (to control AF progression), may motivate patients to initiate lifestyle modification, and may allow for initiation of anticoagulation thereby possibly lowering thromboembolic complications.

Despite growing interest in the role for mass AF screening, there remains some discrepancy in clinical guideline recommendations. AF satisfies most of the criteria outlined by Wilson and Junger (287). Following recent large AF screening studies, the European Society of Cardiology advocated for routine screening for AF in patients ≥65 years either by pulse palpation or by a rhythm strip (57). Recent cost analysis studies have confirmed the cost-effectiveness of this approach (80). However, AF screening is currently not recommended in the UK or US guidelines due to concern of both false positive/false negative findings as well as lack of feasibility (8, 58). We have previously shown that portable ECG devices may provide similar detection rates to 24 hour Holter monitoring (240). Technological advances have also allowed for simpler, more accurate and inexpensive methods of screening such as smartwatches or patches (167). This study adds to the growing body of literature highlighting the feasibility and cost-effectiveness of AF screening, but now proposes a more selective approach.

11.6.2 Echo guided AF screening.

Most AF screening studies to date have assessed opportunistic screening for patients with a predetermined age cut-off (65-75 years) in a variety of settings (primary Care practices, pharmacies, flu vaccination programs, community health programs) (8, 69). These programs have even been adopted by some countries for mass screening (244).

Selecting patients who have undergone a previous echocardiogram may provide an alternative enriched cohort for AF screening. Patients are often referred for TTE based on nonspecific symptoms such as dyspnea. In this cohort of patients, the echocardiogram provides information about the main drivers of risk (age, clinical risk factors and signs of LA remodeling or structural heart disease), which is currently not being utilized clinically. We are proposing targeting mass screening programs to patients at the highest risk, which is a potential way to reduce false positive scan results and minimize costs.

Assessment of LA and LV strain is reproducible, virtually cost-free and requires a modest training commitment prior to implementation. Assessment of myocardial deformation provides a sensitive assessment of LV and LA function which may help identify patients with subclinical LA/LV dysfunction and has important clinical applications in AF and HF (5). When these imaging markers are combined with an individual's clinical risk, they provide a powerful AF risk algorithm which may be very useful in mass screening.

It is not uncommon for echo labs to have databases of thousands of patients who are elderly, have clinical risk factors for AF and have findings of LA enlargement and reduced LV/LA strain. The results from our study have two important clinical applications. First, this group of patients are a suitable cohort to target for AF screening. The results of our analysis suggest that targeting this group provides better cost-effectiveness than selection based only on age. Second, we currently do not have a systematic approach in our TTE reporting to alert referring physicians about the potential for AF. Highlighting this in the report may prompt physicians to routinely screen for AF, thereby increasing the number of patients with the benefits of an early diagnosis.

11.6.3 Assumptions and Limitations.

To our knowledge, no previous study has compared the cost-effectiveness of different AF screening strategies and highlighted the potential use for imaging to guide AF screening. There are several assumptions and limitations in our analysis which may affect the external validity of our results. Like most cost-effectiveness models, data on transition probabilities, utilities and costs were derived from published literature. The complexity of the model required assumptions to be made regarding transition states where there was paucity of evidence.

Subclinical AF has been shown to be associated with increased stroke and mortality risk in an observational cohort study (55). For the purposes of this study, we assumed that clinical outcomes in subclinical AF were equivalent to those with clinically diagnosed AF.

The improvement of AF clinical outcomes with screening requires effective AF detection, anticoagulation treatment of patients diagnosed with AF, and maintenance of these patients on therapy. Our study addresses the first challenge. For this to translate to stroke prevention, we must still address the challenges regarding anticoagulation prescription and compliance.

We made assumptions about the AF detection rate in this cohort, based upon the results of our own AF screening study in which patients had baseline TTE and were risk stratified based on imaging risk (248, 251). We opted for a conservative detection rate of 5%, however based on our previous studies, detection rates may likely be much higher - which would further strengthen the ImagingScreen model. In sensitivity analysis, this approach was more cost-effective than age-based screening, until a high (14%) detection rate was achieved.

Cost data were obtained from predominantly US sources, however in cases where data was limited, we included costs from European countries. Given costs vary according to different countries, this would need to be accounted for when extrapolating these results.

This model along with the transition probabilities will not cater for all AF patients, thus when assessing cost-effectiveness for higher or lower risk cohorts, changes to the transition probabilities will be required. However, it is likely that AF screening in lower risk cohorts is not required and not likely to be cost-effective. Cohorts at higher risk of developing AF will have higher rates of stroke and

cardiovascular events. Therefore, it is likely that an echo-based screening strategy would demonstrate even higher cost-effectiveness than age-based programs.

The screening technology used in this analysis assumes a single lead portable ECG device, which has been used in many AF screening studies to date (8, 70, 71). The model does not take into account the costs related to false positives and the impact this has on patients given the potential for anticoagulation prescription and further investigations. This is an important consideration of any screening test and many AF screening studies are dependent on automated algorithms which may inherently possess this risk. It is also probable that AF detection will increase if the monitoring time is also increased. With the development of newer screening technologies such as smartwatches or monitoring patches, this may subsequently change the model given 1) the difference in costs of these technologies and 2) the ability to monitor for longer time periods thereby potentially increasing AF detection. However, given the focus of our study is more about the target population to screen rather than screening technology and given both screening cohorts will have the same monitoring technology, it is likely that this should not impact the overall results of the model.

11.7 Conclusion

An AF screening program targeting patients who have had a previous TTE with clinical and echocardiographic parameters of AF risk is more cost-effective than age-based screening programs.

11.8 Postscript

The results of this chapter suggest that an echo guided AF screening model may be more cost-effective than using an age-based screening strategy. The development of newer screening technologies such as smartwatches or monitoring patches may change the detection rates and will influence the cost analysis, however, should not impact the overall finding given the screening technology and duration will be similar for both strategies. There are several limitations with our analysis. There is a strong association between age and AF detection. AF detection increases with age and is the strongest predictor, more than choice of screening technology or monitoring period (62). Therefore, the results of our study may change depending on the age of the base-case selected. We decided to compare a group of patients with echocardiogram data available for analysis to other people screened based on age cut-offs as a proof of concept to highlight that using imaging to refine the patient selection may improve cost-effectiveness. I acknowledge that some countries and indeed areas with reduced SES may not have equal access to echocardiograms, which will limit the applicability of this study to those areas.

There are added challenges that will need to be addressed such as the time/costs involved in searching echo databases for suitable patients. There may be a role for artificial intelligence which could help this process. Regardless, commentary about AF risk could be included in TTE reports and it might be easier to identify patients prospectively for AF screening if imaging criteria are fulfilled.

AF detection is strongly dependent on patient selection. Rates of AF may be different in different regions within Australia reflecting differences in individual patient comorbidities, as well as other factors such as regional SES. In the next chapter we investigate the entry pathway of patients into AF screening and explore some of the practical challenges that need to be overcome with AF screening programs.

Chapter 12

Deciding on the most appropriate site and practical aspects to AF screening.

"Atrial Fibrillation Screening – Practical considerations and the impact of recruitment site on detection rates."

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Manuscript: Manuscript under review by European Journal of Preventative Cardiology.

12 Deciding on the most appropriate site and practical aspects to AF screening.

12.1 Preface

Most AF screening programs targeting elderly patients require some level of patient involvement. Patient compliance, cognition and manual dexterity are all potential practical factors which can influence the success of AF screening program. Although much of the literature regarding AF screening has been about how to screen and ways to identify patients at risk of developing AF, there has been very limited discussion about some of these practical matters. The final chapter of this analysis seeks to explore the practical aspects that need to be addressed for AF screening programs to be successful. To do this I compared AF detection rates between patients recruited directly from the community and GP recruitment.

12.2 Abstract

Background: AF screening has been shown to be cost effective however the most appropriate location for patient recruitment is undefined and the practical aspects of screening has not been studied. We investigated the effect of recruitment site with regards to AF detection and investigated practical challenges associated with screening.

Methods: Asymptomatic participants of ≥65 years with >1 AF risk factor (n=445) were recruited from either 1) community setting or 2) general practitioner (GP) setting, were tested at baseline and followed over a median of 15 months for incident AF. Clinical risk was assessed using the CHARGE-AF score. Patients either had clinically diagnosed AF or were diagnosed using a single lead portable ECG monitoring device (5x60 second recordings performed for 1 week). The association between recruitment site and AF detection was studied using logistic regression analysis. A questionnaire addressing the practical aspects to screening was sent to a pilot group of 180 patients.

Results: AF was diagnosed in 45 patients (10%; mean age 70.5±4.2years, male 45%). AF detection was higher in the community cohort compared with the GP cohort (14% vs. 4%, $p<0.001$). In a multivariable logistic regression model, recruitment location was associated with AF independent of LVEF, LAVi and CHARGE-AF score (OR for community cohort 4.28, 95% C.I 1.74 – 10.53, p=0.002). Of the 77/180 questionnaires returned for analysis, 24 (31%) reported difficulty in using the ECG device and 24 (31%) expressed significant anxiety about the results of screening.

Conclusion: Mass AF screening programs are potentially cost-effective and feasible, however appropriate patient selection is vital. There remain added challenges in an elderly population which must be considered including manual dexterity, cognitive impairment, patient anxiety and use of technology.

12.3 Introduction

Atrial fibrillation (AF) is the most common arrhythmia of the elderly (317). The incidence and prevalence continues to rise leading to complications such as stroke and HF, mainly driven by an ageing population along with associated risk factors such as obesity, physical inactivity and diabetes mellitus (18). This will continue to burden our healthcare system with rising hospitalizations and costs (3). Opportunistic screening of AF in recommended by the European Society of Cardiology (57) and the Cardiac Society of Australia and New Zealand for patients ≥ 65 yrs (56). Community screening programs have been implemented across a variety of settings such as pharmacies, flu vaccination programs and community health awareness programs demonstrating feasibility and cost-effectiveness (8, 68, 69, 71). Practical aspects to screening an elderly population have rarely been investigated. Although AF screening is attractive, the most appropriate site for patient recruitment is not known. In this study we compared the difference in AF detection rates between community and GP based screening programs and investigated some of the practical issues of AF screening.

12.4 Methods.

12.4.1 Study population.

AF screening programs were designed with 2 primary sites for patient recruitment: 1) healthy participants from the community and 2) recruitment from GP practices. Patients were recruited from both urban and rural areas in the states of Victoria and Tasmania, Australia (as part of the Tas-ELF and Vic-ELF studies – see chapter 2.1 for details about study inclusion). Asymptomatic participants ≥65 years were recruited if they had ≥1 or more risk factors for AF (hypertension, type 2 diabetes mellitus (T2DM) and obesity (body mass index ≥30). Exclusion criteria included: (1) inability to provide written consent, (2) history of significant valvular disease, (3) known history of heart failure and (4) reduced LV systolic function on baseline echocardiogram (LVEF ≤ 40%). All patients with documented AF on a baseline 12 lead ECG or a history of AF were excluded from the study. All patients were provided written informed consent and approval was obtained from the institution's Human Research Ethics

Committee (University of Tasmania HREC project number H0013333 and Bellberry HREC project number 2016-10-727-A-7).

12.4.2 Data Collection.

Participants undertook a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, past medical history, medication history, baseline examination data was recorded for all participants. Baseline 12 lead ECG and echocardiography were conducted in all participants. Data on regional SES was collected from the Socio-Economic Indexes for Areas (SEIFA) score developed by the Australian bureau of statistics (102).

12.4.3 AF Detection.

Participants were followed for a median of 15 months for incident AF, which was the primary outcome measure. AF was diagnosed using multiple detection methods. Patients with a clinical diagnosis of AF during the follow-up period by primary care physicians was documented. Screening for subclinical AF was performed using a single lead ECG device (Remon RM-100, Semacare, China). The single lead device was used to record 60 second single-lead ECG tracings using three points of finger contact with electrodes, five times per day for one week (i.e. 35 recordings). ECG recordings were then exported as PDF files for interpretation, and all were assessed by a physician. The presence of AF (an irregular rhythm of ≥30 sec with a variable R-R interval and absent P waves) was confirmed by two independent physicians who were blinded to the patient's clinical details. The patient was advised of the recognition of subclinical AF, and further management and investigation was provided by their usual medical practitioner.

12.4.4 Questionnaire.

A questionnaire asking patients about any difficulties during the screening process was sent to a random pilot sample of 180 patients. Data was collected on compliance rate with recordings, patient anxiety and ease of use of the screening device.

12.4.5 Statistical analysis.

All categorical variables are presented as frequencies/percentages and continuous variables presented as means/standard deviation (if normally distributed) or medians/inter-quartile range (if non-parametric). The AF detection rate between community and GP recruitment sites were compared using the chi square test. Logistic regression analysis was used to calculate the effect of recruitment site with regards to AF detection. The impact of regional socioeconomic status was investigated using the Socio-Economic indexes for areas (SEIFA) index of advantage/disadvantage, which is derived from multiple domains from the Australia census data (102). The index is expressed in deciles based on postcode (higher scores reflecting more advantaged areas). Patients were grouped according to the SEIFA index of advantage/disadvantage rank (<5 vs. ≥5) and a Nelson-Aalen cumulative hazard estimate plot was constructed, and the log-rank test used to assess the differences between curves. Analyses were considered to be statistically significant if two-tailed p values were <0.05. Statistical analysis was performed using SPSS v.22 (SPSS, Chicago, IL) and Stata v.13 (StataCorp, College Station, Texas).

12.5 Results

12.5.1 Patient characteristics and AF detection during follow up.

There were 445 subjects included in the study (mean age 70.5±4.2 years, 45% male). Baseline characteristics of participants from both recruitment sites are shown in table 12-1. Both cohorts were similar with regards to age and gender. Participants from the community cohort had higher baseline AF risk (CHARGE-AF score 6.5±6.9% vs. 3.5±3.0%, p<0.001). LAVi at baseline was higher in the GP cohort (34 vs 31 ml/m^2, p=0.003) whilst LV mass was higher in the community cohort (88 vs 73 g/m^2, p<0.001). There were more participants from the community cohort from areas of socioeconomic deprivation (median SEIFA index of advantage/disadvantage 5.0±6.0 vs. 9.0±6.0, p<0.001). During follow up there was 45 patients (10%) overall diagnosed with AF. There was higher AF detection in the community cohort (n=38, 14%) compared with the GP cohort (n=7, 4%), (p<0.001).

Table 12-1 - Summary of baseline characteristics between both patient cohorts.

Demographics	**Community cohort n = 265**	**GP cohort n = 180**	**P Value**
AF Detection n(%)	38 (14)	7 (4)	<0.001
Age - years (SD)	70.3 (4.3)	70.8 (4.1)	0.26
Male n (%)	114 (43)	84 (47)	0.45
Systolic BP mmHg (SD)	140 (15.6)	143 (15.6)	0.02
Diastolic BP mmHg (SD)	82 (10.1)	85 (9.8)	0.001
BMI (kg/m^2) (SD)	29.2 (5.1)	31.8 (5.2)	<0.001
Current Smoking n (%)	5 (2)	7 (4)	0.20
Diabetes Mellitus n (%)	138 (52)	52 (29)	<0.001
Obesity n (%)	109 (41)	117 (65)	<0.001
Hypertension n (%)	196 (74)	157 (87)	0.001
Median CHARGE-AF % (IQR)	6.5 (6.9)	3.5 (3.0)	<0.001
Median CHA_2DS_2-VASC (IQR)	3.0 (2.0)	3.0 (1.0)	0.003
SEIFA Index of advantage/disadvantage (IQR)	5.0 (6.0)	9.0 (6.0)	<0.001
Echocardiographic Parameters			
Ejection Fraction % (SD)	63.7 (5.9)	60.9 (6.4)	<0.001
Global Longitudinal Strain % (SD)	18.8 (2.4)	18.7 (2.6)	0.99
Left atrial volume - indexed ml/m^2 (SD)	31.1 (8.8)	33.7 (9.2)	0.003
Left Ventricular mass – indexed g/m^2 (SD)	87.8 (22.1)	73.1 (19.7)	<0.001

BMI – Body Mass Index IQR – Interquartile range SD – Standard Deviation SEIFA - Socioeconomic Indices for Areas

12.5.2 Association between recruitment site and AF detection.

On univariable logistic regression analysis, the community cohort had higher AF detection compared with the GP cohort (OR 4.14, 95% C.I 1.80 – 9.49, p=0.001). In a multivariable logistic regression model, recruitment location was associated with AF independent of LVEF, LAVi and CHARGE-AF score (OR for community cohort 4.28, 95% C.I 1.74 – 10.53, p=0.002).

12.5.3 Association between regional SES and AF detection.

We investigated the role of regional SES with AF detection to determine if this was the main driver between AF detection rates which was noted between both groups. When the SEIFA index of advantage/disadvantage was added to the logistic regression model, recruitment location was still independently associated with AF, although the effect size decreased (OR 3.38, 95% C.I 1.33 – 8.60, p=0.01). AF detection was higher in areas with reduced socioeconomic status (p=0.005, figure 12.1).

12.5.4 Practical aspects to AF screening.

180 patients from TasELF were given questionnaires to assess acceptability and challenges associated with screening as a pilot study. Data from 77 patients were available for analysis and summarized in figure 12.2. Overall compliance was poor with 42% completing 5 or more ECG recordings daily for 1 week. A significant proportion (31%) reported significant anxiety associated with performing screening and had difficulty using the ECG device.

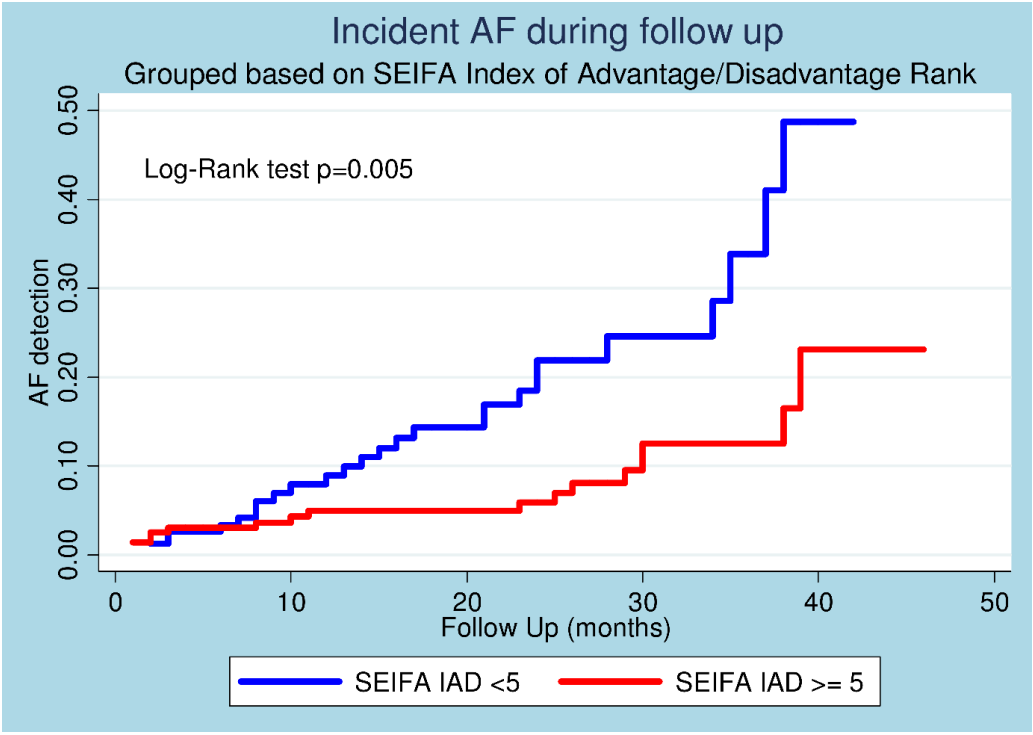

Figure 12.1 - Nelson Aalen curve showing AF detection based on the SEIFA index of advantage/disadvantage rank.

Areas with low SEIFA index of advantage/disadvantage had higher AF detection.

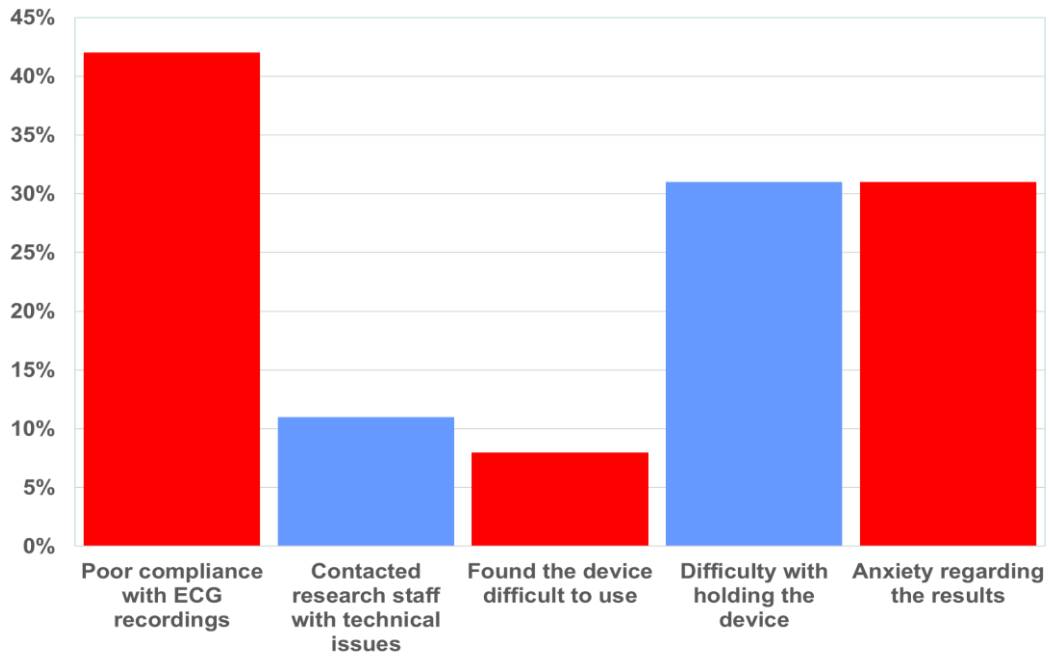

Figure 12.2 - Results of Pilot Study demonstrating common issues experienced by participants with AF screening.

There was a large number of participants who reported issues using the device, anxiety with the results of screening and many were not compliant with the requested 5x recordings per day for 1 week.

12.6 Discussion

The results of our study demonstrated that AF detection was much higher in a community cohort compared with a GP clinic cohort. The results of our pilot study suggest that a large proportion of elderly participants had difficulty in performing ECG screening at home and had anxiety regarding the results.

12.6.1 Who to target for AF screening?

Screening for AF is now recommended in current CSANZ and European guidelines (56, 57). With improvements in technology, screening using single lead ECG devices has been demonstrated to be cost-effective, feasible with a high degree of sensitivity (8, 68, 71, 78). AF remains a major public health issue with a significant rise in hospitalizations placing a tremendous strain on our healthcare system (3). Infrastructure for screening programs are available such as hospital clinics, pharmacies, community health programs and general practices, which have all been shown to be effective places to target AF screening (2).

Much of the attention has been to device technology and the length of monitoring. The recent development of smartwatches and monitoring patches may provide a paradigm shift in how we detect and diagnose AF, allowing for remote monitoring for longer periods of time (166, 167). Deciding on the most appropriate patients to screen is also an important consideration. In our study, despite having two cohorts with similar demographics at baseline, we saw a significant difference in AF detection rates, with much higher AF noted in the community cohort. There are some potential reasons for this. This may be a more vulnerable cohort with a higher burden of comorbidities and AF risk factors. There was a significant difference in regional SES between cohorts (noted in the SEIFA index of advantage/disadvantage). Participants from the community may have poor health literacy and may be from socially disadvantaged areas, which we have previously shown to be associated with AF (248). Those recruited from GP clinics are likely patients with more frequent contact with medical practitioners and may have improved risk factor control and improved health outcomes. Both centers are effective for AF screening programs. However, when we factor in the financial implications and the resources involved in AF screening, targeting community-based recruitment may improve the yield of

screening, thereby improving feasibility and cost-effectiveness. Early diagnosis may be vital in this cohort, where participants may have higher rates of comorbidities, thereby are at most risk for complications associated with AF.

12.6.2 Practical challenges associated with AF screening.

There has been growing advocacy for AF screening, yet there has been limited discussion about the practical challenges associated with screening programs. Although our pilot study had very small numbers it did provide some insights into some of the difficulties which should be overcome. Despite providing in-person demonstrations and written instructions, we had poor compliance rates and had several participants contact the study team with device related issues. Cognitive impairment is often not recognized in clinical settings yet may prove to be an important hurdle. Involvement of family members or automated screening devices such as monitoring patches may be required to address this. Although computer technology is taken for granted in the modern age, for many elderly patients it creates confusion and anxiety. In patients recruited in Tasmania nearly 40% did not have a mobile phone which made it more difficult for them to learn using an ECG device. Most ECG devices also require multiple points of finger contact to create the ECG vector. With elderly patients who have limited manual dexterity and have underlying osteoarthritis, this proved to be a very difficult hurdle. In future, AF screening programs using a smartwatch or monitoring patch may address this problem. The importance of manual dexterity and cognition have not been discussed in detail in other AF screening studies (8, 68, 71). These studies did not report significant issues in these areas. These factors are more of an issue if multi timepoint screening is performed. Although it was not assessed at baseline, it is also possible that our unique patient population may be different to those recruited in other AF screening studies and may be a cohort with reduced baseline cognition and manual dexterity. This is an important area which must be addressed in future AF screening studies.

For some participants seeing their heart rhythm on the device screen can be frightening. Abnormal recordings (ectopy, AF, tachy or bradyarrhythmias) can create anxiety and confusion amongst elderly patients who do not have a clinical nurse or doctor present at the time of the reading. The delay in

analyzing the traces and contacting patients also contributes to this feeling. Patient education is vital to address this. Monitoring patches which do not have a screen may be very useful to address this, as they do not interfere with patients' daily activities.

The results of our study are limited due to the small sample size and limited number of AF outcomes. We do not have the power to make conclusions about the best location for recruitment, however it should serve to highlight that further research in this area is required and raises important practical questions about implementing AF screening programs. There was a difference in regional SES between both cohorts. Despite accounting for this in the multivariable model, there may still be some potential confounders which have contributed to the difference in AF detection which was noted between both groups. Future studies would need to use a similar area for recruitment to try and mitigate this risk. Screening for AF is feasible and ready for the big time. We however need to learn some lessons from recent screening studies, so that we can minimize costs and offer screening to those at greatest need.

12.7 Conclusion

Elderly patients with risk factors have a high prevalence of subclinical AF. AF detection rates may be higher in community-based programs than GP based recruitment. There remain added challenges in an elderly population which must be considered including manual dexterity, cognitive impairment, patient anxiety and use of technology.

12.8 Postscript

AF screening has several potential benefits including early detection and risk factor modification. Cost-effectiveness has been established in previous studies and much of the attention has been on screening technology and the period of monitoring. The differences between AF detection rates in both cohorts demonstrates that the means of patient selection is of critical importance. It supports our findings in chapter 5 as there were differences in regional SES which could have contributed to the differences in AF detection rates observed, but the impact of the pathway to screening is independent of this. One limitation of this study was that there may have been some patients with a previous history of AF which we did not know about, who may be have been accounted as new AF in our analysis. We attempted to minimize this by examining GP medical records and taking detailed patient history at the start of the study and performing a 12 lead ECG prior to recruitment. The sample sizes of the GP recruitment cohort was small and thus we do not have the power in our study to make detailed conclusions about location of screening. We did this analysis as more of a pilot study to show that this may be an area where further research may be required.

We have identified several practical challenges which impacted on the success of our screening program. Overall compliance with device screening was suboptimal with <50% completing the desired number of ECG recordings, which will impact on the AF detection rates. Patients were given demonstrations on using the device and provided written material, yet many had difficulty using the device. Mild cognitive impairment is difficult to recognize in the screening clinic but has a very significant effect on screening as patients need to be actively involved in the screening process. Patient anxiety about abnormal recordings is also a potential issue. Using a wireless monitoring patch appears to be best solution to addressing these challenges. It can be used for up to 2 weeks of continuous monitoring without any patient involvement and the patient is not alerted to any abnormal recordings. The main challenge will the additional costs with these newer screening technologies.

Section V – Discussion and Conclusions

Chapter 13

Discussion and Conclusions

13 Discussion and Conclusions

13.1 Summary of background

AF is a major public health issue and places a tremendous burden on our health care system. It is associated with reduced quality of life and is a major cause of HF and stroke in the community. The prevention of these complications requires early diagnosis which can be achieved through screening programs. In this thesis I have attempted to further refine the patient selection for screening and determine the most appropriate method for screening. The results of this thesis have important clinical implications in how we conduct mass AF screening programs.

13.2 AF detection

One of the primary aims of my thesis was to identify the most appropriate screening technology. I have demonstrated that single lead ECG monitoring devices can replicate the AF detection rates of 24-hour Holter monitors and may be more practical and easier to use for screening programs. Technology in the ECG and monitoring domains have improved exponentially over time. The development of monitoring patches (166) and smartwatches (167) are more attractive alternatives. Not only do they have a high degree of sensitivity for AF detection. More importantly, they have the advantages of not requiring patient involvement and do not interfere was daily activities. As we have demonstrated in chapter 12, manual dexterity and cognition are important considerations, which may limit the feasibility of single lead ECG monitoring devices. There are some challenges with these monitoring devices which need to be addressed. Firstly, we must minimize false negatives as we do not want to commence therapies with potential for harm such as oral anticoagulants. Secondly, we must address patient anxiety which may become a factor when mass screening is adopted. Thirdly, we require a reliable automated algorithm which will enable us to use these devices in a large scale.

13.3 Patient selection

The next aim of my thesis was to determine the most appropriate cohort for screening. The feasibility and effectiveness of screening programs will improve if we are able to refine the target population, leading to an enriched cohort. Most screening studies have adopted either an arbitrary age cut-off or use clinical risk factors such as CHARGE-AF(22). We have identified other novel risk parameters which can be used to identify those most at risk of developing AF and who will most benefit from screening.

In chapter 4 we demonstrated the association between reduced functional capacity and AF risk, independent of other clinical risk parameters. This is an important finding and exercise has also been shown to be protective of AF in other studies (184-186). This may be useful at the bedside to identify those at risk of developing AF. In chapter 5 we demonstrated that regional socioeconomic deprivation was associated with AF independent of LV function and LA size. This is an important finding as socioeconomic deprivation has also been associated with increased risk of cardiovascular disease.

The difficult question is how to translate the findings of this thesis into clinical practice. It can be argued that we should not just offer screening to those from areas of reduced SES. However, the main challenge is to identify the most appropriate cohort for screening. The use of clinical risk factors allows us to characterize patients at high risk at an individual level. Other indices of exercise capacity such as the 6-minute walk test, could be used to alert treating physicians about future AF risk in patients. Regional SES allows us to characterize high risk areas at a population level.

Ideally, AF screening should be offered across the country in both urban and rural settings. However, with limited resources, it is important that these programs target areas with high AF prevalence. Targeting areas with regional socioeconomic deprivation especially in the early pilot stages allows us to further study the feasibility and effectiveness of screening programs. It also importantly improves health literacy, awareness and provides improved health care access to these areas.

13.4 Imaging assessment of AF risk and “atriopathy”

Having determined the best screening technology and refined patient selection, my next aim was to identify novel echocardiographic parameters to assess AF risk and the presence of an underlying

"atriopathy." In chapter 6 I demonstrated that LA pump strain was independent of LV function, therefore providing incremental information about LA function. In chapter 7 I further investigated the relationship between BP and LA function, which can be used to identify those at risk of LA dysfunction. In chapter 8, I investigated how imaging risk parameters could be combined as a risk stratification tool to assist in AF detection. I demonstrated that the presence of LVH, LA enlargement, reduced GLS and LARS was associated with increased AF detection. In chapter 9 we investigated the role of mechanical dispersion as a novel marker of AF risk. In chapter 11 I further investigated the role of an imaging guided screening strategy demonstrating that it was more cost-effective compared with a traditional age-based screening program.

The results of these chapters highlight the importance of imaging in the assessment of AF risk. Routine transthoracic echocardiograms in asymptomatic patients for the purpose of AF risk assessment is not recommended. However, the results of our studies highlight a few important points. Firstly, many patient shave echocardiograms performed for a variety of reasons. Reports should provide some commentary on AF risk as we have the tools available readily in clinical practice. Secondly, the results of previous echocardiogram studies can be used to identify those at risk of developing AF. AF screening programs whilst traditionally taking place in GP clinics or in the community, could also be considered in echo labs where we have access to both clinical and imaging data which can assist in creating an enriched cohort.

The use of speckle tracking allows the assessment of quantitative and qualitative phasic LA function. Recently there has been emerging evidence of stroke and embolic events in patients with an underlying "atriopathy" in the absence of AF (46). AF can be thought of as an end-organ manifestation of the underlying "atriopathy" which occurs due to chronic elevation in LA pressure, negative remodeling and fibrosis. The advantage of strain imaging is that it provides incremental information not only of AF risk but the underlying "atriopathy." Therefore, it provides additional assessment of stroke/thromboembolic risk not just AF risk. This is an important justification for imaging in AF risk assessment. It provides not only assessment of AF risk; it more importantly shows the degree of "atriopathy" which is equally important in stroke assessment. In the future, the development of AF may not be the most important clinical endpoint. Rather, we may be screening patients for "atriopathy" and treating them accordingly.

The ARCADIA study which is currently recruiting is investigating the role of anticoagulation in these patients with “atriopathy” and may provide some important evidence in this field (46).

13.5 Practical aspects to screening

Having identified the most appropriate cohort for screening and investigating the role of imaging in AF risk assessment, my final aim was to assess the practical aspects to screening. There are a number of important considerations which need to be taken into account for screening to be successful. We noted issues with cognition and manual dexterity as well as patient anxiety. These are all important aspects, as we require patient investment for screening programs to be successful. To address this more education and support will be required for patients by staff. The use of monitoring patches and smartwatches can help make screening more passive where it is in the background and automated. This is preferable to single lead ECG monitoring devices which require active patient involvement.

These practical considerations have been underreported previously in clinical studies. To improve our understanding in this area, we need more frequent reporting of these practical issues in future AF screening studies.

13.6 Limitations:

This to my knowledge is one of the first research studies to investigate the use of an echo-guided strategy to improve the feasibility of AF screening. It is also one of the largest studies assessing the association between advanced imaging markers of LA function with AF. There are however several limitations to our research project, which include:

1. Limited AF outcomes due to a short follow up period.
2. Long term follow-up is required to determine if AF screening can reduce rates of stroke and improve long term clinical outcomes.
3. Population selection bias as patients were recruited from radio and newspaper advertising.

4. We had a very well-defined patient cohort with patients specifically recruited from areas of socioeconomic deprivation. Therefore, extrapolation of these results to other cohorts will need to assume external validity.
5. AF outcomes may have been missed as monitoring period was limited (the use of monitoring patches or smartwatches can improve this limitation in future studies).
6. Suboptimal patient compliance (<50% completed the requested 5x60 sec recordings for 2 weeks).
7. Subclinical AF and clinically diagnosed AF have been grouped together in our AF outcomes. Subclinical AF has been shown in observational studies to portend an adverse prognosis with increased all-cause mortality and stroke risk (55), however there is no clinical evidence of a benefit in anticoagulation in this group.
8. LA strain performed by a few operators using the same program. Like other advanced imaging techniques, there is a learning curve with strain analysis which may have contributed to potential errors in the analysis. We measured inter and intra-observer variability to assess this in our individual studies.
9. Lack of standardization between software vendors for strain analysis and intrinsic differences between vendors need to be taken into account.
10. Cost analysis performed may not have taken into account other important costs associated with an imaging guided screening strategy.
11. The results of this project may not be applicable to other regions/countries where echocardiography is not widely available, and the patient population may be different.

13.7 Concluding remarks and areas for future research

In conclusion, targeted AF screening programs can be assisted using a combination of clinical, socioeconomic and imaging parameters. Further research is required to see if this approach is cost-effective and may be associated with reduced AF related complications and improved health outcomes in Australia. Future research should focus on the following:

1. Implementation and cost-effectiveness of newer screening technologies such as smartwatches and monitoring patches.
2. Validation of an imaging guided AF screening model using a prospective cohort study.
3. Long term follow-up of patients following AF screening to assess if there are reduced complications and hospitalizations.
4. Investigate the role of anticoagulation for subclinical AF

14 References

1. Freedman SB, Lowres N. Asymptomatic atrial fibrillation: the case for screening to prevent stroke. JAMA. 2015;314(18):1911-2.

2. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, Albert CM, Anderson CS, Antoniou S, Benjamin EJ. Screening for atrial fibrillation: a report of the AF-SCREEN international collaboration. Circulation. 2017;135(19):1851-67.

3. Gallagher C, Hendriks JM, Giles L, Karnon J, Pham C, Elliott AD, Middeldorp ME, Mahajan R, Lau DH, Sanders P. Increasing trends in hospitalisations due to atrial fibrillation in Australia from 1993 to 2013. Heart. 2019:heartjnl-2018-314471.

4. Cameli M, Mandoli GE, Loiacono F, Sparla S, Iardino E, Mondillo S. Left atrial strain: A useful index in atrial fibrillation. International Journal of Cardiology. 2016;220:208-13.

5. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left atrial structure and function, and left ventricular diastolic dysfunction: JACC state-of-the-art review. Journal of the American College of Cardiology. 2019;73(15):1961-77.

6. Chen-Scarabelli C, Scarabelli TM, Ellenbogen KA, Halperin JL. Device-detected atrial fibrillation: what to do with asymptomatic patients? Journal of the American College of Cardiology. 2015;65(3):281-94.

7. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. Nature Reviews Cardiology. 2016;13:321.

8. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, Bennett AA, Briffa T, Bauman A, Martinez C, Wallenhorst C, Lau JK, Brieger DB, Sy RW, Ben Freedman S. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies: The SEARCH-AF study. Thrombosis and Haemostasis. 2014;111(6):1167-76.

9. Aliot E, Botto GL, Crijns HJ, Kirchhof P. Quality of life in patients with atrial fibrillation: how to assess it and how to improve it. EP Europace. 2014;16(6):787-96.

10. Walters TE, Wick K, Tan G, Mearns M, Joseph SA, Morton JB, Sanders P, Bryant C, Kistler PM, Kalman JM. Psychological Distress and Suicidal Ideation in Patients With Atrial Fibrillation: Prevalence and Response to Management Strategy. Journal of the American Heart Association. 2018;7(18):e005502.

11. PricewaterhouseCoopers. The economic costs of Atrial Fibrillation in Australia. A report for the National Stroke Foundation.; 2010.

12. Kim MH, Johnston SS, Chu B-C, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. Circulation: Cardiovascular Quality and Outcomes. 2011;4(3):313-20.

13. Kim D, Yang P-S, Jang E, Yu HT, Kim T-H, Uhm J-S, Kim JY, Pak H-N, Lee M-H, Joung B. Increasing trends in hospital care burden of atrial fibrillation in Korea, 2006 through 2015. Heart. 2018;104(24):2010-7.

14. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S. Executive summary: heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2014;129(3):399-410.

15. Jørgensen H, Nakayama H, Reith J, Raaschou H, Olsen TS. Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. Neurology. 1997;48(4):891-5.

16. Stewart S, Murphy N, Walker A, McGuire A, McMurray J. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. Heart. 2004;90(3):286-92.

17. Wong CX, Brooks AG, Leong DP, Roberts-Thomson KC, Sanders P. The increasing burden of atrial fibrillation compared with heart failure and myocardial infarction: a 15-year study of all hospitalizations in Australia. Archives of internal medicine. 2012;172(9):739-41.

18. Ball J, Thompson DR, Ski CF, Carrington MJ, Gerber T, Stewart S. Estimating the current and future prevalence of atrial fibrillation in the Australian adult population. Med J Aust. 2015;202(1):32-5.

19. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. Circulation. 2016;133(5):484-92.

20. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable Risk Factors and Atrial Fibrillation. Circulation. 2017;136(6):583-96.

21. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. JAMA. 1994;271(11):840-4.

22. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JD, Janssens AC, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Agarwal SK, McManus DD, Ellinor PT, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kaab S, Couper D, Harris TB, Soliman EZ, Stricker BH, Gudnason V, Heckbert SR, Benjamin EJ. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc. 2013;2(2):e000102.

23. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. Journal of the American College of Cardiology. 2014;64(21):2222-31.

24. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, Somers VK. Obstructive Sleep Apnea, Obesity, and the Risk of Incident Atrial Fibrillation. Journal of the American College of Cardiology. 2007;49(5):565-71.

25. Huxley RR, Misialek JR, Agarwal SK, Loehr LR, Soliman EZ, Chen LY, Alonso A. Physical activity, obesity, weight change, and risk of atrial fibrillation: the Atherosclerosis Risk in Communities study. Circulation: Arrhythmia and Electrophysiology. 2014;7(4):620-5.

26. Sanchis-Gomar F, Perez-Quilis C, Lippi G, Cervellin G, Leischik R, Loellgen H, Serrano-Ostariz E, Lucia A. Atrial fibrillation in highly trained endurance athletes—description of a syndrome. International journal of cardiology. 2017;226:11-20.

27. Rienstra M, McManus DD, Benjamin EJ. Novel risk factors for atrial fibrillation: useful for risk prediction and clinical decision making? Circulation. 2012;125(20):e941-e6.

28. Fox CS, Parise H, D'Agostino Sr RB, Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA. 2004;291(23):2851-5.

29. Thanassoulis G, Massaro JM, O'Donnell CJ, Hoffmann U, Levy D, Ellinor PT, Wang TJ, Schnabel RB, Vasan RS, Fox CS. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study. Circulation: Arrhythmia and Electrophysiology. 2010;3(4):345-50.

30. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation. 1993;88(4):1973-98.

31. Chichlowska KL, Rose KM, Diez-Roux AV, Golden SH, McNeill AM, Heiss G. Individual and Neighborhood Socioeconomic Status Characteristics and Prevalence of Metabolic Syndrome. The Atherosclerosis Risk in Communities (ARIC) Study. Psychosomatic medicine. 2008;70(9):986.

32. Santos AC, Ebrahim S, Barros H. Gender, socio-economic status and metabolic syndrome in middle-aged and old adults. BMC Public Health. 2008;8(1):62.

33. Zöller B, Li X, Sundquist J, Sundquist K. Neighbourhood deprivation and hospitalization for atrial fibrillation in Sweden. Europace. 2013;15(8):1119-27.

34. Misialek JR, Rose KM, Everson-Rose SA, Soliman EZ, Clark CJ, Lopez FL, Alonso A. Socioeconomic status and the incidence of atrial fibrillation in whites and blacks: the Atherosclerosis Risk in Communities (ARIC) study. Journal of the American Heart Association. 2014;3(4):e001159.

35. Muse ED, Wineinger NE, Spencer EG, Peters M, Henderson R, Zhang Y, Barrett PM, Rivera SP, Wohlgemuth JG, Devlin JJ. Validation of a genetic risk score for atrial fibrillation: A prospective multicenter cohort study. PLoS medicine. 2018;15(3):e1002525.

36. Diener H-C, Hart RG, Koudstaal PJ, Lane DA, Lip GYH. Atrial Fibrillation and Cognitive Function: JACC Review Topic of the Week. Journal of the American College of Cardiology. 2019;73(5):612-9.

37. Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Horne BD, Lappe DL. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. Heart Rhythm. 2010;7(4):433-7.

38. de Bruijn RF, Heeringa J, Wolters FJ, Franco OH, Stricker BH, Hofman A, Koudstaal PJ, Ikram MA. Association between atrial fibrillation and dementia in the general population. JAMA Neurology. 2015;72(11):1288-94.

39. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Annals of internal medicine. 2013;158(5_Part_1):338-46.

40. Hoit BD. Left Atrial Size and Function: Role in Prognosis. Journal of the American College of Cardiology. 2014;63(6):493-505.

41. Thomas L, Abhayaratna WP. Left atrial reverse remodeling: mechanisms, evaluation, and clinical significance. JACC: Cardiovascular Imaging. 2017;10(1):65-77.

42. Casaclang-Verzosa G, Gersh BJ, Tsang TS. Structural and functional remodeling of the left atrium: clinical and therapeutic implications for atrial fibrillation. Journal of the American College of Cardiology. 2008;51(1):1-11.

43. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K, Brachmann J. Cryptogenic stroke and underlying atrial fibrillation. New England Journal of Medicine. 2014;370(26):2478-86.

44. Di Tullio MR, Sacco RL, Sciacca RR, Homma S. Left atrial size and the risk of ischemic stroke in an ethnically mixed population. Stroke. 1999;30(10):2019-24.

45. Kamel H, O'Neal WT, Okin PM, Loehr LR, Alonso A, Soliman EZ. Electrocardiographic left atrial abnormality and stroke subtype in the atherosclerosis risk in communities study. Annals of neurology. 2015;78(5):670-8.

46. Kamel H, Longstreth Jr W, Tirschwell DL, Kronmal RA, Broderick JP, Palesch YY, Meinzer C, Dillon C, Ewing I, Spilker JA. The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: rationale and methods. International Journal of Stroke. 2019;14(2):207-14.

47. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. The Lancet. 2009;373(9665):739-45.

48. Chamberlain AM, Agarwal SK, Folsom AR, Soliman EZ, Chambless LE, Crow R, Ambrose M, Alonso A. A clinical risk score for atrial fibrillation in a biracial prospective

cohort (from the Atherosclerosis Risk in Communities [ARIC] study). The American Journal of Cardiology. 2011;107(1):85-91.

49. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A. The cardiovascular health study: design and rationale. Annals of epidemiology. 1991;1(3):263-76.

50. Harris TB, Launer LJ, Eiriksdottir G, Kjartansson O, Jonsson PV, Sigurdsson G, Thorgeirsson G, Aspelund T, Garcia ME, Cotch MF. Age, gene/environment susceptibility–Reykjavik Study: multidisciplinary applied phenomics. American Journal of Epidemiology. 2007;165(9):1076-87.

51. Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bulletin of the World Health Organization. 2008;86:317-9.

52. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). Journal of the American College of Cardiology. 2015;65(20):2159-69.

53. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J. Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2009;361(12):1139-51.

54. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A. Apixaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2011;365(11):981-92.

55. Martinez C, Katholing A, Freedman SB. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. Thrombosis and haemostasis. 2014;112(2):276-86.

56. Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C, Freedman B, Ferguson C, Hall T, Haqqani H, Hendriks J, Hespe C, Hung J, Kalman JM, Sanders P, Worthington J, Yan TD, Zwar N. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. Heart, Lung & Circulation. 2018;27(10):1209-66.

57. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal. 2016;37(38):2893-962.

58. Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, Doubeni CA, Epling JW, Kemper AR, Kubik M. Screening for atrial fibrillation with

electrocardiography: US Preventive Services Task Force recommendation statement. JAMA. 2018;320(5):478-84.

59. United Kingdom National Screening Committee. Recommendation on Atrial Fibrillation Screening in Adults, 2014 2014 [cited 2018. Available from: https://legacyscreening.phe.org.uk/atrialfibrillation.

60. Andrade JG, Verma A, Mitchell LB, Parkash R, Leblanc K, Atzema C, Healey JS, Bell A, Cairns J, Connolly S, Cox J, Dorian P, Gladstone D, McMurtry MS, Nair GM, Pilote L, Sarrazin J-F, Sharma M, Skanes A, Talajic M, Tsang T, Verma S, Wyse DG, Nattel S, Macle L. 2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Canadian Journal of Cardiology. 2018;34(11):1371-92.

61. Joung B, Lee JM, Lee KH, Kim TH, Choi EK, Lim WH, Kang KW, Shim J, Lim HE, Park J, Lee SR, Lee YS, Kim JB, Group KAFGW. 2018 Korean Guideline of Atrial Fibrillation Management. Korean Circ J. 2018;48(12):1033-80.

62. Lowres N, Olivier J, Chao T-F, Chen S-A, Chen Y, Diederichsen A, Fitzmaurice DA, Gomez-Doblas JJ, Harbison J, Healey JS. Estimated stroke risk, yield, and number needed to screen for atrial fibrillation detected through single time screening: a multicountry patient-level meta-analysis of 141,220 screened individuals. PLoS medicine. 2019;16(9):e1002903.

63. Diederichsen SZ, Haugan KJ, Brandes A, Lanng MB, Graff C, Krieger D, Kronborg C, Holst AG, Køber L, Højberg S, Svendsen JH. Natural History of Subclinical Atrial Fibrillation Detected by Implanted Loop Recorders. Journal of the American College of Cardiology 2019;74(22):2771-81.

64. Healey JS, Alings M, Ha A, Leong-Sit P, Birnie DH, de Graaf JJ, Freericks M, Verma A, Wang J, Leong D, Dokainish H, Philippon F, Barake W, McIntyre WF, Simek K, Hill MD, Mehta SR, Carlson M, Smeele F, Pandey AS, Connolly SJ. Subclinical Atrial Fibrillation in Older Patients. Circulation. 2017;136(14):1276-83.

65. Reiffel JA, Verma A, Kowey PR, Halperin JL, Gersh BJ, Wachter R, Pouliot E, Ziegler PD, Investigators ftRA. Incidence of Previously Undiagnosed Atrial Fibrillation Using Insertable Cardiac Monitors in a High-Risk Population: The REVEAL AF Study. JAMA Cardiology. 2017;2(10):1120-7.

66. Kane SA, Blake JR, McArdle FJ, Langley P, Sims AJ. Opportunistic detection of atrial fibrillation using blood pressure monitors: a systematic review. Open Heart. 2016;3(1):e000362.

67. Chan PH, Wong CK, Poh YC, Pun L, Leung WWC, Wong YF, Wong MMY, Poh MZ, Chu DWS, Siu CW. Diagnostic performance of a smartphone-based photoplethysmographic application for atrial fibrillation screening in a primary care setting. Journal of the American Heart Association. 2016;5(e003428):e003428.

68. Kaasenbrood F, Hollander M, Rutten FH, Gerhards LJ, Hoes AW, Tieleman RG. Yield of screening for atrial fibrillation in primary care with a hand-held, single-lead electrocardiogram device during influenza vaccination. Europace. 2016;18(10):1514-20.

69. Proietti M, Mairesse GH, Goethals P, Scavee C, Vijgen J, Blankoff I, Vandekerckhove Y, Lip GY. A population screening programme for atrial fibrillation: a report from the Belgian Heart Rhythm Week screening programme. Europace. 2016:euw069.

70. Halcox JP, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C, Gravenor MB. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study. Circulation. 2017;136(19):1784-94.

71. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. Circulation. 2015;131(25):2176-84.

72. Doliwa PS, Frykman V, Rosenqvist M. Short-term ECG for out of hospital detection of silent atrial fibrillation episodes. Scandinavian Cardiovascular Journal. 2009;43(3):163-8.

73. Battipaglia I, Gilbert K, Hogarth AJ, Tayebjee MH. Screening for atrial fibrillation in the community using a novel ECG recorder. Journal of Atrial Fibrillation. 2016;9(2):29-31.

74. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, Balasubramanian V, Russo AM, Rajmane A, Cheung L. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. New England Journal of Medicine. 2019;381(20):1909-17.

75. Turakhia MP, Ullal AJ, Hoang DD, Than CT, Miller JD, Friday KJ, Perez MV, Freeman JV, Wang PJ, Heidenreich PA. Feasibility of extended ambulatory electrocardiogram monitoring to identify silent atrial fibrillation in high-risk patients: the screening study for undiagnosed atrial fibrillation (STUDY-AF). Clinical Cardiology. 2015;38(5):285-92.

76. Barrett PM, Komatireddy R, Haaser S, Topol S, Sheard J, Encinas J, Fought AJ, Topol EJ. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. The American Journal of Medicine. 2014;127(1):95. e11-95. e17.

77. Freedman B. Screening for atrial fibrillation using a smartphone: is there an app for that? : Am Heart Assoc; 2016.

78. Aronsson M, Svennberg E, Rosenqvist M, Engdahl J, Al-Khalili F, Friberg L, Frykman-Kull V, Levin L-Å. Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording. EP Europace. 2015;17(7):1023-9.

79. Jacobs MS, van Hulst M, Postma MJ, Kaasenbrood F, Tieleman RG. Cost-effectiveness of screening for atrial fibrillation in primary care with a handheld, single-lead electrocardiogram device in the Netherlands. EP Europace. 2016;20(1):12-8.

80. Aronsson M, Svennberg E, Rosenqvist M, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Levin L-Å. Designing an optimal screening program for unknown atrial fibrillation: a cost-effectiveness analysis. Ep Europace. 2017;19(10):1650-6.

81. Lown M, Garrard J, Irving G, Edwards D, Hobbs FR, Mant J. Should we screen for atrial fibrillation? British Journal of General Practice. 2017;67(660):296-7.

82. Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, Picard MH, Polk DM, Ragosta M, Ward RP. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance Endorsed by the American College of Chest Physicians. Journal of the American College of Cardiology. 2011;57(9):1126-66.

83. Blume GG, Mcleod CJ, Barnes ME, Seward JB, Pellikka PA, Bastiansen PM, Tsang TS. Left atrial function: physiology, assessment, and clinical implications. European Heart Journal-Cardiovascular Imaging. 2011;12(6):421-30.

84. Motoki H, Borowski AG, Shrestha K, Troughton RW, Tang WH, Thomas JD, Klein AL. Incremental prognostic value of assessing left ventricular myocardial mechanics in patients with chronic systolic heart failure. Journal of the American College of Cardiology. 2012;60(20):2074-81.

85. Russo C, Jin Z, Elkind MS, Rundek T, Homma S, Sacco RL, Di Tullio MR. Prevalence and prognostic value of subclinical left ventricular systolic dysfunction by global longitudinal strain in a community-based cohort. Eur J Heart Fail. 2014;16(12):1301-9.

86. Mornos C, Muntean D, Mornos A, Crisan S, Petrescu L, Ionac A, Sosdean R, Cozma D. Risk stratification in patients with heart failure: the value of considering both global longitudinal left ventricular strain and mechanical dispersion. Can J Physiol Pharmacol. 2017;95(11):1360-8.

87. Haugaa KH, Grenne BL, Eek CH, Ersboll M, Valeur N, Svendsen JH, Florian A, Sjoli B, Brunvand H, Kober L, Voigt JU, Desmet W, Smiseth OA, Edvardsen T. Strain echocardiography improves risk prediction of ventricular arrhythmias after myocardial infarction. JACC Cardiovasc Imaging. 2013;6(8):841-50.

88. Cameli M, Lisi M, Righini FM, Mondillo S. Novel echocardiographic techniques to assess left atrial size, anatomy and function. Cardiovasc Ultrasound. 2012;10:4.

89. Pathan F, D'Elia N, Nolan MT, Marwick TH, Negishi K. Normal Ranges of Left Atrial Strain by Speckle-Tracking Echocardiography: A Systematic Review and Meta-Analysis. J Am Soc Echocardiogr. 2017;30(1):59-70 e8.

90. Pathan F, Sivaraj E, Negishi K, Rafiudeen R, Pathan S, D'Elia N, Galligan J, Neilson S, Fonseca R, Marwick TH. Use of Atrial Strain to Predict Atrial Fibrillation After Cerebral Ischemia. JACC Cardiovasc Imaging. 2018;11(11):1557-65.

91. Thomas L, Mckay T, Byth K, Marwick TH. Abnormalities of left atrial function after cardioversion: an atrial strain rate study. Heart. 2007;93(1):89-95.

92. Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S, Rao SN, Blauer J, Fish EN, DiBella EV. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation relationship to left atrial structural remodeling detected by delayed-enhancement MRI. Circulation: Cardiovascular Imaging. 2010;3(3):231-9.

93. Di Salvo G, Caso P, Lo Piccolo R, Fusco A, Martiniello AR, Russo MG, D'Onofrio A, Severino S, Calabró P, Pacileo G, Mininni N, Calabró R. Atrial Myocardial Deformation Properties Predict Maintenance of Sinus Rhythm After External Cardioversion of Recent-Onset Lone Atrial Fibrillation. A Color Doppler Myocardial Imaging and Transthoracic and Transesophageal Echocardiographic Study. 2005;112(3):387-95.

94. Doruchowska A, Wita K, Bochenek T, Szydlo K, Filipecki A, Staron A, Wrobel W, Krzych L, Trusz-Gluza M. Role of left atrial speckle tracking echocardiography in predicting persistent atrial fibrillation electrical cardioversion success and sinus rhythm maintenance at 6 months. Advances in medical sciences. 2014;59(1):120-5.

95. Rimbaş RC, Dulgheru RE, Vinereanu D. Methodological Gaps in Left Atrial Function Assessment by 2D Speckle Tracking Echocardiography. Arquivos brasileiros de cardiologia. 2015;105(6):625-36.

96. Mirza M, Caracciolo G, Khan U, Mori N, Saha SK, Srivathsan K, Altemose G, Scott L, Sengupta P, Jahangir A. Left atrial reservoir function predicts atrial fibrillation recurrence after catheter ablation: a two-dimensional speckle strain study. Journal of Interventional Cardiac Electrophysiology. 2011;31(3):197-206.

97. Shih J-Y, Tsai W-C, Huang Y-Y, Liu Y-W, Lin C-C, Huang Y-S, Tsai L-M, Lin L-J. Association of decreased left atrial strain and strain rate with stroke in chronic atrial fibrillation. Journal of the American Society of Echocardiography. 2011;24(5):513-9.

98. Antoni ML, ten Brinke EA, Atary JZ, Marsan NA, Holman ER, Schalij MJ, Bax JJ, Delgado V. Left atrial strain is related to adverse events in patients after acute myocardial infarction treated with primary percutaneous coronary intervention. Heart. 2011;97(16):1332-7.

99. Debonnaire P, Leong DP, Witkowski TG, Al Amri I, Joyce E, Katsanos S, Schalij MJ, Bax JJ, Delgado V, Marsan NA. Left atrial function by two-dimensional speckle-tracking echocardiography in patients with severe organic mitral regurgitation: association with guidelines-based surgical indication and postoperative (long-term) survival. Journal of the American Society of Echocardiography. 2013;26(9):1053-62.

100. Ersbøll M, Andersen MJ, Valeur N, Mogensen UM, Waziri H, Møller JE, Hassager C, Søgaard P, Køber L. The prognostic value of left atrial peak reservoir strain in acute myocardial infarction is dependent on left ventricular longitudinal function and left atrial size. Circulation: Cardiovascular Imaging. 2013;6(1):26-33.

101. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, D'hooge J, Donal E, Fraser AG, Marwick T. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking

echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. European Heart Journal-Cardiovascular Imaging. 2018;19(6):591-600.

102. Australian Bureau of Statistics. Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA), Commonwealth of Australia. [document]. Australian Bureau of Statistics, Commonwealth of Australia.; 2011 [updated 2013-03-28. Available from: http://www.abs.gov.au/ausstats/abs@.nsf/mf/2033.0.55.001.

103. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, Cobb FR, Pryor DB. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). The American Journal of Cardiology. 1989;64(10):651-4.

104. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. American Heart Journal. 1992;124(4):1017-25.

105. D'Hoore W, Sicotte C, Tilquin C. Risk adjustment in outcome assessment: the Charlson comorbidity index. Methods of Information in Medicine. 1993;32(5):382-7.

106. Rabin R, Charro Fd. EQ-SD: a measure of health status from the EuroQol Group. Annals of Medicine. 2001;33(5):337-43.

107. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography. 2015;28(1):1-39 e14.

108. Blessberger H, Binder T. Two dimensional speckle tracking echocardiography: basic principles. Heart. 2010;96(9):716-22.

109. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. The American Journal of Medicine. 1995;98(5):476-84.

110. Vidaillet H, Granada JF, Chyou P-H, Maassen K, Ortiz M, Pulido JN, Sharma P, Smith PN, Hayes J. A population-based study of mortality among patients with atrial fibrillation or flutter. The American Journal of Medicine. 2002;113(5):365-70.

111. Leyden JM, Kleinig TJ, Newbury J, Castle S, Cranefield J, Anderson CS, Crotty M, Whitford D, Jannes J, Lee A, Greenhill J. Adelaide stroke incidence study: declining stroke rates but many preventable cardioembolic strokes. Stroke. 2013;44(5):1226-31.

112. Lau J, Lowres N, Neubeck L, Brieger D, Sy R, Galloway C, Albert D, Freedman S. Performance of an automated iPhone ECG algorithm to diagnose atrial fibrillation in a community AF screening program (search-AF). Heart Lung and Circulation. 2013;22:S205.

113. Watanabe H, Tanabe N, Watanabe T, Darbar D, Roden DM, Sasaki S, Aizawa Y. Metabolic syndrome and risk of development of atrial fibrillation. Circulation. 2008;117(10):1255-60.

114. Dagres N, Anastasiou-Nana M. Atrial Fibrillation and Obesity. Journal of the American College of Cardiology. 2010;55(21):2328-9.

115. Sposato LA, Cipriano LE, Saposnik G, Ruiz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurology. 2015;14(4):377-87.

116. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau DH, Antic NA, Brooks AG. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA. 2013;310(19):2050-60.

117. Chan N, Choy C. Screening for atrial fibrillation in 13 122 Hong Kong citizens with smartphone electrocardiogram. Heart. 2017;103(1):24-31.

118. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.

119. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of Epidemiology and Community Health. 1998;52(6):377-84.

120. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'donnell M, Laupacis A, Côté R. Atrial fibrillation in patients with cryptogenic stroke. New England Journal of Medicine. 2014;370(26):2467-77.

121. Barthélémy JC, Féasson-Gérard S, Garnier P, Gaspoz JM, Costa AD, Michel D, Roche F. Automatic cardiac event recorders reveal paroxysmal atrial fibrillation after unexplained strokes or transient ischemic attacks. Annals of Noninvasive Electrocardiology. 2003;8(3):194-9.

122. Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. Stroke. 2004;35(7):1647-51.

123. Koudstaal PJ, van Gijn J, Klootwijk A, Van Der Meche F, Kappelle L. Holter monitoring in patients with transient and focal ischemic attacks of the brain. Stroke. 1986;17(2):192-5.

124. Hornig C, Haberbosch W, Lammers C, Waldecker B, Dorndorf W. Specific cardiological evaluation after focal cerebral ischemia. Acta Neurologica Scandinavica. 1996;93(4):297-302.

125. Rizos T, Güntner J, Jenetzky E, Marquardt L, Reichardt C, Becker R, Reinhardt R, Hepp T, Kirchhof P, Aleynichenko E. Continuous stroke unit electrocardiographic

monitoring versus 24-hour Holter electrocardiography for detection of paroxysmal atrial fibrillation after stroke. Stroke. 2012;43(10):2689-94.

126. Schuchert A, Behrens G, Meinertz T. Impact of long-term ECG recording on the detection of paroxysmal atrial fibrillation in patients after an acute ischemic stroke. Pacing & Clinical Electrophysiology. 1999;22(7):1082-4.

127. Schaer B, Sticherling C, Lyrer P, Osswald S. Cardiological diagnostic work-up in stroke patients–a comprehensive study of test results and therapeutic implications. European Journal of Neurology. 2009;16(2):268-73.

128. Schaer B, Zellweger M, Cron T, Kaiser C, Osswald S. Value of routine Holter monitoring for the detection of paroxysmal atrial fibrillation in patients with cerebral ischemic events. Stroke. 2004;35(3):e68-e70.

129. Shafqat S, Kelly P, Furie K. Holter monitoring in the diagnosis of stroke mechanism. Internal Medicine Journal. 2004;34(6):305-9.

130. Lazzaro MA, Krishnan K, Prabhakaran S. Detection of atrial fibrillation with concurrent holter monitoring and continuous cardiac telemetry following ischemic stroke and transient ischemic attack. Journal of Stroke & Cerebrovascular Diseases. 2012;21(2):89-93.

131. Grond M, Jauss M, Hamann G, Stark E, Veltkamp R, Nabavi D, Horn M, Weimar C, Köhrmann M, Wachter R. Improved detection of silent atrial fibrillation using 72-hour Holter ECG in patients with ischemic stroke. Stroke. 2013;44(12):3357-64.

132. Stahrenberg R, Weber-Kruger M, Seegers J, Edelmann F, Lahno R, Haase B, Mende M, Wohlfahrt J, Kermer P, Vollmann D, Hasenfu G, Groschel K, Wachter R. Enhanced detection of paroxysmal atrial fibrillation by early and prolonged continuous holter monitoring in patients with cerebral ischemia presenting in sinus rhythm. Stroke. 2010;41(12):2884-8.

133. Ritter MA, Kochhauser S, Duning T, Reinke F, Pott C, Dechering DG, Eckardt L, Ringelstein EB. Occult atrial fibrillation in cryptogenic stroke: detection by 7-day electrocardiogram versus implantable cardiac monitors. Stroke. 2013;44(5):1449-52.

134. Higgins P, MacFarlane PW, Dawson J, McInnes GT, Langhorne P, Lees KR. Noninvasive cardiac event monitoring to detect atrial fibrillation after ischemic stroke: a randomized, controlled trial. Stroke. 2013;44(9):2525-31.

135. Thakkar S, Bagarhatta R. Detection of paroxysmal atrial fibrillation or flutter in patients with acute ischemic stroke or transient ischemic attack by Holter monitoring. Indian Heart Journal. 2014;66(2):188-92.

136. Wachter R, Gröschel K, Gelbrich G, Hamann GF, Kermer P, Liman J, Seegers J, Wasser K, Schulte A, Jürries F. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AF RANDOMISED): an open-label randomised controlled trial. Lancet Neurology. 2017;16(4):282-90.

137. Gumbinger C, Krumsdorf U, Veltkamp R, Hacke W, Ringleb P. Continuous monitoring versus HOLTER ECG for detection of atrial fibrillation in patients with stroke. European Journal of Neurology. 2012;19(2):253-7.

138. Alhadramy O, Jeerakathil TJ, Majumdar SR, Najjar E, Choy J, Saqqur M. Prevalence and predictors of paroxysmal atrial fibrillation on Holter monitor in patients with stroke or transient ischemic attack. Stroke. 2010;41(11):2596-600.

139. Dangayach NS, Kane K, Moonis M. Paroxysmal atrial fibrillation in cryptogenic stroke. Therapeutics and Clinical Risk Management. 2011;7(1):33-7.

140. Gunalp M, Atalar E, Coskun F, Yilmaz A, Aksoyek S, Aksu NM, Sivri B. Holter monitoring for 24 hours in patients with thromboembolic stroke and sinus rhythm diagnosed in the emergency department. Advances in Therapy. 2006;23(6):854-60.

141. Fonseca AC, Brito D, Pinho e Melo T, Geraldes R, Canhao P, Caplan LR, Ferro JM. N-terminal pro-brain natriuretic peptide shows diagnostic accuracy for detecting atrial fibrillation in cryptogenic stroke patients. International Journal of Stroke. 2014;9(4):419-25.

142. Manina G, Agnelli G, Becattini C, Zingarini G, Paciaroni M. 96 hours ECG monitoring for patients with ischemic cryptogenic stroke or transient ischaemic attack. Internal & Emergency Medicine. 2014;9(1):65-7.

143. Tagawa M, Takeuchi S, Chinushi M, Saeki M, Taniguchi Y, Nakamura Y, Ohno H, Kitazawa K, Aizawa Y. Evaluating patients with acute ischemic stroke with special reference to newly developed atrial fibrillation in cerebral embolism. Pacing and Clinical Electrophysiology. 2007;30(9):1121-8.

144. Shibazaki K, Kimura K, Fujii S, Sakai K, Iguchi Y. Brain natriuretic peptide levels as a predictor for new atrial fibrillation during hospitalization in patients with acute ischemic stroke. The American journal of cardiology. 2012;109(9):1303-7.

145. Vandenbroucke E, Thijs V. Diagnostic and therapeutic impact of ambulatory electrocardiography in acute stroke. Acta Neurologica Belgica. 2004;104(1):27-31.

146. Yodogawa K, Seino Y, Ohara T, Hayashi M, Miyauchi Y, Katoh T, Mizuno K. Prediction of atrial fibrillation after ischemic stroke using P-wave signal averaged electrocardiography. Journal of Cardiology. 2013;61(1):49-52.

147. Atmuri K, Hughes A, Coles D, Ahmad O, Neeman T, Lueck C. The role of cardiac disease parameters in predicting the results of Holter monitoring in patients with acute ischaemic stroke. Journal of Clinical Neuroscience. 2012;19(7):965-8.

148. Salvatori V, Becattini C, Laureti S, Baglioni G, Germini F, Grilli P, Guercini F, Filippucci E, Agnelli G. Holter monitoring to detect silent atrial fibrillation in high-risk subjects: the Perugia General Practitioner Study. Internal & Emergency Medicine. 2015;10(5):595-601.

149. Beaulieu-Boire I, Leblanc N, Berger L, Boulanger JM. Troponin elevation predicts atrial fibrillation in patients with stroke or transient ischemic attack. Journal of Stroke and Cerebrovascular Diseases. 2013;22(7):978-83.

150. Dogan U, Dogan EA, Tekinalp M, Tokgoz OS, Aribas A, Akilli H, Ozdemir K, Gok H, Yuruten B. P-wave dispersion for predicting paroxysmal atrial fibrillation in acute ischemic stroke. International Journal of Medical Sciences. 2012;9(1):108.

151. Douen AG, Pageau N, Medic S. Serial electrocardiographic assessments significantly improve detection of atrial fibrillation 2.6-fold in patients with acute stroke. Stroke. 2008;39(2):480-2.

152. Suissa L, Bresch S, Lachaud S, Bertora D, Mahagne MH. Optimal timing and duration of continuous ECG monitoring for detecting atrial fibrillation in stroke patients. Archives of Cardiovascular Diseases Supplements. 2012;4:43-4.

153. Wohlfahrt J, Stahrenberg R, Weber-Kruger M, Groschel S, Wasser K, Edelmann F, Seegers J, Wachter R, Groschel K. Clinical predictors to identify paroxysmal atrial fibrillation after ischaemic stroke. European Journal of Neurology. 2014;21(1):21-7.

154. Engdahl J, Andersson L, Mirskaya M, Rosenqvist M. Stepwise Screening of Atrial Fibrillation in a 75-Year-Old PopulationClinical Perspective. Circulation. 2013;127(8):930-7.

155. Hendrikx T, Hörnsten R, Rosenqvist M, Sandström H. Screening for atrial fibrillation with baseline and intermittent ECG recording in an out-of-hospital population. BMC cardiovascular disorders. 2013;13(1):41.

156. Hendrikx T, Sundqvist M, Sandström H, Sahlin C, Rohani M, Al-Khalili F, Hörnsten R, Blomberg A, Wester P, Rosenqvist M. Atrial fibrillation among patients under investigation for suspected obstructive sleep apnea. PloS One. 2017;12(2):e0171575.

157. Ramkumar S, Yang H, Wang Y, D'elia N, Ochi A, West H, Nolan M, Negishi K, Marwick TH. The Role of Left Atrial and Ventricular Function in Prediction of Atrial Fibrillation: P2-19. Journal of the American Society of Echocardiography. 2017;30(6):B70.

158. Claes N, Goethals M, Goethals P, Mairesse G, Schwagten B, Nuyens D, Schrooten W, Vijgen J. Screening for Atrial Fibrillation (AF) in Belgium: A multicentre trial. European Journal of Cardiovascular Prevention and Rehabilitation. 2011;1):S30.

159. Samol A, Masin M, Gellner R, Otte B, Pavenstädt H-J, Ringelstein EB, Reinecke H, Waltenberger J, Kirchhof P. Prevalence of unknown atrial fibrillation in patients with risk factors. Europace. 2013;15(5):657-62.

160. Chan Ny, Siu CW, Choy CC, Chan CK, editors. Effectiveness of community atrial fibrillation screening in over 10,000 citizens using smartphone electrocardiogram- The AFinder program. ESC Congress; 2017 29th August Barcelona.

161. Doliwa Sobocinski P, Änggårdh Rooth E, Frykman Kull V, von Arbin M, Wallén H, Rosenqvist M. Improved screening for silent atrial fibrillation after ischaemic stroke. EP Europace. 2012;14(8):1112-6.

162. Hendrikx T, Rosenqvist M, Wester P, Sandström H, Hörnsten R. Intermittent short ECG recording is more effective than 24-hour Holter ECG in detection of arrhythmias. BMC cardiovascular disorders. 2014;14(1):41.

163. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH. Subclinical Atrial Fibrillation and the Risk of Stroke. New England Journal of Medicine. 2012;366(2):120-9.

164. Desteghe L, Raymaekers Z, Lutin M, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Vanduynhoven P, Dendale P, Heidbuchel H. Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. Europace. 2016:euw025.

165. Williams J, Pearce K, Benett I, Williams J, Manchester M. The effectiveness of a mobile ECG device in identifying AF: sensitivity, specificity and predictive value. British Journal of Cardiology. 2015;22(2).

166. Steinhubl SR, Waalen J, Edwards AM, Ariniello LM, Mehta RR, Ebner GS, Carter C, Baca-Motes K, Felicione E, Sarich T. Effect of a home-based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation: the mSToPS randomized clinical trial. JAMA. 2018;320(2):146-55.

167. Turakhia MP, Desai M, Hedlin H, Rajmane A, Talati N, Ferris T, Desai S, Nag D, Patel M, Kowey P, Rumsfeld JS, Russo AM, Hills MT, Granger CB, Mahaffey KW, Perez MV. Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: The Apple Heart Study. American Heart Journal. 2019;207:66-75.

168. Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M, Luderitz B. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. Journal of the American College of Cardiology. 2000;36(4):1303-9.

169. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna W, Seward JB, Iwasaka T, Tsang TS. Incidence and mortality risk of congestive heart failure in atrial fibrillation patients: a community-based study over two decades. European Heart Journal. 2006;27(8):936-41.

170. McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. Annals of Internal Medicine. 2003;139(12):1018-33.

171. Ahmed A, Perry GJ. Incident atrial fibrillation and mortality in older adults with heart failure. European journal of heart failure. 2005;7(7):1118-21.

172. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation A study in awake chronically instrumented goats. Circulation. 1995;92(7):1954-68.

173. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. Journal of the American College of Cardiology. 2008;51(8):802-9.

174. Goldberg LR, Jessup M. Stage B heart failure management of asymptomatic left ventricular systolic dysfunction. Circulation. 2006;113(24):2851-60.

175. Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Takemoto Y, Diamond PM, Marra MA, Gersh BJ, Wiebers DO, editors. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. Mayo Clinic proceedings; 2001: Elsevier.

176. Dimitri H, Ng M, Brooks AG, Kuklik P, Stiles MK, Lau DH, Antic N, Thornton A, Saint DA, McEvoy D, Antic R, Kalman JM, Sanders P. Atrial remodeling in obstructive sleep apnea: Implications for atrial fibrillation. Heart Rhythm. 2012;9(3):321-7.

177. Ancona R, Comenale Pinto S, Caso P, D'Andrea A, Di Salvo G, Arenga F, Coppola MG, Sellitto V, Macrino M, Calabrò R. Left atrium by echocardiography in clinical practice: from conventional methods to new echocardiographic techniques. The Scientific World Journal. 2014;2014.

178. Kusunose K, Motoki H, Popovic ZB, Thomas JD, Klein AL, Marwick TH. Independent association of left atrial function with exercise capacity in patients with preserved ejection fraction. Heart. 2012:heartjnl-2012-302007.

179. Gorcsan J, Tanaka H. Echocardiographic assessment of myocardial strain. Journal of the American College of Cardiology. 2011;58(14):1401-13.

180. Edvardsen T, Gerber BL, Garot J, Bluemke DA, Lima JA, Smiseth OA. Quantitative assessment of intrinsic regional myocardial deformation by Doppler strain rate echocardiography in humans validation against three-dimensional tagged magnetic resonance imaging. Circulation. 2002;106(1):50-6.

181. Ciaroni S, Cuenoud L, Bloch A. Clinical study to investigate the predictive parameters for the onset of atrial fibrillation in patients with essential hypertension. American Heart Journal. 2000;139(5):814-9.

182. Dorian P, Paquette M, Newman D, Green M, Connolly SJ, Talajic M, Roy D. Quality of life improves with treatment in the Canadian Trial of Atrial Fibrillation. American Heart Journal. 2002;143(6):984-90.

183. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical Activity and Incidence of Atrial Fibrillation in Older Adults: The Cardiovascular Health Study. Circulation. 2008;118(8):800-7.

184. Azarbal F, Stefanick ML, Salmoirago-Blotcher E, Manson JE, Albert CM, LaMonte MJ, Larson JC, Li W, Martin LW, Nassir R. Obesity, physical activity, and their interaction in incident atrial fibrillation in postmenopausal women. Journal of the American Heart Association. 2014;3(4):e001127.

185. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM, Twomey D, Kalman JM, Abhayaratna WP. Impact of CARDIOrespiratory FITness on arrhythmia recurrence in obese individuals with atrial fibrillation: the CARDIO-FIT study. Journal of the American College of Cardiology. 2015;66(9):985-96.

186. Miller JD, Aronis KN, Chrispin J, Patil KD, Marine JE, Martin SS, Blaha MJ, Blumenthal RS, Calkins H. Obesity, Exercise, Obstructive Sleep Apnea, and Modifiable Atherosclerotic Cardiovascular Disease Risk Factors in Atrial Fibrillation. Journal of the American College of Cardiology. 2015;66(25):2899-906.

187. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, Maclehose R, Konety S, Alonso A. Absolute and Attributable Risks of Atrial Fibrillation in Relation to Optimal and Borderline Risk FactorsClinical Perspective. Circulation. 2011;123(14):1501-8.

188. McLaren L. Socioeconomic status and obesity. Epidemiologic reviews. 2007;29(1):29-48.

189. Fone DL, Farewell DM, White J, Lyons RA, Dunstan FD. Socioeconomic patterning of excess alcohol consumption and binge drinking: a cross-sectional study of multilevel associations with neighbourhood deprivation. BMJ Open. 2013;3(4).

190. Lawani SO, Demerath EW, Lopez FL, Soliman EZ, Huxley RR, Rose KM, Alonso A. Birth weight and the risk of atrial fibrillation in whites and African Americans: the Atherosclerosis Risk In Communities (ARIC) study. BMC cardiovascular disorders. 2014;14(1):69.

191. Sholzberg M, Gomes T, Juurlink DN, Yao Z, Mamdani MM, Laupacis A. The influence of socioeconomic status on selection of anticoagulation for atrial fibrillation. PloS one. 2016;11(2):e0149142.

192. Cameli M, Ciccone MM, Maiello M, Modesti PA, Muiesan ML, Scicchitano P, Novo S, Palmiero P, Saba PS, Pedrinelli R. Speckle tracking analysis: a new tool for left atrial function analysis in systemic hypertension: an overview. Journal of Cardiovascular Medicine. 2016;17(5):339-43.

193. Vieira MJ, Teixeira R, Gonçalves L, Gersh BJ. Left Atrial Mechanics: Echocardiographic Assessment and Clinical Implications. Journal of the American Society of Echocardiography. 2014;27(5):463-78.

194. Saraiva RM, Demirkol S, Buakhamsri A, Greenberg N, Popović ZB, Thomas JD, Klein AL. Left atrial strain measured by two-dimensional speckle tracking represents a new tool to evaluate left atrial function. Journal of the American Society of Echocardiography. 2010;23(2):172-80.

195. Tsai WC, Lee CH, Lin CC, Liu YW, Huang YY, Li WT, Chen JY, Lin LJ. Association of left atrial strain and strain rate assessed by speckle tracking echocardiography with paroxysmal atrial fibrillation. Echocardiography. 2009;26(10):1188-94.

196. Cameli M, Caputo M, Mondillo S, Ballo P, Palmerini E, Lisi M, Marino E, Galderisi M. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. Cardiovasc Ultrasound. 2009;7:6.

197. Eapen ZJ, Greiner MA, Fonarow GC, Yuan Z, Mills RM, Hernandez AF, Curtis LH. Associations between atrial fibrillation and early outcomes of patients with heart failure and reduced or preserved ejection fraction. American Heart Journal. 2014;167(3):369-75. e2.

198. Mountantonakis SE, Grau-Sepulveda MV, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Presence of Atrial Fibrillation is Independently Associated with Adverse Outcomes in Patients Hospitalized with Heart Failure: An Analysis of GWTG-Heart Failure. Circulation: Heart Failure. 2012:CIRCHEARTFAILURE. 111.965681.

199. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. European Heart Journal. 2007.

200. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Smiseth O, Tavazzi L. The task force for the diagnosis and treatment of chronic heart failure of the european society of cardiology: Guidelines for the diagnosis and treatment of chronic heart failure: Reply. European Heart Journal. 2005;26(22):2473-4.

201. Soullier C, Niamkey JT, Ricci J-E, Messner-Pellenc P, Brunet X, Schuster I. Hypertensive patients with left ventricular hypertrophy have global left atrial dysfunction and impaired atrio-ventricular coupling. Journal of hypertension. 2016.

202. Akkaya M, Higuchi K, Koopmann M, Burgon N, Erdogan E, Damal K, Kholmovski E, McGann C, Marrouche NF. Relationship between left atrial tissue structural remodelling detected using late gadolinium enhancement MRI and left ventricular hypertrophy in patients with atrial fibrillation. Europace. 2013;15(12):1725-32.

203. Melenovsky V, Hwang S-J, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circulation: Heart Failure. 2015;8(2):295-303.

204. Peters DC, Duncan JS, Grunseich K, Marieb M, Cornfeld D, Sinusas AJ, Chelikani S. Lower left atrial strain in the presence of regional atrial fibrosis: an MRI study of patients with atrial fibrillation. Journal of Cardiovascular Magnetic Resonance. 2016;18(1):1-2.

205. Harada M, Van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management. Circulation journal: official journal of the Japanese Circulation Society. 2014;79(3):495-502.

206. Chen D, Procter N, Goh V, Liu S, Chua S, Assadi-Khansari B, Stewart S, Horowitz J, Sverdlov A, Ngo D. New onset atrial fibrillation is associated with elevated galectin-3 levels. International Journal of Cardiology. 2016;223:48.

207. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. Journal of the American Society of Echocardiography. 2005;18(12):1440-63.

208. Imanishi J, Tanaka H, Sawa T, Motoji Y, Miyoshi T, Mochizuki Y, Fukuda Y, Tatsumi K, Matsumoto K, Okita Y. Association of Left Atrial Booster-Pump Function with Heart Failure Symptoms in Patients with Severe Aortic Stenosis and Preserved Left Ventricular Ejection Fraction. Echocardiography. 2015;32(5):758-67.

209. Pinheiro AC, Dimaano VL, Sorensen L, Liang H-Y, Luo H-C, Mbiyangandu BK, Abraham R, Abraham T. Left atrial strain rate as a predictor of low exercise capacity in hypertrophic cardiomyopathy patients. Journal of the American College of Cardiology. 2012;59(13s1):E1294-E.

210. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography. 2016;29(4):277-314.

211. Cameli M, Lisi M, Mondillo S, Padeletti M, Ballo P, Tsioulpas C, Bernazzali S, Maccherini M. Left atrial longitudinal strain by speckle tracking echocardiography correlates well with left ventricular filling pressures in patients with heart failure. Cardiovascular Ultrasound. 2010;8(1):14.

212. Caso P, Ancona R, Di Salvo G, Pinto SC, Macrino M, Di Palma V, D'Andrea A, Martiniello A, Severino S, Calabrò R. Atrial reservoir function by strain rate imaging in asymptomatic mitral stenosis: prognostic value at 3 year follow-up. European Heart Journal-Cardiovascular Imaging. 2009;10(6):753-9.

213. Freed BH, Daruwalla V, Cheng JY, Aguilar FG, Beussink L, Choi A, Klein DA, Dixon D, Baldridge A, Rasmussen-Torvik LJ. Prognostic Utility and Clinical Significance of Cardiac Mechanics in Heart Failure With Preserved Ejection Fraction Importance of Left Atrial Strain. Circulation: Cardiovascular Imaging. 2016;9(3):e003754.

214. Helle-Valle T, Opdahl A, Broch K, Gude E, Andreassen A, Smiseth OA, Gullestad L. Left Atrial Strain by Speckle Tracking Echocardiography In Patients with Heart Failure-An Independent and Incremental Predictor of Cardiac Death or Need of Heart Transplantation. Circulation. 2011;124(Suppl 21):A8551-A.

215. Hwang HJ, Choi E-Y, Rhee SJ, Joung B, Lee B-H, Lee S-H, Kim J, Lee M-H, Jang Y, Chung N, Kim SS. Left atrial strain as predictor of successful outcomes in catheter ablation for atrial fibrillation: a two-dimensional myocardial imaging study. Journal of Interventional Cardiac Electrophysiology. 2009;26(2):127-32.

216. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P,

Ovbiagele B, Smith SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Williamson JD, Wright JT. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. 2018;71(19):e127-e248.

217. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, AlMazroa MA, Amann M, Anderson HR, Andrews KG. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012;380(9859):2224-60.

218. Picone DS, Schultz MG, Otahal P, Aakhus S, Al-Jumaily AM, Black JA, Bos WJ, Chambers JB, Chen C-H, Cheng H-M. Accuracy of cuff-measured blood pressure: systematic reviews and meta-analyses. Journal of the American College of Cardiology. 2017;70(5):572-86.

219. Cheng HM, Chuang SY, Sung SH, Yu WC, Pearson A, Lakatta EG, Pan WH, Chen CH. Derivation and validation of diagnostic thresholds for central blood pressure measurements based on long-term cardiovascular risks. Journal of the American College of Cardiology. 2013;62(19):1780-7.

220. Huang CM, Wang KL, Cheng HM, Chuang SY, Sung SH, Yu WC, Ting CT, Lakatta EG, Yin FC, Chou P, Chen CH. Central versus ambulatory blood pressure in the prediction of all-cause and cardiovascular mortalities. Journal of hypertension. 2011;29(3):454-9.

221. Kollias A, Lagou S, Zeniodi ME, Boubouchairopoulou N, Stergiou GS. Association of central versus brachial blood pressure with target-organ damage: systematic review and meta-analysis. Hypertension. 2016;67(1):183-90.

222. McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. European Heart Journal. 2014;35(26):1719-25.

223. Sharman JE, Avolio AP, Baulmann J, Benetos A, Blacher J, Blizzard CL, Boutouyrie P, Chen C-H, Chowienczyk P, Cockcroft JR, Cruickshank JK, Ferreira I, Ghiadoni L, Hughes A, Jankowski P, Laurent S, McDonnell BJ, McEniery C, Millasseau SC, Papaioannou TG, Parati G, Park JB, Protogerou AD, Roman MJ, Schillaci G, Segers P, Stergiou GS, Tomiyama H, Townsend RR, Van Bortel LM, Wang J, Wassertheurer S, Weber T, Wilkinson IB, Vlachopoulos C. Validation of non-invasive central blood pressure devices: ARTERY Society task force consensus statement on protocol standardization. European Heart Journal. 2017;38(37):2805-12.

224. Kobayashi H, Kinou M, Takazawa K. Correlation between the brachial blood pressure values obtained using the cuff method and the central blood pressure values obtained invasively. Internal Medicine. 2013;52(15):1675-80.

225. Negishi K, Yang H, Wang Y, Nolan MT, Negishi T, Pathan F, Marwick TH, Sharman JE. Importance of calibration method in central blood pressure for cardiac structural abnormalities. American Journal of Hypertension. 2016;29(9):1070-6.

226. Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Brooks AG, Worthington M, Rajendram A, Kelly DR, Zhang Y, Kuklik P. Hypertension and atrial fibrillation: evidence of progressive atrial remodeling with electrostructural correlate in a conscious chronically instrumented ovine model. Heart Rhythm. 2010;7(9):1282-90.

227. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, Galderisi M, Marwick T, Nagueh SF, Sengupta PP. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. European Journal of Echocardiography. 2011;12(3):167-205.

228. Millasseau S, Agnoletti D. Non-invasive estimation of aortic blood pressures: a close look at current devices and methods. Current Pharmaceutical Design. 2015;21(6):709-18.

229. Sharman JE, Marwick TH, Gilroy D, Otahal P, Abhayaratna WP, Stowasser M. Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care: principal findings of the BP GUIDE study. Hypertension. 2013;62(6):1138-45.

230. Vaziri SM, Larson MG, Lauer MS, Benjamin EJ, Levy D. Influence of blood pressure on left atrial size: the Framingham Heart Study. Hypertension. 1995;25(6):1155-60.

231. Ramkumar S, Yang H, Wang Y, Nolan M, Negishi T, Negishi K, Marwick TH. Association of the Active and Passive Components of Left Atrial Deformation with Left Ventricular Function. Journal of the American Society of Echocardiography. 2017;30(7):659-66.

232. Benetos A, Thomas F, Bean K, Gautier S, Smulyan H, Guize L. Prognostic value of systolic and diastolic blood pressure in treated hypertensive men. Archives of Internal Medicine. 2002;162(5):577-81.

233. Weber T, Wassertheurer S, Rammer M, Maurer E, Hametner B, Mayer CC, Kropf J, Eber B. Validation of a brachial cuff-based method for estimating central systolic blood pressure. Hypertension. 2011;58(5):825-32.

234. Kelly R, Gibs H, O'ROURKE M, Daley J, Mang K, Morgen J, Avolid A. Nitroglycerin has more favourable effects on left ventricular afterload than apparent from measurement of pressure in a peripheral artery. European heart journal. 1990;11(2):138-44.

235. Matsui Y, Eguchi K, O'Rourke MF, Ishikawa J, Miyashita H, Shimada K, Kario K. Differential effects between a calcium channel blocker and a diuretic when used in combination with angiotensin II receptor blocker on central aortic pressure in hypertensive patients. Hypertension. 2009;54(4):716-23.

236. Manisty CH, Zambanini A, Parker KH, Davies JE, Francis DP, Mayet J, McG Thom SA, Hughes AD. Differences in the magnitude of wave reflection account for differential

effects of amlodipine-versus atenolol-based regimens on central blood pressure: an Anglo-Scandinavian Cardiac Outcome Trial substudy. Hypertension. 2009;54(4):724-30.

237. Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Sanders P, Marwick TH. Relation of functional status to risk of development of atrial fibrillation. The American Journal of Cardiology. 2017;119(4):572-8.

238. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998;98(10):946-52.

239. Sposato LA, Cipriano LE, Saposnik G, Vargas ER, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. The Lancet Neurology.14(4):377-87.

240. Ramkumar S, Nerlekar N, D'Souza D, Pol DJ, Kalman JM, Marwick TH. Atrial fibrillation detection using single lead portable electrocardiographic monitoring: a systematic review and meta-analysis. BMJ open. 2018;8(9):e024178.

241. Claes N, Van Laethem C, Goethals M, Goethals P, Mairesse G, Schwagten B, Nuyens D, Schrooten W, Vijgen J. Prevalence of atrial fibrillation in adults participating in a large-scale voluntary screening programme in Belgium. Acta cardiologica. 2012;67(3):273-8.

242. United Kingdom National Screening Committee: The UK NSC Recommendation on Atrial Fibrillation Screening in Adults: https://legacyscreening.phe.org.uk/atrialfibrillation; 2014 [Available from: https://legacyscreening.phe.org.uk/atrialfibrillation.

243. Wilson JMG, Jungner G. Principles and practice of screening for disease. World Health Organization. 1968.

244. Mairesse GH, Moran P, Van Gelder IC, Elsner C, Rosenqvist M, Mant J, Banerjee A, Gorenek B, Brachmann J, Varma N. Screening for atrial fibrillation: a European heart rhythm Association (EHRA) consensus document endorsed by the heart rhythm Society (HRS), Asia Pacific heart rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca Y Electrofisiología (SOLAECE). Ep Europace. 2017;19(10):1589-623.

245. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013;62(16):e147-e239.

246. Alonso A, Bahnson JL, Gaussoin SA, Bertoni AG, Johnson KC, Lewis CE, Vetter M, Mantzoros CS, Jeffery RW, Soliman EZ. Effect of an intensive lifestyle intervention on atrial fibrillation risk in individuals with type 2 diabetes: the Look AHEAD randomized trial. American Heart Journal. 2015;170(4):770-7. e5.

247. Lowres N, Fitzmaurice DA, Hobbs FDR, Kaasenbrood F, Lee V, Tieleman R, Yan B, Freedman SB. Abstract 20082: Guideline-based Screening for Atrial Fibrillation: Analysis of Yield and Stroke Risk. Circulation. 2017;136(Suppl 1):A20082-A.

248. Ramkumar S, Ochi A, Yang H, Nerlekar N, D'Elia N, Potter EL, Murray IC, Nattraj N, Wang Y, Marwick TH. Association between Socio-Economic Status and Incident Atrial Fibrillation. Internal Medicine Journal. 2019;49(10):1244-51.

249. Movahed M-R, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. International Journal of Cardiology. 2005;105(3):315-8.

250. Delgado V, Di Biase L, Leung M, Romero J, Tops LF, Casadei B, Marrouche N, Bax JJ. Structure and function of the left atrium and left atrial appendage: AF and stroke implications. Journal of the American College of Cardiology. 2017;70(25):3157-72.

251. Ramkumar S, Ochi A, Kawakami H, Yang H, Potter EL, D'Elia N, Negishi T, Negishi K, Marwick TH. Echocardiographic Risk Assessment to Guide Screening for Atrial Fibrillation. Journal of the American Society of Echocardiography. 2019;32(10):1259-67.

252. Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh 3rd E. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35-41.

253. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, Horton K, Ogunyankin KO, Palma RA, Velazquez EJ. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. Journal of the American Society of Echocardiography. 2019;32(1):1-64.

254. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982;143(1):29-36.

255. Cameli M, Lisi M, Focardi M, Reccia R, Natali BM, Sparla S, Mondillo S. Left atrial deformation analysis by speckle tracking echocardiography for prediction of cardiovascular outcomes. The American journal of cardiology. 2012;110(2):264-9.

256. Gibbs H, Freedman B, Rosenqvist M, Al Mahmeed W, Ambrosio G, Camm AJ, Connolly SJ, Gao H, Jacobson B, Jerjes-Sanchez C. P4602Similar clinical outcomes of asymptomatic and symptomatic patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. European heart journal. 2017;38(suppl_1).

257. Guo Y, Wang H, Zhang H, Liu T, Liang Z, Xia Y, Yan L, Xing Y, Shi H, Li S. Mobile Health Technology for Atrial Fibrillation Screening Using Photoplethysmography-Based Smart Devices: The HUAWEI Heart study. Journal of the American College of Cardiology. 2019.

258. Kolek MJ, Graves AJ, Xu M, Bian A, Teixeira PL, Shoemaker MB, Parvez B, Xu H, Heckbert SR, Ellinor PT. Evaluation of a prediction model for the development of atrial fibrillation in a repository of electronic medical records. JAMA cardiology. 2016;1(9):1007-13.

259. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004;110(9):1042-6.

260. Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. Chest. 2012;142(6):1489-98.

261. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation. 1995;91(5):1588-95.

262. Pandozi C, Santini M. Update on atrial remodelling owing to rate; does atrial fibrillation always 'beget' atrial fibrillation? European heart journal. 2001;22(7):541-53.

263. Tsang TS, Gersh BJ, Appleton CP, Tajik AJ, Barnes ME, Bailey KR, Oh JK, Leibson C, Montgomery SC, Seward JB. Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. Journal of the American College of Cardiology. 2002;40(9):1636-44.

264. Fatema K, Barnes ME, Bailey KR, Abhayaratna WP, Cha S, Seward JB, Tsang TS. Minimum vs. maximum left atrial volume for prediction of first atrial fibrillation or flutter in an elderly cohort: a prospective study. European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology. 2009;10(2):282-6.

265. Conen D, Glynn RJ, Sandhu RK, Tedrow UB, Albert CM. Risk factors for incident atrial fibrillation with and without left atrial enlargement in women. International Journal of Cardiology. 2013;168(3):1894-9.

266. Hong J, Gu X, An P, Luo T, Lv Q, Kang J, He Y, Hu R, Liu X, Ma C. Left atrial functional remodeling in lone atrial fibrillation: a two-dimensional speckle tracking echocardiographic study. Echocardiography. 2013;30(9):1051-60.

267. Abhayaratna WP, Fatema K, Barnes ME, Seward JB, Gersh BJ, Bailey KR, Casaclang-Verzosa G, Tsang TS. Left atrial reservoir function as a potent marker for first atrial fibrillation or flutter in persons > or = 65 years of age. American Journal of Cardiology. 2008;101(11):1626-9.

268. Hirose T, Kawasaki M, Tanaka R, Ono K, Watanabe T, Iwama M, Noda T, Watanabe S, Takemura G, Minatoguchi S. Left atrial function assessed by speckle tracking echocardiography as a predictor of new-onset non-valvular atrial fibrillation: results from a prospective study in 580 adults. European Heart Journal - Cardiovascular Imaging. 2012;13(3):243-50.

269. Haugaa KH, Edvardsen T, Leren TP, Gran JM, Smiseth OA, Amlie JP. Left ventricular mechanical dispersion by tissue Doppler imaging: a novel approach for identifying high-risk individuals with long QT syndrome. European Heart Journal. 2009;30(3):330-7.

270. Haugaa KH, Goebel B, Dahlslett T, Meyer K, Jung C, Lauten A, Figulla HR, Poerner TC, Edvardsen T. Risk assessment of ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy by strain echocardiography. J Am Soc Echocardiogr. 2012;25(6):667-73.

271. Haugaa KH, Smedsrud MK, Steen T, Kongsgaard E, Loennechen JP, Skjaerpe T, Voigt JU, Willems R, Smith G, Smiseth OA, Amlie JP, Edvardsen T. Mechanical dispersion assessed by myocardial strain in patients after myocardial infarction for risk prediction of ventricular arrhythmia. JACC Cardiovasc Imaging. 2010;3(3):247-56.

272. Watanabe Y, Nakano Y, Hidaka T, Oda N, Kajihara K, Tokuyama T, Uchimura Y, Sairaku A, Motoda C, Fujiwara M, Kawazoe H, Matsumura H, Kihara Y. Mechanical and substrate abnormalities of the left atrium assessed by 3-dimensional speckle-tracking echocardiography and electroanatomic mapping system in patients with paroxysmal atrial fibrillation. Heart Rhythm. 2015;12(3):490-7.

273. Ciuffo L, Tao S, Gucuk Ipek E, Zghaib T, Balouch M, Lima JAC, Nazarian S, Spragg DD, Marine JE, Berger RD, Calkins H, Ashikaga H. Intra-Atrial Dyssynchrony During Sinus Rhythm Predicts Recurrence After the First Catheter Ablation for Atrial Fibrillation. JACC Cardiovasc Imaging. 2018.

274. Shang Z, Su D, Cong T, Sun Y, Liu Y, Chen N, Yang J. Assessment of left atrial mechanical function and synchrony in paroxysmal atrial fibrillation with two-dimensional speckle tracking echocardiography. Echocardiography. 2017;34(2):176-83.

275. Mochizuki A, Yuda S, Oi Y, Kawamukai M, Nishida J, Kouzu H, Muranaka A, Kokubu N, Shimoshige S, Hashimoto A, Tsuchihashi K, Watanabe N, Miura T. Assessment of left atrial deformation and synchrony by three-dimensional speckle-tracking echocardiography: comparative studies in healthy subjects and patients with atrial fibrillation. Journal of the American Society of Echocardiography. 2013;26(2):165-74.

276. Kobayashi Y, Okura H, Kobayashi Y, Okawa K, Banba K, Hirohata A, Tamada T, Obase K, Hayashida A, Yoshida K. Assessment of atrial synchrony in paroxysmal atrial fibrillation and impact of pulmonary vein isolation for atrial dyssynchrony and global strain by three-dimensional strain echocardiography. J Am Soc Echocardiogr. 2014;27(11):1193-9.

277. Furukawa A, Ishii K, Hyodo E, Shibamoto M, Komasa A, Nagai T, Tada E, Seino Y, Yoshikawa J. Three-Dimensional Speckle Tracking Imaging for Assessing Left Atrial Function in Hypertensive Patients With Paroxysmal Atrial Fibrillation. International Heart Journal. 2016;57(6):705-11.

278. Sakabe K, Fukuda N, Fukuda Y, Morishita S, Shinohara H, Tamura Y. Interatrial dyssynchrony on tissue Doppler imaging predicts progression to chronic atrial fibrillation in patients with non-valvular paroxysmal atrial fibrillation. Heart. 2009;95(12):988-93.

279. Sarvari SI, Haugaa KH, Stokke TM, Ansari HZ, Leren IS, Hegbom F, Smiseth OA, Edvardsen T. Strain echocardiographic assessment of left atrial function predicts recurrence of atrial fibrillation. European Heart Journal - Cardiovascular Imaging. 2016;17(6):660-7.

280. Cho GY, Jo SH, Kim MK, Kim HS, Park WJ, Choi YJ, Hong KS, Oh DJ, Rhim CY. Left atrial dyssynchrony assessed by strain imaging in predicting future development of atrial fibrillation in patients with heart failure. International Journal of Cardiology. 2009;134(3):336-41.

281. Kupczynska K, Michalski BW, Miskowiec D, Kasprzak JD, Szymczyk E, Wejner Mik P, Lipiec P. Incremental value of left atrial mechanical dispersion over CHA2 DS2 - VASc score in predicting risk of thrombus formation. Echocardiography. 2018;35(5):651-60.

282. Russo C, Jin Z, Sera F, Lee ES, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR. Left Ventricular Systolic Dysfunction by Longitudinal Strain Is an Independent Predictor of Incident Atrial Fibrillation: A Community-Based Cohort Study. Circ Cardiovasc Imaging. 2015;8(8):e003520.

283. Bonapace S, Valbusa F, Bertolini L, Zenari L, Canali G, Molon G, Lanzoni L, Cecchetto A, Rossi A, Mantovani A, Zoppini G, Barbieri E, Targher G. Early impairment in left ventricular longitudinal systolic function is associated with an increased risk of incident atrial fibrillation in patients with type 2 diabetes. J Diabetes Complications. 2017;31(2):413-8.

284. Magnani JW, Zhu L, Lopez F, Pencina MJ, Agarwal SK, Soliman EZ, Benjamin EJ, Alonso A. P-wave indices and atrial fibrillation: cross-cohort assessments from the Framingham Heart Study (FHS) and Atherosclerosis Risk in Communities (ARIC) study. American heart journal. 2015;169(1):53-61. e1.

285. Schumacher K, Dagres N, Hindricks G, Husser D, Bollmann A, Kornej J. Characteristics of PR interval as predictor for atrial fibrillation: association with biomarkers and outcomes. Clinical Research in Cardiology. 2017;106(10):767-75.

286. Motoki H, Dahiya A, Bhargava M, Wazni OM, Saliba WI, Marwick TH, Klein AL. Assessment of left atrial mechanics in patients with atrial fibrillation: comparison between two-dimensional speckle-based strain and velocity vector imaging. Journal of the American Society of Echocardiography. 2012;25(4):428-35.

287. Wilson JMG, Jungner G. World Health Organisation. Principles and practice of screening for disease. 1968.

288. Hammoudi N, Duprey M, Régnier P, Achkar M, Boubrit L, Preud'Homme G, Healy-Brucker A, Vignalou J-B, Pousset F, Komajda M. Pretest probability of a normal echocardiography: validation of a simple and practical algorithm for routine use. Archives of cardiovascular diseases. 2014;107(2):105-11.

289. Bassand J-P, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KA, Goldhaber SZ, Goto S, Haas S, Hacke W. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. European Heart Journal. 2016;37(38):2882-9.

290. Johnson ME, Lefèvre C, Collings S-L, Evans D, Kloss S, Ridha E, Maguire A. Early real-world evidence of persistence on oral anticoagulants for stroke prevention in non-valvular atrial fibrillation: a cohort study in UK primary care. BMJ open. 2016;6(9):e011471.

291. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. 2017;70(6):776-803.

292. Nolan MT, Plana JC, Thavendiranathan P, Shaw L, Si L, Marwick TH. Cost-effectiveness of strain-targeted cardioprotection for prevention of chemotherapy-induced cardiotoxicity. International Journal of Cardiology. 2016;212:336-45.

293. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. Value in Health. 2013;16(2):231-50.

294. Harrington AR, Armstrong EP, Nolan Jr PE, Malone DC. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. Stroke. 2013;44(6):1676-81.

295. Diener H-C, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, Xavier D, Di Pasquale G, Yusuf S, group R-Ls. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. The Lancet Neurology. 2010;9(12):1157-63.

296. Kamel H, Johnston SC, Easton JD, Kim AS. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack. Stroke. 2012;43(3):881-3.

297. Hemphill JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score. Stroke. 2001;32(4):891-7.

298. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine. 2011;365(10):883-91.

299. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. New England Journal of Medicine. 2010;362(23):2155-65.

300. Goto S, Angchaisuksiri P, Bassand JP, Camm AJ, Dominguez H, Illingworth L, Gibbs H, Goldhaber SZ, Goto S, Jing ZC. Management and 1-Year Outcomes of Patients With Newly Diagnosed Atrial Fibrillation and Chronic Kidney Disease: Results From the Prospective GARFIELD-AF Registry. Journal of the American Heart Association. 2019;8(3):e010510.

301. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of internal medicine. 2007;146(12):857-67.

302. Schleinitz MD, Weiss JP, Owens DK. Clopidogrel versus aspirin for secondary prophylaxis of vascular events: a cost-effectiveness analysis. The American Journal of Medicine. 2004;116(12):797-806.

303. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation. 2002;106(24):3068-72.

304. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29-322.

305. Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, Wang PJ, Turakhia MP. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Annals of Internal Medicine. 2011;154(1):1-11.

306. Baeten SA, van Exel NJA, Dirks M, Koopmanschap MA, Dippel DW, Niessen LW. Lifetime health effects and medical costs of integrated stroke services-a non-randomized controlled cluster-trial based life table approach. Cost Effectiveness and Resource Allocation. 2010;8(1):21.

307. Gaziano TA, Fonarow GC, Claggett B, Chan WW, Deschaseaux-Voinet C, Turner SJ, Rouleau JL, Zile MR, McMurray JJ, Solomon SD. Cost-effectiveness analysis of sacubitril/valsartan vs enalapril in patients with heart failure and reduced ejection fraction. JAMA cardiology. 2016;1(6):666-72.

308. Göhler A, Geisler BP, Manne JM, Kosiborod M, Zhang Z, Weintraub WS, Spertus JA, Gazelle GS, Siebert U, Cohen DJ. Utility estimates for decision–Analytic modeling in chronic heart failure—Health states based on New York Heart Association classes and number of rehospitalizations. Value in Health. 2009;12(1):185-7.

309. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. Medical Decision Making. 2006;26(4):410-20.

310. Heidenreich PA, Masoudi FA, Maini B, Chou TM, Foster E, Schiller NB, Owens DK. Echocardiography in patients with suspected endocarditis: a cost-effectiveness analysis. The American Journal of Medicine. 1999;107(3):198-208.

311. Holloway R, Witter JD, Lawton K, Lipscomb J, Samsa G. Inpatient costs of specific cerebrovascular events at five academic medical centers. Neurology. 1996;46(3):854-60.

312. Reddy VY, Akehurst RL, Amorosi SL, Gavaghan MB, Hertz DS, Holmes Jr DR. Cost-effectiveness of left atrial appendage closure with the WATCHMAN device compared with warfarin or non–vitamin K antagonist oral anticoagulants for secondary prevention in nonvalvular atrial fibrillation. Stroke. 2018;49(6):1464-70.

313. Kauf TL, Velazquez EJ, Crosslin DR, Weaver WD, Diaz R, Granger CB, McMurray JJ, Rouleau J-L, Aylward PE, White HD. The cost of acute myocardial infarction in the new millennium: evidence from a multinational registry. American Heart Journal. 2006;151(1):206-12.

314. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. Circulation. 2011;123(22):2562-70.

315. Paul SD, Kuntz KM, Eagle KA, Weinstein MC. Costs and effectiveness of angiotensin converting enzyme inhibition in patients with congestive heart failure. Archives of Internal Medicine. 1994;154(10):1143-9.

316. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA. 1996;276(15):1253-8.

317. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim Y-H, McAnulty Jr JH, Zheng Z-J. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129(8):837-47.

15 Appendix

Publications associated with this thesis are attached.

BMJ Open

Atrial fibrillation detection using single lead portable electrocardiographic monitoring: a systematic review and meta-analysis

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ABSTRACT

Objectives Recent technology advances have allowed for heart rhythm monitoring using single-lead ECG monitoring devices, which can be used for early diagnosis of atrial fibrillation (AF). We sought to investigate the AF detection rate using portable ECG devices compared with Holter monitoring.

Setting, participants and outcome measures We searched the Medline, Embase and Scopus databases (conducted on 8 May 2017) using search terms related to AF screening and included studies with adults aged >18 years using portable ECG devices or Holter monitoring for AF detection. We excluded studies using implantable loop recorders and pacemakers. Using a random-effects model we calculated the overall AF detection rate. Meta-regression analysis was performed to explore potential sources for heterogeneity. Quality of reporting was assessed using the tool developed by Downs and Black.

Results Portable ECG monitoring was used in 18 studies (n=117 436) and Holter monitoring was used in 36 studies (n=8498). The AF detection rate using portable ECG monitoring was 1.7% (95% CI 1.4 to 2.1), with significant heterogeneity between studies (p<0.001). There was a moderate linear relationship between total monitoring time and AF detection rate (r=0.65, p=0.003), and meta-regression identified total monitoring time (p=0.005) and body mass index (p=0.01) as potential contributors to heterogeneity. The detection rate (4.8%, 95% CI 3.6% to 6.0%) in eight studies (n=10 199), which performed multiple ECG recordings was comparable to that with 24 hours Holter (4.6%, 95% CI 3.5% to 5.7%). Intermittent recordings for 19 min total produced similar AF detection to 24 hours Holter monitoring.

Conclusion Portable ECG devices may offer an efficient screening option for AF compared with 24 hours Holter monitoring.

PROSPERO registration number CRD42017061021.

Strengths and limitations of this study

- First systematic review comparing single-lead ECG monitoring with 24 hours Holter monitoring for atrial fibrillation (AF) detection.
- Comprehensive literature search and specific inclusion criteria allowing for large patient numbers.
- Heterogeneity among individual studies with regard to patient population, AF definitions and monitoring time.
- Poor reporting of CHA_2DS_2-VASC scores among individual studies.
- Patient compliance unable to be accounted for in this meta-analysis.

Atrial fibrillation (AF) is a leading cause of stroke and heart failure worldwide, and is associated with increased all-cause mortality[1 2] as well as substantial financial cost.[3 4] The prevalence of AF increases with age, exceeding >15% for those aged 85 years and older.[5] The epidemics of obesity, diabetes mellitus and metabolic syndrome have also been associated with the increasing prevalence of AF.[6–8] Up to 20% of patients with stroke have underlying AF, and detection allows the initiation of anticoagulation, which is associated with a significant reduction in stroke recurrence.[9]

Early diagnosis of AF may have several benefits, including individualised lifestyle intervention[10] and anticoagulation, and may be associated with a reduction in complications and healthcare costs. The importance of early diagnosis has been recognised in recent guidelines from the European Society of Cardiology, which recommended opportunistic screening using pulse palpation and 12-lead ECG.[11] However, screening for AF is challenging for several reasons; many patients are asymptomatic or may have atypical symptoms. There are a variety of monitoring techniques available, all of which vary in diagnostic accuracy and sensitivity, and there is no accepted reference standard. Subclinical AF is associated with an increased risk of stroke, cardiovascular disease and all-cause mortality,[12] although there is controversy surrounding the significance of brief paroxysms of AF and the potential benefit of

anticoagulant therapy. Implantable devices are expensive, and not cost-effective for mass screening, and the use of external devices for long periods of monitoring require electrodes, which may be poorly tolerated by patients.

Recent advances in technology have allowed for the development of single-lead portable ECG monitoring devices. Multiple devices are available, all using multiple points of finger contact to create a single-lead ECG trace. The in-built memory of these devices allows for single or multiple time-point screening. Interpretation from a cardiologist or by automated algorithms has achieved high sensitivity and specificity for AF detection.[13–15] Although they have not been incorporated into the latest AF guidelines, the accuracy, ease of use and potential cost-effectiveness of these devices may lead to them having an important role in AF screening. This paper describes a systematic review of the published literature to investigate the overall AF detection rate using portable ECG devices compared with traditional Holter monitoring.

METHODS

Search strategy

We conducted our systematic review and meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (PRISMA).[16] We searched the Medline, Scopus and Embase databases using key terms including 'atrial fibrillation/AF and screening/monitoring and electrocardiographic/Holter monitoring', which were mapped to subject headings. We also searched the reference lists to identify other potential articles. The search was limited to adult human subjects aged >18 years and limited to the English language (see search strategy for Medline database in online supplementary material 1). The study was prospectively registered on the PROSPERO database on 22 April 2017 (CRD42017061021), and the search was conducted on 8 May 2017.

Study selection

Titles and abstracts of studies identified from the search were reviewed by two independent reviewers (SR and DDS). Studies which had a primary aim of AF detection in adult participants were included. We included all cohorts including community screening, those with risk factors and recent stroke. The screening methods included portable single-lead ECG devices or continuous (Holter) monitoring (up to 1 week). We included studies which used single-lead ECG devices for single episode screening or multiple intermittent screening periods. We included conference abstracts if demographic and outcome data were available. We excluded studies if participants were aged <18 years or if other forms of monitoring were used (pacemaker, implantable loop recorders, event recorders, monitoring patches and inpatient telemetry). We also excluded studies where AF detection was not the primary aim.

The primary outcome of interest was the detection rate of new AF using either single-lead intermittent or continuous monitoring. Our secondary objective was to determine the optimal time of intermittent monitoring, which produced equivalent AF detection to continuous monitoring.

Data collection

Full-text manuscripts of studies fitting the inclusion criteria were obtained. Quality of reporting and risk of bias was assessed using the tool developed by Downs and Black.[17] A standardised data-extraction form was used by the reviewers, which included information about the patient demographics, comorbidities, screening strategy, patients with known AF and overall new AF detection rate. Where data were not reported, we attempted to contact the primary authors of the study. Any disagreements between the two reviewers were resolved by consensus or by consulting a third reviewer (THM).

Statistical analysis

The cumulative AF detection rate for continuous and intermittent monitoring and the 95% CI was calculated using a random-effects model. The results were displayed as a forest plot and heterogeneity among the studies was assessed using the I^2 statistic. A subgroup analysis was performed by comparing the cumulative detection rate of single-lead ECG studies, which performed multiple timepoint recordings with 24 hours Holter monitoring studies. Linear regression analysis was used to determine the association between the total monitoring time and AF detection using single-lead ECG devices. This formula was used to determine the monitoring time using single-lead ECG devices to approximate the overall AF detection rate using 24 hours continuous monitoring. Univariate meta-regression analysis was performed to assess the influence of various clinical and screening factors with AF detection. Publication bias was assessed using a funnel plot and the Egger test. Statistical analysis was performed using Stata V.13 (StataCorp, College Station, Texas, USA) with two-tailed p values <0.05 used to denote statistical significance.

Patient and public involvement

Patients were not involved in this review.

RESULTS

Study characteristics

The PRISMA flow chart of our included studies is shown in figure 1 and the search strategy in online supplementary table 1. Our initial search strategy identified 5427 studies, with another 26 identified through other sources. After removing duplicate records, 4122 studies were left. After screening those using the inclusion/exclusion criteria, we identified 111 full-text studies for detailed review, which excluded 59 studies, leaving 52 full-text studies for inclusion in the meta-analysis (see online supplementary

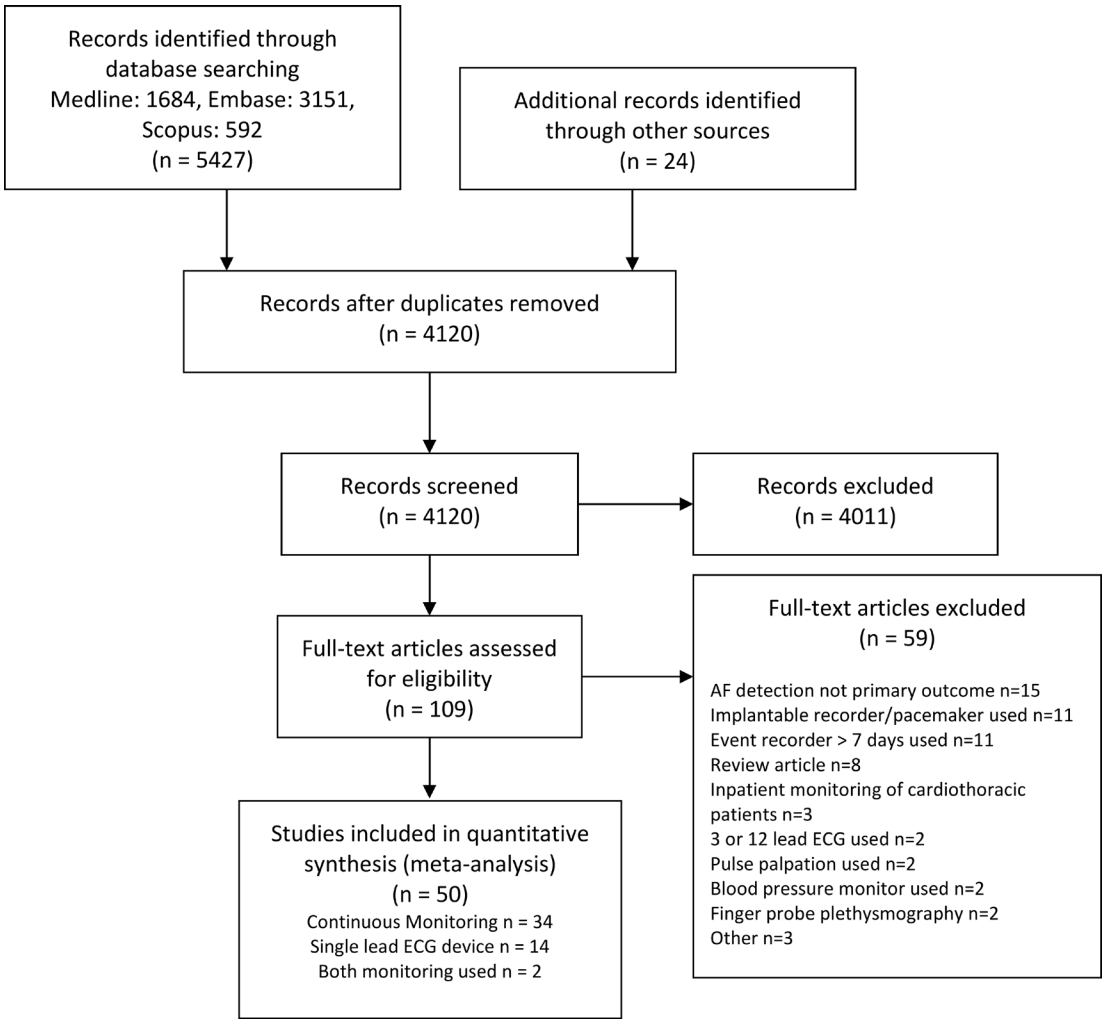

Figure 1 Overview of inclusion and exclusion of studies based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

table 2 for excluded studies). Of the 52 studies included, 34 used continuous (Holter) monitoring (n=8154),[18–51] 16 studies (n=117 092) used single-lead portable ECG monitoring[14 15 52–65] and 2 studies (n=344) used both continuous and intermittent single-lead monitoring for AF detection in a head-to-head comparison.[66 67]

The baseline characteristics of the individual studies is presented in table 1. There was a considerable range in age (54–76 years), and gender (male 29%–77%) between studies. As many studies chose healthy volunteers and other studies focused on patients poststroke or those with AF risk factors, there was significant variation in comorbidities such as diabetes, hypertension and obesity. Stroke risk determined by the CHADS or CHA_2DS_2-VASC score was reported in only 14/52 studies (27%). Of the 52 studies, 36 (69%) were conducted in Europe, 8 (15%) in Asia, 5 (10%) in North America and 3 (6%) in Australia. Nine studies (17%) were retrospective, the remainder all being prospective cohort or randomised controlled trials.

Of the 18 studies using single-lead ECG devices, 10 studies (56%) used a single 10–60 s recording for AF detection while 8 studies (44%) used multiple readings over a 1-week to 52-week period. There were five portable ECG devices used (table 1). Sixteen studies (89%) used healthy participants with risk factors.[14 15 52–61 63–65 67] Two studies assessed patients following stroke or transient ischaemic attack (TIA).[62 66]

Of the 36 studies using continuous (Holter) monitoring, 27 studies (75%) used 24 hours continuous monitoring,[18–23 25–28 33–36 38 39 41–45 47–50 66 67] 4 studies (11%) used 1-week monitoring,[30–32 51] 2 studies (6%) used 48 hours monitoring,[37 46] 2 studies (6%) used 72 hours monitoring[24 29] and 1 study (3%) used 96 hours monitoring.[40]

Overall AF detection

The combined AF detection rate using single-lead ECG monitoring (n=117 436 from 18 studies) was 1.7% (95% CI 1.4% to 2.1%). The cumulative AF detection rate using continuous (Holter) monitoring (n=8498 from 36 studies) was 5.5% (95% CI 4.4% to 6.6%). There was significant heterogeneity between studies (I^2=94% for single-lead ECG monitoring, 87% for Holter monitoring). The overall new AF detection rate is presented in figure 2.

Table 1 Summary of included trials investigating AF detection using single-lead ECG devices or Holter monitoring

Study	n	Country	Type of patients used	Device used	Duration of recording (s)	Frequency of recording/day	Total monitoring (days)	Mean/median age (years)	Male (%)	BMI (kg/m^2)	HTN (%)	DM (%)	IHD (%)	Previous diagnosis of AF (%)	HF (%)	Previous stroke (%)	Mean/median CHADS/CHA$_2$DS$_2$-VASC	Definition of AF	New AF (n)	New AF rate (%)
Lowres *et al*[52]	1000	Australia	Community pharmacy screening	Alive Cor	60	1	0	76	44	NR	62	23	16	10.4	3	7	3.3	Cardiologist interpretation	15	1.5
Svennberg *et al*[53]	7173	Sweden	Community screening (aged 75–76 years)	Zenicor	30	2	14	75	46	25.9	50	11	9.2	9.2	3.4	9	3.4	30 s irregular rhythm without P waves or 2× episodes between 10 and 29 s	218	3
Proietti *et al*[54]	65 747	Belgium	Belgian Heart Week screening	Omron Heartscan HCG-801	30	1	0	58	41	NR	36	21	23	0.5	20	20	2	Irregular R-R interval, no distinct P waves, variable atrial cycle length	603	1.1
Kaasenbrood *et al*[55]	3269	Holland	Influenza vaccination—opportunistic screening	MyDiagnostik	60	1	0	64.1	49	NR	NR	NR	NR	2.6	NR	NR	NR	Cardiologist interpretation×2	37	1.1
Engdahl *et al*[56]	848	Sweden	Community screening (aged 75–76 years) in Halmstad, Sweden	Zenicor	30	2	14	75	43	NR	53	11	NR	9.6	4	10	1.9	30 s duration of irregular rhythm or ≥2 episodes of 10 s or more	40	4.7
Hendrikx *et al*[57]	928	Sweden	GP practices	Zenicor	10	2	28	69.8	50	NR	90.3	31.6	19.8	0	3.7	8.6	2	10 s irregular rhythm without P waves	35	3.8
Hendrikx *et al*[67]	95	Sweden	Referred for presyncope/palpitations	Zenicor	30	2	28	54.1	44	NR	28.4	1.1	8.4	0	0	6.3	1	30 s irregular rhythm without P waves	9	9.5
Chan *et al*[15]	1013	Hong Kong	Patients aged ≥65 years with HTN or diabetes	Alive Cor	60	1	0	68.4	47	NR	90.4	36.6	16.2	2.2	4.4	10.5	3	Cardiologist interpretation	5	0.5
Doliwa Sobocinski *et al*[66]	249	Sweden	Patients post-TIA/stroke	Zenicor	10	2	30	72	57	NR	65	16	20	0	4	25	3	Irregular rhythm of minimum 10 s without visible P waves	15	6
Doliwa Sobocinski P *et al*[14]	606	Sweden	Community event	Zenicor	10	1	0	NR	64	NR	NR	NR	NR	NR	NR	NR	NR	Irregular rhythm without visible P waves	6	1
Ramkumar *et al*[60]	204	Australia	Community aged ≥65 years with one or more risk factor for HF	Remon RM-100	60	5	7	70.1	51	29.1	72.1	56.4	5.9	0	0	NR	3	30 s duration of irregular rhythm with absent P waves	20	9.8
Hendrikx *et al*[58]	201	Sweden	Patients referred to respiratory clinics with suspicion of obstructive sleep apnoea	Zenicor	30	2	14	56	69	30	51	10	9.2	0	4.6	3.1	NR	Irregular supraventricular extra systoles in series for 30 s	13	6.5
Claes *et al*[61]	10 758	Belgium	Community heart rhythm screening programme through medical centres	Omron HeartScan HCG-801	30	1	0	59	38	NR	30.6	8.6	12.2	7.2	7.2	5.4	1	Irregular RR intervals, absence of P waves and variable atrial cycle length (when visible)	167	1.6

Continued

Table 1 Continued

Study	n	Country	Type of patients used	Device used	Duration of recording (s)	Frequency of recording/ day	Total monitoring (days)	Mean/ median age (years)	Male (%)	BMI (kg/ m^2)	HTN (%)	DM (%)	IHD (%)	Previous diagnosis of AF (%)	HF (%)	Previous stroke (%)	Mean/ median CHADS/ CHA_2DS_2-VASC	Definition of AF	New AF (n)	New AF rate (%)
Samol *et al*[62]	132	Germany	Large proportion poststroke/TIA. Also recruited from diabetes, HTN and dyslipidemia clinics	Omron HeartScan HCG-801	30	1	0	64	58	NR	67	27	NR	0	3	49	NR	Cardiologist Interpretation×2	7	5.3
Battipaglia *et al*[63]	855	UK	Community shopping centre screening	MyDiagnostik	15	1	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	7	0.8
Chan and Choy[59]	13122	Hong Kong	Nationwide community screening programme	Alive Cor	30	1	0	64.7	29	23.7	38.2	14.8	2.2	0	0.7	2.8	NR	Software algorithm definition with minimum of 30 s	101	0.8
Chan *et al*[65]	10735	Hong Kong	Nationwide community screening programme	Alive Cor	30	1	0	NR	NR	NR	NR	NR	NR	1.2	NR	NR	NR	Cardiologist interpretation (≥30s)	74	0.7
Halcox *et al*[64]	501	UK	Community based with individuals aged >65 years with CHA2DS2-VASC score≥2	Alive Cor	30	2× per week	365	72.6	48	NR	54	26	14	0	1.0	7.0	3.0	30 s duration of an irregular rhythm without P waves	19	3.8
Gladstone *et al*[18]	277	Canada	Patients admitted with cryptogenic stroke	Holter	Continuous	Continuous	1	73.2	56	NR	67	19.3	14.7	0	7	12.6	NR	30 s or longer duration of irregular rhythm	9	3.2
Barthélémy *et al*[19]	60	France	Consecutive patients admitted with stroke/ TIA	Holter	Continuous	Continuous	1	64.4	55	NR	50	17	NR	0	NR	27	NR	Fibrillatory waves associated with irregular ventricular response ratio at least 30 s duration	8	13.3
Jabaudon *et al*[20]	149	Switzerland	Consecutive patients admitted with stroke/ TIA	Holter	Continuous	Continuous	1	66.9	68	NR	58	16.7	16.8	4.7	NR	16.8	NR	NR	7	4.7
Koudstaal *et al*[21]	100	Holland	Retrospective study of 100 patients admitted with stroke/TIA	Holter	Continuous	Continuous	1	60.9	74	NR	NR	NR	41	NR	NR	NR	NR	NR	5	5
Hornig *et al*[22]	268	Germany	Consecutive patients admitted with stroke/ TIA	Holter	Continuous	Continuous	1	59.1	61	NR	43.7	34	NR	NR	14.9	45	NR	NR	10	3.3
Rizos *et al*[23]	496	Germany	Patients admitted with stroke/TIA	Holter	Continuous	Continuous	1	69	62	NR	78.8	24.6	NR	NR	NR	22.2	3	Cardiologist interpretation (≥30s)	14	2.8
Schuchert *et al*[24]	82	Germany	Consecutive patients admitted with stroke/ TIA	Holter	Continuous	Continuous	3	59.7	57	NR	36.5	NR	17.1	NR	NR	NR	NR	Small irregular baseline undulations of variable amplitudes and morphology at a rate >350/min with an irregular ventiruclar response for at least 1 min	5	6

Continued

Table 1 Continued

Study	n	Country	Type of patients used	Device used	Duration of recording (s)	Frequency of recording/ day	Total monitoring (days)	Mean/ median age (years)	Male (%)	BMI (kg/ m^2)	HTN (%)	DM (%)	IHD (%)	Previous diagnosis of AF (%)	HF (%)	Previous stroke (%)	Mean/ median CHADS/ CHA_2DS_2-VASC	Definition of AF	New AF (n)	New AF rate (%)
Schaer *et al*[25]	241	Switzerland	Consecutive patients admitted with stroke/ TIA	Holter	Continuous	Continuous	1	68.7	59	NR	76	25	41	7	NR	4.6	NR	NR	0	0
Schaer *et al*[26]	425	Switzerland	Retrospective review of patients poststroke/ TIA with Holter monitoring	Holter	Continuous	Continuous	1	67.4	61	NR	NR	NR	NR	NR	NR	1.2	NR	Self-terminating sequence of >30 s of irregular RR intervals and the presence of fibrillatory P waves	9	2.1
Shafqat *et al*[27]	465	Pakistan	Retrospective review of consecutive patients admitted with stroke/TIA	Holter	Continuous	Continuous	1	66.8	56	NR	NR	NR	NR	NR	NR	NR	NR	NR	5	2.4
Lazzaro *et al*[28]	133	USA	Consecutive patients admitted with stroke/ TIA	Holter	Continuous	Continuous	1	63.1	50	NR	70	29.3	18.8	0	NR	2.3	NR	Supraventricular tachyarrhythmia characterised by uncoordinated atrial activation with fibrillatory waves varying in amplitude, shape and timing, replacing consistent P waves and with a duration >30 s	8	6
Grond *et al*[29]	1135	Germany	Patients admitted in seven German centres with stroke/TIA	Holter	Continuous	Continuous	3	67	55	27.4		20.4	7.3	0	5.8	17.4	NR	≥1 period of >30 s duration of an absolute arrhythmia without detectable P waves and without a pattern more consistent with an alternate diagnosis	49	4.3
Stahrenberg *et al*[30]	224	Germany	Consecutive patients admitted with stroke/ TIA	Holter	Continuous	Continuous	7	68	58	27.6	72.9	22.3	14.8	0	5.2	16.2	NR	2x Cardiologist interpretation of software algorithm detection of events	28	12.5
Ritter *et al*[31]	60	Germany	Patients admitted with cryptogenic stroke	Holter	Continuous	Continuous	7	61.8	57	NR	70	11.7	13.3	NR	0	NR	4	Cardiologist interpretation (>30 s)	1	1.7
Higgins *et al*[32]	50	Scotland	Patients admitted with stroke/TIA	Holter	Continuous	Continuous	7	67.1	48	NR	56	8	16	0	NR	NR	NR	Cardiologist interpretation (>30 s)	4	8
Hendrikx *et al*[67]	95	Sweden	Patients investigated for palpitations and presyncope	Holter	Continuous	Continuous	1	54.1	42	NR	28.4	1.1	8.4	0	0	6.3	1	30 s irregular rhythm without P waves	2	2.1

Continued

Table 1 Continued

Study	n	Country	Type of patients used	Device used	Duration of recording (s)	Frequency of recording/ day	Total monitoring (days)	Mean/ median age (years)	Male (%)	BMI (kg/ m^2)	HTN (%)	DM (%)	IHD (%)	Previous diagnosis of AF (%)	HF (%)	Previous stroke (%)	Mean/ median CHADS/ CHA_2DS_2-VASC	Definition of AF	New AF (n)	New AF rate (%)
Thakkar and Bagarhatta[33]	52	India	Consecutive patients admitted with stroke/ TIA	Holter	Continuous	Continuous	1	59.5	77	NR	51.9	23.1	15.4	0	1.7	7.7	NR	30 s irregular rhythm without P waves	3	5.8
Wachter *et al*[34]	198	Germany	Consecutive patients admitted with stroke/ TIA	Holter	Continuous	Continuous	1	73.2	62	NR	80.7	26.4	9.1	0	4.6	21.7	4.8	>30 s rhythm with irregular RR intervals and the presence of fibrillatory P waves	9	5
Gumbinger *et al*[35]	192	Germany	Patients admitted with stroke/TIA	Holter	Continuous	Continuous	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2	1
Alhadramy *et al*[36]	426	Canada	Retrospective review of patients poststroke/ TIA with Holter monitoring	Holter	Continuous	Continuous	1	64.9	48	NR	58.2	14.1	14.1	0	1.6	6.3	NR	Irregular ventricular response in the absence of p waves or with fibrillatory waves	11	2.5
Doliwa Sobocinski *et al*[66]	249	Sweden	Consecutive patients admitted with stroke/ TIA	Holter	Continuous	Continuous	1	72	57	NR	65	16	20	0	4	25	3	Irregular rhythm of minimum 10 s without visible P waves	5	2
Dangayach *et al*[37]	51	USA	Retrospective audit of patients admitted with cryptogenic stroke	Holter	Continuous	Continuous	2	58.2	43	NR	35.3	16	15.7	7.4	NR	NR	NR	NR	15	29.4
Gunalp *et al*[38]	26	Turkey	Patients admitted with ischaemic stroke	Holter	Continuous	Continuous	1	66	69	NR	61	26	31	NR	NR	NR	NR	NR	11	42.3
Fonseca *et al*[39]	80	Portugal	Patients admitted with cryptogenic stroke	Holter	Continuous	Continuous	1	69.3	53	NR	71.3	28.8	11.3	NR	NR	22.5	NR	NR	17	21
Manina *et al*[40]	114	Italy	Patients admitted with cryptogenic stroke	Holter	Continuous	Continuous	4	63.1	NR	NR	52.6	9.6	NR	NR	NR	NR	NR	Irregular ventricular response in the absence of P waves or with fibrillatory waves	29	25.4
Tagawa *et al*[41]	308	Japan	Consecutive patients admitted with ischaemic stroke	Holter	Continuous	Continuous	1	72.6	60	NR	70.1	25.3	NR	20.4	NR	NR	NR	Small irregular baseline undulations of variable amplitude and morphology at a rate of 300–350/ min associated with irregular ventricular response	26	8.4
Shibazaki *et al*[42]	536	Japan	Consecutive patients admitted with ischaemic stroke	Holter	Continuous	Continuous	1	72.4	64	NR	65.9	25.7	9.8	NR	0.3	NR	NR	NR	12	2.2
Vandebroucke and Thijs[43]	136	Belgium	Retrospective audit of patients admitted with ischaemic stroke	Holter	Continuous	Continuous	1	68	52	NR	NR	NR	NR	NR	NR	NR	NR	NR	7	5.1

Continued

Table 1 Continued

Study	n	Country	Type of patients used	Device used	Duration of recording (s)	Frequency of recording/ day	Total monitoring (days)	Mean/ median age (years)	Male (%)	BMI (kg/ m^2)	HTN (%)	DM (%)	IHD (%)	Previous diagnosis of AF (%)	HF (%)	Previous stroke (%)	Mean/ median CHADS/ CHA_2DS_2-VASC	Definition of AF	New AF (n)	New AF rate (%)
Yodogawa *et al*[44]	68	Japan	Consecutive patients admitted with ischaemic stroke	Holter	Continuous	Continuous	1	69.9	54	NR	66.2	14.7	NR	NR	NR	NR	NR	Irregular and uncoordinated atrial electrical activity on surface ECG lasting >30 s	17	25
Atmuri *et al*[45]	140	Australia	Retrospective audit of patients admitted with ischaemic stroke/TIA	Holter	Continuous	Continuous	1	NR	NR	NR	65	20	37.1	18.6	NR	NR	NR	NR	12	8.6
Salvatori *et al*[46]	274	Italy	Cohort study of patients aged ≥65 years with HTN in multiple GP clinics	Holter	Continuous	Continuous	2	70	54	NR	100	15	9	7	4	2.2	NR	Cardiologist interpretation	4	1.5
Beaulieu-Boire *et al*[47]	284	Canada	Consecutive patients admitted with stroke/ TIA	Holter	Continuous	Continuous	1	70.6	52	NR	68.7	26.7	27.4	NR	2.2	22.3	NR	Cardiologist interpretation	18	6.3
Dogan *et al*[48]	400	Turkey	Retrospective review of patients admitted poststroke	Holter	Continuous	Continuous	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	40	10
Douen *et al*[49]	126	Canada	Retrospective review of patients admitted poststroke	Holter	Continuous	Continuous	1	NR	NR	NR	NR	NR	NR	7	NR	NR	NR	NR	9	7.1
Suissa *et al*[50]	354	France	Consecutive patients admitted with ischaemic stroke	Holter	Continuous	Continuous	1	62.4	57	NR	51.1	18.6	NR	0	NR	NR	NR	Cardiologist interpretation	2	0.6
Wohlfahrt *et al*[51]	224	Germany	Patients admitted with ischaemic stroke	Holter	Continuous	Continuous	7	68.5	59	NR	73.2	22.3	15.2	NR	5.4	24.1	NR	>30 s irregular rhythm	29	12.9

AF, atrial fibrillation; BMI, body mass index; DM, diabetes mellitus; GP, general practitioner; HF, heart failure; HTN, hypertension; IHD, ischaemic heart disease.

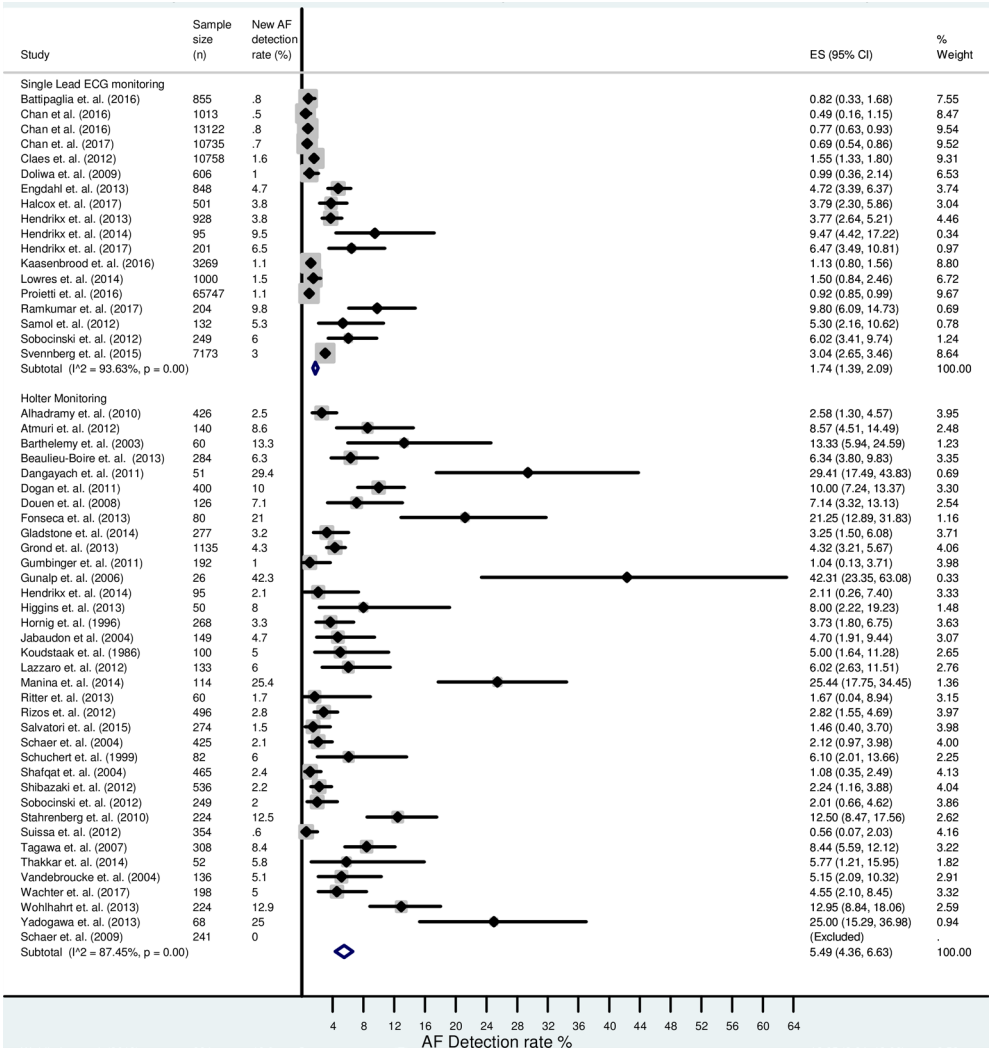

Figure 2 Forest plot showing the overall atrial fibrillation (AF) detection rate between single-lead ECG devices and Holter monitoring.

Comparison of multiple intermittent monitoring with 24 hours Holter

There was significant variation in the monitoring time using both single-lead and Holter monitoring, which contributed to the difference in the cumulative detection rate seen in figure 2. Figure 3 compares the detection rate of multiple intermittent single-lead recordings with 24 hours continuous monitoring, which is used routinely in clinical practice. There were eight studies (n=10 199, mean weighted age 68.8±8.4 years from six studies, 47% male from eight studies) that performed multiple intermittent single-lead ECG recordings and 27 studies (n=6284, mean weighted age 67.8±5.1 years from 23 studies, 58% male from 23 studies) that used 24 hours Holter monitoring. From the data available, the multiple intermittent ECG group had a lower AF risk to the 24 hours Holter group (hypertension 55% (n=8 studies) vs 65% (n=20 studies); diabetes mellitus 15% (n=8 studies) vs 22% (n=20 studies); heart failure 3.3% (n=8 studies) vs 3.9% (n=11 studies); ischaemic heart disease 11% (n=6 studies) vs 19% (n=15 studies) and previous stroke/TIA 9% (n=7 studies) vs 16% (n=15 studies)), respectively. The combined AF detection rate was 4.8% (95% CI 3.6% to 6.0%) using multiple intermittent ECG recordings. The cumulative AF detection rate using 24 hours Holter monitoring was 4.6% (95% CI 3.5% to 5.7%).

Association between monitoring time and AF detection

Using single-lead ECG devices, we found a moderate linear relationship between the total monitoring time and AF detection rate (β=0.13, R^2=0.42). Using this formula, we noted that approximately 19 min of total intermittent monitoring produced similar AF detection to 24 hours continuous monitoring (figure 4). The study by Halcox *et al* was an outlier, with a much lower AF detection rate than other studies (3.8% from 52 min of total monitoring) and this reduced the linear correlation between total monitoring time and AF detection rate.[64] Exclusion of these data led to a stronger linear relationship (β=0.26, R^2=0.80) and a much lower total intermittent monitoring time required (12 min) to produce a similar AF detection rate to 24 hours Holter monitoring.

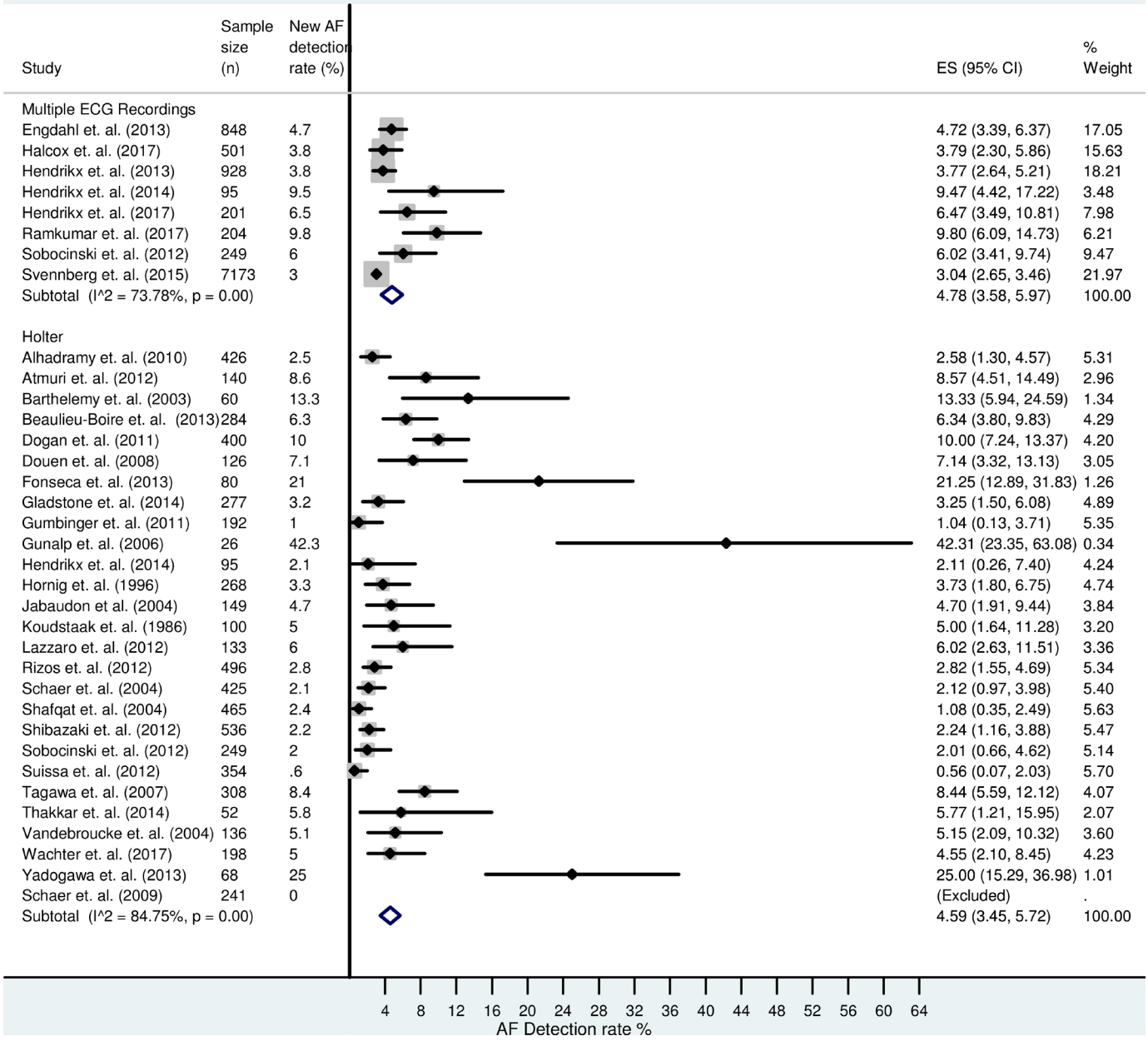

Figure 3 Forest plot comparing the atrial fibrillation (AF) detection rate between 24 hours Holter monitoring and performing multiple intermittent single-lead ECG recordings.

Meta-regression

Sources of heterogeneity in the 18 studies using single-lead ECG monitoring were investigated using meta-regression (table 2). Monitoring time per participant (β=0.11, 95% CI 0.04 to 0.18, p=0.005) and body mass index (β=1.1, 95% CI 0.58 to 1.5, p=0.01) were associated with AF detection.

Sensitivity analysis

A number of outlier studies were observed in the meta-analysis that could influence the cumulative AF detection rate.[37–40 44] Removal of these outlier studies resulted in a reduction in the overall AF detection rate in all Holter studies (table 3) and for 24 hours Holter studies (table 4). When these outlier studies were removed, the overall AF detection rate for 24 hours Holter was 3.86% (95% CI 2.88% to 4.83%), much lower than the detection rate by multiple intermittent ECG recordings using portable single lead devices (4.78%, 95% CI 3.58% to 5.97%). A cumulative meta-analysis (figure 5) did not show any significant variation in the AF detection rate over time using either Holter or single-lead ECG monitoring.

Publication bias

Publication bias was explored using a funnel plot of all included studies (see online supplementary figure 1). There was significant publication bias in both single-lead ECG device and Holter monitoring studies (Egger test, p=0.003 and p<0.001 respectively).

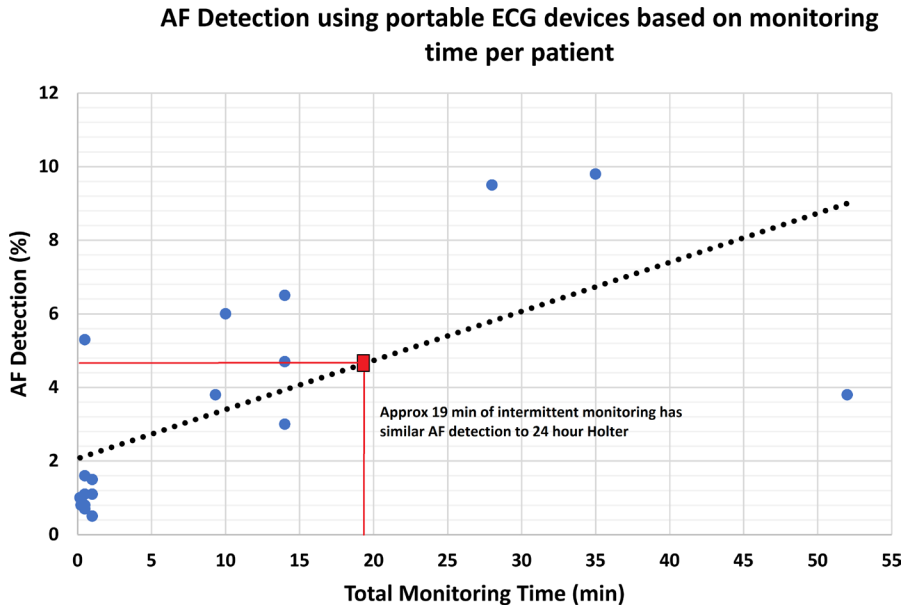

Figure 4 Graph showing the linear relationship between total monitoring time and atrial fibrillation (AF) detection rate in single-lead ECG devices.

Quality of studies

A summary of the quality analysis (see online supplementary table 3) showed that overall quality of reporting was moderate. All studies described the primary objective of the trial and included a summary of the main findings. Detailed comorbidities of the study participants were only adequately reported in 28/52 (54%), and limitations were discussed in 35/52 (67%) of studies. Most had a very selective patient population, 31/52 (60%) were poststroke/TIA cohorts.

DISCUSSION

Our study is the only systematic review that we are aware of that has studied the overall AF detection rate of single-lead portable ECG devices. The results of our systematic review suggest a linear relationship between monitoring time per patient and AF detection rate. Single timepoint screening has an approximate 1% AF detection rate, which can be increased to around 5% when multiple recordings are performed. We noted that approximately 19 min of intermittent monitoring produced similar detection rates to conventional 24 hours continuous Holter monitoring.

Early diagnosis of AF

AF creates a significant burden on both patients as well as the healthcare system. AF will continue to rise in incidence and the costs to the healthcare system will continue to increase, due to ageing, sedentariness and the prevalence of obesity and the metabolic syndrome.[3 68] Early diagnosis offers the possibility for early initiation of treatment, which may reduce the occurrence of the complications and may lead to reduced hospital admissions and associated healthcare costs. Early treatment for AF can be achieved in different ways. Patients with subclinical AF have an increased risk of stroke and cardiovascular

Table 2 Meta-regression analysis for atrial fibrillation (AF) detection (single-lead ECG studies)

Variable	Number of studies	β (95% CI)	P values
Age (years)	15	0.00 (–0.22 to 0.24)	0.95
Monitoring time per participant (min)	18	0.11 (0.04 to 0.18)	0.005
Body mass index (kg/m^2)	4	1.1 (0.58 to 1.5)	0.01
CHADS score (%)	11	–0.13 (–2.6 to 2.4)	0.91
Hypertension (%)	14	0.01 (–0.08 to 0.10)	0.75
Previous diagnosis of AF (%)	16	–0.13 (–0.50 to 0.24)	0.46
Ischaemic heart disease (%)	12	–0.10 (–0.42 to 0.21)	0.48
Previous stroke (%)	13	0.06 (–0.09 to 0.19)	0.45
Male gender	16	0.10 (–0.04 to 0.24)	0.16

Table 3 Outlier studies omitted (all Holter studies) to assess the change to the overall atrial fibrillation (AF) detection rate

Study omitted	Overall AF detection rate (%)	95% CI (%)
Dangayach *et al*[37]	5.27	4.17 to 6.38
Fonseca *et al*[39]	5.26	4.15 to 6.36
Gunalp *et al*[38]	5.32	4.21 to 6.42
Manina *et al*[40]	5.11	4.03 to 6.20
Yadogawa *et al* [44]	5.25	4.14 to 6.35
All studies excluded	4.31	3.36 to 5.26

Table 4 Outlier studies omitted (24 hours Holter) to assess the change to the overall atrial fibrillation (AF) detection rate

Study omitted	Overall AF detection rate (%)	95% CI (%)
Fonseca *et al*[39]	4.30	3.21 to 5.39
Gunalp *et al*[38]	4.39	3.30 to 5.47
Yadogawa *et al*[44]	4.30	3.22 to 5.38
All studies excluded	3.86	2.88 to 4.83

events, like those with established AF.[12 69] Anticoagulation may help reduce the incidence of stroke in this cohort.

The close relationship between metabolic syndrome and AF has encouraged research into the benefits of lifestyle intervention. Aggressive lifestyle intervention in patients with AF undergoing catheter ablation has been reported to lead to a reduction in symptom burden, improved quality of life and the need for repeat ablation procedures.[10] It remains to be tested whether initiation of

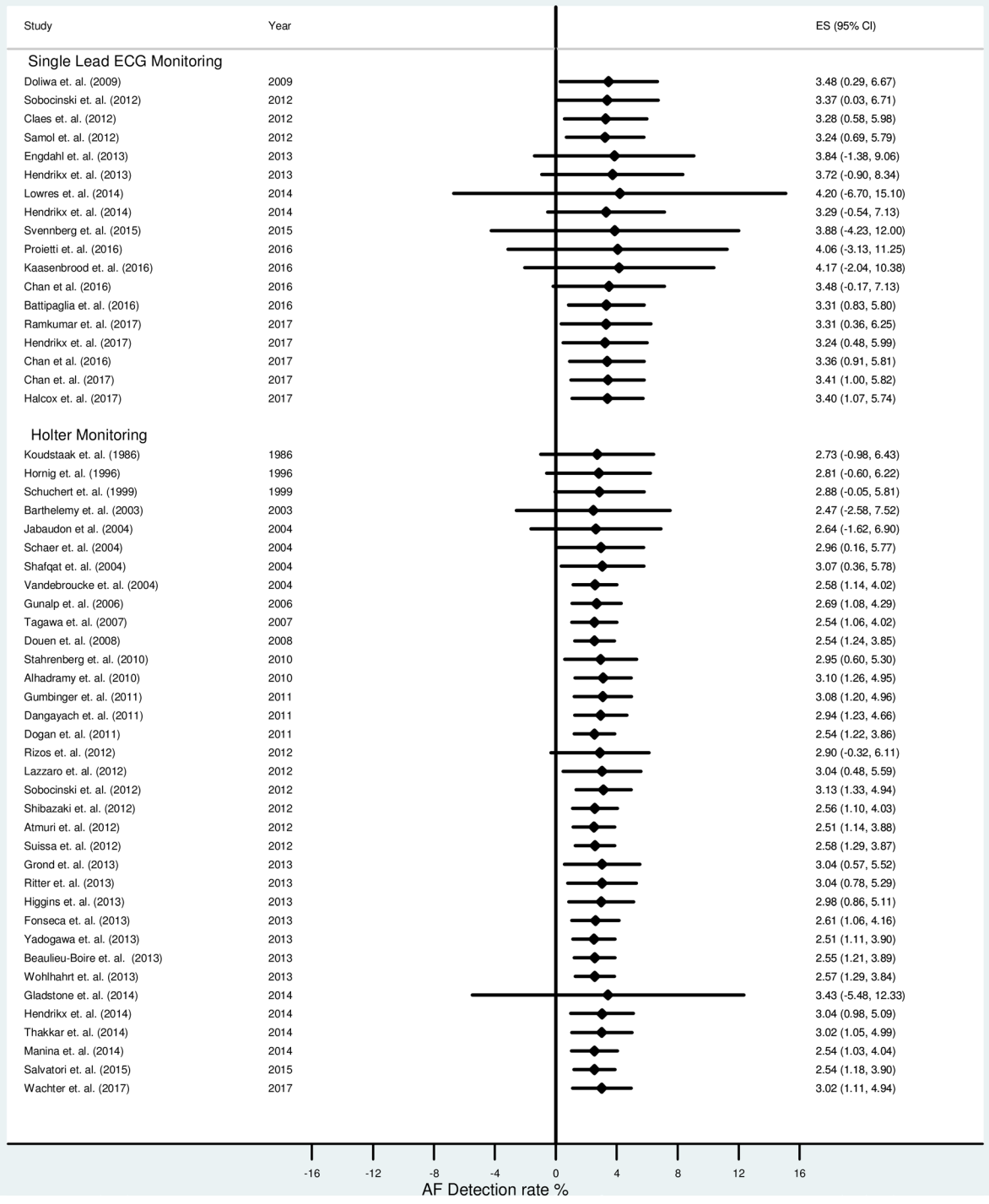

Figure 5 Cumulative meta-analysis showing minimal variation in atrial fibrillation (AF) detection over time using Holter and single-lead ECG devices.

lifestyle intervention and aggressive risk factor modification following the early diagnosis of AF may be associated with positive LA remodelling and reduction of disease progression. Such a process may lead to additional health benefits, including reduction in cardiovascular risk and improvement in exercise capacity.

AF screening and feasibility

AF is a leading cause of stroke and heart failure in the community. As well as an association with increased all-cause mortality, it is associated with reduced quality of life. The availability of preventive therapies, including anticoagulation, has led to increasing recognition of the importance of AF screening for early diagnosis. However, AF screening shares the limitations of screening with other diagnostic tests. The screening tool must have high sensitivity, and needs to be inexpensive and cost-effective. We also need to minimise and have a method of addressing false positives. Current guidelines recommend opportunistic screening using pulse palpation and 12-lead ECG.[11] In a previous systematic review, this was associated with a new AF detection rate of approximately 1%.[5] Pulse palpation may be non-specific in patients with other irregular rhythms such as ventricular ectopy, and 12-lead ECG is only able to capture a single timepoint for screening. There are multiple other methods for AF detection. Continuous Holter monitoring is probably the most commonly used in clinical practice, especially in stroke cohorts. It has the potential advantage of assessing heart rhythm throughout the day and may be useful in detecting nocturnal subclinical AF. However, the disadvantages include the cost of Holter monitoring (especially for mass screening), the inconvenience of leads and electrodes (which may affect compliance) and typical limitation to 1–2 days of capture (as extended periods are more cumbersome and less cost-effective). Other event recorders are again expensive and limited to symptomatic patients. Extended period monitoring using implantable devices have shown promise in the cryptogenic stroke population (where many have been diagnosed with paroxysmal AF),[70] but they are invasive and not feasible for mass screening.

Portable single-lead ECG devices permit multiple 30–60 s recordings to be captured, and downloaded to a computer. These devices have several potential advantages over Holter monitoring. They are leadless and require finger contact (and are hence easy to use and acceptable to patients). They have a high degree of sensitivity for identifying AF.[71–73] Most interface with a web-based cloud system where ECG rhythms can be wirelessly transferred to clinicians, allowing rapid analysis and diagnosis. The development of automated algorithms to detect AF is helpful for mass screening. In two small studies they have demonstrated superior AF detection compared with 24 hours Holter monitoring.[66 67] Although screening using these portable devices are currently not in the latest AF guidelines, they may offer a feasible option for mass screening. Screening using these devices has been demonstrated to be cost-effective.[74 75]

We noted a moderate linear association between monitoring time and AF detection rate. Single timepoint screening for 30–60 s achieved an overall detection rate of approximately 1%. This is no better than what has been reported using pulse palpation or 12-lead ECG, hence does not add any incremental benefit in screening programmes.[5] Multiple intermittent recordings improve AF detection; we found that at least 19 min of total monitoring should be performed to achieve detection rates similar to 24 Holter monitoring.

The linear relationship between monitoring time and AF detection rate (R^2=0.80) and the reproduction of AF detection rates of 24 hours Holter monitoring with only 12 min of intermittent monitoring was possible in our study only after exclusion of an outlier.[64] Despite the inclusion of elderly participants with at least one risk factor for AF, the use of a validated single-lead ECG device and a prolonged monitoring period, that study had a lower AF detection rate (3.8%) than the remaining studies, even using a shorter monitoring period.[53 56 57] Relatively low rates of adherence (only approximately 25% completed 2×30 s ECG recordings every week for the full year of monitoring) may be a potential explanation for the lower AF detection rate noted.[64]

Limitations

There are several challenges inherent in this meta-analysis of studies investigating AF detection. The most important is the target screening population. Most studies did not report the CHADS or CHA_2DS_2-VASC score, a history of previous stroke or other comorbidities. Consequently, it was difficult to ascertain if the risk profiles of patients in these studies were equivalent. Most Holter monitoring studies were performed in the stroke population—which is likely a population with higher AF risk than many studies using portable ECG devices, which recruited mainly healthy participants or those with AF risk factors from the community. The significant heterogeneity among both Holter and portable ECG device studies make it difficult to perform direct comparisons between both groups. The type/duration of monitoring and type of device used will also influence the overall AF detection rate and varied significantly between studies. There are several possible confounders which may not have been taken into account. The validity of the linear regression analysis comparing detection time and rate may be limited due to the significant differences in study population, study design and AF definitions. However, despite these limitations, the analysis may provide some important inferences into AF screening. Multiple intermittent ECG recordings achieved a similar AF detection rate to 24 hours Holter monitoring. This may suggest that in a similar cohort of patients with the same comorbidities,

single-lead intermittent monitoring may be superior for AF detection.

Compared with 24 hours continuous monitoring, single-lead portable ECG monitoring is more patient dependent. Good patient compliance is essential to obtain multiple readings across different timepoints which improves sensitivity. The analysis performed does not take into account patient compliance as this is difficult to assess and poorly reported across the individual studies. Most single-lead device manufacturers have proprietary automated AF detection algorithms, which were used for diagnosis. Not all of these algorithms have had rigorous testing and comparison to a reference standard. It is also difficult to distinguish AF from other supraventricular tachycardias using single-lead ECG devices as the P wave is often not readily discernible. The use of different automated algorithms makes AF definitions non-standardised and can potentially create issues with both overdiagnosis and underdiagnosis.

There are other limitations in this analysis. The efficacy of intermittent monitoring is critically dependent on AF burden and density. All studies varied in their monitoring period and strategy. The linear regression model used was able to determine a total intermittent monitoring time, which produced similar AF detection rates to 24 hours continuous monitoring. However, it is difficult to translate the total monitoring time into an effective monitoring strategy. For example, we are unable to determine from our analysis if 12×60 s recordings over 12 consecutive days is different to 2×60 s recordings daily for six consecutive days. The definitions of AF also vary between studies. Many are based on individual physician interpretation and criteria for diagnosis were not explicitly specified. The duration of AF varied from 10 to 30 s between studies, although a cut-off of 30 s was the most widely adopted practice.

CONCLUSION

Single-lead portable ECG devices may offer an efficient screening option for AF compared with 24 hours Holter monitoring. Total monitoring time is related to AF detection and a total of 19 min may achieve a similar detection rate to 24 hours Holter monitoring.

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REFERENCES

1. Krahn AD, Manfreda J, Tate RB, *et al*. The natural history of atrial fibrillation: Incidence, risk factors, and prognosis in the manitoba follow-up study. *Am J Med* 1995;98:476–84.
2. Vidaillet H, Granada JF, Chyou P, *et al*. A population-based study of mortality among patients with atrial fibrillation or flutter. *Am J Med* 2002;113:365–70.
3. Kim MH, Johnston SS, Chu BC, *et al*. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes* 2011;4:313–20.
4. Leyden JM, Kleinig TJ, Newbury J, *et al*. Adelaide stroke incidence study: declining stroke rates but many preventable cardioembolic strokes. *Stroke* 2013;44:1226–31.
5. Lowres N, Neubeck L, Redfern J, *et al*. Screening to identify unknown atrial fibrillation. A systematic review. *Thromb Haemost* 2013;110:213–22.
6. Watanabe H, Tanabe N, Watanabe T, *et al*. Metabolic syndrome and risk of development of atrial fibrillation. *Circulation* 2008;117:1255–60.
7. Ball J, Thompson DR, Ski CF, *et al*. Estimating the current and future prevalence of atrial fibrillation in the Australian adult population. *Med J Aust* 2015;202:32–5.
8. Dagres N, Anastasiou-Nana M. Atrial Fibrillation and Obesity. *J Am Coll Cardiol* 2010;55:2328–9.
9. Sposato LA, Cipriano LE, Saposnik G, *et al*. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol* 2015;14:377–87.
10. Pathak RK, Middeldorp ME, Lau DH, *et al*. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;64:2222–31.
11. Kirchhof P, Benussi S, Kotecha D, *et al*. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893–962.
12. Martinez C, Katholing A, Freedman SB. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. A cohort study. *Thromb Haemost* 2014;112:276–86.
13. Lau J, Lowres N, Neubeck L, *et al*. Performance of an automated iPhone ECG algorithm to diagnose atrial fibrillation in a community AF screening program (SEARCH-AF). *Heart, Lung and Circulation* 2013;22:S205.
14. Doliwa PS, Frykman V, Rosenqvist M. Short-term ECG for out of hospital detection of silent atrial fibrillation episodes. *Scand Cardiovasc J* 2009;43:163–8.
15. Chan PH, Wong CK, Poh YC, *et al*. Diagnostic performance of a smartphone-based photoplethysmographic application for atrial fibrillation screening in a primary care setting. *J Am Heart Assoc* 2016;5:e003428.
16. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
17. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52:377–84.
18. Gladstone DJ, Spring M, Dorian P, *et al*. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;370:2467–77.
19. Barthélémy JC, Féasson-Gérard S, Garnier P, *et al*. Automatic cardiac event recorders reveal paroxysmal atrial fibrillation after

unexplained strokes or transient ischemic attacks. *Ann Noninvasive Electrocardiol* 2003;8:194–9.
20. Jabaudon D, Sztajzel J, Sievert K, *et al*. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. *Stroke* 2004;35:1647–51.
21. Koudstaal PJ, van Gijn J, Klootwijk AP, *et al*. Holter monitoring in patients with transient and focal ischemic attacks of the brain. *Stroke* 1986;17:192–5.
22. Hornig CR, Haberbosch W, Lammers C, *et al*. Specific cardiological evaluation after focal cerebral ischemia. *Acta Neurol Scand* 1996;93:297–302.
23. Rizos T, Güntner J, Jenetzky E, *et al*. Continuous stroke unit electrocardiographic monitoring versus 24-hour Holter electrocardiography for detection of paroxysmal atrial fibrillation after stroke. *Stroke* 2012;43:2689–94.
24. Schuchert A, Behrens G, Meinertz T. Impact of long-term ECG recording on the detection of paroxysmal atrial fibrillation in patients after an acute ischemic stroke. *Pacing Clin Electrophysiol* 1999;22:1082–4.
25. Schaer B, Sticherling C, Lyrer P, *et al*. Cardiological diagnostic work-up in stroke patients--a comprehensive study of test results and therapeutic implications. *Eur J Neurol* 2009;16:268–73.
26. Schaer BA, Zellweger MJ, Cron TA, *et al*. Value of routine holter monitoring for the detection of paroxysmal atrial fibrillation in patients with cerebral ischemic events. *Stroke* 2004;35:68e–70.
27. Shafqat S, Kelly PJ, Furie KL. Holter monitoring in the diagnosis of stroke mechanism. *Intern Med J* 2004;34:305–9.
28. Lazzaro MA, Krishnan K, Prabhakaran S. Detection of atrial fibrillation with concurrent holter monitoring and continuous cardiac telemetry following ischemic stroke and transient ischemic attack. *J Stroke Cerebrovasc Dis* 2012;21:89–93.
29. Grond M, Jauss M, Hamann G, *et al*. Improved detection of silent atrial fibrillation using 72-hour Holter ECG in patients with ischemic stroke. *Stroke* 2013;44:3357–64.
30. Stahrenberg R, Weber-Krüger M, Seegers J, *et al*. Enhanced detection of paroxysmal atrial fibrillation by early and prolonged continuous holter monitoring in patients with cerebral ischemia presenting in sinus rhythm. *Stroke* 2010;41:2884–8.
31. Ritter MA, Kochhäuser S, Duning T, *et al*, 2013. *Stroke* Occult atrial fibrillation in cryptogenic stroke: detection by 7-day electrocardiogram versus implantable cardiac monitors;44:1449–52.
32. Higgins P, MacFarlane PW, Dawson J, *et al*, 2013. *Stroke* Noninvasive cardiac event monitoring to detect atrial fibrillation after ischemic stroke: a randomized, controlled trial;44:2525–31.
33. Thakkar S, Bagarhatta R. Detection of paroxysmal atrial fibrillation or flutter in patients with acute ischemic stroke or transient ischemic attack by holter monitoring. *Indian Heart J* 2014;66:188–92.
34. Wachter R, Gröschel K, Gelbrich G, *et al*. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-$AF_{RANDOMISED}$): an open-label $_{randomised}$ controlled trial. *Lancet Neurol* 2017;16:282–90.
35. Gumbinger C, Krumsdorf U, Veltkamp R, *et al*, 2012. *Eur J Neurol* Continuous monitoring versus HOLTER ECG for detection of atrial fibrillation in patients with stroke;19:253–7.
36. Alhadramy O, Jeerakathil TJ, Majumdar SR, *et al*. Prevalence and predictors of paroxysmal atrial fibrillation on Holter monitor in patients with stroke or transient ischemic attack. *Stroke* 2010;41:2596–600.
37. Dangayach NS, Kane K, Moonis M. Paroxysmal atrial fibrillation in cryptogenic stroke. *Ther Clin Risk Manag* 2011;7:33–7.
38. Gunalp M, Atalar E, Coskun F, *et al*. Holter monitoring for 24 hours in patients with thromboembolic stroke and sinus rhythm diagnosed in the emergency department. *Adv Ther* 2006;23:854–60.
39. Fonseca AC, Brito D, Pinho e Melo T, *et al*. N-terminal pro-brain natriuretic peptide shows diagnostic accuracy for detecting atrial fibrillation in cryptogenic stroke patients. *Int J Stroke* 2014;9:419–25.
40. Manina G, Agnelli G, Becattini C, *et al*, 2014. *Intern Emerg Med* 96 hours ECG monitoring for patients with ischemic cryptogenic stroke or transient ischaemic attack;9:65–7.
41. Tagawa M, Takeuchi S, Chinushi M, *et al*. Evaluating patients with acute ischemic stroke with special reference to newly developed atrial fibrillation in cerebral embolism. *Pacing Clin Electrophysiol* 2007;30:1121–8.
42. Shibazaki K, Kimura K, Fujii S, *et al*. Brain natriuretic peptide levels as a predictor for new atrial fibrillation during hospitalization in patients with acute ischemic stroke. *Am J Cardiol* 2012;109:1303–7.
43. Vandenbroucke E, Thijs VN. Diagnostic and therapeutic impact of ambulatory electrocardiography in acute stroke. *Acta Neurol Belg* 2004;104:27–31.
44. Yodogawa K, Seino Y, Ohara T, *et al*. Prediction of atrial fibrillation after ischemic stroke using P-wave signal averaged electrocardiography. *J Cardiol* 2013;61:49–52.
45. Atmuri K, Hughes A, Coles D, *et al*. The role of cardiac disease parameters in predicting the results of Holter monitoring in patients with acute ischaemic stroke. *J Clin Neurosci* 2012;19:965–8.
46. Salvatori V, Becattini C, Laureti S, *et al*. Holter monitoring to detect silent atrial fibrillation in high-risk subjects: The perugia general practitioner study. *Intern Emerg Med* 2015;10:595–601.
47. Beaulieu-Boire I, Leblanc N, Berger L, *et al*. Troponin elevation predicts atrial fibrillation in patients with stroke or transient ischemic attack. *J Stroke Cerebrovasc Dis* 2013;22:978–83.
48. Dogan U, Dogan EA, Tekinalp M, *et al*. P-wave dispersion for predicting paroxysmal atrial fibrillation in acute ischemic stroke. *Int J Med Sci* 2012;9:108–14.
49. Douen AG, Pageau N, Medic S. Serial electrocardiographic assessments significantly improve detection of atrial fibrillation 2.6-fold in patients with acute stroke. *Stroke* 2008;39:480–2.
50. Suissa L, Lachaud S, Mahagne MH, *et al*. Optimal timing and duration of continuous electrocardiographic monitoring for detecting atrial fibrillation in stroke patients. *J Stroke Cerebrovasc Dis* 2013;22:991–5.
51. Wohlfahrt J, Stahrenberg R, Weber-Krüger M, *et al*, 2014. *Eur J Neurol* Clinical predictors to identify paroxysmal atrial fibrillation after ischaemic stroke;21:21–7.
52. Lowres N, Neubeck L, Salkeld G, *et al*. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost* 2014;111:1167–76.
53. Svennberg E, Engdahl J, Al-Khalili F, *et al*. Mass screening for untreated atrial fibrillation: the STROKESTOP study. *Circulation* 2015;131:2176–84.
54. Proietti M, Mairesse GH, Goethals P, *et al*. A population screening programme for atrial fibrillation: a report from the Belgian Heart Rhythm Week screening programme. *Europace* 2016;18:euw069–86.
55. Kaasenbrood F, Hollander M, Rutten FH, *et al*. Yield of screening for atrial fibrillation in primary care with a hand-held, single-lead electrocardiogram device during influenza vaccination. *Europace* 2016;18:1514–20.
56. Engdahl J, Andersson L, Mirskaya M, *et al*. Stepwise screening of atrial fibrillation in a 75-year-old populationclinical perspective. *Circulation* 2013;127:930–7.
57. Hendrikx T, Hörnsten R, Rosenqvist M, *et al*. Screening for atrial fibrillation with baseline and intermittent ECG recording in an out-of-hospital population. *BMC Cardiovasc Disord* 2013;13:41.
58. Hendrikx T, Sundqvist M, Sandström H, *et al*. Atrial fibrillation among patients under investigation for suspected obstructive sleep apnea. *PLoS One* 2017;12:e0171575.
59. Chan NY, Choy CC. Screening for atrial fibrillation in 13 122 Hong Kong citizens with smartphone electrocardiogram. *Heart* 2017;103:24–31.
60. Ramkumar S, Yang H, Wang Y, *et al*. The role of left atrial and ventricular function in prediction of atrial fibrillation: P2-19. *Journal of the American Society of Echocardiography* 2017;30:B70.
61. Claes N, Goethals M, Goethals P, *et al*. Screening for atrial fibrillation (AF) in Belgium: a multicentre trial. *European Journal of Cardiovascular Prevention and Rehabilitation* 2011;1:S30.
62. Samol A, Masin M, Gellner R, *et al*. Prevalence of unknown atrial fibrillation in patients with risk factors. *Europace* 2013;15:657–62.
63. Battipaglia I, Gilbert K, Hogarth AJ, *et al*. Screening for atrial fibrillation in the community using a novel ECG recorder. *J Atr Fibrillation* 2016;9:29–31.
64. Halcox JPJ, Wareham K, Cardew A, *et al*. Assessment of remote heart rhythm sampling using the alivecor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study. *Circulation* 2017;136:1784–94. 117.030583.
65. Chan NY, Siu CW, Choy CC, *et al*. Effectiveness of community atrial fibrillation screening in over 10,000 citizens using smartphone electrocardiogram- The AFinder program. *ESC Congress*. Barcelona, 2017.
66. Doliwa Sobocinski P, Anggårdh Rooth E, Frykman Kull V, *et al*. Improved screening for silent atrial fibrillation after ischaemic stroke. *Europace* 2012;14:1112–6.
67. Hendrikx T, Rosenqvist M, Wester P, *et al*. Intermittent short ECG recording is more effective than 24-hour Holter ECG in detection of arrhythmias. *BMC Cardiovasc Disord* 2014;14:41.
68. Stewart S, Murphy NF, Murphy N, *et al*. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 2004;90:286–92.
69. Healey JS, Connolly SJ, Gold MR, *et al*. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;366:120–9.

70. Sanna T, Diener HC, Passman RS, *et al*. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;370:2478–86.
71. Desteghe L, Raymaekers Z, Lutin M, *et al*. Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. *Europace* 2017;19. euw025.
72. Williams J, Pearce K, Benett I, *et al*. The effectiveness of a mobile ECG device in identifying AF: sensitivity, specificity and predictive value. *British Journal of Cardiology* 2015;22.
73. Ben Freedman S, Lowres N. Asymptomatic atrial fibrillation: the case for screening to prevent stroke. *JAMA* 2015;314:1911–2.
74. Aronsson M, Svennberg E, Rosenqvist M, *et al*. Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording. *Europace* 2015;17:1023–9.
75. Jacobs MS, Kaasenbrood F, Postma MJ, *et al*. Cost-effectiveness of screening for atrial fibrillation in primary care with a handheld, single-lead electrocardiogram device in the Netherlands. *Europace* 2018;20:euw285. euw285.

Relation of Functional Status to Risk of Development of Atrial Fibrillation

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Identifying patients at risk is now important as there are demonstrable ways to alter disease progression which could potentially prevent atrial fibrillation (AF) and its complications. We sought whether impaired functional capacity was associated with risk of AF, independent of myocardial dysfunction. In this community-based study, asymptomatic participants aged ≥65 years were recruited if they had ≥1 risk factor (e.g., hypertension, diabetes mellitus, and obesity). Participants underwent baseline echocardiography (including measurement of myocardial mechanics) and six-minute walk test. The CHARGE-AF score was used to calculate 5-year risk of developing AF. Receiver operating characteristic curves were used to assess for independent risk factors for AF. A total of 607 patients (age 71 ± 5 years, men 47%) were studied at baseline and followed for at least 6 months. Patients in the higher AF risk groups were older and had increased rates of hypertension, diabetes mellitus, and ischemic heart disease (p <0.05). Greater AF risk was associated with lower exercise capacity, independent of lower mean global longitudinal strain, global circumferential strain, greater mean E/e' ratio, indexed left atrial volume and LV mass. Multivariate linear regression confirmed association of LV and functional capacity parameters with AF risk. Although functional capacity is impaired in AF, this association precedes the onset of AF. In conclusion, poor functional status is associated with AF risk, independent of LV function. © 2016 Elsevier Inc. All rights reserved. **(Am J Cardiol 2017;119:572−578)**

Atrial fibrillation (AF) is associated with significant morbidity and mortality,[1,2] including stroke, heart failure with impaired and preserved ejection fraction,[3] functional impairment,[4] and poor prognosis.[5] Although the prevalence of AF continues to increase in the aging population, there is currently not a proactive management approach in which patients at risk of AF are identified and treated before the onset of symptoms or complications. Earlier diagnosis of AF might have several benefits. The risk of AF increases after episodes of AF,[6] and this likely contributes to atrial remodeling and altered mechanics.[7] Early diagnosis may allow prevention of complications such as stroke and heart failure, and prevention may avoid the symptoms, impaired quality of life, and overall burden on the health care system associated with AF.[1,2] When implemented early, lifestyle interventions (e.g., weight loss) have been associated with a reduction in symptom burden and improved cardiac remodeling.[8] Such an approach to prevention may be analogous to stage B heart failure,[9] the diagnosis of which in patients with risk factors permits the early implementation of pharmacological therapy and risk factor management to prevent or delay the onset of symptomatic heart failure. The risk factors for AF (hypertension, obesity, and the metabolic syndrome) are common and not specific. We sought whether the detection of impaired functional capacity could better characterize risk of AF.

Methods

This observational cohort study recruited patients from a large community based in Tasmania, which had the primary objective of early detection of heart failure. Asymptomatic participants aged ≥65 years were recruited if they had ≥1 factors, including hypertension (systolic blood pressure >140 mm Hg or preexisting use of antihypertensive medications), type 2 diabetes mellitus (based on self-report of diagnosis or the current use of diabetic medications), obesity (defined as a body mass index ≥30), previous chemotherapy, previous history of coronary artery disease, or family history of heart failure. Exclusion criteria included the following: (1) inability to provide written consent to participate in the study, (2) history of moderate or greater valvular disease, (3) known history of heart failure, (4) reduced left ventricular (LV) systolic function on baseline echocardiogram (LV ejection fraction <40%), (5) contraindications to β blockers and angiotensin-converting enzyme inhibitors, (6) expected life expectancy of <1 year, or (7) inability to acquire interpretable images from baseline echocardiogram. All patients with a known history

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See page 577 for disclosure information.

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Table 1
Baseline characteristics of cohort

Baseline Characteristic	Total Cohort (n = 607)
Age (years) (SD)	70.9 ± 4.8
Men	282 (47%)
Systolic BP (mmHg) (SD)	140.0 ± 16.8
Diastolic BP (mmHg) (SD)	81.8 ± 10.4
BMI (kg/m^2) (SD)	29.4 ± 5.3
Current Smoking	14 (2%)
Diabetes Mellitus	311 (51%)
Obesity	263 (43%)
Hypercholesterolemia	307 (51%)
Hypertension	481 (79%)
Previous history of IHD	47 (8%)
Previous chemotherapy	74 (12%)
Baseline Medications	
Beta blockers	40 (7%)
ACE-I/ARB	405 (67%)
Calcium blockers	129 (21%)
Lipid Lowering drugs	306 (50%)
Anti-platelet agents (aspirin/clopidogrel/ticagrelor/prasugrel)	209 (34%)

Obesity—defined as Body Mass Index $\geq$ 30 kg/m^2.

Table 2
Clinical characteristics of participants in relation to AF risk. There are significant differences in relation to age, sex, blood pressure, diabetes, hypertension, ischemic heart disease, past chemotherapy and current medical therapy

Variable	Low Risk (0-5%) n = 185	Moderate Risk (5-10%) n = 228	High Risk (10-15%) n = 103	Very High Risk (> 15%) n = 91	P Value
Age (years (SD)	68.1 (2.9)	68.9 (3.5)	72.7 (4.0)	76.9 (5.0)	< 0.001
Men	44/185 (24%)	118/228 (52%)	66/103 (64%)	54/91 (59%)	< 0.001
Systolic BP (mmHg) (SD)	136.0 (15.1)	138.8 (14.6)	140.7 (16.4)	150.5 (21.1)	< 0.001
Diastolic BP (mmHg) (SD)	81.0 (10.4)	81.5 (9.8)	82.7 (10.3)	83.2 (12.0)	0.324
BMI (kg/m^2) (SD)	28.9 (4.9)	29.4 (5.4)	30.7 (6.1)	29.3 (4.9)	0.064
Current Smoking	1/185 (0.5%)	5/228 (0.2%)	3/103 (3%)	5/91 (5.4%)	0.077
Diabetes Mellitus n/total	68/185 (37%)	118/228 (52%)	69/103 (67%)	56/91 (62%)	< 0.001
Obesity n/total	75/185 (41%)	96/228 (42%)	51/103 (49.5%)	41/91 (45%)	0.486
Hypercholesterolemia n/total	83/183 (45%)	115/209 (55%)	58/96 (60%)	51/85 (60%)	0.039
Hypertension n/total	126/185 (68%)	181/228 (79%)	88/103 (85%)	86/91 (95%)	< 0.001
Previous history of IHD n/total	3/185 (2%)	15/228 (7%)	14/103 (14%)	15/91 (16%)	< 0.001
Previous chemotherapy n/total	32/185 (17%)	26/228 (11%)	12/103 (12%)	4/91 (4%)	0.020
Baseline Medications					
Beta blockers n/total	8/185 (4%)	15/228 (7%)	9/103 (9%)	8/91 (9%)	0.387
ACE-I/ARB n/total	111/185 (60%)	157/228 (69%)	74/103 (72%)	63/91 (69%)	0.127
Calcium blockers n/total	25/182 (14%)	49/199 (25%)	27/95 (28%)	28/79 (35%)	0.001
Lipid Lowering drugs n/total	85/182 (47%)	111/202 (55%)	59/95 (62%)	51/79 (65%)	0.019
Anti-platelet agents (aspirin.clopidogrel/ticagrelor.prasugrel) n/total	49/182 (27%)	78/200 (39%)	41/93 (44%)	41/79 (52%)	0.001

of AF or documented AF on baseline electrocardiography (ECG) were excluded from the study. All patients were provided written informed consent, and ethics approval was obtained from the institution's Human Research Ethics Committee.

All participants undertook a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, medical history, medication history, and baseline examination data (height, weight, body mass index, and blood pressure were recorded for all participants). Baseline ECG and echocardiography were conducted in all participants.

The CHARGE-AF score[10] uses 12 clinical parameters (age, race, height, weight, systolic/diastolic blood pressure, current smoking, use of antihypertensives, history of diabetes mellitus/myocardial infarction, history of heart failure, ECG data, voltage criteria for left ventricular hypertrophy,

Table 3
Association between AF risk with atrial and left ventricular dysfunction

Independent Variables	Clinical AF risk (CHARGE-AF)						Univariate			Multivariate	
	Low Risk (0-5%) Mean (SD)	Medium Risk (5-10%) Mean (SD)	High Risk (10-15%) Mean (SD)	Very High Risk (> 15%) Mean (SD)	P value	R^2	Standardized Coefficient (β)	ANOVA F statistic (P value)	β	P Value
Male	44/185 (24%)	118/228 (52%)	66/103 (64)	54/91 (59)	< 0.001	0.068	0.260	F(1, 605) = 44.0 (< 0.001)	0.263	<0.001
Ejection Fraction (%)	62.2 (4.8)	60.7 (5.6)	60.2 (6.0)	59.6 (5.9)	0.001	0.018	-0.134	F(1, 599) = 11.0 (0.001)		
Global Longitudinal Strain (%)	-19.1 (2.4)	-18.4 (2.6)	-18.4 (2.5)	-17.6 (2.6)	< 0.001	0.035	0.186	F(1, 605) = 21.6 (< 0.001)	0.125	0.002
Global Longitudinal Strain Rate (s^{-1})	-1.38 (0.24)	-1.33 (0.18)	-1.35 (0.18)	-1.31 (0.20)	0.21	0.009	0.094	F(1, 604) = 5.4 (0.02)		
Global Circumferential Strain (%)	-31.0 (5.7)	-29.5 (5.4)	-28.6 (6.0)	-29.7 (4.9)	0.002	0.004	0.066	F(1, 603) = 2.6 (0.11)		
Global Circumferential Strain Rate (s^{-1})	-2.7 (0.71)	-2.5 (0.62)	-2.5 (0.65)	-2.6 (0.56)	0.263	0.001	0.028	F(1, 603) = 0.47 (0.50)		
E' Average (m/s)	0.076 (0.02)	0.078 (0.02)	0.076 (0.02)	0.070 (0.02)	0.003	0.017	-0.131	F(1, 605) = 10.6 (0.001)		
E/e' (Average septal and lateral)	8.71 (2.4)	8.60 (2.4)	8.98 (2.5)	10.0 (3.1)	< 0.001	0.026	0.162	F(1, 605) = 16.3 (< 0.001)	0.202	<0.001
Left atrial volume (ml/m^2) - indexed	30.1 (9.2)	31.4 (10.0)	32.6 (7.6)	34.7 (10.5)	0.001	0.029	0.170	F(1, 604) = 18.1 (<0.001)		
Left Ventricular mass (g/m^2) – indexed	84.5 (21.4)	92.1 (21.2)	96.1 (23.1)	99.4 (24.8)	< 0.001	0.053	0.230	F(1, 604) = 33.6 (<0.001)		
Multivariate Regression Model						0.124				F (3,603) = 28.5 (<0.001)

and PR interval) to assess 5-year risk of AF. Cardiovascular fitness was assessed using the six-minute walk test (SMWT). This was conducted in marked corridors adjacent to the clinic where the total distance covered over 6 minutes was calculated to the nearest meter. All patients answered questionnaires to assess overall quality of life and function. These included the Duke Activity Status Index (DASI),[11] Minnesota Living with Heart Failure score (MLHF),[12] Charlson Index,[13] and EuroQoL5D Visual Analog Scale.[14]

Echocardiograms were performed by qualified sonographers using the same equipment (Siemens ACUSON SC2000; Siemens Healthcare, California) and transducer (4V1c, 1.25 to 4.5 MHz; 4Z1c, 1.5 to 3.5 MHz). Two-dimensional, M-mode, and Doppler measurements were obtained using techniques outlined by the American Society of Echocardiography. LV dimensions were calculated in both diastole and systole in parasternal long-axis views. LV hypertrophy was defined as LV mass index >115 g/m^2 in men and >95 g/m^2 in women. LV and left atrial (LA) volumes were indexed to body surface area and calculated by the Simpson biplane method. Abnormal LA volume index was defined as $\geq$34 ml/m^2.

Diastolic function was assessed by calculating mitral inflow peak early and late diastolic velocities (E and A wave), deceleration time, and the E/A ratio (ratio <0.8 was used to define for impaired relaxation). The average of septal and lateral mitral annular early diastolic velocity (e') was used to calculate the E/e' ratio (>13 was used to define raised LA filling pressures).

Global longitudinal strain (GLS) was calculated in apical 4-chamber views, and global circumferential strain was calculated in the mid-LV parasternal short-axis view. Velocity vector imaging was used to assess ventricular strain. Manual tracing of the endocardial border of the LV was performed in end systole, and this was tracked during the cardiac cycle.

Patients were split into 4 groups based on AF risk (low 0% to 5%, medium 5% to 10%, high 10% to 15%, and very high >15%). The primary outcome was to assess whether poor functional capacity was an independent risk factor for AF. All categorical variables are presented as frequencies/percentages and continuous variables presented as means/standard deviation (if normally distributed) or medians/interquartile range (if nonparametric). Statistical significance was performed using the chi-square test for categorical data. Analysis of variance was used to assess the interaction between groups. Associations between variables were assessed using linear regression. All variables with p <0.1 in univariate analyses were considered in multivariate models. ROC curves were generated to determine optimal cut-off values of continuous variables. Analyses were considered to be statistically significant if 2-tailed p values were <0.05. Statistical analysis was performed using SPSS version 22 (IBM, Chicago, Illinois).

Results

A total of 607 patients were included (mean ± SD age 70.9 ± 4.8 years, men 47%). Most patients had risk factors for heart failure and AF including type 2 diabetes mellitus (51%), obesity (43%), hypercholesterolemia (51%), and

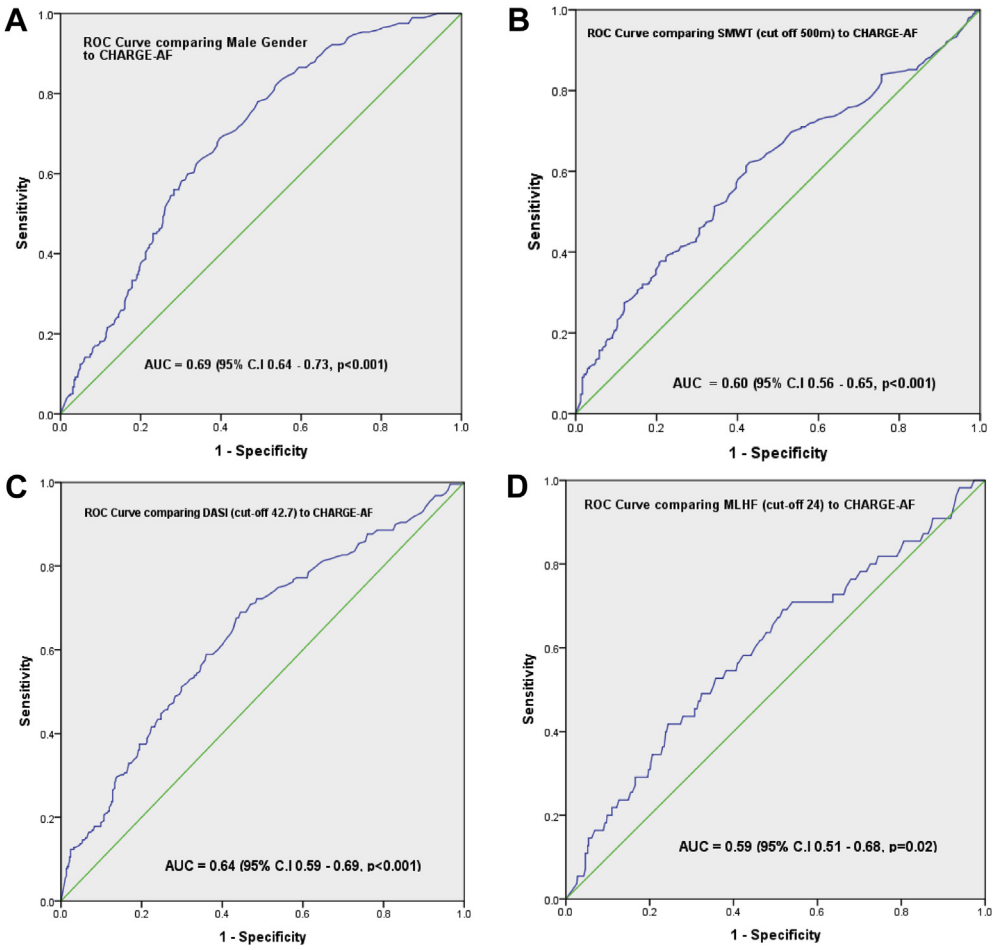

Figure 1. ROC curves comparing functional capacity parameters to AF risk. *(A)* ROC curve comparing male gender to CHARGE-AF. *(B)* ROC curve comparing SMWT cutoff 500 m to CHARGE-AF. *(C)* ROC curve comparing DASI cutoff 42.7 to CHARGE-AF. *(D)* ROC curve comparing MLHF Score cutoff 24 to CHARGE-AF.

hypertension (79%). The median AF risk (CHARGE-AF) was 7.0% (interquartile range 3.5% to 10.5%). Baseline patient characteristics are summarized in Table 1.

Participants were split into 4 groups based on AF risk (low 0% to 5%, medium 5% to 10%, high 10% to 15%, and very high risk >15%; Table 2). Patients with greater AF risk were older, more likely to be men with higher systolic blood pressure and rates of diabetes mellitus, hypercholesterolemia, and ischemic heart disease ($p < 0.05$). Patients with low AF risk had a greater proportion who had previous chemotherapy. There was no statistically significant difference in smoking rates and body mass index between groups.

AF risk was associated with reduced functional capacity (Table 3). SMWT was lower in higher AF risk groups (496 m in low risk vs 432 m in very high risk, $p < 0.001$), and patients with greater AF risk had lower DASI scores ($p < 0.001$) and had more medical comorbidities ($p = 0.04$).

Univariate regression showed clinical AF risk was associated with impaired functional capacity (assessed by SMWT and DASI) and quality of life (EuroQoL5D Visual Analog Scale), Charlson index, and male gender. In a multivariate linear regression model, SMWT ($\beta = -0.188$, $p < 0.001$) was independently associated with clinical AF risk. Using ROC curves, the optimal cutoff for SMWT was 500 m (area under the curve [AUC] 0.60, 95% confidence interval [CI] 0.56 to 0.65, $p < 0.001$), for DASI was 42.7 (AUC 0.64, 95% CI 0.59 to 0.69, $p < 0.001$), and for MLHF was 24 (AUC 0.59, 95% CI 0.51 to 0.68, $p = 0.02$; Figure 1).

The association between AF risk and atrial and LV parameters is presented in Table 4. Greater clinical AF risk was associated with lower ejection fraction ($60 \pm 5.9\%$ vs $62 \pm 4.8\%$ in lowest risk, $p = 0.001$), worse GLS ($-17.6 \pm 2.6\%$ vs $-19.1 \pm 2.4\%$ in lowest risk, $p < 0.001$) and GCS (-29.7 ± 4.9 vs $-31.0 \pm 5.7\%$, $p = 0.002$). Indexed LV mass was noted to be greater in patients with greater AF risk (99.4 ± 24.8 g/m^2 vs 84.5 ± 21.4, $p < 0.001$). AF risk was associated with GLS ($\beta = 0.19$, $p < 0.001$), E/e' ($\beta = 0.16$, $p < 0.001$), and male gender ($\beta = 0.26$, $p < 0.001$). Using ROC curves, the optimal cutoff for GLS was -18% (AUC 0.598, 95% CI 0.552 to 0.643, $p < 0.001$) and that for indexed LA volume was 35 ml/m^2 (AUC 0.586, 95% CI 0.537 to 0.635, $p = 0.001$).

Table 4
Association between AF and functional capacity

Independent Variables	Clinical AF risk (CHARGE-AF					Univariate			Multivariate	
	Low Risk (0-5%) Mean (SD) n = 185	Medium Risk (5-10%) Mean (SD) n = 228	High Risk (10-15%) Mean (SD) n = 103	Very High Risk (> 15%) Mean (SD) n = 91	P value	R^2	Standardized Coefficient (β)	ANOVA F statistic (P value)	β	P Value
Male	44/185 (24)	118/228 (52)	66/103 (64)	54/91 (59)	< 0.001	0.068	0.260	F(1, 605) = 44.0 (< 0.001)	0.306	< 0.001
Six Minute Walk Test (m)	495.8 (89.4)	484.9 (93.7)	438.9 (110.6)	431.8 (117.2)	< 0.001	0.064	-0.253	F(1, 571) = 39.1 (<0.001)	-0.188	< 0.001
Duke Activity Status Index	46.8 (10.5)	44.2 (11.6)	40.2 (13.3)	38.6 (13.5)	< 0.001	0.078	-0.279	F(1, 592) = 50.0 (< 0.001)		
Minnestoa Living with Heart Failure Score	4.7 (10.4)	6.0 (12.1)	9.7 (12.9)	10.8 (16.2)	< 0.001	0.040	0.199	F(1, 590) = 24.3 (<0.001)		
EuroQoL EQ-5D Visual Analogue Score	82.2 (13.8)	80.5 (15.4)	79.8 (15.2)	78.9 (14.8)	0.308	0.007	-0.084	F(1, 590) = 4.21 (0.041)		
Charlson Index	1.8 (2.4)	1.6 (2.0)	2.3 (2.8)	2.2 (2.6)	0.043	0.008	0.087	F(1, 605) = 4.59 (0.033)		
Multivariate Regression Model						0.184			F (6, 562) = 21.2 (<0.001)	

Discussion

This study suggests that AF risk is associated with impaired functional capacity as assessed with the SMWT and less activity (assessed by the DASI), independent of LV function and LV mass. SMWT <500 m as well as DASI <42.7 and MLHF >24 were associated with AF risk.

A number of clinical features are associated with AF, including the metabolic syndrome, hypertension, and type 2 diabetes mellitus. The CHARGE-AF score was developed from a total of 18,556 patients with a wide age range (46 to 94 years) and ethnic diversity (19% African-American) based on pooled data from the Framingham Heart Study,[15] the Atherosclerosis Risk in Communities,[16] and the Cardiovascular Health Study.[17] The bedside clinical score gives a 5-year risk of developing AF using clinical variables including age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive therapy, history of diabetes mellitus/myocardial infarction, and heart failure with overall good model discrimination (C-statistic 0.765, 95% CI 0.748 to 0.781). The CHARGE-AF score has been validated in multiple cohorts, is easy to implement in clinical practice, and can be calculated in the absence of ECG data.[10]

A deficiency in clinical risk scores is that they do not incorporate atrial or LV mechanics or LA size, all of which are implicated in the pathogenesis of AF.[7,18–20] AF risk is associated with reduced atrial reservoir, conduit, and pump strain[21] which is likely a marker of progressive atrial fibrosis and can be used to predict recurrence after catheter ablation[22] or cardioversion.[23] The use of LV strain analysis to predict AF risk is poorly understood. LV regional deformation allows for objective assessment of systolic function.[24] LV strain analysis has important applications for the assessment for cardiomyopathy, myocardial ischemia,[24,25] and assessment for LV dyssynchrony postcardiac resynchronization therapy.[24] Changes to atrial size and fibrosis in the absence of mitral valve disease are often due to progressive changes to the LV including increase in LV mass, higher filling pressures, and concentric remodeling which are commonly associated with age and hypertension and give rise to poor exercise capacity.[26]

We have found in this study that altered myocardial mechanics are independently associated with AF risk. This has several implications for clinical practice. Echocardiography and deformation analysis are noninvasive, easily accessible, and cost effective and can be used in screening programs. This can potentially lead to early diagnosis of AF before the onset of complications such as stroke. The relation between AF and LV mechanics also raises the possibility of AF risk in patients with underlying structural heart disease or a known history of heart failure. AF in these patients is associated with a poorer prognosis; thus, early diagnosis would impact prognosis.[5]

AF is associated with impaired quality of life and poor functional capacity.[2] Restoration of sinus rhythm after pharmacological therapy or catheter ablation may be associated with improvement in New York Heart Association functional class, improvement in quality of life, and modest improvement in exercise capacity.[27] Although the link between AF and quality of life is well understood, it is unclear

if poor functional capacity can contribute to AF risk. Common risk factors for AF such as obesity, hypertension, and type 2 diabetes mellitus are associated with impaired quality of life and reduced exercise capacity.[8,28] Poor exercise capacity could offer a surrogate risk assessment tool in clinical practice to identify patients at risk of AF.

Although the link between AF and quality of life is well understood, previous work has not shown whether poor functional capacity can contribute to AF risk. The results of our study suggest that poor exercise capacity is an independent risk factor for AF. Exercise and weight loss programs have recently been shown to improve AF symptom burden and atrial remodeling.[29] The reasons why poor exercise capacity contributes to AF risk is unclear. Improvement in cardiovascular fitness may have a protective role in AF possibly by preventing atrial remodeling. The strong association between immobility and obesity may lead to altered atrial mechanics and increased atrial size which can create a substrate for arrhythmia. Patients with poor functional capacity are more likely to have associated comorbidities such as hypertension and diabetes mellitus which are known risk factors for AF. Poor exercise capacity could offer a surrogate risk assessment tool in clinical practice to identify patients at risk of AF.

This study has several limitations. There was a potential for population selection bias as patients were recruited with newspaper and radio advertising. In this observational study, our primary outcome measure was to assess AF risk using a validated risk score, rather than following up patients to assess the actual incidence of AF. Showing the association of reduced functional capacity with baseline AF risk is relevant to baseline evaluation.

AF places a huge burden on the health care system and screening programs to identify patients at risk of AF will have increasing importance as there are now ways to alter disease progression which could potentially prevent AF and its complications. Mass screening has the potential to be expensive, so assessment should begin with a clinical risk assessment tool. The association of reduced exercise capacity and functional status with AF risk has 2 implications. It may be a marker of treatable risk, similar to obesity, as well as identifying a patient subgroup appropriate for close monitoring for AF.

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Disclosures

The authors have no conflicts of interest to disclose.

1. Wong CX, Brooks AG, Leong DP, Roberts-Thomson KC, Sanders P. The increasing burden of atrial fibrillation compared with heart failure and myocardial infarction: a 15-year study of all hospitalizations in Australia. *Arch Intern Med* 2012;172:739−741.
2. Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M, Luderitz B. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol* 2000;36:1303−1309.
3. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna W, Seward JB, Iwasaka T, Tsang TS. Incidence and mortality risk of congestive heart failure in atrial fibrillation patients: a community-based study over two decades. *Eur Heart J* 2006;27:936−941.
4. McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. *Ann Intern Med* 2003;139:1018−1033.
5. Ahmed A, Perry GJ. Incident atrial fibrillation and mortality in older adults with heart failure. *Eur J Heart Fail* 2005;7:1118−1121.
6. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* 1995;92:1954−1968.
7. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. *J Am Coll Cardiol* 2008;51:802−809.
8. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau DH, Antic NA, Brooks AG. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* 2013;310:2050−2060.
9. Goldberg LR, Jessup M. Stage B heart failure management of asymptomatic left ventricular systolic dysfunction. *Circulation* 2006;113:2851−2860.
10. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JD, Janssens ACJ. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013;2:e000102.
11. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, Cobb FR, Pryor DB. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989;64:651−654.
12. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. *Am Heart J* 1992;124:1017−1025.
13. D'Hoore W, Sicotte C, Tilquin C. Risk adjustment in outcome assessment: the Charlson comorbidity index. *Methods Inf Med* 1993;32:382−387.
14. Rabin R, Charro Fd. EQ-SD: a measure of health status from the EuroQol Group. *Ann Med* 2001;33:337−343.
15. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009;373:739−745.
16. Chamberlain AM, Agarwal SK, Folsom AR, Soliman EZ, Chambless LE, Crow R, Ambrose M, Alonso A. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol* 2011;107:85−91.
17. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A. The cardiovascular health study: design and rationale. *Ann Epidemiol* 1991;1:263−276.
18. Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Takemoto Y, Diamond PM, Marra MA, Gersh BJ, Wiebers DO. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. *Mayo Clin Proc* 2001;76:467−475.
19. Her A-Y, Kim J-Y, Kim YH, Choi E-Y, Min P-K, Yoon YW, Lee B-K, Hong B-K, Rim S-J, Kwon HM. Left atrial strain assessed by speckle tracking imaging is related to new-onset atrial fibrillation after coronary artery bypass grafting. *Can J Cardiol* 2013;29:377−383.
20. Dimitri H, Ng M, Brooks AG, Kuklik P, Stiles MK, Lau DH, Antic N, Thornton A, Saint DA, McEvoy D, Antic R, Kalman JM, Sanders P. Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. *Heart Rhythm* 2012;9:321−327.
21. Ancona R, Comenale Pinto S, Caso P, D'Andrea A, Di Salvo G, Arenga F, Coppola MG, Sellitto V, Macrino M, Calabrò R. Left atrium

by echocardiography in clinical practice: from conventional methods to new echocardiographic techniques. *ScientificWorldJournal* 2014;2014:451042.
22. Mirza M, Caracciolo G, Khan U, Mori N, Saha SK, Srivathsan K, Altemose G, Scott L, Sengupta P, Jahangir A. Left atrial reservoir function predicts atrial fibrillation recurrence after catheter ablation: a two-dimensional speckle strain study. *J Interv Card Electrophysiol* 2011;31:197−206.
23. Thomas L, Mckay T, Byth K, Marwick TH. Abnormalities of left atrial function after cardioversion: an atrial strain rate study. *Heart* 2007;93:89−95.
24. Gorcsan J, Tanaka H. Echocardiographic assessment of myocardial strain. *J Am Coll Cardiol* 2011;58:1401−1413.
25. Edvardsen T, Gerber BL, Garot J, Bluemke DA, Lima JA, Smiseth OA. Quantitative assessment of intrinsic regional myocardial deformation by Doppler strain rate echocardiography in humans validation against three-dimensional tagged magnetic resonance imaging. *Circulation* 2002;106:50−56.
26. Ciaroni S, Cuenoud L, Bloch A. Clinical study to investigate the predictive parameters for the onset of atrial fibrillation in patients with essential hypertension. *Am Heart J* 2000;139:814−819.
27. Dorian P, Paquette M, Newman D, Green M, Connolly SJ, Talajic M, Roy D. Quality of life improves with treatment in the Canadian trial of atrial fibrillation. *Am Heart J* 2002;143:984−990.
28. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, Somers VK. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;49:565−571.
29. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;64:2222−2231.

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ORIGINAL ARTICLES

Association between socioeconomic status and incident atrial fibrillation

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Abstract

Background: Low socioeconomic status is associated with cardiovascular diseases, and an association with atrial fibrillation (AF) could guide screening.
Aim: To investigate if indices of advantage/disadvantage (IAD), index of education/occupation (IEO) and index of economic resources were associated with incident AF, independent of risk factors and cardiac function.
Methods: We studied community-based participants aged ≥65 years with AF risk factors (n = 379, age 70 ± 4 years, 45% men). The CHARGE-AF score (a well validated AF risk score) was used to assess 5-year risk of developing AF. Participants also had baseline echocardiograms. IAD, IEO and index of economic resources were obtained from the 2011 Socio-Economic Indexes for Areas score, in which higher decile ranks indicate more advantaged areas. Patients were followed up for incident AF (median 21 (range 5–31) months), with AF diagnosed by clinical review, including 12-lead electrocardiogram (ECG), as well as single-lead portable ECG monitoring used to record 60 s ECG tracings five times/day for 1 week. Cox proportional hazards models were used to assess the association between socioeconomic status and incident AF.
Results: Subjects with AF (n = 50, 13%) were more likely to be male (64 vs 42%, P = 0.003) and had higher CHARGE-AF score (median 7.1% (5.2–12.8%) vs 5.3% (3.3–8.6%), P < 0.001). Areas with lower socioeconomic status (IAD and IEO) had a higher risk of incident AF independent of LV function and CHARGE-AF score (hazard ratio for IAD 1.16, 95% confidence interval 1.05–1.29, P = 0.005 and hazard ratio for IEO 1.18, 95% confidence interval 1.07–1.30, P = 0.001).
Conclusion: Regional socioeconomic status is associated with risk of incident AF, independent of LV function and clinical risk. This association might permit better regional targeting of prevention.

Introduction

Atrial fibrillation (AF) is associated with stroke, heart failure, increased all-cause mortality[1,2] and substantial financial cost.[3,4] The epidemics of obesity, diabetes mellitus and metabolic syndrome have been associated with the increasing prevalence of AF, which has become a significant population health problem.[5–7] The early diagnosis of AF may lead to individualised lifestyle intervention[8] and anticoagulation, and these steps may be associated with a reduction in complications and healthcare costs. The development of hand-held electrocardiogram (ECG) screening devices,[9–15] has increased the feasibility of AF screening. Appropriate selection of patients for screening is of critical importance; the

Abbreviations: AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; ECG, electrocardiogram; HR, hazard ratio; IAD, index of advantage/disadvantage; IEO, index of education/occupation; IER, Index of Economic Resources; LV, left ventricular; SEIFA, Socio-Economic Indices for Areas; T2DM, type II diabetes mellitus.

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development of a risk assessment score,[16,17] based on the link between AF and clinical risk factors, is an important component of identifying individual patients at risk. The introduction of a screening programme should also involve consideration of which communities are at risk.

Socioeconomic deprivation is strongly associated with increased risk of metabolic syndrome and coronary artery disease,[18–20] beyond its association with reduced healthcare access. Low household income influences dietary choices, psychological well-being and is associated with a sedentary lifestyle.[21] Poor literacy and education levels may affect treatment adherence and risk awareness. There may also be higher rates of substance and alcohol abuse in deprived areas.[22] However, the association between socioeconomic deprivation and AF risk is controversial, with reports of an association of lower household income with increased AF risk,[23] balanced by other evidence that neighbourhood deprivation and socioeconomic disparities were not independently associated with AF.[24] The purpose of this study was to assess the association of regions of socioeconomic deprivation with risk of incident AF.

Methods

Study population

This prospective observational cohort study recruited participants from both urban and rural settings in Tasmania (an island located south of the Australian mainland) and Victoria (a larger State in the south of mainland Australia). Apart from the major cities (Hobart and Launceston), much of Tasmania is geographically isolated, with limited access to healthcare.[25] Participants from the community ≥65 years were recruited if they had one or more AF/heart failure (HF) risk factors, including hypertension (systolic blood pressure (BP) >140 mmHg or preexisting use of antihypertensive medications), type 2 diabetes mellitus (T2DM, based on self-report of diagnosis or the current use of diabetic medications) and obesity (body mass index ≥30). Subjects were excluded if they were unable to provide written consent, had known HF or left ventricular (LV) systolic dysfunction, moderate/severe valvular disease or life expectancy <1 year. All patients with a history of AF and anticoagulation or were noted to have AF during baseline 12-lead ECG and echocardiograms were excluded. All patients were provided written informed consent and the study protocol conforms with the ethical guidelines of the 1975 Declaration of Helsinki and approval was obtained from the Tasmanian Human Research Ethics Committee (HREC project number H0013333). The study was registered on the Australian and New Zealand clinical trials registry (ACTRN12614000080628).

Clinical findings

Participants provided a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, past medical history, medication history and baseline examination data (height, weight, body mass index, BP) was recorded for all participants. Baseline 12-lead ECG and echocardiography were conducted in all participants, and patients with previously unrecognised HF were excluded. Assessment of AF risk was performed using the CHARGE-AF score.[17] Exercise capacity was assessed using the 6-minute walk test.

Assessment of socioeconomic status

All participants had information collected on education level. The Socio-Economic Indexes for Areas (SEIFA) score is derived from several domains of national census data (including education, housing, household income, employment and occupation) to provide a multidimensional assessment of socioeconomic status based on postcode. This was used to describe the regional variations of participants' overall socioeconomic status.[25]

The SEIFA score has three main indices: an index of advantage/disadvantage (IAD, based on income, occupation and housing), an index of education/occupation (IEO, based on education and occupation) and an index of economic resources (IER, based on individual income, mortgage repayments, rental return and family income). These indices are expressed to deciles, with the lowest scoring 10% of areas given a decile number of 1 and the highest 10% of areas are given a decile number of 10. Hence, higher scores reflect more advantaged areas.[25]

AF follow up

AF was diagnosed using multiple detection methods. All participants had baseline and follow-up assessment, including a 12-lead ECG and echocardiogram. In the interim, any patients diagnosed with AF by local physicians were documented. Screening for subclinical AF was performed using a single-lead ECG device (Remon RM-100; Semacare, Shenzhen, China). The single-lead device was used to record 60-s single-lead ECG tracings using three points of finger contact with electrodes, five times per day for 1 week (i.e. 35 recordings). ECG recordings were then exported as PDF files for interpretation, and all were assessed by a physician. The presence of AF (an irregular rhythm of ≥30 s with a variable R-R interval and absent P waves) was confirmed by two

independent physicians who were blinded to the patient's clinical details. The patient was advised of the recognition of subclinical AF, and further management and investigation was provided by their usual medical practitioner.

Outcome measures

Our primary outcome measure was the overall proportion of the cohort with new onset AF during the follow-up period.

Statistical analysis

All categorical variables are presented as frequencies/percentages, and continuous variables presented as means/standard deviation (if normally distributed) or medians/interquartile range (if nonparametric). Patients with incident AF were compared with those remaining in sinus rhythm. Groups were compared using the Chi-squared test for categorical data and the independent two sample t-test for continuous data. Patients were grouped according to the SEIFA rank (<5 vs ≥5) and Nelson–Aalen cumulative hazard estimate plots were constructed, and the log-rank test used to assess the differences between curves. A Cox proportional hazards regression analysis was used to calculate the adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the association between each socioeconomic index and incident AF. Clinically relevant model covariates included CHARGE-AF score, global longitudinal strain, gender and indexed left atrial volume. The follow-up time was the time from the initial baseline clinical assessment to the completion of portable device screening or the date of diagnosis of AF (whichever came first). Analyses were considered to be statistically significant if two-tailed P values were < 0.05. Statistical analysis was performed using SPSS v.22 (SPSS, Chicago, IL, USA) and Stata v.13 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

The baseline characteristics of the 379 subjects included in the study (mean age 70 ± 4 years, 45% male) are summarised in Table 1. Thirteen participants (3%) had a previous diagnosis of paroxysmal AF. Cardiovascular risk factors (including T2DM, obesity, hypercholesterolaemia and hypertension) were highly prevalent. There was a large proportion of participants with low education levels (43% had not completed high school and approximately three in four had not completed university education). Most participants were recruited from areas with socioeconomic deprivation (median IAD 5 ± 6, median IEO 5 ± 6 and median IER 4 ± 5).

AF during follow up

Over a median follow up of 21 months (range 5–31 months), 50 patients (13%) were diagnosed with AF. Of these, 37 patients (9.8%) were diagnosed with incident AF, 23 of whom (6%) were diagnosed with portable ECG monitoring while 14 (4%) were diagnosed by local physicians during the follow-up period or had AF during hospitalisations. Table 2 compares the characteristics of those with AF and sinus rhythm; new onset AF was more likely in men, and in those with a higher CHARGE-AF score and those from socioeconomically deprived areas ($P < 0.05$).

Table 1 Baseline characteristics of the overall cohort

Demographics	n = 379
Age (SD) (years)	70.3 (4.2)
Male, *n* (%)	169 (45)
Systolic BP (SD) (mmHg)	140.6 (15.9)
Diastolic BP (SD) (mmHg)	82.5 (9.9)
Heart rate (SD) (b.p.m.)	68.7 (10.8)
BMI (SD) (kg/m^2)	29.8 (5.2)
Current/previous smoking, *n* (%)	182 (48)
Diabetes mellitus, *n* (%)	176 (46)
Obesity, *n* (%)	176 (46)
Hypercholesterolaemia, *n* (%)	205 (54)
Hypertension, *n* (%)	293 (77)
Previous history of IHD, *n* (%)	16 (4)
Previous history of AF, *n* (%)	13 (3)
Previous chemotherapy, *n* (%)	36 (10)
Median 6-min walk test (IQR) (m)	504 (96)
Median CHARGE-AF (IQR) (%)	6.8 (6.6)
Median CHA_2DS_2-VASC (IQR) (%)	3.0 (2.0)
Echocardiographic parameters	Mean (SD)
Ejection fraction (SD) (%)	62.8 (6.2)
Global longitudinal strain (SD) (%)	−18.8 (2.5)
E/e' (average of lateral and septal) (SD)	8.7 (2.5)
Left atrial volume, indexed (SD) (mL/m^2)	31.5 (9.1)
Left ventricular mass, indexed (SD) (g/m^2)	88.8 (21.7)
Social factors	
Median SEIFA Index of Advantage/Disadvantage (IQR)	5 (6.0)
Median SEIFA Index of Education/Occupation (IQR)	5 (6.0)
Median SEIFA Index of Economic Resources (IQR)	4 (5.0)
Completed high school, *n* (%)	214/375 (57)
Completed university, *n* (%)	88/376 (23)

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; IHD, ischaemic heart disease; IQR, interquartile range; SEIFA, Socio-Economic Indexes for Areas.

Association between socioeconomic status and AF risk

SEIFA data were available in 370/379 participants (with 48 AF outcomes). Table 3 summarises the features associated with AF risk, including increased age, male gender, reduced global longitudinal strain, increased left atrial volume and socioeconomic deprivation. Those who developed AF had lower median SEIFA indices than those in sinus rhythm (IAD (4.0 (range 2–6) vs 5.0 (range 3–8), P = 0.005), IER (4.0 (range 2–5) vs 5.0 (range 3–8), P = 0.002) and IEO (3.5 (range 2–7) vs 6.5 (range 2–8), P = 0.02)). There were no differences in AF rates noted in participants with high school or tertiary level education. In a multivariable model, adjusted for gender, clinical risk factors, LV function and left atrial volume, increased incident AF risk was associated with disadvantaged areas (HR for IAD = 1.16, 95% CI 1.05–1.29, P = 0.005) and areas with lower education/occupation levels (HR for IEO = 1.18, 95% CI 1.07–1.30, P = 0.001) (Fig. 1, Table 3). Areas with lower economic resources were not independently associated with increased incident AF risk (HR for IER = 1.11, 95% CI 0.99–1.24, P = 0.08).

Discussion

The results of our study suggest that a significant number of elderly people in the community with risk factors have subclinical AF. Regional socioeconomic deprivation is associated with AF independent of other clinical risk factors and cardiac function. Areas with higher household income, higher rates of education and employment were associated with reduced risk of incident AF.

Socioeconomic status and AF

Socioeconomic deprivation is well established as a risk factor for metabolic syndrome and cardiovascular disease,[18–20] but the association between socioeconomic status and AF is less clear. A large Swedish study did not find an independent association between socioeconomic status and hospitalised AF,[24] although an association was found in women.[24] The ARIC cohort found that low family income was associated with increased risk of AF,[23] with lower education levels associated with increased AF risk in women.[23] After adjusting for confounders, we found that regional indices of low

Table 2 Comparison of baseline characteristics between patients with AF and sinus rhythm

Demographics	Atrial fibrillation n = 50	Sinus rhythm n = 329	P Value
Age (SD) (years)	71.3 (5.0)	70.1 (4.0)	0.12
Male, n (%)	32 (64)	137 (42)	0.003
Systolic BP (SD) (mmHg)	135.5 (18.3)	141.4 (15.3)	0.01
Diastolic BP (SD) (mmHg)	82.6 (11.2)	82.5 (9.7)	0.99
BMI (SD) (kg/m^2)	29.3 (4.7)	29.9 (5.3)	0.39
Current/previous smoking, n (%)	24 (48)	158 (48)	1.0
Diabetes mellitus, n (%)	27 (54)	149 (45)	0.25
Obesity, n (%)	19 (38)	157 (48)	0.419
Hypercholesterolaemia, n (%)	25/47 (53)	180/321 (56)	0.71
Hypertension, n (%)	38 (76)	255 (78)	0.81
Previous history of IHD, n (%)	5 (10)	11 (3.3)	0.03
Median CHARGE-AF (IQR) (%)	7.1 (7.6)	5.3 (5.3)	<0.001
Median CHA_2DS_2-VASC (IQR)	3.0 (2.0)	3.0 (2.0)	0.93
Functional capacity			
Six-min walk test (SD) (m)	498 (102)	508 (98)	0.50
Social factors			
Median SEIFA Index of Advantage/Disadvantage (IQR)	4 (4.0)	5.0 (5.0)	0.005
Median SEIFA Index of Education/Occupation (IQR)	3.5 (5.0)	6.5 (6.0)	0.02
Median SEIFA Index of Economic Resources (IQR)	4.0 (3.0)	5.0 (5.0)	0.002
Completed high school, n (%)	28 (56)	186/325 (57)	0.87
Completed university, n (%)	8 (16)	80/326 (25)	0.18
Echocardiographic parameters			
Ejection fraction (SD) (%)	60.7 (7.2)	63.2 (5.9)	0.01
Global longitudinal strain (SD) (%)	−17.7 (3.3)	−19.0 (2.3)	0.01
E/e' (average of lateral and septal) (SD)	8.6 (2.7)	8.8 (2.5)	0.67
Left atrial volume, indexed (SD) (mL/m^2)	34.0 (10.3)	31.1 (8.9)	0.03
Left ventricular mass, indexed (SD) (g/m^2)	93.6 (23.3)	87.8 (21.3)	0.10

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; IHD, ischaemic heart disease; IQR, interquartile range; SEIFA, Socio-Economic Indexes for Areas.

Table 3 Cox regression analysis showing association between socioeconomic status and AF

Independent variables	Unadjusted hazard ratio (95% CI)	*P*- value	Adjusted hazard ratio (95% CI)	*P*-value
Age (years)	1.06 (1.00–1.12)	0.048		
Male gender	2.44 (1.37–4.36)	0.003	1.78 (0.96–3.31)	0.07
Body mass index (kg/m^2)	1.01 (0.95–1.06)	0.83		
Systolic blood pressure (mmHg)	0.98 (0.96–0.99)	0.02		
Diastolic blood pressure (mmHg)	1.01 (0.98–1.04)	0.51		
Type 2 diabetes mellitus	1.33 (0.75–2.34)	0.32		
Obesity	0.90 (0.51–1.59)	0.71		
Hypertension	0.99 (0.52–1.91)	0.99		
Ejection fraction (%)	0.93 (0.90–0.97)	0.001		
Global longitudinal strain (%)	1.21 (1.09–1.36)	0.001	**1.22 (1.08–1.38)**	**0.002**
Left atrial volume, indexed (mL/m^2)	1.05 (1.02–1.08)	0.002	**1.04 (1.01–1.07)**	**0.01**
Left ventricular mass, indexed (g/m^2)	1.01 (0.99–1.02)	0.02		
Six-min walk test (m)	1.00 (0.99–1.00)	0.87		
CHARGE-AF Score (%)	1.04 (0.99–1.09)	0.10	0.98 (0.92–1.03)	0.37
CHA_2DS_2-VASC Score	0.98 (0.71–1.34)	0.89		
SEIFA Index of Advantage/Disadvantage	1.15 (1.04–1.27)	0.007	**1.16 (1.05–1.29)**	**0.005**
SEIFA Index of Education/Occupation	1.17 (1.06–1.28)	0.001	**1.18 (1.07–1.30)**	**0.001**
SEIFA Index of Economic Resources	1.11 (0.99–1.25)	0.07	1.11 (0.99–1.24)	0.08
Completed high school	0.67 (0.39–1.18)	0.17		
Completed university	0.55 (0.26–1.16)	0.12		

Multivariable model adjusted for gender, CHARGE-AF score, left atrial volume and global longitudinal strain. Bold indicates variables that are independently associated with AF ($P < 0.05$). AF, atrial fibrillation; CI, confidence interval; SEIFA, Socio-Economic Indexes for Areas.

income/education were associated with AF in both sexes. The use of regional indices of socioeconomic status provides a basis of using geographic location in planning screening, in a way that using individual income or educational data would be inaccessible.

There may be several mechanisms by which socioeconomic status can affect AF risk and management. AF has been strongly associated with metabolic syndrome and obesity,[5,7] both of which are strongly influenced by socioeconomic status. Household income and education levels influence dietary habits and physical activity levels. Interestingly, in our study despite high rates of obesity, T2DM and hypertension at baseline, we did not see any significant difference in these markers in participants with AF compared with those in sinus rhythm. It is possible that could be due to our small sample size and limited follow up. These markers are components of the CHARGE-AF score, where we did note a higher score in those with AF compared with those in sinus rhythm. It is possible that even though the overall rates between both groups were similar, those who developed AF may have poorly controlled risk factors or may have individuals with multiple risk factors present, hence creating incremental risk. Children born to parents of low socioeconomic status have higher risk of low birth weight which has been shown to be associated with AF risk.[26] The higher rates of alcohol and substance abuse in areas of socioeconomic deprivation are both associated with AF risk.[22] There may be added challenges such as poor health awareness in this cohort and issues relating to poor adherence, as limited household income may influence decisions made on anticoagulation and other pharmacological therapy.[27] Irrespective of the mechanisms involved, socioeconomic status appears to be associated with AF and in our study, it was as important a risk factor as left atrial volume and LV function.

Early diagnosis of AF and community screening

AF creates a significant burden on both patients and the healthcare system. For patients, it is associated with increased risk of stroke and HF as well as causing symptoms and impaired quality of life. AF seems likely to continue to increase in incidence and the costs to the healthcare system will continue to increase.[1,3,6] Early diagnosis might be achieved by community screening programmes, but successful AF screening requires both an appropriate diagnostic tool as well as careful selection of the at-risk population.

The incident AF rate of 9.8% in this study – higher than previously reported in the literature[9,10,15] – is attributable to not only age and clinical risk factors for AF, but also social vulnerability. Elderly, socially isolated patients with poor access to affordable healthcare, limited household income and poor education levels are often encountered in hospital following the complications of AF. Early diagnosis offers the possibility for early initiation of treatment which may offset

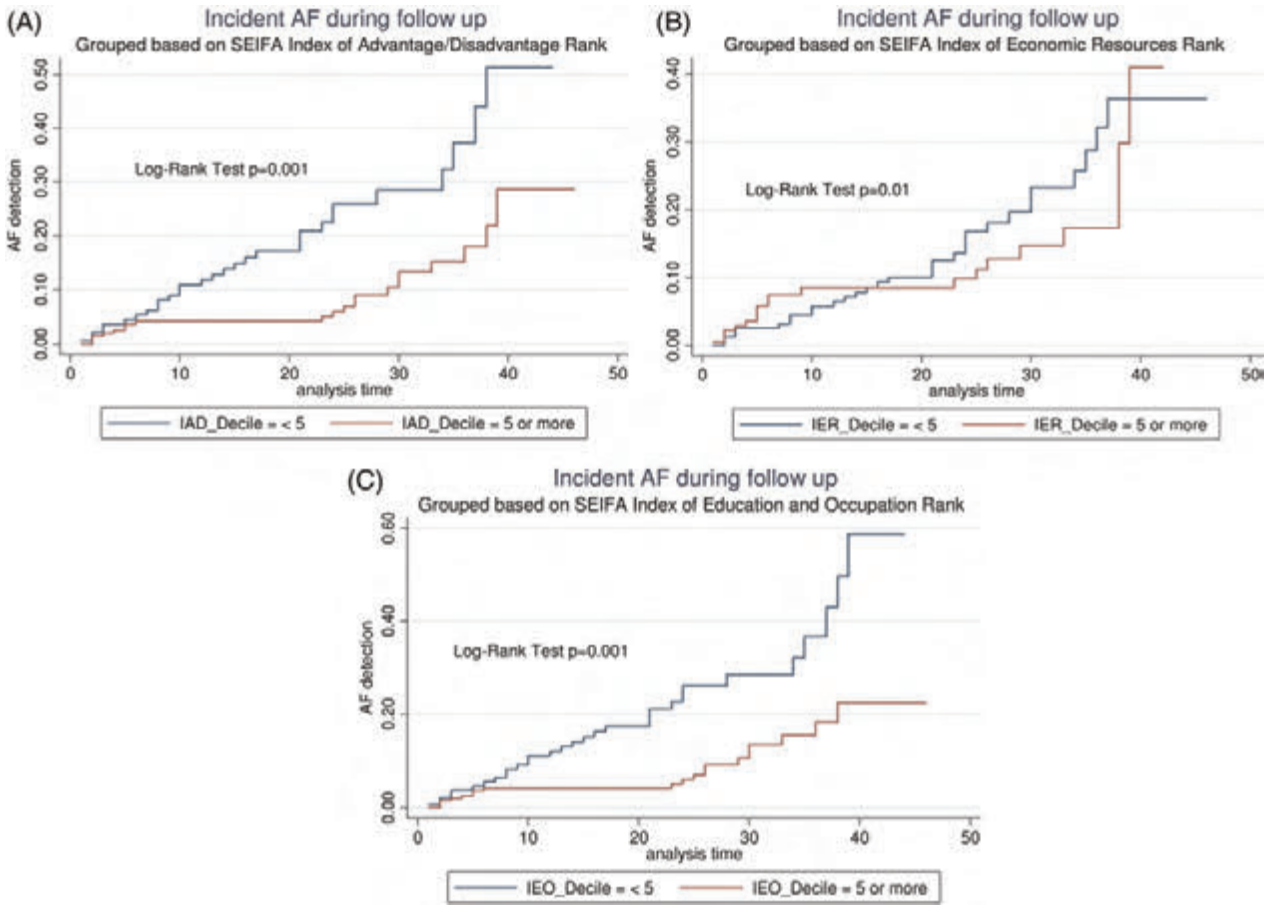

Figure 1 Nelson–Aalen curves showing incident atrial fibrillation (AF) diagnosis based on (A) index of advantage/disadvantage (IAD) decile rank; (——), IAD_Decile = <5; (——), IAD_Decile = 5 or more, (B) index of economic resource (IER) decile rank; (——), IER_Decile = <5; (——), IER_Decile = 5 or more and (C) index of education/occupation (IEO) decile rank; (——), IEO_Decile = <5; (——), IEO_Decile = 5 or more.

some of the complications which may lead to reduced hospitalisations and associated healthcare costs. Patients with subclinical AF and atrial tachyarrhythmias have an increased risk of stroke and cardiovascular events similar to those with established AF,[28,29] and anticoagulation may help reduce the incidence of stroke in this cohort. Active lifestyle intervention may lead to a reduction in symptom burden and in the need for repeat ablation procedures and an improvement in quality of life.[8] Initiation of lifestyle intervention and risk factor modification following early diagnosis of AF may be associated with positive LA remodelling, which may reduce disease progression and produce additional health benefits, including reduction in cardiovascular risk and improvement in exercise capacity.

Clinical implications

The results of our study have several important clinical implications. We have demonstrated a significant burden of subclinical AF in elderly people with risk factors. We have also demonstrated that AF screening using portable ECG monitoring is feasible. The finding that low regional socioeconomic status is associated with increased AF risk has important implications for mass screening. Screening programmes conducted in these areas will likely yield higher detection rates, improving cost-effectiveness and providing access to early intervention programmes to those at the highest risk of complications and hospitalisations.

Limitations

There are several limitations of our study. There is a potential for population selection bias as participants were recruited with newspaper and radio advertising. Selection bias may influence the rates of clinically diagnosed AF in the cohort. Patients from areas of high socioeconomic status who may have better access to healthcare and improved health literacy may present

more frequently for review, potentially resulting in higher rates of clinically diagnosed AF. Our patient sample was small, and we had a limited number of AF outcomes. Our patient population was predominantly white Australian, and our results are not generalisable to the indigenous population or other ethnicities. Our screening for subclinical AF was done for a 1-week period of intermittent ECG monitoring, and it is possible that resulted in some AF outcomes to be potentially missed. Our study focused on the assessment of regional socioeconomic status as we investigated the implications to a community AF screening programme. Hence, the results of our study cannot be used for individual risk assessment. Our cohort study is unable to establish causality. Intervention studies are required in the future to determine if socioeconomic deprivation is a risk factor for AF and if community-based interventions can result in reduced AF incidence.

Conclusion

Elderly patients with risk factors have a high prevalence of subclinical AF, especially in regions of socioeconomic deprivation. The finding that socioeconomic deprivation is independently associated with incident AF suggests that additional resources and access to healthcare are needed in selected communities to improve health outcomes.

References

1 Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba follow-up study. *Am J Med* 1995; **98**: 476–84.

2 Vidaillet H, Granada JF, Chyou P-H, Maassen K, Ortiz M, Pulido JN *et al*. A population-based study of mortality among patients with atrial fibrillation or flutter. *Am J Med* 2002; **113**: 365–70.

3 Kim MH, Johnston SS, Chu B-C, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes* 2011; **4**: 313–20.

4 Leyden JM, Kleinig TJ, Newbury J, Castle S, Cranefield J, Anderson CS *et al*. Adelaide stroke incidence study: declining stroke rates but many preventable cardioembolic strokes. *Stroke* 2013; **44**: 1226–31.

5 Watanabe H, Tanabe N, Watanabe T, Darbar D, Roden DM, Sasaki S *et al*. Metabolic syndrome and risk of development of atrial fibrillation. *Circulation* 2008; **117**: 1255–60.

6 Ball J, Thompson DR, Ski CF, Carrington MJ, Gerber T, Stewart S. Estimating the current and future prevalence of atrial fibrillation in the Australian adult population. *Med J Aust* 2015; **202**: 32–5.

7 Dagres N, Anastasiou-Nana M. Atrial fibrillation and obesity. *J Am Coll Cardiol* 2010; **55**: 2328–9.

8 Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D *et al*. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014; **64**: 2222–31.

9 Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J *et al*. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost* 2014; **111**: 1167–76.

10 Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP study. *Circulation* 2015; **131**: 2176–84.

11 Engdahl J, Andersson L, Mirskaya M, Rosenqvist M. Stepwise screening of atrial fibrillation in a 75-year-old population clinical perspective. *Circulation* 2013; **127**: 930–7.

12 Kaasenbrood F, Hollander M, Rutten FH, Gerhards LJ, Hoes AW, Tieleman RG. Yield of screening for atrial fibrillation in primary care with a hand-held, single-lead electrocardiogram device during influenza vaccination. *Europace* 2016; **18**: 1514–20.

13 Proietti M, Mairesse GH, Goethals P, Scavee C, Vijgen J, Blankoff I *et al*. A population screening programme for atrial fibrillation: a report from the Belgian heart rhythm week screening programme. *Europace* 2016; **18**: 1779–86.

14 Halcox JP, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C *et al*. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study. *Circulation* 2017; **136**: 1784–94.

15 Chan N, Choy C. Screening for atrial fibrillation in 13 122 Hong Kong citizens with smartphone electrocardiogram. *Heart* 2017; **103**: 24–31.

16 Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ *et al*. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors - clinical perspective. *Circulation* 2011; **123**: 1501–8.

17 Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB *et al*. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013; **2**: e000102.

18 Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. *Circulation* 1993; **88**: 1973–98.

19 Santos AC, Ebrahim S, Barros H. Gender, socio-economic status and metabolic syndrome in middle-aged and old adults. *BMC Public Health* 2008; **8**: 62.

20 Chichlowska KL, Rose KM, Diez-Roux AV, Golden SH, McNeill AM, Heiss G. Individual and neighborhood socioeconomic status characteristics and prevalence of metabolic syndrome. The atherosclerosis risk in communities (ARIC) study. *Psychosom Med* 2008; **70**: 986–92.

21 McLaren L. Socioeconomic status and obesity. *Epidemiol Rev* 2007; **29**: 29–48.

22 Fone DL, Farewell DM, White J, Lyons RA, Dunstan FD. Socioeconomic patterning of excess alcohol consumption and binge drinking: a

cross-sectional study of multilevel associations with neighbourhood deprivation. *BMJ Open* 2013; **3**: e002337.
23 Misialek JR, Rose KM, Everson-Rose SA, Soliman EZ, Clark CJ, Lopez FL *et al*. Socioeconomic status and the incidence of atrial fibrillation in whites and blacks: the atherosclerosis risk in communities (ARIC) study. *J Am Heart Assoc* 2014; **3**: e001159.
24 Zöller B, Li X, Sundquist J, Sundquist K. Neighbourhood deprivation and hospitalization for atrial fibrillation in Sweden. *Europace* 2013; **15**: 1119–27.
25 Australian Bureau of Statistics. *Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA), Commonwealth of Australia*. Canberra: Australian Bureau of Statistics, Commonwealth of Australia; 2011 [cited 2013 Mar 28]. Available from URL: http://www.abs.gov.au/ausstats/abs@.nsf/mf/2033.0.55.001
26 Lawani SO, Demerath EW, Lopez FL, Soliman EZ, Huxley RR, Rose KM *et al*. Birth weight and the risk of atrial fibrillation in whites and African Americans: the atherosclerosis risk in communities (ARIC) study. *BMC Cardiovasc Disord* 2014; **14**: 69.
27 Sholzberg M, Gomes T, Juurlink DN, Yao Z, Mamdani MM, Laupacis A. The influence of socioeconomic status on selection of anticoagulation for atrial fibrillation. *PLoS One* 2016; **11**: e0149142.
28 Martinez C, Katholing A, Freedman SB. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. *Thromb Haemost* 2014; **112**: 276–86.
29 Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A *et al*. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012; **366**: 120–9.

Association of the Active and Passive Components of Left Atrial Deformation with Left Ventricular Function

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Background: Left atrial (LA) strain imaging enables the quantitative assessment of LA function. The clinical relevance of these measurements is dependent on the provision of information incremental to the left ventricular (LV) evaluation. The aim of this study was to test the hypothesis that LA pump function but not reservoir function is independent of measurement of LV mechanics.

Methods: Echocardiography was undertaken in a community-based study of 576 participants ≥65 years of age with one or more risk factors (e.g., hypertension, diabetes mellitus, obesity). Strain analysis was conducted using a dedicated software package, using R-R gating. LV function was classified as normal in the presence of global longitudinal strain (GLS) (≤−18%) or global circumferential strain (GCS) (≤−22%). The associations between GLS or GCS and LA reservoir, conduit, and pump strain were assessed using univariate and multivariate linear regression.

Results: Patients (mean age 71 ± 5 years, 54% women) with reduced GLS had higher blood pressure and rates of diabetes and obesity ($P < .05$). LA reservoir strain and conduit strain were lower in the group with impaired GLS (38.2 ± 7.3% vs 39.9 ± 6.4% [$P = .004$] and 18.7 ± 5.7% vs 20.5 ± 5.1% [$P < .001$], respectively), but there was no difference in LA pump strain (19.5 ± 5.5% vs 19.3 ± 4.6%, $P = .72$). GLS was independently associated with LA reservoir and conduit strain ($P < .05$) but not independently associated with LA pump strain ($P = .91$). Reduced GCS was associated with a larger body mass index, male sex, and diabetes ($P < .05$). There were no differences in LA reservoir, conduit, and pump strain in patients with normal and abnormal GCS ($P > .05$).

Conclusions: The application of LA strain is specific to the component measured. LA pump strain is independent of LV mechanics. (J Am Soc Echocardiogr 2017;30:659-66.)

Keywords: Strain, Left atrium, Atrial function, Left ventricle

There is increasing recognition of the importance of altered left atrial (LA) function, incremental to LA dilatation, and the feasibility of its assessment has increased with the application of strain imaging to LA function.[1-3] Although there are currently no standardized guidelines with regard to electrocardiographic (ECG) gating, image acquisition, or analysis techniques,[3,4] this parameter is reliable and reproducible[2,3] and is able to quantify the contributions of reservoir, conduit, and active pump function.[5]

LA strain imaging can be used as part of the assessment of left ventricular (LV) diastolic function,[6-8] but it is unclear as to whether it provides incremental information to other echocardiographic measures of diastolic function such as mitral inflow or mitral annular velocities. Because LA reservoir and conduit function reflect underlying LV function, there has been some skepticism about the utility of LA strain compared with other markers of LV strain, such as global longitudinal strain (GLS)[1,2,9,10]; indeed, atrial and ventricular volumes reciprocate at different phases in the cardiac cycle. In contrast, LA contractile strain is a measure of LA systolic function relative to LA load as it fills the left ventricle and pulmonary veins. Hence, although LA pump function contributes approximately 30% to LV filling during end-diastole (and even more in older patients), it is less dependent on LV function.[3,11] The loss of the LA "kick" is also believed to contribute to symptoms of heart failure (HF) in patients with atrial fibrillation (AF).[12,13] Given the important physiologic role of the LA pump, we hypothesized that atrial pump strain was independent of LV strain.

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METHODS

Study Population

In this prospective, observational cohort study, we recruited patients from a large community-based study in Australia, which had the primary objective of early detection of HF in the community. Asymptomatic

Abbreviations
AF = Atrial fibrillation
ECG = Electrocardiographic
GCS = Global circumferential strain
GLS = Global longitudinal strain
HF = Heart failure
LA = Left atrial
LV = Left ventricular

participants ≥65 years of age were recruited if they had one or more risk factors, including hypertension (systolic blood pressure > 140 mm Hg or preexisting use of antihypertensive medications), type 2 diabetes mellitus (on the basis of self-report of diagnosis or the current use of diabetic medications), and obesity (defined as body mass index ≥ 30 kg/m^2). Exclusion criteria were (1) inability to provide written consent to participate in the study, (2) history of moderate or greater valvular disease, (3) known history of HF, (4) reduced LV systolic function on baseline echocardiography (LV ejection fraction < 40%), (5) contraindications to β-blockers and angiotensin-converting enzyme inhibitors, (6) life expectancy < 1 year, and (7) inability to perform strain analysis or acquire interpretable images from baseline echocardiography. All patients with known histories of AF or documented AF on baseline electrocardiography were excluded from the study. All patients were provided written informed consent, and approval was obtained from the institution's human research ethics committee.

Clinical Findings

All participants undertook a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, medical history, medication history, and baseline examination data (height, weight, body mass index, and blood pressure) was recorded for all participants. Baseline electrocardiography and echocardiography were conducted in all participants.

Echocardiography

All echocardiographic examinations were performed by qualified sonographers using the same equipment (Siemens Acuson SC2000, Siemens Medical Solutions USA, Mountain View, CA) and transducers (4V1c [1.25–4.5 MHz] and 4Z1c [1.5–3.5 MHz]). Two-dimensional, M-mode, and Doppler measures were obtained using standard techniques outlined by the American Society of Echocardiography. LV dimensions were calculated in both diastole and systole in parasternal long-axis views. LV hypertrophy was defined as LV mass index > 115 g/m^2 in men and >95 g/m^2 in women. LV and LA volumes were indexed to body surface area and calculated using the Simpson biplane method. Abnormal LA volume index was defined as ≥34 mL/m^2.

Diastolic function was assessed by calculating mitral inflow peak early and late diastolic velocities (E and A waves, respectively), deceleration time, and the E/A ratio (a ratio < 0.8 was used to define impaired relaxation). Mitral annular early diastolic velocity using Doppler tissue imaging (e′) was calculated in both septal and lateral and averaged to calculate the E/e′ ratio (>13 was used to define increased LA filling pressures).

GLS was calculated in the apical four-chamber view, and global circumferential strain (GCS) was calculated in the mid-LV parasternal short-axis view. Velocity Vector Imaging was used to assess ventricular strain. Manual tracing of the endocardial border of the left ventricle was performed in end-systole, and this was tracked during the cardiac cycle. LA reservoir, conduit, and pump strain was assessed using speckle-tracking imaging by an external third-party software program (Image Arena; TomTec Imaging Systems, Munich, Germany). Apical four- and two-chamber images were selected with a frame rate of 60 to 80 frames/sec. The endocardial border of the left atrium was manually traced, and strain analysis was performed using the LV strain algorithm, with the average of both the four- and two-chamber values. The reference point for image analysis was taken at the onset of the QRS complex (R-R gating; Figure 1). Patients with poor image quality, such that strain analysis could not be performed, were excluded. All strain measurements were performed by two investigators. Reproducibility was assessed using a random sample of 20 patients, and the mean percentage difference was calculated.

HF Follow-Up

All participants were followed using questionnaires, phone calls, and follow-up clinical visits at a median time of 12 months (interquartile range, 6 months). HF symptoms were assessed using the Framingham criteria. We included patients with HF with reduced ejection fraction and those with HF with preserved ejection fraction, per criteria outlined by the European Society of Cardiology.[14,15] All patients were reviewed by a cardiologist in the clinic, and information was collected regarding symptoms and examination findings. Patients underwent echocardiography to confirm the presence of HF.

Statistical Analysis

Patients were split into two groups on the basis of GLS (cutoff −18%) and GCS (cutoff −22%). All categorical variables are presented as frequencies and percentages, and continuous variables are presented as mean ± SD (if normally distributed) or as medians and interquartile ranges (if nonparametric). Statistical significance was assessed using the χ^2 test for categorical data and the independent-sample t test for continuous data. Simple linear regression was used to identify associations between LV function and clinical parameters with LA reservoir, conduit, and pump strain. All variables with P values < .10 in univariate analyses were considered in multivariate regression models. Cox proportional-hazard models were used to assess for the association between LA strain and incident HF. Analyses were considered to be statistically significant if two-tailed P values were <.05. Statistical analysis was performed using SPSS version 22 (SPSS, Chicago, IL).

RESULTS

Baseline Characteristics

A total of 576 patients were included in the study (mean age, 70.7 ± 4.7 years; 46% men). The majority of patients had type 2 diabetes mellitus (52%), obesity (43%), hypercholesterolemia (54%), and hypertension (79%). Mean values of LA reservoir, conduit, and pump strain were 39.3 ± 6.8%, 19.8 ± 5.4%, and 19.4 ± 5.0%, respectively. A summary of baseline patient characteristics is shown in Table 1.

Associations of Impaired LV Strain

Participants were split into two groups on the basis of GLS (normal, ≤−18%; n = 352). Table 2 shows that patients with abnormal GLS were older, were more likely to be male, hypertensive, and obese, and were more likely to have diabetes mellitus. LA reservoir and conduit strain was reduced in the group with abnormal GLS (reservoir strain, 38.2 ± 7.3% vs 39.9 ± 6.4% [P = .004]; conduit strain, 18.7 ± 5.7% vs 20.5 ± 5.1% [P < .001]). There were no significant differences with regard to LA pump strain (19.5 ± 5.5% vs 19.3 ± 4.7%, P = .72).

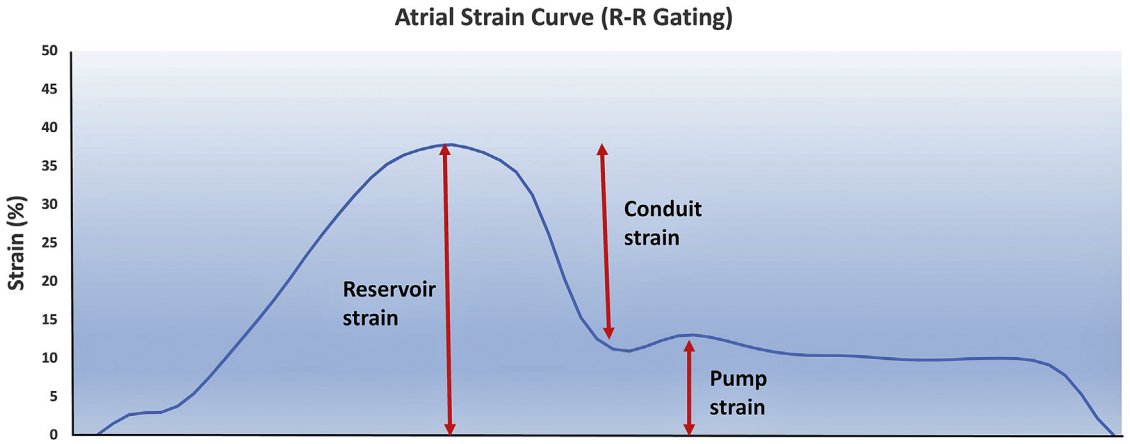

Figure 1 Components of LA strain.

Participants were also split into two groups on the basis of GCS (normal, ≤−22% [n = 533]; abnormal, >−22% [n = 43]) (Table 3). Patients with abnormal GCS were more likely to be male and to have higher body mass index and rates of diabetes mellitus and ischemic heart disease ($P < .05$). Groups were not different with respect to LA reservoir (39.3 ± 6.8% vs 39.0 ± 7.3%, $P = .83$), conduit (19.9 ± 5.3% vs 19.0 ± 6.5%, $P = .30$), and pump (19.4 ± 5.0% vs 20.0 ± 5.3%, $P = .38$) strain.

Associations of LA and LV Function

LA reservoir strain was independently associated with GLS ($r = 0.16$, $\beta = -0.13$, $P = .001$). GCS was not associated with reservoir strain. LA reservoir strain was associated with E/e′ ratio ($r = 0.16$, $\beta = -0.12$, $P = .004$) and LV mass ($r = 0.14$, $\beta = -0.09$, $P = .03$) independent of age ($r = 0.26$, $\beta = -0.21$, $P < .001$). It was not associated with A wave or deceleration time ($P > .05$) (Table 3).

LA conduit strain was independently associated with GLS ($r = 0.21$, $\beta = -0.14$, $P = .01$). GCS was not independently associated with conduit strain. LA conduit strain was associated with E wave ($r = 0.14$, $\beta = 0.21$, $P < .001$) and A wave ($r = 0.11$, $\beta = -0.19$, $P < .001$), independent of age ($r = 0.23$, $\beta = -0.18$, $P < .001$). It was not associated with deceleration time or LV mass ($P > .05$) (Table 4).

LA pump strain was associated with E wave ($r = 0.10$, $\beta = -0.23$, $P < .001$) and A wave ($r = 0.12$, $\beta = 0.24$, $P < .001$) independent of age ($r = 0.10$, $\beta = -0.13$, $P = .002$). There was no association noted between LA pump strain and ventricular strain (GLS, $r = 0.005$, $P = .91$; GCS, $r = 0.0$, $P = .99$). LA pump strain was not independently associated with deceleration time or LV mass ($P > .05$) (Table 5; Figure 2).

Association between LA Function and Incident HF

Among 478 of 576 patients with follow-up data available for analysis (median follow-up 12 ± 6 months), 54 (11%) developed new incident HF. LA function was not independently associated with new incident HF (reservoir strain, $P = .28$; conduit strain, $P = .38$; pump strain, $P = .66$).

Reproducibility

Reproducibility was assessed by blinded strain measurements in a random sample of 20 patients. All measurements were done by the same two investigators (S.R. and T.N.), and the mean of the absolute value of differences between measurements was calculated. For GLS and GCS, the mean differences were 0.7 ± 0.7% and 4.0 ± 3.9%, respectively. For LA strain, the mean differences were 8.0 ± 7.0% for reservoir strain, 5.4 ± 4.1% for conduit strain, and 5.6 ± 4.6% for pump strain. Intraobserver variability was assessed by one investigator (S.R.), who repeated LA strain measurements in the same 20 patients at a different time point. The mean differences for LA strain were 3.8 ± 2.9% for reservoir strain, 2.7 ± 1.4% for conduit strain, and 2.7 ± 1.4% for pump strain.

DISCUSSION

The results of our study suggest that GLS was independently associated with LA reservoir and conduit strain but was not independently associated with LA pump strain. GCS was not found to be associated with LA strain. LA strain was associated with diastolic function but not independently associated with incident HF.

LA Physiology

The left atrium is thin walled, with a high degree of compliance, which allows it to stretch during the reservoir phase.[11] Therefore, in ventricular systole, the left atrium acts as a reservoir for blood flow from the pulmonary circulation. The elasticity of the left atrium allows it to return to normal size during the conduit and pump phases.[3] The independent association of LV GLS with reservoir function is a reflection of how LV pathology is associated with higher LV filling pressures, increased LA pressure and tension, and impaired LA compliance.[16] The maladaptive compensatory changes of the thin-walled left atrium in response to high pressures[17-19] leads to progressive pathologic changes, including fibrosis as a response to inflammatory mediators,[6,20,21] resulting in reduced reservoir function.

One of the main functions of the left atrium is acting as a passive conduit during early diastole, which contributes up to 35% of ventricular filling.[22] An essential aspect to normal conduit function is a pressure gradient across the mitral valve that occurs during LV relaxation.[11] The association of impaired GLS with reduced conduit strain in our study is a reflection of the contribution of a stiff LV to a lower LA-LV gradient.[16]

LA contraction at the end of diastole is influenced by age, LV relaxation, atrial preload, and LV end-diastolic pressure (afterload). The LA pump contributes approximately 30% of ventricular filling, which can be higher in older patients.[11,23] The LA pump has an important role in

Table 1 Baseline demographics and echocardiographic parameters (N = 576)

Baseline patient characteristic	Value
Demographics	
Age (y)	70.7 ± 4.7
Men	264/576 (46)
Systolic BP (mm Hg)	140.0 ± 16.8
Diastolic BP (mm Hg)	81.8 ± 10.4
Heart rate (beats/min)	66.8 ± 10.5
BMI (kg/m^2)	29.4 ± 5.2
Current smoking	13/576 (2)
Diabetes mellitus	297/576 (52)
Obesity	249/576 (43)
Hypercholesterolemia	293/545 (54)
Hypertension	457/576 (79)
History of IHD	42/576 (7)
Previous chemotherapy	70/576 (12)
Medications	
β-blockers	40/576 (7)
ACE inhibitors/angiotensin receptor blockers	385/576 (67)
Calcium blockers	123/526 (23)
Lipid-lowering agents	291/529 (55)
Antiplatelet agents	196/525 (37)
Echocardiographic parameters	
Ejection fraction (%)	63.6 ± 5.9
GLS (%)	−18.5 ± 2.5
GCS (%)	−29.8 ± 5.5
E/e′ ratio (average of lateral and septal)	8.9 ± 2.6
LA volume index (mL/m^2)	31.8 ± 9.4
LV mass index (g/m^2)	91.7 ± 22.9
Atrial reservoir strain (%)	39.3 ± 6.8
Atrial conduit strain (%)	19.8 ± 5.4
Atrial pump strain (%)	19.4 ± 5.0

ACE, Angiotensin-converting enzyme; *BMI*, body mass index; *BP*, blood pressure; *IHD*, ischemic heart disease.
Data are expressed as mean ± SD or as *n*/*N* (percentage).

ventricular filling when conduit function is reduced. In the early stages of diastolic dysfunction, the left atrium is able to compensate for reduced conduit function by an increased "atrial kick" at end-diastole.[11] Although patients can remain asymptomatic during this phase, they have less functional reserve. Reduced LA strain has been shown to be associated with reduced exercise capacity.[24-26] Patients who lose the "atrial kick," such as those who develop AF and those who develop tachycardia (associated with reduced diastolic filling time), can manifest symptoms of HF and decompensate acutely.[1,2,11]

Measurement of LA Strain

Several concerns are relevant to LA strain measurement. There are limited guidelines or consensus on image acquisition, ECG gating, and what parameters to measure.[2,23] LA strain measurement may be operator dependent and time consuming, as the thin endocardial border is difficult to track.[23] The calculation of LA strain must be done using a LV strain algorithm, as software vendors have yet to develop a dedicated algorithm.[2] In contrast, GLS is more robust, has been validated in different populations to assess for subclinical LV dysfunction, and can be used to assess prognosis in patients admitted with myocardial infarction and HF.[27,28]

What Factors Influence LA Pump Function?

In our study, we have attempted to highlight the importance of the atrial pump, as most studies have focused on LA reservoir strain. We have shown that in comparison with reservoir and conduit function, the atrial pump is less associated with LV function. This suggests that there may be other mechanisms that can influence atrial pump function.

LA function is influenced mainly by LV systole and relaxation: because reservoir and conduit function are reflections of changes to the left ventricle, the independent value of LA contractile strain might be expected but has not been proved.[1,5,9,10] The LA pump involves the interplay of multiple factors.[3,29] In our study, we have emphasized that LA pump function is independent of LV function.

The first component influencing pump function is atrial preload. Pulmonary venous flow is a determinant of LA volume and therefore atrial ejection. Second, there is a codependence among the three components of LA strain. LA reservoir function is influenced by LV compliance and descent of the LV base during diastole but also by LA systole. In elderly patients, changes to LV compliance and impaired relaxation reduce conduit strain, and the left atrium may compensate by ejecting a larger volume during end-diastole, until the eventual loss of LA reserve may lead to symptoms of HF. This interdependence among the three components of LA function demonstrates an indirect influence of LV function on pump function. Third, the LA pump is influenced by LV end-diastolic pressure (afterload), as the left atrium must pump blood across a higher pressure gradient.

In our study, we attempted to highlight the importance of the LA pump. Despite the indirect involvement of the left ventricle in LA function, outlined by the mechanisms above, our results demonstrate that LA pump function is not directly dependent on LV function. To further understand the physiology of the LA pump and the various influencing factors, further research combining LA strain with invasive hemodynamic data will allow us to better understand this relationship.

LA Strain and Association with Diastolic Function

Current echocardiographic assessment of diastolic function is based primarily on assessment of mitral inflow velocities, early diastolic mitral annular velocity, and assessment of LA volume.[30] The novel role of LA strain in assessment of diastolic function is mentioned in the latest American Society of Echocardiography guidelines, but there is acknowledgment of current limitations.[30] In our study, we have demonstrated a close relationship between diastolic function and LA strain. The left atrium acts as a reservoir during ventricular systole, and we noted that reservoir function was associated with E/e′ ratio. This suggests that the ability of the left atrium to stretch and act as a reservoir is directly influenced by the pressure within the left atrium as well as the LV-LA gradient. Conduit function was associated with both the E and A waves, suggesting a close relationship with LV relaxation and filling pressures rather than LA size. LA pump function was not associated with LV mass or LV strain and was closely associated with the E and A waves. This suggests that pump function is not influenced primarily by LV function and is influenced by other external factors that directly influence LA function.

Table 2 Baseline characteristics for groups with normal and reduced GLS (cutoff −18%) and GCS (cutoff −22%)

Variable	GLS > −18% (*n* = 224)	GLS ≤ −18% (*n* = 352)	*P*	GCS > −22% (*n* = 43)	GCS ≤ −22% (*n* = 533)	*P*
Age (y)	71.2 ± 4.4	70.4 ± 4.7	.007	70.4 ± 4.0	70.8 ± 4.7	.65
Men	127/224 (57)	137/352 (39)	<.001	30/43 (70)	234/533 (44)	.001
Systolic BP (mm Hg)	142.3 ± 19.6	138.7 ± 14.6	.02	138.1 ± 17.8	140.2 ± 16.7	.43
Diastolic BP (mm Hg)	84.2 ± 10.4	80.3 ± 10.1	<.001	83.3 ± 10.6	81.7 ± 10.4	.31
Heart rate (beats/min)	69.2 ± 11.2	65.3 ± 9.8	<.001	72.6 ± 11.6	66.4 ± 10.3	<.001
BMI (kg/m^2)	29.9 ± 5.5	29.1 ± 5.0	.08	31.7 ± 6.1	29.2 ± 5.1	.003
Current smoking	9/224 (4)	4/352 (1)	.02	1/43 (2)	12/533 (2)	.97
Diabetes mellitus	151/224 (67)	146/352 (42)	<.001	31/43 (72)	266/533 (50)	.005
Obesity	111/224 (49)	138/352 (39)	.02	23/43 (54)	226/533 (42)	.16
Hypercholesterolemia	121/210 (58)	172/335 (51)	.15	20/37 (54)	273/508 (54)	.97
Hypertension	178/224 (80)	279/352 (79)	.95	35/43 (81)	422/533 (79)	.73
History of IHD	21/224 (9)	21/352 (6)	.13	7/43 (16)	35/533 (7)	.02
Previous chemotherapy	28/224 (13)	42/352 (12)	.84	6/43 (14)	64/533 (12)	.71
Ejection fraction (%)	61.8 ± 6.8	64.8 ± 4.9	<.001	58.8 ± 8.1	64.0 ± 5.5	<.001
GLS (%)	−16.1 ± 1.6	−20.1 ± 1.5	<.001	−16.7 ± 2.4	−18.7 ± 2.5	<.001
GCS (%)	−28.7 ± 6.0	−30.4 ± 5.0	<.001	−20.0 ± 1.7	−30.6 ± 4.9	<.001
E/e′ (average septal and lateral)	9.0 ± 2.8	8.8 ± 2.5	.40	8.7 ± 2.7	8.9 ± 2.6	.53
LA volume index (mL/m^2)	32.6 ± 9.9	31.2 ± 9.0	.10	30.1 ± 7.6	31.9 ± 9.5	.23
LV mass index (g/m^2)	95.9 ± 24.9	89.0 ± 21.1	.001	96.5 ± 23.4	91.3 ± 22.8	.15
Atrial reservoir strain (%)	38.2 ± 7.3	39.9 ± 6.4	.004	39.0 ± 7.3	39.3 ± 6.8	.83
Atrial conduit strain (%)	18.7 ± 5.7	20.5 ± 5.1	<.001	19.0 ± 6.5	19.9 ± 5.3	.30
Atrial pump strain (%)	19.5 ± 5.5	19.3 ± 4.7	.72	20.0 ± 5.3	19.4 ± 5.0	.38

BMI, Body mass index; *BP*, blood pressure; *IHD*, ischemic heart disease.
Data are expressed as mean ± SD or as *n*/*N* (percentage). GLS ≥ −18 refers to values less negative than −18%, and GCS ≥ −22 refers to values less negative than −22%.

Table 3 Associations of atrial reservoir strain and LV mechanics and diastolic function

	Univariate			Multivariate		
Variable	Unstandardized coefficient (95% CI)	Standardized β	*P*	Unstandardized coefficient (95% CI)	Standardized β	*P*
Age	−0.38 (−0.49 to −0.26)	−0.26	<.001	−0.31 (−0.43 to −0.19)	−0.21	<.001
GLS	−0.44 (−0.66 to −0.22)	−0.16	<.001	−0.36 (−0.57 to −0.14)	−0.13	.001
GCS	−0.08 (−0.18 to 0.02)	−0.07	.12			
E/e′ ratio	−0.43 (−0.64 to −0.21)	−0.16	<.001	−0.31 (−0.52 to −0.10)	−0.12	.004
E wave	1.51 (−2.0 to 5.0)	0.04	.40			
A wave	−0.12 (−3.1 to 2.8)	−0.003	.94			
Deceleration time	0.0 (−0.01 to 0.01)	0.0	.99			
LV mass index	−0.04 (−0.07 to −0.02)	−0.14	.001	−0.03 (−0.05 to −0.003)	−0.09	.03

CI, Confidence interval.
Multivariate-adjusted R^2 = 0.10, P < .001.

Usefulness of LA Strain Compared with Other Echocardiographic Markers of Diastolic Function

The use of transmitral Doppler and annular tissue Doppler imaging in the echocardiographic evaluation of diastolic function is constrained by a number of situations in which the measurements confounded by other disease processes (e.g., mitral annular calcification, mitral regurgitation). LA strain has a few advantages over Doppler tissue imaging: it is angle independent,[4] and it provides quantitative assessment of the various active and passive components of LA function, potentially including regional function.[4,5] As discussed previously, the main disadvantages are the lack of consensus guidelines on image acquisition, ECG gating, and variable software vendor algorithms.[3,4] We have noted in our study the close correlation between some LA strain parameters and other markers of diastolic function. Interestingly, however, there was no significant difference in E/e′ ratio or LA volume between both normal and abnormal LV

Table 4 Associations between atrial conduit strain and LV mechanics and diastolic dysfunction

	Univariate			Multivariate		
Variable	Unstandardized coefficient (95% CI)	Standardized β	*P*	Unstandardized coefficient (95% CI)	Standardized β	*P*
Age	−0.27 (−0.36 to −0.17)	−0.23	<.001	−0.21 (−0.30 to −0.11)	−0.18	<.001
GLS	−0.44 (−0.62 to −0.27)	−0.21	<.001	−0.31 (−0.48 to −0.13)	−0.14	.001
GCS	−0.08 (−0.16 to 0.002)	−0.08	.06	−0.02 (−0.10 to 0.06)	−0.02	.57
E/e′ ratio	−0.28 (−0.45 to −0.11)	−0.13	.001	−0.31 (−0.52 to −0.10)		
E wave	4.9 (2.1 to 7.7)	0.14	.001	7.1 (4.0 to 10.2)	0.21	<.001
A wave	−3.3 (−5.6 to −0.92)	−0.11	.007	−5.5 (−8.1 to −3.0)	−0.19	<.001
Deceleration time	−0.01 (−0.02 to 0.002)	−0.06	.15			
LV mass index	−0.02 (−0.04 to 0.0)	−0.08	.05	−0.01 (−0.03 to 0.01)	−0.04	.36

CI, Confidence interval.
Multivariate-adjusted R^2 = 0.12, P < .001.

Table 5 Associations between atrial pump strain and LV mechanics and diastolic dysfunction

	Univariate			Multivariate		
Variable	Unstandardized coefficient (95% CI)	Standardized β	*P*	Unstandardized coefficient (95% CI)	Standardized β	*P*
Age	−0.11 (−0.20 to −0.02)	−0.10	.01	−0.14 (−0.23 to −0.05)	−0.13	.002
GLS	0.01 (−0.15 to −0.17)	0.005	.91			
GCS	0.0 (−0.08 to 0.08)	0.0	.99			
E/e′ ratio	−0.14 (−0.30 to 0.02)	−0.07	.08			
E wave	−3.3 (−5.9 to −0.69)	−0.10	.01	−7.2 (−10.1 to −4.3)	−0.23	<.001
A wave	3.1 (0.94–5.3)	0.12	.005	6.3 (3.8–8.7)	0.24	<.001
Deceleration time	0.01 (−0.002 to 0.02)	0.06	.15			
LV mass index	−0.02 (−0.04 to −0.003)	−0.10	.02	−0.02 (−0.03 to 0.001)	−0.07	.07

CI, Confidence interval.
Multivariate adjusted R^2 = 0.07, P < .001.

strain groups, despite differences in LA reservoir and conduit strain. It is possible that LA strain analysis has greater sensitivity in detecting early pathologic changes in LA function. This may be analogous to the greater sensitivity of LV strain compared with standard systolic markers of LV dysfunction.[27]

There are also certain clinical situations in which assessment of LA strain may offer incremental information. Fibrosis is the hallmark of LA remodeling. LA strain has also been correlated with LA stiffness and fibrosis,[6,31] thus allowing noninvasive assessment. In patients with HF, LA reservoir strain is associated with exercise capacity[26] and has higher sensitivity than E/e′ ratio in predicting LV filling pressures.[32] LA strain may be useful in predicting AF recurrence following cardioversion.[33] Compared with traditional markers of diastolic function, LA reservoir strain provides additional prognostic information in AF, myocardial infarction, and mitral valve disease.[11,34-38]

Clinical Implications

LA reservoir strain is an important prognostic marker in predicting both mortality and HF end points in both HF with preserved ejection fraction[35] and HF with reduced ejection fraction,[36] and LA strain is also associated with reduced exercise capacity in HF with reduced ejection fraction.[26] However, in this study, LA function was not associated with new-onset HF. It is possible that patients with LA dysfunction without significant LV dysfunction can compensate and hence do not manifest symptoms.

As discussed above, LA reservoir strain is an alternative marker of LV diastolic function that may be of value in patients with symptoms of HF who have indeterminate diastolic function from Doppler tissue imaging. In patients with HF, LA reservoir strain can be used for prognostication and prediction of exercise capacity.[26,35]

The results of our study suggest that LA contractile function is independent of LV function. In patients with new-onset AF with normal LA volumes, measurement of contractile strain may help delineate underlying abnormal LA function. LA strain may also be useful to predict recurrence of AF after cardioversion or catheter ablation.[33,39]

There are several sources of variability of LA strain that should be resolved. The utility and feasibility of LA strain in routine clinical practice are still undefined. Standardized guidelines on ECG gating and image acquisition techniques may help provide more uniform measurements and reduce variability. Nomenclature for LA strain should be standardized so that results across studies can be compared. Development of a dedicated LA strain algorithm by external software vendors may help improve accuracy, reduce measurement time, and reduce error. We also need consensus definition of normal LA strain values across age groups to make it easier to identify patients with abnormal measurements.

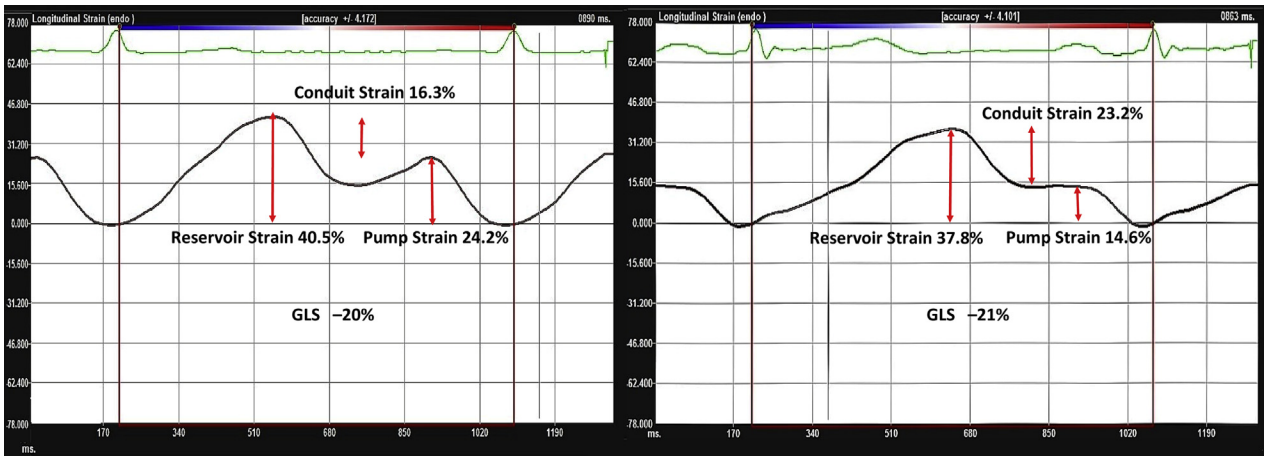

Figure 2 Variability of LA pump strain in two patients with similar GLS and LA reservoir strain.

The results of our study also highlight several areas that may be of interest for future research. Linking LA strain to LA remodeling and fibrosis may offer further insight into the "atriopathy" that develops in conditions such as hypertension and obesity. LA strain appears to be of value in prediction of AF, but a prospective study could better establish this parameter in decision making. A comparison of LA strain with LA voltage mapping could help identify whether strain may offer a noninvasive method of identifying LA negative and positive remodeling. There is a potential role for LA strain in predicting stroke risk in patients with AF, incremental to clinical risk scores.

Limitations

The limitations of our study include potential for population selection bias, as patients were recruited using newspaper and radio advertising. Ventricular and atrial strain were both measured using speckle-tracking but using software from different manufacturers (albeit very similar). The primary reason for this was to allow rapid assessment for subclinical LV dysfunction using the on-cart software for clinical assessment. Although the use of different strain analysis techniques from different vendors has been previously shown to create inconsistencies and errors, this problem has been substantially ameliorated by recent efforts to improve concordance.[3] Thus, we do not think that this difference in software influenced our assessment of the associations between LV and LA function.

LA strain imaging, like other imaging techniques, is operator dependent. In our study, there was approximately 8% difference in LA reservoir strain and approximately 5% to 6% difference in conduit and pump measurements during our validation study.

CONCLUSIONS

LA strain is not a single entity. The American Society of Echocardiography and European Association of Echocardiography recommendations for the evaluation of LV diastolic function[30] describe associations between LV systolic and diastolic strain and LA strain and LV diastolic function. However, LA strain is not merely duplicative of LV diastolic function: the results of this study emphasize that LA pump strain is independent of LV function. Changes to atrial pump function are not dependent primarily on changes to the left ventricle and may be due to the development of an underlying "atriopathy."

REFERENCES

1. Cameli M, Mandoli GE, Loiacono F, Dini FL, Henein M, Mondillo S. Left atrial strain: a new parameter for assessment of left ventricular filling pressure. Heart Fail Rev 2016;21:65-76.
2. Cameli M, Mandoli GE, Loiacono F, Sparla S, Iardino E, Mondillo S. Left atrial strain: a useful index in atrial fibrillation. Int J Cardiol 2016;220:208-13.
3. Vieira MJ, Teixeira R, Gonçalves L, Gersh BJ. Left atrial mechanics: echocardiographic assessment and clinical implications. J Am Soc Echocardiogr 2014;27:463-78.
4. Saraiva RM, Demirkol S, Buakhamsri A, Greenberg N, Popović ZB, Thomas JD, et al. Left atrial strain measured by two-dimensional speckle tracking represents a new tool to evaluate left atrial function. J Am Soc Echocardiogr 2010;23:172-80.
5. Cameli M, Ciccone MM, Maiello M, Modesti PA, Muiesan ML, Scicchitano P, et al. Speckle tracking analysis: a new tool for left atrial function analysis in systemic hypertension: an overview. J Cardiovasc Med 2016;17:339-43.
6. Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S, et al. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation relationship to left atrial structural remodeling detected by delayed-enhancement MRI. Circ Cardiovasc Imaging 2010;3:231-9.
7. Tsai WC, Lee CH, Lin CC, Liu YW, Huang YY, Li WT, et al. Association of left atrial strain and strain rate assessed by speckle tracking echocardiography with paroxysmal atrial fibrillation. Echocardiography 2009;26:1188-94.
8. Shih JY, Tsai WC, Huang YY, Liu YW, Lin CC, Huang YS, et al. Association of decreased left atrial strain and strain rate with stroke in chronic atrial fibrillation. J Am Soc Echocardiogr 2011;24:513-9.
9. Cameli M, Caputo M, Mondillo S, Ballo P, Palmerini E, Lisi M, et al. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. Cardiovasc Ultrasound 2009;7:6.
10. Cameli M, Lisi M, Righini FM, Mondillo S. Novel echocardiographic techniques to assess left atrial size, anatomy and function. Cardiovasc Ultrasound 2012;10:4.
11. Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol 2014;63:493-505.
12. Eapen ZJ, Greiner MA, Fonarow GC, Yuan Z, Mills RM, Hernandez AF, et al. Associations between atrial fibrillation and early outcomes of patients

with heart failure and reduced or preserved ejection fraction. Am Heart J 2014;167:369-75.e2.
13. Mountantonakis SE, Grau-Sepulveda MV, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure: an analysis of GWTG-Heart Failure. Circ Heart Fail 2012;5:191-201.
14. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539-50.
15. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, et al. The task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology: guidelines for the diagnosis and treatment of chronic heart failure: reply. Eur Heart J 2005;26:2473-4.
16. Soullier C, Niamkey JT, Ricci JE, Messner-Pellenc P, Brunet X, Schuster I. Hypertensive patients with left ventricular hypertrophy have global left atrial dysfunction and impaired atrio-ventricular coupling. J Hypertens 2016;34:1615-20.
17. Akkaya M, Higuchi K, Koopmann M, Burgon N, Erdogan E, Damal K, et al. Relationship between left atrial tissue structural remodelling detected using late gadolinium enhancement MRI and left ventricular hypertrophy in patients with atrial fibrillation. Europace 2013;15:1725-32.
18. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail 2015;8:295-303.
19. Peters DC, Duncan JS, Grunseich K, Marieb M, Cornfeld D, Sinusas AJ, et al. Lower left atrial strain in the presence of regional atrial fibrosis: an MRI study of patients with atrial fibrillation. J Cardiovasc Magn Reson 2016;18:1-2.
20. Harada M, Van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management. Circ J 2014;79:495-502.
21. Chen D, Procter N, Goh V, Liu S, Chua S, Assadi-Khansari B, et al. New onset atrial fibrillation is associated with elevated galectin-3 levels. Int J Cardiol 2016;223:48.
22. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.
23. Rimbaş RC, Dulgheru RE, Vinereanu D. Methodological gaps in left atrial function assessment by 2D speckle tracking echocardiography. Arq Bras Cardiol 2015;105:625-36.
24. Imanishi J, Tanaka H, Sawa T, Motoji Y, Miyoshi T, Mochizuki Y, et al. Association of left atrial booster-pump function with heart failure symptoms in patients with severe aortic stenosis and preserved left ventricular ejection fraction. Echocardiography 2015;32:758-67.
25. Pinheiro AC, Dimaano VL, Sorensen L, Liang HY, Luo HC, Mbiyangandu BK, et al. Left atrial strain rate as a predictor of low exercise capacity in hypertrophic cardiomyopathy patients. J Am Coll Cardiol 2012;59:E1294.
26. Kusunose K, Motoki H, Popovic ZB, Thomas JD, Klein AL, Marwick TH. Independent association of left atrial function with exercise capacity in patients with preserved ejection fraction. Heart 2012;98:1311-7.
27. Gorcsan J, Tanaka H. Echocardiographic assessment of myocardial strain. J Am Coll Cardiol 2011;58:1401-13.
28. Edvardsen T, Gerber BL, Garot J, Bluemke DA, Lima JA, Smiseth OA. Quantitative assessment of intrinsic regional myocardial deformation by Doppler strain rate echocardiography in humans validation against three-dimensional tagged magnetic resonance imaging. Circulation 2002;106:50-6.
29. Blume GG, Mcleod CJ, Barnes ME, Seward JB, Pellikka PA, Bastiansen PM, et al. Left atrial function: physiology, assessment, and clinical implications. Eur Heart J Cardiovasc Imaging 2011;12:421-30.
30. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314.
31. Her AY, Choi EY, Shim CY, Song BW, Lee S, Ha JW, et al. Prediction of left atrial fibrosis with speckle tracking echocardiography in mitral valve disease: a comparative study with histopathology. Korean Circ J 2012;42:311-8.
32. Cameli M, Lisi M, Mondillo S, Padeletti M, Ballo P, Tsioulpas C, et al. Left atrial longitudinal strain by speckle tracking echocardiography correlates well with left ventricular filling pressures in patients with heart failure. Cardiovasc Ultrasound 2010;8:14.
33. Di Salvo G, Caso P, Lo Piccolo R, Fusco A, Martiniello AR, Russo MG, et al. Atrial myocardial deformation properties predict maintenance of sinus rhythm after external cardioversion of recent-onset lone atrial fibrillation. A color Doppler myocardial imaging and transthoracic and transesophageal echocardiographic study. Circulation 2005;112:387-95.
34. Caso P, Ancona R, Di Salvo G, Pinto SC, Macrino M, Di Palma V, et al. Atrial reservoir function by strain rate imaging in asymptomatic mitral stenosis: prognostic value at 3 year follow-up. Eur Heart J Cardiovasc Imaging 2009;10:753-9.
35. Freed BH, Daruwalla V, Cheng JY, Aguilar FG, Beussink L, Choi A, et al. Prognostic utility and clinical significance of cardiac mechanics in heart failure with preserved ejection fraction importance of left atrial strain. Circ Cardiovasc Imaging 2016;9:e003754.
36. Helle-Valle T, Opdahl A, Broch K, Gude E, Andreassen A, Smiseth OA, et al. Left atrial strain by speckle tracking echocardiography in patients with heart failure—an independent and incremental predictor of cardiac death or need of heart transplantation. Circulation 2011;124:A8551.
37. Ersbøll M, Andersen MJ, Valeur N, Mogensen UM, Waziri H, Møller JE, et al. The prognostic value of left atrial peak reservoir strain in acute myocardial infarction is dependent on left ventricular longitudinal function and left atrial size. Circ Cardiovasc Imaging 2013;6:26-33.
38. Mirza M, Caracciolo G, Khan U, Mori N, Saha SK, Srivathsan K, et al. Left atrial reservoir function predicts atrial fibrillation recurrence after catheter ablation: a two-dimensional speckle strain study. J Interv Card Electrophysiol 2011;31:197-206.
39. Hwang HJ, Choi EY, Rhee SJ, Joung B, Lee BH, Lee SH, et al. Left atrial strain as predictor of successful outcomes in catheter ablation for atrial fibrillation: a two-dimensional myocardial imaging study. J Interv Card Electrophysiol 2009;26:127-32.

Echocardiographic Risk Assessment to Guide Screening for Atrial Fibrillation

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Background: Although atrial fibrillation (AF) is a significant population health burden, and an avoidable cause of stroke, AF screening remains controversial. The aim of this study was to investigate whether coincidental echocardiography could provide information about patients at risk for AF.

Methods: Asymptomatic participants ≥65 years of age with more than one AF risk factor ($N = 445$) undergoing echocardiography for risk evaluation were followed over a median of 15 months for incident AF. Left atrial volume index (LAVi), left ventricular (LV) global longitudinal strain (GLS; absolute value), left atrial (LA) strain, and LV mass were measured. During the follow-up period, AF was diagnosed clinically by primary care physicians or by using a single-lead portable electrocardiographic monitoring device (five 60-sec recordings performed by participants over 1 week).

Results: AF was diagnosed in 45 patients (10%; mean age, 70.5 ± 4.2 years; 55% women). AF detection was higher in those with LV hypertrophy, GLS < 16%, LAVi > 34 mL/m^2, and LA reservoir strain < 34%. GLS, LAVi, and LA reservoir strain were independently associated with AF ($P < .05$). Those with AF had reduced GLS, higher LAVi, and higher LV mass ($P < .05$), but LA strain was similar in both groups ($P > .05$). GLS and LAVi were the strongest predictors, and cut points of 14.3% for GLS and 39 mL/m^2 were associated with increased risk for developing AF. Those with all four risk parameters (LV hypertrophy, GLS < 16%, LA reservoir strain < 34%, and LAVi > 34 mL/m^2) had a 60% AF detection rate, compared with 7% without these features ($P = .004$).

Conclusion: Echocardiography is widely used in patients at risk for AF, and simple LV and LA measurements may be used to enrich the process of AF screening. (J Am Soc Echocardiogr 2019;32:1259-67.)

Keywords: Atrial fibrillation, Strain, Left atrium, Screening

The magnitude of atrial fibrillation (AF) as a population health problem is increasing, driven by the aging population and the rise of AF risk factors, including obesity, physical inactivity, and diabetes mellitus.[1,2] The consequences of AF include debilitating symptoms and reduced quality of life. Complications such as stroke, heart failure (HF), and cognitive impairment are associated with increased all-cause mortality[3,4] and place a substantial cost burden on the health care system.[5,6] The early diagnosis of AF allows individualized lifestyle intervention, which has been shown to reduce AF burden.[7] The initiation of anticoagulation could be associated with reduced complications and hospitalizations.

Several screening technologies for AF offer an opportunity for early diagnosis, but they need to be accurate, reproducible, and cost effective. Standard electrocardiographic (ECG) monitoring has limited value for detection of new AF,[8] and longer term monitoring is limited by poor adherence. Invasive options such as loop recorders

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Abbreviations

AF = Atrial fibrillation

ECG = Electrocardiographic

GLS = Global longitudinal strain

HF = Heart failure

HR = Hazard ratio

LA = Left atrial

LAVi = Left atrial volume indexed to body surface area

LV = Left ventricular

LVH = Left ventricular hypertrophy

are expensive and unsuitable for screening. Single-lead portable ECG devices are unobtrusive (and consequently acceptable for patients) and sensitive for identifying AF.[9-11] The development of automated algorithms to detect AF with these devices may allow mass screening. In two small studies, they have demonstrated superior AF detection compared with 24-hour Holter monitoring,[12,13] and a systematic review demonstrated similar AF detection rates to 24-hour Holter monitoring.[14] The use of these devices in screening studies has provided AF detection rates of 1% to 5%[15-19] and has been demonstrated to be cost effective.[18,20]

Although opportunistic screening for AF is recommended in current European guidelines using both pulse palpation and assessment of a rhythm strip,[21] routine AF screening is not recommended in the United Kingdom[22] or the United States.[23] This is because although AF screening satisfies most of the criteria for mass screening,[24,25] concerns persist about both false-positive and false-negative results.[26] The appropriate selection of patients could reduce the number of false-positive results by avoiding low-risk patients. Clinical risk scores for AF aid in this process, but imaging parameters provide important clues in risk assessment.[27] As echocardiography is widely performed for other reasons in patients at risk for AF,[28] we sought to determine whether this information could provide an opportunity to assess AF risk and thereby guide AF screening.

METHODS

Study Population

Participants in this prospective observational cohort study were healthy, asymptomatic subjects recruited into a community HF screening study in the Victorian and Tasmanian communities. Recruitment was by several methods, including from community centers and local medical clinics and through radio and newspaper advertising. Asymptomatic participants ≥65 years of age were recruited if they had one or more risk factors for AF, including hypertension (systolic blood pressure > 140 mm Hg or preexisting use of antihypertensive medications), type 2 diabetes mellitus (on the basis of self-report of diagnosis or the current use of diabetic medications), and obesity (defined as a body mass index ≥ 30 kg/m^2). Exclusion criteria were (1) inability to provide written consent to participate in the study, (2) history of moderate or greater valvular disease, (3) known history of HF on the basis of the 2013 American Heart Association/American College of Cardiology guidelines,[29] (4) reduced LV systolic function on baseline echocardiogram (left ventricular [LV] ejection fraction ≤ 40%), (5) contraindications to β-blockers and angiotensin converting enzyme inhibitors, (6) life expectancy of <1 year, and (7) inability to acquire interpretable images for performance of strain analysis from the baseline echocardiogram. All patients with documented AF on baseline 12-lead electrocardiography or histories of AF were excluded from the study. Patients were recruited from both urban and rural environments. All patients were provided written informed consent, and approval was obtained from the institution's human research ethics committee (University of Tasmania human research ethics committee project H0013333 and Bellberry human research ethics committee project 2016-10-727-A-7).

Clinical Assessment

Participants undertook a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, medical history, medication history, and baseline examination data (height, weight, body mass index, and blood pressure) was recorded for all participants. Baseline 12-lead electrocardiography and echocardiography were conducted in all participants. Clinical AF risk assessment was performed using a validated AF risk score (the CHARGE-AF score) that includes 12 clinical parameters (age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive drugs, history of diabetes mellitus or myocardial infarction, history of HF, and ECG data [voltage criteria for LV hypertrophy (LVH), and PR interval]) to assess 5-year risk for AF.[27]

Assessment of Risk on the Basis of Imaging

All echocardiographic examinations were performed by qualified sonographers using the same equipment (Siemens ACUSON SC2000; Siemens Healthcare, Mountain View, CA) and transducers (4V1c, 1.25–4.5 MHz; 4Z1c, 1.5–3.5 MHz). Two-dimensional, M-mode, and Doppler measures were obtained using standard techniques outlined by the American Society of Echocardiography. LV dimensions were calculated in both diastole and systole in parasternal long-axis views. LVH was defined as LV mass index > 115 g/m^2 in men and >95 g/m^2 in women. Left atrial (LA) volume was indexed to body surface area (LAVi) and calculated using the Simpson biplane method. Abnormal LAVi was defined as ≥34 mL/m^2.

Global longitudinal strain (GLS) measurements were obtained from apical four-chamber, two-chamber, and long-axis views. GLS was analyzed using Velocity Vector Imaging (syngo VVI; Siemens Medical Solutions USA, Mountain View, CA). All measurements were performed online by averaging strain measurements from the three views. Manual tracing of the endocardial LV border was performed in end-systole, and this was tracked during the cardiac cycle. Abnormal GLS was defined as <16% (absolute values were used throughout the study). Patients with poor image quality, in whom GLS could not be assessed, were excluded.

LA reservoir, conduit, and pump strain were assessed offline using speckle-tracking imaging using an external third-party software program (ImageArena; TomTec, Munich, Germany). Apical four- and two-chamber images were selected with a frame rate of 60 to 80 frames/sec. The endocardial border of the left atrium was manually traced, and strain analysis was performed using the LV strain algorithm, using the average of the four- and two-chamber values. The reference point for image analysis was taken at the onset of the QRS complex (R-R gating). All strain measurements were performed by two investigators. If more than one of the six LA segments could not be tracked, the sample was excluded. We used a cut point of 34% for LA reservoir strain to determine high risk for AF.

Interobserver reliability was assessed by a second operator who performed strain measurement in a random sample of 20 participants and was blinded to all clinical and imaging data. Intraobserver reliability was assessed by the primary author (S.R.), who performed

HIGHLIGHTS

- Screening may reduce complications and healthcare costs of AF.
- Coincidental echo findings may increase the efficiency of AF screening.
- LAVi >34 ml/m^2, LVH, LA reservoir strain ≥34% and LVGLS ≥16% are markers of AF risk.

repeated strain measurements in a random sample of 20 patients at a different time point. The mean percentage difference was calculated.

Outcomes

Participants were followed for a median of 15 months for incident AF, which was the primary outcome measure. AF was diagnosed using multiple detection methods. Patients with clinical diagnosis of AF during the follow-up period by primary care physicians (confirmed on 12-lead electrocardiography or Holter monitoring) were documented. Screening for subclinical AF was performed using a single-lead ECG device (Remon RM-100; Semacare, Beijing, China). Screening was performed within the first month of recruitment into the study. The single-lead device was used to record 60-sec single-lead ECG tracings using three points of finger contact with electrodes, five times per day for 1 week (i.e., 35 recordings). ECG recordings were then exported as PDF files for interpretation, and all were assessed by a physician. The presence of AF (an irregular rhythm of ≥30 sec with a variable R-R interval and absent P waves) was confirmed by two independent physicians who were blinded to the patient's clinical details. The patient was advised of the recognition of subclinical AF, and further management and investigation was provided by their usual medical practitioner.

Statistical Analysis

All categorical variables are presented as frequencies and percentages, and continuous variables are presented as mean ± SD (if normally distributed) or as median (interquartile range; if nonparametric). Patients with incident AF were compared with those in sinus rhythm. Groups were compared using the χ^2 test for categorical data and the independent two-sample *t* test for continuous data. Patients were then grouped on the basis of four imaging parameters of AF risk (LAVi, presence of LVH, GLS, and LA reservoir strain) on the basis of the cutoffs defined earlier. Nelson-Aalen cumulative hazard estimate plots were constructed for groups on the basis of the baseline risk parameters, and the log-rank test was used to assess the differences between curves. The AF rate was compared between those at the highest risk and those with the lowest risk using the χ^2 test. Cox proportional-hazards regression analysis was used to calculate the hazard ratios (HRs) and 95% CIs for the association between each risk parameter and incident AF. The follow-up time was the time from the initial baseline clinical assessment to the completion of portable device screening or the date of diagnosis of AF (whichever came first).

Classification and regression tree analysis was performed to identify appropriate discriminatory cut points to identify those at risk for developing AF. Analyses were considered to be statistically significant if two-tailed *P* values were <.05. Statistical analysis was performed using SPSS version 22 (SPSS, Chicago, IL), SPSS Modeler version 18.1 (SPSS), and Stata version 13 (StataCorp, College Station, Texas).

Table 1 Baseline characteristics of the overall cohort (*N* = 445)

Variable	Value
Demographics	
Age (y)	70.5 ± 4.2
Sex, male (%)	198 (45)
Systolic BP (mm Hg)	141 ± 15.7
Diastolic BP (mm Hg)	83 ± 10.1
Heart rate (beats/min)	69 ± 10.7
BMI (kg/m^2)	30.3 ± 5.3
Current smoking	12 (3)
Diabetes mellitus	190 (43)
Obesity	226 (51)
Hypercholesterolemia	244/434 (55)
Hypertension	353 (79)
History of IHD	16 (4)
History of stroke/TIA	26 (6)
6-min walk distance m*	474 (98)
CHARGE-AF score (%)*	5.1 (5.1)
CHA_2DS_2-VASc score (%)*	3.0 (2.0)
Echocardiographic parameters	
Ejection fraction (%)	62.6 ± 6.3
GLS (%): absolute value	18.8 ± 2.5
E/e′ (average of lateral and septal)	8.8 ± 2.4
LAVi (mL/m^2)	32.2 ± 9.1
LV mass indexed (g/m^2)	81.8 ± 22.4
LA reservoir strain (%) (*n* = 417)	37.5 ± 7.0
LA conduit strain (%) (*n* = 417)	18.2 ± 5.5
LA pump strain (%) (*n* = 417)	19.3 ± 5.1

BMI, Body mass index; *BP*, blood pressure; *IHD*, ischemic heart disease; *TIA*, transient ischemic attack.
Data are expressed as mean ± SD or number (percentage) except as indicated.
*Median (interquartile range).

RESULTS

Patient Characteristics

The baseline characteristics of the 445 subjects included in the study (mean age, 70.5 ± 4.2 years; 45% men) are summarized in Table 1. Cardiovascular risk factors (including type 2 diabetes mellitus, obesity, hypercholesterolemia, and hypertension) were highly prevalent. There was a large proportion of participants with low education levels (43% had not completed high school, and approximately three in four had not completed a tertiary level of education). LA strain could be measured in 417 of 445 patients (94%).

AF during Follow-Up

An overview of patient recruitment and AF detection is summarized in Figure 1. Over a median follow-up period of 15 months (range, 5–27 months), 45 patients (10%) were diagnosed with AF, 28

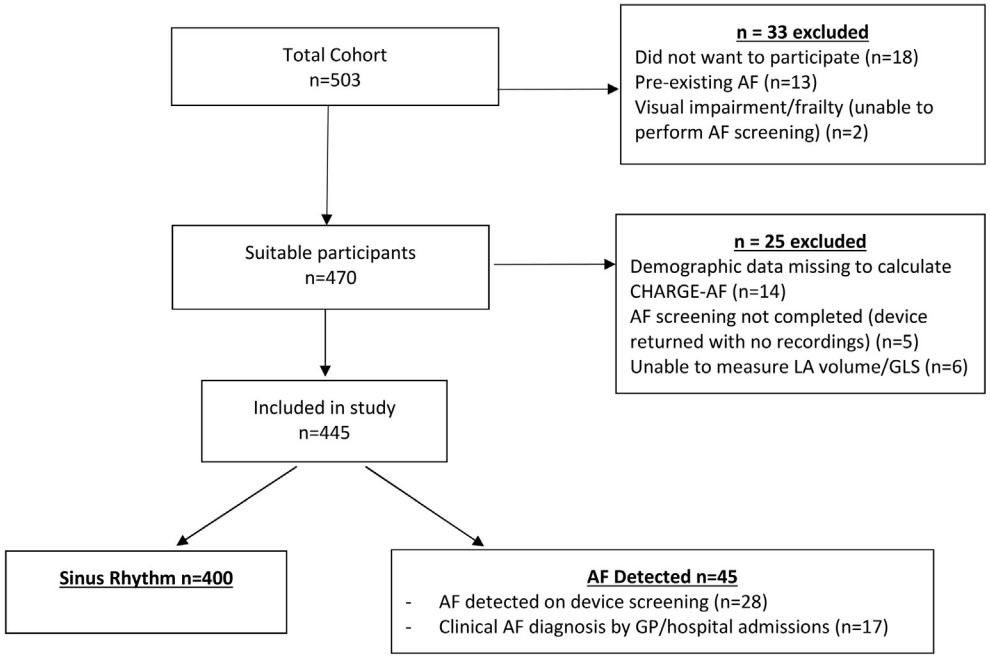

Figure 1 Flowchart showing patient recruitment in the study. *GP*, general practitioner.

(6%) with portable ECG monitoring and 17 (4%) by local physicians during the follow-up period. Among the 417 patients with measurable LA strain, there were 42 AF outcomes. Table 2 compares the characteristics of those with AF and sinus rhythm; new-onset AF was more likely in men and in those with higher CHARGE-AF scores, reduced GLS, and increased LAVi and LV mass ($P < .05$). There were no significant differences in LA strain between both groups ($P > .05$).

AF Detection on the Basis of Risk Parameters

Participants were grouped on the basis of the four risk parameters highlighted earlier (LAVi, presence of LVH, GLS, and LA reservoir strain). Grouping participants on the basis of these risk parameters resulted in a range of AF detection rates (0%–60%), with the presence of more positive risk parameters associated with higher AF detection rates (Table 3, Figure 2).

Table 4 and Figures 3 and 4 summarize the association between the risk parameters and AF. When patients were grouped on the basis of abnormal LAVi (cutoff 34 mL/m^2), GLS (cutoff 16%), and LA reservoir strain (cutoff 34%), higher AF detection was noted in the abnormal groups (Figure 3; $P < .05$ for all). Participants were then grouped on the basis of the total number of baseline risk parameters (LAVi, LA reservoir strain, LVH, and GLS; Figure 4). AF detection was higher with the presence of more baseline risk parameters ($P = .004$). Participants with all four risk parameters had a higher AF detection rate compared with those without any risk parameters (60% [three of five] vs 7% [11 of 160], $P = .004$).

On univariate analysis, abnormal LAVi, LA reservoir strain, and GLS were all associated with AF ($P < .05$), but LA pump strain was not associated with AF ($P = .86$). LA reservoir strain along with LA pump strain was included in the multivariate model (LA conduit strain was not included given the possibility of collinearity when included with GLS). In a multivariate model, abnormal LAVi, GLS, and LA reservoir strain were independently associated with AF (abnormal LAVi HR, 2.01 [95% CI, 1.06–3.81; $P = .03$]; abnormal GLS HR, 2.46 [95% CI, 1.21–5.00; $P = .01$]; and abnormal LA reservoir strain HR, 2.14 [95% CI, 1.04–4.38; $P = .04$]). LA pump strain and presence of LVH were not independently associated with AF ($P > .05$).

The classification and regression tree analysis identified three discriminatory nodes as predictors of AF. A GLS cut point of 14.3% was identified ($P = .02$). In those with GLS $\leq$ 14.3%, a second discriminatory node using LAVi (cut point of 39 mL/m^2) was identified ($P = .01$). The intermediate group with LAVi $\leq$ 39 mL/m^2 could then be discriminated using a third node: LA reservoir strain with a cut point of 33.9% ($P = .01$). This correctly identified 91% of participants.

The results of the classification and regression tree analysis can potentially be incorporated into an AF risk stratification algorithm. Participants with GLS $>$ 14.3% can be categorized as "low risk," in whom AF screening has low detection rates and may not be required. In those with GLS $\leq$ 14.3, LAVi $>$ 39 mL/m^2 can be used to classify the "high-risk" group, in which AF screening may have high detection rates. In the intermediate group (GLS $<$ 14.3% and LAVi $\leq$ 39 mL/m^2), LA reservoir strain can be used with a cut point of 34% to reclassify patients as "moderate to high" risk (LA reservoir strain $<$ 34%) versus "low to moderate" risk (LA reservoir strain $>$ 34%). Screening should be considered in the moderate- to high-risk group.

Reproducibility

Interobserver variability was assessed using blinded strain measurements in a random sample of 20 patients. All measurements were done by the same two investigators (S.R. and T.N.), and the mean of the absolute value of differences between measurements was calculated. For GLS, the mean $\pm$ SD difference between was 0.7 $\pm$ 0.7%. For LA strain, the mean difference was 8.0 $\pm$ 7.0% for LA reservoir strain, 5.4 $\pm$ 4.1% for LA conduit strain, and 5.6 $\pm$ 4.6% for LA pump strain. Intraobserver variability was assessed by the primary investigator (S.R.), who repeated GLS measurements in a random sample of 20 patients at a different time point. The mean

Table 2 Comparison of baseline characteristics between patients with AF and those in sinus rhythm

Demographics	AF *n* = 45	Sinus rhythm *n* = 400	*P* value
Age (y)	71.7 ± 5.3	70.3 ± 4.1	.11
Sex, male (%)	27 (60)	171 (43)	.03
Systolic BP (mm Hg)	134 ± 15.6	142 ± 15.5	.002
Diastolic BP (mm Hg)	82 ± 11.0	83 ± 10.0	.38
BMI (kg/m^2)	29.6 (5.2)	30.3 (5.3)	.34
Current smoking	2 (4)	10 (3)	.45
Diabetes mellitus	21 (47)	169 (42)	.57
Obesity	18 (40)	208 (52)	.12
Hypercholesterolemia	24/43 (56)	220/391 (56)	.96
Hypertension	36 (80)	317 (79)	.91
History of IHD	5 (11)	11 (3)	.004
History of TIA/stroke	2 (4)	24 (6)	.63
Median CHARGE-AF score (%)*	6.6 (8.2)	4.8 (4.7)	.001
Median CHA_2DS_2-VASc score*	3.0 (2.0)	3.0 (2.0)	.52
Functional capacity			
Median 6-min walk distance (m)*	488 (110.8)	473 (98)	.22
Echocardiographic parameters			
Ejection fraction (%)	60.9 ± 7.3	62.7 ± 6.1	.06
GLS %	18.0 ± 3.4	18.8 ± 2.4	.04
E/e′ (average of lateral and septal)	8.5 ± 2.5	8.8 ± 2.4	.52
LAVi (mL/m^2)	34.8 ± 10.4	31.9 ± 8.9	.04
LV mass indexed (g/m^2)	93.3 ± 25.2	80.5 ± 21.7	.002
LA strain	(*n* = 42)	(*n* = 375)	
LA reservoir strain (%)	36.5 ± 8.0	37.7 ± 6.9	.33
LA conduit strain (%)	17.6 ± 5.3	18.3 ± 5.6	.49
LA pump strain (%)	18.9 ± 6.9	19.4 ± 4.9	.68

BMI, Body mass index; *BP*, blood pressure; *IHD*, ischemic heart disease; *TIA*, transient ischemic attack.
Data are expressed as mean ± SD or number (percentage) except as indicated.
*Median (interquartile range).

Table 3 Summary of AF detection on the basis of risk groups

LVH	LAVi	GLS	LA reservoir strain	*n* (*N* = 417)	AF detected, *n* (%) (*N* = 42)
No	Normal (<34 mL/m^2)	Normal (≥16%)	Normal (≥34%)	160	11 (7)
			Low (<34%)	44	1 (2)
		Low (<16%)	Normal (≥34%)	22	4 (18)
			Low (<34%)	11	2 (18)
	Increased (≥34 mL/m^2)	Normal (≥16%)	Normal (≥34%)	65	6 (9)
			Low (<34%)	38	4 (11)
		Low (<16%)	Normal (≥34%)	5	0 (0)
			Low (<34%)	8	1 (13)
Yes	Normal (<34 mL/m^2)	Normal (≥16%)	Normal (≥34%)	18	3 (17)
			Low (<34%)	5	0 (0)
		Low (<16%)	Normal (≥34%)	2	0 (0)
			Low (<34%)	1	0 (0)
	Increased (≥34 mL/m^2)	Normal (≥16%)	Normal (≥34)	19	2 (11)
			Low (<34%)	11	4 (36)
		Low (<16%)	Normal (≥34%)	3	1 (33)
			Low (<34%)	5	3 (60)

Patients were divided into high and low risk for LVH, LAVi, GLS, and LA reservoir strain. Cutoffs used were (LVH: 115 g/m^2 for men and 95 g/m^2 for women; LAVi 34 mL/m^2; GLS 16%; and LA reservoir strain 34%).

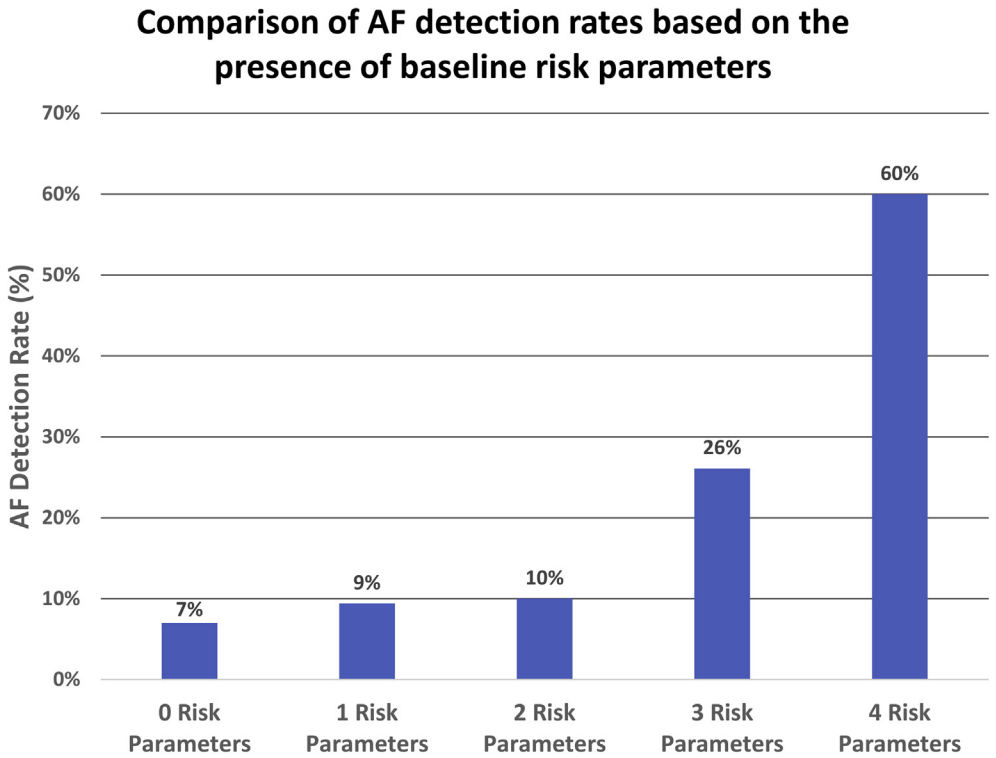

Figure 2 Comparison of AF detection on the basis of the presence of baseline risk parameters: risk parameters defined on the basis of cutoff for LVH (LV indexed mass ≥ 115 g/m^2 for men and ≥95 g/m^2 for women), LAVi ≥ 34 mL/m^2, GLS < 16%, and LA reservoir strain < 34%.

Table 4 Cox regression analysis showing association between risk parameters and AF

Independent variable	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Abnormal GLS	2.79 (1.40–5.56)	.003	2.46 (1.21–5.00)	.01
Abnormal LAVi	2.17 (1.18–3.98)	.01	2.01 (1.06–3.81)	.03
Abnormal LA reservoir strain	2.13 (1.13–4.03)	.02	2.14 (1.04–4.38)	.04
Presence of LVH	1.59 (0.82–3.09)	.17	1.22 (0.60–2.49)	.58
LA pump strain (%)	0.99 (0.93–1.06)	.86	1.04 (0.97–1.11)	.25

Multivariate model contained abnormal LAVi (cutoff 34 mL/m^2), abnormal GLS (cutoff 16%), abnormal LA reservoir strain (cutoff 34%), presence of LVH and LA pump strain (*n* = 417; AF outcomes, *n* = 42).

difference for GLS was 0.8 ± 0.6%. The mean difference for LA strain was 3.8 ± 2.9% for LA reservoir strain, 2.7 ± 1.4% for LA conduit strain, and 2.7 ± 1.4% for LA pump strain.

DISCUSSION

Many at-risk individuals undergo echocardiography for other reasons, therefore the incidental finding of these risk parameters can be used to alert referring physicians to future AF risk. The results of our study suggest that individuals with more imaging risk parameters have a higher likelihood of AF. In our study, we found that reduced LA reservoir strain, reduced GLS, and increased LAVi were independently associated with AF. Targeted screening using portable single-lead ECG devices can capture a significant proportion of patients with subclinical AF.[15,19]

Early Diagnosis of AF

AF is a leading cause of stroke and HF, placing a tremendous burden on the health care system with rising costs and hospitalizations.[5,30,31] Patients with asymptomatic (or subclinical) AF have been shown to have increased all-cause mortality and increased stroke risk in a large cohort study.[32] Early diagnosis has several potential benefits. Even in the early stages, AF is not a benign condition and is associated with long-term morbidity and mortality.[32] The early diagnosis of AF serves as an important warning to both the patient and the treating physician and may prompt important discussions about risk factor modification, improve treatment adherence, and allow closer monitoring of "high risk" patients. Aggressive risk factor modification and weight loss has been shown to be equivalent to an antiarrhythmic drug in patients with established AF,[7,33] although incident AF was not reduced with intensive weight loss in a large randomized trial. Early diagnosis might prompt improvement in physical activity and reduction in blood pressure, cholesterol, and blood glucose levels, all of which have cardiovascular benefits.[34] Anticoagulation may have a role in stroke and systemic embolism prevention in this cohort of patients, but this has not been assessed in a large randomized trial.

Improving AF Detection in Screening Programs

For mass screening to be viable, an efficient screening process with a high AF detection rate is required. The main focus of screening has been three factors: device technology, patient age, and clinical risk factors. Age is the biggest risk factor for AF, so many screening studies have used population-based screening methods

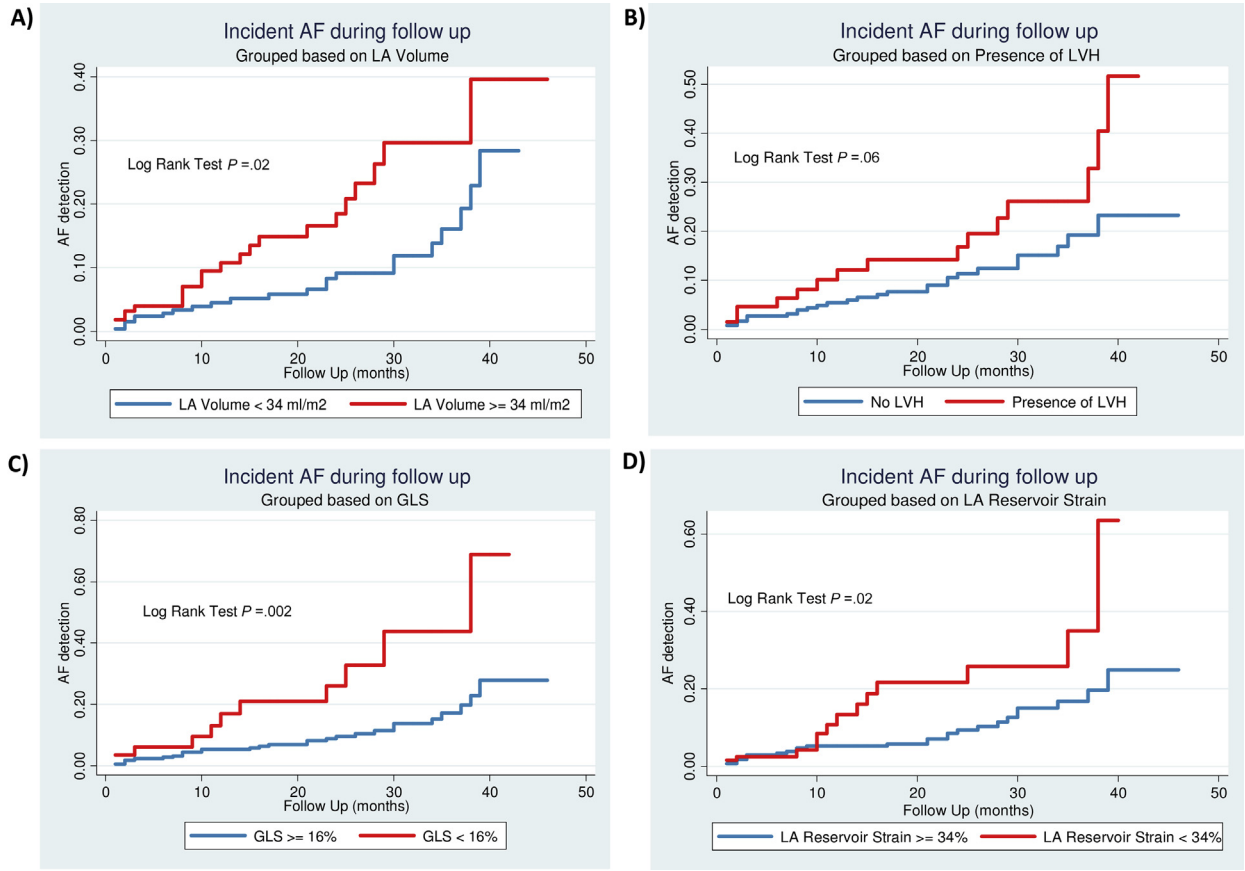

Figure 3 Nelson-Aalen curves showing AF detection on the basis of baseline risk parameters. (**A**) LA volume (groups <34 mL/m^2 and ≥34 mL/m^2), (**B**) LVH (groups with no LVH and presence of LVH), (**C**) GLS (groups ≥16% and <16%), and (**D**) LA reservoir strain (groups ≥34% and <34%).

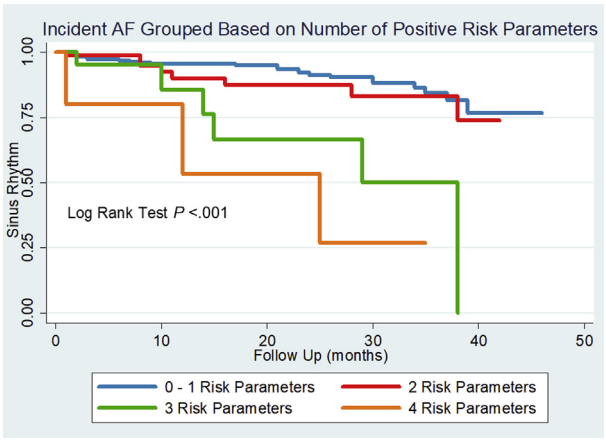

Figure 4 Kaplan-Meier curve showing AF detection on the basis of the number of positive baseline risk parameters: risk parameters defined on the basis of cutoff for LAVi ≥ 34 ml/m^2, GLS < 16%, LVH (LV indexed mass ≥ 115 g/m^2 for men and ≥95 g/m^2 for women), and LA reservoir strain < 34%.

based on an age cutoff of 65 or 75 years.[15,19] Lowres *et al.*[35] showed an increase in AF detection rates from approximately 1% in the 65- to 69-year-old cohort to >3% in patients >85 years of age after combining four large AF screening cohorts. Clinical risk factors associated with AF and stroke risk can also increase the detection rate. Use of an age-based population screening strategy may improve sensitivity by screening a larger cohort but reduces efficiency, as many patients will have normal results. The use of clinical risk scores such as CHARGE-AF can help identify those who benefit the most from screening.[27] This is a simple bedside scoring system using several risk parameters, providing a 5-year AF risk assessment that has been validated in several large multiethnic cohorts.[27] Combining an age-based cutoff with clinical risk factors results in increased AF rates and, more important, translates into implementation of pharmacological treatments, as all participants will qualify for anticoagulation (i.e., CHA_2DS_2-VASC score ≥ 2). Single–time point screening has a new AF detection rate of approximately 1%, which can be increased with multiple–time point screening over a 1- to 2-week period.[15,18] We have previously investigated the role of other AF risk factors, such as physical activity and socioeconomic deprivation.[2,36]

The Use of Echocardiography in Risk Assessment

In this study, those with increased LAVi and reduced GLS and LA reservoir strain were at higher risk for developing AF. We noted a higher AF detection rate in those with LA reservoir strain < 34%, implying that strain below the normal range is associated with AF (albeit acknowledging the emerging consensus about the "normal" range for LA reservoir strain). Nonetheless, a few patients were noted to have AF despite high LA reservoir strain values. These results may have offset those with reduced LA reservoir strain, explaining the similarity of mean LA reservoir strain in both the AF and sinus rhythm

groups. This surprising finding—we expected a difference between the groups—may also be explained by the wide range of LA reservoir strain values and the small sample of patients with AF (with insufficient power to show a difference).

Although the traditional use of echocardiography in AF follows a confirmed clinical diagnosis of AF (to determine the etiology of AF, guide management, and provide important prognostic information),[37] many individuals at risk for AF undergo echocardiography for other reasons, such as investigation of hypertension, cardiac murmur, or perioperative risk. However, there is no systematic method in traditional echocardiography reporting to alert referring physicians to AF risk. Targeting a group with echocardiographic risk features with portable ECG monitoring may be associated with high AF detection rates. Nonetheless, AF risk assessment is complex, so the next step would be to create a multiparameter risk assessment strategy incorporating clinical, imaging, and socioeconomic markers of risk.

Limitations

The limitations of our study include the potential for population selection bias, as patients were recruited with newspaper and radio advertising. Our cohort was relatively small, resulting in a small number of AF outcomes, with a very selective patient population; hence adaption of these findings to a large screening population would need to assume external validity. The small number of AF outcomes also limited the number of covariates in our multivariate model, so it is possible that other potential confounders were not accounted for. AF detection was based on the use of a single-lead portable ECG device for a 1-week period. It is possible that we missed subclinical AF in some patients, and extended monitoring may increase the AF detection rate. Detailed cost analysis was not performed in our study. Cutoff values for GLS and LA strain used in this study were arbitrary. We did not collect data from local practitioners on anticoagulation prescription following a diagnosis of AF and hence were unable to assess the impact of early diagnosis. We did not perform long-term follow-up to assess if those with subclinical AF had similar clinical outcomes to those with clinically diagnosed AF.

CONCLUSION

Elderly patients with risk factors have a high prevalence of subclinical AF. Baseline risk assessment using echocardiographic parameters of LV and LA function can be used to improve AF detection rates and could be relevant to the implementation of population screening programs.

REFERENCES

1. Ball J, Thompson DR, Ski CF, Carrington MJ, Gerber T, Stewart S. Estimating the current and future prevalence of atrial fibrillation in the Australian adult population. Med J Aust 2015;202:32-5.
2. Ramkumar S, Yang H, Wang Y, Nolan M, Negishi K, Sanders P, et al. Relation of functional status to risk of development of atrial fibrillation. Am J Cardiol 2017;119:572-8.
3. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death. Circulation 1998;98:946-52.
4. Vidaillet H, Granada JF, Chyou P-H, Maassen K, Ortiz M, Pulido JN, et al. A population-based study of mortality among patients with atrial fibrillation or flutter. Am J Med 2002;113:365-70.
5. Kim MH, Johnston SS, Chu B-C, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. Circ Cardiovasc Qual Outcomes 2011;4:313-20.
6. Stewart S, Murphy N, Walker A, McGuire A, McMurray JJV. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. Heart 2004;90:286-92.
7. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol 2014;64:2222-31.
8. Sposato LA, Cipriano LE, Saposnik G, Vargas ER, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2015;14:377-87.
9. Desteghe L, Raymaekers Z, Lutin M, Vijgen J, Dilling-Boer D, Koopman P, et al. Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. Europace 2017;19:29-39.
10. Williams J, Pearce K, Benett I, Williams J, Manchester M. The effectiveness of a mobile ECG device in identifying AF: sensitivity, specificity and predictive value. Br J Cardiol 2015;22.
11. Freedman SB, Lowres N. Asymptomatic atrial fibrillation: the case for screening to prevent stroke. JAMA 2015;314:1911-2.
12. Hendrikx T, Rosenqvist M, Wester P, Sandström H, Hörnsten R. Intermittent short ECG recording is more effective than 24-hour Holter ECG in detection of arrhythmias. BMC Cardiovasc Disorders 2014;14:41.
13. Doliwa Sobocinski P, Änggårdh Rooth E, Frykman Kull V, von Arbin M, Wallén H, Rosenqvist M. Improved screening for silent atrial fibrillation after ischaemic stroke. EP Europace 2012;14:1112-6.
14. Ramkumar S, Nerlekar N, D'Souza D, Pol DJ, Kalman JM, Marwick TH. Atrial fibrillation detection using single lead portable electrocardiographic monitoring: a systematic review and meta-analysis. BMJ Open 2018;8:e024178.
15. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP study. Circulation 2015;131:2176-84.
16. Proietti M, Mairesse GH, Goethals P, Scavee C, Vijgen J, Blankoff I, et al. A population screening programme for atrial fibrillation: a report from the Belgian Heart Rhythm Week screening programme. Europace 2016;18:1779-86.
17. Claes CVL N. Prevalence of atrial fibrillation in adults participating in a large-scale voluntary screening programme in Belgium. Acta Cardiologica 2012;67:273.
18. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, et al. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. Thromb Haemost 2014;111:1167-76.
19. Halcox JP, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C, et al. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study. Circulation 2017;136:1784-94.
20. Aronsson M, Svennberg E, Rosenqvist M, Engdahl J, Al-Khalili F, Friberg L, et al. Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording. Europace 2015;17:1023-9.
21. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-962.
22. United Kingdom National Screening Committee. The UK NSC recommendation on atrial fibrillation screening in adults. Available at: https://legacyscreening.phe.org.uk/atrialfibrillation. Accessed July 18, 2019.
23. Curry S, Krist A, Owens D, Barry M, Caughey A, Davdison K, et al. Screening for atrial fibrillation with electrocardiography: US Preventive Services Task Force recommendation statement. JAMA 2018;320:478-84.
24. Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva, Switzerland: World Health Organization; 1968.

25. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, et al. Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. Circulation 2017;135:1851-67.
26. Mairesse GH, Moran P, Van Gelder IC, Elsner C, Rosenqvist M, Mant J, et al. Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE). Europace 2017;19:1589-623.
27. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc 2013;2:e000102.
28. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved vs. reduced ejection fraction. Circulation 2016;122:484-92.
29. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.
30. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995;98:476-84.
31. Leyden JM, Kleinig TJ, Newbury J, Castle S, Cranefield J, Anderson CS, et al. Adelaide stroke incidence study: declining stroke rates but many preventable cardioembolic strokes. Stroke 2013;44:1226-31.
32. Martinez C, Katholing A, Freedman SB. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. Thromb Haemost 2014;112:276-86.
33. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). J Am Coll Cardiol 2015;65:2159-69.
34. Alonso A, Bahnson JL, Gaussoin SA, Bertoni AG, Johnson KC, Lewis CE, et al. Effect of an intensive lifestyle intervention on atrial fibrillation risk in individuals with type 2 diabetes: the Look AHEAD randomized trial. Am Heart J 2015;170:770-7.e5.
35. Lowres N, Fitzmaurice DA, Hobbs FDR, Kaasenbrood F, Lee V, Tieleman R, et al. Abstract 20082: guideline-based screening for atrial fibrillation: analysis of yield and stroke risk. Circulation 2017;136:A20082.
36. Ramkumar S, Ochi A, Yang H, Nerlekar N, D'Elia N, Potter EL, et al. Association between socio-economic status and incident atrial fibrillation. Intern Med J 2019. In press.
37. Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance Endorsed by the American College of Chest Physicians. J Am Coll Cardiol 2011;57:1126-66.

Left Atrial Mechanical Dispersion Assessed by Strain Echocardiography as an Independent Predictor of New-Onset Atrial Fibrillation: A Case-Control Study

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Background: Left atrial (LA) enlargement is associated with atrial fibrillation (AF), but new-onset AF often occurs in the absence of LA enlargement. AF may be related to myocardial fibrosis, and even though left ventricular fibrosis is associated with mechanical dispersion, this phenomenon is not well studied in AF. We hypothesized that detection of LA dysfunction and mechanical dispersion using strain echocardiography is useful for predicting new-onset AF.

Methods: Baseline echocardiography was performed at entry in 576 community-based participants at risk of heart failure or AF. In this case-control study, we compared 35 individuals with new-onset AF (age 70 ± 4 years; 57% men) over 2 years of follow-up with 35 age- and sex-matched individuals who did not develop AF from the same cohort. Using speckle-tracking echocardiography, we measured the LA strain in each of 12 segments in the two- and four-chamber views. LA mechanical dispersion was defined as the SD of time to peak positive strain corrected by the R-R interval (SD-TPS, %).

Results: There was no significant difference in LA volume index (32.5 ± 9.2 mL/m^2 vs 29.5 ± 8.3 mL/m^2; P = .16); patients with new-onset AF had significantly worse LA pump strain (16.6% ± 4.3% vs 20.6% ± 4.3%; P < .01) and reservoir strain (31.4% ± 7.7% vs 38.0% ± 7.3%; P < .01) than those without AF. SD-TPS was significantly higher in patients with AF than in those without it (6.3% ± 2.3% vs 3.9% ± 1.6%; P < .01). SD-TPS was independently associated with new-onset AF after adjustment for patient characteristics, LA volume, and strain (hazard ratio = 1.26; 95% CI, 1.10-1.45; P < .01). In the nested Cox models, the model based on the LA volume and strain for predicting new onset AF was significantly improved by adding SD-TPS (P < .01).

Conclusions: LA dispersion obtained from strain echocardiography seems to provide incremental information about LA volume and function in the prediction of new-onset AF and warrants testing in a larger study. (J Am Soc Echocardiogr 2019;■:■-■.)

Keywords: Atrial fibrillation, Echocardiography, Strain, Left atrium, Dispersion

Atrial fibrillation (AF) is the most common serious arrhythmia, and its increasing incidence reflects the aging population.[1,2] Risk stratification for the development of this arrhythmia has a potential public health impact, because the recognition of AF is often delayed and the major complication of AF (stroke) is potentially preventable with anticoagulation. Transthoracic echocardiography has played an important role in assessing this remodeling because it is noninvasive, highly accessible, and portable.

AF is a progressive disease that facilitates its own persistence through the process of atrial remodeling[3]; both left atrium (LA) structural and functional remodeling are associated with AF.[4,5] LA enlargement is a well-known predictor for new-onset AF,[6-8] but AF is often observed in patients without LA enlargement because functional impairment precedes morphological changes.[9,10] Strain echocardiography can accurately assess regional myocardial function, and impaired LA strain is a marker of AF risk.[11-13] Myocardial strain may also be used to measure the timing of contraction, and several studies have revealed an association between left ventricular (LV) mechanical dispersion and ventricular arrhythmias.[14-16] Disturbances in the timing of LA contraction reflect the presence of atrial fibrosis and electrophysiological

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Abbreviations

ACE = Angiotensin-converting enzyme

AF = Atrial fibrillation

AUC = Area under the receiver operating characteristic curve

CHARGE-AF = Cohorts for Heart and Aging Research in Genomic Epidemiology Atrial Fibrillation

ECG = Electrocardiogram

GCS = Global circumferential strain

GLS = Global longitudinal strain

HF = Heart failure

HR = Hazard ratio

LA = Left atrium, atrial

LAVI = Left atrial volume index

LV = Left ventricle, ventricular

LVEF = Left ventricular ejection fraction

ROC = Receiver operating characteristic

SD-TPS = Standard deviation of the time to peak strain

disorders,[17,18] for example, intra-atrial dyssynchrony during sinus rhythm is an independent predictor of recurrence after the first AF ablation.[18] Building on this, we hypothesized that measurement of LA mechanical dispersion could be a useful biomarker to stratify the risk for new-onset AF. The purpose of this study was to quantify the association and impact of LA dispersion on the incidence of new-onset AF and to assess whether LA dispersion provided additional predictive information toward new-onset AF over LA enlargement and dysfunction.

METHODS

Study Population

This case-control study was derived from a prospective, observational cohort study, which had the primary objective of early detection of heart failure (HF) and AF. This community-based cohort included asymptomatic individuals older than 65 years with more than one risk factor including hypertension (systolic blood pressure >140 mm Hg or preexisting use of antihypertensive medications), type 2 diabetes mellitus (based on self-reports of diagnosis or the current use of diabetic medications), obesity (body mass index ≥ 30), previous chemotherapy, and family history of HF. Exclusion criteria were (1) inability to provide written consent to participate in the study, (2) history of moderate or greater valvular disease, (3) known history of HF, (4) reduced left ventricle (LV) systolic function on baseline echocardiography (LV ejection fraction [LVEF] < 40%), (5) contraindications to beta-blockers and angiotensin-converting enzyme inhibitors (ACE), (6) life expectancy < 1 year, and (7) inability to perform strain analysis or acquire interpretable images from baseline echocardiography. All patients provided written informed consent, and approval was obtained from the institution's human research ethics committee. From this initial cohort, we excluded all patients with known histories of AF or with documented AF on baseline electrocardiography, leaving 576 eligible individuals for inclusion into our study.

Clinical Data

We obtained clinical histories from all participants, and they answered questionnaires to assess their overall health status at the start of the study. Clinical parameters (sociodemographic variables, medical history, medication history, and baseline examination data) were comprehensively assessed. Using these data, we computed the CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology Atrial Fibrillation)[19] and CHA_2DS_2-VASc scores. We also performed baseline electrocardiography and echocardiography in all participants at entry.

Recognition of AF

Incident AF was identified over a median follow-up of 15 months. All patients were followed clinically, and a clinical diagnosis of AF was sought on the basis of history and confirmed by 12-lead ECG. In addition, a single-lead ECG device using three points of finger contact (Remon RM-100, Semacare, China) was used to record 60-second single-lead ECG tracings, five times per day for 1 week. AF was identified as an irregular rhythm of ≥30 seconds with a variable R-R interval and absent P waves, confirmed by two independent physicians who were blinded to the patient's clinical details. The patient was advised of the recognition of subclinical AF, and further management and investigation were provided by their usual medical practitioner.

Conventional Echocardiography

All echocardiographic examinations were performed by qualified sonographers using the same equipment (Siemens Acuson SC2000, Siemens Medical Solutions, Mountain View, CA) and transducers (4V1c [1.25-4.5 MHz] and 4Z1c [1.5-3.5 MHz]) during sinus rhythm. Conventional echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography.[20,21] Early and late diastolic mitral annular tissue velocity (e′ and a′) were measured in the apical four-chamber view, with the sample volume positioned at both the septal and lateral mitral annuli and being the average of these two values. LA volume was calculated using the biplane method of disks (Simpson's modified rule) and indexed to body surface area (LA volume index [LAVI]).

Strain Analysis

All strain parameters were assessed by speckle-tracking imaging using an external third-party software program (Research Arena; TomTec Imaging Systems, Munich, Germany). After manual tracing of the LA and LV endocardial border, the dedicated software automatically tracked the myocardium throughout the cardiac cycle. All tracking was reviewed to ensure that it was appropriate and a true representation of LA and LV motion. LV global longitudinal strain and global circumferential strain were measured using standard methodologies.[22] The strain curves of the global and regional LA wall were generated by the software automatically, and the reference point for image analysis was taken at the onset of the QRS complex (R-R gating) as has been described elsewhere.[23] Apical four- and two-chamber images were selected with a frame rate of 60-80 frames/sec, and strain results were obtained by averaging the two views. The resulting atrial strain curve provided two peaks consistent with reservoir and contractile strain, and the difference between these was conduit strain (Figure 1A). LA mechanical dispersion was defined as the SD of time to peak positive strain (SD-TPS) from the 12 LA segments (Figure 1B). We corrected the SD-TPS by the R-R interval to derive SD-TPS as a percentage of the R-R interval. Higher values of SD-TPS are thought to suggest a greater degree of LA dispersion. Patients without interpretable images, such as those with incomplete strain measurements, were excluded from this study. All echocardiographic analysis was performed by one investigator experienced with strain imaging who was blinded to the patient characteristics and the outcome.

HIGHLIGHTS

- Left atrial (LA) mechanical dispersion is a useful predictor of atrial fibrillation.
- This predictive value is superior and incremental to traditional predictors.
- LA dispersion may detect the early LA remodeling regardless of LA enlargement.

Statistical Analysis

Continuous variables are expressed as mean ± SD or median (interquartile range), and categorical variables are shown in percentages. The significance of differences between the groups was assessed using Student's *t*-test for data with normal distribution, and the Mann-Whitney *U*-test was used for data that were not normally distributed. For categorical variables, the χ^2-test or Fisher's exact test was used, as appropriate. Univariable and multivariable linear regression analyses were used to evaluate the associations between SD-TPS and other echocardiographic parameters. Univariable and multivariable Cox regression analysis was used to assess independent predictors for new-onset AF. The independence and robustness of SD-TPS were examined using several models. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated for each echocardiographic variable, and the value closest to the corner of the ROC curve determined the optimal cutoff for the ability of the variables to discriminate between patients with and without new-onset AF. Kaplan-Meier survival analyses with follow-up censored at 40 months were performed for participants with SD-TPS above and below an optimal cutoff in a previous study.[24]

The incremental value of SD-TPS in the overall group was assessed in three modeling steps using nested models. Covariate selection for model entry was based on clinical experience and identification of known correlates. The first step consisted of fitting a multivariable model based on the CHARGE-AF score and LAVI. LA reservoir strain was then included in the second step and SD-TPS in the third step. The incremental value of SD-TPS over baseline clinical characteristics and conventional LA factors for predicting new-onset AF was determined by calculating the improvement in the global χ^2 statistic. Reclassification was evaluated to assess the incremental benefit of adding SD-TPS to the model on the basis of LA volume and function with net reclassification improvement. Inter- and intraobserver variability for LA reservoir strain and SD-TPS were studied in a random sample of 10 patients, and the mean of the absolute value of differences between measurements was calculated. In addition, the mean differences and limits of agreement between measurements were assessed using Bland-Altman plots.

All statistical analyses were performed using a standard statistical software package (SPSS ver. 21, SPSS, Chicago, IL; and R version 3.5.0, https://www.r-project.org). All *P* values reported are from two-sided tests, and values $< .05$ were considered statistically significant.

RESULTS

Patient Characteristics

Among 576 patients, new-onset AF developed in 35 participants (mean age, 70 ± 4 years; 57% men, 49% paroxysmal AF, and 51% nonparoxysmal AF) over 2 years of follow-up, and we age and sex matched 35 individuals who did not develop AF from the same cohort to act as controls. Thus, we performed our final analyses with data from a total of 70 participants (Table 1). Most patients had type 2 diabetes mellitus (54%), obesity (44%), hypercholesterolemia (48%), and hypertension (76%), but the average values for LAVI, LA, and LV function were in the normal range. Table 1 also shows a comparison of baseline characteristics and echocardiographic parameters between the patients with and without new-onset AF. Although there was no significant difference in LAVI (32.5 ± 9.2 vs 29.5 ± 8.3 mL/m^2; $P = .16$), the patients with new-onset AF had significantly worse LA pump strain (16.6% ± 4.3% vs 20.6% ± 4.3%; $P < .01$) and reservoir strain (31.4% ± 7.7% vs 38.0% ± 7.3%, $P < .01$) than those without AF. SD-TPS was significantly higher in the patients with AF than in those without it (6.3% ± 2.3% vs 3.9% ± 1.6%; $P < .01$). Figure 1B shows representative cases of LA strain curves and SD-TPS in the four-chamber view for patients with and without new-onset AF.

Association between SD-TPS and Other Echocardiographic Parameters

The association between SD-TPS and other echocardiographic parameters was evaluated using univariable and multivariable linear regression analyses (Table 2 and Supplemental Table 1, available at www.onlinejase.com). In the multivariable analysis, SD-TPS was associated with LVEF ($r = -0.38$, $\beta = -0.27$; $P = .03$) and LA reservoir strain ($r = -0.39$, $\beta = -0.27$; $P = .04$). LA pump and conduit strain were excluded from the multivariable models because of collinearity.

Predictors of New-Onset AF

In the univariable Cox regression analysis, new-onset AF was associated with LAVI, LA reservoir strain, and SD-TPS (Table 3). The independent association of SD-TPS with new-onset AF was examined using three different models. SD-TPS had a consistently significant association with new-onset AF in every model, and the hazard ratios (HRs) were similar (1.28-1.37). In addition, SD-TPS was independently associated with new-onset AF after adjusting for CHARGE-AF score, LAVI, and LA reservoir strain (HR = 1.26; 95% CI, 1.10-1.45; $P < .01$; Figure 2). We also confirmed the independent association of LA reservoir strain with new-onset AF using the same models (Supplemental Table 2, available at www.onlinejase.com and Figure 2).

Table 4 summarizes the ROC curve analysis results. SD-TPS and LA reservoir strain were identified as echocardiographic predictors with high AUC (0.80 for SD-TPS and 0.75 for LA reservoir strain), with the AUC for SD-TPS being the highest. Using the previously defined SD-TPS cutoff of 5.3%,[24] patients with new-onset AF were identified with a sensitivity of 65.7% and specificity of 85.7%. The AF-free survival was significantly better in those with SD-TPS <5.3% than in those with SD-TPS ≥5.3% (log-rank $P < .01$; Figure 3A).

Incremental Value of SD-TPS

Figure 2 and Supplemental Figure 1 (available at www.onlinejase.com) show the incremental benefit of using sequential Cox models for the prediction of new-onset AF. In Figure 2, a model based on clinical and conventional echocardiographic variables including CHARGE-AF scores and LAVI ($\chi^2 = 5.3$) was significantly improved by addition of LA reservoir strain ($\chi^2 = 17.8$; $P < .01$) and further improved by adding SD-TPS ($\chi^2 = 27.5$; $P < .01$).

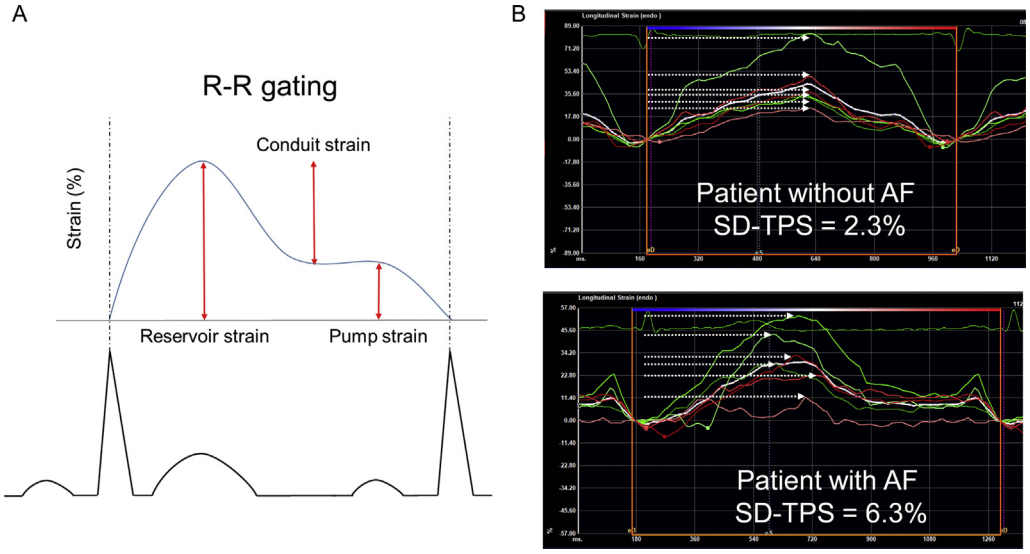


Figure 1 Measurements of LA strain. The left panel shows the LA strain components **(A)**. The right panel shows the measurements of LA dispersion and representative cases in patients with and without AF **(B)**. *White arrows* indicate contraction durations defined as the time from the end diastole (the R wave on the electrocardiogram) to the maximal time of positive deformation in each LA segment. SD-TPS was calculated as the SD of time to peak and expressed as a percentage of the R-R interval. The patients with new-onset AF showed higher SD-TPS.

The addition of SD-TPS to a risk classification model based on LAVI or LA reservoir strain alone resulted in the correct reclassification of patients without new-onset AF to the low-risk category (net reclassification improvement, 0.26 and 0.17, respectively; both $P < .05$; Tables 5 and 6). Moreover, adding SD-TPS to the combined LAVI and LA reservoir strain model resulted in a significantly improved reclassification (net reclassification improvement, 0.14; $P = .04$; Table 7).

Reproducibility

Reproducibility was assessed by blinded strain measurements in a random sample of 10 patients. Interobserver variability was assessed by two investigators, and the mean of the absolute value of differences between measurements was calculated (Supplemental Figure 2, available at www.onlinejase.com). For LA reservoir strain and SD-TPS, the mean differences were 3.8% ± 3.1% and 0.5% ± 0.3%, respectively. Intraobserver variability was assessed by one investigator, who repeated LA strain at a different time point. For LA reservoir strain and SD-TPS, the mean differences were 2.3% ± 1.5% and 0.6% ± 0.4%, respectively.

DISCUSSION

The principal finding of this study was that LA mechanical dispersion assessed by speckle-tracking echocardiography is a useful predictor of new-onset AF, superior and incremental to and independent of clinical risk factors and conventional echocardiographic predictors including LA enlargement and dysfunction.

LA Dispersion as a Predictor of New-Onset AF

During the past 10 years, myocardial mechanical dispersion assessed by strain echocardiography has emerged as a useful tool to evaluate supraventricular and ventricular arrhythmias. Haugaa *et al.*[14-16] have demonstrated that mechanical dispersion assessed in the LV is an independent and powerful predictor for ventricular arrhythmias in a variety of cardiovascular diseases. Similarly, LA dispersion is greater in patients with AF than in healthy individuals[24-27] and increases in proportion to the duration of AF.[25] LA dispersion predicts progression from paroxysmal to persistent AF[28] and may predict recurrent AF after catheter ablation.[26,29] Importantly, LA dispersion can also detect LA functional impairment and asynchrony in patients without LA enlargement[24,26,29,30]—indeed, in the present study, the average LAVI in the patients with new-onset AF was within the normal range. However, despite studies showing the association between LA dispersion and AF,[24-30] only one previous study has linked LA dispersion to incident AF—but this used tissue Doppler imaging and was limited to patients with HF.[30] To our knowledge, this is the first study demonstrating that LA dispersion assessed by speckle-tracking echocardiography predicts the future development of new AF in a community-based cohort.

LA strain is inversely associated with LA fibrosis detected by cardiac magnetic resonance,[1,13] and these imaging markers are related to AF burden.[13] Furthermore, LA dispersion was a more specific marker of LA scarring evaluated by cardiac magnetic resonance than LA volume and global function in the patients undergoing AF ablation.[18] In a study of electroanatomical mapping and LA strain in patients undergoing AF ablation, LA dispersion was significantly increased in patients with low-voltage zones and the severity of LA dispersion was related to the LA conduction delay.[17]

Clinical Implications

The findings in this study suggest that LA dispersion assessed by speckle-tracking echocardiography could be a useful biomarker to estimate LA structural and electrical remodeling regardless of LA enlargement. In addition, recent studies demonstrated that LA dispersion has an incremental value over the CHA_2DS_2-

Table 1 Baseline characteristics

Variables	All patients (*N* = 70)	AF (*n* = 35)	No AF (*n* = 35)	*P* value
Demographics				
Age, years	70 ± 4	70 ± 4	70 ± 4	
Sex, male	40 (57)	20 (57)	20 (57)	
BSA, m^2	1.9 ± 0.2	2.0 ± 0.2	1.9 ± 0.2	.82
BMI, kg/m^2	29.5 ± 4.6	29.7 ± 5.0	29.4 ± 4.3	.79
Heart rate, bpm	67.3 ± 12.0	69.1 ± 13.5	65.5 ± 10.2	.21
Type 2 diabetes mellitus	38 (54)	19 (54)	19 (54)	≥.999
Obesity	31 (44)	14 (40)	17 (49)	.47
Hypercholesterolemia	32 (48)	15 (45)	17 (50)	.71
Hypertension	53 (76)	27 (77)	26 (74)	.78
CHA_2DS_2VASc score	3.0 ± 1.0	3.1 ± 0.9	3.0 ± 1.0	.71
CHARGE-AF score	8.3 (5.0-12.7)	6.9 (5.1-12.2)	8.7 (4.8-14)	.49
Medication				
ACE inhibitors or ARBs	44 (63)	20 (57)	24 (69)	.32
β-blockers	7 (10)	5 (14)	2 (6)	.43
Calcium blocker	16 (26)	5 (16)	11 (37)	.06
Lipid lowering drugs	33 (53)	15 (47)	18 (60)	.30
Antiplatelet agents	19 (31)	9 (28)	10 (33)	.66
Echocardiographic parameters				
LVEF, %	62.7 ± 6.2	61.3 ± 6.3	64.1 ± 5.8	.058
GLS, %	−18.5 ± 2.7	−18.1 ± 3.3	−18.8 ± 1.9	.46
GCS, %	−29.9 ± 5.4	−29.9 ± 5.8	−30.0 ± 5.0	.94
E/e'	8.9 ± 2.7	8.6 ± 2.6	9.1 ± 2.8	.44
LV mass index	81.8 ± 17.0	81.7 ± 18.2	82.0 ± 16.0	.94
LAVI, mL/m^2	31.0 ± 8.8	32.5 ± 9.2	29.5 ± 8.3	.16
LA pump strain, %	18.6 ± 4.7	16.6 ± 4.3	20.6 ± 4.3	<.01
LA conduit strain, %	16.0 ± 5.2	14.8 ± 4.9	17.1 ± 5.4	.06
LA reservoir strain, %	34.7 ± 8.1	31.4 ± 7.7	38.0 ± 7.3	<.01
SD-TPS, %	5.1 ± 2.3	6.3 ± 2.3	3.9 ± 1.6	<.01

ARB, Angiotensin receptor blocker; *BMI*, body mass index; *BSA*, body surface area; *GCS*, global circumferential strain; *GLS*, global longitudinal strain. SD-TPS is expressed as a percentage of the R-R interval.
Data are expressed as mean ± SD, *n* (%), or median (interquartile range).
P value is for patients with and without AF.

Table 2 Associations of SD-TPS and other echocardiographic parameters

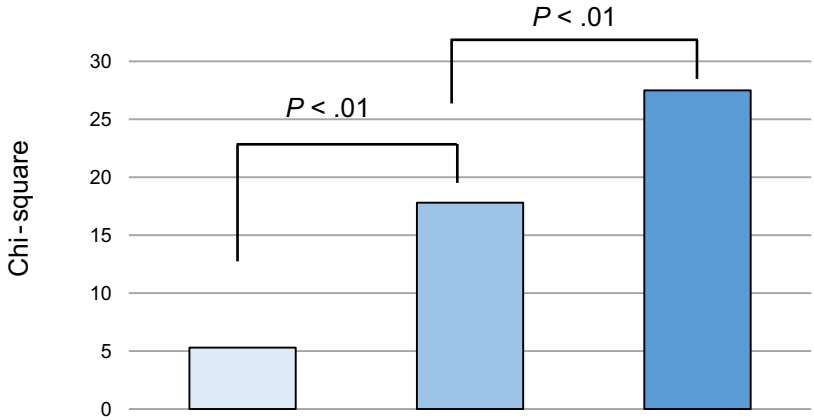
	Univariable			Multivariable		
Variables	Unstandardized β (95% CI)	Standardized β	*P* value	Unstandardized β (95% CI)	Standardized β	*P* value
LVEF	−0.144 (−0.227 to -0.060)	−0.384	<.01	−0.101 (−0.190 to −0.013)	−0.271	.03
GCS	0.036 (−0.068 to 0.140)	0.083	.49			
GLS	0.292 (0.098 to 0.486)	0.342	<.01	0.118 (−0.095 to 0.330)	0.138	.27
E/e'	0.187 (−0.015 to 0.388)	0.219	.07			
LAVI	0.051 (−0.011 to 0.114)	0.196	.10	0.012 (−0.050 to 0.075)	0.047	.69
LA pump strain	−0.123 (−0.238 to −0.007)	−0.249	.04			
LA reservoir strain	−0.109 (−0.173 to -0.046)	−0.385	<.01	−0.076 (−0.147 to −0.004)	−0.266	.04

GCS, Global circumferential strain; *GLS*, global longitudinal strain. SD-TPS is expressed as a percentage of the R-R interval.

Table 3 Univariable and multivariable cox regression analysis for new-onset AF

	Univariable		Multivariable					
			Clinical model		Medical model		Echo model	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
BMI, per 1 kg/m^2 increase	1.00 (0.94-1.07)	.94	0.96 (0.89-1.04)	.30				
CHA_2DS_2-VASc score, per 1-point increase	1.05 (0.76-1.45)	.79	0.97 (0.65-1.44)	.87				
CHARGE-AF score, per 1-point increase	0.97 (0.90-1.04)	.41	0.96 (0.88-1.05)	.35				
ACE inhibitors or ARBs	1.58 (0.81-3.10)	.18			1.89 (0.85-4.21)	.12		
β-blockers	0.57 (0.22-1.50)	.26			0.52 (0.16-1.66)	.27		
Calcium blocker	1.58 (0.61-4.09)	.35			1.80 (0.67-4.86)	.25		
LVEF, per 1% increase	0.96 (0.91-1.01)	.08					1.02 (0.96-1.08)	.59
LAVI, per 1 mL/m^2 increase	1.04 (1.00-1.07)	.04					1.00 (0.95-1.08)	.88
LA reservoir strain, per 1% increase	0.92 (0.88-0.96)	<.01					0.93 (0.86-0.99)	.02
SD-TPS, per 1% increase	1.32 (1.17-1.50)	<.01	1.37 (1.20-1.59)	<.01	1.37 (1.21-1.56)	<.01	1.28 (1.08-1.51)	<.01

ARB, Angiotensin receptor blocker; *BMI*, body mass index; *GLS*, global longitudinal strain. SD-TPS was corrected by the R-R interval to derive SD-TPS as a percentage of the R-R interval.



Variable	Model 1 Chi-square = 5.3 HR (95%CI), *P* value	Model 2 Chi-square = 17.8 HR (95%CI), *P* value	Model 3 Chi-square = 27.5 HR (95%CI), *P* value
CHARGE-AF score (per 1 point increase)	0.96 (0.90-1.04), *P* = .33	0.93 (0.86-1.01), *P* = .07	0.93 (0.85-1.00), *P* = .06
LAVI (per 1 ml/m^2 increase)	**1.04 (1.00-1.07), *P* = .03**	1.00 (0.96-1.04), *P* = .81	1.00 (0.96-1.05), *P* = .99
LA reservoir strain (per 1 % increase)		**0.90 (0.85-0.95), *P* < .01**	**0.92 (0.86-0.98), *P* < .01**
SD-TPS (per 1% increase)			**1.26 (1.10-1.45), *P* < .01**

Figure 2 Incremental value of SD-TPS over existing indices. A comparison is made with CHARGE-AF score, LAVI, and LA reservoir strain in risk stratification for new-onset AF. SD-TPS was corrected by the R-R interval to derive SD-TPS as a percentage of the R-R interval.

VASc score for predicting the risk of thrombus formation in patients with AF.[31] Based on these findings, the mean age (70 years) and CHA_2DS_2-VASc score (3.0) of the current cohort would suggest a significant risk of stroke if the individuals had AF, and better risk stratification may facilitate decision-making about AF prevention and follow-up for early diagnosis. LA dispersion might have the potential to contribute to the risk stratification for incident AF and for thrombus formation.

Table 4 AUC for ROC analysis of echocardiographic variables

Variables	AUC	95% CI	*P* value	Optimal cutoff	Sensitivity, %	Specificity, %	PPV, %	NPV, %
SD-TPS, %	0.80	0.69-0.90	<.01	5.3	65.7	85.7	82.1	71.4
LA reservoir strain, %	0.75	0.63-0.87	<.01	36.8	82.9	65.7	70.7	79.3
LVEF, %	0.62	0.49-0.76	.08	63.6	71.4	54.3	61.0	65.5
LAVI, mL/m^2	0.59	0.46-0.73	.18	28.9	62.9	51.4	56.4	58.1
GLS, %	0.55	0.41-0.69	.46	−17.6	45.7	71.4	61.5	56.8

GLS, Global longitudinal strain; *NPV*, negative predictive value; *PPV*, positive predictive value.

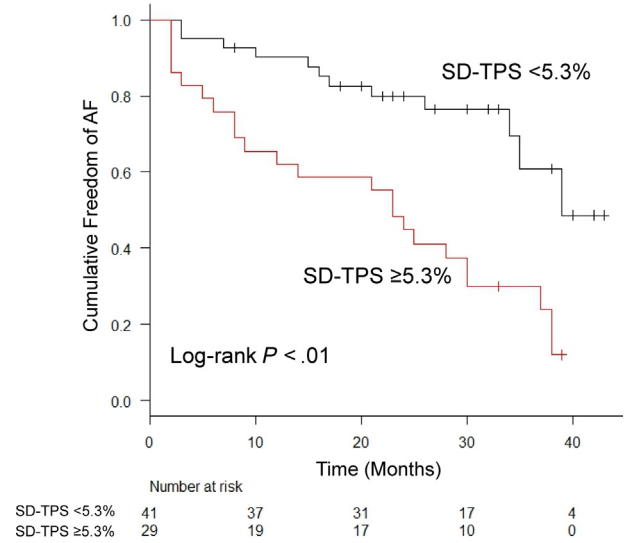


Figure 3 Kaplan-Meier curves showing freedom from new-onset AF. Patients with SD-TPS ≥ 5.3% had more AF events than patients with SD-TPS < 5.3% (*P* < .01). SD-TPS was corrected by the R-R interval to derive SD-TPS as a percentage of the R-R interval.

Table 5 Net reclassification table: The addition of SD-TPS to the model based on LAVI

Variables	LAVI + SD-TPS		Reclassified		Net correctly reclassified, %
	Low risk	High risk	Increased risk*	Decreased risk*	
No new-onset AF (*n* = 35)					
LAVI					
Low risk	0	0	0	11	31.4
High risk	11	24			
New-onset AF (*n* = 35)					
LAVI					
Low risk	0	0	0	2	−5.7
High risk	2	33			Net reclassification improvement = 0.26 (*P* < .01)

The risk for new-onset AF was stratified into low (0% to < 20%) and high risk (≥20%). The net reclassification improvement is the sum of correctly reclassified individuals with and without new-onset AF.
*The number of individuals who were reclassified upward and downward, respectively.

Table 6 Net reclassification table: The addition of SD-TPS to the model based on LA reservoir strain

Variables	LA reservoir strain + SD-TPS		Reclassified		Net correctly reclassified, %
	Low risk	High risk	Increased risk*	Decreased risk*	
No new-onset AF (*n* = 35)					
LA reservoir strain					
Low risk	5	0	0	7	20.0
High risk	7	23			
New-onset AF (*n* = 35)					
LA reservoir strain					
Low risk	1	0	0	1	−2.9
High risk	1	33			Net reclassification improvement = 0.17 (*P* = .02)

The risk for new-onset AF was stratified into low (0% to < 20%) and high risk (≥20%). The net reclassification improvement is the sum of correctly reclassified individuals with and without new-onset AF.
*The number of individuals who were reclassified upward and downward, respectively.

Limitations

There are several limitations in the present study. First, the current study is a case-control study of a small selected group. The sampling of relatively small numbers may explain the absence of association of AF with well-established links such as LV hypertrophy and dysfunction.[32,33] Further prospective multicenter studies are needed to confirm the external validity of our findings—especially cutoffs—and translate LA dispersion into risk stratification for AF. Second, the number of AF cases in the cohort may have been underestimated because some AF events are asymptomatic and intermittent monitoring may miss AF episodes. Third, we did not compare LA strain and dispersion with electrocardiographic parameters such as P wave duration and PR intervals, which are also established predictors of AF.[34,35] Fourth, it was difficult to select the optimal LA dispersion cutoff for predicting new-onset AF—the normal LA dispersion range is unknown and we applied a cutoff from a previous cross-sectional study.[24] Although our cutoff value of SD-TPS was completely consistent with the result of this previous study,[24] ROC analysis in this study was used to derive optimal cutoff values and report those values in the same derivation cohort, rather than in an

Table 7 Net reclassification table: The addition of SD-TPS to the model based on LAVI and LA reservoir strain

Variables	LAVI + LA reservoir strain + SD-TPS		Reclassified		
	Low risk	High risk	Increased risk*	Decreased risk*	Net correctly reclassified (%)
No new-onset AF (n = 35)					
LAVI + LA reservoir strain					
Low risk	5	0	0	6	17.1
High risk	6	24			
New-onset AF (n = 35)					
LAVI + LA reservoir strain					
Low risk	1	0	0	1	−2.9
High risk	1	33			
				Net reclassification improvement = 0.14 (P = .04)	

The risk for new-onset AF was stratified into low (0% to < 20%) and high risk (≥20%). The net reclassification improvement is the sum of correctly reclassified individuals with and without new-onset AF.
*The number of individuals who were reclassified upward and downward, respectively.

independent group of patients. This cutoff should be verified in other cohorts. Fifth, a specific software for evaluating LA strain by speckle-tracking is not yet available; therefore, we analyzed LA strain using software for evaluating the LV. Vendor differences arising from differences between edge-tracking and speckle-tracking[36] may affect the cutoff of LA strain and SD-TPS. Finally, although strain imaging, like other imaging techniques, is operator dependent, there was no evidence of operator differences during our validation study (Supplemental Figure 2, available at www.onlinejase.com).

CONCLUSION

LA dispersion assessed by speckle-tracking echocardiography is a predictor of new-onset AF, superior and incremental to and independent of clinical risk factors and conventional echocardiographic predictors including LA enlargement and dysfunction.

SUPPLEMENTARY DATA

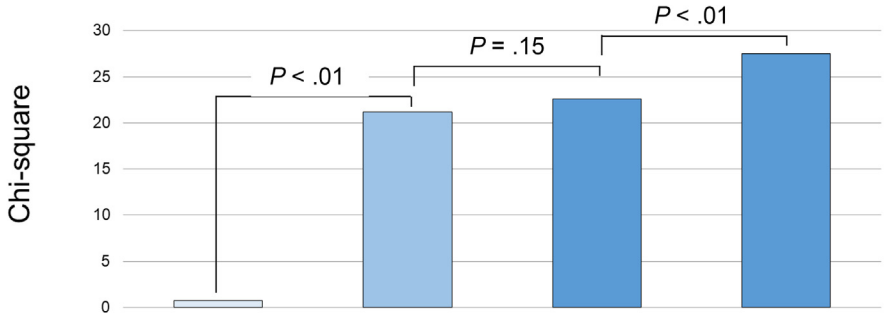
Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2019.06.002.

REFERENCES

1. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042-6.
2. Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. Chest 2012;142:1489-98.
3. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 1995;91:1588-95.
4. Pandozi C, Santini M. Update on atrial remodelling owing to rate: does atrial fibrillation always "beget" atrial fibrillation? Eur Heart J 2001;22:541-53.
5. Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol 2014;63:493-505.
6. Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Takemoto Y, et al. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. Mayo Clinic Proc 2001;76:467-75.
7. Tsang TS, Gersh BJ, Appleton CP, Tajik AJ, Barnes ME, Bailey KR, et al. Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. J Am Coll Cardiol 2002;40:1636-44.
8. Fatema K, Barnes ME, Bailey KR, Abhayaratna WP, Cha S, Seward JB, et al. Minimum vs maximum left atrial volume for prediction of first atrial fibrillation or flutter in an elderly cohort: a prospective study. Eur J Echocardiogr 2009;10:282-6.
9. Conen D, Glynn RJ, Sandhu RK, Tedrow UB, Albert CM. Risk factors for incident atrial fibrillation with and without left atrial enlargement in women. Int J Cardiol 2013;168:1894-9.
10. Hong J, Gu X, An P, Luo T, Lv Q, Kang J, et al. Left atrial functional remodeling in lone atrial fibrillation: a two-dimensional speckle tracking echocardiographic study. Echocardiography 2013;30:1051-60.
11. Abhayaratna WP, Fatema K, Barnes ME, Seward JB, Gersh BJ, Bailey KR, et al. Left atrial reservoir function as a potent marker for first atrial fibrillation or flutter in persons > or = 65 years of age. Am J Cardiol 2008;101:1626-9.
12. Hirose T, Kawasaki M, Tanaka R, Ono K, Watanabe T, Iwama M, et al. Left atrial function assessed by speckle tracking echocardiography as a predictor of new-onset non-valvular atrial fibrillation: results from a prospective study in 580 adults. Eur Heart J Cardiovasc Imaging 2012;13:243-50.
13. Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S, et al. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI. Circ Cardiovasc Imaging 2010;3:231-9.
14. Haugaa KH, Edvardsen T, Leren TP, Gran JM, Smiseth OA, Amlie JP. Left ventricular mechanical dispersion by tissue Doppler imaging: a novel approach for identifying high-risk individuals with long QT syndrome. Eur Heart J 2009;30:330-7.
15. Haugaa KH, Goebel B, Dahlslett T, Meyer K, Jung C, Lauten A, et al. Risk assessment of ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy by strain echocardiography. J Am Soc Echocardiogr 2012;25:667-73.
16. Haugaa KH, Smedsrud MK, Steen T, Kongsgaard E, Loennechen JP, Skjaerpe T, et al. Mechanical dispersion assessed by myocardial strain in patients after myocardial infarction for risk prediction of ventricular arrhythmia. JACC Cardiovasc Imaging 2010;3:247-56.
17. Watanabe Y, Nakano Y, Hidaka T, Oda N, Kajihara K, Tokuyama T, et al. Mechanical and substrate abnormalities of the left atrium assessed by 3-dimensional speckle-tracking echocardiography and electroanatomic mapping system in patients with paroxysmal atrial fibrillation. Heart Rhythm 2015;12:490-7.
18. Ciuffo L, Tao S, Gucuk Ipek E, Zghaib T, Balouch M, Lima JAC, et al. Intra-atrial dyssynchrony during sinus rhythm predicts recurrence after the first catheter ablation for atrial fibrillation. JACC Cardiovasc Imaging 2019;12:310-9.
19. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc 2013;2:e000102.
20. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107-33.

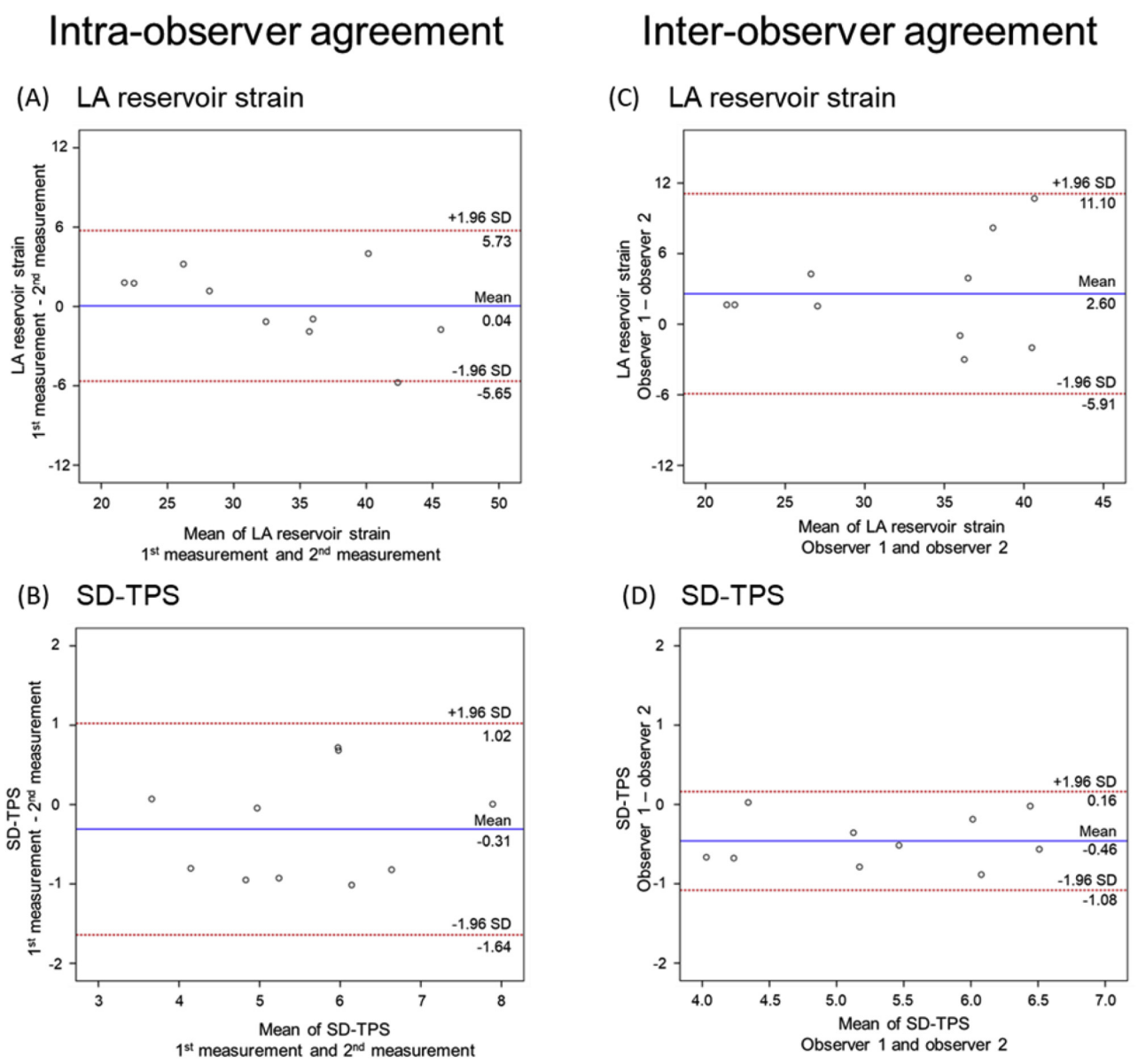
21. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.
22. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. J Am Soc Echocardiogr 2011;24:277-313.
23. Pathan F, D'Elia N, Nolan MT, Marwick TH, Negishi K. Normal ranges of left atrial strain by speckle-tracking echocardiography: a systematic review and meta-analysis. J Am Soc Echocardiogr 2017;30:59-70.e8.
24. Shang Z, Su D, Cong T, Sun Y, Liu Y, Chen N, et al. Assessment of left atrial mechanical function and synchrony in paroxysmal atrial fibrillation with two-dimensional speckle tracking echocardiography. Echocardiography 2017;34:176-83.
25. Mochizuki A, Yuda S, Oi Y, Kawamukai M, Nishida J, Kouzu H, et al. Assessment of left atrial deformation and synchrony by three-dimensional speckle-tracking echocardiography: comparative studies in healthy subjects and patients with atrial fibrillation. J Am Soc Echocardiogr 2013;26:165-74.
26. Kobayashi Y, Okura H, Kobayashi Y, Okawa K, Banba K, Hirohata A, et al. Assessment of atrial synchrony in paroxysmal atrial fibrillation and impact of pulmonary vein isolation for atrial dyssynchrony and global strain by three-dimensional strain echocardiography. J Am Soc Echocardiogr 2014;27:1193-9.
27. Furukawa A, Ishii K, Hyodo E, Shibamoto M, Komasa A, Nagai T, et al. Three-dimensional speckle tracking imaging for assessing left atrial function in hypertensive patients with paroxysmal atrial fibrillation. Int Heart J 2016;57:705-11.
28. Sakabe K, Fukuda N, Fukuda Y, Morishita S, Shinohara H, Tamura Y. Interatrial dyssynchrony on tissue Doppler imaging predicts progression to chronic atrial fibrillation in patients with non-valvular paroxysmal atrial fibrillation. Heart 2009;95:988-93.
29. Sarvari SI, Haugaa KH, Stokke TM, Ansari HZ, Leren IS, Hegbom F, et al. Strain echocardiographic assessment of left atrial function predicts recurrence of atrial fibrillation. Eur Heart J Cardiovasc Imaging 2016;17:660-7.
30. Cho GY, Jo SH, Kim MK, Kim HS, Park WJ, Choi YJ, et al. Left atrial dyssynchrony assessed by strain imaging in predicting future development of atrial fibrillation in patients with heart failure. Int J Cardiol 2009;134:336-41.
31. Kupczynska K, Michalski BW, Miskowiec D, Kasprzak JD, Szymczyk E, Wejner Mik P, et al. Incremental value of left atrial mechanical dispersion over CHA2 DS2-VASc score in predicting risk of thrombus formation. Echocardiography 2018;35:651-60.
32. Russo C, Jin Z, Sera F, Lee ES, Homma S, Rundek T, et al. Left ventricular systolic dysfunction by longitudinal strain is an independent predictor of incident atrial fibrillation: a community-based cohort study. Circ Cardiovasc Imaging 2015;8:e003520.
33. Bonapace S, Valbusa F, Bertolini L, Zenari L, Canali G, Molon G, et al. Early impairment in left ventricular longitudinal systolic function is associated with an increased risk of incident atrial fibrillation in patients with type 2 diabetes. J Diabetes Complications 2017;31:413-8.
34. Magnani JW, Zhu L, Lopez F, Pencina MJ, Agarwal SK, Soliman EZ, et al. P-wave indices and atrial fibrillation: cross-cohort assessments from the Framingham Heart Study (FHS) and Atherosclerosis Risk in Communities (ARIC) study. Am Heart J 2015;169:53-61.
35. Schumacher K, Dagres N, Hindricks G, Husser D, Bollmann A, Kornej J. Characteristics of PR interval as predictor for atrial fibrillation: association with biomarkers and outcomes. Clin Res Cardiol 2017;106:767-75.
36. Motoki H, Dahiya A, Bhargava M, Wazni OM, Saliba WI, Marwick TH, et al. Assessment of left atrial mechanics in patients with atrial fibrillation: Comparison between two-dimensional speckle-based strain and velocity vector imaging. J Am Soc Echocardiogr 2012;25:428-35.

APPENDIX



Variable	Model 1 Chi-square = 0.7 HR (95%CI), *P* value	Model 2 Chi-square = 21.2 HR (95%CI), *P* value	Model 3 Chi-square = 22.6 HR (95%CI), *P* value	Model 4 Chi-square = 27.5 HR (95%CI), *P* value
CHARGE-AF score (per 1 point increase)	0.97 (0.91-1.04), *P* = .41	0.96 (0.89-1.03), *P* = .23	0.95 (0.88-1.02), *P* = .15	0.93 (0.85-1.00), *P* = .06
SD-TPS (per 1% increase)		**1.34 (1.18-1.53), *P* < .01**	**1.32 (1.16-1.51), *P* < .01**	**1.26 (1.10-1.45), *P* < .01**
LAVI (per 1 ml/m^2 increase)			1.03 (0.99-1.07), *P* = .13	1.00 (0.96-1.05), *P* = .99
LA reservoir strain (per 1 % increase)				**0.92 (0.86-0.98), *P* < .01**

Supplemental Figure 1 Incremental value of SD-TPS over existing indices. A comparison is made with CHARGE-AF score, LAVI, and LA reservoir strain in risk stratification for new-onset AF.



Supplemental Figure 2 Bland-Altman plots of intraobserver agreement for LA reservoir strain (**A**) and standard deviation of time to peak strain (TPS; **B**), and interobserver agreement for LA reservoir strain (**C**) and standard deviation of TPS (**D**).

Supplemental Table 1 The results of linear regression analysis

Variables	*r*	*P* value
LVEF	–0.384	<.01
GCS	0.083	.49
GLS	0.342	<.01
E/e'	0.219	.07
LAVI	0.196	.10
LA pump strain	–0.249	.04
LA reservoir strain	–0.385	<.01

The strength of the relation between SD-TPS and other echocardiographic parameters was expressed using *r* value. *GCS*, Global circumferential strain; *GLS*, global longitudinal strain.

Supplemental Table 2 Univariable and multivariable cox regression analysis for new-onset AF

	Univariable		Multivariable					
			Clinical model		Medical model		Echo model	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
BMI	1.00 (0.94-1.07)	.94	0.98 (0.91-1.06)	.65				
CHA_2DS_2VASc score	1.05 (0.76-1.45)	.79	0.86 (0.57-1.30)	.47				
CHARGE-AF score	0.97 (0.90-1.04)	.41	0.94 (0.86-1.03)	.16				
ACE inhibitors or ARBs	1.58 (0.81-3.10)	.18			1.64 (0.79-4.03)	.16		
β-blockers	0.57 (0.22-1.50)	.26			1.37 (0.40-4.69)	.61		
Calcium blocker	1.58 (0.61-4.09)	.35			1.50 (0.56-4.05)	.42		
LVEF	0.96 (0.91-1.01)	.08					1.02 (0.96-1.08)	.59
LAVI	1.04 (1.00-1.07)	.04					1.00 (0.95-1.08)	.88
LA reservoir strain	0.92 (0.88-0.96)	<.01	0.90 (0.85-0.94)	<.01	0.91 (0.87-0.96)	<.01	0.93 (0.86-0.99)	.02
SD-TPS	1.32 (1.17-1.50)	<.01					1.28 (1.08-1.51)	<.01

ARB, Angiotensin receptor blocker.

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IMAGING VIGNETTE

Left Atrial Strain Performance and its Application in Clinical Practice

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THERE IS INCREASING EVIDENCE OF THE IMPORTANCE OF LEFT ATRIAL (LA) FUNCTION INCREMENTAL TO atrial dilatation. The feasibility of LA function assessment has increased with the development of LA strain (1). Although the use of atrial strain is ready to spread beyond its research application, many clinicians are unfamiliar with the process of strain acquisition and continue to rely on other atrial parameters (e.g., LA volume, A-wave velocity). The purpose of this paper is to facilitate the acquisition of atrial strain for clinicians by illustrating its application with the most commonly used software.

Currently, most vendors use strain software that was originally developed for left ventricular strain. **Figures 1 to 4** show the steps to obtain this using machines with the most widely available software. In collaboration, we used the experience of more than 1,000 cases of LA strain analysis to develop a method of 8 steps that are common to all vendors: 1) image acquisition and/or selection; 2) electrocardiographic orientation "reference" (**Figure 5**); 3) detection and marking of fiducial landmarks; 4) detection and tracing of the endocardial border (**Figure 6**); 5) adjustment of regions of interest (**Figure 7**); 6) evaluating tracking quality; 7) excluding segments of inadequate and/or poor tracking; and 8) repeating in more than 1 view and then averaging to minimize error.

Atrial strain has now been evaluated in multiple conditions, especially heart failure and atrial fibrillation (2). In heart failure, LA strain has been used in the assessment and staging of diastolic dysfunction (**Figure 8**) and filling pressure (**Figure 9**). The assessment of atrial contractile function (**Figure 10**) may be pertinent to risk evaluation in atrial fibrillation.

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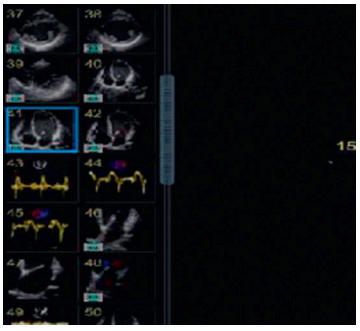
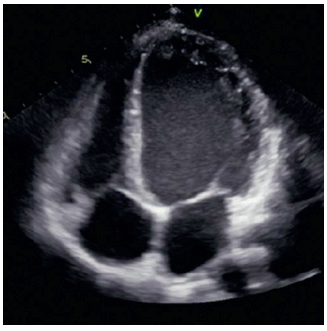
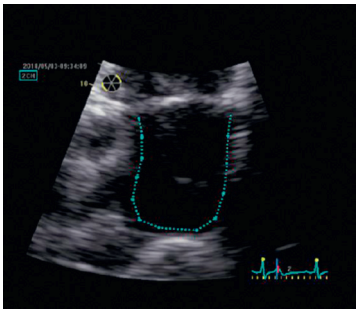
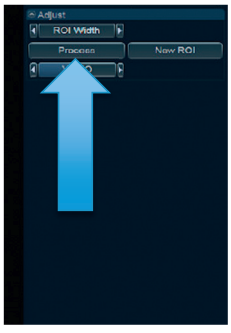
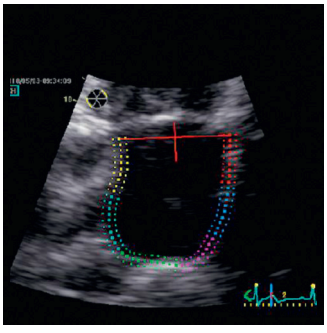
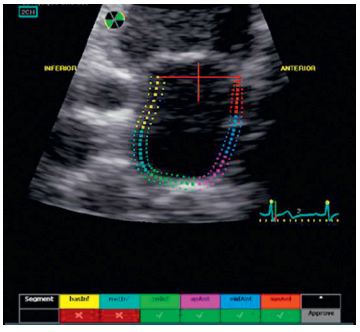
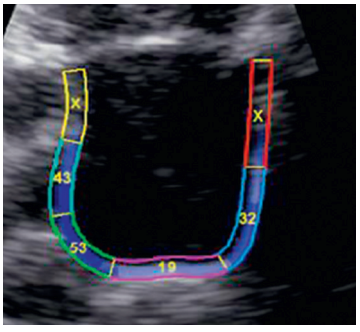
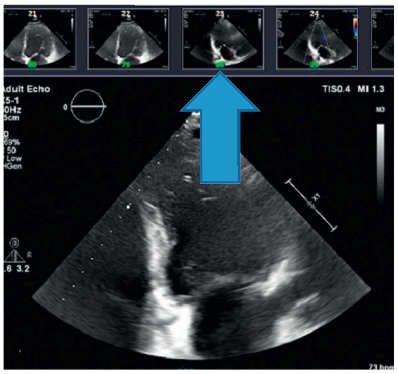
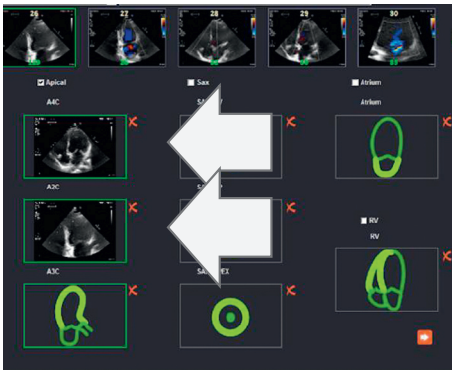
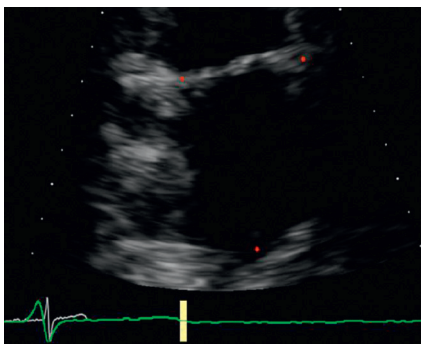
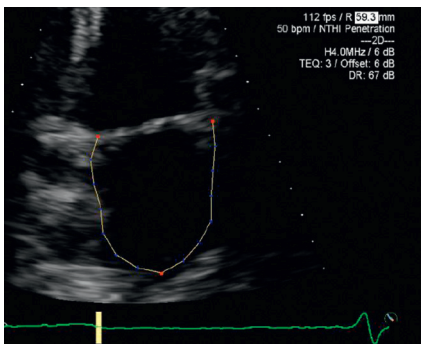
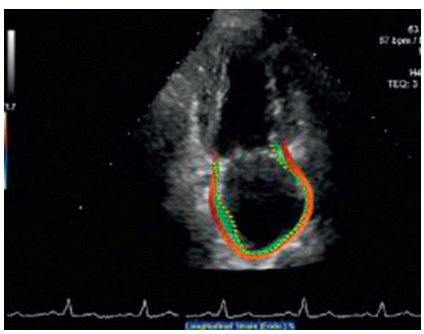
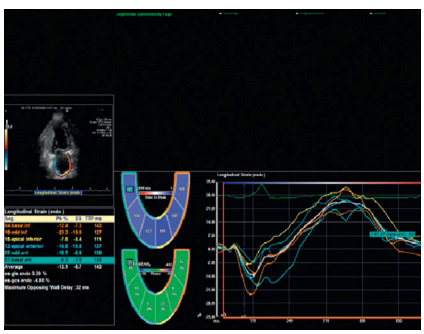
FIGURE 1 Steps of Performing Atrial Strain With ECHOPAC (GE Health Care, Milwaukee, Wisconsin)

Image selection/ acquisition. Left image shows available images to choose from (Choose the apical 4 chamber /or 2 chamber). Right image shows the chosen image. (Double click on the image you want to analyze)		
Detection of fiducial landmark and tracing endocardial border. Left image shows steps to perform LA strain. Right image shows manual endocardial tracking starting and finishing with the mitral valve insertion points		
Adjustment of ROI. Left image shows ROI adjustment icon, Click the ROI width to adjust ROI. Right image shows the thickness of the analyzed segment		
Evaluation of tracking quality and exclude poorly tracked segments. Left and right images show poorly tracked segments. The assessment of tracking quality involves visual assessment and adjustment of the linear contour Please see online video 2 to see examples of tracking		

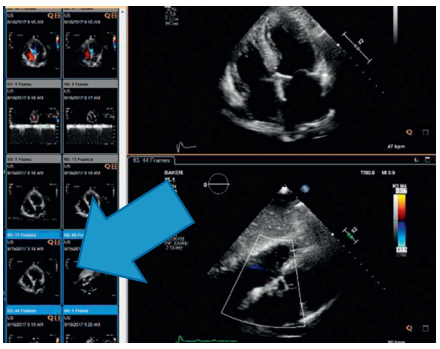
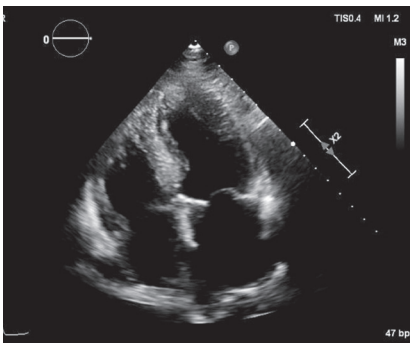
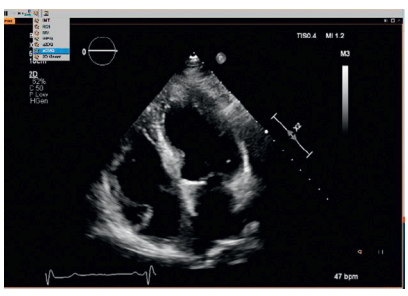
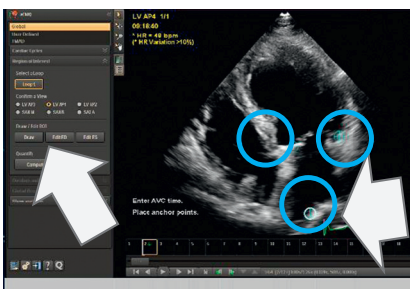
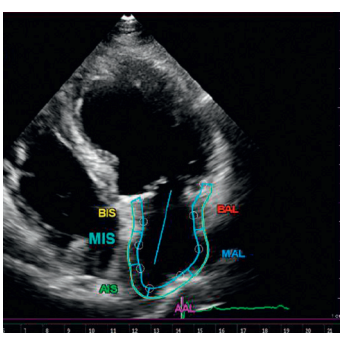
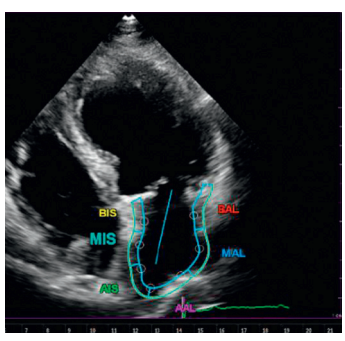
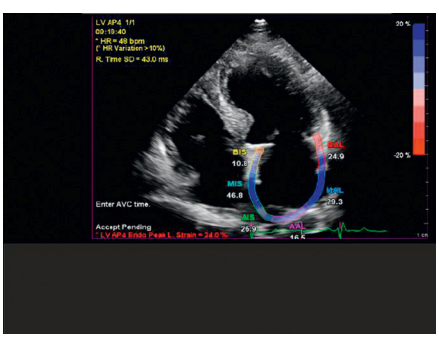
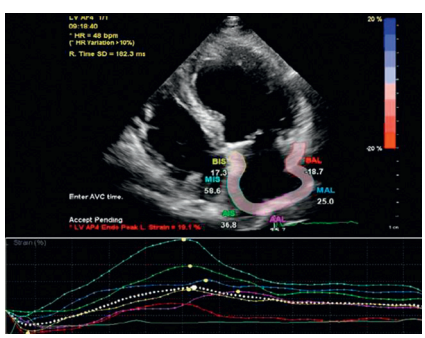
Videos 1 and 2 illustrate the steps and tracking. LA = left atrial; ROI = region of interest.

FIGURE 2 **Steps of Performing Atrial Strain With TOMTEC (Siemens, Malvern, Pennsylvania)**

Image selection/ Acquisition. Left image shows available images to choose from. Right image shows selected images. Drag the image you want to analyze in the provided boxes for the apical 4 chamber and 2 chamber accordingly. (Note we use the boxes provided for LV strain)		
Detection of fiducial landmark and endocardial border. Left image shows the fiducial landmarks, click both mitral annuluses and then right click roof of LA. Right image shows automatic completion of endocardial border tracking		
Evaluation of tracking quality and exclude poorly tracked segments. Left image shows tracking. Right image shows LA strain graph. The assessment of tracking quality involves visual assessment and adjustment of the linear contour Please see online video 3 to see an examples of tracking		

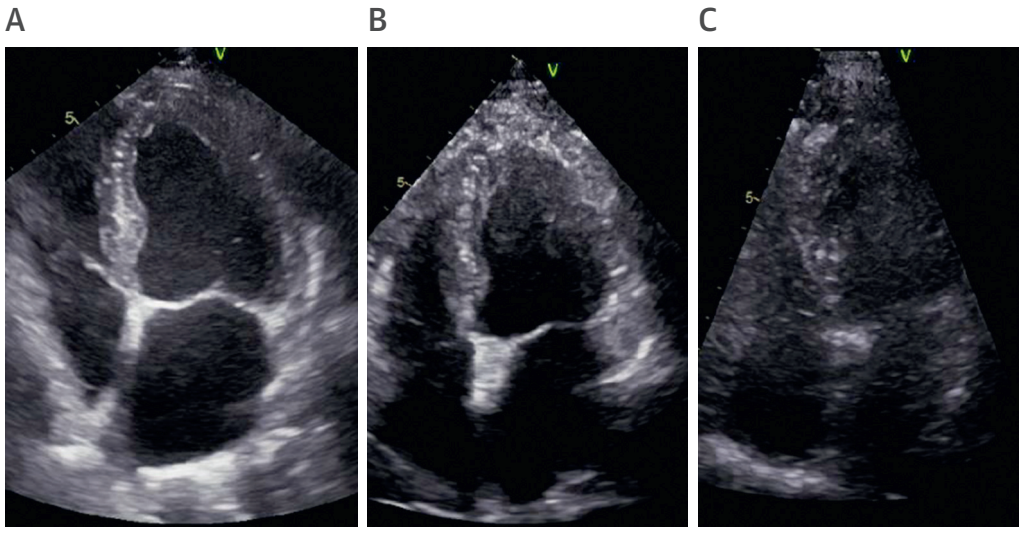
Video 3 illustrates tracking. LV = left ventricular; other abbreviation as in **Figure 1**.

FIGURE 3 Steps of Performing Atrial Strain With QLAB (Philips, Andover, Massachusetts)

Image selection/ acquisition. Left image shows available images to choose from (Choose the apical 4 chamber /or 2 chamber). Right image shows the chosen image. (Double click on the image you want to analyze)		
Detection of fiducial landmark and endocardial border. Left image – clicking CMQ allows a semi-automated tracing by marking three fiducial landmarks. Right image click "draw" then click both mitral annuluses and then click the roof of LA		
Adjustment of ROI. Left image shows ROI Thickness. Right image shows the thickness analyzed segment after adjustment. For adjustment simply click on the outer line to decrease or increase thickness		
Evaluation of tracking quality and exclude poorly tracked segments. Left image shows tracking. Right image shows LA strain graph. The assessment of tracking quality involves visual assessment and adjustment of the linear contour. Please see video 4.		

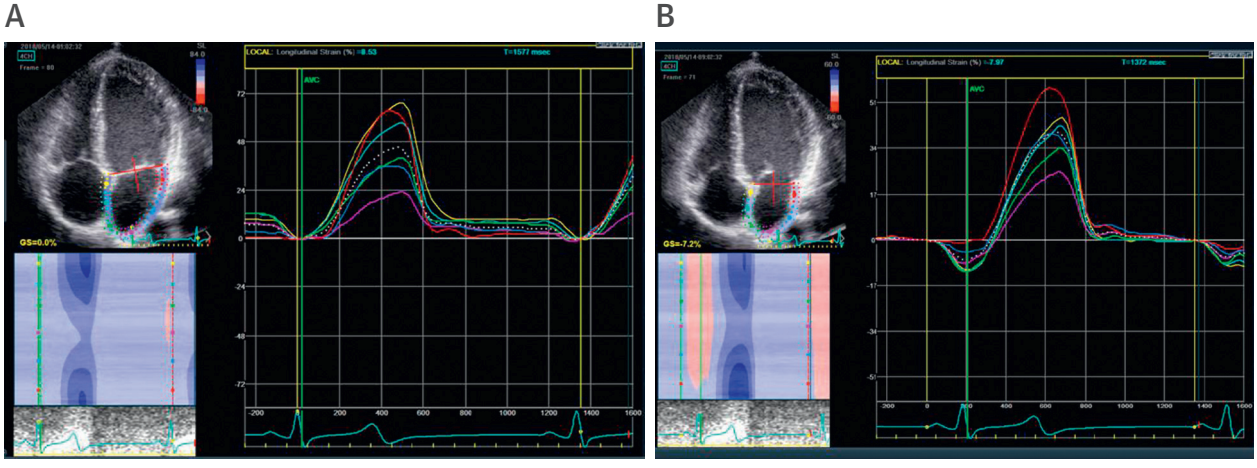
Video 4 illustrates tracking. CMQ = cardiac motion quantification; LA = left atrium/atrial; other abbreviations as in **Figure 1**.

FIGURE 4 **Image Quality**



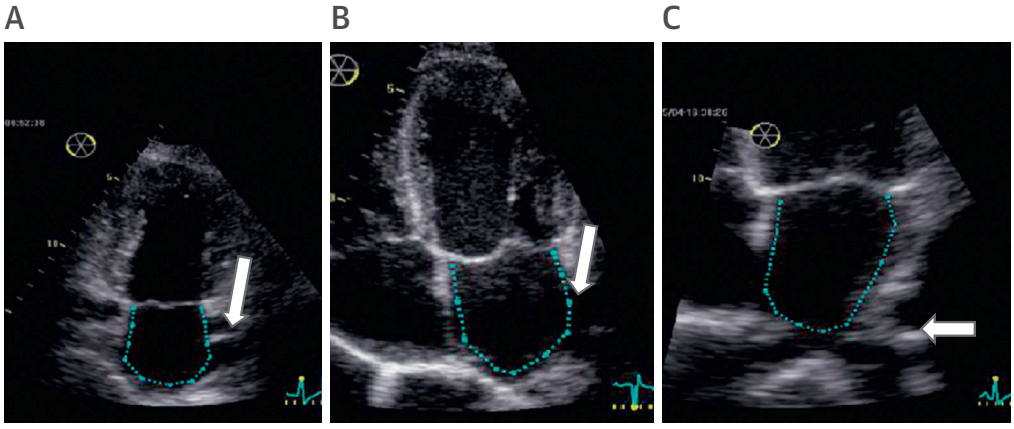
(A) The image is considered adequate for LA strain measurement. The part of intra-atrial septum and entry of right lower pulmonary vein might not track well, but **(B)** global longitudinal strain is still measurable. **(C)** The quality of image 3 is too poor to analyze. (Videos 5, 6, and 7). Note: Acquire and/or select images of dedicated apical 4 and 2 chambers that have a visible endocardial border throughout the cycle to assess tracking quality. Optimize gain, depth and avoid foreshortening. Atrial strain can still be measured when 1 or 2 segments are not visible due to artifacts. Abbreviation as in Figure 1.

FIGURE 5 **Gating the Strain Image**



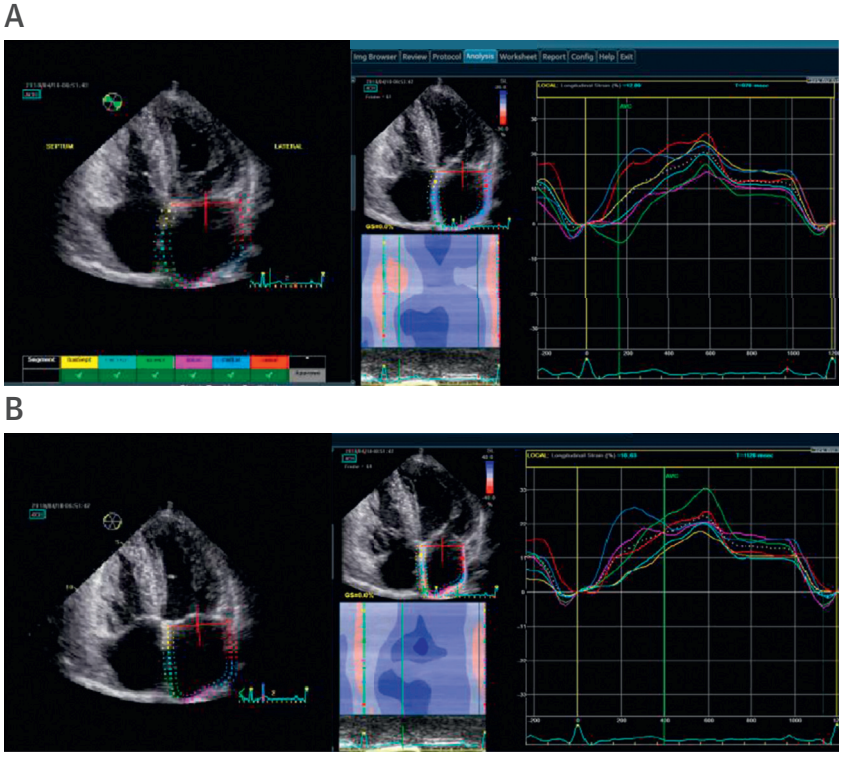
(A) Atrial strain using R-R gating. **(B)** Atrial strain using P-P gating. Note: Most vendors measure the atrial strain reference frame of zero strain from R-R by default. However, some vendors offer changing the electrocardiographic orientation to P-P; in addition, LA strain from either approach can be converted into the other. We recommend using R-R for the purposes of diastolic assessment and P-P in case of atrial contractile function assessment.

FIGURE 6 Tracing Borders



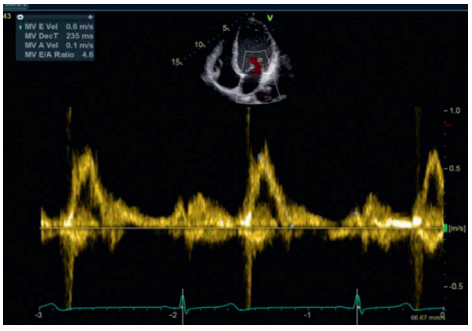
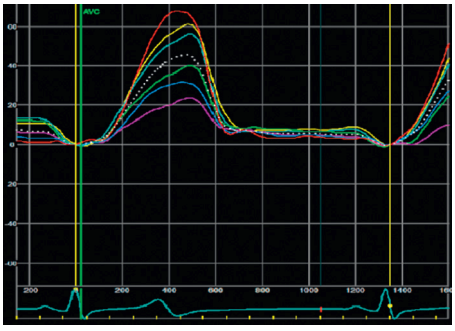
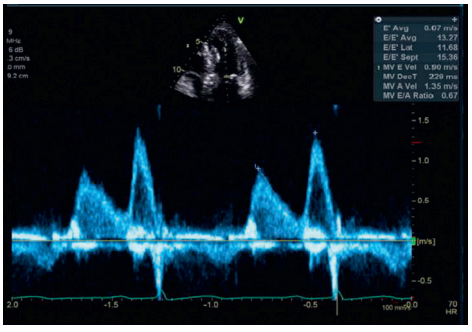
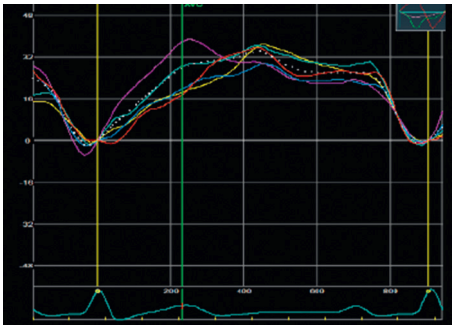
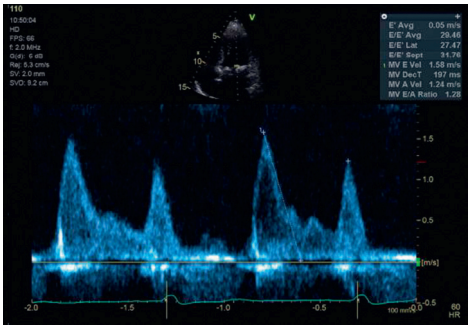
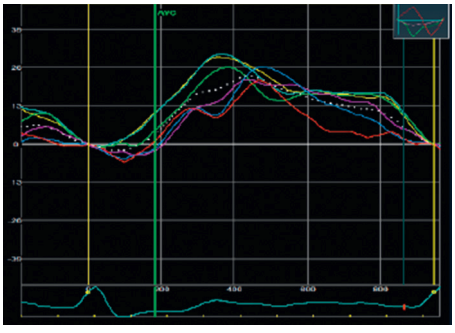
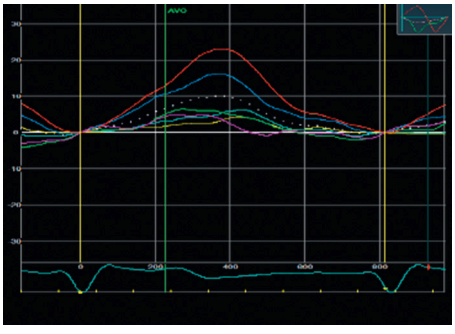
(A) Apical 2-chamber view with **arrow** pointing to left atrial appendage (LAA). **(B)** Apical 4-chamber view with **arrow** pointing to right lower pulmonary vein. **(C)** Apical 4 chamber view with **arrow** pointing to the left lower pulmonary vein. Note: Trace the LA endocardial border, extrapolating across the pulmonary veins, and/or LAA orifices, up to the opposite mitral annulus side. In the semiautomated software, only choose the mitral annulus and roof of the LA in apical 4- and 2-chamber views. Abbreviation as in Figure 1.

FIGURE 7 Defining the ROI



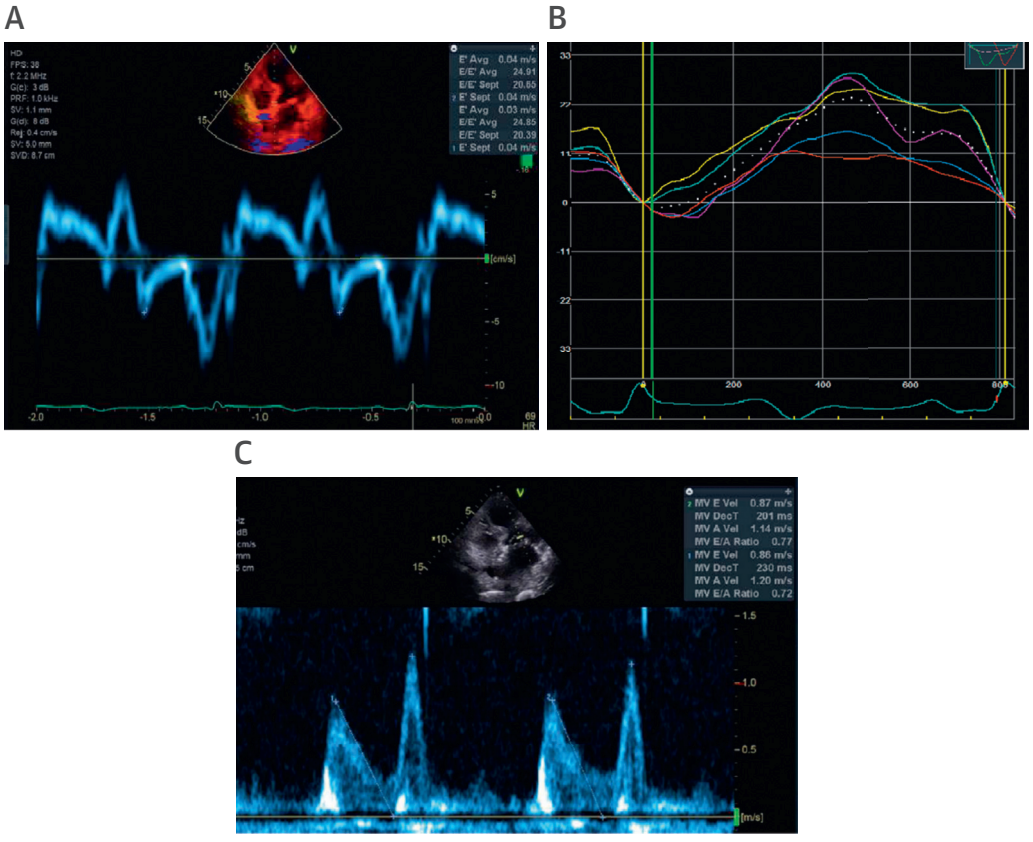
Same patient shown in the other figures. **(A)** Thick ROI as provided by software without adjustment (reservoir strain 21% and contractile strain 12%). **(B)** ROI after adjustment (reservoir strain 25% and atrial contraction 15%. ROI of the LA is defined by the endocardial border (inner contour of the LA wall), and the epicardial border (outer contour of the LA wall, or in the case of the atrial septum, the opposite edge of the septum). A default width of 3 mm is recommended. LA strain can be underestimated if ROI is not adjusted. Abbreviations as in Figure 1.

FIGURE 8 **Gradation of Atrial Reservoir Strain at Each Stage of Diastolic Dysfunction**

a. Normal (reservoir strain 45%)		
b. Delayed relaxation (reservoir strain 33%)		
Grade II diastolic dysfunction (Pseudonormal) (reservoir strain 24%)		
Grade III diastolic dysfunction (restrictive) (reservoir strain 10%)		

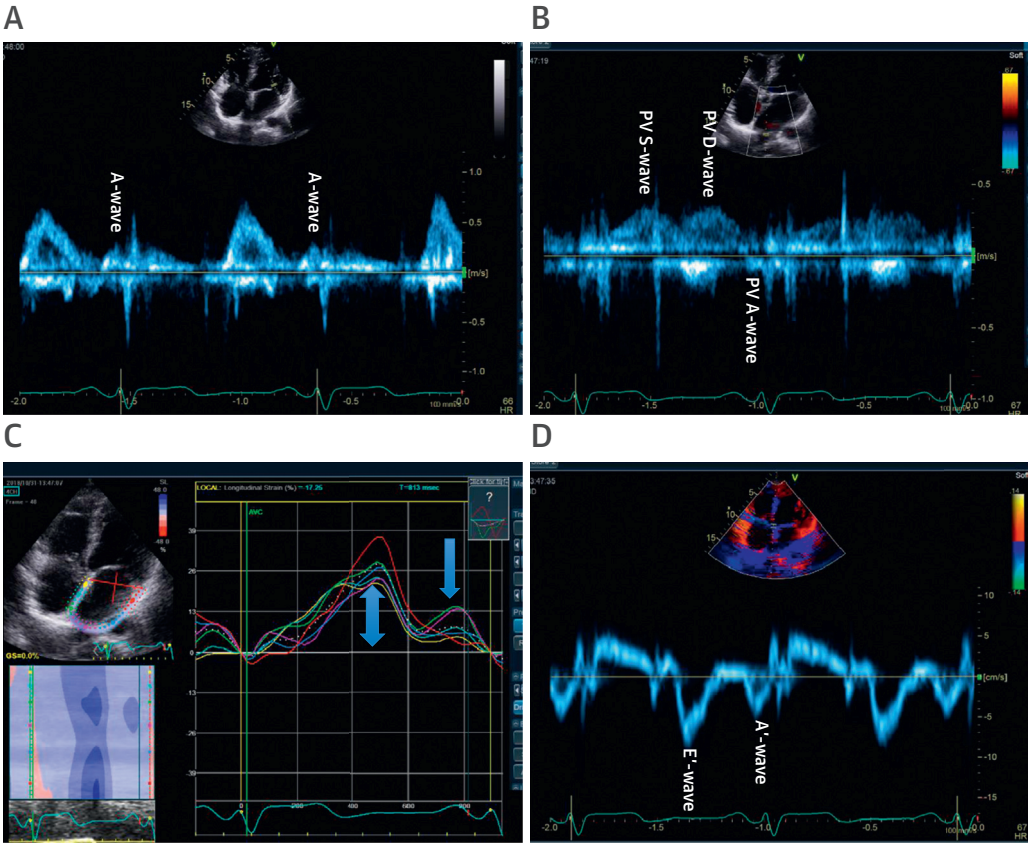
At each stage, there is a progressive decrement of reservoir strain.

FIGURE 9 **Use of LA Strain for Estimation of Increased LV Filling Pressure**



(A) Tissue Doppler. **(B)** Atrial strain. **(C)** Mitral inflow. There is an inverse relation between E/e′ and atrial strain. Filling pressure estimated by tissue Doppler is increased (E/e′: 24). Total LA strain (reservoir strain) of 22% is decreased. Abbreviations as in Figures 1 and 2.

FIGURE 10 Application for Assessment of Atrial Function



Different modes to assess atrial stunning in a patient 10 min post-cardioversion for atrial fibrillation. **(A)** Pulsed wave Doppler of mitral valve inflow, showing a small A-wave. **(B)** Pulmonary venous Doppler, showing a decrease in the pulmonary vein S-wave and in the AR wave. **(C)** Atrial strain curve, showing decrease in reservoir strain (28%; expected range: 35% to 40%), and a small LA booster pump (8%; expected range: 16% to 19%). **(D)** Tissue Doppler and mitral valve annular velocity, showing small a′. Abbreviation as in Figure 1.

REFERENCES

1. Badano LP, Kolias TJ, Muraru D. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2018;19:591–600.

2. Buggey J, Hoit BD. Left atrial strain: measurement and clinical application. Curr Opin Cardiol 2018;33:479–85.

KEY WORDS atrial function, atrial strain, global longitudinal strain

APPENDIX For supplemental videos, please see the online version of this article.

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Use of echocardiography to stratify the risk of atrial fibrillation: comparison of left atrial and ventricular strain

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Aims Although both left atrial (LA) and ventricular (LV) dysfunction has been accepted as an important risk factor of atrial fibrillation (AF), usefulness of LA and LV strain has not been fully compared for prediction of AF. The aims of this study were to clarify the associations of both LA and LV strain with AF and to compare their predictive values in the risk stratification for AF.

Methods and results We evaluated 531 consecutive patients (median age 67 years, 56% male), with no history of AF who underwent echocardiography after cryptogenic stroke. Standard echocardiographic parameters were measured, and speckle-tracking was used to measure LA (reservoir, pump, and conduit strain) and LV strain (global longitudinal strain, GLS). The baseline clinical and echocardiographic parameters of the patients who developed AF and those who did not were compared. Median 36 months of follow-up, 61 patients (11%) had newly diagnosed AF. LA pump strain and GLS were significantly and independently associated with AF and provided incremental predictive value over clinical and standard echocardiographic parameters. Areas under the receiver-operating curves for GLS (0.841) were comparable to LA pump (0.825) and reservoir (0.851) strain. However, predictive value of both strains was different between patients with and without LA enlargement at the time of transthoracic echocardiography screening. LA strain was more useful than LV strain in patients with normal LA volumes, while LV strain was more useful than LA strain in patients with abnormal LA volumes.

Conclusion Both LA and LV strain are significantly and independently associated with AF and provide incremental predictive value over clinical and standard echocardiographic parameters. However, priorities of strain assessment are different depends on patients' condition at the time of echocardiography.

Keywords atrial fibrillation • echocardiography • speckle-tracking • atrial strain • ventricular strain

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and has an increasing prevalence that reflects the ageing population.[1,2] Because of the association of AF with stroke, heart failure, and overall mortality,[3] preventive steps may have a public health impact, but their effective delivery will need to be based on risk stratification.

Left atrial (LA) and left ventricular (LV) structural and functional cardiac abnormalities, including chamber dilatation, systolic/diastolic dysfunction, and valvular failure are all potential risk marker.[4–8] Among standard transthoracic echocardiography (TTE) parameters, LV ejection fraction (LVEF), *E*/*e*′, and LA volume are well-established,[9,10] but AF often occurs in the absence of reduced LVEF and LA enlargement. The detection of subclinical dysfunction with strain echocardiography has emerged as a useful imaging technique,[11,12] and LA and LV strain can improve the prediction of adverse cardiovascular events compared with standard TTE.[13–19] However, although LA strain is a powerful predictor for AF,[16–19] its assessment is complicated, time-consuming and not yet established. In contrast, LV global longitudinal strain (GLS) is more robust and easier than LA

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strain[20] and has been validated in different population to assess for subclinical LV dysfunction and can provide predictive value for a variety of cardiovascular disease, including AF.[13–15,21,22] However, usefulness of both LA and LV strain has not been fully compared for prediction of AF. The aims of this study were to clarify the associations of both LA and LV strain with AF and to compare their predictive values in the risk stratification for AF.

Methods

Study population

We used a database of consecutive patients admitted and diagnosed as a cryptogenic stroke at Royal Hobart Hospital from 2010 to 2014. All patients met the recent criteria of cryptogenic stroke.[23] Patients exclusions were (i) history of AF or AF diagnosis prior to the TTE; (ii) an alternative cause of cerebral ischaemia was identified, including severe carotid stenosis, left-sided cardiac mass or thrombus, left-sided endocarditis, or atrial septal aneurysm with patent foramen ovale; (iii) only transoesophageal echocardiography was performed; (iv) images were inadequate for strain analysis. We retrospectively evaluated clinical risk factors and standard and strain echocardiographic parameters to determine the association of each parameter with newly diagnosed AF. All clinical and outcome data were collected by reviewing electronic medical records, admission codes, clinic correspondence, and cardiac investigations (electrocardiogram, telemetry, Holter, and cardiac implantable electronic device reports). The primary outcome was newly diagnosed AF detected by any cardiac monitoring during follow-up. The study was approved by the Tasmanian Health and

Table 1 Baseline characteristics for all patients and subgroups with normal (LAVI < 34 mL/m^2) and abnormal (LAVI ≥ 34 mL/m^2) LA volumes

	All patients (n = 531)	Normal LA volume (n = 290)	Abnormal LA volume (n = 241)	P-value[a]
Clinical parameters				
Age (years)	67 (56–78)	62 (52–74)	72 (60–81)	<0.01
Male	296 (56)	157 (54)	139 (58)	0.41
Height (cm)	169 (161–173)	168 (161–173)	170 (161–173)	0.55
Weight (kg)	77 (69–87)	78 (70–87)	76 (68–86)	0.46
BSA (m^2)	1.9 (1.8–2.0)	1.9 (1.8–2.0)	1.9 (1.8–2.0)	0.63
SBP (mmHg)	133 (122–144)	132 (120–140)	135 (125–145)	0.18
DBP (mmHg)	72 (70–80)	73 (70–80)	70 (68–80)	0.06
Heart rate (bpm)	68 (61–76)	70 (62–78)	66 (60–74)	<0.01
Type 2 diabetes mellitus	100 (19)	52 (18)	48 (20)	0.56
Hypertension	368 (69)	184 (63)	184 (76)	<0.01
Heart failure	14 (3)	3 (1)	11 (5)	0.01
Myocardial infarction	63 (12)	28 (10)	35 (15)	0.08
Valvular disease	23 (4)	7 (2)	16 (7)	0.02
CHA_2DS_2-VASc score	4 (3–5)	4 (3–5)	5 (3–6)	<0.01
CHARGE-AF score	4.6 (1.6–13.7)	3.2 (1.0–8.6)	7.5 (2.8–17.3)	<0.01
Standard echocardiographic parameters				
LAVI (mL/m^2)	33.1 (26.5–40.1)	27.3 (22.6–30.9)	42.0 (37.3–47.8)	<0.01
E velocity (cm/s)	67 (56–81)	67 (55–78)	69 (56–83)	0.13
A velocity (cm/s)	74 (59–91)	73 (60–89)	75 (58–92)	0.70
e' (cm/s)	7.0 (5.5–8.5)	7.4 (5.9–9.0)	6.2 (4.9–8.0)	<0.01
E/e'	9.5 (7.4–13.2)	8.8 (7.1–11.2)	11.1 (8.2–14.7)	<0.01
LV mass index (g/m^2)	92.3 (76.6–112.7)	85.3 (71.0–103.1)	101.2 (84.1–119.5)	<0.01
LVEF (%)	61.8 (53.9–66.3)	62.5 (56.6–67.3)	61.0 (51.6–65.7)	0.02
Strain echocardiographic parameters				
LA pump strain (%)	14.6 (12.0–17.3)	15.1 (12.9–17.9)	13.8 (10.4–16.7)	<0.01
LA conduit strain (%)	16.1 (11.6–20.8)	17.3 (12.9–21.7)	14.5 (10.5–19.8)	<0.01
LA reservoir strain (%)	31.9 (25.6–37.0)	33.3 (28.4–39.2)	29.3 (23.0–35.0)	<0.01
GLS (%)	-20.6 (-22.2 to -18.5)	-21.2 (-22.5 to -19.2)	-19.9 (-21.9 to -17.3)	<0.01
Events during follow-up				
AF	61 (11)	21 (7)	40 (17)	<0.01

Data are expressed as median (interquartile range) or number (percentage).
AF, atrial fibrillation; BSA, body surface area; DBP, diastolic blood pressure; GLS, global longitudinal strain; LA, left atrium; LAVI, left atrial volume index; LV, left ventricle; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.
[a]P-value compared with patients with normal and abnormal LA volumes.

Medical Human Ethics Research Committee (HERC reference no. H0015502).

Clinical variables

We obtained all relevant clinical variables from all patients to assess their overall health status at baseline. Clinical parameters (physical characteristics, medical history, cardiac risks, and baseline examination data) were comprehensively assessed. Using these data, we computed the CHA_2DS_2-VASc and CHARGE-AF scores. The CHARGE-AF score used clinical parameters (age, race, height, weight, systolic and diastolic blood pressure, current smoking, treatment of hypertension, diabetes, history of myocardial infarction and heart failure, and electrocardiogram data) to assess 5-year risk of AF.[24]

Echocardiographic assessment

All echocardiographic examinations were performed by experienced sonographers using commercially available ultrasonography systems. Standard echocardiographic parameters, measured according to the recommendations of guidelines,[9,10] included LA volume, LV mass, and LV systolic/diastolic function. LA volume and LV mass were indexed to body surface area [LA volume index (LAVI) and LV mass index]. Normal LA volume was defined as LAVI < 34 mL/m^2.[10]

All strain parameters were assessed using speckle-tracking imaging by an external third-party software programme (TomTec Imaging Arena, Munich, Germany). After manual tracing of the LA and LV endocardial border, the dedicated software automatically tracked the myocardium throughout the cardiac cycle. All tracking was reviewed to ensure that it was appropriate and a true representation of LA and LV motion. GLS was measured using standard methodologies.[20] LA pump, conduit, and reservoir strain were averaged from the apical four-chamber and two-chamber views.[16,25] The reference point for image analysis was taken at the onset of the QRS complex (R-R gating).[16,25] Patients without interpretable images, such as those with incomplete strain measurements, were excluded from this study. In all patients, conventional and strain parameters were obtained in sinus rhythm at baseline.

Statistical analysis

All categorical variables are presented as frequencies and percentage, and continuous variables are expressed as median and interquartile range. Statistical significance of differences between the groups was assessed using Student's *t*-test for data with normal distribution, and the Mann–Whitney *U* test was used for data that were not normally distributed. For categorical variables, the χ^2 test or Fisher's exact test was used, as appropriate. Simple linear regression was used to evaluate the associations between LA and LV strain. Univariable and multivariable Cox regression analysis was used to assess independent association with newly diagnosed AF. The independence and robustness of parameters were examined using several models. Receiver-operating characteristic (ROC) curve analysis was performed on clinical and imaging predictors of AF, and the area under the curve (AUC) was also calculated.

The incremental predictive values of LA and LV strain over clinical and standard echocardiographic parameters were assessed using multivariable nested Cox regression models, comparison of AUCs, and reclassification. In the nested Cox regression models, the incremental values of LA and LV strain were assessed in two steps in overall and subgroups (patients with normal and abnormal LA volumes). Covariate selection for model entry was based on clinical experience and identification of known correlates. The incremental values of LA and LV strain for predicting AF were determined by calculating the improvement in the global χ^2 statistic. ROC analyses were performed to compare the strength of the models by comparisons of AUC. Reclassification was evaluated to assess the incremental benefit of adding GLS or LA strain to the model on the basis of baseline clinical and standard echocardiographic parameters with net reclassification improvement (NRI). Finally, the optimal risk stratification for AF was evaluated using a Classification and Regression Tree (CART) analysis in patients with normal and abnormal LA volumes, respectively.

Reproducibility was assessed in 20 randomly selected patients. Inter- and intra-observer variability were evaluated by having the same observer and another experienced reader repeat the analysis, and they are reported as inter-class correlation coefficients (ICCs).

All statistical analyses were performed using a standard statistical software package [SPSS version 21 (SPSS, Chicago, IL, USA) and R version 3.5.0 (https://www.r-project.org)]. A *P*-value <0.05 was considered statistically significant.

Table 2 Univariable Cox regression analysis for association with AF in all patients

Variables	HR (95% CI)	*P*-value
Clinical parameters		
Age (years)	1.08 (1.06–1.11)	<0.01
Female	1.33 (0.80–2.19)	0.27
Height (cm)	0.98 (0.96–1.01)	0.15
Weight (kg)	0.98 (0.96–1.00)	0.016
BSA (m^2)	0.22 (0.07–0.71)	0.011
SBP (mmHg)	0.99 (0.97–1.01)	0.26
DBP (mmHg)	0.95 (0.92–0.98)	<0.01
Heart rate (bpm)	0.98 (0.93–1.04)	0.50
Type 2 diabetes mellitus	1.10 (0.58–2.07)	0.78
Hypertension	2.34 (1.19–4.62)	0.014
Heart failure	7.10 (3.37–14.9)	<0.01
Myocardial infarction	1.27 (0.723–2.23)	0.41
Valvular disease	3.53 (1.60–7.78)	<0.01
CHA_2DS_2-VASc score	1.76 (1.48–2.09)	<0.01
CHARGE-AF score	1.10 (1.07–1.13)	<0.01
Standard echocardiographic parameters		
LAVI (mL/m^2)	1.04 (1.02–1.06)	<0.01
E velocity (cm/s)	1.00 (0.99–1.01)	0.87
A velocity (cm/s)	1.01 (0.99–1.02)	0.30
e′ (cm/s)	0.73 (0.63–0.84)	<0.01
E/*e′*	1.10 (1.06–1.15)	<0.01
LV mass index (g/m^2)	1.01 (1.00–1.02)	0.054
LVEF (%)	0.98 (0.96–1.00)	0.085
Strain echocardiographic parameters		
LA pump strain (%)	0.78 (0.74–0.82)	<0.01
LA conduit strain (%)	0.86 (0.83–0.90)	<0.01
LA reservoir strain (%)	0.88 (0.85–0.90)	<0.01
GLS (%)	1.24 (1.19–1.30)	<0.01

AF, atrial fibrillation; BSA, body surface area; CI, confidence interval; DBP, diastolic blood pressure; GLS, global longitudinal strain; HR, hazard ratio; LA, left atrium; LAVI, left atrial volume index; LV, left ventricle; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Table 3 Multivariable Cox regression analysis for association with AF in all patients

Variables	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Clinical parameters						
Female	1.15 (0.68–1.94)	0.60	1.11 (0.60–2.06)	0.74		
CHARGE-AF	1.05 (1.05–1.11)	<0.01	1.08 (1.04–1.12)	<0.01	1.07 (1.03–1.11)	<0.01
LA parameters						
LAVI (mL/m^2)	0.99 (0.98–1.01)	0.54			1.00 (0.98–1.03)	0.84
LA pump strain (%)	0.85 (0.77–0.93)	<0.01	0.83 (0.77–0.90)	<0.01	0.83 (0.77–0.90)	<0.01
LA reservoir strain (%)	0.99 (0.93–1.04)	0.59				
LV parameters						
e′ (cm/s)						
E/e′			1.01 (0.96–1.06)	0.72	1.01 (0.95–1.07)	0.77
LV mass index (g/m^2)						
LVEF (%)			1.04 (1.00–1.07)	0.026	1.04 (1.01–1.07)	0.018
GLS (%)	1.10 (1.02–1.18)	0.017	1.18 (1.08–1.28)	<0.01	1.18 (1.08–1.29)	<0.01

Model 1 adjusted with clinical (gender and CHARGE-AF score) and LA echocardiographic (LAVI and LA reservoir strain) parameters.
Model 2 adjusted with clinical (gender and CHARGE-AF score) and LV echocardiographic (*E*/e′ and LVEF) parameters.
Model 3 adjusted with multi mixed parameters (CHARG-AF score, LAVI, *E*/e′, and LVEF).
CI, confidence interval; GLS, global longitudinal strain; HR, hazard ratio; LA, left atrium; LAVI, left atrial volume index; LV, left ventricle; LVEF, left ventricular ejection fraction.

Results

Patient characteristics and AF events

A total of 531 patients who underwent standard echocardiographic and both LA and LV strain measurements were included in this study (*Table 1*). Most patients had hypertension (69%) and high CHA_2DS_2-VASc score [median 4 (3–5)], but most values for LA size, and LA and LV function were within the normal range. Over a median of 36 (19–54) months following the presentation with a cryptogenic stroke, AF was newly diagnosed in 61 patients (11%). The median delay between the stroke event and diagnosis of AF was 7 (1–19) months. Patients with AF had more risk factors of AF and worse LA and LV function than those without (Supplementary data online, *Table S1*). In patients with AF, the minimum CHARGE-AF score was 2.1 (Supplementary data online, *Figure S1*).

Predictive value of standard and strain echocardiographic parameters for AF

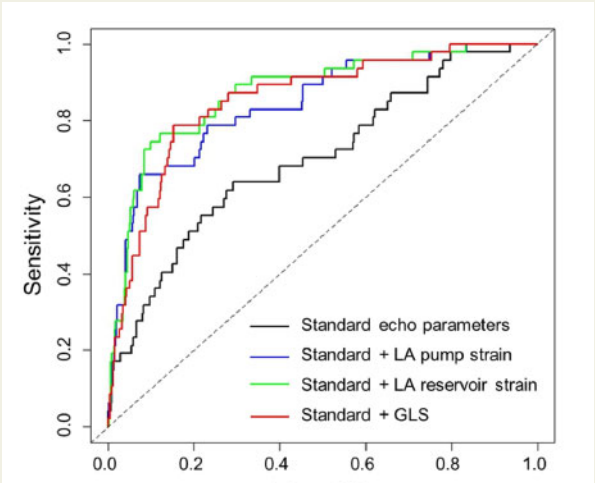
In the univariable Cox regression analysis, AF was significantly associated with a variety of clinical and TTE parameters (*Table 2*). Multivariable Cox regression analysis revealed that CHARGE-AF score, LA pump strain, and GLS were independently associated with AF (*Table 3*). The robustness of these parameters was examined using three different models, and all three variables had a consistently significant association with AF in every model and hazard ratios were similar (CHARGE-AF score, 1.05–1.08; LA pump strain, 0.83–0.85; and GLS, 1.10–1.18, respectively). LA reservoir strain was not independently associated with AF because of a collinearity between LA reservoir strain and GLS (Supplementary data online, *Table S2*). The predictive value of clinical and TTE parameters is summarized in Supplementary data online, *Table S3*. The AUC for strain echocardiographic parameters were higher than clinical and standard TTE parameters. Importantly, the AUC for GLS (0.841) was comparable to LA pump (0.825) and reservoir (0.851) strain.

Incremental predictive value of LA and LV strain

ROC analysis for the association with AF showed that the AUCs of standard TTE parameters (LVEF, *E*/e′, and LAVI) plus one of each strain (LA pump strain, LA reservoir strain, and GLS) models were significantly better than that of the standard TTE model (*Figure 1*). Moreover, the addition of GLS or LA pump strain to a risk classification model based on clinical and standard TTE parameters (CHARGE-AF score, LVEF, *E*/e′, and LAVI) led to further significant reclassification improvements (adding GLS, NRI = 0.264; $P < 0.01$ and adding LA pump strain, NRI = 0.221; $P < 0.01$, respectively) (Supplementary data online, *Table S4*). Finally, we assessed sequential Cox models for the prediction of newly diagnosed AF (*Figure 2*). *Figure 2A* revealed that the initial model based on clinical and standard TTE parameters (CHARGE-AF score, LVEF, *E*/e′, and LAVI) was significantly improved by the addition of LA pump strain and further improved by adding GLS. Interestingly, the same initial model was also significantly improved by the addition of GLS and further improved by adding LA pump strain (*Figure 2B*).

The priorities of LA and LV strain for AF risk screening in patients with and without LA enlargement

We also conducted a subgroup analysis between patients with normal and abnormal LA volumes. Patients with abnormal LA volumes were older and had more risk factors of AF and worse LA and LV function than those with normal LA volumes (*Table 1*). The incidence rate of AF was significantly higher in patients with abnormal LA volumes than those with normal LA volumes. In the subgroup analysis,



AUC

	AUC	95% CI
Standard echo parameters	0.699	0.616-0.782
Standard + LA pump strain	0.843	0.780-0.905
Standard + LA reservoir strain	0.873	0.817-0.929
Standard + GLS	0.853	0.796-0.911

AUC comparison

	P value
Standard vs. Standard + LA pump strain	0.001
Standard vs. Standard + LA reservoir strain	<0.001
Standard vs. Standard + GLS	<0.001

Standard echo parameters: LVEF, E/e', LAVI.

Figure 1 Results of receiver-operating characteristic curve analysis for prediction newly diagnosed AF in all patients. AF, atrial fibrillation; AUC, area under the curve; GLS, global longitudinal strain; LA, left atrium; LAVI, left atrial volume index.

the independent association of each parameter was evaluated using five different models (Supplementary data online, *Table S5*). In patients with abnormal LA volumes, GLS and LA pump strain had consistently significant association with newly diagnosed AF in every model. However, in patients with normal LA volumes, GLS was not an independent predictor for AF and only LA pump strain was significantly and independently associated with AF. Supplementary data online, *Table S3* shows the results of ROC curve analysis in patients with normal and abnormal LA volumes. Interestingly, in patients with normal LA volumes, AUC for CHARGE-AF was higher than any other imaging parameters. On the other hand, AUC for GLS was the highest in patients with abnormal LA volumes. Supplementary data online, *Figure S2* shows a series of nested Cox proportional hazards models to evaluate the incremental prognostic values of GLS or LA pump strain over CHARGE-AF, and either of LVEF, *E/e'*, LA reservoir strain, and GLS or LA pump strain in both subgroups. All these models were significantly improved by the addition of GLS and LA pump strain in patients with abnormal LA volumes (Supplementary data online, *Figure S2B*). However, GLS provided no incremental value, and only LA pump strain had an incremental predictive value for AF in patients with normal LA volumes (Supplementary data online, *Figure S2A*). In addition, we assessed ROC analysis and reclassification in both subgroups (*Figure 3* and Supplementary data online, *Tables S6* and *S7*). In patients with normal LA volumes, only LA pump strain had an incremental predictive value for AF over standard TTE parameters (*Figure 3A* and Supplementary data online, *Table S6*). On the other hand, in patients with abnormal LA volumes, GLS also had an incremental predictive value as well as LA strain (*Figure 3B* and Supplementary data online, *Table S7*). Finally, we assessed the priority of both LA and LV strain after standard TTE evaluation for AF risk screening using CART analysis in subgroups (*Figure 4*). In patients with normal LA volumes, the first node was LA pump strain, and the second nodes were both GLS (*Figure 4A*). With LA enlargement, the first node was GLS and the second nodes were both LA pump strain (*Figure 4B*).

Reproducibility

The ICC value for intra-observer variability for GLS, LA pump strain, and LA reservoir strain were 0.95, 0.96, and 0.90, respectively. Those ICC values for inter-observer variability were 0.82, 0.95, and 0.86, respectively.

Discussion

This analysis identified that both LA and LV strain assessed by speckle-tracking were significantly and independently associated with AF in patients with cryptogenic stroke. Moreover, both strains provided the incremental predictive value over clinical and standard TTE parameters and the other measurement of strain. Interestingly, predictive value of both strains was different between patients with and without LA enlargement at the time of TTE screening. LA strain was more useful than LV strain in patients with normal LA volumes, while LV strain was more useful than LA strain in patients with abnormal LA volumes. This study also identified that the contribution of echocardiographic screening was limited in patients with very low risk of AF (CHARGE-AF score < 2.1), so additional strain measurement may be unnecessary in these patients.

Biomarkers for risk stratification of AF

The causes of AF are multifactorial, so a comprehensive assessment is necessary for the risk stratification for AF. In addition to a variety of clinical scores,[24,26] LA and LV structural and functional abnormalities have been used as predictors for AF.[4–6,17,18,21,22] Generally, LA parameters have been accepted as the most powerful predictors, with recent studies demonstrating that LA strain can detect impairment of LA function without LA enlargement and has incremental predictive value for AF over LA enlargement in a variety of cardiac conditions.[16–19] In contrast, despite the role of LV dysfunction as an established predictor for AF, previous studies have not reported an association of LVEF with AF. This finding may reflect the insensitivity of LVEF for mild LV systolic dysfunction. However, we can now assess subclinical LV dysfunction using speckle-tracking, and GLS has powerful prognostic value even if LVEF is preserved.[13,15] Recent studies have suggested GLS to be an independent predictor of AF.[21,22] The present study firstly investigated a comparison of both strains for the risk stratification of AF, and identified that GLS was independently associated with AF and provided incremental predictive value over clinical and LA parameters, including LA strain.

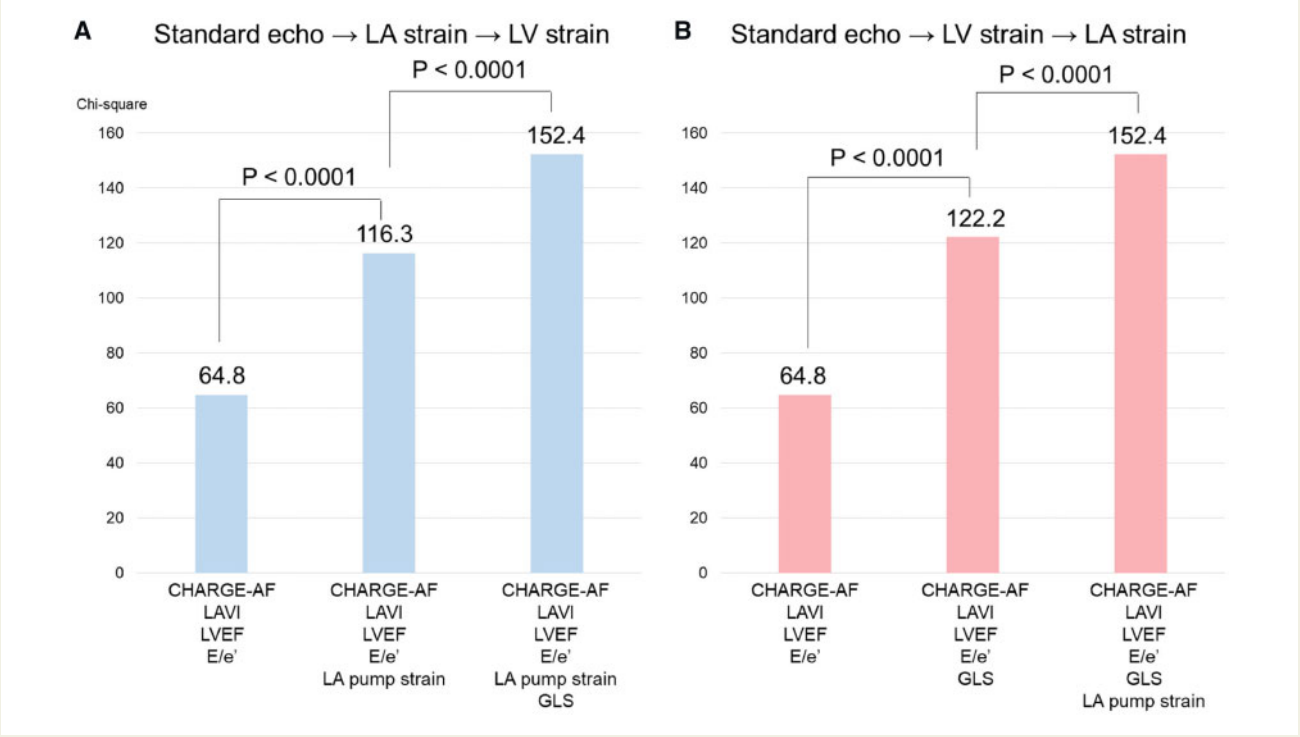


Figure 2 Results of sequential Cox models for the prediction of newly diagnosed AF. (*A*) The initial model based on clinical and standard TTE parameters was significantly improved by the addition of LA pump strain and further improved by adding GLS. (*B*) The same initial model was also significantly improved by the addition of GLS and further improved by adding LA pump strain. AF, atrial fibrillation; GLS, global longitudinal strain; LA, left atrium; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction.

Close relationship between LA and LV mechanics

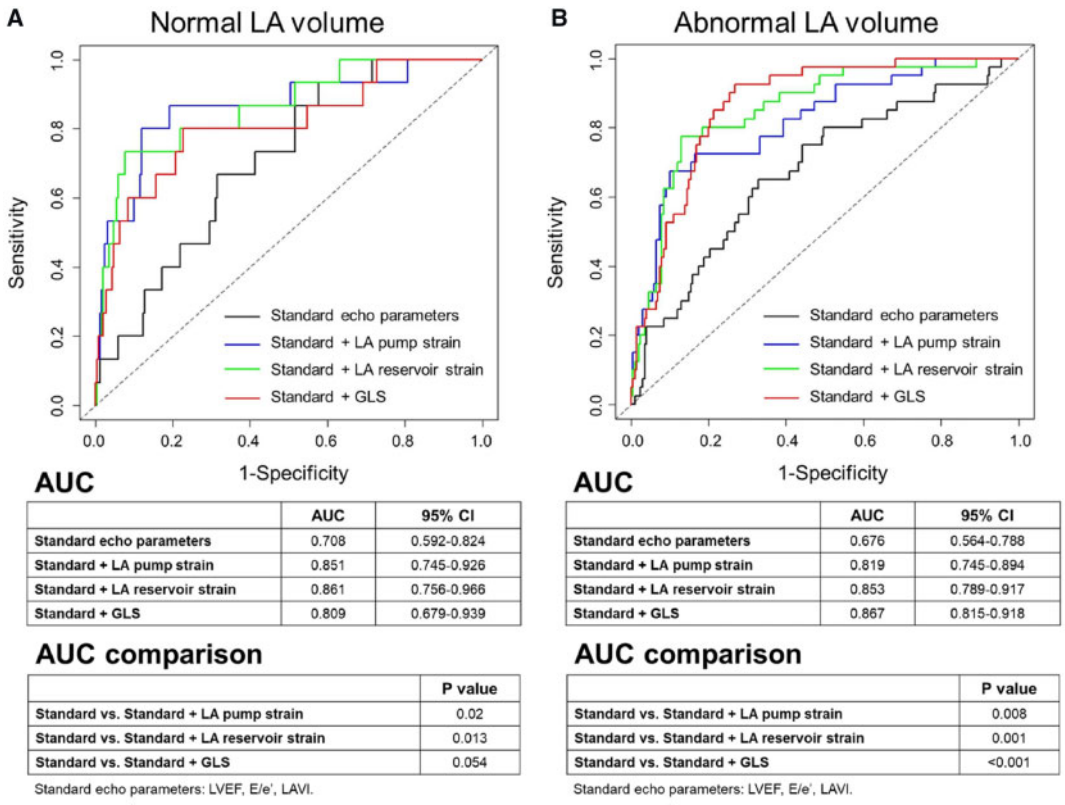
There is a close interplay of LA and LV mechanics because LA function is influenced mainly by LV systole and relaxation.[25,27–30] Barbier *et al.*[27] investigated the determinants of LA reservoir function using an animal model, and verified that LA reservoir function was influenced by LV long-axis shortening. Furthermore, in 843 patients with acute myocardial infarction, Ersboll *et al.*[28] identified the strong correlation between LA reservoir strain and GLS. The results of our study was consisted with previous findings (Supplementary data online, *Table S2*), which suggested that LA reservoir strain as the reflection of LV longitudinal function. On the other hand, LA pump function is less dependent on LV mechanics.[12,27,30] Indeed, LA pump strain was independent of GLS in this study (Supplementary data online, *Table S2*). That was because we attempted to highlight the importance of LA pump strain in this study despite of the fact that most previous studies focused on LA reservoir strain.

Comparison of predictive values between LA and LV strain

The present study revealed that usefulness of both strain measurement was different depends on existing LA enlargement. In patients with LA enlargement, AF was thought to be mainly caused by LA remodelling associated with LV dysfunction because these patients had more traditional AF risks and worse LV function than those with normal LA volumes. That is why priority of GLS was superior to LA pump strain in this subgroup. On the other hand, only LA pump strain not GLS was significantly associated with AF in patients without LA enlargement. In this subgroup, their LV function was completely preserved at the study point, so predictive value of GLS was limited. In addition, some patients in this subgroup might have an atriopathy as the cause of AF (called as lone AF) because these patients were younger and had less risk factors than those with LA enlargement.[19,31] Hubert *et al.*[19] compared LA and LV function between patients with lone AF and healthy controls and identified that there was no significant difference of LVEF and GLS between two groups. Hence, LA strain, rather than GLS was strongly associated with AF. Our results are consistent with these findings. Moreover, Wijesurendra *et al.*[31] proposed that lone AF may be a tissue-specific manifestations of upstream idiopathic cardiomyopathy and AF contributes to make LV function worse via adverse haemodynamics. These findings suggest that LA strain, not LV strain should be assessed when the aetiology of AF is suspected to be atriopathy.

Clinical implications

We summarized our findings as a flowchart for risk stratification of AF in *Figure 5*. At the first place, our results suggested that TTE evaluation is not always essential for risk stratification of AF because no AF occurred in patients with very low AF risk (CHARGE-AF score < 2.1). There has been an ongoing increase the use of echocardiography,[32,33] which has led to increasing healthcare cost and more



AUC

	AUC	95% CI
Standard echo parameters	0.708	0.592-0.824
Standard + LA pump strain	0.851	0.745-0.926
Standard + LA reservoir strain	0.861	0.756-0.966
Standard + GLS	0.809	0.679-0.939

AUC comparison

	P value
Standard vs. Standard + LA pump strain	0.02
Standard vs. Standard + LA reservoir strain	0.013
Standard vs. Standard + GLS	0.054

Standard echo parameters: LVEF, E/e', LAVI.

AUC

	AUC	95% CI
Standard echo parameters	0.676	0.564-0.788
Standard + LA pump strain	0.819	0.745-0.894
Standard + LA reservoir strain	0.853	0.789-0.917
Standard + GLS	0.867	0.815-0.918

AUC comparison

	P value
Standard vs. Standard + LA pump strain	0.008
Standard vs. Standard + LA reservoir strain	0.001
Standard vs. Standard + GLS	<0.001

Standard echo parameters: LVEF, E/e', LAVI.

Figure 3 Results of receiver-operating characteristic curve analysis for prediction newly diagnosed AF in patients with normal LA volumes (LAVI < 34 mL/m^2) (*A*) and patients with abnormal LA volumes (LAVI ≥ 34 mL/m^2) (*B*). AUC, area under the curve; GLS, global longitudinal strain; LA, left atrium; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction.

burden on cardiologists and sonographers. Our strategy may contribute to control overuse of TTE and to improve patients care. When patients have considerable AF risk, TTE screening can provide incremental information for predicting AF over clinical risks. The flowchart shows the more effective and efficient TTE strategy for risk stratification of AF based on our results. Importantly, although GLS provided no incremental value in the patients with normal LA volumes, its predictive value was comparable to LA strain. The assessment of GLS is better established and less time consuming than LA strain, so GLS may be an alternative to LA strain in patients with inability to acquire interpretable LA images or assess LA strain. Long-term remote monitoring for AF is now possible using mobile technologies and implantable recorders, so the selection of patients for these tests may be facilitated by our findings.

Study limitations

There are several study limitations to be addressed. First, the presence study was conducted using a very specific cohort of patients with cryptogenic stroke, so this selection bias may influence external validity in other settings. Further studies using other cohort are needed. In addition, the cut-off values provided by CART analyses in each parameter also need to be externally validated in further studies. Second, for detection of AF during follow-up, most patients were monitored using conventional methods without implantable cardiac monitors in this cohort (only two AF events were detected by implantable cardiac devices). Although our incident rate was similar to previous studies,[34] recent studies demonstrated that detection rates of AF followed using implantable cardiac monitors were higher than those using conventional monitoring in patients with cryptogenic stroke.[34,35] Thus, the number of AF cases is likely underestimated. Finally, strain imaging, like other imaging techniques, is operator-dependent. However, strain computation was feasible in 87% of echocardiograms. We analysed LA strain using software for evaluating the LV, but the difference between vendors and few dedicated atrial strain packages should be considered.

Conclusions

Both LA and LV strain are significantly and independently associated with AF and can provide incremental predictive value over clinical and standard echocardiographic parameters in patients with considerable AF risk.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

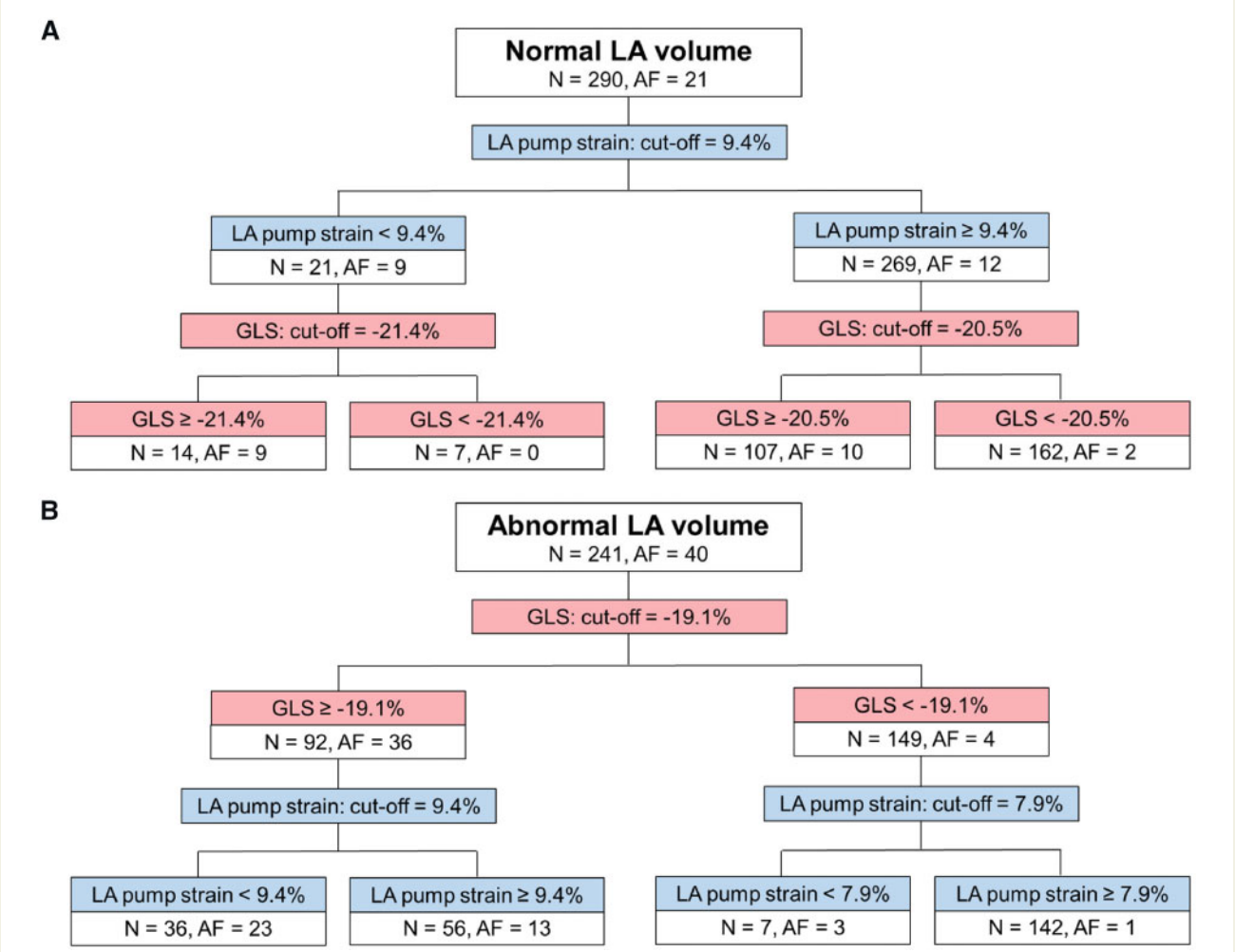


Figure 4 Classification and Regression Tree (CART) analysis between patients with normal LA volumes (LAVI < 34 mL/m^2) (*A*) and abnormal LA volumes (LAVI ≥ 34 mL/m^2) (*B*). AF, atrial fibrillation; GLS, global longitudinal strain; LA, left atrium; LAVI, left atrial volume index.

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References

1. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS *et al*. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;**110**:1042–6.
2. Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. *Chest* 2012;**142**:1489–98.
3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M *et al*. Executive summary: heart disease and stroke statistics–2016 update: a report from the American Heart Association. *Circulation* 2016;**133**:447–54.
4. Cha YM, Redfield MM, Shen WK, Gersh BJ. Atrial fibrillation and ventricular dysfunction: a vicious electromechanical cycle. *Circulation* 2004;**109**:2839–43.
5. Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Takemoto Y *et al*. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. *Mayo Clin Proc* 2001;**76**:467–75.
6. Tsang TS, Gersh BJ, Appleton CP, Tajik AJ, Barnes ME, Bailey KR *et al*. Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. *J Am Coll Cardiol* 2002;**40**:1636–44.
7. Fatema K, Barnes ME, Bailey KR, Abhayaratna WP, Cha S, Seward JB *et al*. Minimum vs. maximum left atrial volume for prediction of first atrial fibrillation or flutter in an elderly cohort: a prospective study. *Eur J Echocardiogr* 2009;**10**:282–6.
8. Vlachos K, Letsas KP, Korantzopoulos P, Liu T, Georgopoulos S, Bakalakos A *et al*. Prediction of atrial fibrillation development and progression: current perspectives. *World J Cardiol* 2016;**8**:267–76.
9. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA *et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;**22**:107–33.
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–70.
11. Marwick TH. Methods used for the assessment of LV systolic function: common currency or tower of Babel? *Heart* 2013;**99**:1078–86.
12. Hoit BD. Left atrial size and function: role in prognosis. *J Am Coll Cardiol* 2014;**63**:493–505.
13. Motoki H, Borowski AG, Shrestha K, Troughton RW, Tang WH, Thomas JD *et al*. Incremental prognostic value of assessing left ventricular myocardial mechanics in patients with chronic systolic heart failure. *J Am Coll Cardiol* 2012;**60**:2074–81.
14. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart* 2014;**100**:1673–80.

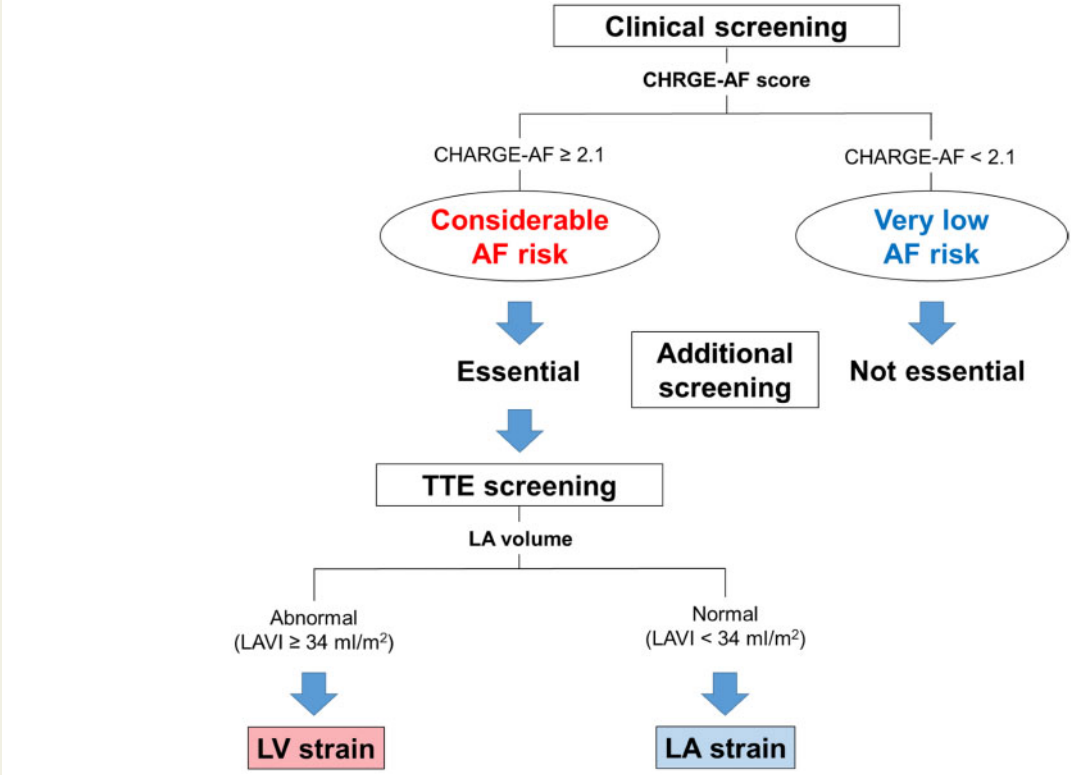

Figure 5 The AF risk stratification strategy using clinical and echocardiographic findings. AF, atrial fibrillation; LA, left atrium; LAVI, left atrial volume index; TTE, transthoracic echocardiography.

15. Russo C, Jin Z, Elkind MS, Rundek T, Homma S, Sacco RL *et al.* Prevalence and prognostic value of subclinical left ventricular systolic dysfunction by global longitudinal strain in a community-based cohort. *Eur J Heart Fail* 2014;**16**:1301–9.
16. Pathan F, Sivaraj E, Negishi K, Rafiudeen R, Pathan S, D'Elia N *et al.* Use of atrial strain to predict atrial fibrillation after cerebral ischemia. *JACC Cardiovasc Imaging* 2018;**11**:1557–65.
17. Hirose T, Kawasaki M, Tanaka R, Ono K, Watanabe T, Iwama M *et al.* Left atrial function assessed by speckle tracking echocardiography as a predictor of new-onset non-valvular atrial fibrillation: results from a prospective study in 580 adults. *Eur Heart J Cardiovasc Imaging* 2012;**13**:243–50.
18. Abhayaratna WP, Fatema K, Barnes ME, Seward JB, Gersh BJ, Bailey KR *et al.* Left atrial reservoir function as a potent marker for first atrial fibrillation or flutter in persons > or = 65 years of age. *Am J Cardiol* 2008;**101**:1626–9.
19. Hubert A, Galand V, Donal E, Pavin D, Galli E, Martins RP *et al.* Atrial function is altered in lone paroxysmal atrial fibrillation in male endurance veteran athletes. *Eur Heart J Cardiovasc Imaging* 2018;**19**:145–53.
20. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G *et al.* Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Eur J Echocardiogr* 2011;**12**:167–205.
21. Russo C, Jin Z, Sera F, Lee ES, Homma S, Rundek T *et al.* Left ventricular systolic dysfunction by longitudinal strain is an independent predictor of incident atrial fibrillation: a community-based cohort study. *Circ Cardiovasc Imaging* 2015;**8**: e003520.
22. Bonapace S, Valbusa F, Bertolini L, Zenari L, Canali G, Molon G *et al.* Early impairment in left ventricular longitudinal systolic function is associated with an increased risk of incident atrial fibrillation in patients with type 2 diabetes. *J Diabetes Complications* 2017;**31**:413–18.
23. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ *et al.* Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;**13**:429–38.
24. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB *et al.* Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013;**2**: e000102.
25. Vieira MJ, Teixeira R, Goncalves L, Gersh BJ. Left atrial mechanics: echocardiographic assessment and clinical implications. *J Am Soc Echocardiogr* 2014;**27**: 463–78.
26. Alonso A, Norby FL. Predicting atrial fibrillation and its complications. *Circ J* 2016;**80**:1061–6.
27. Barbier P, Solomon SB, Schiller NB, Glantz SA. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. *Circulation* 1999; **100**:427–36.
28. Ersboll M, Andersen MJ, Valeur N, Mogensen UM, Waziri H, Moller JE *et al.* The prognostic value of left atrial peak reservoir strain in acute myocardial infarction is dependent on left ventricular longitudinal function and left atrial size. *Circ Cardiovasc Imaging* 2013;**6**:26–33.
29. Cameli M, Mandoli GE, Loiacono F, Dini FL, Henein M, Mondillo S. Left atrial strain: a new parameter for assessment of left ventricular filling pressure. *Heart Fail Rev* 2016;**21**:65–76.
30. Ramkumar S, Yang H, Wang Y, Nolan M, Negishi T, Negishi K *et al.* Association of the active and passive components of left atrial deformation with left ventricular function. *J Am Soc Echocardiogr* 2017;**30**:659–66.
31. Wijesurendra RS, Liu A, Eichhorn C, Ariga R, Levelt E, Clarke WT *et al.* Lone atrial fibrillation is associated with impaired left ventricular energetics that persists despite successful catheter ablation. *Circulation* 2016;**134**:1068–81.
32. Fonseca R, Otahal P, Wiggins N, Marwick TH. Growth and geographical variation in the use of cardiac imaging in Australia. *Intern Med J* 2015;**45**:1115–27.
33. Fonseca R, Jose K, Marwick TH. Understanding decision-making in cardiac imaging: determinants of appropriate use. *Eur Heart J Cardiovasc Imaging* 2018;**19**: 262–8.
34. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA *et al.* Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**: 2478–86.
35. Ziegler PD, Rogers JD, Ferreira SW, Nichols AJ, Richards M, Koehler JL *et al.* Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world cryptogenic stroke population. *Int J Cardiol* 2017;**244**:175–9.