Targeted echocardiographic screening for subclinical left ventricular dysfunction to prevent incident heart failure

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A thesis submitted for the degree of *Doctor of Philosophy*

Monash University 2020

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The Baker Heart and Diabetes Institute

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Supervision

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Abstract

Background: Heart failure (HF) is a global disease that has reached epidemic proportions. Its aetiologies are many but in high-income countries, ageing coupled with cardiovascular risk factors set the scene for an often-insidious process. An asymptomatic phase of left ventricular dysfunction (LVD), detectable by echocardiography, precedes symptom onset. Identification and treatment of this phase has proven beneficial in preventing the onset of symptomatic HF. However, our understanding of LVD pathophysiology and phenotypes, how LVD is echocardiographically detected, and how it is treated has evolved. So must our approach to targeted intervention.

Hypothesis: Screening individuals at high risk of HF using advanced echocardiographic techniques to identify LVD that prompts treatment, will reduce incident heart failure.

Aims

i. Identify the most appropriate screening population based on predicted HF risk
ii. Explore whether a pre-screening test; a novel signal-processed ECG, is superior to clinical risk prediction
iii. Establish the role of and appropriate cut-offs for echocardiographic deformation (strain) imaging of the left ventricle and left atrium in the definition of subclinical LVD
iv. Test a process of selection for echocardiographic screening coupled with echo-guided spironolactone therapy to reduce incident HF

Methods: The main methodology will be echocardiographic techniques to identify HF, and the primary hypothesis will be tested in a community-based randomized controlled trial (RCT) of elderly (≥65 years) with ≥ 1 non-ischemic risk factor for HF. Randomisation will be to either advanced echocardiographic evaluation plus spironolactone if LVD is present, or usual care. The primary outcome is incident heart failure based on Framingham criteria with the secondary outcomes of functional capacity and change in LV function. Other chapter analyses (excluding literature review and meta-analysis) will use cross-sectional data from the RCT or longitudinal data from a similar community cohort previously collected in Tasmania combined with the RCT.

Results and Conclusions: HF risk is heterogenous and addition of socioeconomic status, functional capacity and comorbidities not considered in established clinical HF risk scores offer improvement. Strain imaging provides a reliable and prognostically important evaluation of LV systolic and diastolic function. Spironolactone therapy

instituted on detection of early subclinical LVD cannot be advocated due to poor tolerability.

Declaration

This thesis is an original work of my research and 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: ELIZABETH POTTER

Date: 2/12/2020

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 3 submitted publications. The core theme of the thesis is screening for and treatment of subclinical left ventricular dysfunction. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the imaging research team of the Baker Heart and Diabetes Institute under the supervision of Professor 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.

In the case of *all chapters excluding 1, 8 and 10 (not published or submitted)* my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of contribution	Co-author(s), Monash student Y/N
2	Impact of socioeconomic status incident heart failure and left ventricular dysfunction: Systematic review and meta-analysis	Published Eur Heart J Qual Care Clin Outcomes, 2019 https://doi.org/10.1093/ehjqcco/qcy047	70% - study concept and design, data gathering/appraisal/extraction, statistical analysis, manuscript preparation and editing	Ingrid Hopper – 5% data appraisal, manuscript editing Jonathan Sen – 10% data extraction Agus Salim – 5% statistical oversight Thomas Marwick – 10% study concept, manuscript editing	No
3	Machine learning interpretation of energy waveform ECG: a screening test for asymptomatic left ventricular dysfunction	Submitted JACC: Cardiovascular Imaging	65% - study concept and design, data collection, analysis, manuscript preparation and editing	Carlos Rodriguez – 10% data analysis, manuscript editing David Ascher – 5% data analysis, manuscript editing Walter Abhayaratna – 2% data collection and manuscript editing Partho Sengupta – 3% data collection and manuscript editing Thomas Marwick – 15% study concept and design, manuscript preparation and editing	No
4	Measurement of functional capacity to discriminate clinical from subclinical heart failure in patients ≥65 years old.	Published Am J Cardiol, 2020 https://doi.org/10.1016/j.amjcard.2020.03.051	60% - study concept and design, data collection, statistical analysis, manuscript preparation and editing	Hong Yang – 10% data collection Leah Wright – 8% data collection Bing Wang – 2% data collection Thomas Marwick – 20% study concept and design, data analysis, manuscript preparation and editing	No
5	Assessment of left ventricular function by echocardiography: The	Published JACC: Cardiovascular Imaging, 2018 https://doi.org/10.1016/j.jcmg.2017.11.017	65% - design, data collection, manuscript preparation and editing	Thomas Marwick – 35% concept, design, manuscript preparation and editing	No

	case for routinely adding global longitudinal strain to ejection fraction				
6	Normal range of global longitudinal strain in the elderly: The impact of subclinical disease	Epub ahead of print JACC: Cardiovascular Imaging, 2020 https://doi.org/10.1016/j.jcmg.2020.07.014	65% - concept, design, data collection and analysis, manuscript preparation	Leah Wright – 5% data collection Hong Yang – 5% data collection Thomas Marwick 25% – concept, manuscript editing	No
7	Association of asymptomatic diastolic dysfunction assessed by left atrial strain with incident heart failure	Published JACC: Cardiovascular Imaging, 2020 https://doi.org/10.1016/j.jcmg.2020.04.028	65% - concept, design, data collection and analysis, manuscript preparation	Satish Ramkumar – 5% data collection Hiroshi Kawakami – 3% data collection Hong Yang – 3% data collection Leah Wright – 2% data collection Tomoko Negishi – 2% data collection Thomas Marwick – 20% concept, design, manuscript preparation and editing	SR – Yes Otherwise no
9	Association of subclinical heart failure and atrial fibrillation with mild cognitive impairment: Implications for screening	Submitted, BMJ Open	70% - concept, design, data collection and analysis, manuscript preparation and editing	Satish Ramkumar – 10% data collection Leah Wright – 5% data collection Thomas Marwick – 15% concept, manuscript editing	SR – Yes Otherwise no

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

Student name: Elizabeth Potter

Student signature: **Date: 2/12/2020**

I 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 name: Thomas Marwick

Main Supervisor signature: **Date: 2/12/2020**

Publications during candidature

First author

1. Potter EL, Yang H, Wright L, Wang B, Marwick TH. Measurement of Functional Capacity to Discriminate Clinical from Subclinical Heart Failure in Patients ≥65 Years of Age. Am J Cardiol 2020; 127: 84-91.

2. 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. J Am Coll Cardiol Img 2020; 13(11): 2316-2326.

3. Potter EL, Wright L, Yang H, Marwick TH. Normal Range of Global Longitudinal Strain in the Elderly: The Impact of Subclinical Disease. J Am Coll Cardiol Img 2020. Epub ahead of print https://doi.org/10.1016/j.jcmg.2020.07.014.

4. Potter EL, Hopper I, Sen J, Salim A, Marwick TH. Impact of socioeconomic status on incident heart failure and left ventricular dysfunction: systematic review and meta-analysis. Eur Heart J Qual Care Clin Outcomes 2019; 5(2): 169-179.

5. Potter EL and Marwick TH. Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction. J Am Coll Cardiol Img 2018; 11(2): 260-274.

6. Potter EL, et al. Evaluation of pharmacist-led physician-supported inpatient deprescribing model in older patients admitted to an acute general medical unit. Austral J Ageing 2019; 38(3): 206-210.

Contributing author

7. Ramkumar S, Pathan F, Kawakami H, Ochi A, Yang, H, **Potter EL**, Marwick TH. Impact of disease stage on the performance of strain markers in the prediction of atrial fibrillation. Int J Cardiol 2020. Epub ahead of print 10.1016/j.ijcard.2020.09.057

8. Nerlekar N, Thakur U, Lin A, Koh J, **Potter EL**, Liu D, Muthalaly, RG, Rashid HN, Cameron JD, Dey D, Wong DTL (2020). The Natural history of Epicardial Adipose Tissue Volume and Attenuation: A long-term prospective cohort follow-up study. Nat Sci Reports 10(1): 7109.

9. 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. J Am Soc Echocardiogr 2019; 32(10): 1259-1267.

10. 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 2018; 49 (10), 1244-1251.

Conference presentations

(First author only)

ACC Scientific Sessions 2018

Poster presentation - Potter EL, Perrera N, Wang Y, Marwick TH. *Cognitive impairment is not associated with asymptomatic left ventricular dysfunction as assessed by global longitudinal strain in elderly patients at risk of heart failure.*

ESC Congress 2018

Best poster presentation – Potter EL, Yang H, Marwick TH. *Roles of abnormal filling pattern and myocardial dysfunction in development of overt heart failure in at-risk elderly subjects.*

Poster presentation - Potter EL, Yang H, Marwick TH. *Recognition of Stage Heart Failure in the community: Combined assessment with six-minute walk test and echocardiography.*

CSANZ Annual Scientific Sessions 2018

Oral presentation – Potter EL, Ramkumar S, Yang H, Marwick TH. *Left Atrial Strain and Incident Heart Failure: Validation of LA strain-defined diastolic dysfunction grade and comparison with current ASE guidelines.*

Oral presentation – Potter EL, Yang H, Marwick TH. *Identification of early Stage C Heart Failure in the Community: Combined Assessment with Six-Minute Walk Test and Echocardiography*

Poster presentation – Potter EL, Yang H, Marwick TH. *Risk of heart failure in the elderly: Roles of impaired relaxation and myocardial dysfunction*

ACC Scientific Sessions 2019

Poster presentation – Potter EL, Marwick TH. *Detection of Stage B Heart Failure in the Community Using Energy Waveform ECG*

ESC Congress 2019

Poster presentation – Potter EL, Ramkumar S, Kawakami H, Wright L, Marwick TH. *Preclinical Diastolic Dysfunction Assessed by Left Atrial Strain and Association with Incident Heart Failure*

Poster presentation – Potter EL, Rodrigues C, Ascher D, Marwick TH. *Machine learning applied to energy waveform ECG for prediction of subclinical myocardial dysfunction*

ACC Scientific Sessions 2020

Poster presentation - Potter EL, Rodrigues C, Ascher D, Marwick TH. *Machine learning applied to energy waveform ECG for prediction of subclinical LV dysfunction in the community*

ESC Congress 2020

Poster presentation – Potter EL, Woessner M, Marwick TH. *Reduced NT-proBNP threshold for risk prediction in high-risk elderly with subclinical heart failure: Support from cardiopulmonary exercise testing*

CSANZ Annual Scientific Sessions 2020

Poster presentation – Potter EL, Woessner M, Neil C, Marwick TH, Howden E. *Cardiopulmonary exercise testing identifies reduced ventilatory efficiency in subclinical heart failure*

Poster presentation - Potter EL, Woessner M, Marwick TH. *Reduced NT-proBNP threshold for risk prediction in high-risk elderly with subclinical heart failure: Support from cardiopulmonary exercise testing*

AHA Scientific Sessions 2020

Poster presentation - Potter EL, Woessner M, Neil C, Marwick TH, Howden E. *Ventilatory Inefficiency associated with Stage A Heart Failure*

Scholarships, awards, and funding

This research was supported by an Australian Government Research Training Program (RTP) Scholarship as well as a Monash Graduate Research Excellence scholarship. Prior to securing this funding, I was supported by a Baker Institute Bright Sparks Scholarship.

Additional funding:

- *2018 Cardiac Society of Australia and New Zealand ASM Travelling Fellowship*
- *2018 Monash University Travel Grant*

Acknowledgements

Firstly, I would like acknowledge Prof Tom Marwick. Without his supervision and support this work would not have been possible. I have received an outstanding research education and one that was given with generosity, despite the huge demands on his time. From continually challenging and inspiring me to diligently removing dangling participles, Tom has ensured I am now well positioned as a future clinician-researcher. I look forward to our ongoing collaboration.

I thank A/Prof Ingrid Hopper for the perspective on work and life she has offered throughout this process. Her practical advice and encouragement have meant a lot. I thank A/Prof Chris Neil for reaching out to me and diverting me down this path. As part of Tom's team, I have been fortunate to work with Dr Leah Wright, sonographer extraordinaire, whose expertise I have called on many times during this PhD. I would like to thank Lisa Riddell for her work wrangling myself and the rest of the PhD students (amongst her numerous other responsibilities) into Tom's schedule and I apologise for reliably running over time in meetings! I have found camaraderie in the cosy PhD room aka the fishbowl. There I have made great friends while cursing reviewers/statistics/closing of good cafes and celebrating publications and any glimmers of hope! The Vic-ELF trial team have been a pleasure to work with – Joanne Harris, Georgia Stephenson and Mary Woessner.

Collaborations within the Baker Heart and Diabetes Institute have been vital, and I thank Dr Erin Howden, Mr Carlos Rodrigues and A/Prof David Ascher for their expertise and time.

During this PhD I have had the unwavering support of my husband John and the happy distraction of welcoming my first child Hugh. With their support I have developed, not with great ease, the ability to balance research, clinical work, and a young family. The fiercely insightful Ruth Bader Ginsburg attributed her law school success to her baby daughter. Long before the term 'work-life balance' was coined she wrote: "*Each part of my life provided respite from the other and gave me a sense of proportion that classmates trained only on law studies lacked."* Spot on RBG.

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Abbreviations

6MWT = six-minute walk test

6MWD = six-minute walk distance

ACE-I = angiotensin converting enzyme inhibitor

AF = atrial fibrillation

AMI = acute myocardial infarction

AS = aortic stenosis

ALVD = asymptomatic left ventricular dysfunction

AR = aortic regurgitation

ARB = angiotensin receptor blocker

ARIC = atherosclerosis risk in communities

AUC = area under curve

BP = blood pressure

BMI = body mass index

BNP = B-type natriuretic peptide

BSA = body surface area

CAD = coronary artery disease

CART = classification and regression tree

COPD = chronic obstructive pulmonary disease

CHD = coronary heart disease

CI = confidence interval

CMR = cardiac magnetic resonance imaging

CTRCD = cancer therapeutics related cardiac dysfunction

CVD = cardiovascular disease

CWT = continuous wave transforms

DASI = Duke activity status index

DD = diastolic dysfunction

DM = diabetes mellitus

ECG = electrocardiogram

GDMT = guideline directed medical therapy

ewECG = energy waveform ECG

GLS = global longitudinal strain

HCM = hypertrophic cardiomyopathy

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

IHD = ischemic heart disease

IMD = index of multiple deprivation

IQR = interquartile range

IR = impaired relaxation

IRR = incidence rate ratio

LA = left atrium

LAE = left atrial enlargement

LARS = left atrial reservoir strain

LARS-DD = left atrial reservoir strain-defined diastolic dysfunction

LAVI = left atrial volume indexed to body surface area

LGE = late gadolinium enhancement

LVD = left ventricular dysfunction

LVDD = left ventricular diastolic dysfunction

LVH = left ventricular hypertrophy

MCI = mild cognitive impairment

METS = metabolic equivalents

MoCA = Montreal cognitive assessment

MR = mitral regurgitation

NT-proBNP = N-terminal pro B-type natriuretic peptide

OR = odd ratio

PHQ = patients health questionnaire

RAS = renin-angiotensin system

RF = random forest

ROC = receiver operating characteristic

RR = respiratory rate

SAHF = Stage A HF

SBHF = Stage B HF

SCHF = Stage C HF

SCI = silent cerebral infarct

SD = standard deviation

SES = socioeconomic status

SEIFA = socioeconomic indexes for areas

T2DM = type 2 diabetes mellitus

$\dot{V}O_2$ = oxygen uptake

Preface

Heart failure (HF) is a major cause of morbidity and mortality both worldwide and in Australia. The prevalence of HF in the Australian population is around 2% and at least the same proportion, particularly in at risk groups, will have asymptomatic or subclinical left ventricular dysfunction (LVD); a prelude to symptomatic HF (1). HF risk factors, such as type 2 diabetes mellitus and obesity are rising at an alarming rate and this threatens to increase the burden of HF (2). At present two thirds of patients with HF are over the age of 65 (1). This not only has implications for future upwards trends in HF prevalence but for the medical complexity of affected individuals. This thesis will focus on this age group.

Not all patients with HF risk factors will develop HF, but those who go on to develop subclinical LVD are at significantly high risk (3-8). This asymptomatic but manifest stage of disease offers a window for intervention and therefore prevention (9). Identification of subclinical LVD requires echocardiographic imaging. However, at present, standard of care of those with HF risk factors (excluding ischemic heart disease) does not include echocardiography. Neither consensus appropriate use criteria nor Medicare rebate criteria endorse echocardiography for detection of LVD in selected diabetic, obese and hypertensive patients where clinical signs and symptoms are absent (10). The reason for this discrepancy is that we currently lack evidence that shows benefit from early intervention in a non-ischemic subclinical LVD population.

The first step in building this evidence is selecting those with HF risk factors, who have the highest HF risk, for assessment of cardiac function i.e. targeted echocardiographic screening. Given that 82% of over 67 year-olds in the community either have HF risk factors (with normal LV function) or subclinical LVD (the majority would not have this identified routinely) (11), the economic consequence of screening the majority of this age group is prohibitive. Accurate risk prediction tools are therefore needed to, in the first instance, direct recruitment for clinical trials, and subsequently (should benefit be proven) direct echocardiographic screening both on an individual and population level. Also critical at the selection for screening stage is the determination of symptomatic status. As early symptoms may be unrecognized or dismissed, an objective measure would be preferable, and this thesis investigates functional capacity assessment in this role.

The second step is to utilize suitable echocardiographic parameters to identify subclinical LVD. Current guideline definitions are insensitive to early signals of myocardial disease and presumably the earliest stages are the most amenable to treatment. Strain imaging or speckle-tracking echocardiography measures myocardial deformation during the cardiac cycle and is a reliable and prognostically robust measure of LV systolic function. Abnormalities in the most well studied strain measure, LV global longitudinal strain (GLS) are apparent in the presence of normal LV ejection fraction and confer a poorer prognosis (12). Left atrial (LA) strain is emerging as a single measure of LV diastolic function and diastolic dysfunction should be considered part of the subclinical LVD definition. This thesis will advance understanding of the use of strain imaging in defining and directing therapy in subclinical LVD.

Finally, once early LVD is defined and detected, the question becomes if and what therapeutic intervention will be of benefit. The ultimate metric of benefit would be reduced rates of progression to symptomatic HF. Secondary outcomes – functional capacity and cardiac function are also relevant. In this thesis a randomized trial, the Victorian study of Echocardiographic detection of Left ventricular dysFunction (Vic-ELF), will test a strategy of screening, detection, and treatment.

Aims

The aims of this thesis are to:

i. Refine selection for echocardiographic screening for LV dysfunction
    a. Evaluate non-traditional markers of HF risk – socioeconomic status, functional capacity.
    b. Evaluate the discriminative ability of an established HF risk score, derived from the general population, in the population of interest and establish if it can be improved upon.
ii. Evaluate the ability of a novel signal-processed ECG technology as a pre-screening tool for subclinical LVD
iii. Advance understanding of the use of strain imaging in subclinical LVD
    a. Does LV global longitudinal strain decline with age?
    b. What is the independent prognostic significance of left atrial strain and how can it be used in the assessment of diastolic function?
    c. How can strain imaging integrate into clinical decision-making in subclinical LVD?
iv. Establish whether echocardiography-guided spironolactone therapy prevents incident HF in elderly with HF risk factors
    a. Establish whether this strategy improves functional capacity and cardiac function.
v. Investigate the potential impact of cognitive impairment on a screening and management process and whether there are links with strain markers of subclinical LVD

Thesis Structure

The thesis is structured into 5 thematic parts. The first 3 parts are arranged in sequence to mirror the steps in the strategy of HF prevention proposed in this thesis. The fourth part circles back to risk prediction based on results from part 1 and part 3. An illustration of the thesis structure is shown (Figure 1-0).

Chapter 1 – The burden of HF is introduced along with the paradigm surrounding its evolution and progression. This sets the framework for defining and identifying a subclinical phase which offers a window for specific interventions. Current evidence for screening is appraised and knowledge gaps identified.

PART 1: How should we select patients for subclinical LV dysfunction screening?

Chapter 2 – The impact of socioeconomic status (SES) on incident heart failure and LVD is systematically reviewed and meta-analyzed. The effect size for difference metrics of individual level and area level SES are determined. The aim is to be able to estimate what the impact may be on an individuals' risk (independent of traditional risk factors), which could be incorporated into risk prediction tools as well as to geographically direct HF prevention programs.

Chapter 3 – One prior study suggests that functional capacity may be a HF risk marker (13). Furthermore, it is important to ensure that those who are potentially suitable for screening do not already have unrecognized HF symptoms. To investigate whether there is an objective marker of symptom status in apparent subclinical LVD, the independent prognostic importance of reduced functional capacity with regards incident HF is analyzed. Reduced functional capacity – as a marker of an early symptomatic state – is measured by the Duke activity status index (questionnaire) and the six-minute walk test. This aims to improve on HF guidelines that advocate for patients with LVD to self-appraise their symptom status, which may be insensitive for several reasons. If early symptoms exist, then this has implications for disease stage and management. Longitudinal data from the RCT (chapter 8) and a comparable Tasmanian trial (Tas-ELF (14)) are used.

Chapter 4 – Moving on from risk prediction as a selection method, this chapter investigates the ability of a novel screening test that could be applied prior to echocardiogram. The purpose is to detect manifest disease using a standard surface ECG that has been signal processed. Signal processing aims to reveal abnormalities not appreciable on the standard trace, however hundreds of variables are generated. A supervised machine-learning method was used for this high dimensionality data to evaluate accuracy of prediction of, but most importantly sensitivity for, known LVD. Data came from the baseline ECGs and echocardiograms recorded as part of the RCT (Chapter 8) and validated with an external dataset.

PART 2: Echocardiographic measures to identify subclinical LV dysfunction

Chapter 5 – This contemporary narrative review presents evidence in support of incorporating LV global longitudinal strain (GLS), a sensitive marker of LV systolic dysfunction, into routine echocardiographic practice and the definition of subclinical LVD. The utility of GLS is as a strong prognostic and complementary metric to LV ejection fraction (LVEF) but its uptake into routine practice is compromised by limited data regarding impact on clinical decision-making. Chapter 8 seeks to address this gap in knowledge.

Chapter 6 – The impact of aging on the reference range for GLS is uncertain. This chapter establishes whether ageing beyond the age of 65, in the absence of myocardial disease (elevated NT-proBNP), is associated with decline in GLS. GLS is compared by age tertiles further divided by NT-proBNP (normal/elevated) using cross-sectional data from chapter 8 in combination with Tasmanian (Tas-ELF) data. The analysis supports the single-cut-off for abnormal GLS used in chapter 8.

Chapter 7 – While GLS is a measure of LV systolic function, left atrial reservoir strain (LARS), a measure of LA reservoir function (passive stretch during LA filling), reflects LV diastolic function and may precede other diastolic abnormalities, particularly LA remodelling. This chapter establishes the independent prognostic value of LARS with respect to incident HF and how it could be integrated into current diastolic function guidelines. While the findings of this chapter contribute to growing evidence of the

utility of this measure, for the purposes of this thesis LARS will not be used in the definition of subclinical LVD tested in the RCT (chapter 8).

PART 3: Trialling a risk-based strategy of heart failure prevention

Chapter 8 – This chapter tests the central hypothesis of the thesis. It is an RCT (the VICtorian study of Echocardiographic detection of subclinical LV dysFunction; Vic-ELF) with a PROBE design that tests whether randomisation to advanced echocardiography (strain imaging and detailed diastolic assessment) to identify subclinical LVD – triggering spironolactone treatment, prevents incident HF compared to standard echocardiography and continued primary care. Recruitment will take place in the community via primary care and advertising. The population of interest has two important features: 1) a history or symptoms of ischemic heart disease (IHD) must be absent as patients with IHD routinely undergo echocardiography (thus a screening strategy is not applicable to them) and 2) an LVEF of <40% and/or >moderate valve disease (although fulfilling criteria for subclinical LVD) are exclusions based on established guideline-directed management in these scenarios.

Selection will be on the basis of age ≥65 years with at least one non-ischemic HF risk factor (hypertension, type 2 diabetes mellitus or obesity). There must be no symptoms or signs of existing heart failure. At least intermediate risk of LVD must be present based on six-minute walk test (6MWT) and the atherosclerosis risk in communities (ARIC) HF risk score (13). The primary outcome is incident heart failure assessed by Framingham criteria. Secondary outcomes are functional capacity (6MWT) and change in LV function. Importantly the tolerability of spironolactone in this elderly cohort will be assessed.

Chapter 9 – This chapter investigates the prevalence of mild cognitive impairment (MCI) in the screening population given the potential impact on self-management that may be required as a result of LVD detection, as well as on the design of a formal screening program. A Vic-ELF sub-study is detection of subclinical atrial fibrillation (AF), using hand-held single electrode ECG devices, and the effect of cognitive impairment on adherence to self-monitoring is investigated. A novel association between MCI and subclinical AF is sought as well as between MCI and LV GLS and LARS. The latter is to build on conflicting evidence of association between cardiac and

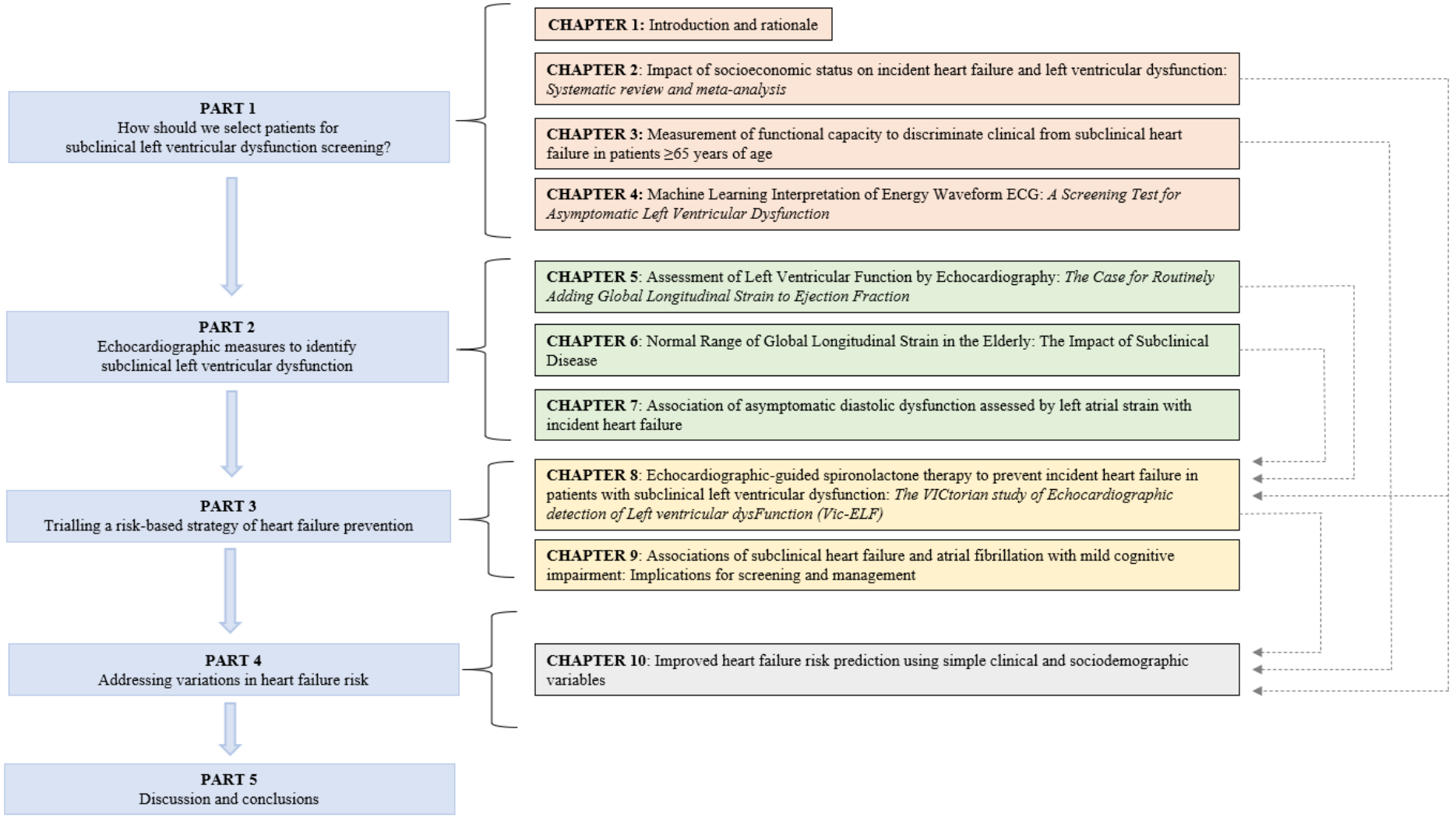
brain function, independent of vascular risk factors. This cross-sectional study uses baseline Vic-ELF data.

PART 4: Addressing variations in heart failure risk

Chapter 10 – To address the observed differences in rate of incident HF between Vic-ELF and Tas-ELF as well as the discrepancy between predicted HF rate, calculated by the ARIC HF risk score, this study combines longitudinal data from the trials to evaluate improvements in risk prediction gained by the inclusion of readily available clinical (AF, chronic obstructive pulmonary disease), functional capacity (Duke activity status index, 6MWT), psychological (depression, anxiety), SES (SEIFA score) and geographic (remoteness index) variables. As well as a new predictive model, a classification and regression tree (CART) analysis is undertaken to evaluate a sequence of importance of such variables in differentiating high from low risk, that may inform on approaches to screening.

Chapter 11 – Chapter 11 concludes the thesis by appraising the significance of the findings and how they could be further investigated.

Figure 1-0: Thesis structure. Dotted grey lines indicate where findings influence rationale and content of subsequent chapters.



1 Introduction and rationale

1.1 The epidemiology of heart failure

Heart failure (HF) is a major cause of morbidity and mortality both worldwide and in Australia. The prevalence of HF in the Australian population is estimated to be between 1-2%, and at least the same proportion have asymptomatic left ventricular dysfunction (LVD), a prelude to overt symptomatic HF (1). These data are in line with other countries particularly the United States (US) (15). Approximately 30,000 people per year in Australia are newly diagnosed with HF (16) but more recent estimates put this number at 61,000 (17). Major risk factors for heart failure include coronary heart disease (CHD), hypertension, type 2 diabetes mellitus (T2DM) and obesity. In the past 40 years advances in treatment and prevention of CHD have resulted in a 70% reduction in CHD death rates, and incidence has been largely stable (18,19). There is therefore increased survivorship with ongoing risk of consequent heart failure. More significant, however, is the impact of rises in prevalent obesity and T2DM. In Australia, 32% of adults are obese (20) and in the past 20 years the prevalence of T2DM has risen by 42% in the elderly (> 65 years) (20).

Significant pharmacotherapeutic advances in HF have translated into declining death rates (21). Furthermore, population studies in the US (i.e. Olmstead County and the Framingham Heart Study (FHS)), demonstrated that between 1979 and 2000 the incidence of HF either remained stable or even declined to a small degree amongst women (22,23). Conversely, when incidence in the elderly alone is considered, it appears that incidence is rising. Between 1970 and 1994 the age-standardized incidence of HF in a US population of ~10, 000 over 65 years old, increased by 14%. (24). In a more recent UK study of 4 million individuals from 2002-2014, age-standardized HF incidence declined by 7%, although an increase in incidence was observed for the very elderly (25). Indeed, the effect of rising rates of obesity and T2DM on incident HF may not yet be apparent. Nonetheless, data consistently demonstrate that prevalence of HF is increasing. The aforementioned UK study observed a 23% increase in prevalence (25) and US data projections made in 2013 suggest HF prevalence will increase 43% by 2030, a conservative estimate given this projection only accounted for population aging (26).

The ‘heart failure epidemic’ is felt most acutely by socioeconomically deprived members of society, with many studies demonstrating socioeconomic gradients in

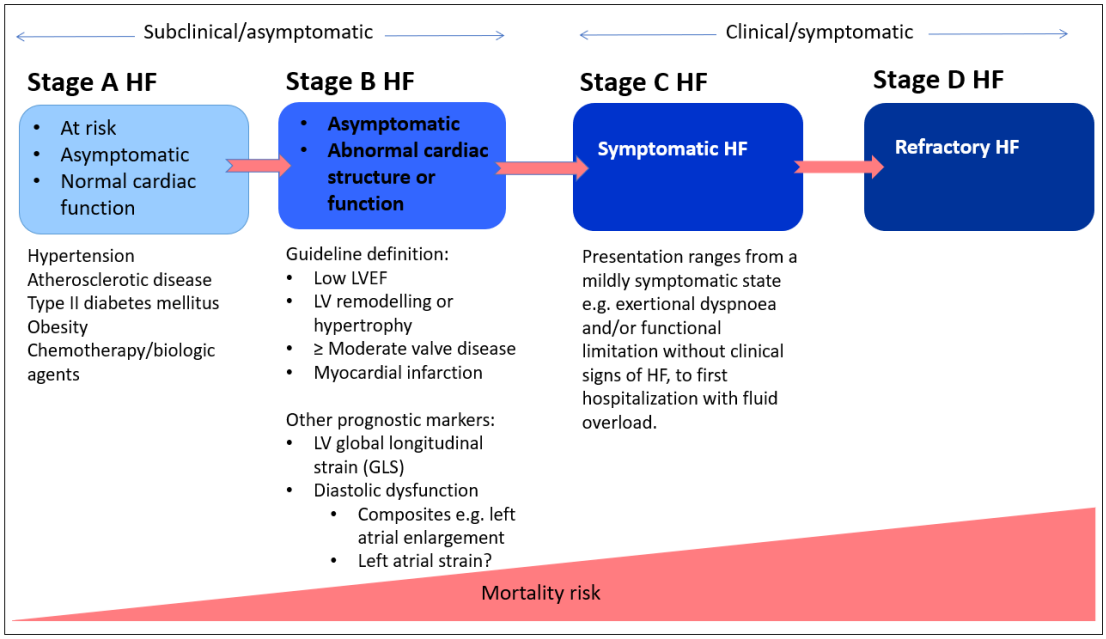
incident HF by several measures of socioeconomic status (SES) (25,27). However, how this knowledge, either on an individual or health policy-level, is to be best used for preventive purposes is not well studied.

Age is the leading risk factor for HF, indeed two thirds of HF sufferers are over the age of 65 (1). This not only has implications for future upwards trends in HF prevalence but for the medical complexity of affected individuals. In the space of 12 years from 2002 the average number of comorbidities accompanying incident HF rose by 2 (25). This limits treatment options for several reasons that include increased likelihood of drug side-effects and interactions, as well as reduced physical and cognitive capacity to engage with non-pharmacological interventions.

1.2 Stages of heart failure

The classification of heart failure has evolved in recent years. Firstly, the observation that left ventricular ejection fraction (LVEF) is normal in approximately 50% of those with the clinical syndrome of HF gave rise to the delineation of heart failure with HF with preserved ejection fraction (HFpEF) (as opposed to HF with reduced ejection fraction (HFrEF)). An important feature of HFpEF is LV diastolic dysfunction. Secondly, the American College of Cardiology/American Heart Association (ACC/AHA) 4 stages of HF (A-D) (28) is a classification based on presence or absence of symptoms and/or abnormalities in cardiac structure and function, that champions the notion of HF evolution as a continuum, starting with an at risk state (Stage A) escalating to severe symptomatic HF (Stage D) (Figure 1-1). This is supported by increasing levels of biomarkers of myocardial dysfunction and mortality across stages (29).

Figure 1-1: Stages of heart failure development first outlined the in ACC/AHA guidelines for heart failure diagnosis and therapy. Here, the definition of SBHF could be refined by additional measures and there is emphasis on identification of an early symptomatic state.



Thus, there is a framework to target populations with early detection and therapeutic strategies. Stage A HF (SAHF) is defined by risk factors alone, e.g. hypertension, diabetes or obesity, and normal cardiac structure and function (Figure 1-1). Management of SAHF centres on risk factor modification. Stage B heart failure (SBHF) is defined as asymptomatic LVD. Guidelines describe the echocardiographic abnormalities that define this stage as being limited to an LVEF <40%, left ventricular hypertrophy (LVH) or remodelling and ≥ moderate valvular disease. However, most would consider subclinical diastolic dysfunction, as fulfilling SBHF criteria (11) given its prognostic association with symptomatic or Stage C HF (SCHF) (5,30,31). Diastolic dysfunction is inferred non-invasively by impaired LV relaxation and subsequent elevation in left atrial pressure, and requires a multiparametric echocardiographic assessment (32). In the asymptomatic stages some of these measures appear to be especially predictive of incident HF e.g. left atrial (LA) enlargement (33,34). Measures of LA function e.g. LA strain, may add incremental information to LA structure, but are yet to enter mainstream echocardiography. Assessment of LV systolic function should not be limited to LVEF, which infers function based on the relative volume of LV end diastolic volume ejected during systole. A more sensitive and direct method is

the systolic deformation of the LV myocardium which can be tracked and measured using the speckle-like nature of the echocardiographic image, known as speckle-tracking echocardiography (STE). In the longitudinal plane this measure is termed global longitudinal strain (GLS). The evidence base in support of GLS as a superior, reproducible (35,36) and prognostic systolic marker in a arrange of scenarios, is robust (37). However, GLS is yet to be incorporated into routine clinical practice (outside cardio-oncology), in part due to sparse data supporting GLS-directed management (37).

Risk of symptomatic HF (and mortality) is greater for SBHF than SAHF, consistent with a progression through stages. Data from the Framingham Heart Study looked at asymptomatic LVD (ALVD) defined by visual LVEF estimation of ≤50% and found ALVD was associated with an almost 5-fold risk of incident HF (hazard ratio [HR] 4.7, 95% CI 2.7-8.1) and this rose at HR of 7.8 (95% CI 3.9-15.6) in those with an LVEF <40% (6). The comparator group was a mix of SAHF (mostly hypertensive patients) and those with no classical risk factors, so this may have magnified the increase in risk associated with SBHF vs. SAHF. Conversely, some of the comparator group may have had unmeasured LVD e.g. diastolic dysfunction. Similarly, a meta-analysis evaluating progression from both asymptomatic LV systolic dysfunction (defined variable by levels of LVEF) and LV diastolic dysfunction found that these individual states were associated with rates of incident HF of 1.5-16.3 per 100 person-years and 1.2-3.7 per 100 person-years, respectively (7). This corresponded to a hazard ratio of 4.64 (95% CI 2.2-9.81) and 1.71 (95% CI 1.34-2.18) for systolic and diastolic dysfunction, respectively. These data provide a useful guide to risk associated with SBHF and reinforce the notion of asymptomatic LVD as a HF precursor.

Apparent SAHF however should not be considered a no-risk state and we do not have good data on risk of incident HF in this group. Indeed, the estimate from the control group of the aforementioned meta-analysis was an incidence rate of 0.1-2.4 per 100 person-years, although this group was not exclusively SAHF. Normal and recovered LV function has been associated with incident HF risk in several studies (5,7,38). This observation suggests: 1) that traditional echocardiographic measures of LV function are insensitive, 2) non-cardiac pathophysiological processes may be contributing or, 3) cardiovascular insults can occur after index echocardiography. What is clear, however, is that the definition of SBHF needs expanding.

1.3 Targets for preventive therapies

One approach to prevention is selecting individuals at highest risk of disease and applying preventive therapies. This is especially preferable when pharmacological therapies are involved. In the case of HF prevention there are two ways to conceptualize risk assessment for the purposes of directing treatment. Firstly, determination of risk of future HF and secondly, risk defined by subclinical but manifest disease i.e. SBHF. These approaches will be discussed, and the best approach may be a combination of both.

There have been 29 HF risk scores generated from population data, although only 5 have been externally validated (39,40). The Atherosclerosis Risk In Communities (ARIC) HF risk score has demonstrated the greatest discriminatory ability (AUC 0.797) and requires simple clinical data (41). The clinical impact of HF risk scores is unknown as none have been clinically implemented. Very few risk scores have included biomarker or echocardiographic variables, and the benefit of either of these has been modest, except perhaps for those at intermediate risk (42). On adding echocardiography to the Health ABC HF score there was a 18.8% improvement (net reclassification index) in HF risk categorization (based on movement between risk category) (42). This was greater than for the addition of biomarker (N-terminal pro-B-type natriuretic peptide (NT-proBNP)) alone, although the two combined saw a 24.5% improvement. Furthermore, the benefit of adding biomarkers and echocardiography was greatest (35.7%) for those at intermediate risk (5-20% 5-year risk).

SBHF is at present a therapeutic target owing to randomized, placebo-controlled trials in the 1990s and early 2000s demonstrating benefit in treatment of asymptomatic LVD defined by a reduced LVEF. Guideline directed medical therapy (GDMT) for SBHF is angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) and beta blockers (43). The trials of ACE-I in asymptomatic LVD predominately included patients following AMI with the definition of LVD being LVEF $\leq$ 35% or $\leq$ 40% (9,44,45). They demonstrated a 29-37% reduction in incident HF, as well as mortality benefit. Evidence for beta-blockers in terms of progression to symptomatic HF is much weaker. A retrospective analysis of the SAVE trial (captopril vs. placebo) (44), demonstrated a 21% reduction in incident HF (46), while a post-hoc analysis of the SOLVD prevention trial (enalapril vs. placebo in asymptomatic LVD) (9) demonstrated beta-blocker use (in combination with enalapril) was associated with

a relative reduction of 34% for cardiovascular death, although incident HF was not an endpoint (47).

More recently, treatment of SBHF, based on early functional abnormalities has shown promise (14). This trial moved the definition of systolic dysfunction from reduced LVEF to reduced longitudinal strain and excluded LVEF <40%. Additionally, diastolic dysfunction (grade ≥1) was included in the definition and meeting either criteria prompted instruction to the primary care physician to initiate (or up-titrate) ACE inhibition or beta-blockade. While on an intention-to-treat basis this was a negative trial, in the 43% in whom therapy was initiated, the hazard ratio for incident HF (using Framingham criteria) was 0.23 (95% CI 0.05-0.95, p=0.04) compared to those who underwent standard echocardiography and routine follow-up. SBHF has clear management implications, however, echocardiography (and the attendant cost if applied to a large section of the population) is required to identify it, and this will be discussed in more detail in the next section.

The focus on treating subclinical LVD should not detract from the importance of treating individual risks factors/SAHF for HF prevention, which is also advocated by guidelines (43). Hypertension is a well described example, with clear benefits of treatment on development and progression of LVH and incident HF (48-50). However, treatment of hypertension needs to be somewhat tailored to the endpoint that is being prevented, which is clinically problematic (51,52). In this scenario demonstration of subclinical LVD may be helpful to guide therapy. Hypertension is also an example of where some SBHF therapies are already indicated regardless of LV function, as is the case post AMI and in T2DM with proteinuria. However, there is no premise for pharmacological therapy in SAHF defined by obesity alone. Nor is there much evidence for intensification of or additions to therapy in hypertension or T2DM with SBHF, above what is required to optimally control blood pressure and proteinuria, respectively.

Taken together, there is proven benefit in using SBHF to direct treatment, but it is uncertain who should undergo echocardiographic screening to identify it. Clinical risk assessment based on a validated risk score is appealing. However, if SBHF is the trigger for specific therapeutic interventions, then there is also the question of how high-risk individuals with normal cardiac function should be managed.

1.4 Screening

Appropriate use criteria do not currently endorse echocardiography for detection of LVD in SAHF per se, unless for example, there are signs of hypertensive heart disease (10), or in the European setting, diabetes (53). In Australia, the Medical Benefits Scheme does not reimburse transthoracic echocardiography for assessment of LV dysfunction in the asymptomatic patient. Of note echocardiography is endorsed and is routine following AMI, explaining why these patients are not considered in this thesis. In community clinical practice therefore, SBHF is not routinely differentiated from SAHF and this raises the question of screening.

SBHF fulfils some but not all criteria for screening (54). While SBHF is an asymptomatic state associated with high risk of progression to symptomatic HF, there is evidence that it's natural history includes remaining stable and even re (5). Once manifest, HF is burdensome to the individual and on healthcare resources, with an approximate annual cost in Australia of $2.7 billion (17). Furthermore, the 5-year survival is only 53% (although this may be somewhat improved by emerging therapies) (55,56). Echocardiography is a safe, acceptable, and accurate test and there is evidence that treatment of LV dysfunction identified by echo that improves outcomes, albeit by a definition of SBHF that is not comprehensive. However, there is less evidence for cost effectiveness. Screening with echocardiography has been deemed cost effective in populations where the incidence of LVD, defined by LVEF <40%, is at least 1%, with a cost per quality-adjusted life years (QALYS) of $22,300 in men and $77,700 in women (57). This was after demonstration of elevated B-type natriuretic peptide (BNP) – another step in the process. If echocardiography alone was used the cost per QALYS in men rose to $123,500. While a two-step process incorporating natriuretic peptides may therefore seem appealing, the sensitivity of BNP, at a range of cut-offs and accounting for age and sex, is far too low (<55%) for screening purposes (58). The cost-effectiveness of echocardiography alone would likely be much improved if a limited scan, restricted to quantification of LV function was used (59). The sensitivity of cost-effectiveness to the prevalence of LVD (57) may also be overcome by expanding the definition of SBHF to include diastolic dysfunction and reduced GLS, however given there is no evidence for therapeutic benefit in these settings, economic evaluations cannot be conducted.

Natriuretic peptides are however emerging as part of HF risk assessment. ACC/AHA guidelines give measurement of natriuretic peptides a class IIa

recommendation for evaluation of the patient at high-risk of developing HF, to better direct GDMT and specialist cardiovascular care (60). This recommendation comes primarily from the STOP-HF randomized trial conducted in primary care (61). Patients (mean age 65 years) with a least one HF risk factor were randomized to receive usual primary care or BNP testing. If BNP was >50pg/ml (41%), echocardiography was undertaken followed by specialist cardiovascular care. In the intervention arm there was a significant reduction in the combined endpoint of LVD (systolic [LVEF<50%] and diastolic [E/e' >15]) with or without HF (adjusted OR 0.57, 95% CI 0.38-0.86, p=0.007), although when HF alone was considered, the reduction was not significant (OR 0.48, 95% CI, 0.20-1.20; p=0.12) possibly due to a lack of power. Slightly increased use of renin-angiotensin system (RAS) modifying therapies was noted at follow-up in the intervention arm. The exact therapy or management, and on what basis e.g. echocardiographic or other test abnormalities, was not specified. There may have also been improved care in the intervention group regardless of echocardiographic abnormalities. Nevertheless, this trial demonstrates that risk stratification (in this case using another test, BNP), echocardiography and therapy is beneficial in prevention of progression through HF stages. What remains to be established is the optimal components of this 3-stage strategy, particularly how best to select high risk individuals and the therapeutic strategy.

PART 1: How should we select patients for subclinical left ventricular dysfunction screening?

2 Impact of socioeconomic status on incident heart failure and left ventricular dysfunction: Systematic review and meta-analysis

Published as: Potter EL, Hopper I, Sen J, Salim A, Marwick TH. Impact of socioeconomic status on incident heart failure and left ventricular dysfunction: systematic review and meta-analysis. Eur Heart J Qual Care Clin Outcomes 2019;5:169-179.

2.1 Preface

While those with SAHF are at risk of LV dysfunction not all will progress to LV dysfunction and HF, thus echocardiographically screening all individuals with SAHF is of low value. HF risk scores are an attractive tool for selection for screening, especially those containing easily acquired clinical and anthropometric data. Of the all the risk scores, however, none have evaluated or incorporated socioeconomic status (SES), measures of which are readily available from the individual or their geography and have been reported to confer elevated risk. The following meta-analysis aims to quantify this risk as well as determine the nature of variation in risk with different SES metrics.

2.2 Abstract

Socioeconomic status (SES) is recognizably linked with incident heart failure (HF) risk and the association of SES with geography presents a potential target for geographical location of preventive health services. To better inform policy we sought to quantify the independent association between SES and incident HF and investigate differences by type of SES measure.

MEDLINE and EMBASE were searched up to August 2018. Observational studies and randomized trials reporting adjusted HF incidence by stratified socioeconomic measures were included. Effect sizes reflected HF incidence in the lowest versus highest SES stratum and were pooled using a random-effects model. Low SES referred to the lowest resource stratum, the definition of which varied across studies: meta-analysis was only performed where strata were comparable. Statistical heterogeneity was assessed using the I^2 statistic. Eleven studies comprising 6,308,006 individuals and 104,217 HF events found that low SES was associated with an increase in risk of incident HF ranging between 43% and 87% depending on SES measure, with an overall estimate of 62% (hazard ratio [HR] 1.62, 95% CI 1.50-1.76). By individual measure, HRs of 1.66 (95% CI 1.3-2.11), 1.87 (95% CI 1.33-2.62) and 1.54 (95% CI 1.22-1.95) were observed for education, income and occupation respectively. For area-level indexes, HRs were 1.43 (95% CI 1.2-1.69) (Carstairs index) and 1.61 (95% CI 1.56-1.65) (index of multiple deprivation).

Low SES assessed by all common measures confers independent risk for incident HF. These findings carry implications for the design and delivery of HF prevention programs.

2.3 Introduction

Heart failure (HF) presents an increasing health burden with prevalence projected to rise by 43% by 2030 due to population aging alone (26). In tackling this epidemic, strategies are needed that select high-risk individuals for detailed evaluation of cardiac function but also address population level drivers of incident HF. Cardiovascular disease risk scoring under estimates risk in those with low socioeconomic status (SES) (62,63). While it may be appealing to add a measure of SES to risk scores to select individuals for screening, it is possible that this approach alone will be insufficient to impact HF incidence over time as it does not address the complex causes of social health inequalities (64). Understanding the magnitude of increased HF risk will help inform on screening delivery e.g. location, and also on wider reaching health policies that aim to reduce the health impacts of social disadvantage (65).

Socioeconomic indicators are considered as individual or area-based and there is no consensus on a single or composite best indicator (66). SES includes the individual measures of education, income and occupational status, which have shown reliable relationships with cardiovascular outcomes (67). Small area measures categorizing social support, access to medical care and residential environments are less consistently related and variably categorized. Multi-parametric indexes incorporating census data have been developed. For example, the index of multiple deprivation (IMD) is measure of relative deprivation for small areas based on seven weighted deprivation domains (68). Similarly, the Carstairs index, includes four indicators of disadvantage (low occupational social class, overcrowded households, male unemployment and lack of car ownership) (69).

The increase in HF risk associated with low SES has been approximated at 30-50% (27). However, adjustment for traditional cardiovascular risk factors has not been universal and effect sizes have not been meta-analyzed (27). Thus, the precise degree of risk associated with low SES and its independence from established risk factors is unclear. Furthermore, risk may differ by the type of measure SES used.

Accordingly, we conducted a systematic review and meta-analysis to examine the independent contribution of SES to risk of incident HF and whether risk differs by SES measure. As a secondary outcome the association of SES with echocardiographic left ventricular dysfunction (LVD) was investigated.

2.4 Methods

2.4.1 Literature search

MEDLINE and EMBASE electronic databases were searched using Ovid® to August 2018. Respective MeSH and Emtree terms are detailed in the Appendix. Searches were restricted to human studies and English language. Reference mining of articles undergoing full-text review was undertaken as well as grey literature searching. Appeals to authors were made when data within an otherwise suitable study was incomplete.

2.4.2 Study selection

Prospective and retrospective studies and randomized controlled trials (RCTs) reporting incident HF outcome by stratified socioeconomic measures were deemed suitable for inclusion. Studies were excluded if 1) there was no description of how HF at baseline was excluded; 2) effect size was not adjusted for HF risk factors (age and sex at a minimum), and 3) the exposure was not a true measure of SES (see below). Multiple publications from the same dataset were included if there was a difference in SES measure and if the same measure was used, the study with the most adjusted effect estimate was chosen. After exclusions based on title or abstract review, two investigators independently undertook full text reviews for eligibility (E.L.P and I.H) with a third investigator designated to resolve disputes (T.H.M).

2.4.3 Socioeconomic status assessment

We assessed the following individual level SES measures; education, income/wealth, occupation and composites, as well as area level measures. Studies using exposures without a well-defined connection to socioeconomic status e.g. air pollution, were excluded.

2.4.4 Quality and risk of bias assessment

We used the Newcastle-Ottawa quality assessment scale for cohort studies (70). Briefly, this scale assesses three domains: selection, comparability, and outcome. Each domain is broken down into quality indicators. We gave each study an overall quality rating (high, intermediate or low) (Appendix Table 2-6: Quality assessment using the Newcastle-Ottawa quality assessment scale (9). *indicates the study has met criteria for the relevant quality indicator.).

2.4.5 Data extraction

Two investigators (E.L.P and J.S) independently extracted data from eligible studies. Data were extracted on study characteristics including year of publication, setting, name of dataset used (e.g. Atherosclerosis Risk in Communities [ARIC]), number of participants, duration of follow-up, exclusion criteria and cardiovascular risk factors. The type of SES measure, how it was stratified and how the strata were compared were recorded along with number of incident HF events, HF adjudication method and risk factors adjusted for in effect size estimation. We extracted multivariable-adjusted hazard ratio (HR), relative risk (RR), odds ratio (OR) or incidence rate ratio (IRR) (with 95% confidence intervals [C.I.]) for HF incidence by lowest versus highest SES stratum, with calculation of reciprocal values where a highest versus lowest estimate was reported. For LVD, only effect sizes for clinically relevant echo parameters with maximal adjustment (if any) for confounders were extracted. For longitudinal studies, baseline echocardiographic measures were selected.

2.4.6 Data synthesis and statistical analysis

Studies were grouped by SES measure for meta-analysis and an effect estimate for SES overall was also computed. To minimize clinical heterogeneity, we only included studies in the meta-analysis that had categorized SES variables in similar ways and had divided individuals into a similar number of categories or strata. The latter has bearing on the effect size, whereby more strata may result in greater effect size given comparison of more extreme groups. If the difference in number of strata between studies (within an SES group) was >2 we excluded the study with the least strata. Meta-analysis was not possible for echo markers of LVD as there was no consistent SES measure between studies reporting echo parameters.

We used maximally adjusted HRs and 95% CI as the individual study effect size. One study reported relative risk (71), one reported odds ratio (72) and one incidence rate ratio (25). These were considered comparable estimators of risk given the relatively low prevalence (1-2%) of HF in the populations studied. Combining these measures of association has been reported previously (73). Where studies reported separate effect sizes by a dichotomous variable e.g. gender, we included both reported effect sizes in the meta-analysis. A random-effects model was used to generate the summary estimate from pooled effect estimates and 95% CIs, for each SES measure and overall. Due to the small number of studies, assessment for publication bias was

not feasible or meaningful, so was not attempted. Analyses were conducted using standard software ('metan' command in STATA, StataCorp 2017. College Station, TX: StataCorp LLC). We used the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) checklist for reference on methods and reporting standards.

2.5 Results

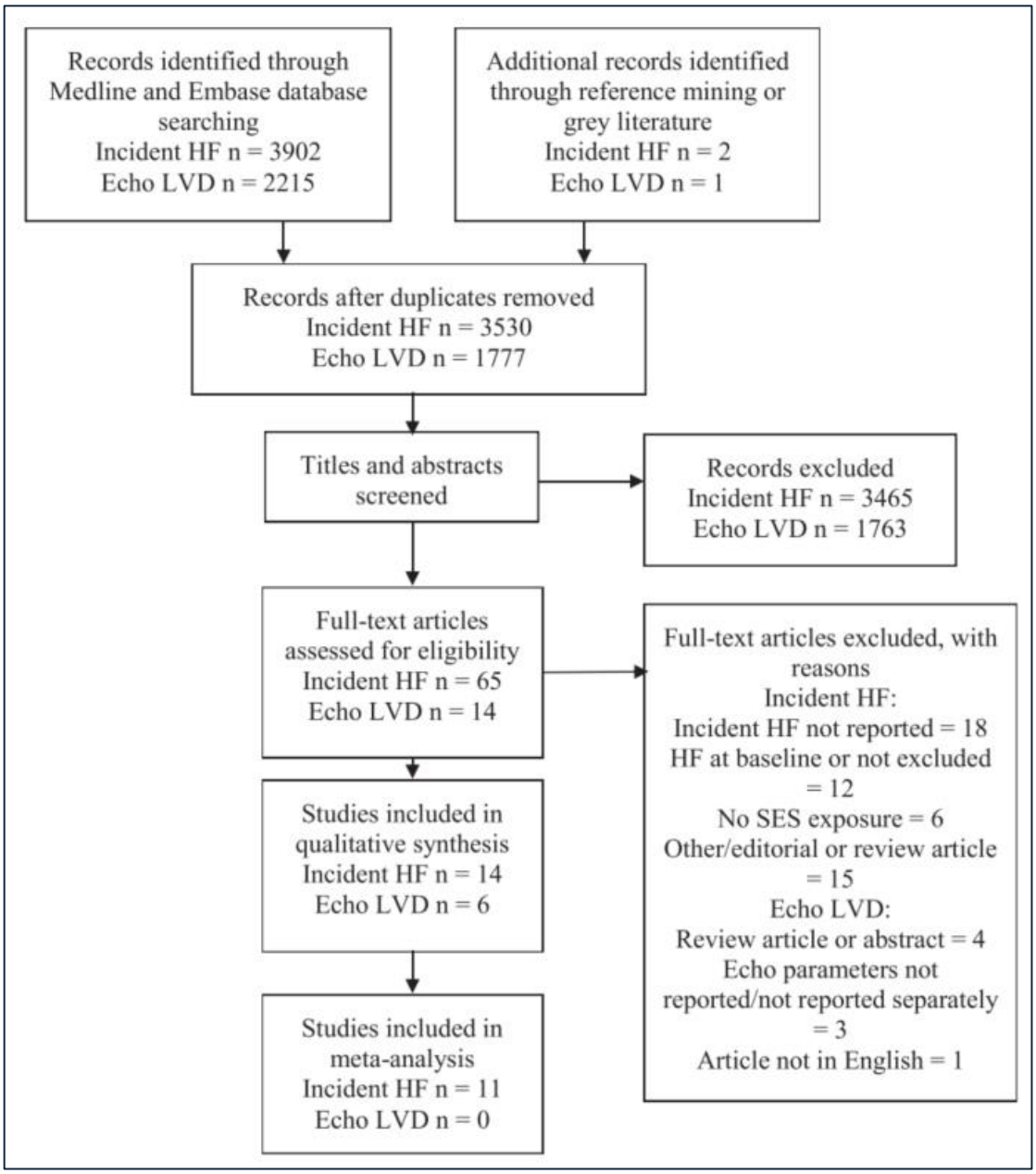
2.5.1 Study selection

Of 3530 studies identified through the search strategy for the outcome of incident HF, sixty-five underwent full-text review (Figure 2-1). After exclusions, fourteen studies were included for qualitative synthesis (71,72,74-85) and eleven for meta-analysis (Roberts, Cuthbertson and Akwo et al, excluded). Of 1776 studies identified through the search strategy for the outcome of echocardiographic LVD, fourteen underwent full-text review and six were included (Figure 2-1).

2.5.2 Study characteristics

Table 2-1 and Table 2-2 illustrate study characteristics and outcomes for the fourteen studies reporting association between SES and incident HF. Populations studied were limited to the USA, Europe (UK and Scandinavia) and Israel and included 6,356,821 individuals and 126,479 incident HF events (6,308,006 individuals and 104,217 events included in the meta-analysis). One study exclusively included those with established coronary heart disease (CHD) (77), while the remainder studied general populations with two studies exclusively in men (80,82) and five excluding prior CVD or MI (74,76,78,80,82). In terms of study design, there were eleven prospective studies, two retrospective studies and one RCT. The commonest SES measure reported, by number of studies, was education (n=5, 44,251 subjects) followed by occupation (n=4, 16,100 subjects) and income (n=2, 25,343 subjects). In two studies an individual-level composite was constructed, and four studies used standardized area-level SES indexes: the Carstairs index (n=2, 323,143 subjects) and the IMD (n=2, 5,929,77 subjects). One study used area level education as defined by the proportion of individuals with less than high school education, as well as the proportion of individuals living in poverty, although poverty was not defined (83).

Figure 2-1: Flow-diagram showing literature search outcome and study-selection process.



HF – heart failure, LVD – left ventricular dysfunction, SES – socioeconomic status.

Table 2-1:Characteristics of included studies for incident heart failure outcome.

Study	Year	Country	Design	Population	Mean age (SD)	Sex (% female)	Sample size	Follow-up (yrs.)
Cuthbertson et al. (83)	2018	USA	Observational, prospective (ARIC)	General population, ≥65 yrs.	72 (7.4)	60	109, 756	3.9
Akwo et al. (84)	2018	USA	Observational, prospective (SCCS)	General population, 40-79 yrs.	55.5 (10.4)	62.7	26, 818	5.2
Conrad et al.(25)	2017	UK	Observational, retrospective	General population, >16yrs.	76.7 (12.6)	49	3,992,417	12
Fretz et al.(74)	2016	USA	Observational, prospective (ARIC)	General population, 48-67yrs., no CHD or stroke	56.7 (5.7)	57	11,441	20
Ramsey et al.(75)	2014	UK	Observational, prospective (British Regional Heart Study)	General male population, 60-79 yrs.	68.8 (6)	0	3836	10
Pujades-Rodriguez et al.(76)	2014	UK	Observational, retrospective	General population, >30yrs., no CVD	47.2 (15.4)	50.5	1,937,360	5.5
Benderly et al.(77)	2013	Israel	RCT (Benzafibrate Infarction Prevention Study)	CHD, 45-74 yrs.,	61 (6.7)	9	2951	7.9
Christensen et al.(78)	2011	Denmark	Observational, prospective (Copenhagen City Heart Study)	General population, no prior MI	51 (12)	55	13,902	21
Roberts et al.(79)	2010	USA	Observational, prospective (ARIC)	General population, 48-67yrs.	53 (5.7)	59	11,022	17
Schaufelberger et al.(80)	2007	Sweden	Observational, prospective	General male population, no MI or stroke	51.6 (2.3)	0	6999	28

			(multifactor Primary Prevention Study)					
Stewart et al.(81)	2006	Scotland	Observational, prospective (Renfrew/Paisley Study)	General population, 45-64yrs.	-	54	15,402	20
Ingelsson et al.(82)	2006	Sweden	Observational, prospective (Uppsala Longitudinal Study of Adult Men)	General male population, > 50yrs., no MI or valvular disease	-	0	2314	29.6
McAlister et al.(72)	2004	Scotland	Observational, prospective	General population in primary care	-	-	307,741	1
He et al.(71)	2001	USA	Observational, prospective (NHANES I Epi study)	General population, 25-74yrs.	50 (15.3)	59	13,643	19

ARIC – Atherosclerosis Risk in Communities, CHD – coronary heart disease, CVD – cardiovascular disease, RCT – randomized controlled trial, MI – myocardial infarction, SCCS – Southern Community Cohort Study, NHANES – National Health and Nutrition Examination Study

Table 2-2: Exposures and outcomes for included studies for incident heart failure outcome.

Study	SES variables	Assessment of HF	Events	Effect size (95% CI)	Covariates in ES adjustment
Cuthbertson et al. (83)	Education IP diagnosis OP diagnosis Poverty IP diagnosis OP diagnosis	Hospital discharge code (IP), healthcare common procedure code (OP)	17,204	 IRR 1.18 (1.12-1.25) IRR 1.21 (1.11-1.32) IRR 1.24 (1.17-1.32) IRR 1.22 (1.11-1.35)	Age, sex, race, community
Akwo et al. (84)	Neighbor-hood deprivation index	Medical claim ICD code	4300	HR 1.12 (1.07-1.18)	Age, sex, race, smoking, alcohol, physical activity, BMI, diabetes, hypertension, cholesterol, MI. Income, education
Conrad et al.(25)	Index of multiple deprivation	Medical record, primary care and hospital	93,074	IRR 1.61 (1.58-1.68)	Age, sex
Fretz et al.(74)	Income Low hs-cTnT High hs-cTnT Education Low hs-cTnT High hs-cTnT	Hospital discharge code, annual interview	1628	 HR 1.61 (1.38-1.89) HR 3.54 (2.66-4.72) HR 1.43 (1.24-1.64) HR 3.08 (2.38-3.99)	Age, sex, race, cholesterol, SBP, DBP, BP treatment, diabetes, eGFR, LVH, BMI, physical activity, alcohol, tobacco consumption
Ramsey et al.(75)	Occupation Composite†	Health records, verified by review	229	HR 1.42 (0.79-2.56) HR 2.01 (1.21-3.34)	Smoking, alcohol, SBP, HDL, BMI, diabetes

Pujades-Rodriguez et al.(76)	Index of multiple deprivation Women Men	Hospital discharge code	3130	 HR 1.55 (1.42-1.7) HR 1.63 (1.48-1.79)	Age, sex, ethnicity, Smoking, cholesterol, SBP, BMI, diabetes
Benderly et al.(77)	Education Occupation	Cardiologist assessment/ examination, AERs, hospitalization	511	HR 1.32 (1.01-1.72) HR 1.3 (0.79-1.74)	Age, sex, obesity, diabetes, metabolic syndrome, PVD, hypertension, number of Mis
Christensen et al.(78)	Education Income* Women Men	Hospital discharge code	2190	HR 1.64 (1.37-2) HR 1.49 (1.12-1.96) HR 1.5 (1.24-1.85)	Age, sex, SBP, BMI, diabetes, smoking, physical inactivity
Roberts et al.(79)	Composite[§] African American White	Patient interview and hospital discharge code	758	 HR 1.32 (0.9-1.96) HR 1.39 (1.11-1.75)	Age, sex, BMI, diabetes, hypertension, CHD, LVH, alcohol, health insurance
Schaufelberger et al.(80)	Occupation	Hospital discharge record**	554	HR 1.58 (1.14-2.18)	Age, smoking, SBP, BMI, physical activity, diabetes, alcohol, treatment for hypertension or dyslipidemia

Stewart et al.(81)	Carstairs index	Hospital discharge code**	628	HR 1.39 (1.04-2.01)	BP, BMI, serum cholesterol, glucose, stroke, MI, cardiomegaly, LBBB, FEV_1
Ingelsson et al.(82)	Education	Hospital discharge code, physician review of record for validation	282	HR 1.98 (1.07-3.68)	Hypertension, diabetes, smoking, LVH (ECG), smoking, dyslipidemia, interim MI
	Occupation			HR 1.55 (1.0-2.35)	
McAlister et al.(72)	Carstairs index	Primary care records**	609	OR 1.44 (1.18-1.75)	Age, sex
He et al.(71)	Education	Hospital discharge code	1382	RR 1.22 (1.04-1.42)	Age, ethnicity, CHD

IRR – incident rate ratio, HR – hazard ratio, RR –relative risk, IP – inpatient, OP – outpatient, hs-cTnT – high sensitivity cardiac troponin T, SBP – systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index, eGFR – estimated filtration rate, LVH – left ventricular hypertrophy, PVD – peripheral vascular disease, HDL – high density lipoprotein, MI – myocardial infarction, LBBB –left bundle branch block, FEV1 – forced expiratory volume in one second, CHD – coronary heart disease.

† Occupation, education, car and house ownership, pension, availability of central heating. § Income, occupation, home ownership. * only adjusted for age and time period. **>90% validity for HF diagnosis.

Finally, one study used a non-standardized, i.e. not used by a governmental body, area level index termed the Neighbourhood Deprivation Index (NDI) comprising eleven variables (84). Identification of incident HF was predominantly by medical record review (n=4) or hospital discharge coding (n=8) with one study using clinical assessment along with medical records (77). Most studies used multiple cardiovascular covariates in adjustments for effect size with only two studies adjusting only for age and sex (72,85). Baseline variables for each study are displayed in the appendix (Table 2-5). On quality assessment, eight studies were of high quality and four were intermediate (Appendix Table 2-6).

For the secondary outcome of echocardiographic LVD, six studies were identified (Table 2-3). All studies were in general populations. Four used education, one used income and two used occupation as an SES measure. Echo parameters reported included left ventricular hypertrophy (LVH) and LV mass index (LVMi) (n=6), E/e' (n=2) with one study reporting LV dilatation, LV ejection fraction (LVEF) <50% and diastolic dysfunction (DD) (78).

2.5.3 SES and incident HF

Table 2-4 shows how each study stratified the SES measures. The purpose of this was to evaluate consistency in the SES measure between studies within the same group and therefore decide on appropriateness of meta-analysis. For education, four of the five studies were grouped into three categories with relatively similar cut-points with one study having two categories. Based on our pre-specified criteria all five were therefore appropriate to combine in meta-analysis. For occupation there was the most variability in stratification and one study (Benderly et al.), which had only two strata, was excluded. Two studies reporting composite SES measures could not be pooled given the differences in component SES measures as well as the questionable applicability of arbitrary composites. The study by Akwo et al, which reported the NDI, was excluded from meta-analysis because the effect size was not expressed as a comparison of low vs. high NDI group (or vice versa). However, the findings did support neighbourhood deprivation as a contributor to HF risk, not only independent of established risk factors, but also of individual education and income. The area level estimates for education and poverty (Cuthbertson et al. (83)) were not included in the meta-analysis as they were not multifactorial as were the other area-level measures thus would risk introducing heterogeneity at least for this sub-group effect size estimate.

The pooled HR for incident HF due to low SES assessed by education and income was 1.66 (95% CI 1.30-2.11) and 1.87 (95% CI 1.33-2.62), respectively. (Figure 2-2). Both summary estimates demonstrated a high degree of statistical heterogeneity (I^2 87.6%, p<0.001 and 89.2%, p<0.001 respectively). In both groups there was a higher HR for a subgroup with elevated (≥14 ng/L) plasma high-sensitivity troponin T (hs-cTnT) from the study by Fretz et al (74). A sensitivity analysis removing this high-risk group reduced the HR for education to 1.44 (95% CI 1.26-1.64) with reduced but still moderate statistical heterogeneity, I^2=53.7%, p=0.07. For income, the summary effect was also reduced (HR 1.55, 95% CI 1.39-1.74) and heterogeneity was eliminated (I^2=0%, p=0.8) (Appendix Figure 2-3). For occupation, the pooled HR for incident HF was 1.54 (95% CI 1.22-1.95, I^2=0%, p=0.952). For area-level indexes, low SES by the Carstairs index and IMD was associated with a pooled HR of 1.43 (95% CI 1.2-1.69, I^2 0%, p=0.857) and 1.61 (95% CI 1.56-1.65), respectively. Overall, the HR for incident HF for low SES by any measure was 1.62 (95% CI 1.50-1.76) with significant statistical heterogeneity (I^2=77.3%, p<0.001). Again, with the removal of subgroups with high hs-cTnT heterogeneity fell to I^2 =23.8% and overall effect size fell to HR 1.54 (95% CI1.47-1.61) (Appendix Figure 2-3).

Table 2-3: Characteristics of and outcome in included studies for echocardiographic LVD outcome. Effect sizes (ES) for low SES vs. high SES.

Study	Year	Country	Population	Sample size	SES measure	Echo parameters	Effects size (mean difference, proportion or HR, [95% CI])	Covariates in ES adjustment
Kubota at al.**(86)**	2017	USA	General population, 45-64yrs. 56% F (ARIC)	13,948	Education	LVH	5 vs. 2%, p<0.001	Unadjusted
Laitinen et al.**(87)**	2017	Finland	General population, 34-49yrs., 54%F (The Cardiovascular Risk in Young Finns Study)	1214	Income (family)	LVMi ($g/m^{2.7}$)	1.5 (0.2-2.8)	Age, SBP, BMI, lipid profile, glucose, smoking, own SES in adulthood
						E/e'	0.2 (0-0.5)	
				1222	Occupation (parental, per unit increase in status)	LVMi ($g/m^{2.7}$)	-0.3 (-0.6-0)	Age, SBP, BMI, lipid profile, glucose, smoking, own SES in adulthood
						E/e'	-0.05 (-0.1 – 0.01)	
Medenwald et al.**(88)**	2016	Germany	General population, 50-87yrs., 44% F	1436	Education			Age, neighbourhood
					Women	LVMi (g/m)	15.6 (5.6-25.7)	
						LVEF	-3.3 (-5.7-0.8)	
					Men	LVMi (g/m)	2.6 (-11.7-16.8)	
						LVEF	-1.7 (-4.9-1.6)	
Murray at al.**(89)**	2016	UK	General population, 60-64yrs. 52% F	1638	Occupation	LVMi ($g/m^{2.7}$)	1.46 (0.78-2.14)	BMI, SBP, DBP, alcohol, smoking, cholesterol, HR, HbA1c
						E/e'	0.25 (0.09-0.41)	

Christensen et al.**(78)**	2011	Denmark	General population, mean age 59.8 yrs., 55% F, no prior MI (Copenhagen City Heart Study)	3589	Education	LVH LV dilatation LVEF <50% Severe DD	HR 1.23 (0.88-1.72) HR 2.13 (1.32-3.45) HR 1.12 (0.7-1.79) HR 2.86 (1.02-7.69)	Age, sex, SBP, DBP, treated hypertension, diabetes, BMI, smoking, alcohol, lipids, physical activity, family history MI
Rodriguez et al.**(90)**	2004	USA	General population, >40yrs., 61%F, prior MI excluded (Northern Manhattan Study)	1916	Education	LVMi ($g/m^{2.7}$) Blacks Whites Hispanics Overall	 5.3 (0.45-10.2) 0.0 (-4.4-4.4) 1.0 (-2.65-4.65) 3.1 (1.22-4.98)	Age, sex, SBP, diabetes, physical activity, BMI

HR – hazard ratio, F – female, ARIC – atherosclerosis risk in communities, SBP – systolic blood pressure, DPB – diastolic blood pressure, BMI – body mass index, LVH – left ventricular hypertrophy, LVMi – left ventricular mass indexed, LVEF – left ventricular ejection fraction, HR – heart rate, MI – myocardial infarction, DD – diastolic dysfunction.

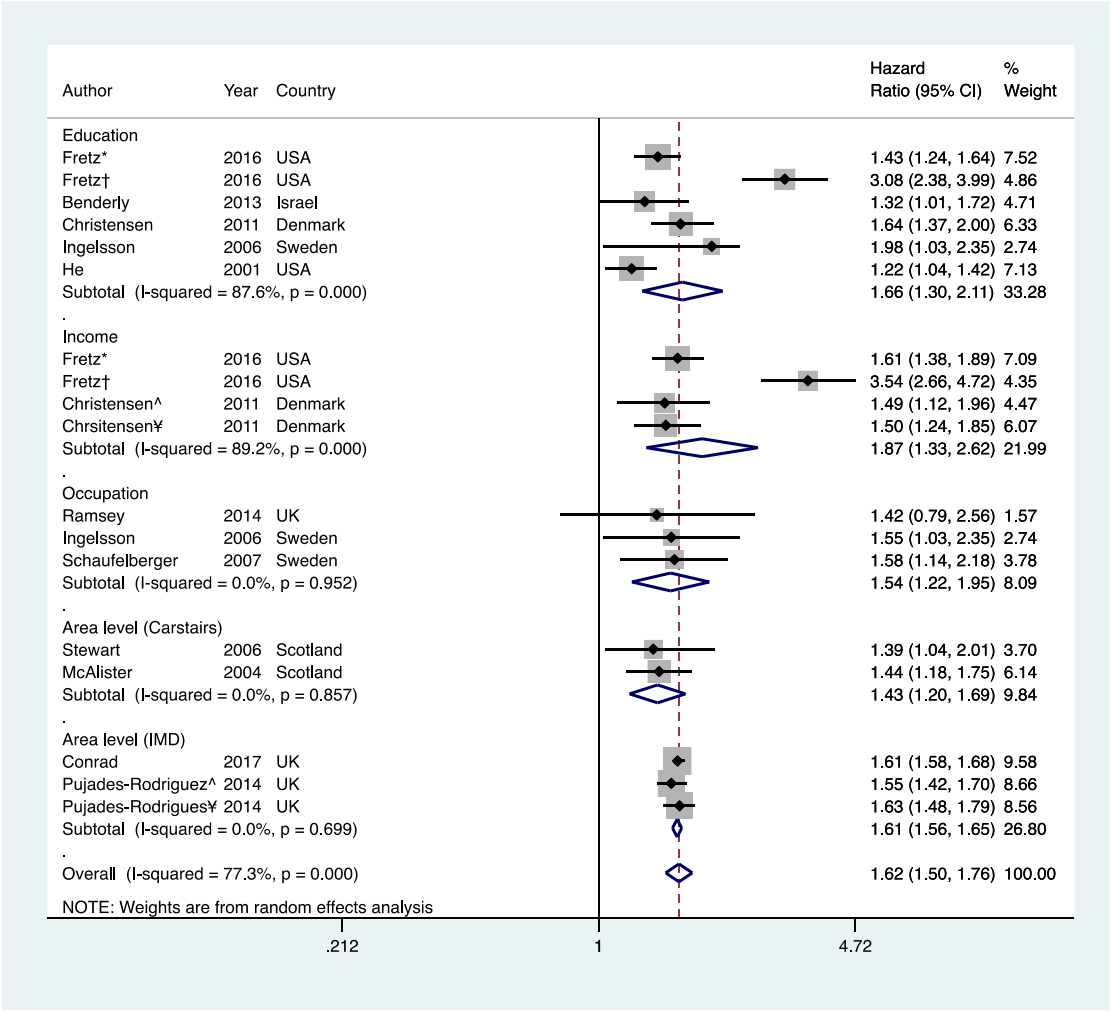
Table 2-4: Studies included in systematic review (incident HF outcome) grouped by socioeconomic status (SES) measure with description of how the measure was stratified to help determine suitability for meta-analysis.

SES measure	Study	Strata	Description of strata	Included
Education				
	Fretz (USA)	3	<12th grade, 12th grade or other diploma, college	Yes
	Benderly (Israel)	3	Elementary school, high/secondary school, academic	Yes
	Christensen (Denmark)	3	<8, 8-10, >10 yrs.	Yes
	Ingelsson (Sweden)	3	Elementary school, high/secondary school, college, or graduate exam	Yes
	He (USA)	2	< 12yrs., >12 yrs.	Yes
Income				
	Fretz (USA)	3	Low <16,000, mid 16,000-34,000, high >35,000 (USD)	Yes
	Christensen (Denmark)	3	Low, med, high (cut-offs not specified)	Yes
Occupation				
	Ramsey (UK)	4	Registrar generals social class classification	Yes
	Benderly (Israel)	2	Blue collar vs. white collar/academic	No, to few strata
	Ingelsson (Sweden)	3	Laborers, clerical/sales/nurses, professionals	Yes
	Schaufelberger (Sweden)	5	Swedish socioeconomic classification system, Socio-Economic Index (SEI). Un/semi-skilled, skilled, foremen in industrial production/non-manual, intermediate non-manual, professionals, executives, high civil servants	Yes
Composites				
	Ramsey (UK)	5	Education, occupation, car and house ownership, pension, central heating	No, composites not comparable
	Roberts (USA)	6	Mid-to older adulthood SEP – income, occupation, homeownership status	As above

Area-level (census data for 'area')				
Poverty	Cuthberts-on (USA)	3	Proportion in poverty. Low (0-0.054), med (0.055-0.088), high (0.089-0.37)	No
Education	Cuthbertson (USA)	3	Proportion > high school education. Low (0-0.25), med (0.026-0.42), high (0.43-0.78)	No
NDI	Akwo (USA)	NA†	11 indicators covering 3 domains – social indicators, health and income, education	No
IMD	Conrad (UK)	5	Income, employment, health deprivation, education, barriers to social services, crime; scored, divided into quintiles	Yes
IMD	Pujades-Rodriguez (UK)	5	As above	Yes
Carstairs index	Stewart (Scotland)	7	low social class, lack of car ownership, overcrowding, male unemployment, 6 quantiles	Yes
Carstairs index	McAlister (Scotland)	5	As above, quintiles	Yes

IMD – index of multiple deprivation, NDI – Neighbourhood deprivation index. † effect size per 1 interquartile increase in NDI

Figure 2-2: Meta-analysis of effect estimates for incident heart failure grouped by type of socioeconomic status measure.



* low high-sensitivity troponin T, † high high-sensitivity troponin T, ^women, ¥men

2.5.4 SES and echocardiographic features of LVD

Studies using education reported several parameters of LV structure and function (Table 2-3). Low educational status was significantly associated with LVH (5% vs. 2%, p<0.001 and HR 1.23, 95% CI 0.88-1.72, respectively), higher mean LV mass index (LVMi), as well as LV dilatation (HR 2.13, 95% CI 1.32-3.45), reduced LV ejection fraction and diastolic dysfunction (DD). One study reported a higher mean LVMi difference for low SES females vs. males (15.6 g/m, 95% CI 5.6-25.7 vs. 2.6 g/m 95% CI -11.7-16.8). While this effect was only adjusted for age, interestingly women had a better cardio-metabolic profile. The association between low education and LVMi varied significantly by ethnicity, with whites displaying no difference and blacks the most (5.3 g/m$^{2.7}$, 95% CI 0.45-10.2) (90). Low income was also associated

with a mean increase in LVMi as well as DD evidenced by a modest increase in mean E/e' (mean difference 0.2, 95% CI 0-0.5) (87). Finally, low occupation status also saw small increases in mean LVMi and E/e'. Inconsistency between the SES measures used, as well as their definition and stratification (Appendix Table 2-7), and the echo parameters reported, precluded meta-analysis for echocardiographic markers of LVD.

2.6 Discussion

Our review demonstrates a consistent association between socioeconomic deprivation and increased risk of HF, independent of traditional risk factors and by all commonly used individual measures and area-level indexes of SES. The overall increase in risk associated with socioeconomic deprivation by any measure of SES was 62%. This is the first meta-analysis to specifically address the outcome of incident HF (rather than CVD composites) and to assess several SES exposures. The effect of education and income on a composite cardiovascular outcome, including HF (not exclusively *incident* HF) has been meta-analyzed previously (91). The risk ratios for this composite by low vs. high education status (1.5, 95% CI 1.17-1.92) and low vs. high income (1.17, 95% CI 0.96-1.44) can therefore not be extrapolated to purely incident HF. Indeed, both these estimates are lower than our findings, particularly for income.

We found few studies examining the association between low SES and echocardiographic markers of LVD. Reported effect sizes are variable and suggest heterogeneity by sex and ethnicity, with the limited data suggesting that the effect of low SES may be greater for females. Overall, there is a trend supporting an association between socioeconomic disadvantage and LVD as would be expected given the association with stage C HF. However, it could not be determined whether a similar SES gradient exists for stage B HF.

Clinical heterogeneity in our meta-analysis overall effect estimate clearly derives from the combination of different SES measures, so our estimate of a 62% increase in risk must be interpreted with this caveat in mind. However, given there is no standardized measure we believe this estimate to be a representative and meaningful statistic. Other sources of clinical heterogeneity include differing HF definitions, although most studies used hospital discharge codes (some with complimentary sources) and one used primary care records (McAlister et al, Carstairs index). However, no statistical heterogeneity was found for the Carstairs index sub-group estimate

(Figure 2-2). Statistical heterogeneity in the overall effect estimate was largely due to the study by Fretz et al, that reported risk dichotomized by troponin level. When the small high risk group (n=438) was excluded from the meta-analysis, statistical heterogeneity fell from I^2=77.3% to I^2=23.8%, a level not considered significant (92). It may be argued that for a more general population the effect size estimate from the meta-analysis excluding this group (HR 1.54) (Appendix Figure 2-3) is more appropriate. However, we chose to report the original estimate (HR 1.62) that included high-risk individuals given that the underlying risk in the types of populations for which we foresee this data being applied (see 'Clinical and Public Health Implications') is likely to be high. Furthermore, we chose a random effects meta-analysis given the statistical heterogeneity to give a more conservative estimate with wider confidence intervals (95% CI 1.50-1.76). In contrast, no statistical heterogeneity was observed for both the area level indexes (Carstairs and IMD) as well as occupation. For the Carstairs index, despite differing HF adjudication methods (hospital discharge codes vs. primary care records), both studied representative samples of the general Scottish population. Similarly, for the IMD the same general population (UK) was studied, although one study excluded those with CVD. Furthermore, both used data from the Clinical Practice Research Datalink (CPRD), although Pujades-Rodriguez et al. used complimentary sources.

Overall, the quality of studies included in meta-analysis was high, as assessed by the Newcastle-Ottawa scale for cohort studies, which has demonstrated content validity and 'fair' overall inter-rater reliability (93). Retrospective studies contributed the majority of individuals, and while generally considered of lower quality, data were derived from government statistics and hospital coding or health records.

Understanding potential mechanisms mediating a causal relationship between low SES and HF is important in designing preventive strategies and for broadening understanding of HF pathophysiology. It is well known that behavioral HF risk factors namely physical inactivity, poor diet, smoking and medication non-adherence are more prevalent among the socioeconomically disadvantaged (67). In our review these were somewhat adjusted for although none of the studies adjusted for diet or medication adherence, factors that are difficult to measure. Therefore, a proportion of excess HF risk associated with low SES may be attributed to unmeasured adverse health behaviors. Indeed, data from the Women's Health study found that only 50% of the association between low education and high CVD events could be attributed to higher prevalence

of traditional risk factors which included smoking, alcohol use and physical activity (94). Health literacy, healthcare access and utilization vary by SES (95,96) and these factors may contribute to detrimental health behaviors such as reduced adherence to medication and low uptake of health screening. Psychobiological mediators include chronic autonomic and neuroendocrine activation (97,98), and resulting arterial inflammation, evidenced by SES gradients in inflammatory biomarkers (99,100), as well as stress-related insulin resistance (101) may contribute to poor CVD outcomes. While this may be significant in CHD-related HF, involvement of inflammatory pathways in non-ischemic HF, are not well defined.

2.6.1 Clinical and public health implications

The benefit of incorporating a measure of SES into risk scoring for CHD was demonstrated in a study using the Framingham risk score (FRS) (102). Using the standard FRS, those with high vs. low SES had a predicted risk of 3.7% vs. 3.9% while the observed event rate was 3.2% vs. 5.6% respectively. With the addition of SES, the predicted risk vastly improved to 3.1% and 5.2%. Evidently the addition of SES mitigates the underestimation in risk inherent in current CAD scoring systems (62,63,102) but similar studies looking at HF risk prediction models are lacking. Currently, the most accurate HF risk prediction tool is the Atherosclerotic Risk in Communities (ARIC) HF risk score and this could provide the base comparator (41). However, we feel our findings are most relevant to health policy makers in two ways. Firstly, HF prevention strategies in high-risk individuals (based on traditional clinical risk factors, cardiac imaging, biomarkers) are being evaluated (13,14,61,103) and if proven effective and economically viable, implementation into areas of highest risk would be priority. Our findings support priority for deprived areas. Secondly, they support wider reaching policies to address the social disadvantages that contribute to high HF incidence in low SES groups. Examples of effective policies include those that improve access to healthcare e.g. home visiting programs thus mitigating financial (cost of travel etc.) and even educational disadvantage/low health literacy (health education can be delivered) (65), and policies that address behavioral determinants e.g. financial benefits to enable healthy food choices (65). A recent guidance paper for future health policy in the United States details these and other strategies for reducing health disparities (104). Such a ‘population strategy’ (64) may complement efforts to identify and treat high-risk individuals. The latter hinges upon uptake, behavioral modification,

and adherence to treatments, all of which are significant challenges for socioeconomically deprived individuals.

A unique feature of our study is risk quantification by different SES measures, important when using SES for purposes previously described. If the purpose is health resource allocation, then area-level indices are the most feasible. Furthermore, the finding from Akwo et al, that the socioeconomic position of a neighborhood (from census data pertaining to housing, education, income and occupation) adds risk that is independent of an individual's education or income, supports these indices as robust measures. For the individual, e.g. risk scoring; an individual SES measure is more appropriate. Our study demonstrates variability in magnitude of HF risk by type of individual level measure (range HR 1.54-1.87). The effect estimate for education (HR 1.66) may be the most accurate given this was the largest dataset. Education is easy to measure, relatively standardized across countries and regions, less open to misreporting and applies to everyone. Furthermore, education is conceivably more closely linked to health literacy, which is known to impact health outcomes (105). For example, health literacy has been shown to mediate the association between older age and worse HF outcomes (106). Interestingly, one study found that disparities in traditional risk factors fully explain the association between low SES and increased CVD risk when assessed by income but not by education (94). While this is inconsistent with our analysis, it may suggest that education more holistically captures features of SES that confer risk.

2.6.2 Limitations

Our meta-analysis is limited by the relatively small number of studies within each SES measure group. Two studies, Conrad et al, and McAlister et al, (both reporting area-level SES indexes), only adjusted their effect sizes for age and sex, limiting inference about the size if the true independent effect of SES for these two measures. However, no statistical heterogeneity was observed in the sub-group meta-analysis for either index. While we endeavored to only combine studies within each measure of SES if definitions and stratifications were comparable (Table 3), we acknowledge that some variability existed, and this introduces clinical heterogeneity. The studies are all from populations in the developed world, predominantly the United States and northern Europe, thus findings may not apply to other geographical regions. Indeed, in developing countries mortality has been found to be minimally impacted by level of education (107). Detection bias resulting from differences in outcome assessment is an

important consideration and there was some variability in HF adjudication methods in our study. The majority of studies used hospital discharge coding/records that may miss events that do not result in hospitalization, and coding may be prone to error. However, of the seven studies that used hospital coding for adjudication, three were complemented by patient review/interview and one had a previously proven >90% validity for HF diagnosis. Three studies used hospital records, of these, two were complemented by either a secondary source or manual record review, and one method had demonstrated a prior >90% validity for HF diagnosis. Thus, while there was some variability in method of outcome adjudication, the quality of individual study outcome assessment was high overall.

2.7 Conclusion

Low SES is consistently and independently associated with increased risk of incident HF in high-income nations regardless of the type of common SES measure used. Further work is needed to address mediators of this association in the HF population and how SES could improve HF risk stratification. As data emerge on benefits of HF screening, the immediate utility of our observation pertains to allocation of health resources.

2.8 Postscript

The immediate impact of this meta-analysis should be on risk factor management in existing public health approaches to cardiovascular prevention (including HF prevention), and importantly access to these services. However, directly incorporating any of the effect sizes into a HF risk score for individual risk estimation is more problematic. Firstly, studies came from a limited number of countries and healthcare systems. Secondly, the interaction between SES measures remains unknown and is likely complex. To refine the use of SES as a risk metric, further work on such interactions is required, bearing in mind this may be country specific.

Evaluation of the contribution of SES in our Australian population of interest will be investigated in detail in chapter 10. SES is not the only less well recognized risk factor. The next chapter will expand on the role of functional capacity both as a risk marker and a symptom discriminator.

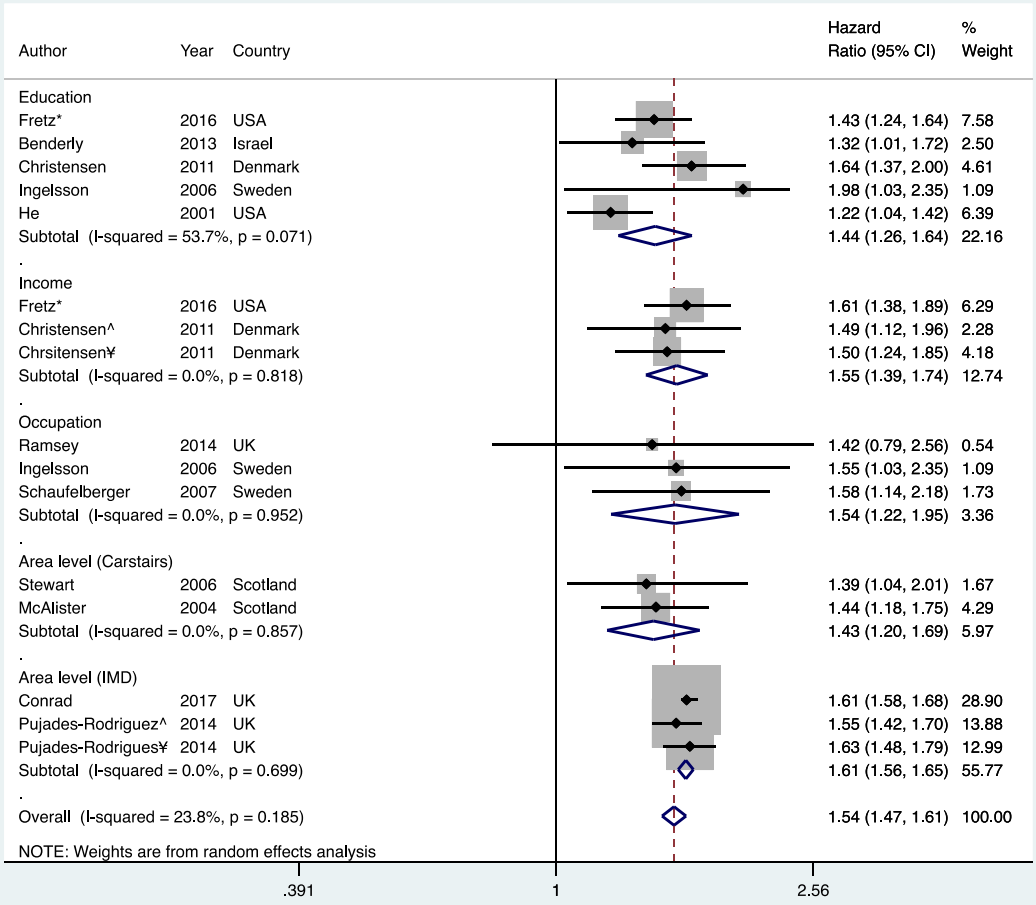
2.9 Appendix

Search terms

MEDLINE: MeSH terms "Heart failure,' 'Cardiomyopathies,' 'Ventricular dysfunction, left,' and 'Echocardiography,' 'Heart Ventricles/[Anatomy and Histology, Diagnostic Imaging, Physiopathology],' 'Ventricular dysfunction, left/[Diagnostic Imaging, Physiopathology],' 'Ventricular Function, Left,' AND 'Socioeconomic factors,' 'Social class,' 'Healthcare disparities,' 'Health status disparities,' 'Educational status,' 'Occupations,' 'Financial status,' 'Income,' 'Censuses,' 'Residence characteristics' and 'Poverty' were used along with text-words 'financial*', 'wealth' and 'deprivation'.

EMBASE: Emtree terms 'Heart failure,' 'nonischemic cardiomyopathy, 'cardiomyopathy,' 'diabetic cardiomyopathy,' 'ischemic cardiomyopathy,' 'congestive cardiomyopathy,' 'heart ventricle function/di, ep,' 'Echocardiography,' 'heart left ventricle function,' ' heart ventricle,' AND 'Socioeconomics,' 'Social class,' 'Social status,' 'Health disparity,' 'Educational status,' 'Occupation,' 'Career mobility,' 'Income' and 'Poverty' were used along with text-words 'wealth*,' 'job*' and 'deprivation.

Figure 2-3: Meta-analysis of effect estimates for incident heart failure grouped by type of socioeconomic status measure, with removal of the elevated hs-TnT subgroup from the study by Fretz et al.



* low high-sensitivity troponin T (hs-TnT), ^women, ¥men

Table 2-5: Participant characteristics for studies included in meta-analysis of SES and incident HF..

Study	CHD/MI (%)	Hypertension (%)	SBP (SD)	DPB (SD)	Diabetes-es (%)	HbA1c*/glucose (SD)	Obesity (%)	BMI (SD)	Smoking (%)	Dyslipidemia (%)	Total Chol mmol/l	Alcohol abuse (%)	Low physical activity (%)
Conrad	49	67	133 (21)	-	22	-	32	-	13	28	-	-	-
Fretz	0	28	121 (19)	72.2 (10.2)	13.3	5.7*(1)	28	-	21.8	-	5.4	-	-
Ramsey	0	-	150 (24)	-	10.4	-	16	-	12	-	-	18.8	32.8
Pujades-Rodriguez	0	53.3	130 (19)	78 (10.3)	2.6	-	20	26.4 (5.2)	20.3	-	5.4 (1.2)	-	-
Benderly	100	47	135 (16)	82 (8)	11	-	17	27 (3.4)	12	-	5.5 (0.5)	-	-
Christensen	0	6 (treated)	136 (21)	-	2.8	-	-	24.8 (3.8)	62	-	6 (1.2)	-	18
Roberts	2.8	37	-	-	10.8	-	30	-	23	-	-	-	-
Schaufelberger	0	5.3 (treated)	149 (22)	-	2	-	-	25.5 (3.2)	50.2	-	6.5 (1.15)	7	25
Stewart	2.8	-	149 (23)	85 (13)	-	5 (1.4)	-	25.8 (3.9)	67	-	-	-	-

Ingelsson	17.8	42.6	-	-	5.6	-	-	25 (3.2)	51	-	6.9 (1.3)	-	-
McAlister	-	-	-	-	-	-	-	-	-	-	-	-	-
He	5.3	28.5	134 (24)	-	3.8	-	-	25.7 (4.9)	36	31.7	5.73 (1.24)	-	43

Table 2-6: Quality assessment using the Newcastle-Ottawa quality assessment scale (9). *indicates the study has met criteria for the relevant quality indicator.

A maximum of one star can be awarded per indicator signifying a quality criterion is satisfied (a maximum of two stars for comparability). To achieve a 'high' rating the study must have achieved a star for all of the quality indicators within each domain. An intermediate rating was assigned when ≥50% quality indicators within each domain achieved a star.

Study	**Overall rating (high/intermediate/low)**	**Selection**				**Comparability**	**Outcome**		
		Representativeness of the exposed cohort	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design or analysis (max 2 stars)**	**Assessment of outcome**	**Was follow-up long enough for outcome to occur?**	**Adequacy of follow-up of cohorts**
Conrad	High	*	*	*	*	**	*	*	*
Fretz	High	*	*	*	*	**	*	*	*
Ramsey	Intermediate	*	*	*	*	**	*	*	Follow-up rate <80%
Pujades-Rodriguez	Intermediate	*	*	*	*	**	*	*	No statement
Benderly	Intermediate	Selected group – CHD	*	*	*	**	*	*	*
Christensen	High	*	*	*	*	**	*	*	*
Roberts	High	*	*	*	*	**	*	*	*

Schaufelberger	High	*	*	*	*	**	*	*	*
Stewart	High	*	*	*	*	**	*	*	*
Ingelsson	High	*	*	*	*	**	*	*	*
McAlister	Intermediate	*	*	*	*	**	*	< 2yrs	*
He	High	*	*	*	*	**	*	*	*

Table 2-7: Description of SES measures for studies included in qualitative synthesis for LVD outcome.

SES measure	Study	Strata	Description of strata
Education			
	Kubota	6	Grade school, high school no graduation, high school with graduation, vocational school, college +/- graduation, graduate or professional school
	Medenwald	4	Low (9-10 yrs.), medium low (11-13 yrs.), medium high (14-17 yrs.), high (18-20 yrs.)
	Christensen	3	<8 yrs., 8-10 yrs., >10yrs.
	Rodriguez	4	< high school, completed high school, some college, ≥ college graduate
Income			
	Laitinen	3	Parental in childhood converted to present day value (is USD). Low ≤ $14,600, medium > $14,600 to ≤ $32,000 and high > $32,000
Occupation			
	Laitinen	5	Parental occupation, 1, farmers; 2, lower manual; 3, upper manual; 4, lower non-manual; and 5, upper non-manual
	Murry	2	Father/head of household's occupation. Registrar General's 6 levels dichotomized for analysis (for life accumulation models for LVMi and E/e') into manual vs. non-manual

3 Measurement of Functional Capacity to Discriminate Clinical from Subclinical Heart Failure in Patients ≥65 Years of Age

Published as: Potter EL, Yang H, Wright L, Wang B, Marwick TH. *Measurement of Functional Capacity to Discriminate Clinical from Subclinical Heart Failure in Patients ≥65 Years of Age*. Am J Cardiol 2020; 127: 84-91.

3.1 Preface

The previous chapter was concerned with increasing the probability that those we select to screen will develop HF. However, just as important in the optimal selection for screening is the second criterion for SBHF; that is the absence of symptoms. Symptoms are subjective, may not be reported and may be (unwittingly) avoided e.g. by reducing one's level of physical activity. Conversely, a simple but objective measure of functional capacity could be considered a 'stress test' for symptoms, and if positive indicates that such individuals should be considered different from most SBHF patients, and that SCHF is imminent.

3.2 Abstract

We sought to show that reduced functional capacity (FC) in subclinical HF portends a higher risk of clinically overt HF (stage C HF [SCHF]). We studied this by obtaining the Duke activity status index (DASI) and six-minute walk distance (6MWD) in 814 individuals (age 70 [IQR 67-74] years, 51% female) with non-ischemic subclinical HF. Reduced FC was defined as: a) DASI-derived metabolic equivalents <7, b) 6MWD <2 standard deviations below the age-based normative mean (excluding those with mobility impairment) and c) reduced 6MWD with reclassification where DASI was discordant. Based on reduced FC and left ventricular dysfunction (LVD), subjects were classified into; 1) Stage A HF (SAHF; no LVD nor reduced FC), 2) SAHF with reduced FC, 3) Stage B HF (SBHF; LVD without reduced FC) and 4) early SCHF (eSCHF; LVD with reduced FC). Outcome was assessed by Kaplan-Meier survival estimates and Cox proportional hazard ratios. With reduced FC determined by 6MWD and DASI, 436 (58%) had SAHF, 80 (11%) had SAHF-reduced FC, 182 (24%) had SBHF and 52 (7%) had eSCHF. After a median follow-up of 13 months [IQR 11-19]), 76 (9%) developed HF - 6% of SAHF, 10% of SAHF-reduced FC, 9% of SBHF and 37% of eSCHF ($p<0.001$). After adjustment (for HF risk score, atrial fibrillation, pulmonary disease and therapy), the hazard ratio for development of overt HF in eSCHF was 5.92 (95% CI 2.92-11.54, $p<0.001$) compared with SAHF and 3.08 (95% CI 1.47-6.47, $p=0.003$) compared with SBHF. In conclusion, reduced functional capacity in the setting of apparent subclinical LVD predicts short-to-medium term progression to overt HF, analogous to a symptomatic state and should be considered eSCHF.

3.3 Introduction

Diagnosing heart failure (HF) early in its clinical course permits institution of therapy to reduce hospitalizations, improve quality of life and reduce mortality (28). However, HF is often diagnosed at first hospitalization. The absence of signs of HF in the early stages of HF means that symptom status is critically important. Symptoms in the elderly (i.e. ≥65 years old) may be difficult to recognize, due to factors including sedentary lifestyle, reduced mobility secondary to musculoskeletal pathology and misattribution of symptoms to 'old age.' Reduced functional capacity i.e. the reduced ability to perform physical work, is a hallmark of stage C heart failure (SCHF) and reduced functional capacity (FC), quantified by peak oxygen uptake (VO_2max), has shown strong prognostic utility (108-110). Such testing can be challenging in the elderly. Conversely, the Duke Activity Status Index (DASI) and six-minute walk distance (6MWD) offer a simple assessment of functional capacity (111), that correlates with VO_2max and is associated with outcomes (112-115). However, the role of FC evaluation in subclinical HF, particularly asymptomatic LV dysfunction or Stage B heart failure (SBHF), is unclear. We hypothesized that apparently asymptomatic subjects with reduced FC, determined by DASI and 6MWD, combined with echocardiographic evidence of left ventricular dysfunction (LVD) are at increased risk of incident overt heart failure in the short term and may therefore warrant classification as early SCHF (eSCHF).

3.4 Methods

We studied 814 individuals from community cohorts with non-ischemic HF risk factors in Tasmania and Victoria, Australia. Recruitment was from the community through advertising and via primary care. Participants were ≥65 years old and had one or more HF risk factors (hypertension [self-reported diagnosis including treatment or blood pressure ≥140/90mmHg], type 2 diabetes mellitus [self-reported diagnosis] or obesity [body mass index, BMI ≥30kg/m^2]). Patients with a prior diagnosis, symptoms or clinical signs of HF (by study physician review) or ≥ moderate valve disease were excluded. Those with LVEF of <40% were excluded, given clear guideline directed management implications,(43) although there is a low incidence of reduced LVEF (0.4%) in asymptomatic individuals with HF risk factors (11). We also excluded patients with symptoms of ischemic heart disease because of the increased risk of HF in this population and the likelihood of such participants receiving specialist care,

imaging and therapies (43). All participants gave written informed consent, and the relevant Human Research Ethics Committees approved the study.

Participants underwent physician assessment at baseline, with documentation of HF risk factors, comorbidities, medications and the DASI questionnaire (114). From the clinical assessment, the Atherosclerosis Risk in Communities (ARIC) HF risk score (41) was calculated with modification to enable calculation of 4 year risk and inclusion of ages >75 years, as previously described.(13) Included in the risk score are age, smoking status, race, BMI, blood pressure, heart rate, ischemic heart disease, treatment for hypertension and diabetes status. Serum N-terminal prohormone brain natriuretic peptide (NT-proBNP) was measured by electrochemiluminescence immunoassay using an Elecsys instrument (Cobas e 601, Roche Diagnostics, Basel, Switzerland) using Elecsys ProBNP III assay kits with a lower limit of detection of 5pg/ml). Due to the rural nature of much of the community recruitment, facilities for bio-specimen collecting and processing were not available for all participants.

A 6MW test was performed indoors on a flat, 25m marked track and in line with the American Thoracic Society guidelines (111) and at test conclusion the Borg dyspnoea scale was administered. Participants were also asked whether they felt their walking speed was limited by the presence of pain, a musculoskeletal or neurological condition (referred to hereafter as mobility impairment). Age is a significant determinant of 6MWD over 60 years of age and international normative data for age ranges 60-69 and 70-80 years have been reported (116). Reduced 6MWD (i.e. reduced FC) was defined as 2 standard deviations below the age-bracket mean 6MWD. Reduced 6MWD was 399m, 372m and 327m for ages 65-69, 70-80 and >80 years, respectively (116).

Resting 2-dimensional and Doppler echocardiography was performed with standard equipment (ACUSON SC2000, Siemens Healthcare, Mountain View, CA) and transducer (4V1c, 1.25 to 4.5 MHz; 4Z1c, 1.5 to 3.5 MHz) in accordance with American Society of Echocardiography (ASE) guidelines.(117) A vector-velocity imaging algorithm (Syngo VVI, Siemens Healthcare, Mountain View, CA) was used for global longitudinal strain (GLS) quantification and averaged from apical, 2-, 3- and 4-chamber views. Diastolic dysfunction was diagnosed using current ASE/EACVI recommendations (32), based on mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, septal and lateral mitral annular early diastolic velocities (e') and E/e' ratio. Biplane method of disks (Simpson's modified rule) was

used for left atrial volume quantification and indexed to body surface area. Left ventricular mass was calculated using the 2-dimensional linear method and indexed to body surface area; LVH was defined as left ventricular mass index (LVMI) >95 g/m^2 in women and >115 g/m^2 in men. LVD was defined as any of reduced GLS (≤ 16%), diastolic dysfunction or LVH. An LVEF of 40-50% in the absence of LVD (as defined herein) did not constitute LVD/stage A HF given that its relationship with mortality is similar to LVEF >50% (37,118).

The study population was divided into four groups: 1) Stage A HF (SAHF; no LVD nor reduced FC), 2) SAHF-reduced FC, 3) Stage B HF (SBHF; LVD without reduced FC) and 4) early SCHF (eSCHF; LVD with reduced FC) (LVD-reduced FC). We determined these groups in three ways and compared outcomes. Firstly, outcomes were analyzed with reduced FC defined by a DASI estimated metabolic equivalents (METS) of <7, which corresponded to <25 percentile in our study population. Secondly, outcomes were analyzed with reduced FC defined by abnormal 6MWD (as described above). Thirdly, outcomes were analyzed based on reduced FC by 6MWD but those with discordant DASI METS were reclassified e.g. those with no LVD and reduced 6MWD (SAHF-reduced FC) but with DASI METS ≥6 would be reclassified as SAHF.

Follow-up was by symptom questionnaires and study physician review every 6 months with a maximum total follow-up duration of 2 years. Incident HF was adjudicated by the Framingham criteria (119). HF diagnoses made external to the trial underwent record review by two physicians and date of diagnosis was recorded.

Continuous variables are presented as medians with interquartile ranges (IQR) or means ± standard deviation, based on distribution testing using the Shapiro-Wilk test. Categorical variables are presented as frequencies and percentages. Differences between two independent groups were determined using χ^2 and unpaired t-test for categorical and continuous variables respectively. One-way analysis of variance (ANOVA, or Kruskall-Wallis for non-normally distributed continuous variables) and χ^2 were used to examine the relationship of variables across >2 groups. Hochberg adjustment was made for multiple pairwise comparisons. Predictors of HF were determined using Cox proportional hazards ratio after ensuring the proportional hazards assumption was satisfied. Multivariable adjustments were made using clinically significant covariates. Effect sizes are expressed as hazard ratios with 95% confidence

intervals (CI). Ability of Cox models to discriminate HF outcome was assessed with Harrell's c-statistic. Survival analysis for HF-free survival was conducted using the Kaplan-Meier estimate and differences in survival distributions were assessed using the log-rank test. Statistical significance was defined as a two-tailed p value <0.05. Analyses were conducted using STATA 15.1 (StataCorp, College Station, TX).

3.5 Results

A total of 814 subjects (median age 70 [IQR 67-74 years], 51% women) with HF risk factors were followed for 13 months (11-19 months). Median DASI was 45 (IQR 37-51), corresponding to METS of 8.3 (IQR 7.3-9), which was abnormal in 161 (20%). Mobility impairment that affected walking speed was reported in 63 (7.7%) participants, including 4 who could not complete 6MW testing. Excluding those with mobility impairment, mean 6MWD was 469±89m and was abnormal in 95 (13%) subjects. Correlation between DASI and 6MWD was moderate (r=0.55, appendix Figure 3-3) and agreement between methods for determining reduced FC was fair (kappa statistic 0.3, p<0.001). LVD was observed in 254 (31%), including 86 (11%) with LVH, 171 (21%) with reduced GLS and 127 (16%) with diastolic dysfunction (with 22% with indeterminate diastolic function).

Incident HF occurred in 76 subjects (9%); echocardiographic assessment was completed for 65 of these subjects demonstrating 59 (95%) had preserved LVEF.

HF stages were assessed using DASI and 6MWD. Table 3-1 shows baseline characteristics by HF stage determined by DASI; 463 (57%) had SAHF, 97 (12%) had SAHF-reduced FC, 190 (23%) had SBHF and 64 (8%) had eSCHF. Within the SAHF groups, SAHF-reduced FC were significantly older than SAHF alone. However, there was no significant difference in average age between SBHF and eSCHF. eSCHF was associated with a significantly higher proportion of type II diabetes mellitus, atrial fibrillation and compared with SAHF, a higher BMI. Interestingly, ARIC HF risk was similar between SAHF-reduced FC and SBHF although significantly different between other groups. SAHF and SBHF did not differ by either measure of functional capacity (DASI and 6MWD). The median Charlson comorbidity index (age-excluded) was low (i.e. 1 or 2) for all groups, but higher in eSCHF. While E/e' was higher in eSCHF (10 [8-13] vs. 9 [7-11], there was no significant difference in other echocardiographic risk markers between those with eSCHF and SBHF.

For HF stages determined by 6MWD, which excluded 63 subjects with mobility impairment (total n=751), the proportion with reduced FC was 13% (versus 20% by DASI) (Table 3-2). Similar associations were observed as for Table 3-1. In particular, there was no significant difference in ARIC risk score between SAHF-reduced FC and SBHF.

Table 3-1: Clinical, echocardiographic and outcome data by heart failure group determined by DASI.

Variable	**SAHF (n=463)**	**SAHF-rFC (n=97)**	**SBHF (n=190)**	**eSCHF (n=64)**	**p-value**
Age (years, IQR)	69 (67-72)	72 (69-76)	71 (67-74)	73 (70-79)	<0.001*
Men	225 (49%)	33 (34%)	108 (57%)	29 (45%)	0.003
Hypertension	377 (81%)	79 (81%)	160 (84%)	51 (80%)	0.8
Type II Diabetes Mellitus	183 (40%)	49 (51%)	96 (51%)	47 (73%)	<0.001
Atrial Fibrillation	14 (3%)	1 (1%)	18 (9.5%)	10 (16%)	<0.001
Chronic obstructive pulmonary disease	24 (5%)	11(11%)	8 (4%)	4 (6%)	0.08
Angiotensin converting enzyme inhibitor/receptor blocker	335 (76%)	69 (74%)	131 (71%)	50 (83%)	0.24
Beta-blocker	24 (5%)	5 (5%)	23 (12%)	9 (14%)	0.06
Heart rate (bpm ± SD)	68 ± 11	69 ± 10	69 ± 12	70 ± 11	0.76
SBP (mmHg ± SD)	140 ± 15	139 ± 15	142 ± 31	142 ± 20	0.36
BMI (kg/m^2, IQR)	29 (26-32)	32 (27-35)	30 (27-33)	31 (27-35)	<0.001†
ARIC HF risk score (% ± SD)	6 ± 5	10 ± 8	9 ± 8	14 ± 9	<0.001Ŧ
DASI-METS (IQR)	9 (8-9)	6.3 (5.2-6.6)	8 (7.6-9)	5.9 (5.1-6.6)	<0.001§
6MWD (meters ± SD)	484 ± 77	393 ± 89	476 ± 79	381 ± 111	<0.001§
Mobility impairment	26 (6%)	17 (18%)	8 (4%)	12 (19%)	<0.001

Charlson comorbidity index (IQR)^	1 (0-1)	1 (0-2)	1 (0-2)	2 (1-4)	<0.001
Echocardiographic parameters					
Left ventricular mass index (g/m^2 ± SD)	85 ± 20	82 ± 19	98 ± 26	98 ± 27	<0.001¶
Left ventricular ejection fraction, (%, IQR)	64 (61-68)	63 (60-69)	61 (56-65)	58 (53-66)	<0.001¶
Global longitudinal strain (% ± SD)	19 ± 1.8	19 ± 1.6	16 ± 2.5	16 ± 3	<0.001¶
E/e' (IQR)	8 (7-10)	8 (7-10)	9 (7-11)	10 (8-13)	<0.001**
Left atrial volume index (ml/m^2, IQR)	30 (25-37)	29 (24-37)	33 (26-42)	39 (29-45)	<0.001¶
Incident heart failure	27 (6%)	11 (11%)	17 (9%)	21 (33%)	<0.001

SAHF – Stage A HF, rFC – reduced functional capacity, SBHF – Stage B HF, eSCHF – early Stage C HF. ^ age not included.
Pairwise comparisons: * NS for SBHF vs. eSCHF, † significant for SAHF vs. others, ₸ NS for SAHF vs. SAHF-rFC and SAHF-rFC vs. SBHF, § NS for SAHF vs. SBHF and SAHF-rFC vs. eSCHF, ¶ NS for SAHF vs. SAHF-rFC and SBHF vs. eSCHF, ** significant for eSCHF vs. others.

We now present three means of defining eSCHF and describe HF incidence and risk. The incidence of HF during follow-up was 33% for eSCHF determined by DASI, compared with 6%, 11% and 9% for SAHF, SAHF-reduced FC and SBHF respectively (p<0.001) (Table 3-1). There was reduced HF-free survival with worsening DASI (log-rank χ^2-test 27.7, p<0.001) (Figure 3-1a). The adjusted hazard ratio (HR) for HF in the eSCHF group defined by DASI was 5.41 (95% CI 2.77-10.54, p<0.001) with SAHF as the reference category (Table 3-3, adjusted for ARIC HF risk score, atrial fibrillation, chronic obstructive pulmonary disease, angiotensin converting enzyme inhibitor use, angiotensin receptor blocker use and beta-blocker therapy) (c-statistic 0.72). The magnitude of increased risk for SAHF-reduced FC (HR 2.05) and SBHF (HR 1.88) was of borderline significance. With SBHF as the reference category the HR for HF remained significantly increased for eSCHF (HR 2.95, 95% CI 1.44-6.03, p=0.003). There was also no significant difference in HF risk for SAHF-reduced FC (HR 1.12, 95% CI 0.50-2.49, p=0.78). The incidence of HF was 22% for eSCHF determined by 6MWD, compared with 5%, 16% and 14% for SAHF, SAHF-reduced FC and SBHF respectively (p<0.001) (Table 3-2). There was reduced HF-free survival with worsening 6MWD (log-rank χ^2-test 21.2, p<0.001) (Figure 3-1b).

The HR for HF in the eSCHF group defined by 6MWD was 3.36 (95% CI 1.34-8.38, p=0.009) (c-statistic 0.72). However, with SBHF as the reference category the increased HF risk in the eSCHF failed to reach statistical significance (HR 1.14, 95% CI 0.47-2.76, p=0.77). In contrast to eSCHF by DASI, the increased HF risk associated with reduced FC compared with SAHF, was greater for both SAHF-reduced FC (HR 2.36 [95% CI 1.03-5.43, p=0.004] and SBHF (HR 2.94 [95% CI 1.62-5.32, p<0.001]). The difference in risk between SAHF-reduced FC and SBHF was not statistically significant (HR 0.80, 95% CI 0.35-1.82, p=0.6).

Figure 3-1: Heart failure free survival by early HF sub-classifications. Reduced functional capacity (rFC) determined by (a) Duke activity status index (DASI)-derived METS <7, (b) reduced six-minute walk distance (6MWD) and (c) reduced 6MWD with reclassification for discordant DASI.

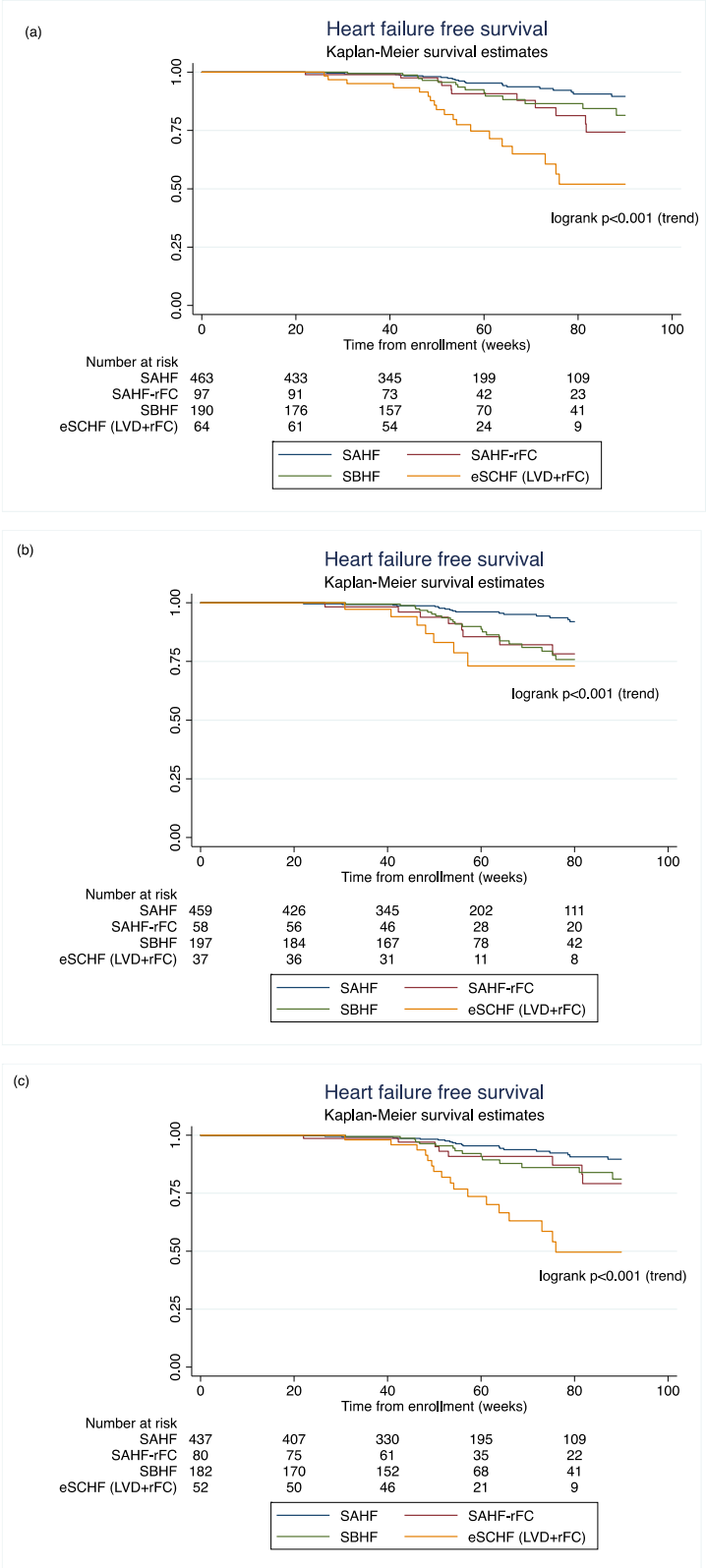


Table 3-2: Clinical, echocardiographic and outcome data by heart failure (HF) group determined by six-minute walk test.

Variable	**SAHF (n=459)**	**SAHF-rFC (n=58)**	**SBHF (n=197)**	**eSCHF (n=37)**	**p-value**
Age (years, IQR)	70 (67-72)	72 (68-75)	71 (68-75)	71 (68-77)	<0.001*
Men	214 (47%)	21 (36%)	108 (54%)	16 (43%)	0.06
Hypertension	373 (81%)	47 (81%)	169 (86%)	27 (73%)	0.24
Type II Diabetes Mellitus	174 (38%)	33 (57%)	107 (54%)	27 (73%)	<0.001
Atrial Fibrillation	12 (3%)	0 (0%)	17 (9%)	5 (14%)	<0.001
Chronic obstructive pulmonary disease	23 (5%)	5 (9%)	9 (5%)	2 (5%)	0.67
Angiotensin converting enzyme inhibitor/receptor blocker	330 (74%)	42 (76%)	140 (73%)	27 (77%)	0.92
Beta-blocker	19 (4%)	5 (9%)	26 (13%)	2 (5%)	<0.001
Heart rate (bpm ± SD)	68 ± 11	70 ± 9	69 ± 12	72 ± 11	0.3
SBP (mmHg ± SD)	140 ± 15	138 ± 13	140 ± 18	145 ± 16	0.34
BMI (kg/m^2, IQR)	28 (26-32)	33 (27-36)	30 (27-33)	31 (29-40)	<0.001†
ARIC HF risk score (% ± SD)	6 ± 5	12 ± 9	9 ± 7	16 ± 12	<0.001**
DASI-METS (IQR)	8 (7.6-9)	7 (5.7-8.3)	8.2 (7.3-8.9)	6.6 (5-7.3)	<0.001Ŧ
6MWD (meters ± SD)	493 ± 66	321 ± 58	488 ± 63	295 ± 78	<0.001^^
Charlson comorbidity index (IQR)^	1 (0-1)	1 (0-2)	1 (0-2)	1 (1-3)	<0.001

Echocardiographic parameters					
Left ventricular mass index (g/m^2 ± SD)	84 ± 20	84 ± 21	97 ± 26	102 ± 27	<0.001§
Left ventricular ejection fraction, (%, IQR)	64 (61-68)	65 (60-68)	61 (57-66)	60 (55-65)	<0.001§
Global longitudinal strain (% ± SD)	20 ± 1.9	19 ± 1.6	16 ± 2.6	16 ± 3.2	<0.001§
E/e' (IQR)	8 (7-10)	8 (7-9)	9 (7-11)	10 (9-11)	0.001¶
Left atrial volume index (ml/m^2, IQR)	30 (25-37)	29 (24-37)	34 (27-42)	35 (26-42)	<0.001§
Incident heart failure	25 (5%)	9 (16%)	28 (14%)	8 (22%)	<0.001

Mobility impairment affecting walking speed (n=30) excluded. ^ age not included.
Pairwise comparisons: *significant for SAHF vs. other groups, † non-significant (NS) for SAHF-rFC vs. eSCHF and SBHF vs. eSCHF, ** NS for SAHF-rFC vs. SBHF, Ŧ NS SAHF-rFC vs. eSCHF, ^^ NS SAHF vs, SBHF or SAHF-rFC vs. eSCHF, § NS for SAHF vs. SAHF-rFC and SBHF vs. eSCHF, ¶ significant only for SAHF and SAHF-rFC vs. eSCHF.

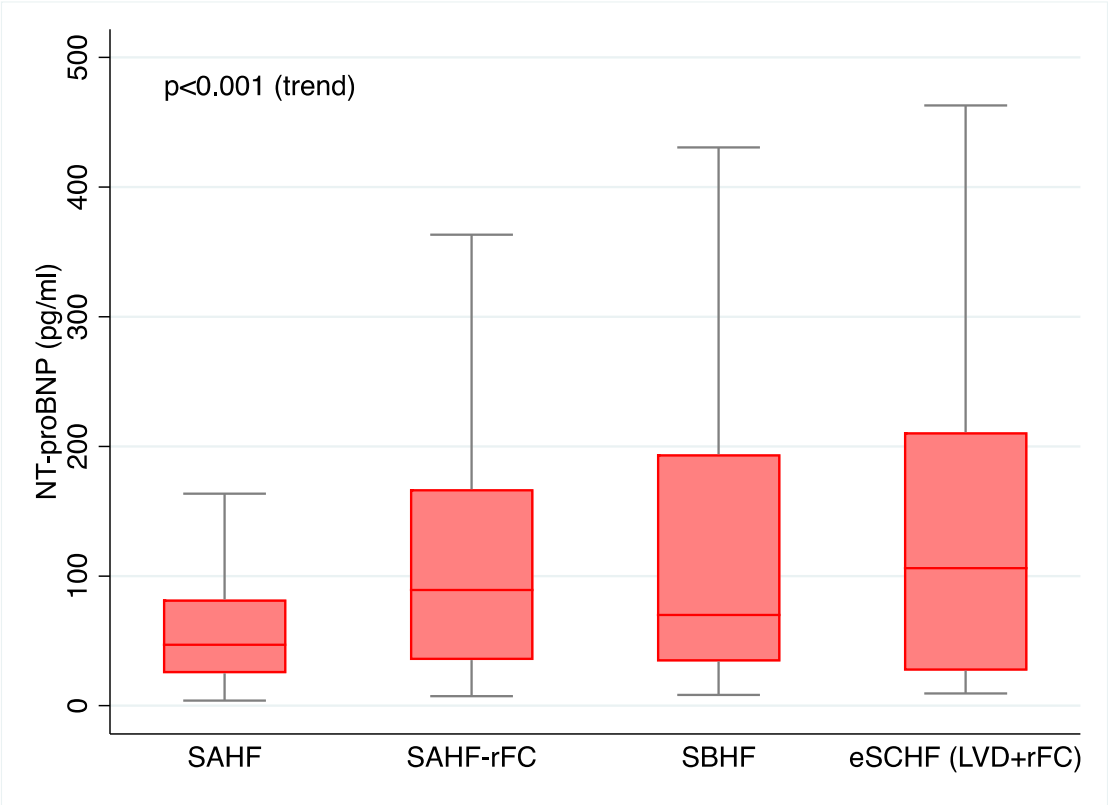
Using the 6MWD-based classification, reclassification was undertaken where there was discordant FC based on DASI (Appendix Table 3-4). After reclassification, there were 437 subjects classified as SAHF (58%), 80 (11%) as SAHF-reduced FC, 182 (24%) as SBHF, and 52 (7%) as eSCHF. Incident HF occurred in 37% with eSCHF, in contrast to 5% with SAHF 10% with SAHF-reduced FC and 9% with SBHF ($p<0.001$) (Appendix Table 3-5). Survival analysis (Figure 3-1c) again demonstrated a significant trend for reduced HF-survival across groups (log-rank χ^2-test 27.2, $p<0.001$). The adjusted HR for incident HF for the eSCHF group was 5.92 (95% CI 2.93-11.96, $p<0.001$) and remained significant with SBHF as the reference group (HR 3.08, 95% CI 1.47-6.47, $p=0.003$) (Table 3-3) (c-statistic 0.71). By this classification, SBHF also had a similar risk to SAHF (HR 1.92 (0.98-3.76, $p=0.056$).

Of the 814 subjects in this analysis, baseline NT-proBNP was available for 445 (55%) (Appendix Table 3-6). The proportion of participants for whom NT-proBNP was available did not differ between SAHF (56%), SAHF-reduced FC (49%), SBHF (47%) and eSCHF (52%; $p=0.15$). The average NT-proBNP was 55 pg/ml (IQR 27-108pg/ml) and was significantly higher for those who developed incident HF (143 [IQR 61-218]) compared with those who did not (50 [26-101], $p<0.001$). The average NT-proBNP was least in SAHF with normal FC and imaging (47 [25-82]), and greater in those with SAHF-reduced FC (89 [35-167]), SBHF (70 [34-194]) and eSCHF (106 [27-211], $p<0.001$) (Figure 3-2). Adjusted pairwise comparisons showed a significant difference in average NT-proBNP for SAHF vs. all other groups individually. No other significant differences were found (Appendix Table 3-7).

Table 3-3: Cox regression for incident heart failure (HF) by HF group, adjusted for Atherosclerosis Risk in Communities (ARIC) HF risk score, AF, COPD, angiotensin converting enzyme inhibitor, angiotensin receptor blocker and beta-blocker therapy. Reduced functional capacity (rFC) determined by DASI, 6MWT or both. Stage A HF (SAHF) as reference category (top) and stage B HF (SBHF) as reference category (bottom).

	Duke activity status index (DASI)-derived METS <7		**Reduced six-minute walk test (6MWT)**		**6MWT with reclassification by DASI METS <7 if rFC discordant.**	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
SAHF	Reference category		Reference category		Reference category	
SAHF-rFC	2.05 (0.98-4.31)	0.06	2.36 (1.03-5.43)	0.04	1.82 (0.79-4.17)	0.16
SBHF	1.83 (0.94-3.55)	0.07	2.94 (1.62-5.32)	<0.001	1.92 (0.98-3.76)	0.056
eSCHF (LVD + rFC)	5.41 (2.77-10.54)	<0.001	3.36 (1.34-8.38)	0.009	5.92 (2.93-11.96)	<0.001
SBHF	Reference category		Reference category		Reference category	
SAHF	0.55 (0.28-1.06)	0.07	0.34 (0.19-0.62)	<0.001	0.52 (0.27-1.01)	0.056
SAHF-rFC	1.12 (0.50-2.49)	0.78	0.80 (0.35-1.82)	0.6	0.94 (0.39-2.27)	0.9
eSCHF (LVD + rFC)	2.95 (1.44-6.03)	0.003	1.14 (0.47-2.76)	0.77	3.08 (1.47-6.47)	0.003

Figure 3-2: NT-proBNP by early HF sub-classifications. Reduced functional capacity (rFC) determined reduced 6MWD with reclassification for discordant DASI.



However, NT-proBNP was higher for those with reduced FC, irrespective of LVD (50pg/ml [26-95] vs. 91pg/ml [35-192] for normal FC vs. reduced FC respectively, p<0.001). In 78 cases (60%) of those with LVD and available NT-proBNP, NT-proBNP was <125pg/ml. However, 4 (5%) of these individuals developed HF, so while this is a lower rate that for LVD overall (38/254, 15%), risk associated with LVD and normal natriuretic peptide levels remained significant.

3.6 Discussion

In this prospective, community study of asymptomatic subjects ≥65 years old and at risk of HF, we demonstrated that sub-classification by functional capacity could refine prediction of overt SCHF. Incident HF developed in 22-37% of those with LVD and reduced FC, depending on whether the DASI, 6MWD or a combination of these methods was used. These subjects had significantly worse HF-free survival over 18 months, and after adjustment for confounders were 4.9 to 6.5 times more likely to develop HF compared with SAHF. Compared with SBHF, eSCHF patients were up to 3 times more likely to develop HF. We found that classification based on the DASI better selected those at increased risk (eSCHF) compared with the 6MWD alone. Our

classification of subclinical and early HF by functional capacity and LVD was further supported by sequentially higher natriuretic peptide level. Overall, our evidence suggests that reduced FC in the setting of SBHF may be considered equivalent to an early symptomatic state. A second important finding is the similar prognosis of SAHF with reduced FC, and SBHF with normal functional capacity. This near equivalence in risk conferred by reduced FC in the absence of LVD, and LVD alone has not previously been reported. Indeed, while mechanisms and co-existing pathologies implicated in progression of SBHF to SCHF are under investigation (7,31), less is known about risk markers in SAHF. This is of importance as the ARIC study showed that prevalence of SAHF and SBHF in the elderly is 82% (11). In our study, SAHF was twice as prevalent as SBHF and accounted for the same number of incident HF outcomes. Thus, while there may be economic and resource barriers to targeting the larger SAHF group for HF preventive strategies, it contributes significantly to new HF diagnoses. Here we show that a simple and cheap assessment of functional capacity may assist in such therapeutic targeting by identifying those at increased risk.

Given the barriers to symptom recognition and reporting in the elderly, objective testing of functional capacity is appealing. Studies in cancer patients and the general public have shown that symptom normalization e.g. attributing symptoms to age or lack of physical fitness, is common (120,121) and there is overall lack of awareness of symptom significance (122). Furthermore, the medical symptom lexicon - even terms such as “breathless” - seems to have limited understanding (120). Therefore, even if a patient is directly questioned there is risk of miscommunication.

We presented 2 methods of functional assessment for 2 reasons: firstly, to establish the utility of both an objective test and a somewhat subjective one, and secondly, to give clinicians choice of the most appropriate method for their individual patients and resources. The DASI is particularly useful in those whose walking speed is impacted by a musculoskeletal problem, but still maintain a high level of habitual physical activity, e.g. swimming. Conversely, a more quantitative assessment of functional capacity, such as 6MWD, may be preferable for monitoring change over time. If 6MWD is the preferred method, our data indicate that DASI should be evaluated concurrently to ensure optimal risk stratification.

While early SCHF (or Stage C1) is not referenced in HF guidelines (28), it has been described with differing definitions (11,29). For example, data from Olmsted County that split SCHF into C1 (mildly symptomatic; exercise limitation due to

dyspnoea or fatigue but not fulfilling Framingham criteria), and C2 (fulfilling Framingham criteria) (29), the mean BNP concentration in the Stage C1 group was double that of SBHF. The C1 sub-group accounted for 82% of SCHF and had a 5-year survival of 78% compared to 96% for SBHF and 60% for Stage C2. These data demonstrate that a mildly symptomatic state is associated with worse outcomes than being truly asymptomatic. However, there was no recognition of competing pathologies in the aforementioned study, and there remains the problem of symptom specificity. In a population where obesity, a smoking history and deconditioning are prevalent, the exclusion of non-cardiac dyspnoea and coronary artery disease are important. Our data build on this work by demonstrating worse outcomes in those with apparent SBHF who exhibit reduced objective and reported functional capacity but who do not report symptoms and do not to fulfil Framingham criteria. We propose such individuals could also be considered Stage C1 HF. Indeed, ACC/AHA HF guidelines (28) acknowledge the importance of early HF detection and identify the problem of unrecognized exercise intolerance. They advise that SBHF patients be asked to undertake self-surveillance for such, however, formal assessment as outlined in our study may offer a more robust solution.

The ACCF/AHA HF staging paradigm (A-D) describes a continuum from an at risk state to overt HF (28). The inclusion of subclinical stages serves to highlight the importance of early identification and management of those at increased risk. The continuing rise in HF prevalence(26) reinforces the importance of preventive efforts. A surprising finding of this study is the similar risk to progression to SCHF conferred by SAHF-reduced FC and LVD with normal FC. While mechanisms behind this observation were not investigated it is possible that these individuals were manifesting early impairment in peripheral oxygen extraction, as described in the majority of patients with HF with preserved ejection fraction (123). Conversely, this group may have had cardiac dysfunction that our current methods of detection are unable to detect.

Our data specifically apply to a subjectively asymptomatic population and expand understanding of the clinical utility of the DASI and 6MWD beyond advanced HF stages (108,109). It would be reasonable for the standard of care for all those with SAHF to undergo DASI or a 6MWD, which is simple, safe (124), cheap and may even be done remotely (125). Even without imaging, recognition of SAHF-reduced FC, could promote intensive risk factor management and monitoring in primary care. Where SBHF is diagnosed when echocardiography is not undertaken for symptom

interrogation (e.g. preoperative assessments, electrocardiographic abnormalities, surveillance for cardiotoxicity), DASI and 6MWD could refine risk assessment.

There are some limitations to discuss. The accuracy of the effect size estimates is limited by small group size especially in the group of interest, eSCHF. Our study population did not include those with established CAD or reduced LVEF (<40%), although these individuals would likely receive specialist care and more guideline-directed therapy and may have less to gain from this program. Given the relatively low burden of chronic disease in our cohort, our findings are not applicable to the multi-morbid elderly who may have competing pathologies and health priorities. The choice of cut-off for reduced functional capacity based on DASI-METs may not be appropriate for all populations and indeed the mean METS for this cohort were likely higher than the general population. NT-proBNP was not available in all cases and results would have been strengthened by comprehensive biomarker evaluation. However, we did show a trend of increasing NT-proBNP as HF stage (SAHF to eSCHF) advanced and those who did not have NT-proBNP measured were not systematically different than those who did (Appendix Table 3-6).

3.7 Conclusion

The DASI and 6MWD offer simple assessment of functional capacity and refine risk stratification in the subclinical stages of HF. In particular, reduced DASI and 6MWD predict short-to-medium term progression to overt HF in SBHF, analogous to a symptomatic state and should be considered early SCHF or Stage C1. Furthermore, in SAHF, reduced functional capacity identifies a group at similar risk of HF evolution as those with SBHF. Incorporation of functional capacity evaluation with 6MWD and/or DASI should be considered in the elderly with subclinical HF.

3.8 Postscript

The adoption of reduced functional capacity as an early symptom equivalent will depend on whether it is incorporated in management guidelines. This will not be immediate and will likely require supporting data. Alternatively, reduced functional capacity should be at least considered a risk factor for HF. Therefore, despite this chapter focussing on whether an individual has progressed past SBHF, it has also supported the adoption of this novel risk factor that could be used as part of a screening strategy. 6MWD has been previously reported as part of a decision tree analysis to stratify HF risk and presence of echocardiographic abnormalities (13). This work

indicated that functional capacity contributed to risk of LVD and HF. However, this chapter significantly advances understanding of the importance of reduced functional capacity by demonstrating its independent association with HF risk in the setting of both normal and abnormal resting cardiac function, and suggesting that LVD and reduced functional capacity are risk equivalents. This is an intriguing observation that suggests early impairments in integrated cardiopulmonary and metabolic systems. In chapter 8 as part of the RCT, an exclusion step will include measurement of 6MWD (along with the ARIC HF risk score) to identify low risk individuals, although using the cut-off identified by the aforementioned decision tree analysis.

These findings also raise the possibility of using objective evidence of manifest disease to direct selection for echocardiography. This theme is investigated in the next chapter.

3.9 Appendix

Table 3-4: Reclassification of discordant individuals based on DASI-METS. Individuals in the cells in orange were reclassified.

	Classification based on rFC by reduced 6MWT			
	SAHF	SAHF-rFC	SBHF	eSCHF
DASI-METS ≥ 7	404	33	165	17
DASI-METS <7	55	25	32	20

Table 3-5: Incident HF by HF group after reclassification (above).

	SAHF (n=437)	**SAHF-rFC (n=80)**	**SBHF (n=182)**	**eSCHF (n=52)**	**p-value**
Incident HF (%)	26 (5)	8 (10)	17 (9)	19 (37)	<0.001

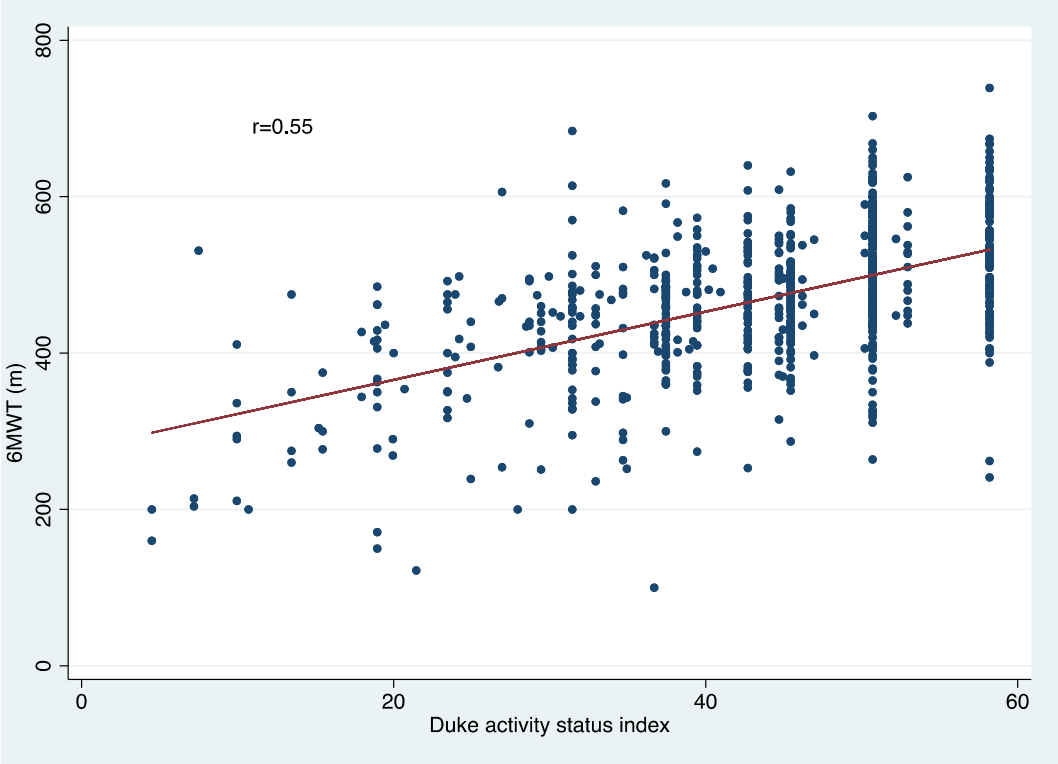
Table 3-6: Characteristics by NT-proBNP status.

	NT-proBNP unavailable	**NT-proBNP available**	**p-value**
Age, yrs. (IQR)	70 (67-74)	70 (68-74)	0.37
Male gender (%)	183 (50)	212 (48)	0.58
Hypertension (%)	305 (83)	362 (81)	0.64
Type II Diabetes (%)	177 (48)	198 (44)	0.32
Obesity (%)	172 (47)	231 (52)	0.12
AF (%)	11 (3)	32 (7)	0.008
COPD (%)	18 (5)	29 (7)	0.32
ACE-I/ARB (%)	251 (68)	334 (81)	<0.001
Beta-blocker (%)	22 (6)	39 (9)	0.13
Heart rate, bpm (SD)	67 (11)	70 (11)	<0.001
SBP, mmHg (SD)	141 (16)	139 (15)	0.09
BMI, kg/m^2 (IQR)	29 (26-33)	30 (27-33)	0.1
ARIC HF risk score, % (SD)	8 (8)	8 (7)	0.54
DASI-METS (IQR)	8 (7-9)	8 (7-9)	0.22
6MWT, m (SD)	468 (103)	459 (78)	0.18
Mobility impairment (%)	15 (4)	48 (11)	<0.001
LVMI, g/m^2 (SD)	93 (22)	83 (23)	<0.001
LVEF, % (IQR)	64 (60-67)	62 (58-67)	0.02
GLS, % (SD)	18 (2.7)	18 (2.5)	0.9
E/e' (IQR)	9 (7-10)	8 (7-10)	0.36
LAVI, ml/m^2 (IQR)	30 (25-38)	32 (26-39)	0.009
Incident HF (%)	49 (13)	27 (6)	<0.001

Table 3-7: Pairwise comparisons of median NT-proBNP between HF groups (t-statistic and p-value [bold]).

	SAHF	SAHF-rFC	SBHF
SAHF-rFC	-3.947015		
	0.0002		
SBHF	-4.792703	0.148054	
	0.0000	**0.8824**	
eSCHF	-3.541327	-0.116940	-0.261107
	0.0009	**0.4535**	**1.0000**

Figure 3-3: Correlation between Duke activity status index and the six-minute walk test (6MWT).



4 Machine Learning Interpretation of Energy Waveform ECG: A Screening Test for Asymptomatic Left Ventricular Dysfunction

Submitted as: Potter EL, Rodrigues C, Ascher D, Abhayaratna W, Sengupta P, Marwick TH. *Machine learning interpretation of energy waveform ECG: a screening test for asymptomatic left ventricular dysfunction* (J Am Coll Cardiol Imag)**.**

4.1 Preface

The previous chapters focussed on patient data to explore how risk and therefore suitability for screening could be refined. This chapter asks if a preliminary test prior to echocardiographic screening could be beneficial. The test in question is a standard electrocardiogram which has been signal processed. Importantly, it is compared to other candidates; the ARIC HF risk score, NT-proBNP and standard ECG. Indeed, using evidence of manifest disease, i.e. signal-processed ECG abnormalities, would be expected to effectively identify high-risk individuals.

4.2 Abstract

Aims. Asymptomatic left ventricular dysfunction (LVD) has management implications, but routine echocardiographic detection is not undertaken in stage A heart failure (SAHF). Signal processing of the surface ECG using continuous wave transforms (CWT) can identify abnormal myocardial relaxation. We sought whether machine-learning from CWT-processed "energy waveform" ECG (ewECG) could identify subclinical systolic and diastolic LVD.

Methods. EwECG and echocardiography were undertaken in 398 participants with SAHF. Reduced global longitudinal strain (GLS≤16%)), diastolic abnormalities (E/e'>15, left atrial enlargement with E/e'>10 or impaired relaxation) or LV hypertrophy defined LVD. EwECG feature selection and supervised machine-learning by Random Forest (RF) classifier was undertaken with 643 CWT-derived features and the atherosclerosis risk in communities (ARIC) heart failure risk score.

Results. The ARIC score and 18 CWT features were selected to build a RF predictive model for LVD in a training data set (n=287, 60% female, median age 71(68-74) years). Model performance was tested in an independent group (n=111, 49% female, median age 61(59-66) years), demonstrating 85% sensitivity and 72% specificity (AUC 0.83,95% CI 0.74-0.92). With ARIC score removed, sensitivity was 88% and specificity, 70% (AUC 0.78,95% CI 0.70-0.86). RF models for reduced GLS and diastolic abnormalities included similar features but sensitivities were unsuitable for screening. Conventional candidates for LVD screening (ARIC score, NT-proBNP and standard automated ECG analysis) had inferior discriminative ability. EwECG would reduce echocardiography in SAHF by 56% while missing 12% of LVD cases.

Conclusion. Machine-learning applied to ewECG has suitable sensitivity for a screening test for LVD and would reduce the number of echocardiograms by over half.

4.3 Introduction

The echocardiographic recognition of structural and functional cardiac abnormalities among patients with Stage A heart failure (SAHF, patients with HF risk factors) identifies asymptomatic LV dysfunction (LVD), and thereby guides therapy (28). Despite this routine echocardiography is rarely performed in SAHF, other than in coronary artery disease (CAD) (53,126). No viable screening test has evolved to better direct selection for echocardiography.

Standard 12-lead electrocardiography (ECG) is a potential initial investigation in SAHF. A range of ECG abnormalities, e.g. arrhythmias, conduction disturbances and voltage patterns, may relate to underlying LV dysfunction. The potential for a form of signal processing, known as continuous wavelet transform (CWT), to reveal abnormalities in a standard ECG signal has been recognized for over 20 years (127,128). However, only recently have patterns in CWT-processed ECG signals or 'energy waveform ECG (ewECG)' been demonstrated to predict functional LV abnormalities, specifically abnormal relaxation (129). That study of symptomatic patients applied machine-learning to several hundred CWT measures to determine ewECG test performance, with impressive results (129). Recording an ewECG requires no additional time or expertise and simultaneously displays a standard 12-lead ECG trace, making it a feasible test for use in the community. However, although there is an association between repolarization measures and abnormal myocardial relaxation (130), whether prior findings extend to the detection of asymptomatic systolic and diastolic LV dysfunction in populations at risk of HF is unknown. Indeed, the most appropriate use of this technology would be as a screening test to guide definitive echocardiographic assessment. We hypothesized that machine-learning algorithms applied to ewECG data could identify LVD in a community population at risk of HF, and that depolarization and repolarization CWT features were associated with systolic and diastolic dysfunction (DD) respectively.

4.4 Methods

4.4.1 Study participants

Participants were recruited from the community as part of the ongoing Victorian Study of Echocardiographic detection of Left ventricular dysFunction (Vic-ELF; ACTRN 12617000116325), in Melbourne, Australia. Participants were aged ≥65 years with at least one of the following HF risk factors; obesity (BMI ≥30 kg/m^2), type 2

diabetes mellitus or hypertension (systolic blood pressure ≥140mmHg or on medication). Exclusion criteria included LV ejection fraction (LVEF) ≤40%, known symptomatic heart failure (or diagnosed at baseline screening), known coronary artery disease (CAD; excluded due to the routine use of echocardiographic assessment in this group), moderate or greater valvular heart disease, renal impairment and symptoms of HF.

A group of de-identified external participants formed the test dataset (n=111). All had at least one cardiovascular risk factor (without established disease) and came from Canberra (Australian National University Medical School), Australia (n=79); New York, NY (Icahn School of Medicine), and Morgantown, WV (University of West Virginia), USA (n=32). This geographical heterogeneity aimed to test model generalizability. The relevant institutional review boards approved the study and participants gave written informed consent.

4.4.2 Clinical measures

Baseline measures and procedures pertinent to this sub-study included: body mass index, resting averaged systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), documentation of cardiovascular risk factors, comorbidities and medications. Clinical data were used to calculate the 4 year risk of incident symptomatic HF using the Atherosclerosis Risk in Communities (ARIC) HF risk score, which has demonstrated utility in risk stratification in subclinical HF (13). Biochemical markers of renal function and N-terminal pro-brain natriuretic peptide (NT-proBNP) were also measured.

4.4.3 Standard electrocardiography and energy waveform ECG

Subjects underwent ewECG evaluation using standard ECG lead placement (MyoVista Version 2.0, HeartSciences, Southlake, TX). The MyoVista ewECG interface displays a standard 12-lead ECG trace as well as an automated diagnostic interpretation based on the University of Glasgow 12-lead ECG interpretive analysis algorithm, which provides both quantitative parameters and qualitative interpretations (131,132). The ECG signal is deconstructed by CWT mathematics, and presented graphically in an energy scalogram (red [high energy] to blue [low energy]) depicting an energy distribution by time (x-axis) and frequency (y-axis) (the “energy waveform”) (Figure 4-1). Energy is expressed as CWT coefficients (a measure of agreement between wavelet and signal at varying scales), rather than a discrete energy

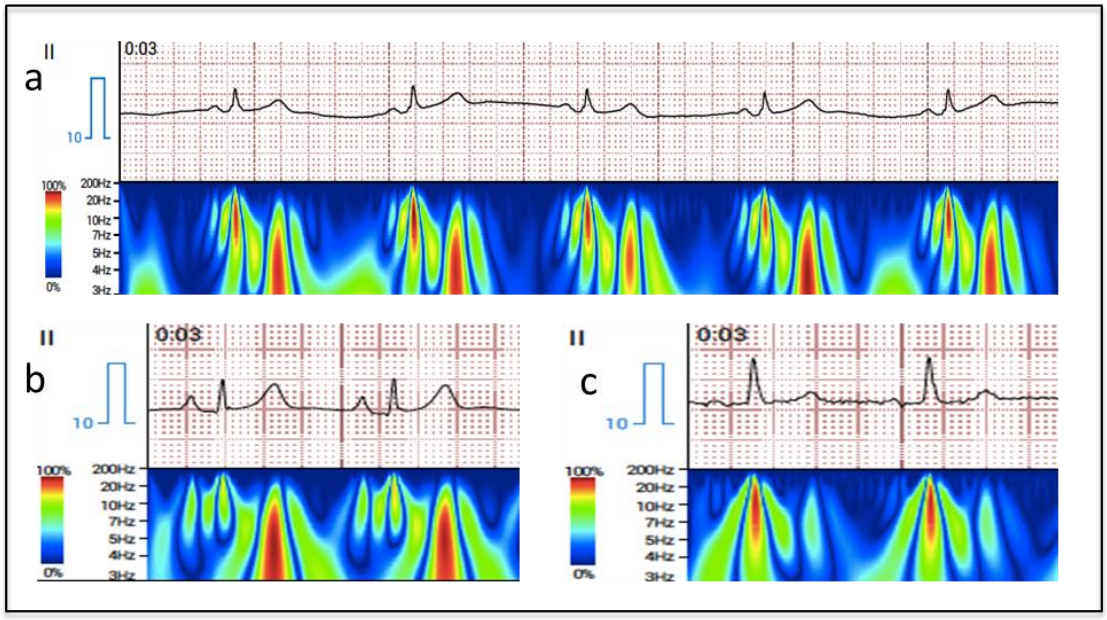
measurement (133). A total of 643 CWT features (energies, frequencies and ratios) at defined points in the cardiac cycle as well as energy spectrum features (ratios of certain harmonics within the energy spectrum) for the 16-second recording window, are generated by proprietary software. CWT features throughout the cardiac cycle are generated, and the equipment's internal analysis algorithms use T-wave-related features to make predictions regarding diastolic function. However, as our prior work demonstrated the existing automated interpretative algorithms to be insufficiently sensitive to detect LVD (134), we used the complete CWT output.

4.4.4 Machine-learning classification model

A supervised machine-learning approach was used to test for LVD status. We used the Random Forest (RF) classifier algorithm, built with 100 trees, using the module Scikit-learn (Python Software Foundation, https://www.python.org/) (135). Given the high dimensionality of the data, including the fact that ewECG features were more numerous than subjects, we undertook a process of feature selection to identify those features with the most predictive information relevant to LVD (Appendix Figure 4-4). All CWT features plus the ARIC HF risk score were offered in feature selection. The ARIC score was offered to evaluate importance of this easily attainable clinical variable against ewECG.

The feature selection approach evaluated the performance of all individual *N* features and selected the best performing in the first round. Then, each of the remaining *N-1* features was paired with the previously selected one to identify the pair that gave the best performance. This process was repeated until all features were selected and the combination of features that provided the best performance was ascertained. Other approaches were tested but were less successful (Appendix). We also evaluated feature importance, indicating the contribution made by each feature to the model's predictive performance. Practically, higher importance means that the decision-making error associated with a feature in the nodes across all decision trees in the forest is less than using other features in other nodes.

Figure 4-1: Conventional ECG traces and corresponding ewECG scalograms after signal processing using CWT. a) a normal ewECG [determined by MyoVista proprietary software and our machine-learning algorithm]. Echocardiogram was normal. b) Predicted abnormal by our machine-learning algorithm. Participant had abnormal systolic function (GLS 15%), of potential significance is the lower energy associated with the QRS and c) Predicted abnormal by our machine-learning algorithm. Participant had diastolic dysfunction, note low energy associated with the T wave.



A 5-fold cross validation was used to internally validate model performance with subsequent external validation on the separate/test dataset. The output of the RF model is a continuous probability score with a default threshold of 50% for dichotomising predicted outcome e.g. LVD vs. no LVD. When evaluating the performance on the external dataset, modification of this probability threshold was investigated to see if performances could be optimised. Unless otherwise stated, the default threshold was found to be optimal.

Echocardiography. On the same day as ewECG a transthoracic 2-D and Doppler echocardiographic study was performed using standard equipment (ACUSON SC2000, Siemens Healthcare USA, Mountain View, CA) and transducer (4V1c, 1.25 to 4.5 MHz; 4Z1c, 1.5 to 3.5 MHz) in accordance with American Society of Echocardiography guidelines. LV systolic function was assessed by global longitudinal strain (GLS) computed using speckle-tracking (Syngo VVI, Siemens Healthcare USA, Mountain View, CA). GLS was the average of regional strains in the apical 2-chamber, 4-chamber and long axis views. Diastolic function was assessed by measuring mitral

inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, septal and lateral mitral annular early diastolic velocities (e') and the E/e' ratio. LAVi was calculated from maximal LA volume using biplane images and indexed to body surface area. Left ventricular hypertrophy (LVH) was defined as LVMi >95 g/m^2 in women and >115 g/ m^2 in men. LVD was defined by either i) abnormal structure (LVH), ii) abnormal GLS ≤16%, or borderline GLS (17-18%) with impaired relaxation (IR) or left atrial enlargement (LAE), iii) diastolic dysfunction (E/e' >15 or E/e'>10 with LAE or IR with LAE).

We developed predictive models for: a) LVD, b) systolic dysfunction (GLS≤16%), c) diastolic dysfunction.

4.4.5 Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) depending on distribution after visual assessment. Between group differences for categorical data were tested using Pearson's chi-square, and for continuous variables the independent t-test or Wilcoxon rank-sum test was used depending on normality of distribution. Because the most important characteristic of a screening test is high sensitivity, cut-points were selected with the minimal number of false positives at a sensitivity closest to 90%. Discriminatory performance predictive models were assessed using area under receiver operating characteristic curve (ROC AUC). To evaluate the incremental utility of the machine learning models compared with the ARIC HF risk score as a base model, continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI) were calculated. CNRI measures improvements in probabilities within events (i.e. increased probability) and non-events (i.e. decreased probabilities), with the addition of, in this case, the machine-learning models (136). IDI reflects the difference in discrimination slopes (probabilities for events minus non-events) between 2 models and is reported herein as the absolute IDI (137). For all analyses, statistical significance was defined as a two-tailed p value <0.05. Analyses were conducted using STATA 15.1 (StataCorp, College Station, TX).

4.5 Results

4.5.1 Participants

Overall, we included 398 participants (57% female, median age 69 (66-73) years) and of these, 171 (43%) had LVD. Baseline characteristics by HF stage are shown in Table 4-1. Compared with SAHF, LVD was associated with older age, a higher proportion of hypertension, T2DM, increased heart rate and systolic blood pressure, and higher ARIC HF risk score. The proportion of an 'abnormal' Glasgow ECG analysis summary was 15% and 36% for SAHF and LVD, respectively ($p<0.001$). All echocardiographic measures differed significantly between HF stages.

4.5.2 Prediction of LVD by conventional methods

The ARIC HF risk score had an AUC of 0.72 (95% CI 0.67-0.77) for LVD discrimination. An optimized cut-point for sensitivity was identified as an ARIC HF risk score of 2.6, providing 90% sensitivity and 40% specificity. Similarly, the AUC for NT-proBNP was 0.53 with an optimized cut-off of 21pg/ml providing a sensitivity of 88% and specificity of 14%. Lastly, an abnormal ECG by Glasgow analysis had a sensitivity and specificity of 36% and 85%, respectively. In those with available NT-proBNP, adding NT-proBNP to ARIC HF risk score (AUC 0.65 [95% CI 0.59-0.71]) did not significantly improve discriminatory ability vs. ARIC alone (AUC 0.63 [95% CI 0.56-0.69], p=0.18). Furthermore, the addition of both NT-proBNP and abnormal ECG by Glasgow analysis did not significantly improve discriminatory ability (AUC 0.67 [95% CI 0.61-0.74], p=0.06) (Appendix Figure 4-5).

Table 4-1: Baseline characteristics by subclinical heart failure stage.

	Stage A HF (n=227)	**LV dysfunction (n=171)**	**p-value**
Clinical and biomarkers			
Age, yrs. (IQR)	68 (62-71)	71 (68-75)	<0.001
Gender (% female)	137 (60)	90 (40)	0.08
Hypertension (%)	185 (82)	152 (90)	0.04
Type II Diabetes Mellitus (%)	41 (18)	60 (35)	<0.001
Atrial fibrillation (%)	9 (4)	13 (8)	0.12
Systolic BP, mmHg (SD)	138 (15)	142 (15)	0.01
Diastolic BP, mmHg (SD)	82 (9)	83 (11)	0.13
Heart rate, beats per min (SD)	63 (9)	66 (10)	0.002
BMI, g/m^2 (SD)	31 (5)	32 (6)	0.09
ACE-I/ARB* (%)	118 (75)	118 (73)	0.64
Beta-Blockers* (%)	17 (11)	25 (15)	0.22
NT-proBNP†, pg/ml (IQR)	51 (30-94)	59 (33-101)	0.39
ARIC HF risk score (IQR)	3.6 (1.22-6.6)	7.1 (3.8-12.9)	<0.001
Standard ECG abnormalities			
Atrial fibrillation (%)	1 (0.4)	4 (2.3)	0.09
LBBB (%)	0 (0)	3 (1.6)	0.05
LV hypertrophy (%)	7 (3)	10 (6)	0.18
Abnormal ECG (per Glasgow analysis) (%)	35 (15)	62 (36)	<0.001
Echocardiographic measures			
LV mass index, g/m^2 (SD)	67 (16)	71 (22)	0.01
LV ejection fraction, % (SD)	64 (6)	61 (7)	<0.001
Global longitudinal strain, % (IQR)	20 (18.9-21)	17 (15.4-18.6)	<0.001
E/A ratio (SD)	0.95 (0.28)	0.80 (0.24)	<0.001
Average e', cm/s (SD)	8.1 (1.7)	7.1 (1.9)	<0.001

Average E/e' (IQR)	8.3 (7.2-9.8)	9.3 (7.3-11.7)	0.003
LAVI, ml/m^2 (IQR)	30 (25-34)	37 (29-42)	<0.001

HF – heart failure, LV – left ventricular, BP – blood pressure, BMI – body mass index, ACE-I/ARB – angiotensin converting enzyme inhibitor/receptor blocker, NT-proBNP – N terminal pro B-type natriuretic peptide, ARIC – Atherosclerosis Risk In Communities, LBBB – left bundle branch block, LAVI – left atrial volume indexed to body surface area. *not available in the Canberra group. †available only in the training dataset.

4.5.3 Prediction of LVD by Random Forest classifier using ewECG

Of the 398 subjects, 287 (72%) were used to train the RF prediction model and 111 (28%) were used to test model performance. Compared with the training dataset, subjects in the test dataset were significantly younger and there was a lower proportion of females, as well as participants with hypertension and diabetes. Furthermore, SBP, DBP and ARIC HF risk were significantly lower. The prevalence of the LVD composite was 23% in the test dataset compared to 51% in the training dataset ($p<0.001$) and a similar pattern was observed for abnormal GLS and diastolic abnormalities (Appendix Table 4-4).

The ARIC HF risk score was selected during feature selection along with 18 CWT features to train an RF model (Table 4-2). At a probability threshold of 0.51 (optimized for sensitivity), the sensitivity and specificity of the model for prediction of LVD on the test dataset were 85% and 72%, respectively (ROC AUC 0.83 (95% CI 0.74-0.92) (Table 4-3). With ARIC removed from the model, the optimized sensitivity and specificity for detection of LVD were 88% and 70%, respectively (ROC AUC 0.78 (95% CI 0.67-0.88), $p=0.32$ for difference between models) (Table 4-3, Figure 4-2). For a prevalence of 43%, this corresponded to a negative predictive value of 89% (95% CI 78-95%) and positive predictive value of 69% (95% CI 60-77%). Incremental improvements in prediction were seen for both RF models compared with the ARIC HF risk score alone, as assessed by cNRI and IDI. For the RF model incorporating ARIC, cNRI was 0.79 (95% CI 0.23-1.17) and IDI 0.09 (95% CI 0.012-0.24). For the model incorporating only ewECG features cNRI was 0.94 (95% CI 0.46-1.29) and IDI 0.11 (0.017-0.255).

The RF classifiers were inspected to reveal their node features. For the LVD predictive model, features were temporally associated with both depolarization and repolarization and included several features derived from the energy/power spectrum i.e. certain ratios of harmonics within the power spectrum throughout cardiac cycles (Table 4-2).

4.5.4 Prediction of low global longitudinal strain by ewECG, using the Random Forest classifier

When the features from the predictive model for LVD were used to train a predictive model for low GLS (≤16%), this was not able to identify any cases of low GLS (Appendix Table 4-5). After repeating feature selection, 16 features were found to confer peak predictive power (Appendix Table 4-6), and performance on the test dataset showed a sensitivity of 57% and a specificity of 90% (Table 4-3). However, the proportion with low GLS in the test dataset (6%) was significantly lower than the training dataset (19%, p=0.002), which is of significance in interpreting model performance. The CWT features selected for the low GLS model were predominantly power spectrum and repolarization features (ARIC HF risk score was not selected). Nine out of the 16 features were chosen for the LVD model.

4.5.5 Prediction of diastolic abnormalities by ewECG, using the Random Forest classifier

Overall, 91 (23%) exhibited diastolic abnormalities, with a significantly lower proportion in the test versus training dataset (13% vs. 27%, p=0.002, respectively [Appendix Table 4-4]). Again, features from the LVD predictive model trained for diastolic abnormalities were unable to discriminate (Appendix Table 4-5). After repeated feature selection, a model with 14 features produced a sensitivity of 50% and a specificity of 90% (Table 4-3). Features selected for inclusion in the model included power spectrum and repolarization features as well as one depolarization-related features that also occurred in the LVD model (ARIC HF risk score was not selected) (Appendix Table 4-7). Ten out of the 14 features were also chosen for the LVD model.

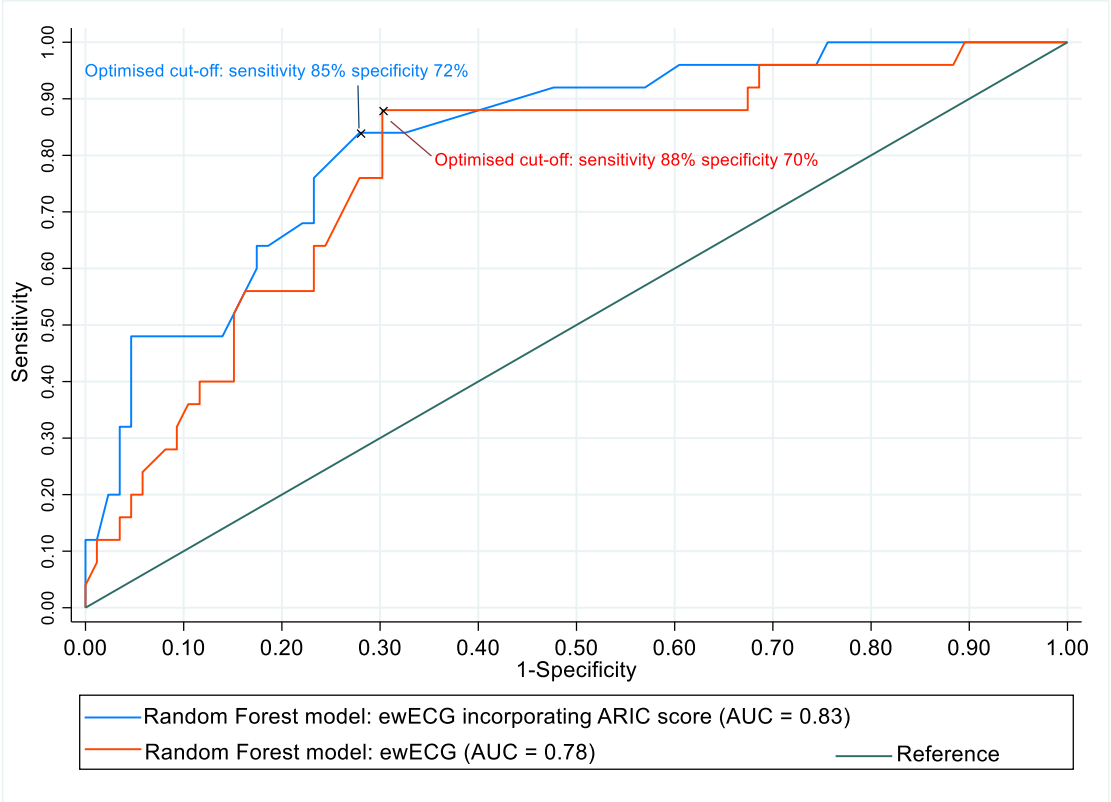
Table 4-2: Model features and relative importance (as a proportion of 1) for predicting LV dysfunction.

CWT feature description	**ECG Lead(s)**	**Variable importance**
Repolarization late measure (RV) below specified threshold		0.01
Repolarization early measure (RV) below specified threshold		0.01
Repolarization late measure ratio exceeded for RV/LV		0.002
Sum of Depolarization measures from Q, R and S waves divided by heart rate	aVF	0.1
Early repolarization is too low (below specified threshold)	V5	0.098
Frequency during minimum energy in early repolarization	V5, V6	0.056, 0.055
Minimum energy at peak repolarization	II	0.095
Frequency during maximum energy in early repolarization	V6	0.09
Frequency during minimum energy in late repolarization	V4, II	0.051, 0.065
Frequency during Repolarization late measure	I, aVF	0.086, 0.092
Polarity of R wave	aVR	0.012
Power spectrum (harmonic) amplitude of the first 4 harmonic peaks is too low	II, V1	0.008, 0.01
Power spectrum (harmonic) amplitudes of the first 4 peaks is too high	II, III, V4, aVR	0.005, 0.006, 0.005, 0.003
Power spectrum (harmonic) 4th peak amplitude is greater than the 3rd peak	aVF, V5	0.018, 0.015

Power spectrum (harmonic) 5th peak amplitude is greater than the 1st peak	II, III, V1, V3	0.013, 0.014, 0.017, 0.013
Power spectrum (harmonic) 5th peak amplitude is greater than the 3rd peak	V4, V6	0.011, 0.009
Power spectrum (harmonic) 1st peak amplitude is too low	V2, V3	0.007, 0.012
Power spectrum (harmonic) 3rd peak amplitude is too low	I, aVL	0.011, 0.015

LV – left ventricular, CWT – continuous wave transform, ECG – electrocardiogram, RV – right ventricular

Figure 4-2: Performance of the random forest classifier model utilizing energy waveform ECG features with and without ARIC-HF risk score, for prediction of LV dysfunction.



4.5.6 Impact of ewECG on a screening process for LVD

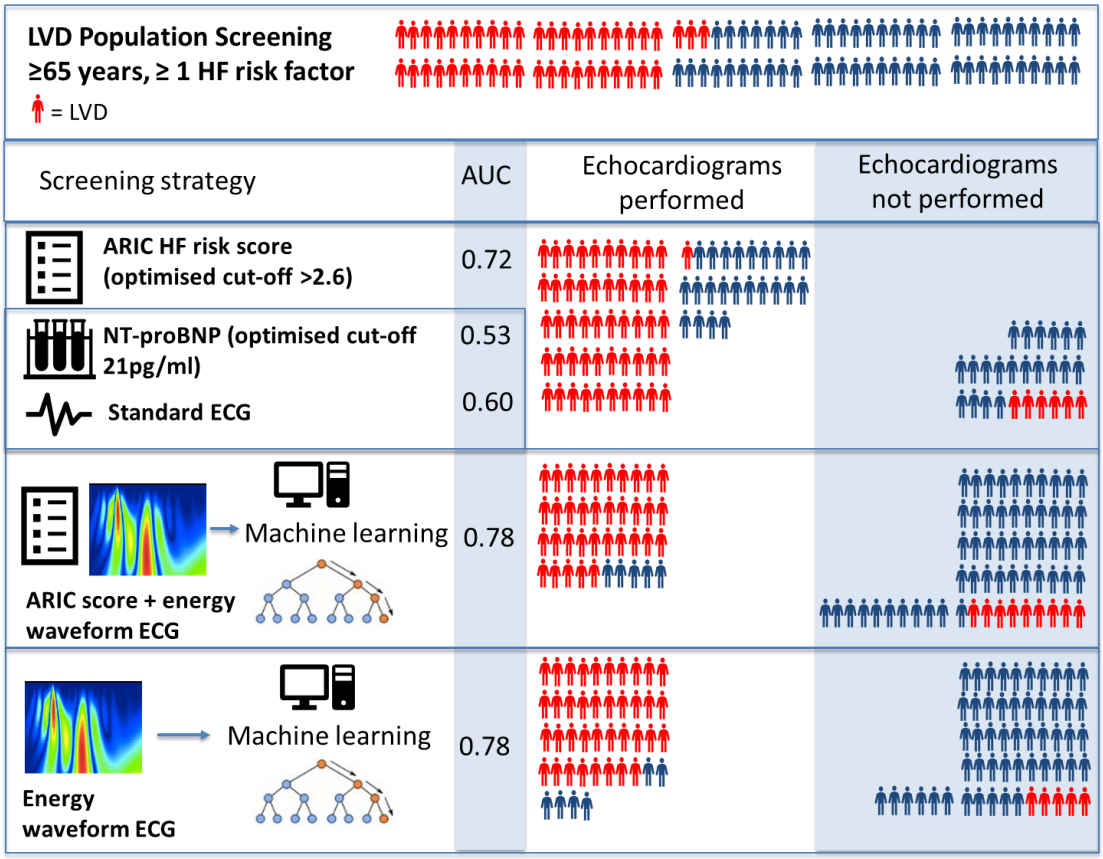
On the basis of greatest sensitivity for LVD identification, the RF ewECG model without the ARIC HF risk score was considered most optimal. Use of this ewECG-based model to select people for echocardiography could reduce the number of echocardiograms by 56% ([true negatives + false negatives]/total screened x 100). However, 12% of cases of LVD would be missed. Alternatively, the RF model incorporating ARIC score and ewECG, would result in a 60% reduction in echocardiograms but would miss 16% of cases of LVD. By comparison, using the best of the conventional methods i.e. ARIC HF risk score ≥2.6, echocardiograms would be reduced by only 27% and 11% of LVD cases would be missed (Figure 4-3).

Table 4-3: Performance of random forest classifier models for predicting LV dysfunction, low global longitudinal strain (GLS) alone and diastolic abnormalities.

Prediction target: LV dysfunction **Model components: ewECG features + ARIC HF risk score**		
	Training (n=287)	**Test (n=111)**
Sensitivity	67%	85%
Specificity	68%	72%
ROC AUC (95% CI)	0.71 (0.64-0.77)	0.83 (0.74-0.92)
F-score	0.68	0.60
Prediction target: LV dysfunction **Model components: ewECG features**		
	Training	**Test**
Sensitivity	66%	88%
Specificity	60%	70%
ROC AUC (95% CI)	0.66 (0.59-0.72)	0.78 (0.67-0.88)
F-score	0.64	0.59
Prediction target: Low GLS		
	Training	**Test**
Sensitivity	35%	57%
Specificity	95%	90%
ROC AUC (95% CI)	0.67 (0.58-0.76)	0.65 (0.37-0.93)
F-score	0.45	0.36
Prediction target: Diastolic abnormalities		
	Training	**Test**
Sensitivity	36%	50%
Specificity	94%	90%
ROC AUC 95% (CI)	0.69 (0.62-0.76)	0.62 (0.42-0.82)
F-score	0.47	0.45

LV – left ventricular, ewECG – energy waveform electrocardiogram, ARIC – Atherosclerosis Risk in Communities, HF – heart failure, ROC – receiver operating characteristic curve, AUC – area under curve.

Figure 4-3: Comparison of strategies for LVD screening showing impact on number of echocardiograms indicated as a result of screening and number of missed cases of LV dysfunction.



4.6 Discussion

The application of signal processing (CWT), to a conventionally acquired ECG signal provides a viable screening test for LV dysfunction. In our cohort of people at-risk of HF, our machine-learning (RF) algorithm provided 88% sensitivity and 70% specificity for detection of LVD, outperforming a clinical risk score, biomarkers and an established automated ECG analysis algorithm. Furthermore, we highlighted that CWT features required for identification of LVD differed slightly according to LV abnormality e.g. reduced systolic function or diastolic abnormality. The best performing model was for prediction of a composite measure of LVD. There was no significant difference between a machine-learning model that incorporated clinical information i.e. the ARIC HF risk score, compared with ewECG features alone. To simplify a process such as screening it would be valid to omit calculation of this risk score. If implemented as a screening test, ewECG could reduce routine echocardiograms by 56% in screening for LVD. This is important given the 82%

prevalence of subclinical HF in the community in those over 67 years (11). For the United States this would mean approximately 40 million people would be eligible for screening and ewECG could reduce the number of echocardiograms by around 23 million (138).

4.6.1 Electrocardiography and myocardial dysfunction

Structural and metabolic cardiac pathology manifesting as electrocardiographic abnormalities is well accepted. However, abnormalities may be too subtle for either the human reader or standard analytics to detect (131). Accordingly, a recent study used artificial intelligence (AI) (convolutional neural networks) applied to standard ECG digital data to predict LVD (defined as LVEF $\leq$ 35%) with a sensitivity of 89%, specificity of 83% and AUC of 0.93 (139). Interestingly, those with a "false positive" result were 4 times as likely to develop LVD during 4-year follow-up, suggesting the AI could recognize early abnormalities. Another approach extracted advanced ECG (A-ECG) parameters (3D ECG parameters, QRS/T wave complexity parameters) including variability analysis (5-minute high fidelity ECG recording) as well as conventional ECG measures to devise a prediction score for myocardial disease (140). The authors demonstrated that a 5-parameter A-ECG score (derived using a feature selection technique and logistic regression) had 83% sensitivity and 93% specificity for LVD (LVEF<50%) in a group of predominately male subjects with either CAD or LVH. Interestingly, none of the features used in this score required an extended duration, high sample rate recording, and as such could be attained from a conventionally recorded ECG, after advanced analytics. These works and ours, demonstrate a growing body of evidence supporting the feasibility of electrocardiographic identification of LVD.

4.6.2 Continuous wavelet transforms processing and cardiac disease

Wavelet transforms have been applied to the ECG signal for measurement of intervals, noise reduction and importantly identification of abnormalities (141). One of the first applications was identification of ventricular late potentials (VLPs), micro-voltage deflections after (and sometimes within) the QRS complex that are often obscured by noise (128,141). The detection of VLPs using CWT improved prediction of post-infarction ventricular arrhythmias from 52-72% and 64-76% for inferior and anterior infarctions, respectively, compared to standard signal filtering (142). Wavelet transforms have also revealed electrical similarities (abnormal frequency content)

within the QRS complex in congenital and acquired long QT syndrome, providing insight into shared electro-pathophysiology (143).

While CWT-processed ECG has demonstrated value by revealing known or suspected electrical abnormalities, there are limited data on a direct association between CWT-processed ECG features and cardiac *function*. Associations between standard ECG features and cardiac dysfunction has focused on long QT syndrome, which is associated with increased isovolumetric relaxation time, altered tissue Doppler velocity profiles and mechanical dispersion (144,145). Furthermore, the interval from T-wave peak to T-wave end (TpTe) is increased in DD assessed by mitral inflow and tissue Doppler velocities (130). At the molecular level, DD is partly related to low amplitude calcium transients secondary to reduced calcium uptake into, and leakage from, the sarcoplasmic reticulum (146,147). Given calcium is a key modulator of the action potential duration, disturbances in the electrical signal on the surface ECG may be apparent in LV dysfunction. It follows that detailed decomposition of the ECG signal from a diseased myocardium may reveal characteristic abnormalities, and indeed, the machine-learning model using only ewECG features provided accurate detection of LVD. Recently CWT-processed ECG (as used in our study) has shown 80% sensitivity and 84% specificity for abnormal relaxation, assessed by low e' (AUC 0.9) in a cohort of patients presenting with symptoms of CAD (129). As in our study, a machine learning approach (random forest classifier) was used but with far more features (n=257), owing to different methodologies. Furthermore, in a larger patient cohort with similar characteristics (e.g. suspected CAD or indication for LV function evaluation) (n=1202), a machine learning algorithm was trained with ewECG features to quantitatively predict e' (148). This algorithm was able to discriminate guideline-defined thresholds with an AUC of 0.84, and given the model generated a continuous output for e', inaccuracies associated with age-based declines could be avoided. While we chose cut-offs, there is no suggestion that in normal aging GLS declines (149), and our definition of diastolic dysfunction would be inclusive of signs of early disease prior to elevations in left atrial pressure. We also believe that our study population is the most appropriate choice for testing and application of this technology i.e. where echocardiography may not be strictly indicated.

The benefit of our machine-learning method, as opposed to an AI approach (e.g. neural networks), is the potential for interrogation of the model to provide mechanistic insight. We were interested to see whether systolic dysfunction was exclusively,

temporally associated with depolarization features, which it was not. This may not be surprising for two reasons: 1) the surface ECG is a simplification of electrical activity spreading across the complex 3D structure of the heart and body and 2) early LV systolic dysfunction and diastolic dysfunction often coexist (150,151). The predictive model for diastolic abnormalities included measures from depolarization as well as repolarization, and most of the features within the low GLS and diastolic models also appeared in the composite LVD model. Clearly, investigation concerning the association between LV dysfunction and specific CWT signatures is in its infancy and is likely to be facilitated by machine-learning algorithms.

4.6.3 Screening for LV dysfunction

The detection of subclinical LVD fulfills some but not all criteria for screening (54). On an individual and population health level, HF is burdensome, and its natural history involves an early asymptomatic stage that is readily detected by abnormal GLS and DD, which carry risk of symptomatic HF and mortality (30,34,152,153), analogous to standard markers of impaired LV function (29,34). In terms of treatment, guideline-advocated therapies (ACE-I, ARBs and beta-blockers) significantly improve outcomes (9,154,155), not only in populations with ischemic cardiomyopathy with reduced ejection fraction (EF), but also in subjects with reduced GLS and diastolic abnormalities with preserved EF, where intensification of cardioprotective therapies may reduce progression to symptomatic HF (14).

Although echocardiography is safe and accurate, cost and access may be problematic. The cutoffs that we have developed with ewECG have a sufficiently high sensitivity for use in screening, and the test is low risk and acceptable to patients. The sensitivity of ewECG in our study is superior to both mammography in breast cancer screening, and fecal occult blood tests for colorectal cancer screening, although specificity is lower (156-158). However, the risks associated with further testing after a positive ewECG (i.e. echocardiography) are far lower than for colonoscopy, for example. Nonetheless, further work with ewECG will need to include integration of machine-learning algorithms into the device's software to enable immediate interpretation and guide decision-making, and integration of ewECG into clinical workflows.

The alternative is the use of natriuretic peptides (NP) (e.g. BNP ≥50 pg/ml) to guide therapy. Intensification of RAS and beta-blockade in diabetics with NT-proBNP

>125 pg/ml has been shown to reduce cardiovascular (CV) hospitalizations compared with usual care (RR 0.52, 95% CI 0.4-0.68) (159). However, although previous work has shown NP-based therapy reduces asymptomatic LVD in individuals >40 years with CV risk factors (adjusted OR 0.6, 95% CI 0.39-0.93), that study showed no significant difference in HF hospitalization over the 4.2 year mean follow-up (61). Indeed, we found that NT-proBNP had poor screening performance. An inherent problem of BNP in this setting is that levels are artefactually reduced in the setting of obesity. Thus, the role of NT-proBNP in a screening role in this population remains unclear.

4.6.4 Limitations

Machine-learning models are inherently limited by the amount of data available to train the algorithm. Continued acquisition of ewECG data will continue to improve our models. We demonstrated that models differ between targets; performance for one cardiac abnormality in one population should not be extrapolated to others. The poor performances observed for prediction of diastolic abnormalities and early systolic dysfunction are likely due to the small number of abnormal studies available for the algorithm to train; as well as the fact that the over-represented group (in this case normal studies) is, by chance, more likely to be predicted. Our study is cross-sectional and therefore we do not know what proportion will go on to develop symptomatic heart failure, or whether ewECG varies between those who do or do not progress. Furthermore, it is unknown whether ewECG can reveal abnormalities before the onset of early LVD or in the subset of patients who fail to exhibit resting echocardiographic abnormalities prior to manifesting HF. It also remains to be seen whether ewECG can predict incident HF.

4.7 Conclusion

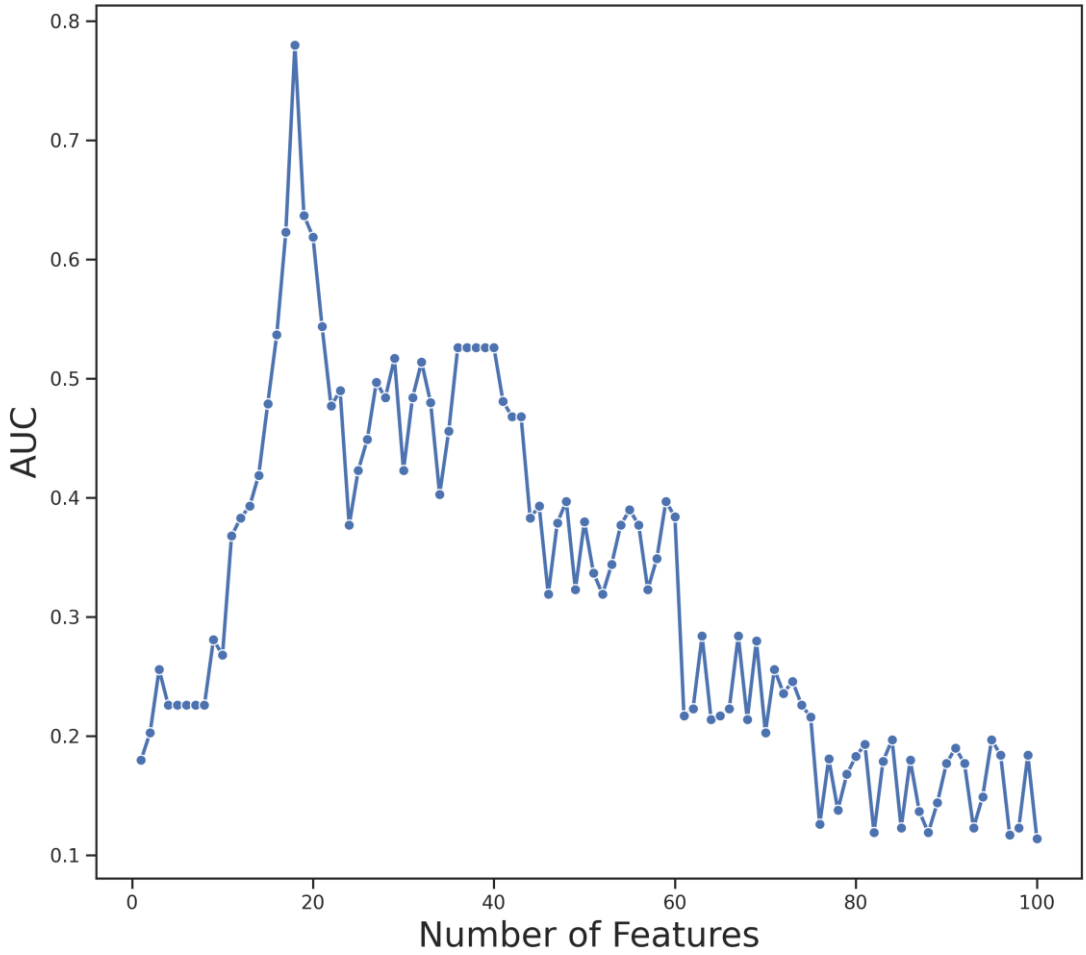
Echocardiography is necessary in patients at risk of subclinical LV dysfunction, who are at increased risk of HF. Advanced analysis of a routinely acquired ECG using CWT signal processing and machine learning provides a suitably sensitive screening test for detection of LVD. Should such screening be adopted, it could reduce the number undergoing echocardiography by over half.

4.8 Postscript

EwECG provides a promising pre-screening step but at present its true value in this setting is unclear given the sample size of this analysis. The reliance on an external machine learning algorithm is also a barrier to its implementation. Given that the ewECG technology used in this study is commercial and proprietary, there is only limited scope for us to influence the development of the system for our purposes.

4.9 Appendix

Figure 4-4: Graphical representation of feature selection with AUC for discrimination of LVD with progressive number of model features.



With reference to other feature selection processes evaluated:

1. Removing features that have a **low variance**. This is a baseline approach that removes features that have the same value for all entries or in which the variability across the data is too low (more than 80% of entries have the exact same value). This sort of feature is meaningless given it does not differentiate between classes. Here we were able to reduce the number of features to only 287.

2. Using **Recursive Feature Elimination.** This approach is similar to the method selected in the manuscript. However, this algorithm considers the weights/importance assigned to each feature by an external classifier at each round of feature selection until a number X of features is selected. Here we tested this approach using X = 100 and X = 50. Below are the performances for each type targeting the SBHF class. Neither performed well.

X = 100 features

	Training (278)	**Blind test (111)**
Sensitivity	58%	56%
Specificity	53%	66%
AUC	0.55	0.61

X = 50 features

	Training (278)	**Blind test (111)**
Sensitivity	64%	68%
Specificity	55%	69%
AUC	0.60	0.68

Reference: Guyon, I., Weston, J., Barnhill, S., & Vapnik, V et al. Gene selection for cancer classification using support vector machines. Mach. Learn. 2002. 46; (1-3), 389–42

Figure 4-5: Comparison of logistic regression model discrimination for ARIC HF risk score alone and the combination of ARIC HR risk score, NT-proBNP and abnormal conventional ECG analysis.

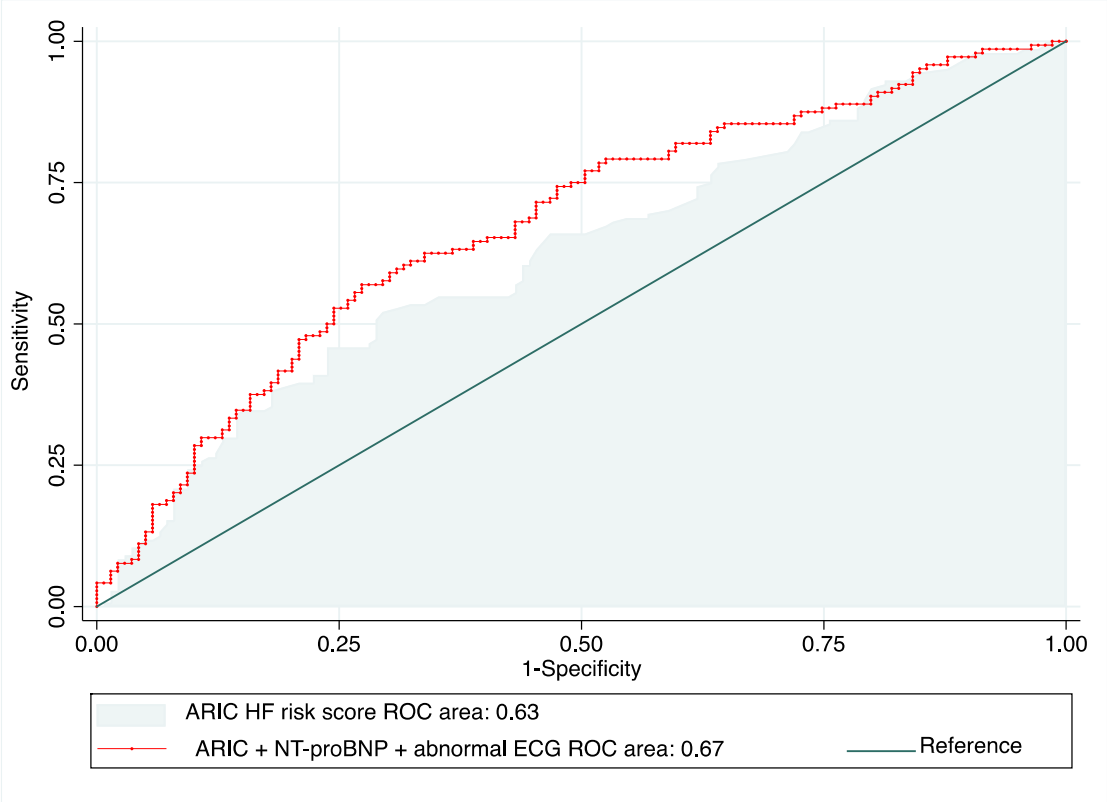


Table 4-4: Baseline and Outcome characteristics by training versus test dataset.

	Training (n=287)	**Test (n=111)**	**p-value**
Age, yrs. (IQR)	71 (68-74)	61 (59-66)	<0.001
Gender (% female)	171 (60)	54 (49)	0.05
Hypertension (%)	252 (88)	85 (77)	0.005
Type II Diabetes Mellitus (%)	92 (32)	9 (8)	<0.001
Systolic BP, mmHg (SD)	142 (14)	134 (16)	<0.001
Diastolic BP, mmHg (SD)	84 (9)	79 (10)	<0.001
Heart rate, beats per min (SD)	65 (9)	64 (10)	0.48
BMI, g/m^2 (SD)	32 (6)	31 (5)	0.23
ARIC HF risk score (IQR)	6.3 (3.8-10.6)	1.2 (0.8-2.6)	<0.001
Standard ECG abnormalities			
Atrial fibrillation (%)	5 (1.7)	0 (0)	0.16
LBBB (%)	3 (1)	0 (0)	0.28
LV hypertrophy (%)	15 (5)	2 (1.8)	0.13
Abnormal ECG (per Glasgow analysis) (%)	81 (28)	16 (14)	0.004
Echocardiographic measures			
LV mass index, g/m^2 (SD)	68 (20)	69 (17)	0.53
LV hypertrophy (%)	17 (6)	4 (4)	0.35
LV ejection fraction, % (SD)	63 (7)	62 (5)	0.65
Global longitudinal strain, % (IQR)	19 (17-20)	20 (18-21)	<0.001
GLS ≤ 16% (%)	54 (19)	7 (6)	0.002
E/A ratio (SD)	0.83 (0.22)	1.03 (0.33)	<0.001
Average e', cm/s (SD)	7.8 (1.9)	7.4 (1.7)	0.03
Average E/e' (IQR)	8 (7-10)	9 (8-11)	0.001
LAVI, ml/m^2 (IQR)	35 (30-41)	25 (22-31)	<0.001
Diastolic abnormality (%)	77 (27)	14 (13)	0.002

LV dysfunction (%)	146 (51)	25 (23)	<0.001

LV – left ventricular, BP – blood pressure, BMI – body mass index, ARIC – Atherosclerosis Risk In Communities, HF – heart failure, LBBB – left bundle branch block, LAVI – left atrial volume indexed to body surface area

Table 4-5: Performance of a model trained with the same features as for LVD prediction.

Prediction target: Low GLS		
	Training	Test
Sensitivity	0%	0%
Specificity	100%	100%
AUC	0.50	0.50
Prediction target: Diastolic abnormalities		
Sensitivity	3%	7%
Specificity	98%	98%
AUC	0.50	0.53

Table 4-6: Model features and importance for predicting low global longitudinal strain (≤ 16%).

CWT feature description	ECG Lead(s)	Feature importance
Repolarization late measure (LV) below specified threshold		0.013
Repolarization late measure ratio exceeded for RV/LV		0.004
Repolarization early measure ratio exceeded for RV/LV		0.005
Repolarization late measure (RV) below specified threshold		0.01
Repolarization early measure minus repolarization late measure above threshold		0.035
Repolarization early measure (RV) below specified threshold		0.01
Repolarization early measure minus repolarization late measure less than specified threshold		0.012
Repolarization early measure (LV) less than specified threshold		0.011
Polarity of R wave	V6, 1	0.017, 0.037
Power spectrum (harmonic) amplitude of the first 4 harmonic peaks is too high	V4, V5	0.015, 0.018
Power spectrum (harmonic) 4th peak is greater than the 3rd peak	V2	0.035
Power spectrum (harmonic) amplitude of the first 4 peaks is too low	III, aVR	0.05, 0.019
Power spectrum (harmonic) 1st peak is too low	V2, aVF	0.02, 0.036
Power spectrum (harmonic) 3rd peak is too low	V6	0.04
Power spectrum (harmonic) actual ratio of 2nd peak to the first 1st peak	V5	0.527
Power spectrum (harmonic) 2nd peak is greater than the 1st peak	I, V5, aVL	0.028, 0.029, 0.039

Table 4-7: Model features and importance for predicting diastolic abnormalities.

CWT feature description	ECG Lead(s)	Feature importance
Repolarization late measure (RV) below specified threshold		0.01
Repolarization early measure (RV) below specified threshold		0.01
Repolarization early measure minus repolarization late measure above threshold		0.011
Repolarization early measure minus repolarization late measure less than specified threshold		0.012
Repolarization early measure (LV) less than specified threshold		
Sum of Depolarization measures from Q, R and S waves divided by heart rate	aVL	0.301
Frequency of minimum energy in late repolarization	V6	0.104
Frequency of the Repolarization late measure	V4	0.069
Polarity of R wave	aVL, II	0.028, 0.045
Power spectrum (harmonic) amplitude of the first 4 harmonic peaks is too high	aVL, V1, V5, V6, III	0.014, 0.026, 0.015, 0.0, 0.009
Power spectrum (harmonic) amplitude of the first 4 peaks is too low	V4, V5, V6, aVR, aVF, I, II	0.019, 0.013, 0.009, 0.011, 0.022, 0.016, 0.01
Power spectrum (harmonic) 1st peak is too low	V4, V5, V6, aVR, III	0.024, 0.018, 0.02, 0.021, 0.017
Power spectrum (harmonic) 3rd peak is too low	V3, V4, V6	0.034, 0.026, 0.018
Power spectrum (harmonic) 4th harmonic peak is greater than the 3rd peak	V2	0.023

PART 2: Echocardiographic measures to identify subclinical left ventricular dysfunction

5 Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction

Published as: Potter EL and Marwick TH. *Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction*. J Am Coll Cardiol Img 2018; 11(2): 260-274

5.1 Preface

SBHF due to systolic dysfunction is defined as an LVEF <40%. This is insensitive given that strain imaging that can detect reductions in LV systolic function despite a preserved ejection fraction. This thesis proposes that reduced GLS i.e. strain imaging of the left ventricle in the longitudinal plane, be an additional criterion for SBHF. However, despite GLS being a reliable technique it is yet to enter mainstream clinical practice outside of cardio-oncology. Therefore, for the purpose of promoting its adoption into routine echocardiography, this chapter lays out the substantive data in support of its prognostic significance both in our population of interest and in others.

5.2 Abstract

Left ventricular (LV) ejection fraction (LVEF) is a simple measure of global systolic function that pervades the risk evaluation and management of many cardiovascular diseases. However, this parameter is limited by not only technical challenges, but also pathophysiologic entities where the ratio of stroke volume to LV cavity size is preserved. The assessment of global longitudinal strain (GLS) from speckle-tracking analysis of two-dimensional echocardiography has become a clinically feasible alternative to LVEF for the measurement of myocardial function. Evidence gathered over the last decade has shown GLS to be more sensitive to LV dysfunction (LVD) than EF, and to provide additional prognostic information. The technology is validated, reproducible within an acceptable range and widely available. GLS has been proposed as the test of choice in guidelines for monitoring of asymptomatic cardiotoxicity related to chemotherapy. It also has the potential to improve risk stratification, redefine criteria for disease classification as well as determine treatment in asymptomatic LVD due to a variety of aetiologies. GLS provides utility across the spectrum of heart failure (and LVEF) as well as in the evaluation of valvular heart disease. There is a strong case for incorporation of GLS into clinical decision-making. This review appraises the evidence addressing the utility of GLS as a complementary metric to LVEF for incorporation into mainstream clinical practice.

5.3 Introduction

The noninvasive assessment of ventricular function remains central to modern cardiology. The volume-based measurement of left ventricular ejection fraction (LVEF) is fundamentally different from direct measurement of myocardial

motion by tissue Doppler imaging and myocardial deformation, and the reliability and precision of these measurements are also different. In the era of precision medicine, patient-specific measurements are used to make decisions about therapies in individual patients, as well as guidance across patient populations. Moreover, the current era is also marked by the emergence of heart failure with preserved ejection fraction (HFpEF)—in which ejection fraction (EF) is not useful prognostically—as the predominant form of heart failure (HF) (160). In this contemporary review, LVEF and strain are compared to evaluate the benefits of combining these complementary techniques.

5.4 Markers of global LV systolic function

5.4.1 Ejection fraction

Despite differences between techniques, left ventricular ejection fraction (LVEF) has remained a cornerstone of therapeutic decisions that are related to myocardial performance. A variety of LVEF thresholds are pertinent to the initiation of cardioprotective pharmacotherapies and device therapies in HF, as well as the timing of surgery for mitral and aortic regurgitation (43,161).

However, LVEF can be normal despite LV dysfunction (LVD) in the presence of LV hypertrophy and small LV cavity size, where a normal EF may hide a small stroke volume. Moreover, 2-dimensional (2D) echocardiography, the most common imaging modality by which LVEF is determined, has inherent limitations relating to LV cavity border tracing and geometric assumptions. Although fore-shortening has more impact on estimation of LV volumes than EF, this phenomenon needs to be born in mind with sequential measurements.

5.4.2 LV global strain

Strain describes deformation of the myocardium that occurs during the cardiac cycle in the longitudinal, circumferential, and radial planes. These vectors result from the obliquely and oppositely orientated subendocardial and epicardial myofibers which generate an apical counter clockwise twist and a basal clockwise twist driving torsional ventricular contraction (162,163). Strain is a dimensionless index of a change in length between two points: Strain (ε) = L-Lo/Lo (where Lo=baseline length, L = length after deformation). Measurement of strain-rate (SR, the change of strain over time) is accurate when imaging is possible at high temporal resolution.

During systole the LV undergoes longitudinal and circumferential shortening (denoted by a negative value) and radial thickening (denoted by a positive value). Despite initial hopes that this method would improve the quantification of regional function, this application has been disappointing. In contrast, the derivation of global longitudinal strain (GLS) from averaging multiple regions has overcome the effects of regional noise and provided a remarkably robust systolic function marker. Detailed practical and technical guidance relating to strain measurement have been recently published (164,165). For the purposes of this review 'strain' will refer to Lagrangian strain by speckle-tracking echocardiography which has superseded Doppler-based measurement (natural strain). In the interests of simplicity, GLS values herein will not be preceded by a negative sign.

The accuracy of strain has been validated experimentally against in vivo measurement with sonomicrometry, and clinically against magnetic resonance-tagging techniques (166-169). Precision (or reliability) refers to the measurement reproducibility when the test is repeatedly applied under identical conditions. The presence of minimal variance in a reliable test implies that alteration can be interpreted as true signal of pathological change. The larger variability of EF over GLS means that the use of GLS carries an advantage in relation to reclassification, both at baseline (Figure 5-1A) and in sequential follow-up (Figure 5-1B). Although association exists between the accuracy of GLS measurement and readers' experience, echocardiographers with no experience in strain imaging have high precision (intraclass correlation co-efficient 0.975; 95% confidence interval [CI]: 0.912,0.998), similar to that of expert readers (0.996; 95%CI: 0.988,1.000; p=0.0002) (170).

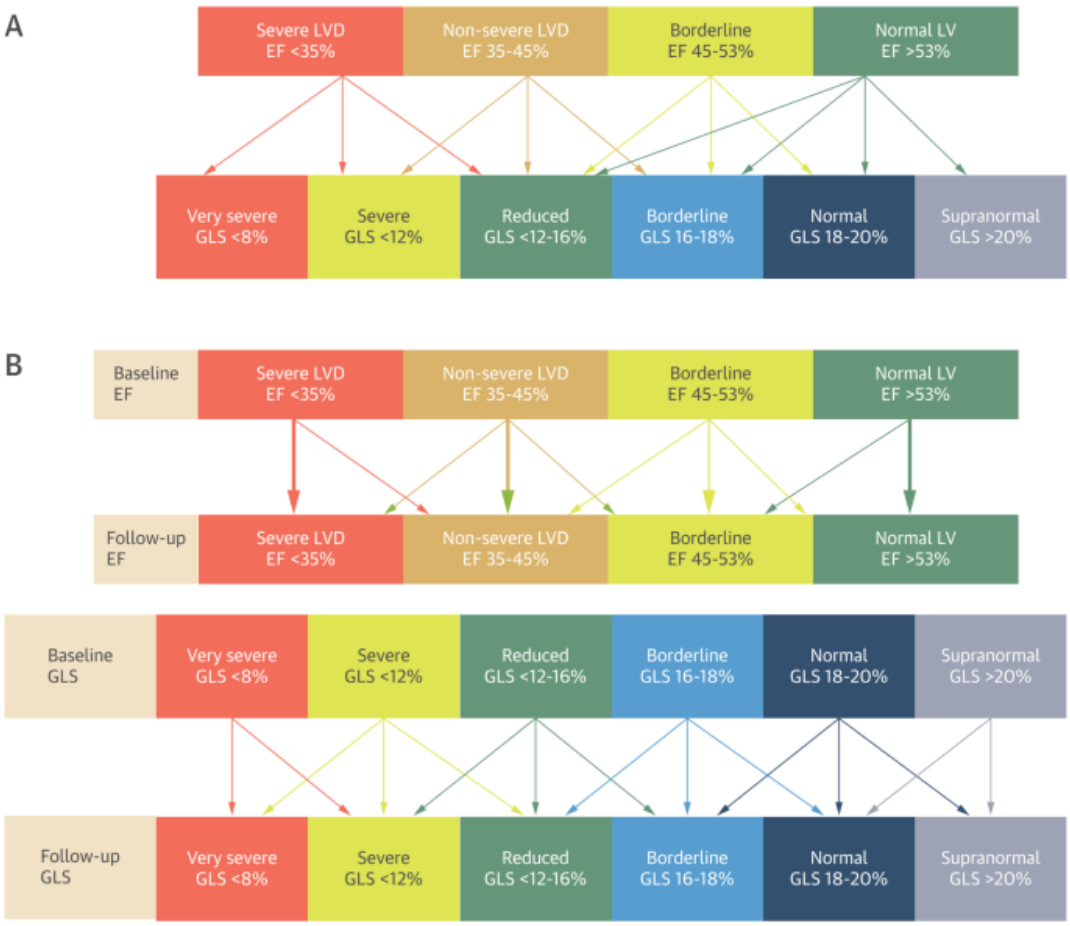
The early phases of the development of strain was marked by significant inter-vendor variability, and vendor-independent software was used to circumvent this problem (171). Since the consensus paper from the European Association of Cardiovascular Imaging (EACVI)/American Society of Echocardiography (ASE) Industry Task Force (172), inter-vendor differences in strain measurements have markedly reduced, to levels similar to (or less than) that of standard parameters including LVEF (35,36).

5.4.3 Reference ranges

Although the normal range of LVEF is >53%, most prognostic value is present when EF is <40%, with very little prognostic information provided in the mild or

borderline ranges (Figure 5-2). Normal reference ranges for GLS have been determined by meta-analysis of study control groups and healthy volunteers (173). In 24 studies involving 2,597 subjects, normal values ranged from 15.9 to 22.1% (mean 19.7%; 95% CI 20.4 to 18.9%). Meta-regression for sources of inter-study variability in strain values found systolic blood pressure to be a significant contributor. Strain declines with age (without significant drop in LVEF) (174), but gender has a more significant impact on normal strain values. In the general population (without cardiovascular disease or traditional risk factors) the absolute GLS difference between men and women is >1% (175,176).

Figure 5-1: Reclassification with GLS. (A) Global longitudinal strain (GLS) may reclassify baseline function at every level of impaired ejection fraction (EF), especially in the normal left ventricle. (B) On a longitudinal basis, the test-retest variability of ejection fraction compromises the ability to reclassify function. GLS is more reproducible and more able to reclassify function in sequential follow-up. In both situations, more extensive reclassifications are available but less common.



5.5 Clinical value from functional evaluation with strain

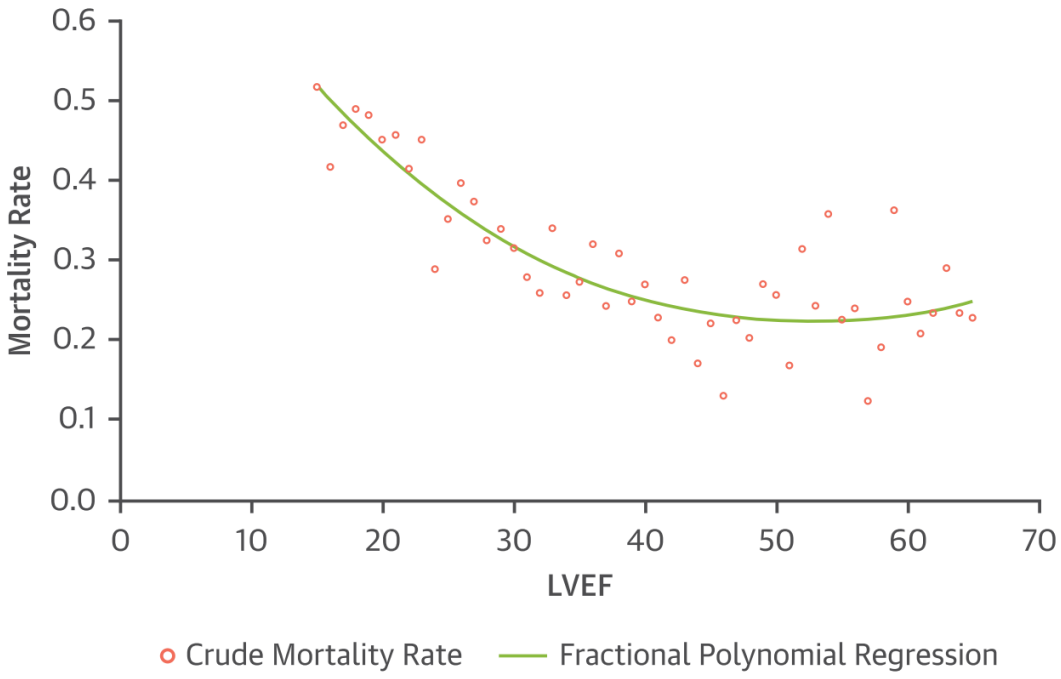
5.5.1 Risk prediction

Reductions in LVEF portend worse cardiovascular outcomes (118,177-179). Although there is an inverse relationship between LVEF and all-cause mortality rate, this plateaus at an EF of 40-45%, above which EF is unrelated to mortality (Figure 5-2) (118). Despite this, heart failure (HF) patients have a similar 1-year mortality irrespective of whether they have preserved (HFpEF) or reduced ejection fraction (HFrEF) (180). In contrast, GLS is a correlate of mortality, independent of and incremental to LVEF in patients with HFrEF (153,181,182). GLS adds significant incremental predictive value for mortality in patients with LVEF >35% (Figure 5-3). A meta-analysis of 5721 subjects across 16 studies of various cardiac diseases has

confirmed that GLS is a stronger predictor than LVEF of all-cause mortality and a composite of cardiac death, HF hospitalization and malignant arrhythmias (153).

Strain imaging has also shown prognostic utility over traditional imaging markers of LV function after acute myocardial infarction (AMI) (183). In 603 patients in the VALIANT (Valsartan in Acute Myocardial Infarction Study) echo sub-study, longitudinal SR provided prognostic value for the prediction of all-cause mortality, independent and incremental to clinical variables and LVEF, and circumferential SR identified patients at risk of LV remodelling.

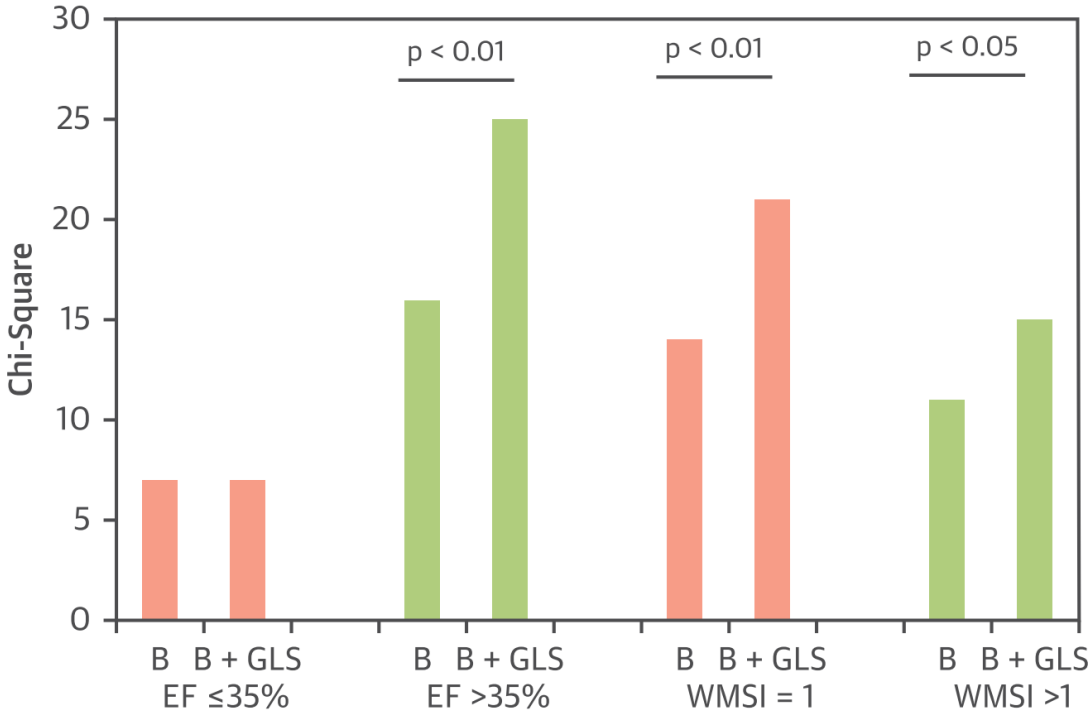
Figure 5-2: Relationship of LVEF with unadjusted all-cause mortality rate. This figure summarizes mortality versus left ventricular ejection fraction (LVEF) in the Digitalis Investigation Group (DIG) trial. Reprinted with permission from Curtis et al (118).



Population-based data also support the prognostic importance of abnormal GLS. Risk of composite AMI, HF and cardiovascular death appears to be 3 times greater for highest versus lowest GLS quartiles. GLS improved the predictive ability of Framingham risk score in a Danish population while natriuretic peptides did not (152). In an elderly population without HF, the prevalence of strain-defined LVD (with a normal EF) was 16.8% compared to 4.2% with abnormal EF. After adjustment for clinical variables, hemodynamic and imaging parameters, the respective hazard ratios

(HR) for cardiovascular events were 2.39 (95% CI 1.2-4.77, p=0.017) and 3.51 (95% CI 1.25-9.88, p=0.014) (184).

Figure 5-3: Association of mortality with GLS. The model chi-square for prediction of mortality when global longitudinal strain (GLS) is added to baseline variables (B), dichotomized by both EF ≤35% or >35% and wall motion score index (WMSI) of 1 or >1. Baseline clinical variables are diabetes mellitus, age, and hypertension based on independent univariable predictors. Data from Stanton et al (153).



5.5.2 Asymptomatic LV dysfunction

Increases in cancer survivorship and the use of cardiotoxic biologic- and chemotherapies, as well as the burden of HF risk factors in the aging population are all drivers of increasing risk of cardiotoxicity. The incidence of CTRCD (defined as a decrement of >10 LVEF percentage points to below 53%) ranges from 13-42% depending on risk profiles, cumulative anthracycline dose and therapy combinations (185,186). Impairments in GLS precede reductions in LVEF, with a 10-15% relative change in GLS early in treatment being predictive of subsequent EF reduction (187). Accordingly, GLS measurement is incorporated into consensus guidelines for abnormal (cardiotoxic) response as a >15% relative reduction in GLS from baseline (185). Whether the use of GLS to guide early cardioprotective therapy results in improved clinical outcomes remains to be established. Nevertheless, it is evident that GLS detects

early subclinical LVD in this population, where long term rates of HF and disease reversibility, particularly with anthracycline-based regimens, are unknown.

5.6 Asymptomatic valve disease

Current guidelines have recently emphasized a classification system analogous to that of HF, including an asymptomatic phase with subclinical LVD.

5.6.1 Aortic stenosis (AS)

Aortic valve replacement may be considered for severe AS and impaired LVEF, even in the absence of cardiac symptoms (161). However, LVEF is an insensitive marker of LV systolic function, especially so in the setting of LV hypertrophy. Impaired LV longitudinal function correlates with LV fibrosis and is associated with poor symptomatic recovery and even deterioration following surgery for symptomatic severe AS (188). Hence, in asymptomatic severe AS with normal EF (>50%), reduced strain (GLS <15%) has an association with mortality and symptom-driven valve replacement, independent of and incremental to standard severity indices (189). Strain imaging in this setting has the potential to provide pathophysiological insights and improve risk prediction, perhaps enabling selection of patients who would gain survival benefit from earlier intervention than guidelines currently recommend.

5.6.2 Mitral regurgitation (MR)

As with AS, guideline-directed surgical management for asymptomatic severe MR incorporates LVEF, with the aim of intervention before LVD develops. However, EF is poorly representative of LV contractile function in MR, and this is reflected by a "supra-normal" LVEF cut-off (≤60%) (161). In severe primary MR, preoperative GLS impairment (<18%) is a strong independent predictor of post-operative LVD (LVEF <50%) irrespective of preoperative EF (190,191).

5.6.3 Aortic regurgitation (AR)

The risk of failing to recognize LV dysfunction is less in AR than MR, because the LV does not eject into the low-pressure left atrium. Consequently, a policy of "watchful waiting" remains the norm in severe asymptomatic AR with preserved EF without LV dilatation. Nonetheless, post- surgical recovery is dependent upon the duration of impaired LV function (192). Hence, the identification of impaired systolic function by reduced GLS prior to LVEF decline might support more vigilant surveillance or earlier valve replacement. Furthermore, interpreting subtle symptoms in patients can be challenging and adjunct objective echocardiographic markers may assist

in decision-making. Symptomatic patients with moderate to severe and severe AR with preserved LVEF demonstrate significantly lower GLS than asymptomatic individuals and control subjects, even after controlling for loading conditions by normalizing GLS to LV end diastolic volume (193). Asymptomatic patients with AR that develop a surgical indication exhibit significantly lower GLS versus those that do not (15.7±2.0 versus 17.6±2.7%, p=0.009), despite the lack of difference in conventional echo parameters including LVEF and clinical variables apart from age (194). GLS is independently associated with need for AV surgery after adjustment for clinical variables and LV volumes; a GLS of ≥19.3% can rule out need for AV surgery with a negative predictive value (NPV) of 100%. An optimized cut-off (Table 5-1) of ≤ 17.4% has been defined for risk of progression during conservative management.

5.7 Symptomatic LVD with preserved EF

While HFpEF has been considered in clinical trials as a single entity, it seems more probable that this disease represents a variety of disease phenotypes, which may be distinguished on the basis of clinical and echocardiographic features. Impaired longitudinal systolic function has been demonstrated in HFpEF and asymptomatic diastolic dysfunction by tissue Doppler and strain imaging (150,151). Abnormal strain is found in around 50-60% of HFpEF (12), probably more with an ischemic etiology (151). Although isolated GLS reduction was rare (6%) in the TOPCAT trial, reduced strain (to ≤15.8%) was associated with higher risk of cardiovascular death and HF hospitalization, and added incremental ability to clinical and standard echocardiographic variables for the prediction of cardiovascular death (12).

The importance of assessment of diastolic function is increasing with the rising prevalence of HFpEF, but despite integration of several indices, a significant proportion of cases are found to be indeterminate. Measurement of left atrial (LA) strain follows the same principles as for GLS and has good inter-observer agreement (r=0.94) (195). Left atrial (LA) strain correlates with invasively measured LV filling pressures and may facilitate the detection and grading of diastolic dysfunction. LA reservoir strain decreases sequentially and significantly with rising diastolic dysfunction grades, and cut-off values were able to discriminate grades with excellent accuracy (195). LA strain holds promise in diastolic evaluation but further validation of cut-off values in larger and more diverse patient groups is warranted.

Table 5-1: Significance of GLS in different patient populations

Study	Design	n	Population	Outcome	GLS cut-off (%)	Size of effect or test performance	Analysis software
Yingchoncharoen et al.(173)	Meta-analysis	2,597	Healthy controls	N/A. Determination of reference range	15.9-22.1 (mean 19.7; 95% CI 20.4-18.9)	N/A	Various
Cheng et al.(175)	Prospective, observational	739	Healthy population cohort (no CVD or traditional RFs)	N/A. Determination of reference range by age group/gender	Mean: M 20.2±2.7, F 22.0±3.2 Lower reference limits (age 45-54) M 15.2 (95%CI 25.1,4.1) F 17.1 (95%CI 27.5,5.1) Lower reference limits (age 75-84) M 14.4 (95%CI 27.6,0.7) F 14.4 (95%CI 27.2,1.8)	N/A	2D Cardiac Performance analysis v1.1, TOMTEC Imaging Systems
Zhang et al.(181)	Prospective, observational	416	HFrEF	Composite (all-cause mortality, transplantation and VAD placement)	≤6.5, lowest tertile vs. ≥ 9.6, highest tertile	HR=3.9; 95% CI, 2.5-6.1 p<0.001	TOMTEC Imaging Systems
Sengelov et al.(182)	Retrospective	1,065	HFrEF	All-cause mortality	Lowest tertile vs. highest tertile (cut-offs not specified) Per 1% GLS decrease	HR=38; 95% CI, 2.3-5.1 p< 0.001 HR=1.15; 95% CI, 1.04-1.27 p=0.008	EchoPAC v12 (GE Healthcare)
Stanton et al.(153)	Retrospective	546	Unselected (established CV	All-cause mortality	12	Same event free survival as LVEF <35%	EchoPAC v8 (GE Healthcare)

			disease or risk factors)				
Biering-Sørensen et al.(152)	Prospective, observational	1296	General population	HF AMI CVD	<15.8, lowest quartile vs. >20.4, highest quartile	HR=4.7; 95% CI, 2.0–5.4; *p*<0.001 HR=3.7; 95% CI, 1.4–10.0; *p*=0.010 HR=2.2; 95% CI, 1.1–4.6; *p*=0.027	EchoPAC v2008 (GE Healthcare)
Russo et al.(196)	Prospective, observational	708	General population (>50 years old)	Composite (AMI, vascular death, stroke)	<14.7	HR=2.39; 95% CI, 1.20–4.77 (vs. healthy reference sample)	Philips QLAB Advanced Quantification v 8.1
Plana et al.(185)	ASE/EACI guideline	N/A	Cardiotoxic cancer therapy	Cardiotoxicity	>15% *relative* reduction from baseline	N/A	Various
Lee et al.(197)	Prospective, observational	95	Hypertension	CVD, HF, AMI, Stroke	<17.6*	Worse event free survival *p*=0.016	EchoPAC PC 2013 (GE Healthcare)
Holland et al.(198)	Prospective, observational	230	Diabetes Mellitus (Type 2)	All-cause mortality and hospitalization	<18.9	Worse event free survival *p*=0.03	EchoPAC v9 (GE Healthcare)
Chen et al.(199)	Prospective, observational	247	Diabetes Mellitus (Type 2)	Composite (CVD, HF hospitalization, AMI, Stroke)	<17.9	Worse event free survival *p*=0.01	EchoPAC v108.1.5 (GE Healthcare)
Weidemann et al.(188)	Prospective	58	Symptomatic AS	Severe fibrosis, lack of functional improvement post AVR	<10	Mean GLS corresponding to outcome	EchoPAC (GE Healthcare)
Yingchoncharoen et al.(189)	Prospective, observational	79	Asymptomatic AS	CVD and symptom driven AVR	≤15	Worse event free survival *p*=0.009	Syngo VVI (Siemens)
Olsen et al.(200)	Prospective	33	Moderate or severe asymptomatic AR	Disease progression versus stability	≤18	Sens 88%, spec 60%. AUC 0.72	EchoPAC PC 6.1.1 (GE Healthcare)

Ewe et al.(194)	Prospective	49	Moderate to severe and severe asymptomatic AR	Disease progression versus stability	≤17.4	Sens 77%, Spec 57%. AUC 0.70	EchoPAC 110.0.0(GE Healthcare)
Mascle et al.(190)	Prospective	88	Severe MR undergoing MVR	Post-op LVD (LVEF <50%)	<18	OR=4.2; 95% CI, 1.4–13; *p*= 0.009)	EchoPAC PC (GE Healthcare)
Witkowski et al.(201)	Prospective	233	Moderate-severe MR undergoing MVR	LV dysfunction (LVEF <50%) at long term follow-up	<19.9	Sens 90%, spec 79%. AUC 0.88 (95% CI, 0.83-0.93)	EchoPAC 108.1.5 (GE Healthcare)
Shah et al.(12)	Prospective	447	HFpEF	Composite (cardiovascular death, HF hospitalization, aborted cardiac arrest)	<15.8	HR=2.14; 95% CI, 1.26–3.66; *p*=0.005	NR
Liu et al.(202)	Prospective	400	HCM	Composite (new onset ventricular arrhythmia, HF, cardiac transplantation, all-cause death	<10 vs. > 16	HR=4.0; 95% CI, 1.5-10.5; p=0.006	EchoPAC 112 (GE Healthcare)
Ng et al.(203)	Prospective	424	ICD (primary prevention)	All-cause mortality Appropriate ICD discharge	<9.9§ <9.9§	Worse event free survival *p*=0.046 Worse event free survival *p*=0.088	EchoPAC v7.0.0 (GE Healthcare)
Biering-Sørensen et al.(204)	Prospective	296	Chest pain (low-intermediate risk)	CAD (≥ 70% stenosis)	18.4	NPV 89%, PPV 50% Sens 74%, spec 58%	EchoPAC (GE Healthcare)
Choi et al.(205)	Prospective	96	Suspected CAD	CAD, high risk	<17.9	NPV 85%, PPV 71% Sens 78.9%, spec 79.3%	EchoPAC BT 06.6.1.0 (GE Healthcare)

			(normal regional motion, LVEF >50%)	(LMCA stenosis, 3 vessel disease)			
Liou et al.(206)	Meta-analysis	1385	CAD (suspected, stable, ACS)	CAD (≥ 50% stenosis)	"Abnormal" per individual study definition. (mean 16.5, 95% CI 15.8,17.3)	Sens 74%, spec 72%. AUC 0.81	EchoPAC, various versions
Dhalslett et al.(207)	Prospective	64	Suspected NSTEACS	CAD (> 50% stenosis)	21	NPV 92%, PPV 74% Sens 93%, spec 78%	EchoPAC v112 (GE Healthcare)
Antoni et al.(208)	Prospective, observational	659	Post-AMI	All-cause mortality	<15.1	HR=4.5 (95% CI, 2.1-9.7)	EchoPAC v7.0.0 (GE Healthcare)

CI – confidence interval, RF - risk factors, M – male, F – female, VAD – ventricular assist device, HFrEF heart failure with reduced ejection fraction, HF – heart failure, AMI – acute myocardial infarction, CVD – Cardiovascular death, N/A – not applicable, NR – not reported, AS – aortic stenosis, AR – aortic regurgitation, AVR – aortic value replacement, MR – mitral regurgitation, MVR – mitral value replacement, OR – odds ratio, HR – hazard ratio, RR – relative risk, CAD – coronary artery disease, HCM – hypertrophic cardiomyopathy, HFpEF – heart failure with preserved ejection fraction, ICD – implantable cardioverter defibrillator, LMCA – left main coronary artery, sens – sensitivity, spec - specificity.*epicardial longitudinal strain, § peri-infarct strain

5.8 Symptomatic LVD with reduced EF

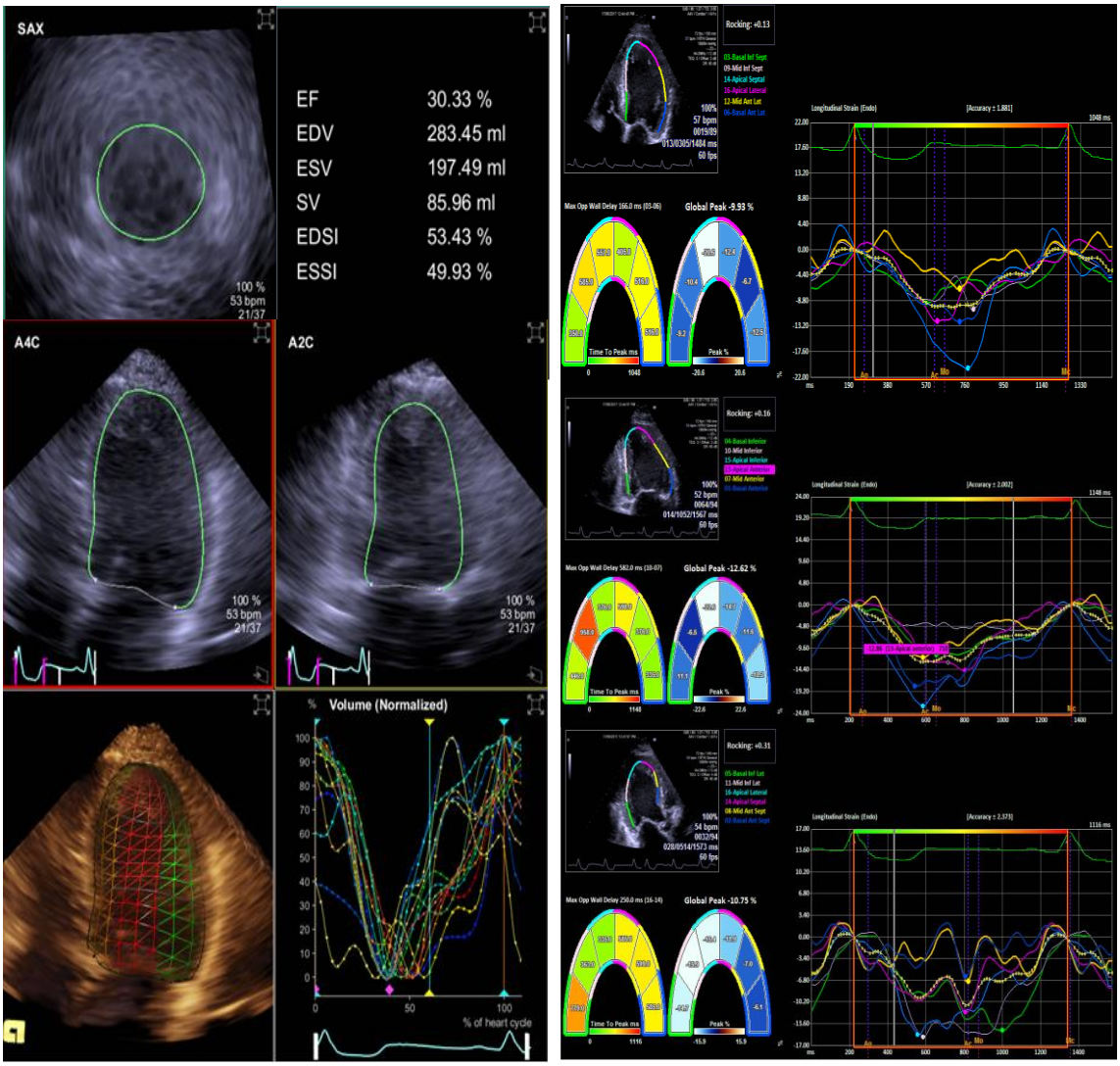
LVEF determines eligibility for primary prevention implantable defibrillator devices after AMI and cardiac resynchronization in HFrEF, but many patients suffer ventricular arrhythmias despite preserved EF. While EF has clear prognostic value in HFrEF, GLS still carries incremental prognostic value. In established ischemic cardiomyopathy, peri-infarct strain is the only independent predictor for ventricular tachycardia and fibrillation (HR 1.22, 95%CI 1.09,1.36) (203), and specific scar sites identified by regional strain may be more pro-arrhythmogenic than others (209). Mechanical dispersion, evidenced by variation in the time to maximal deformation in segmental strain curves (Figure 5-4) reflects heterogenous electrical conduction and thus an arrhythmogenic substrate in cardiomyopathies, channelopathies, and IHD (210). A dispersion cut-off of ≥47ms has 88% sensitivity and 62% specificity for ventricular tachycardia and sudden cardiac death.

Furthermore, guidance of LV pacing lead placement by speckle-tracking is associated with improved outcomes (211,212). Compared with standard placement, pacing a region with greatest mechanical delay (to improve dyssynchrony) and away from areas of severely reduced strain (presumed scar) reduces HF admissions and mortality (HR 0.48, 95% CI 0.28-0.82, p=0.006) (212).

5.9 Hypertrophy

In patients with non-obstructive hypertrophic cardiomyopathy (HCM), imaging provides information on the differential diagnosis as well as prognosis (213). Overt LVD is uncommon but heralds a dire prognosis. Reduction of GLS to 15% in a HCM patient cohort with normal LVEF is associated with fibrosis (214,215). Reduced GLS is the strongest independent predictor of fibrosis assessed by late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR); in the presence of LGE, GLS was 11.8±2.8%, compared with 15±1.7% in its absence (216). Furthermore reduced GLS has prognostic significance in HCM with preserved LVEF (202,216,217); GLS was the strongest independent predictor of outcome (ventricular arrhythmia, heart failure, transplant and all cause death) in a recent study 400 HCM subjects followed for >3 years (202). GLS <10% portended 4 times the risk compared with GLS >16% and there was significantly worse event free survival when subjects were dichotomized by a GLS cut-off of 16% (p=0.004).

Figure 5-4: Reduced GLS in the setting of impaired LVEF. In this patient with symptomatic heart failure with reduced left ventricular ejection fraction (LVEF 30%, left), global longitudinal strain (GLS) was reduced to 11%. This figure also shows both spatial and temporal variation in the 4-, 2- and 3-chamber views.



The differential diagnosis of LV wall thickening due to HCM includes athletic LVH, hypertensive heart disease, and infiltrations. The pattern of reduction of strain can help to distinguish these conditions, with apical sparing in amyloidosis (218), posterolateral defects in Fabry's disease (219) and reduced septal strain in classical HCM.

5.10 Regional LV dysfunction

Resting measurement of strain is helpful in the detection and assessment of IHD when LVEF is normal and when visible resting wall motion abnormalities are absent. This information is based on regional as well as global deformation. "Bull's-eye" strain plots provide an accessible display of data. Post-systolic shortening is an important

marker of ischemic tissue, so the use of end-systolic rather than peak strain is helpful in IHD.

Animal models of induced coronary ischemia have demonstrated regional strain reductions that correlate with region and degree of coronary occlusion (220). In humans with stable coronary artery disease (CAD) both lesion-specific regional strain and GLS are reduced (204). Evidence of basal segment involvement (strain <17.4%), has a sensitivity and specificity of 79% for detection of extensive CAD (left main or 3-vessel), with discriminatory value exceeding those of apical segments or GLS (205). Relative apical-sparing has been observed in left main stenosis compared with 1- or 2-vessel disease despite similar GLS (204). Selective strain imaging of myocardial layers in the longitudinal orientation is also associated with underlying CAD (visual angiographic stenosis ≥ 50%) (221).

Although CAD is inherently a regional disease, abnormal GLS (mean 16.5%, 95% CI 15.8-17.3) detects moderate-severe CAD with a 74% sensitivity and 72% specificity, and good discriminatory value (area under ROC curve 0.81) (206). The addition of resting GLS to exercise ECG and conventional echo indices in patients with low-intermediate risk chest pain (with normal LVEF) improves prediction of severe CAD and may therefore have a role in work-up of this common presenting symptom (206).

Non-ST elevation acute coronary syndromes remain a diagnostic challenge because occluded vessels - especially in the posterior circulation - may not produce ST elevation. In acute presentations, the presence of significant CAD (≥50% diameter stenosis on invasive coronary angiography) is predicted by both peak systolic segmental and GLS (area-under ROC curve of 0.86 and 0.89, respectively). A GLS <21% had a negative predictive value of 92% for exclusion of significant CAD (207). Lesion-specific regional circumferential strain is able to identify coronary occlusion within an hour of presentation with high sensitivity and specificity (222).

Following AMI, GLS may improve risk prediction for all-cause mortality and cardiovascular composite endpoints when LVEF is in the intermediate range (208). Reduced GLS can predict infarct size; a GLS <15% independently predicts infarct mass ≥30g with a sensitivity and specificity of 83% and 93% respectively (223).

5.11 Barriers to the incorporation of GLS into clinical practice

5.11.1 Evidence base

Myocardial strain provides prognostic information that is independent and incremental to standard parameters in a range of clinical scenarios. Improvements in myocardial strain have been demonstrated in hypertensive heart disease, obesity and metabolic syndrome following treatment with spironolactone (224). However, there is an urgent need to link the adoption of strain to improving outcomes by informing decisions.

Current guidelines for the assessment of chemotherapy-related cardiotoxicity advocate formal cardiology evaluation based on GLS cut-offs at baseline, as responding to a GLS reduction relative to an individual's baseline measurement is better justified than use of an absolute cut-off (175,185). The recognition of clinically significant abnormal values is more difficult, as the parameter is influenced by age, gender and loading conditions. Indeed, abnormal GLS has been variably defined based on underlying pathology and outcomes (Table 5-1). In proposing a GLS cut-off, it would be prudent to select a lower threshold than normal reference range to maximize specificity for adverse outcomes across common disease/at risk groups. A gender influence appears consistent in healthy populations but impact on outcomes in disease states is not well established. In addition, gender and age based reference ranges quoted in some data have large confidence intervals (165) (Table 5-1).

5.12 Technical considerations

The feasibility of GLS has been improved by the wide availability of post-processing algorithms. However, as with the adoption of all new technologies, inertia needs to be overcome by education and training. While the learning curve for an echocardiographer to obtain appropriate images is small, it warrants a process of validation and audit (170). User education is needed for general physicians and general practitioners, who typically share the care of multi-morbid and community-based patients with SBHF and HFpEF, in whom strain has much to offer.

The previous variability in measurements between various manufacturers was a significant barrier to the adoption of this method, because it prevented adoption of a standardized normal range, and meant that the use of different echo machines from one visit to the next provided (or obscured) differences. While use of the same manufacturer

is advisable from visit to visit, this cause of variability has been substantially reduced since the conclusion of a concordance process (36).

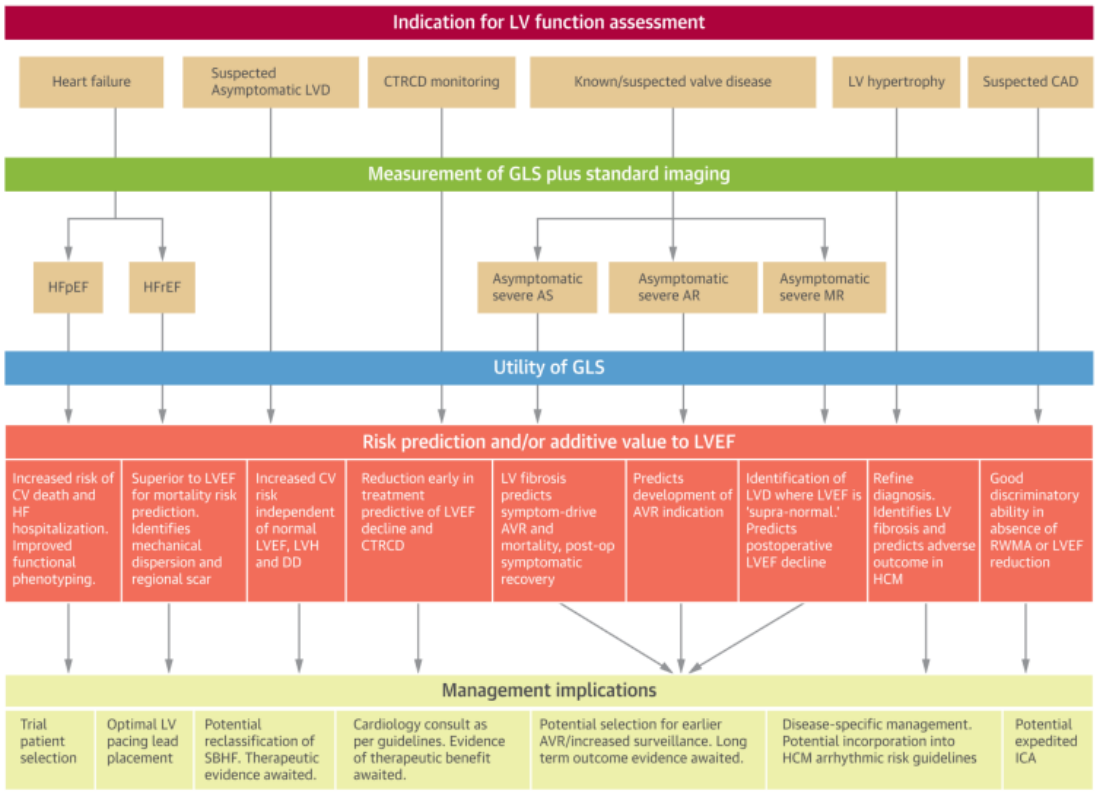
5.13 Conclusions

The measurement of global systolic function is essential in risk assessment and management of all patients with cardiac disease. GLS improves detection of systolic dysfunction beyond LVEF and has revealed additional pathology in scenarios where diastolic dysfunction has been considered the singular or defining abnormality. Reduced GLS has a consistent independent association with adverse outcomes, and its use now is well justified for the purpose of risk evaluation (Figure 5-5). In general, however, the evidence is still being developed to link GLS measurements with changes in management (Figure 5-5). The role that GLS holds in current cardio-oncology recommendations is the exception, and even there, further work on a consensus definition of abnormal absolute values and/or relative changes in GLS and their application in individual disease states is needed. Nonetheless, in addition to cardio-oncology, the value of strain in optimizing LV lead placement exemplifies how the technique can bring unique information to enhance existing management. Its promise in the diagnosis of HFpEF and the recognition of SBHF will extend the contribution of GLS outside of specialist centres because these disease burdens are ubiquitous in the wider community.

The escalating prevalence of obesity and DM as well as population aging are projected to increase the burden of subclinical LVD. Early detection of LVD and initiation of cardioprotective therapy holds promise in the effort to reverse the HF epidemic but large-scale randomized trial evidence is awaited. Routine GLS measurement in this setting will increase the proportion of patients identified as having disease. The adoption of strain imaging therefore raises questions not only around its incorporation into HF staging, but also how imaging resources are allocated to large numbers of patients who are ‘at risk’ but in whom imaging is not presently indicated. Health economic considerations will need to include evaluation of the entire disease management pathway.

Although LVEF will remain a cornerstone of LV function assessment, the addition of GLS enables detailed phenotyping and improved risk assessment and is a tool for present and future therapeutic advancement.

Figure 5-5: Prognostic and management implications of abnormal strain measurement in common clinical scenarios.



5.14 Postscript

This comprehensive narrative review highlights the gaps in knowledge regarding the implementation of GLS. Importantly, its role as a marker of subclinical LVD needs to be supported by evidence that intervention based on GLS measurement is beneficial. This sets the background for one of the hypotheses of the randomized trial reported in chapter 8. However, decisions in medicine are usually made by categorizing patients, and binary cut-offs are inherent in this work. The next chapter addresses how we might go about categorizing GLS in the identification of SBH

6 Normal Range of Global Longitudinal Strain in the Elderly: The Impact of Subclinical Disease

Published as: Potter EL, Wright L, Yang H, Marwick TH. *Normal Range of Global Longitudinal Strain in the Elderly: The Impact of Subclinical Disease*. J Am Coll Cardiol Img 2020. Epub ahead of print https://doi.org/10.1016/j.jcmg.2020.07.014.

6.1 Preface

The prior chapter presented the supporting evidence for the clinical application of GLS. However, there remains uncertainty around the impact of normal ageing on GLS. Understanding of this impact will be crucial in designating a cut-off that triggers treatment in the RCT (chapter 8), which will recruit subjects aged ≥65 years. It is known that GLS >-16% is abnormal and <-18% is normal (and measurements in between are borderline) (225) and the following analysis will establish whether normal aging across the 60th to 80th decades should change these cut-offs.

6.2 Background

The ability to designate normal GLS is central to the incorporation of left ventricular (LV) global longitudinal strain (GLS) into clinical practice (225). While it has been proposed that GLS increases (i.e. becomes less negative) with age, individuals ≥65 years have been underrepresented in normal range studies (226). Moreover, as only 5% of community elderly are free of cardiovascular risk factors (11), the evaluation of 'normal' elderly is challenging - exclusion of those with risk factors is not representative, while their inclusion may incorporate subclinical disease. Elevated N-terminal prohormone brain natriuretic peptide (NT-proBNP) identifies individuals with subclinical disease who are at high risk of developing LV dysfunction and heart failure (HF) (60). To establish whether GLS increases with normal aging we examined the effects of age on GLS in a group of asymptomatic volunteers ≥ 65 years old with HF risk factors, stratified by elevated NT-proBNP.

6.3 Methods

Participants were selected from two community cohorts of elderly (≥65 years old) in Tasmania and Victoria, Australia, and recruited after obtaining informed consent following approval by relevant Human Research Ethics Committees. For inclusion, subjects had ≥1 non-ischemic risk factor for HF, without established HF or ≥ moderate valvular disease, and included in this analysis if N-terminal prohormone brain natriuretic peptide (NT-proBNP) measurement was available. Serum NT-proBNP was measured by electrochemoluminescence immunoassay (Cobas e 601, Roche Diagnostics, Basel, Switzerland) using Elecsys ProBNP III assay kits. Elevated NT-proBNP (>125pg/ml in sinus rhythm and >375pg/ml in atrial fibrillation) defined subclinical myocardial disease. Resting 2D and Doppler echocardiography was performed (ACUSON SC2000, Siemens Healthcare, Mountain View, CA) in

accordance with current guidelines (117). GLS quantification by vector-velocity imaging (Syngo VVI, Siemens Healthcare, Mountain View, CA) was averaged from apical 2-, 3- and 4-chamber views. Participants were divided into age tertiles to assess trends in GLS with advancing age. Tertiles were further divided by elevated NT-proBNP. The reference group was the first age tertile with normal NT-proBNP. To determine the effect of 'normal' aging, GLS in the reference group was compared with the third age tertile with normal NT-proBNP. To determine whether an increase in GLS with age could be attributed to myocardial disease we compared the reference group with the third tertile with elevated NT-proBNP.

6.4 Results

In the 455 participants (age 70 (68-74), 52% female), mean GLS was -18±3% (reduced >-16% in 85 (19%)), and NT-proBNP was 58pg/ml (IQR 28-110pg/ml) (elevated in 88 (20%)). Age tertile 1 (65-68 years), tertile 2 (69-72 years) and tertile 3 (73-88 years) had similar risk factor profiles, but showed a gradation of subclinical HF, with respective NT-proBNP levels of 39 pg/ml (20-79), 56 (33-101) and 87 (42-185) ($p<0.001$). However, there was no increase in GLS with advancing age (-18±3, -19±3 and -18±3 in tertiles 1-3, respectively, $p=0.06$).

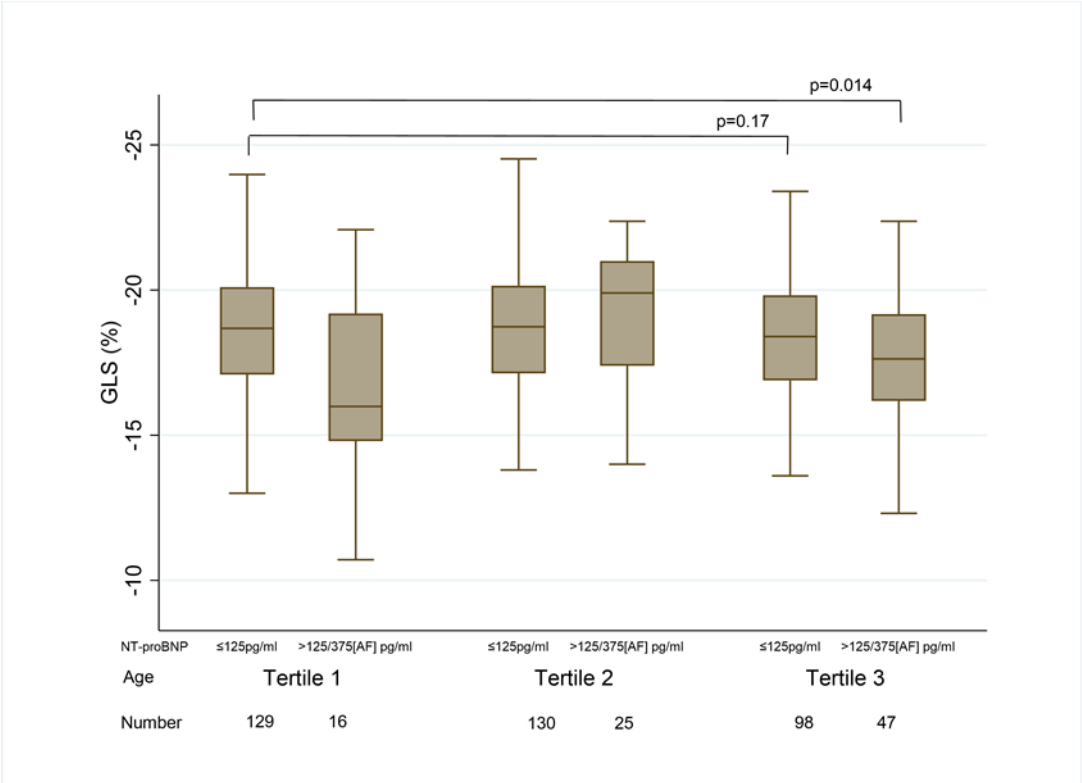
Figure 6-1 shows GLS did not differ with advancing age alone. However, an increase in GLS was seen with advancing age plus elevated NT-proBNP. Similarly, the proportion with GLS >-16% did not increase with age alone but did with advancing age and elevated NT-proBNP (18 (14%) vs. 21 (21%), $p=0.14$ and 15 (32%), $p=0.007$, respectively). In the 375 participants with normal NT-proBNP, mean GLS was -18.6±2.4% and on exclusion of those with GLS >-16% (n=85), mean GLS was -19.3±1.8%. Age was neither a univariable nor a multivariable predictor of GLS (β -0.03, 95% CI -0.08-0.02, $p=0.22$, adjusted for diabetes, hypertension, BMI, smoking, IV chemotherapy and NT-proBNP).

6.5 Conclusions

Our data suggest that reference intervals for GLS should not be age-specific between the ages of 65-88 years and decline is associated with subclinical myocardial disease. In the NORRE study, GLS did not significantly differ by age group, although age was an independent predictor of GLS (226). Furthermore, in those ≥ 60 years (n=95) GLS was -22.4±2.9 (women) and -21.4±2.2 (men). In contrast we report a lower mean GLS of -19±1.8% which may be due to differing study populations (healthy

versus HF risk factors) or different vendors. Nonetheless, we demonstrate that aging is not associated with reductions in LV function by GLS.

Figure 6-1: GLS across advancing age tertiles subcategorized by elevated NT-proBNP. Whiskers correspond to maximum and minimum values.



6.6 Postscript

These data support a single cut-off for abnormal GLS, regardless of age, that can be used direct treatment. This further endorses GLS as a well-defined and understood measure of systolic function. Strain imaging, however, is less well understood in the evaluation of diastolic function. The next chapter seeks to address this by investigating the prognostic implications and the practical application of left atrial strain.

7 Association of asymptomatic diastolic dysfunction assessed by left atrial strain with incident heart failure

Published as: 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*. J Am Coll Cardiol Img 2020; 13(11): 2316-2326.

7.1 Preface

The prior 2 chapters in this section evaluated GLS as an additional echocardiographic measure to identify subclinical LV dysfunction. This chapter moves away from the LV to evaluate function of the left atrium (LA) as another prognostically relevant measure with the potential to contribute to the SBHF definition. Strain imaging of the LA in the reservoir phase, i.e. passive stretch during LA filling may provide ventricular diastolic information. Whether this is incremental to LA volume for the prediction of incident HF is uncertain. If an independent association exists, it must then be determined how LA reservoir strain could be clinically implemented into the well-established and multiparametric assessment of diastolic function.

7.2 Abstract

Background. Left atrial reservoir strain (LARS) measures passive LA stretch and is a sensitive marker of left ventricular (LV) diastolic dysfunction (DD). The potential contribution of LARS to diastolic assessment is unclear.

Objectives. To establish the association of LARS with incident heart failure (HF), and the impact of substituting LARS for LA volume index (LAVI) in diastolic assessment.

Methods. Baseline clinical and echocardiographic assessments were obtained in 758 asymptomatic, community-dwelling elderly subjects (age 70 [67-74] years, 53% women) with non-ischemic HF risk factors. LARS-defined DD (LARS-DD) was assessed by speckle-tracking echocardiography, and grades were assigned as normal (>35%), grade 1 (25-35%) and grade 2 (≤24%. DD grade using current recommendations was compared with grading using LARS <24% in place of LAVI >34 ml/m^2. Patients were followed for up to 2 years for incident HF.

Results. LA strain analysis was feasible in 738 (97%); average LARS was 39 (34-43) %. Incident HF was associated with LARS-DD grade; 8 (36%) of those with grade 2+, 14 (10%) with grade 1 and 39 (9%) with normal function (p<0.001). LARS-DD grade 2+ predicted incident HF after adjustment for clinical and echocardiographic markers (adjusted HR 2.5 [95% CI 1.02-6.3], p=0.049); there was no significant HF risk associated with LARS-DD grade 1. Dichotomized abnormal LARS <24% had an adjusted HR of 2.9 (95% CI 1.25-6.79, p=0.013). Substituting LARS for LAVI provided a 75% reduction in indeterminate diastolic function; all were re-categorized

as normal. There was no increased risk associated normal diastolic function by this grading compared to conventional grading (C-statistic = 0.76 for both models).

Conclusions. LARS-DD grade 2+ is associated with incident HF in the elderly, independent of LAVI. The substitution of LARS for LAVI reduces the number of indeterminate cases without impacting prognosis in normal diastolic function and grade 1 DD.

7.3 Introduction

Heart failure (HF) remains a problem of increasing prevalence (26). Asymptomatic diastolic dysfunction (DD) refers to degrees of impaired left ventricular (LV) relaxation and subsequent elevation in left atrial pressure, in the absence of HF symptoms and portends increased risk of progression to symptomatic HF (7). Current recommendations (32) for echocardiographic diagnosis and grading of DD have increased specificity but increased the number of patients identified as indeterminate (227). The consequence is that subclinical LV dysfunction may be unrecognized in some individuals at risk of HF (stage A HF [SAHF]), who may progress to HF.

Left atrial (LA) volume index (LAVI) is a component of the multi-parametric diagnosis and grading of DD (32), and an independent predictor of incident HF (33). However, deterioration in LA function occurs before structural changes, so use of functional assessment may improve diagnostic and therefore prognostic accuracy (228-230). Assessment of LA function by LA reservoir strain (LARS), a measure of myocardial deformation during LA filling using 2D speckle-tracking echocardiography (STE), provides a more sensitive left atrial marker of DD than LAVI (231,232). Moreover, as LA reverse remodelling i.e. improvement in LA size and function (233,234), is inconsistent, LA volume may better reflect past than current LA pressure. In contrast, LARS provides a more contemporaneous LA measure of diastolic function and therefore be better correlated with prognosis. A lower limit of normal LARS in healthy individuals has been defined (235) and ranges of LARS values to discriminate DD grade have been validated against diastolic guidelines (195) thus providing potential for LARS to simplify the multi-parametric DD assessment (32). There are conflicting data on the incremental prognostic value of LARS to impaired LV global longitudinal strain (GLS), in HF with preserved ejection fraction (236,237). It is presently unclear whether abnormal baseline LARS is associated with incident HF in subclinical HF, a population where prevalence of indeterminate DD is likely to be high.

Accordingly, we sought to 1) investigate the association between LARS-defined DD (LARS-DD) grade and incident HF, including a single cut-off for abnormal LARS and, 2) use LARS in place of LAVI in conventional diastolic function assessment and assess impact on the proportion and prognosis of DD grade, in particular regarding indeterminate diastolic function.

7.4 Methods

7.4.1 Study population

Subjects were recruited from community advertising and primary care practices in Tasmania and Victoria, Australia. Individuals aged ≥65 years were included if they had ≥1 HF risk factor –hypertension (self-reported diagnosis including treatment or blood pressure ≥140/90mmHg), type 2 diabetes mellitus, obesity (body mass index ≥ 30kg/m^2), or previous intravenous chemotherapy/biologic therapy for breast cancer. Patients were ineligible if patient interview, symptom questionnaire or clinical examination identified existing HF, known coronary artery disease (CAD) or life expectancy <1 year, or if at least moderate valve disease and LVEF <40% were identified by echocardiography. Height, weight, heart rate, six-minute walk test (6MWT), and relevant comorbidities and medications were recorded at baseline. All subjects provided written informed consent and the study was approved by the relevant Human Research Ethics Committee.

7.4.2 Standard assessment of diastolic function

Standard transthoracic 2-D and Doppler echocardiographic studies were performed using standard equipment (SC2000, Siemens Healthcare USA, Mountain View, CA) and transducer (4V1c, 1.25 to 4.5 MHz; 4Z1c, 1.5 to 3.5 MHz) in accordance with ASE guidelines (117). Diastolic function was assessed by measuring mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, septal and lateral mitral annular early diastolic velocities (e') and the E/e' ratio. Multiple echocardiographic windows were used to screen for tricuspid regurgitation and maximal velocity recorded with spectral Doppler. LAVI was calculated using the biplane method of disks and indexed to body surface area. Diastolic function was assessed using 2016 American Society of Echo/European Association of Cardiovascular Imaging (ASE/EACVI) recommendations for the evaluation of LV diastolic function (32).

7.4.3 Assessment of LA strain

LARS was assessed using STE using a third-party software program (TOMTEC-Arena™ (Version TTA2), 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 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 R wave (R-R gating). Patients with poor image quality, where strain analysis could not be performed, were excluded. If tracking was inadequate in one (but no more than one) segment, it was excluded. Reproducibility was assessed by two blinded investigators (SR and HK) using a random sample of 50 patients.

7.4.4 Diastolic function assessment using LARS

Where LARS measurement was feasible, a LARS-DD grade was assigned based on previously validated cut-offs (195): >35% (normal), 25-35% (grade 1), 19-24% (grade 2), <19% (grade 3); grades 2 and 3 combined for analysis. Baseline clinical and echocardiographic variables and HF outcome were compared by DD grade. The impact of replacing LAVI with LARS was based on a cut-off of <24% (195,235).

7.4.5 Outcome adjudication

Participants were followed for up to 2 years using questionnaires, telephone calls and in-person clinic reviews. HF was diagnosed by physicians based on Framingham criteria (119).

7.4.6 Statistical analysis

Continuous variables are presented as median with interquartile ranges (IQR) or mean±standard deviation, based on distribution testing using the Shapiro-Wilk test. Categorical variables are presented as frequencies and percentages. Differences between two independent groups were determined using $\chi 2$ and unpaired t-test for categorical and continuous variables, respectively. One-way analysis of variance (ANOVA) (or Kruskall Wallis for non-normally distributed continuous variables) and $\chi 2$ were used to examine the relationship of variables across >2 groups. For comparison of paired data at baseline and follow-up a paired t-test or Wilcoxon sign-rank test was used depending on normality of distribution. Kaplan-Meier survival estimates were used to examine HF-free survival by diastolic function group, and differences in survival distributions were assessed using the log-rank test. Duration of survival

analysis was determined by a minimum ongoing group size of 8-10. Variables with a p-value <0.1 in univariable analysis were selected for inclusion in multivariable Cox modeling. All variables from the baseline assessment (Table 7-1) were considered for inclusion. Ability of Cox models to predict HF outcome was assessed with Harrell's c-statistic. Effect sizes are expressed as hazard ratios (HR) with 95% confidence intervals (CI). Statistical significance was defined as a two-tailed p value <0.05. Analyses were conducted using STATA 15.1 (StataCorp, College Station, TX).

7.5 Results

7.5.1 Patient selection

Seven hundred and fifty-eight subjects (age 70 [IQR 67-74] years, 47% male) were followed over 12 (IQR 9-17) months. Of these, 738 (97%) had imaging suitable for LA strain measurement with an average LARS of 39 (IQR 34-43) %.

7.5.2 LARS-DD grade

Of the 738 subjects in whom LAS measurement was feasible, 526 (71%) had normal diastolic function, 189 (26%) had LARS-DD grade 1 and 23 (3%) had LARS-DD grade 2+. Clinical variables associated with increased LARS-DD grade were increased age, systolic and diastolic blood pressure, as well atrial fibrillation and reduced functional capacity (Table 7-1). Increased LARS-DD grade was associated with impaired LVEF and GLS, increased LAVI and LV mass index (LVMI) (Table 7-1).

7.5.3 Prognostic significance of LARS-DD grade

Incident HF occurred in 61 (10%), most frequently manifest as HF with preserved EF (HFpEF) (in 48 of 53 [91%] undergoing follow-up echocardiography). HF was associated with a significantly greater increase in both E/e' and LAVI than in those without HF (Figure 7-1); most of those with incident HFpEF had ≥ 2 abnormal diastolic parameters (Appendix Table 7-5). Incident HF significantly increased with higher LARS-DD grade with 41 (8%), 16 (8%) and 7 (30%) of those with normal, grade 1 and grade 2+, respectively (p=0.001) (Table 7-1). There was significantly worse HF-free survival for LARS-DD grade 2+ (LARS <24%) compared with other patients (log-rank $\chi 2$ 12.7 p=0.002) (Figure 7-2), but no difference between those with normal diastolic function (LARS >35%) and LARS-DD grade 1 (LARS 24-35%). LARS-DD grade 2+ (HR 3.54, 95% 1.58-7.93, p=0.002) but not LARS-DD grade 1 (HR 0.85, 95% CI 0.47-1.54, p=0.59) was associated with HF, compared to normal diastolic function.

After adjustment for potential confounders including age, heart rate, BMI, diabetes mellitus, 6MWT, GLS, E/e, LVMI and LAVI, LARS-DD grade 2+ reduced remained independently associated with incident HF (HR 2.44 [95% CI 1.01-5.9], p=0.049) (Table 7-2).

Abnormal LARS (<24%) had an adjusted HR of 2.9 (95%1.25-6.79, p=0.013) for incident heart failure (Table 7-3). When echocardiographic covariates were dichotomized the risk associated with abnormal LARS was maintained. The only other echocardiographic risk marker that was independently predictive of HF was reduced GLS (HR 2.28, 95% CI 1.29-3.99, p=0.004).

Figure 7-1: Change in E/e' and left atrial volume index (LAVI) between baseline and follow-up in subjects who did not develop HF versus those who did develop heart failure. Incident HF was associated with a significantly higher mean increase in both E/e' and LAVI.

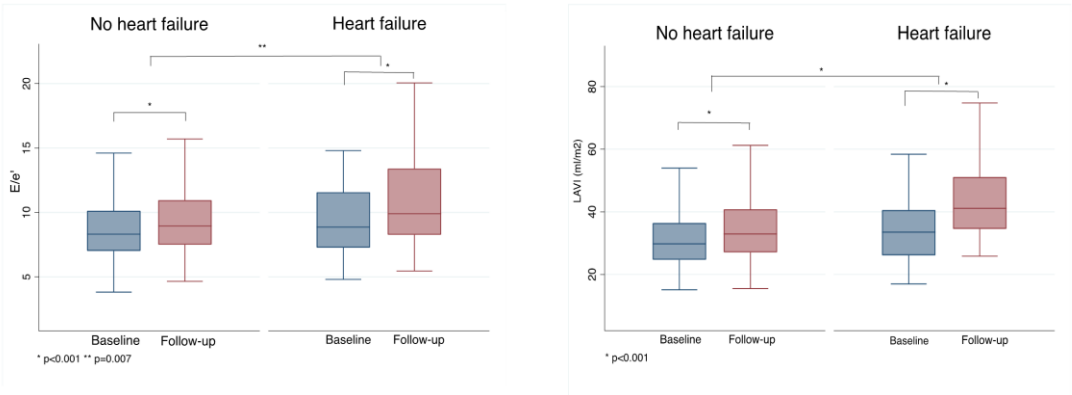


Table 7-1: Baseline characteristics and heart failure (HF) outcome by left atrial strain (LAS) diastolic dysfunction grade.

	LA strain diastolic dysfunction grade			
No. Subjects	0 (526)	1 (189)	≥2 (23)	p-value
Age, yrs. (IQR)	70 (67-73)	71 (68-75)	73 (70-79)	<0.001
Gender, male (%)	257 (49)	81 (43)	10 (43)	0.34
Hypertension (%)	425 (81)	162 (86)	21 (91)	0.16
Diabetes Mellitus (%)	250 (48)	79 (42)	10 (43)	0.39
Cardiotoxic chemotherapy (%)*	44 (8)	12 (6)	1 (4)	0.56
Atrial Fibrillation (%)	32 (6)	20 (11)	5 (21)	0.005
BMI, g/m^2 (IQR)	29 (26-33)	30 (27-34)	29 (27-35)	0.09
Heart rate (IQR)	68 (61-76)	68 (61-76)	66 (58-71)	0.42
SBP, mmHg (IQR)	139 (128-148)	141 (131-151)	144 (130-165)	0.04
DBP, mmHg (SD)	82 (10)	84 (10)	88 (12)	<0.001
ACE-I/ARB (%)	359 (68)	130 (69)	16 (70)	0.98
Beta-blocker (%)	31 (6)	24 (13)	3 (13)	0.008
Functional capacity, 6MWD, m (IQR)	478 (423-525)	457 (408-497)	447 (402-502)	0.004
Echo parameters				
LAS, % (IQR)	41 (38-45)	31 (29-33)	21 (19-22)	<0.001
LVEF, % (IQR)	63 (60-67)	62 (58-67)	61 (55-63)	0.001
GLS, % (IQR)	19 (17-20)	19 (17-20)	17 (15-20)	0.02
E/A (IQR)	0.8 (0.68-0.93)	0.74 (0.64-0.91)	0.78 (0.64-1.2)	0.05
DT, ms (IQR)	243 (210-277)	247 (214-283)	232 (210-261)	0.5
e' cm/s (IQR)	7.8 (6.7-8.9)	6.7 (5.8-7.9)	7.3 (6.0-8.7)	<0.001†

E/e' (IQR)	8.2 (6.9-10)	9 (7-11)	8.3 (6-11)	0.003†
TR V_{max}, m/s (IQR)**	2.2 (2-2.4)	2.2 (2-2.45)	2.4 (2.2-2.5)	0.07
LAVI, ml/m^2 (IQR)	30 (26-37)	34 (27-40)	42 (35-50)	<0.001
LVMI g/m^2 (IQR)	76 (66-89)	81 (66-94)	93 (75-107)	0.003
Incident HF (%)	41 (8)	16 (8)	7 (30)	0.001

IQR – interquartile range, SD- standard deviation, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, ACE-I/ARB – angiotensin converting enzyme inhibitor/receptor blocker, 6MWD – 6 minute walk distance, LVEF – left ventricular ejection fraction, GLS – global longitudinal strain, DT – deceleration time, TR Vmax – maximal velocity of tricuspid regurgitation, LAVI – left atrial volume indexed to body surface area, LVMI – left ventricular mass indexed to body surface area. * 15 participants were included on the basis of prior cardiotoxic chemotherapy alone. ** feasible in 88%. † pairwise comparison significant for normal vs. grade 1.

Figure 7-2: Heart failure-free survival by LA reservoir strain (LARS) -defined diastolic dysfunction (DD) grade. LARS-DD grade 2+ demonstrates significantly worse HF-free survival while normal function and LARS-DD grade 1 are similar.

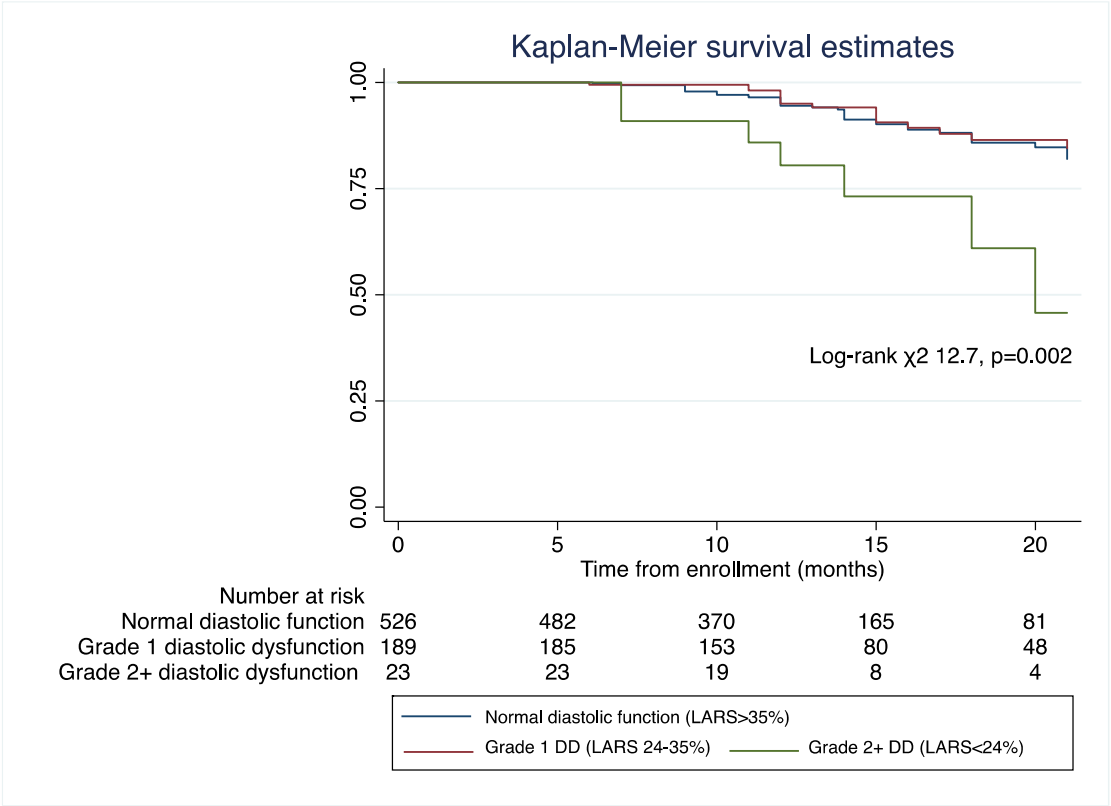


Table 7-2: Multivariable predictors of heart failure in 590 subjects with LA strain measurement.

	Univariable		**Multivariable**	
	HR (95% CI)	p-value	HR (95% CI)	p-value
LARS-DD grade				
Normal diastolic function	ref		ref	
1	0.85 (0.47-1.54)	0.59	0.64 (0.33-1.26)	0.2
≥ 2	3.54 (1.58-7.93)	0.002	2.44 (1.01-5.9)	0.049
Age, years	1.06 (1.01-1.11)	0.018	1.04 (0.99-1.12)	0.3
Gender, male	1.18 (0.71-1.96)	0.64		
Hypertension	1.37 (0.59-3.2)	0.46		
Diabetes Mellitus	3.23 (1.89-5.53)	<0.001	2.63 (1.45-4.76)	0.001
BMI, kg/m2	1.1 (1.04-1.13)	<0.001	1.08 (1.03-1.13)	0.002
AF	0.96 (0.35-2.67)	0.94		
Cardiotoxic chemotherapy	1.11 (0.44-2.77)	0.23		
Heart rate, beats/min	0.97 (0.95-0.99)	0.03	0.97 (0.94-0.99)	0.02
SBP, mmHg	1.00 (0.99-1.01)	0.83		
ACE-I/ARB	1.16 (0.63-2.11)	0.63		
6MWT, m	0.99 (0.993-0.998)	0.003	0.99 (0.99-1.002)	0.71
LVEF, %	0.98 (0.94-1.02)	0.28		
GLS, %	0.86 (0.78-0.94)	0.001	0.9 (0.81-1.01)	0.07
e', cm/s	0.93 (0.79-1.09)	0.35		
E/e'	1.1 (1.01-1.2)	0.033	1.08 (0.98-1.18)	0.14
TR Vmax, m/s	1.7 (0.85-3.55)	0.13		
LAVI, ml/m^2	1.02 (1.00-1.05)	0.05	0.98 (0.95-1.02)	0.33
LVMI, g/m^2	1.02 (1.01-1.04)	<0.001	1.02 (1.00-1.03)	0.047

LARS-DD – left atrial reservoir strain-defined diastolic dysfunction, BMI – body mass index, SBP – systolic blood pressure, ACE-I – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, 6MWT – 6 minute walk test, AF- atrial fibrillation, GLS – global longitudinal strain, TR Vmax – maximal velocity of tricuspid regurgitation, LAVI – left atrial volume indexed to body surface area, LVMI – left ventricular mass indexed to body surface area.

Table 7-3: Multivariable Cox models for abnormal LARS (<24%) and risk of incident HF. Controlling for significant univariables (left) and with the echocardiographic univariables dichotomized (right).

	HR (95% CI)	**p-value**		**HR (95% CI)**	**p-value**
LARS <24%	2.9 (1.25-6.79)	0.013	**LARS<24%**	2.86 (1.19-6.87)	0.019
Age, years	1.04 (0.98-1.1)	0.18	**Age**	1.02 (0.96-1.08)	0.47
Diabetes Mellitus	2.74 (1.52-4.9)	0.001	**Diabetes Mellitus**	2.8 (1.56-5.05)	0.001
BMI, kg/m^2	1.08 (1.03-1.13)	0.003	**BMI**	1.08 (1.03-1.14)	0.001
Heart rate, beats/min	0.97 (0.94-0.99)	0.018	**Heart rate**	0.96 (0.94-0.99)	0.007
6MWT, m	1.0 (0.99-1.002)	0.64	**6MWT**	0.99 (0.99-1.00)	0.44
GLS, %	0.9 (0.81-1.00)	0.07	**GLS ≤ 16%**	2.27 (1.29-3.99)	0.004
E/e'	1.06 (0.97-1.16)	0.22	**E/e'>14**	1.69 (0.71-4.04)	0.23
LAVI, ml/m^2	0.98 (0.96-1.01)	0.31	**LAVI >34**	1.39 (0.77-2.52)	0.27
LVMI, g/m^2	1.01 (0.99-1.02	0.07	**LVH**	1.24 (0.6-2.55)	0.56

LARS – left atrial reservoir strain-defined diastolic dysfunction, BMI – body mass index, 6MWT – 6 minute walk test, GLS – global longitudinal strain, LAVI – left atrial volume indexed to body surface area, LVMI – left ventricular mass indexed to body surface area, LVH – left ventricular hypertrophy.

7.5.4 Impact of replacing LA volume index with LA reservoir strain

Normal diastolic function (n=396, 52%), indeterminate function (n=141, 19%), grade 1 DD (n=195, 26%) and grade 2+ DD (n=26, 3%) were identified by conventional grading (Appendix Table 7-6). Left atrial enlargement (LAE, LAVi >34ml/m^2) occurred in 281 subjects (37%). While the highest proportion of LAE was seen in Grade 2+ DD (92%), 86% of those with indeterminate function had LAE, double the proportion in grade 1 DD (43%). This was not explained by a significant difference in AF prevalence across groups (p=0.11), nor a difference in LARS feasibility across diastolic function grade (Appendix Table 7-6). LARS decreased significantly with worsening diastolic function, but compared with LAE, the proportion of reduced LARS was far smaller (n=23, 3%). The proportion of those with LAE and normal LARS was 93% (257/276) and 99% (458/462) of those with normal LAVI had normal LARS.
Reassignment of diastolic function using LARS in place of LAVI resulted in a 75% reduction in the proportion of indeterminate cases from (18.6% to 4.7%), driven by 113 indeterminate individuals being reassigned normal diastolic function (Figure 7-3). While there was a net reduction in indeterminate cases, 2 normal and 6 grade 2+ individuals became indeterminate. As 10 grade 2+ individuals were also downgraded to grade 1, the proportion of grade 2+ was reduced by 65% to 9 individuals.

Using conventional grading with LAVI (Table 7-4), 25 (6%) of those with baseline normal diastolic function developed incident HF, compared with 11 (8%) with indeterminate function and 23 (12%) of grade 1 DD (p=0.03). By comparison, when using LARS in place of LAVI, incident HF developed in 33 (7%) of normal diastolic function, 4 (11%) with indeterminate diastolic function and 25 (13%) of those with grade 1 DD (p=0.03). Of the 113 indeterminate cases that were reassigned normal diastolic function, 8 (7%) developed HF. Of the 16 grade-2+ DD that were downgraded, 2 developed HF.

Figure 7-3: Comparison of diastolic function grades by grading method. Reassignment of diastolic function from (A) using conventional diastolic function recommendations to (B) LA reservoir strain used in place of LA volume index. Total number of individuals in A is 758 and in B is 738 (the number in which LARS measurement was feasible). Numbers in boxes are absolute numbers of individuals changing group. HF – incident HF.

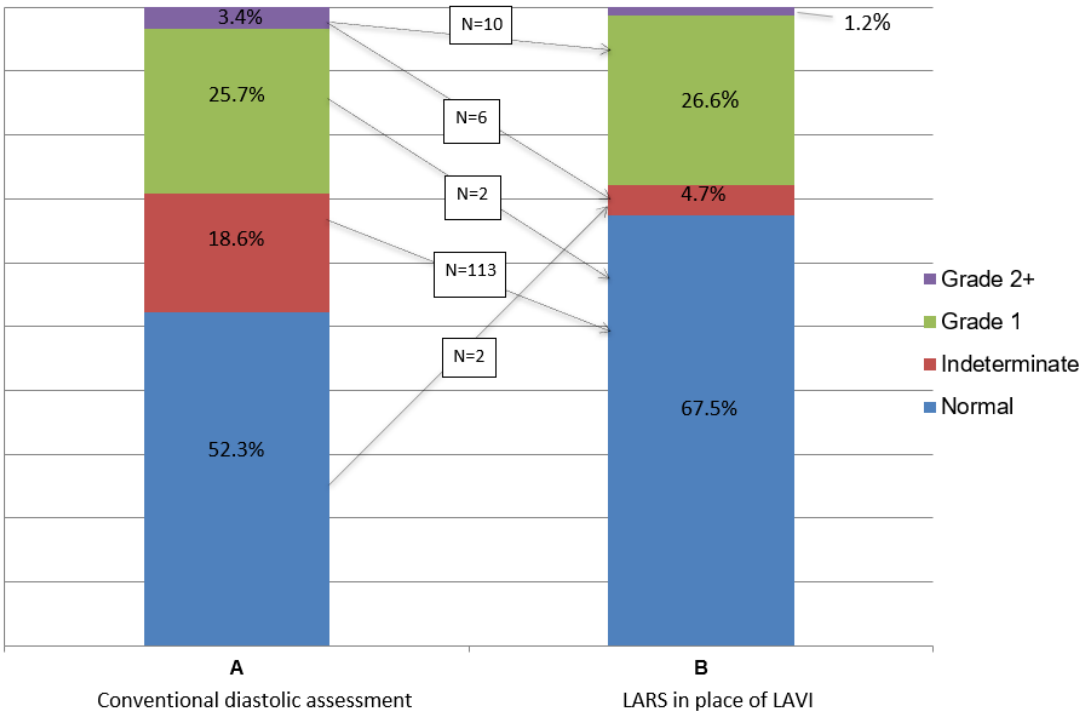


Table 7-4: Hazard ratios for incident heart failure by conventional diastolic function assessment and using LA reservoir strain (LARS) in place of LA volume index (LAVI).

	Conventional diastolic function grading					
	n	**Incident HF† (%)**	**HR (95% CI)**	**p-value**	**HR* (95% CI)**	**p-value**
Normal diastolic function	396	25 (6)	ref		ref	
Indeterminate diastolic function	141	11 (8)	1.36 (0.67-2.75)	0.4	1.01 (0.48-2.14)	0.95
Grade 1 DD	195	23 (12)	2.43 (1.42-4.16)	0.001	1.45 (0.72-2.91)	0.29
Grade 2+ DD	26	5 (19)	**		**	
	LARS replacing LAVI					
	n	**Incident HF† (%)**	**HR (95% CI)**	**p-value**	**HR* (95% CI)**	**p-value**
Normal diastolic function	498	33 (7)	ref		ref	
Indeterminate diastolic function	35	4 (11)	0.58 (0.08-4.3)	0.6	0.57 (0.07-4.3)	0.58
Grade 1 DD	196	25 (13)	2.58 (1.47-4.5)	0.001	1.82 (0.85-3.88)	0.12
Grade 2+ DD	9	2 (22)	****		****	

† p=0.03 (conventional grading), p=0.03 (LARS replacing LAVI) *Adjusted for age, diabetes mellitus, body mass index, heart rate, six-minute walk distance, global longitudinal strain and LV mass index. ** combined with grade 1 for Cox regression due to low number of events.

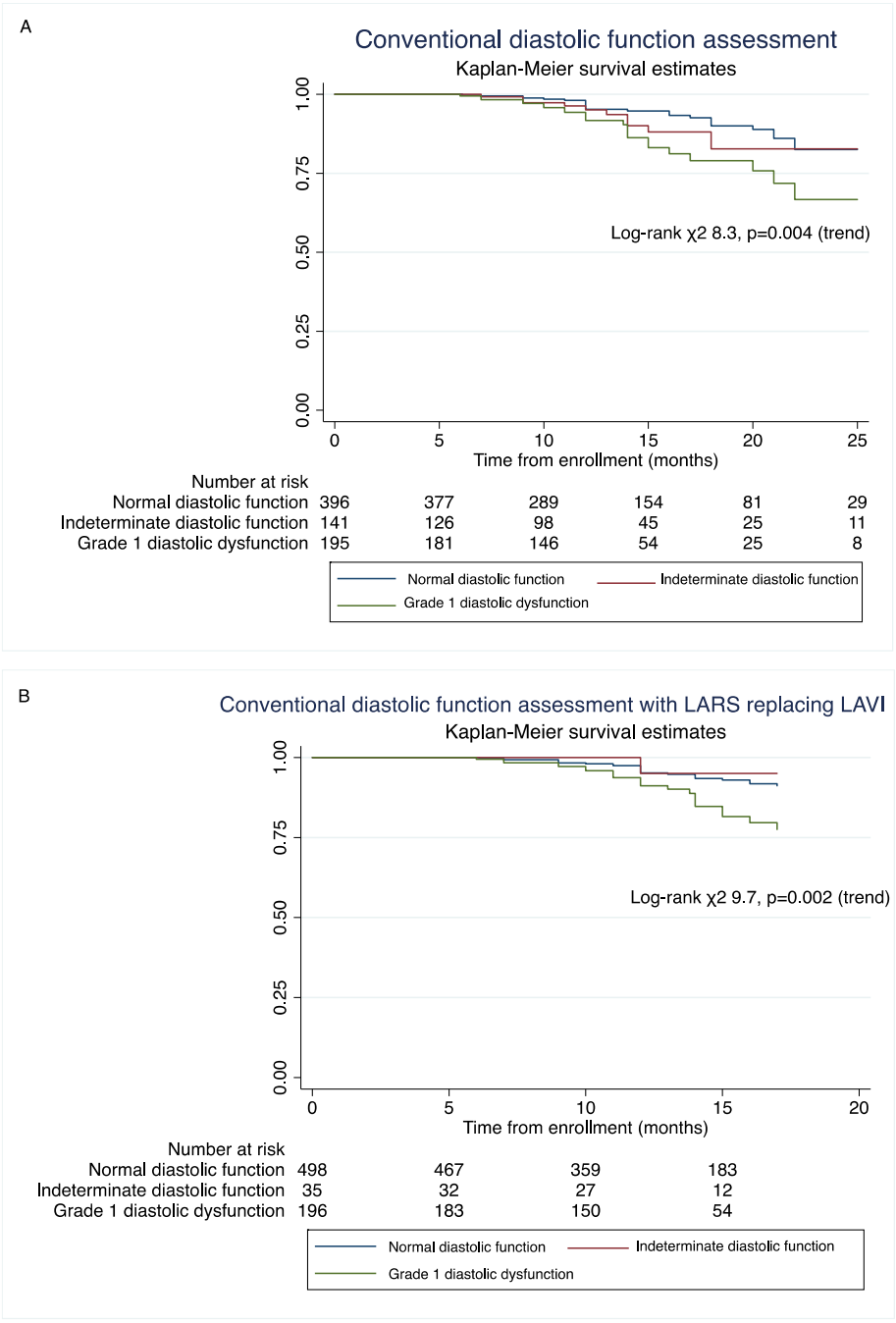
Figure 7-4 compares HF-free survival for the two diastolic grading methods. Both methods saw a significant difference in HF-free survival between normal diastolic function and grade 1 diastolic dysfunction.

For Cox regressions hereafter grade 2+ is combined with grade 1 given the low number of absolute events in the former group. The unadjusted HR for HF for conventionally graded indeterminate function was 1.36 (95% CI 0.67-2.75, p=0.4), and for grade 1+ DD was 2.43 (95% CI 1.42-4.16, p=0.001). After adjustment (as per Table 7-2 model minus LAVI and E/e') the risk was attenuated in the indeterminate group (HR 1.01 [95% CI 0.48-2.14], p=0.95) and grade 1+ DD (HR 1.45 [95% CI 0.72-2.91], p=0.29). With reduced LARS used in place of increased LAVI, the unadjusted HR for HF for indeterminate DD was 0.58 (95% CI 0.08-4.3, p=0.6) and for grade 1+ DD was 2.58 (95% CI 1.47-4.5, p=0.001). After adjustment, the HRs were 0.57 (95% CI 0.07-4.3, p=0.58) and 1.82 (95% CI 0.85-3.88 p=0.12) for indeterminate and grade 1+ DD, respectively (Table 7-4). When all DD groups including grade 2+ DD were modelled (rather than being combined with grade 1), multivariable regression showed grade 2+ DD to have a non-significant HR of 2.04 (95% CI 0.74-5.6, p=0.17) for incident HF.
In multivariable Cox models of conventional and LARS-based grading, with diastolic function dichotomized as normal or abnormal, the c-statistic for both multivariable regression models was 0.76. This reassures that despite 113 indeterminate cases being reassigned normal diastolic function, there was no difference in the adjusted risk between the two grading methods.

7.5.5 Reproducibility

The inter-observer variability for LARS and LAVI was 6.8±5.5% and 5.9±3.3ml/m^2, respectively. The inter-observer LARS-DD grade agreement was 76% and conversely, disagreement was 24% therefore 177 of 738 would be reclassified. For normal versus abnormal LARS (cut-off 24%) there was 94% agreement. Intra-observer variability of one investigator (SR) who repeated LA strain measurements in 20 patients at a different time point was 3.8±2.9%.

Figure 7-4: Heart failure-free survival by diastolic function grading method. HF-free survival by diastolic function using conventional recommendations (A) and using conventional recommendations but replacing abnormal left atrial volume index (LAVI) with abnormal left atrial reservoir strain (LARS) (B).



7.6 Discussion

In an elderly population with subclinical HF, grade 2+ DD determined by LARS alone was associated with double the risk of incident HF after adjustment for clinical and echocardiographic risk markers including LAVI. Furthermore, the risk of HF after designating abnormal LARS as worse than 24% (235) was almost 3-fold. However,

there was no apparent difference in risk of HF between grade 1 DD and normal diastolic function when determined by LARS. The impact of replacing increased LAVI with reduced LARS in conventional diastolic function assessment was also investigated on the premise that LARS may more closely reflect changes in DD severity compared with structural enlargement. The result was a 75% reduction in the number of indeterminate cases that were mostly reassigned to normal diastolic function. In comparison to LARS used in place of LAVI, the risk associated with indeterminate grade was higher for conventional grading while the risk associated with grade 1 DD was lower. LARS grading had negligible impact on the proportion of incident HF across groups. Nor could we find evidence of an increase in risk associated with normal diastolic function as a result of the reassignment of a significant number of indeterminate cases to this group.

7.6.1 Evaluation of DD

The current recommendations for diastolic function assessment provide algorithms for diagnosis of diastolic dysfunction (presence, absence or indeterminate [algorithm a]) and also for identification of elevated filling pressures and therefore grading of DD where LVEF is reduced or there is strong clinical suspicion of myocardial disease (algorithm b) (32). The new guidelines are more easily applied clinically than the 2009 recommendations but result in a larger proportion of patients with indeterminate diastolic function - the majority of whom (79%) would have been previously classified as having DD (227). Accordingly current recommendations result in a dramatically lower prevalence of DD (227,238) whilst demonstrating lower sensitivity for invasively measured, elevated filling pressure in symptomatic populations (239,240). The 19% prevalence of indeterminate diastolic function in our cohort was similar so the 15% previously reported in a general population aged >45 years (227). Leaving this significant proportion of those at risk of DD unclassifiable is problematic in clinical decision-making.

7.6.2 LA strain and diastolic dysfunction

LARS (as opposed to conduit or pump strain) represents the passive stretch of LA during ventricular systole as it receives blood from the pulmonary veins. The predominant pathophysiological process that reduces LARS is thought to be the elevation in LA pressure resulting from impaired ventricular relaxation. However, there is also evidence supporting a direct LA fibrotic effect in the setting of diabetes mellitus,

independent of LVDD. LVDD usually accompanies systolic dysfunction and LARS has been significantly associated with LV-GLS previously. While it might be questioned whether LARS needs evaluation if reduced LV-GLS is found, our study demonstrates that reduced LARS has prognostic significance in addition to LV-GLS. This may lend support to the idea of direct atrial damage compounding LVDD, and the high prevalence of diabetes in our study (46%) may have contributed to this finding.

Understanding of LA remodelling and LA reverse remodelling is still evolving. Mechanistically, aberrations in myocardial energetics result in a decline in function that may precede LAE in the process of LA remodelling (232,241,242). However, studies that inform on the process of functional and structural LA *reverse* remodelling, are limited. After successful radiofrequency ablation (RFA), improvements in both LA function and size have been observed at 3 months (233), although it is unclear whether these improvements happened consecutively. In a cross-sectional study of hypertensive patients, LA function was normal in those treated with renin-angiotensin system (RAS) inhibition but only if LA size was normal (234). Those treated with other antihypertensive agents had abnormal LA function regardless of LA size. This suggests that LA reverse remodelling may depend on the degree of structural abnormality. In hypertensive patients commenced on irbesartan, LARS significantly improved after 6 months, while LA volume significantly improved after 12 months (243).

In our study only 2.7% had abnormal LARS, far lower than the proportion with abnormal LAVI (37%). Indeed, most of those with LAE had normal LARS (93%), suggesting LA *reverse* remodelling. Unfortunately, given the small number of subjects with LAE and abnormal LARS (n=19), comparing HF risk between those undergoing presumed atrial reverse remodelling and those still remodelled, was not feasible. In contrast, in another study population with LVDD risk factors, 37% had abnormal LARS (<23%) while only 15.5% had LAE (231). Mean LARS was far lower than in our study (27±10 vs. 39[34-43]) despite mean LAVI also being lower (27±10 vs. 30[25-37]). This might suggest that subjects were in the process of atrial remodelling rather than reverse remodelling. The reasons for the inconsistency with our findings are uncertain but may lie in differences in study population, especially established HF and coronary artery disease. Future studies should confirm that LA functional recovery precedes structural recovery.

7.6.3 Clinical implications

While LARS is referenced in the current diastolic function recommendations, there is no consensus regarding if or how it should be used to determine diastolic function. There is evidence to support a relationship between LARS and clinical symptoms, severity of DD (195) and invasively measured LV filling pressures (244). Our study builds on current evidence by demonstrating the prognostic significance of reduced LARS in patients at risk of HF, independent of clinical and echocardiographic risk markers including LAVI. Despite our finding that LARS correlates with HF risk better than conventional grading, it remains mechanistically undefined whether LARS should be used as a single parameter for DD assessment given the potential for influence by LA fibrosis (245).

Management of asymptomatic DD focuses on risk factor control and investigation for co-morbidities associated with progression to HFpEF (31). A diagnosis of DD rather than indeterminate diastolic function may therefore prompt intensification of therapy, investigation for relevant comorbidities and a more proactive approach to confirming a truly asymptomatic state. By substituting LARS for LAVI, we found that indeterminate cases could be reduced by 75% without significantly affecting the relationships between diastolic function and prognosis. This approach may enhance diagnostic clarity.

7.6.4 Limitations

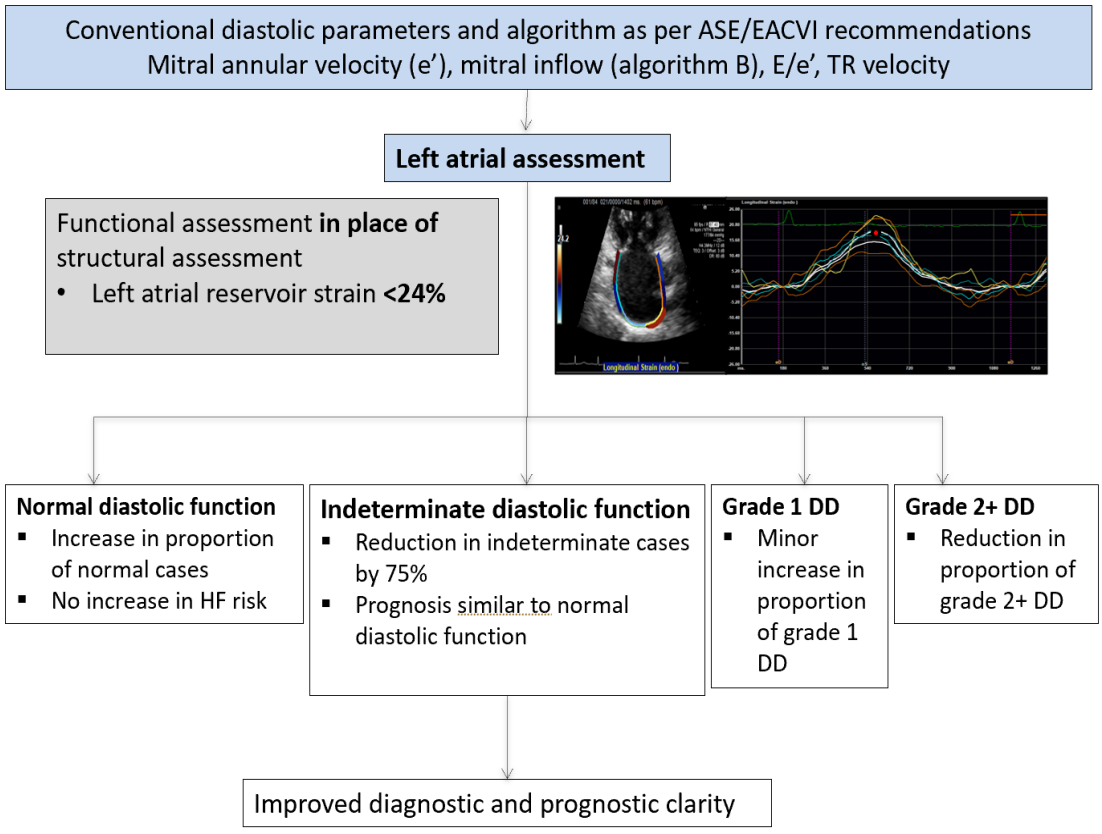
Our study had a short follow-up duration so risk differences between LAS-DD grades beyond the period of study are unknown. We observed only a small number of cases with moderate-severe DD and this limits the accuracy of the risk estimate associated with this LARS-DD grade. A larger cohort or one with a different risk profile may improve upon our findings for this DD grade. The exclusion of CAD, and lack of systematic characterization of renal impairment and chronic obstructive pulmonary disease - important risk factors for asymptomatic DD and progression to HFpEF (31) – may compromise extrapolation to other populations. Furthermore, while cardiotoxic chemotherapy was an inclusion criterion, this the sole inclusion qualifier for only 15 (2.5%) subjects, so our findings may not be generalizable to chemotherapy-related cardiotoxicity. We found that 3% of studies could not be analyzed for LARS due to poor image quality. However, traditional diastolic parameters have several recognized limitations, for example the elevation in E/e’ seen with mitral annular calcification, which shares risk factors with DD. Consistency in LA strain measurement is a concern,

however, a consensus document standardizing LA deformation imaging and other instructive articles are now available (246,247).

7.7 Conclusion

LARS is a feasible parameter in the assessment of DD in community subjects at risk of HF and may complement conventional diastolic assessment. LARS-DD grade 2+ is independently associated with incident HF. Substituting LARS for LAVI in current algorithms for DD grading, significantly reduces the number of diastolic assessments deemed indeterminate, due to reassignment of indeterminate cases to normal diastolic function, without impacting risk prediction (Figure 7-5).

Figure 7-5: Algorithm for combining LARS with existing diastolic parameters. The use of functional rather than structural LA assessment provides a major reduction in the proportion of indeterminate diastolic dysfunction and increases in the proportion of studies identified as normal or showing grade 1 dysfunction, with parallel improvement in prognostic assessment.



7.8 Postscript

At the beginning of this chapter, it was proposed that LARS may contribute to the definition of SBHF as a marker of diastolic dysfunction. The study demonstrates that incorporation of LARS into the multiparametric diastolic assessment is valid both practically and prognostically, so this proposal can be accepted. It was not concluded that LARS *replace* recommended diastolic assessment as reduced LARS could potentially occur independently of diastolic dysfunction but distinguishing such a process from early diastolic dysfunction would be exceedingly difficult. Nevertheless, the findings do not preclude the use of LARS as a standalone measure conferring increased HF risk and it may well be a simpler singular approach to diastolic assessment despite the problem mentioned. There is also support for the utility of LARS in symptomatic populations where it discriminates HFpEF from non-cardiac dyspnoea significantly better than any other diastolic measure (248), or abnormalities such as LV hypertrophy and reduced GLS. The accumulating evidence of its diagnostic and prognostic ability coupled with its feasibility may eventually lead to a singular LARS-based diastolic assessment.

What would further support the use of LARS is longitudinal data demonstrating deterioration prior to LA remodelling and as was suggested in the chapter, recovery prior to reverse remodelling (if this occurs). A cross-sectional study published after completion of this chapter demonstrated that adolescents with obesity or T2DM show early signs of decline in atrial function assessed by LARS, while there is no difference in LA size (249). While this supports the notion of LA function deterioration prior to remodelling, again there was no longitudinal evaluation.

The chapters in this part of thesis reinforce some of the echocardiographic methodology of the RCT (chapter 8). However, LARS and its integration into diastolic assessment will not be used as part of the SBHF definition in this trial. The focus is more on filling the last link in the evidence gap in use of GLS, that is, its ability to direct clinical decision making.

7.9 Appendix

Table 7-5: Individual echocardiographic parameters in participants with incident HFpEF. 1= satisfies criterion.

ID	EA <0.8 or >2	Septal e'<7 or lateral e' <10	E/e' >14	LAVI >34ml/m^2	Total diastolic abnormalities	LVH	GLS ≤16%
28	0	1	0	0	1	0	0
107	0	1	0	1	2	0	0
110	0	1	0	1	2	0	0
117	1	0	0	1	2	0	0
121	0	0	1	1	2	1	0
135	1	1	0	1	3	0	0
140	1	1	0	1	3	1	0
156	1	1	0	1	3	0	0
198	0	1	0	0	1	1	0
231	0	0	1	1	2	0	1
232	0	0	1	1	2	1	0
251	1	1	0	1	3	1	0
272	0	1	0	0	1	0	0
290	1	1	0	0	2	0	0
295	0	0	0	1	1	1	1
317	1	0	0	1	2	0	0
323	1	1	0	0	2	0	0
330	0	0	0	1	1	1	1
331	1	0	0	1	2	0	0
338	0	1	1	1	3	0	0
355	0	0	0	0	0	0	0
358	1	1	0	1	3	0	1
368	0	0	1	1	2	0	1
403	1	0	1	1	3	1	1
412	1	1	0	0	2	0	1

417	1	1	0	1	3	1	0
433	0	1	0	1	2	0	0
443	1	0	1	1	3	0	0
444	1	0	1	1	3	0	0
467	0	1	0	1	2	0	0
472	0	0	1	0	1	0	0
475	1	0	1	0	2	0	1
519	0	1	0	1	2	0	0
554	0	1	0	1	2	0	1
597	1	1	0	1	3	0	0
631	1	0	0	1	2	1	1
646	1	1	0	1	3	0	0
694	1	0	1	1	3	1	1
706	1	1	0	1	3	0	0
732	0	1	0	1	2	0	0
736	0	1	0	1	2	0	0
738	1	1	0	1	3	0	0
739	1	1	0	0	2	0	1
753	0	1	0	1	2	0	0
787	0	0	0	1	1	0	0
789	1	1	0	1	3	0	1
791	1	1	0	1	3	0	0
879	1	0	1	1	3	1	0

Table 7-6: Baseline characteristics and heart failure (HF) outcome by ASE/EACVI diagnostic algorithm for diastolic function in 758 subjects.

	Diastolic function assessment				
	Normal (396)	Indeterminate (141)	Grade 1 DD (195)	Grade 2+ DD (26)	-value
Age, yrs. (IQR)	69 (67-73)	71 (68-75)	71 (68-75)	74 (71-78)	<0.001
Gender, male (%)	173 (44)	71 (50)	91 (47)	16 (62)	0.1
Hypertension (%)	316 (80)	123 (87)	164 (84)	22 (85)	0.2
Diabetes Mellitus (%)	167 (42)	55 (39)	112 (57)	14 (54)	0.001
AF (%)	24 (6)	11 (8)	21 (11)	4 (15)	0.11
BMI, g/m^2 (IQR)	29 (26-33)	29 (26-34)	30 (26-34)	31 (27-35)	0.15
Heart rate (IQR)	69 (61-76)	65 (60-71)	68 (60-77)	64 (61-75)	0.005
SBP, mmHg (IQR)	140 (129-149)	142 (131-150)	140 (129-150)	142 (132-162)	0.33
DBP, mmHg (IQR)	82 (75-88)	82 (75-89)	83 (77-91)	79 (72-88)	0.06
ACE-I/ARB (%)	277 (70)	93 (66)	132 (68)	11 (42)	0.52
Beta-blocker (%)	17 (4)	14 (10)	19 (8)	8 (31)	<0.001
Echo parameters					
e' cm/s (IQR)	8 (7-9)	7 (6-8)	7 (6-8)	6 (5-8)	<0.001
E/e' (IQR)	8 (7-9)	9 (8-11)	8 (7-10)	14 (14-16)	<0.001
TR V$_{max}$ (IQR)	2.2 (2-2.4)	2.3 (2-2.4)	2.2 (2-2.4)	2.7 (2.2-3)	0.001
LAVI, ml/m^2 (IQR)	27 (24-32)	39 (36-44)	32 (26-40)	40 (37-45)	<0.001
LAVI >34ml/m^2 (%)	52 (13)	122 (86)	83 (43)	24 (92)	<0.001
LARS not feasible (%)	11 (3)	2 (1.4)	6 (3)	1 (4)	0.8
LARS†, % (IQR)	40 (36-44)	39 (34-43)	37 (30-42)	34 (30-40)	<0.001
LARS † <24% (%)	4 (1)	3 (2)	15 (8)	1 (4)	<0.001
GLS ≤ 16% (%)	3 (0.8)	3 (2)	135 (69)	7 (26)	<0.001
LVH (%)	0 (0)	4 (2.8)	71 (36)	4 (15)	<0.001
Ar-A duration >30ms (%)	34 (11)	23 (23)	22 (15)	4 (20)	0.03
Incident HF (%)	25 (6)	11 (8)	23 (12)	5 (19)	0.03

IQR – interquartile range, AF – atrial fibrillation, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, ACE-I/ARB – angiotensin converting enzyme inhibitor/receptor blocker, LARS – left atrial reservoir strain, LVEF – left ventricular ejection fraction, GLS – global longitudinal strain, DT – deceleration time, TR Vmax – maximal velocity of tricuspid regurgitation, LAVI– left atrial volume indexed to body surface area, LVMI – left ventricular mass indexed to body surface area, Ar-A – pulmonary vein atrial flow duration minus mitral A wave duration. † total n=738.

PART 3: Trialling a risk-based strategy of heart failure prevention

8 Echocardiographic-guided spironolactone therapy to prevent incident HF in patients with subclinical left ventricular dysfunction: The VICtorian study of Echocardiographic detection of Left ventricular dysFunction (Vic-ELF).

In preparation for submission as: Potter E, Stephenson G, Wright L, Marwick T. *Echocardiographic-guided spironolactone therapy to prevent incident HF in patients with subclinical left ventricular dysfunction.* Am J Cardiol.

8.1 Preface

The concept of early identification of cardiac dysfunction as being crucial to effective preventive strategies has been demonstrated in an on-treatment analysis of a single randomized trial, Tas-ELF (14). The choice of intervention following identification of reduced GLS or diastolic abnormalities remains unclear. It is expected that ACE-I, ARBs and perhaps beta-blockers would confer benefit, and this was demonstrated in the Tas-ELF on-treatment analysis. However, the majority of those with SAHF e.g. patients with hypertension or diabetes, should already be receiving RAS therapies at a dose to optimally control blood pressure and treat microalbuminuria. While up-titration is an option, this may not be well tolerated, particularly in the elderly. Similarly, commencement of ACE-I or ARBs may be problematic in normotensive SAHF (e.g. due to obesity). Alternatively, spironolactone may be an attractive option given it has demonstrated mortality benefit in established HF and in the SBHF setting has favourable effects on cardiac function, with little effect on blood pressure. Evidence for the efficacy of the sodium-glucose cotransporter-2 (SGLT-2) inhibitors, a new diabetic treatment, in reducing incidence of worsening HF and cardiovascular death is now established in HFrEF (although not prior to conception of this thesis) (250,251). Whether SGLT-2 inhibitors applied in SBHF could prevent progression to SCHF warrants investigation.

In the RCT presented here, risk was enriched in 2 ways. First, recruitment was exclusively in the Western suburbs of Melbourne, where relative socioeconomic disadvantage is an important contributor to HF risk. Second, risk was also quantified with ARIC-HF risk score and 6MWT. The cut-offs used have been previously shown in a decision tree analysis to identify intermediate to high HF risk, albeit in a relatively small sample, but one with the same characteristics as our population of interest (13). At time of RCT design, the results of chapter 3 (“Measurement of functional capacity to discriminate clinical from subclinical heart failure in patients ≥65 years of age”) were not known and therefore these findings are not integrated into the selection process for this RCT.

8.2 Abstract

Background. Subclinical left ventricular dysfunction (LVD) is a prelude to symptomatic heart failure (HF). We hypothesized that spironolactone would prevent incident HF among patients with echocardiographically-detected subclinical LVD.

Methods. Asymptomatic, community-dwelling subjects aged ≥ 65 years old, with at least one non-ischemic HF risk factor (hypertension, type 2 diabetes mellitus or obesity) underwent echocardiography. Systolic dysfunction was defined by abnormal global longitudinal strain (GLS ≤16%). Diastolic dysfunction was defined by E/e'>15 or left atrial enlargement [LAE] with E/e' >10, impaired relaxation [E/A <0.8, IR] or borderline GLS (16-18%). Patients were randomly assigned (1:1) to echocardiography-guided therapy (subclinical LVD triggered spironolactone therapy), or usual care. The primary outcome was incident HF defined by Framingham criteria at 24 months. Secondary outcomes were change in functional capacity by 6-minute walk test (6MWT) and change in LV function.

Results. The trial was stopped due to the rate of spironolactone discontinuation (55%), after recruitment of 349 participants (age 70 years [68-73], 201 (58%) women). Discontinuation was primarily due to decline in renal function. Of the 310 participants who completed follow-up, 7 (4%) in the intervention arm vs. and 4 (2.3%) in the usual care arm experienced incident HF and there was no difference in HF-free survival between arms (log-rank χ^2 1.04, p=0.38). Decline in 6MWT distance was -3±76m vs. -17±70m for intervention vs. usual care (p=0.28). There was no difference in the proportion with persistent or new LVD between intervention and usual care (52 (48%) vs. 57 (51%), p=0.68). Mean change in GLS was -0.24±2.7% for usual care versus 0.23±2.5% for intervention (p=0.2). In a sub-analysis of 109 patients with baseline LVD and a follow-up, LVD resolved in 16 of 26 (61%) treated with spironolactone, compared to 24 of 83 (29%) who did not (p=0.003).

Conclusion. The use of spironolactone to reduce incident HF in elderly patients with subclinical LVD was ineffective because of poor toleration of therapy.

8.3 Introduction

The rising prevalence, and in some demographics incidence, of heart failure (HF) demands preventive efforts (15,23,25,26). HF evolution is considered a continuum (28), starting with risk factors alone (Stage A HF, SAHF), progressing to left ventricular dysfunction (LVD) – deemed Stage B HF (SBHF) and finally the symptomatic syndrome of HF. This paradigm of stepwise progression may be particularly valid in HF of non-ischemic etiology and early targeted therapy in SBHF may halt progression. Asymptomatic diastolic dysfunction is a prelude to HF with preserved ejection fraction (HFpEF) (5,30), and reduced LV global longitudinal strain (GLS), an early marker of systolic dysfunction, has prognostic significance above LV ejection fraction (LVEF) (37). Both provide early triggers for preventive therapies, incremental to reduced LVEF and remodeling, which are the principal characteristics of SBHF. Furthermore, asymptomatic reduced LVEF is rare in the community (11).

Spironolactone, a mineralocorticoid antagonist (MRA), is an attractive pharmacological intervention in this scenario. Pharmacologically, it inhibits myocardial fibrosis (252) and partly through this mechanism demonstrates clinical efficacy above angiotensin converting enzyme inhibition (ACE-I) in HF with reduced ejection fraction (HFrEF), where a large proportion exhibit persistently high aldosterone levels (253,254). Furthermore, treatment with ACE-I may be associated with a rise in aldosterone (255). Practically, many SAHF patients with hypertension and diabetic nephropathy already receive angiotensin blockade, and those with obesity (and are normotensive) may not tolerate the more potent antihypertensive effects of ACE-I.
Accordingly, we undertook a randomized controlled trial in a population with non-ischemic HF risk factors to determine whether identification of early echocardiographic measures of LV dysfunction i.e. reduced GLS and diastolic abnormalities, and subsequent treatment with spironolactone would reduce incident HF.

8.4 Methods

8.4.1 Study design

The Victorian Study of Echocardiographic detection of Left ventricular dysFunction [Vic-ELF; ACTRN 12617000116325) was a prospective randomized open, blinded endpoint (PROBE) trial. Recruitment was undertaken through primary care and community advertising in the state of Victoria, Australia between April 2017, and June 2019. Reporting of the trial followed CONSORT guidelines (256).

8.4.2 Participant selection

Prior Australian work has demonstrated that in the community elderly SAHF population, the prevalence of LVD by similar definition is ~50%, with annual HF incidence of 10-12% in the presence of LVD (14). This is compared to a 5% incidence with normal LV function. On this basis and with follow-up of 2 years, randomization of 650 participants would give 80% power to detect a 10% absolute difference in incident HF accepting a 5% chance of type I error.

Patients were eligible if they were ≥ 65 years, with at least one risk factor; hypertension (self-reported diagnosis including treatment or blood pressure ≥140/90mmHg), type 2 diabetes mellitus or obesity (body mass index ≥ 30kg/m^2). Known ischemic heart disease was excluded given the routine use of echocardiography in this setting and the trial would potentially serve as evidence for screening in at-risk individuals. Patients were also ineligible if patient interview and clinical examination identified existing HF, life expectancy <1 year, systolic blood pressure ≤ 110mmHg, or if at least moderate valve disease and LVEF <40% were identified by echocardiography, given the clear management implications of the latter (60). Existing treatment with spironolactone or other potassium sparing diuretic as well as estimated glomerular filtration rate (eGFR) < 60ml/min and serum potassium ≥ 5mmol/l were exclusions. All subjects provided written informed consent and the study was approved by the relevant Human Research Ethics Committee (Bellberry, HREC number 2016-10-727).

8.4.3 Clinical measures

We recorded height, weight, waist and hip circumference, heart rate, blood pressure (average of three resting measures), and relevant comorbidities and medications. The Charlson comorbidity index was calculated to quantify the comorbid burden of participants, (with the exclusion of age) (257). N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured (Alere Triage, Alere, San Diego, CA) along with renal biochemistry. To assess functional capacity, the Duke Activity Status Index questionnaire; DASI (converted into metabolic equivalents) and six-minute walk test (6MWT) were conducted, in accordance with standard procedures (111). The ARIC risk score was calculated from clinical variables (41). Subjects were excluded if they were found to be low risk, based on ARIC HF risk score ≤9.5% (4-year risk) and 6MWT ≥ 501m (13).

8.4.4 Echocardiography

Standard transthoracic 2-D and Doppler echocardiographic studies were performed using standard equipment (SC2000, Siemens Healthcare USA, Mountain View, CA) and transducer (4V1c, 1.25 to 4.5 MHz; 4Z1c, 1.5 to 3.5 MHz) in accordance with ASE guidelines (117). A vector-velocity imaging algorithm (Syngo VVI, Siemens Healthcare, Mountain View, CA) was used for global longitudinal strain (GLS) quantification and averaged from apical, 2-, 3- and 4-chamber views. GLS will be displayed without a negative sign so that higher GLS indicates better myocardial function. Diastolic function was assessed by measuring mitral inflow, peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, septal and lateral mitral annular early diastolic velocities (e') and the E/e' ratio. Left atrial volume was calculated using the biplane method of disks and indexed to body surface area (LAVI). LVD was defined as GLS ≤ 16%, diastolic abnormalities (E/e'>15, E/e' >10 with left atrial enlargement [LAE] or impaired relaxation [E/A <0.8, IR] with LAE), or borderline GLS (17%) with IR or LAE.

8.4.5 Randomisation and study drug

Participants were block randomized to the intervention or usual care. In the intervention arm, identification of subclinical LVD (as defined herein) triggered initiation of spironolactone. Spironolactone was commenced a dose of 25mg. Participants were advised to ensure adequate hydration. At 2 weeks post commencement the participant was reviewed to document side-effects, postural blood pressure measure, weight, and measurement of renal biochemistry. Biochemistry and clinical review were repeated at 3, 6, 12, 24 months. Spironolactone was ceased if eGFR fell below 60 ml/min, if there was a persistent decline in eGFR by >25% despite dose reduction (to 12.5mg), hyperkalaemia (serum potassium ≥ 5.2 mmol/L), symptomatic or asymptomatic orthostatic blood pressure drop (>20mmHg systolic, >10mmHg diastolic) or other side-effects intolerable by the participant. The drug could be suspended in the event of intercurrent illness. Adherence to medication was assessed by pill count. Non-adherence was defined as taking <80% of prescribed medication, in line with the reported adherence rate (to medication classes including aldosterone receptor antagonists) required to avoid hospitalization with complications of hypertension including heart failure and cardiomyopathy (258). In the usual care arm, the echocardiogram methods and reporting were the same as for the intervention, and

the report was sent to the participants' primary care doctor. A yearly report was submitted to an external data safety and monitoring board.

8.4.6 Outcomes

The primary outcome was incident HF diagnosed by a blinded study physician using Framingham criteria, as previously described (119). Participants were reviewed in person at 6, 12, and 24-months. Owing to the impact of COVID-19, final reviews were brought forward and conducted by phone (n=191, 62%). If HF symptoms were reported participants were then reviewed in person (n=8). This arrangement significantly impacted the ability to ascertain complete follow-up anthropometric, functional, and biochemical measures. HF diagnosed external to the study was adjudicated by 2 blinded physicians using hospital discharge summaries or primary care notes. Secondary outcomes were 1) change in functional capacity measured by 6MWT and, 2) change in LV function (as change in GLS or as the proportion of those with persistently normal LV function or resolved LVD vs those with persistent LVD or evolution of LVD).

8.4.7 Statistical analysis

Continuous variables are presented as median with interquartile ranges (IQR) or mean±standard deviation, based on distribution testing using the Shapiro-Wilk test. Categorical variables are presented as frequencies and percentages. Differences between two independent groups were determined using χ^2 and unpaired t-test for categorical and continuous variables, respectively. For comparison of paired data at baseline and follow-up a paired t-test or Wilcoxon sign-rank test was used depending on normality of distribution. Kaplan-Meier survival estimates were used to examine HF-free survival by randomisation group, and differences in survival distributions were assessed using the log-rank test. Logistic regression was used to examine predictors of spironolactone discontinuation. Effect sizes are expressed as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was defined as a two-tailed p value <0.05. Analyses were conducted using STATA 15.1 (StataCorp, College Station, TX).

8.5 Results

8.5.1 Participant characteristics and follow-up

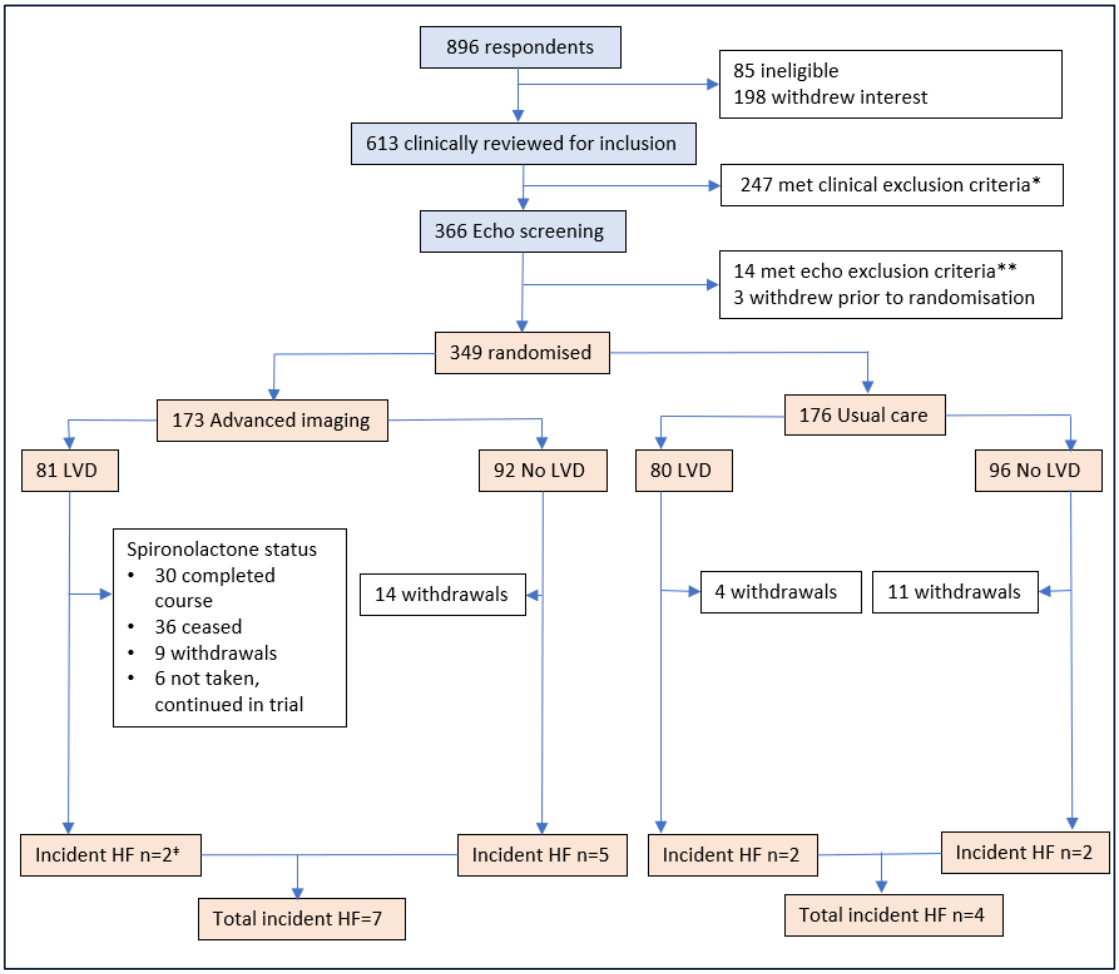
Of the 896 subjects that responded from primary care recruitment and community advertising, 613 were clinically reviewed for inclusion (Figure 8-1). Of these, 247 met clinical exclusion criteria (most common reasons being: low risk status

(57%), eGFR <60ml/min (24%), SBP <110mm Hg (8%) and undiagnosed HF (6%)). After excluding 14 based on echocardiographic criteria, we randomized 349 (age 70 years [68-73], 201 (58%) women). After randomization of 349, the high proportion of spironolactone discontinuation was identified as being likely to lead to futility, and the data safety and monitoring board advised to cease recruitment.

Overall, 161 (46%) exhibited LVD. As a proportion of all participants, 23% had diastolic abnormalities, 17% had low GLS and 14% had borderline GLS with IR or LAE (Figure 8-2 displays the overlap between subgroups). There were 11 participants with LVEF between 40-50%, and 9 of these fulfilled the trial criteria for LVD. Baseline characteristics were similar between randomisation arms, although there was a higher proportion of dyslipidemia and ex- or current smoking in the intervention arm (Table 8-1). Conversely, NT-proBNP and the proportion of those taking beta-blockers was significantly higher in the usual care arm.

The total number of withdrawals was 39 (Appendix, Table 8-7). The intervention arm had a higher study withdrawal rate compared with usual care (14% vs 9%, p=0.11) but only 2 of the 24 withdrawals from the intervention arm cited spironolactone as a reason. Follow-up duration did not differ by randomisation to intervention vs. usual care (23 months [14-25] vs. 22 months [13-25], p=0.35) (Table 8-1).

Figure 8-1: Vic-ELF consort diagram



*144 (57%) low risk, 60 (24%) eGFR <60ml/min, 20 (8%) Systolic BP <110mm Hg, 16 (6%) existing HF without prior diagnosis, 8 (3%) NYHA >2, 2 (1%) MRA contraindication, 3 (1%) prior MI. ** 6 > moderate valvular disease, 7 poor image quality, 1 LV ejection fraction <40%. ‡ both events in participants who ceased spironolactone.

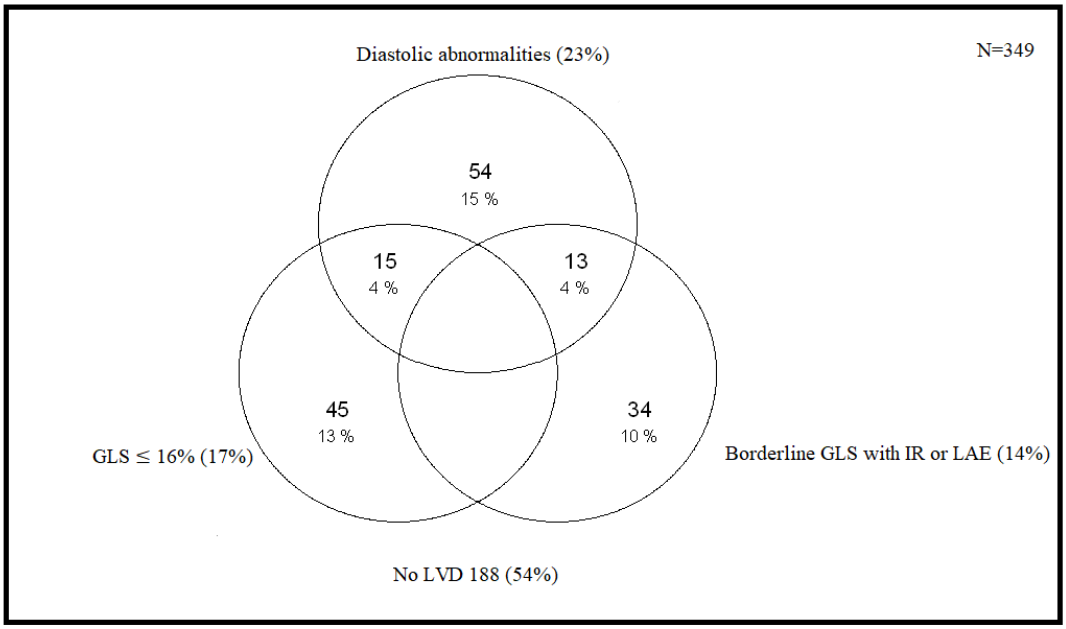
Table 8-1: Baseline characteristics by randomisation arm.

	Usual care (n=176)	**Intervention (n=173)**	**p-value**
Age, years (IQR)	70 (68-73)	70 (67-73)	0.36
Gender, female (%)	98 (56)	103 (60)	0.47
Hypertension (%)	157 (89)	145 (84)	0.14
Type II diabetes mellitus (%)	55 (31)	56 (32)	0.82
Obesity (%)	104 (59)	117 (68)	0.1
Atrial fibrillation (%)	10 (6)	14 (8)	0.38
Dyslipidemia (%)	99 (57)	119 (69)	0.02
Ever smoker (%)	69 (39)	86 (50)	0.048
ACE-I/ARB (%)	144 (82)	131 (76)	0.16
Thiazide diuretic (%)	56 (32)	46 (27)	0.28
Beta-blocker (%)	25 (14)	13 (8)	0.045
Calcium channel blocker (%)	59 (34)	58 (34)	0.99
Total number of medications (IQR)	4 (3-6)	4 (3-6)	0.1
Systolic blood pressure, mm Hg (SD)	144 (30)	140 (15)	0.14
Diastolic blood pressure, mm Hg (SD)	85 (9)	83 (9)	0.1
Heart rate, bpm (SD)	72 (11)	72 (11)	0.65
Body mass index, kg/m^2 (SD)	31 (6)	32 (5)	0.33
Waist-hip ratio (SD)	0.92 (0.09)	0.93 (0.09)	0.64
6MWT, m (SD)	440 (55)	434 (53)	0.27
NT-proBNP, pg/ml (IQR)	62 (34-108)	50 (26-93)	0.04
Serum potassium, mmol/litre (SD)	4.4 (0.34)	4.4 (0.35)	0.89
Serum creatinine, µmol/litre (SD)	72 (15)	74 (13)	0.37
Estimated glomerular filtration rate, ml/min (IQR)	81 (9)	80 (9)	0.33
Charlson comorbidity index (IQR)	0 (0-1)	1(0-1)	0.34
DASI-METS (IQR)	8.1 (7.3-9)	8.2 (7.3-9)	0.97
PHQ-9 (IQR)	0 (0-0.5)	0 (0-1)	0.73
GAD-7 (IQR)	0 (0-1)	1 (0-1)	0.37
Montreal cognitive assessment score (IQR)	27 (25-29)	27 (25-29)	0.72
Echocardiographic measures			
LV ejection fraction, % (SD)	62 (7)	62 (6)	0.8

Global longitudinal strain, % (SD)	19 (3)	18 (2)	0.32
LV mass index, g/m^2 (SD)	70 (19)	71 (21)	0.74
E/A (SD)	0.86 (0.26)	0.82 (0.22)	0.12
Early diastolic mitral annulus velocity (e'), cm/s (SD)	7.5 (1.6)	7.7 (1.9)	0.31
E/e' (IQR)	8.3 (7.0-10.5)	8.2 (6.7-10.1)	0.27
LA volume index, ml/m^2 (IQR)	33 (29-42)	34 (28-40)	0.87
LV dysfunction (%)	80 (45)	81 (47)	0.8
Study withdrawal (%)	15 (9)	24 (14)	0.11
Follow-up duration, months (IQR)	23 (14-25)	22 (13-25)	0.35

IQR – interquartile range, SD – standard deviation, ACE-I - angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, DASI-METS – Duke activity status index metabolic equivalents, NT-proBNP - N-terminal pro-B-type natriuretic peptide, LV – left ventricular, LA – left atrial.

Figure 8-2: Categorization and cross-over of left ventricular dysfunction (LVD) subgroups in all study participants.



GLS – global longitudinal strain, IR – impaired relaxation, LAE – left atrial enlargement.

8.5.2 Spironolactone therapy

In the intervention arm, 81 (47%) had LVD. Of these participants, 9 (5 prior to commencing the drug) withdrew, and 6 did not take the drug but continued in the study (Figure 8-1). Of the 66 remaining subjects that were prescribed spironolactone, 30

(45%) completed the study course, while 36 (55%) ceased before follow-up was complete. Therefore, of those that commenced spironolactone, 45% tolerated the drug.

The duration of spironolactone therapy was 23 months (IQR 17-24) in those who completed, versus 2 months (IQR 0.7-6.5) in those who ceased spironolactone. There was 99.95% (IQR 98-100) adherence to spironolactone in those who completed the course, and none met criteria for non-adherence. The most frequent reason for discontinuation was decline in eGFR, with 10 (15.2%) experiencing a decline to <60ml/min, and 6 (9.1%) seeing a decline of >25% from baseline (Table 8-2). The median time to discontinuation for these reasons was 3 (IQR 0.6-6) months and 2 (0.7-6) months, respectively. All recovered with cessation of spironolactone. There was only 1 case of hyperkalaemia, while hypotension, problematic urinary frequency and gynaecomastia or nipple pain were more frequent causes of discontinuation (Table 8-2).

Compared with those in the usual care arm, those who completed the spironolactone course did not exhibit a significant increase in serum potassium or creatinine, nor a deterioration in eGFR (-3.7±9.5ml/min vs. -3.9±10.5ml,min, respectively, p=0.92) (Table 8-3). Similarly, no clinically or statistically significant differences were observed in change in blood pressure, heart rate and weight from baseline to follow-up between these two groups (Table 8-4).

Table 8-2: Reasons for spironolactone discontinuation in all participants who commenced treatment (n=66).

Indication for spironolactone discontinuation	**Number of participants (%)**
Estimated glomerular filtration rate decline to <60ml/min	10 (15.2)
Estimated glomerular filtration rate decline by >25% (but not to <60ml/min)	6 (9.1)
Hypotension or orthostatic hypotension	6 (9.1)
New urinary frequency	5 (7.6)
Gynecomastia or nipple pain	4 (6.1)
Hyperkalaemia (serum potassium ≥ 5.2mml/l)	1 (1.5)
Other	4 (6.1)

Table 8-3: Change in biochemical measures from baseline to follow-up in participants who tolerated spironolactone versus those in the usual care arm.

	Usual care (n=62)	**Spironolactone (n=30)**	**p-value**
Change in serum potassium, mmol/litre	-0.08±0.40	0.04±0.50	0.22
Change in serum creatinine, µmol/litre	3.5±11.9	1.9±15.1	0.56
Change in eGFR, ml/min	-3.7±9.5	-3.9±10.5	0.92

eGFR - estimated glomerular filtration rate.

Table 8-4: Change in hemodynamic and weight measures from baseline to follow-up in participants who tolerated spironolactone versus those in the usual care arm.

	Usual care (n=116)	**Spironolactone (n=25)**	**p-value**
Change in systolic BP, mm Hg (n=116)	-6±20	-7±15	0.93
Change in diastolic BP, mm Hg	-8±14	-6±9	0.49
Change in heart rate, bpm	0.6±10	-1±8	0.49
Change in weight, kg *	-1.03±4.3	-1.72±4.1	0.43

*follow-up data not available for all **usual care n=148, spironolactone n=30.

Significant univariable predictors of spironolactone discontinuation were age (OR 1.18 (95% CI 1.04-1.34), p=0.01), angiotensin-converting-enzyme-inhibitor (ACE-I) or angiotensin receptor blocker (ARB) use (OR 7.33 (95% CI 1.82-29.42), p=0.005), and total number of medications (OR 1.22 (95% CI 1.005-1.48), p=0.044) (Table 8-5). ACE-I/ARB use was the only variable that remained significant after multivariable adjustment (OR 5.53 (95% CI 1.28-23.98), p=0.02).

Table 8-5: Predictors of Spironolactone discontinuation.

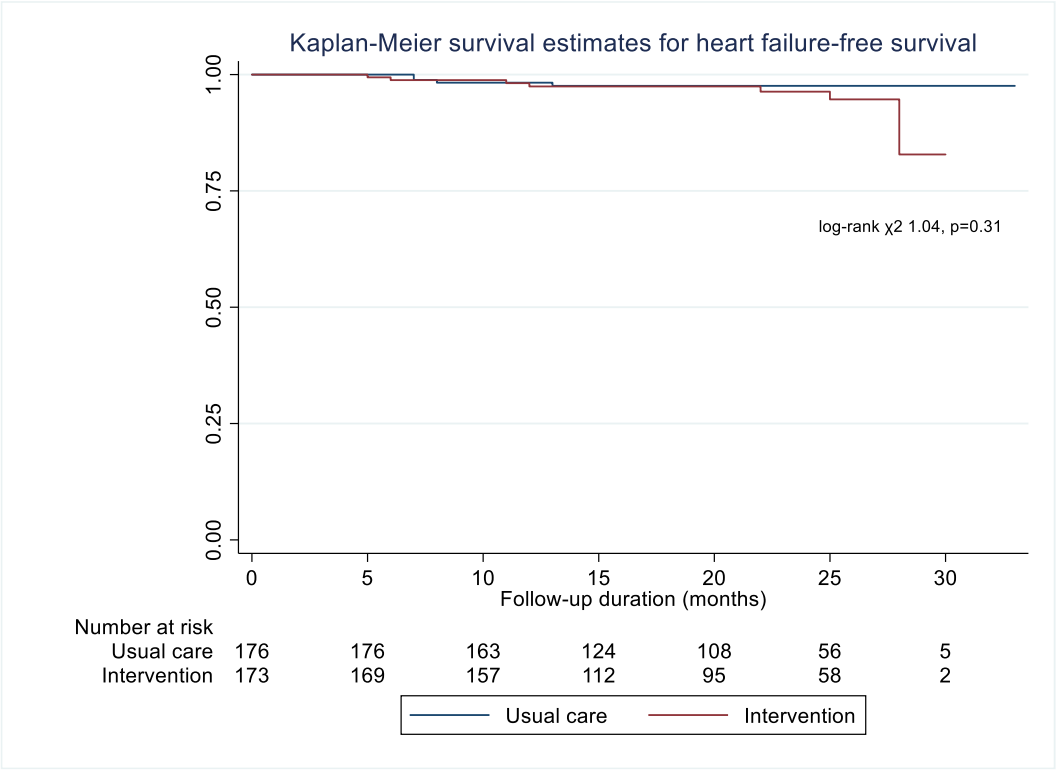
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age, years	1.18 (1.04-1.34)	0.01	1.12 (0.99-1.28)	0.08
Female gender	0.60 (0.22-1.59)	0.36		
Hypertension	4.25 (0.79-22.88)	0.09		
Type II diabetes mellitus	0.66 (0.24-1.83)	0.42		
Comorbidity index	1.17 (0.76-1.82)	0.48		
ACE-I or ARB	7.33 (1.82-29.42)	0.005	5.53 (1.28-23.98)	0.02
Number of medications	1.22 (1.005-1.48)	0.044	1.17 (0.95-1.45)	0.14
Systolic blood pressure, mm Hg	1.02 (0.97-1.04)	0.7		
Body mass index, kg/m^2	0.97 (0.89-1.07)	0.56		
Serum potassium, mmol/litre	0.76 (0.20-2.90)	0.69		
Serum creatinine, µmol/litre	1.02 (0.99-1.06)	0.23		
Estimated glomerular filtration rate, ml/min	0.96 (0.9-1.02)	0.16		

OR – odds ratio

8.5.3 Primary outcomes

Of the 310 participants who completed follow-up, 11 (3.6%) experienced incident HF; 7 were in the intervention arm and 4 in the usual care arm. There was no significant difference in HF-free survival between the two arms (log-rank χ^2 1.04, p=0.38) (Figure 8-3). Given the low number of outcomes, Cox regression for incident HF was not attempted.

Figure 8-3: Heart failure free survival by treatment arm.



8.5.4 Secondary outcomes

A follow-up 6MWT was able to be conducted in 135 (72 in usual care and 63 in the intervention arm). On an intention-to-treat basis there was a non-significant trend towards a smaller decline in 6MWT distance in the intervention arm (-17±70m vs. -3±76m, p=0.28, for usual care vs. intervention, respectively). A similar trend was observed for functional capacity assessed by DASI-METS (n=305) (-0.50±1.3 vs. -0.2±1.4, p=0.09, for usual care vs. intervention, respectively).

Follow-up echocardiography was able to be conducted in 220 participants. Of these, 112 (51%) were in the usual care arm and 108 (49%) were in the intervention arm. Of those in the intervention arm 52 (48%) had LVD at baseline and only 26 completed treatment with spironolactone. Overall, of the 220 participants undergoing follow-up echocardiography, 71 (33%) had persistently normal LV function and 40 (18%) showed resolution of LVD. Conversely, 69 (31%) exhibited persistent LVD and 40 (18%) developed LVD. There was no difference in the proportion of those with persistence or development of LVD between usual care and intervention (57 (51%) vs.

52 (48%), p=0.68, respectively), and this observation was the same for both men and women (Table 8-6).

Mean change in GLS was -0.24±2.7% for usual care versus 0.23±2.5% for intervention, p=0.2 (Table 8-6). For men (n=99) mean change in GLS was 0.04±2.7% for usual care versus -0.05±2.6% for intervention, p=0.86. While for women (n=121) there was a trend towards GLS decline in the usual care arm versus improvements in the intervention arm, (ΔGLS -0.51±2.7% vs. 0.44±2.9%, p=0.06, respectively).

8.5.4.1 Echocardiographic outcomes by spironolactone treatment

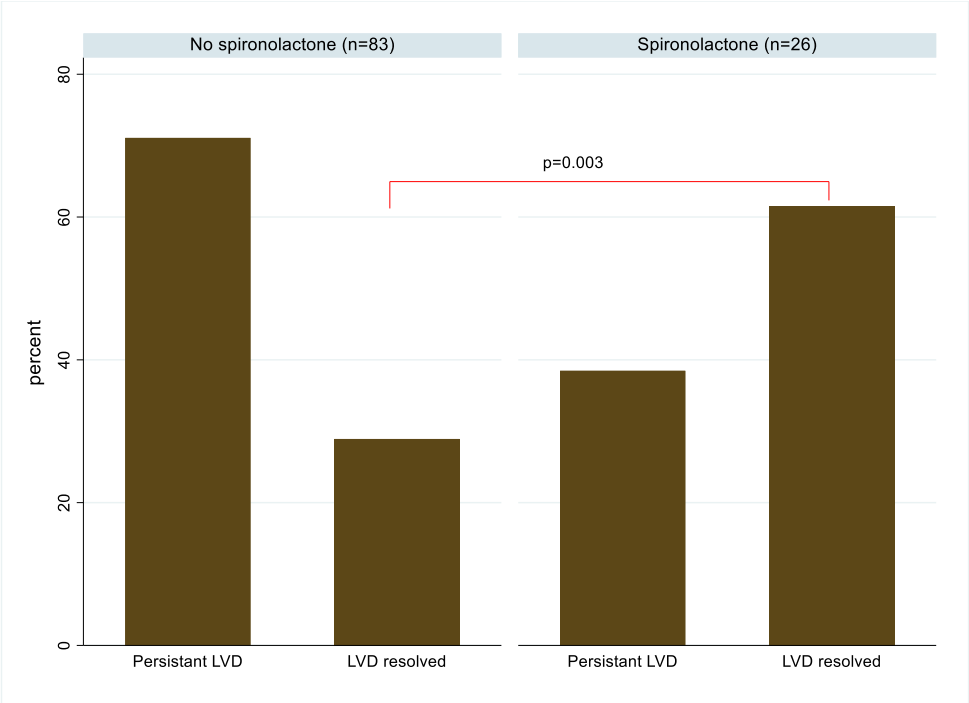
To evaluate whether the high rate of spironolactone discontinuation could have impacted the echocardiographic secondary outcomes, a sub-analysis comparing subjects taking spironolactone versus not taking spironolactone was undertaken. Given that spironolactone was only indicated in the presence of LVD (in the intervention arm), only patients with baseline LVD and a follow-up echo were considered (n=109). Of these, 26 were treated with spironolactone and 83 were not. LVD resolved in 16 (61%) of those who took spironolactone resolved compared with 24 (29%) of those not taking spironolactone (p=0.003) (Figure 8-4). The mean absolute change in GLS for those taking spironolactone was 1.6±2.3 vs. 0.6±3 for those not taking spironolactone (p=0.1).

Table 8-6: Changes in LV function and echocardiographic parameters by randomisation and gender.

	Usual care (n=112)			**Intervention (n=108)**			
	All	Men	Women	All	Men	Women	p-value
Secondary echo outcomes							
Persistently normal LV function or resolved LVD (%)	55 (49)	22 (41)	33 (57)	56 (52)	21 (47)	35 (56)	0.68, 0.55*, 0.88‡
Persistence or development of LVD (%)	57 (51)	32 (59)	25 (43)	52 (48)	24 (53)	28 (44)	0.68, 0.55*, 0.88‡
Δ GLS, %	-0.24±2.7	0.04±2.7	-0.51±2.7	0.23±2.5	-0.05±2.6	0.44±2.9	0.2, 0.86*, 0.06‡
	All	Men	Women	All	Men	Women	p-value
Other echo measures							
Δ LV ejection fraction, %	-0.1±8.1	-0.9±8.8	0.6±7.5	1.11±7.8	1.7±8.8	0.7±7.6	0.25, 0.14*, 0.94‡
Δ LV mass index, g/m^2	14±22	15±23	14±21	9±18	7±20	10±17	0.05, 0.06*, 0.38‡
Δ e', cm/s	1.1±3.2	0.6±1.7	1.5±4.2	0.4±2.1	0.6±1.9	0.3±2.2	0.08, 0.94*, 0.04‡
Δ E/e'	-0.7 (-2.3-0.44)	-0.7 (-2.3-0.26)	-0.7 (-2.4-0.7)	-0.5 (-2-1)	-0.06 (-1.8-0.9)	-0.6 (-2.3-1)	0.36, 0.34*, 0.7‡
Δ LAVI, ml/m^2	4 (-2-11)	5 (-0.1-13)	3 (-2-9)	7 (-0.3-12)	9 (2-12)	5 (-2-12)	0.18, 0.42*, 0.25‡

LVD – left ventricular dysfunction, GLS – global longitudinal strain, LAVI – left atrial volume index. * men, ‡women.

Figure 8-4: Trajectory of LV dysfunction by study drug status. Those in the spironolactone group completed the study course of spironolactone.



8.6 Discussion

In this randomized trial of echocardiography-guided spironolactone therapy we were unable to establish benefit in terms of a reduction in incident HF. The overall HF event rate was significantly lower than anticipated and only 45% of those in whom spironolactone was indicated, tolerated the drug. The risk of incident HF in elderly patients with risk factors is heterogenous. While LVD resolved in patients who took spironolactone, the poor tolerability of spironolactone indicates that it is not a feasible intervention - and especially not in those already taking an ACE-I or ARB.

8.6.1 Progression of subclinical LVD

Two relevant considerations in understanding the progression of subclinical to symptomatic HF is *how* it occurs on a cellular and molecular level, and in *whom* it is most likely to occur. Such understanding must inform therapeutic trials aimed at preventing such progression. The accepted paradigm of transition from subclinical LVD to overt HF states that cardiomyocyte hypertrophy becomes predominantly of the maladaptive type that is associated with fibrosis and cardiomyocyte loss with resulting pump failure (259). This paradigm relates to HFrEF but in HFpEF (the likely HF phenotype the patients in this trial are at risk of) LV remodelling and associated dysfunction is mediated via inflammation and microvascular endothelial dysfunction,

especially in the early stages (260). The pivotal role of inflammation in HFpEF has led to trials of anti-inflammatory therapy and research in this area is ongoing (261). Such work is vital for a condition with no effective treatment and may also lead to therapies for the subclinical phase. Several non-cardiovascular comorbidities including renal dysfunction, COPD and anaemia have been implicated in progression of subclinical diastolic dysfunction (DD) to HFpEF (8,262). Of note, COPD seems to be particularly associated with progression to HFpEF (8). Most of these data are observational therefore precluding conclusions of causality. Furthermore, the mechanisms by which these non-cardiovascular comorbidities cause or contribute to the HF syndrome, above that of shared symptoms, is unclear although may relate to systemic inflammation (260). There is a dose-response relationship between DD grade or DD grade progression, and incident HF (5). However, in some patients with subclinical DD, echocardiographic abnormalities do not worsen (and may even improve) prior to symptom onset (5,262). This could suggest that peripheral HF abnormalities are contributing. Risk of progression also relates to the underlying etiology of subclinical LVD. Indeed, subclinical LVD in people with diabetes appears to progress at a higher rate compared with other aetiologies (30). Taken together, the underlying cause as well as comorbidities appear to influence progression of subclinical HF. This has two implications for future trials of HF prevention in those with subclinical LVD. First, populations could be enriched for a higher HF risk than that observed in our study. Second, comorbidities should be considered, both in terms of influence on risk but also how these could be sought and modified for preventive effect.

8.6.2 Role of spironolactone in subclinical LVD

To our knowledge, this is the first trial to assess efficacy of aldosterone antagonism in subclinical LVD with a hard, clinical endpoint of incident HF. Spironolactone has favourable effects on cardiac function in several cohorts with cardiovascular risk factors but without symptomatic HF. In a study of 80 patients with metabolic syndrome and background ACE-I or ARB therapy, randomisation to spironolactone versus placebo saw significant improvements in several echocardiographic parameters including GLS, LV mass index, E/e' and left atrial dimension, after 6 months (263). This was accompanied by a significant reduction in circulating markers of fibrosis compared with placebo. Those with worse baseline GLS saw the greatest degree of improvement in strain and reduction in fibrotic markers.

There have been similar findings in, obese patients without other comorbidities (264). Although this may not be extrapolated to other populations given the association between obesity and hyperaldosteronism. In established HFpEF, the ALDO-DHF trial found that randomisation to spironolactone versus placebo resulted in a statistically significant (although clinically small) decline in E/e' and LV mass index compared with placebo, but did not change overall grade of DD and did not improve peak oxygen uptake (265). In a subgroup analysis of the TOPCAT trial, of those with both baseline and follow-up echocardiography recruited in the Americas (n=64), GLS improved significantly after adjustment for baseline characteristics in those treated with spironolactone versus placebo (12). Therefore, there is some evidence of improvement in GLS with spironolactone therapy, but whether this translates into improved outcomes in subclinical LVD remains unknown.

Critical to the potential role of spironolactone in this setting is its tolerability. The rate of discontinuation was high in our study due to pre-specified stoppage criteria. Primarily this related to declines in renal function i.e. eGFR decline by >25% or to <60ml/min. Comparison with other studies is difficult owing to differing patient characteristics and different definitions around renal function impairment. In the aforementioned study of metabolic syndrome, mean baseline creatinine was normal (82µmol/l) and there was no significant rise after 6 months and no patients discontinued spironolactone (263). While this cohort was younger (mean age 59 ± 11 years), baseline therapies were similar, and the prevalence of diabetes was higher (58%). The criteria for discontinuation on renal grounds was a creatinine >310 µmol/l, which would represent a significant kidney injury that could not be outweighed by potential benefit. In the ALDO-DHF trial, mean baseline eGFR was only slightly less than in our study. Spironolactone was associated with a greater proportion of patients with a decline in renal function (36% versus 21%, p=0.001), defined as a reduction in eGFR of >15% or to <30ml/min (265). Discontinuation or reduction in dose was only indicated if eGFR dropped to <20ml/min, although only gynaecomastia and hyperkalaemia were significantly associated with discontinuation. Again, in our cohort, permitting this degree of decline in renal function would be an unacceptable risk. Interestingly, spironolactone has been reported to be well tolerated in non-diabetic chronic kidney disease (mean eGFR of 49 ± 12 ml/min, age 54 ± 12 years) with concomitant ACE-I or ARB therapy (266). Less than 5% exhibited 'clinically significant' (>25%) reductions in eGFR over 40 weeks of spironolactone treatment and most were in the first 4 weeks.

We saw double the rate of discontinuation for this reason and the timing of this extended to 6 months. Future work should address whether in certain scenarios spironolactone could be safe and clinically effective as therapy in subclinical LVD e.g. in obesity without co-existing ACE-I/ARB treatment, which we found to be independently associated with need to discontinue spironolactone.

8.6.3 Limitations

Under recruitment by around 50% of target, due to trial stoppage for safety, was a major limitation that prevented testing of our hypothesis. However, we believe that the low incident HF rate and poor drug tolerability would have had a similar impact despite adequate powering. In those that tolerated spironolactone we found excellent adherence; however, adherence was based on pill counts rather than an objective biochemical measure and therefore may not have been reliable. Our design of the usual care arm in which the primary care provider was provided with the echo results may have prompted intensification of therapy and therefore lessened the potential effect of the intervention. Finally, while we recruited participants who had no history or symptoms of IHD, it was not definitively excluded, therefore applying our findings to a purely non-ischemic population is problematic.

8.7 Conclusion

This trial did not confirm that identification of subclinical LVD (defined by reduced GLS and diastolic abnormalities), and subsequent treatment with spironolactone, reduced incident symptomatic HF. The main reasons for this were the low rate if incident HF and the low tolerability of spironolactone, primarily related to reductions in renal function. Subsequent intervention trials in SBHF should study patients at greater risk of progression, with alternative therapeutic approaches.

8.8 Postscript

Although patients at risk of HF based on age and risk factors might be expected to develop adverse renal responses to spironolactone, the magnitude of side-effects in this trial was surprising. It seems unlikely that spironolactone could be a first-line pharmacological approach to HF prevention.

Patients with the SBHF profile assessed in this study are more likely to develop HFpEF than HFrEF. Cardioprotective therapies in this setting might best be selected based on the underlying pathophysiology and be personalised to comorbidities, both cardiovascular and non-cardiac, implicated in progression of HF. Trialling of new

pharmacological therapies may require careful phenotyping and prespecified analyses on this basis, acknowledging that this may require large sample sizes. A holistic, team approach combining risk factor control, investigation for relevant comorbidities, addressing physical inactivity and novel therapeutics will ultimately result in greatest benefit. Regardless of what the intervention may be, an important consideration regarding tolerance and adherence in the elderly, apart from pharmacokinetic and physical concerns, is cognition. Like established HF, any therapy in subclinical HF will require self-management and as a first step engagement with a screening process. The next chapter investigates the potential impacts of mild cognitive impairment on subclinical HF and AF screening.

8.9 Appendix

Table 8-7: Study withdrawals

Reason	N (%)
No reason given/other	11 (28)
Other commitments (caring for others, employment)	8 (21)
Moved away/difficulty travelling	7 (18)
Intercurrent health problem	6 (15)
Failed to attend appointments	3 (8)
Changed mind about taking spironolactone	2 (5)
Bereavement	2 (5)

9 Associations of subclinical heart failure and atrial fibrillation with mild cognitive impairment: Implications for screening

Submitted as: Potter EL, Ramkumar S, Wright L, Marwick TH. *Association of subclinical heart failure and atrial fibrillation with mild cognitive impairment: Implications for screening*. BMJ: Open

9.1 Preface

Screening for and managing LVD in the elderly presents problems relating to comorbidity, particularly cognitive impairment. Practically, the extent of cognitive impairment and the impact it may have on screening should be investigated with the intent to mitigate barriers to participation in these patients. Cognitive impairment is quite prevalent but is not necessarily a prelude to dementia, as around 60% of those affected either improve or remain stable. Therefore, it should not be considered a competing mortality risk and HF prevention remains important. In addition, the onset of overt HF precipitates cognitive decline, so prevention is arguably more relevant in those already cognitively impaired.

Vic-ELF participants underwent cognitive assessment at baseline. Some were also involved in an AF screening sub-study and therefore the association between cognition and adherence to AF screening as well as detection of subclinical AF is also presented here.

9.2 Abstract

Objectives. Effective identification and management of subclinical left ventricular dysfunction (LVD) and subclinical atrial fibrillation (AF) by screening elderly populations might be compromised by mild cognitive impairment (MCI). We sought to characterize the prevalence and profile of MCI and evaluate associations with LV and left atrial dysfunction and AF, in a trial of screening for subclinical LVD and AF.

Design. Cross-sectional.

Setting. Australian, community-based intervention trial.

Participants. Adults aged ≥ 65 years with ≥ 1 non-ischemic LVD risk factors (n=337).

Outcome measures. The Montreal cognitive assessment (MoCA) was obtained Subclinical LVD was defined as echocardiographic global longitudinal strain (GLS) ≤16%, diastolic dysfunction or left ventricular hypertrophy; abnormal left atrial reservoir strain (LARS) was defined as <24%. Subclinical AF was detected using a single-lead portable electrocardiographic device in those without pre-existing AF who gave consent (n=293).

Results. Subclinical LVD was found in 155 (46%), abnormal LARS in 9 (3.6%) and subclinical AF in 11 (3.8%). MoCA score consistent with MCI (<26) was found in 101 (30%); executive function (69%) and delayed recall (93%), were the most frequently abnormal domains. Compared with normal cognition, MCI was associated with non-adherence to AF screening (25% vs 40%, p=0.01). In multivariable logistic regression modelling, educational achievement, systolic blood pressure, body mass index and waist-to-hip ratio were independently associated with MCI. However, neither subclinical AF nor any measure of cardiac dysfunction, were associated with MCI.

Conclusions. The 30% prevalence of MCI among elderly subjects with risk factors for subclinical LVD and AF has important implications for screening strategies and management. However, MCI is not associated with subclinical myocardial dysfunction nor subclinical AF.

9.3 Introduction

Mild cognitive impairment (MCI) describes test-based evidence of cognitive impairment without significant compromise to independent functioning (267). It is a prelude to dementia - a major contributor to mortality and morbidity in our ageing population (268). Heart failure (HF) and atrial fibrillation (AF) increase risk of cognitive impairment (269,270), with between 54% and 74% of HF patients affected (271). Furthermore, MCI in HF compromises self-management and leads to worse outcomes (272). Early detection and prevention of HF and AF may consequently serve to reduce the burden of MCI. Trials evaluating screening for subclinical left ventricular dysfunction (LVD) and AF, should incorporate cognitive assessment, not only to inform future screening and prevention strategies but to elucidate clinical associations and mechanisms.

Cognitive impairment in HF is associated with medial temporal lobe atrophy and lower cerebral grey matter volume on neuroimaging (273,274), changes that are more marked compared with those with risk factors but without HF. Whether this is the case in the subclinical phase of HF failure i.e. LVD without HF symptoms, is uncertain. Vascular risk factors, particularly hypertension, predispose to cerebral small-vessel disease, lacunar infarcts and compromise auto-regulatory responses that maintain cerebral perfusion (271). Limited data suggest subclinical LVD is independently associated with MCI (275), In addition, reduced systolic function assessed by global longitudinal strain (GLS) has been associated with silent cerebral infarcts, independent of vascular risk factors (196). Left atrial (LA) enlargement has been linked with MCI but this does not appear independent of AF, particularly in longitudinal analyses (276). AF may exert its effect on cognitive function via silent cerebral infarcts, presumably due to cardiogenic embolism. The impact of subclinical AF (asymptomatic AF, unrecognized without screening) or LA function on cognition are unknown.

Should screening programs for subclinical HF and AF be advocated, the cognitive status of the target population must be quantified to inform effective program design and implementation. Furthermore, the presence of an independent link between subclinical LV and LA dysfunction, subclinical AF, and cognitive impairment remains unclear. Accordingly, assessment of cognitive function was undertaken at baseline in participants enrolled in the Victorian Study of Echocardiographic detection of Subclinical Left Ventricular Dysfunction (Vic-ELF) to establish a) prevalence and

profile of MCI in this population and b) identify associations between MCI and left ventricular (LV) function, LA function and subclinical AF.

9.4 Methods

9.4.1 Study population

All subjects were participants in the Victorian Study of Echocardiographic detection of Subclinical Left Ventricular Dysfunction (Vic-ELF; ACTRN:12617000116325). Baseline data were used for this cross-sectional sub-study. Subjects were recruited from the community via primary care and advertising. Those who were asymptomatic and ≥ 65 years with hypertension (self-reported, on medication or systolic blood pressure (SBP) ≥140/90mm Hg), type II diabetes mellitus or obesity (BMI ≥ 30kg/m^2) were eligible for inclusion. Those with a history or symptoms of HF or ischemic heart disease (based on existing clinical indication for echocardiography), LV ejection fraction ≤40%, > moderate valvular disease or oncologic life expectancy <1 year were excluded. The study was approved by a Human Research Ethics Committee (Bellberry, HREC number 2016-10-727) and all participants gave written informed consent.

9.4.2 Patient and public involvement

Patients were not involved in study design and no evaluation of patient involvement burden was undertaken. All participants will receive information regarding the impact of the research findings after study conclusion.

9.4.3 Clinical assessment

Comprehensive medical and medication history were taken along with clinical examination. Heart rate, resting averaged blood pressures, body mass index (BMI), waist and hip circumference and serum N-terminal pro-brain natriuretic peptide (NT-proBNP) were recorded along with a six-minute walk test to assess functional capacity, in accordance with standard procedure (111). Patient–reported functional capacity was assessed using the Duke activity score index (DASI). Health-related quality of life, depression and anxiety were evaluated with the EQ-5D-5L, generalized anxiety disorder 7-item scale (GAD-7) and the patient health questionnaire-9 (PHQ-9), respectively. Habitual physical activity was measured (n=201) using waist-worn accelerometers (ActiLife, ActiGraph, Pensacola, FL) for 7 days. Recordings of less than 4 days were excluded, leaving a total of 190 suitable for analysis.

9.4.4 Cognitive assessment

The MoCA was conducted in accordance with instructions (277). In brief the MoCA is a short (10-12 minutes) office-based assessment that evaluates the cognitive domains of executive and visuospatial function; attention, concentration and working memory; short term memory, language skills and orientation. It is validated in ages 55-85 years and is the preferred screening tool for mild cognitive impairment (278). MCI is diagnosed by a score of <26/30. Graded severity levels of 18-25, 10-17 and <10, are suggested for mild, moderate and severe cognitive impairment respectively, although supportive data are lacking. Therefore, all cognitive impairment will be referred to as MCI. A deficit in a domain is defined herein as ≥1 point deficit in that domain. MoCA result was unknown to the investigator (SR) evaluating subclinical AF and atrial function.

9.4.5 Echocardiography

Resting 2D and Doppler echocardiography was performed with standard equipment (ACUSON SC2000, Siemens Healthcare USA, Mountain View, CA) and transducer (4V1c, 1.25 to 4.5 MHz; 4Z1c, 1.5 to 3.5 MHz) in accordance with guidelines (117). A vector-velocity imaging algorithm (Syngo VVI, Siemens Medical Solutions, Siemens Healthcare USA, Mountain View, CA) was used for GLS quantification and averaged from apical, 2-, 3- and 4-chamber views. Diastolic function was assessed by measuring mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, septal and lateral mitral annular early diastolic velocities (e') and E/e' ratio. Biplane method of disks (Simpson's modified rule) was used for left atrial volume quantification and indexed to body surface area (LAVI). Diastolic dysfunction was diagnosed using current recommendations (32). Left ventricular mass (LVM) was calculated using the 2D linear method and indexed to body surface area. LVH was defined as LVMI (LVM indexed to body surface area) 95 g/m^2 in women, 115 g/m^2 in men. Subclinical LVD was defined as presence of GLS ≤16%, DD or LVH.

LA reservoir strain (LARS) was assessed by speckle-tracking using a third-party software program (TOMTEC-Arena™ (Version TTA2), 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 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). Abnormal LARS was defined as <24 %.

9.4.6 Atrial fibrillation screening and echocardiographic risk markers for AF

Participants without a history of atrial fibrillation or flutter were asked to provide separate consent (n=293). Screening for subclinical AF was performed using a portable, single-lead ECG device (Remon RM-100; Semacare, Beijing, China) using three finger contact electrodes. Recordings lasted 60-seconds and were undertaken 3 times per day for 2 weeks (i.e. 42 recordings). Instructions were given verbally face-to-face and in written form. Battery failure, device malfunction or problems relating to dexterity were recorded. ECG recordings were exported as PDF files for interpretation, and all were assessed by a physician. The presence of AF was defined as an irregular rhythm of ≥30 sec with a variable R-R interval and absent P waves.

A stepwise risk stratification tool for atrial fibrillation using GLS, LAVI and LA reservoir strain (LARS) has been devised (279). GLS >14.3% determines low risk; GLS <14.3% and LAVI >39ml/m^2 determines high risk; GLS <14.3% and LAVI ≤39ml/m^2 determines intermediate risk, which can be reclassified to intermediate-high if LARS <33.9%. Participants were dichotomised by low/intermediate or high (including intermediate-high) risk based on these criteria. Association between this risk assessment with MCI was assessed individually and combined with detected subclinical AF i.e. a group combining those at high risk of subclinical AF plus those with detected subclinical AF.

9.4.7 Statistical analysis

Continuous variables are presented as median with interquartile ranges (IQR) or mean ± standard deviation, based on distribution testing using the Shapiro-Wilk test. Categorical variables are presented as frequencies and percentages. Differences between two independent groups were determined using χ^2 and unpaired Student's t-test for categorical and continuous variables, respectively. Variables with a p-value <0.1 in univariable analysis were selected for inclusion in multivariable logistic regression modelling. Effect sizes are expressed as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was defined as a two-tailed p-value <0.05. Analyses were conducted using STATA 15.1 (StataCorp, College Station, TX).

9.5 Results

9.5.1 Participant characteristics

Of the 337 subjects (age 70 years (68-73), 58% female), 292 (87%) had hypertension with a median duration of 13 years, 108 (32%) had type 2 diabetes mellitus with a median duration of 8 years and 214 (64%) were obese (Table 9-1). The majority (65%) were dyslipidemic, a significant proportion were current or ex-smokers (45%) and a small proportion had a history of stroke or transient ischemic attack (6%) and alcohol abuse (7%). On average, the group spent 66% of waking time sedentary with levels of moderate to physical activity (MVPA) falling well below guideline recommendations. Serum NT-proBNP was, on average, in the low risk range i.e. <125pg/ml (51pg/ml (30-100)).

9.5.2 Characteristics of cognitive impairment and relation to LV function

With regards cognitive assessment by MoCA, 101 (30%) exhibited MCI with an overall average MoCA score of 27 (25-29). Of the 101 participants with MCI, severity staging showed none with severe cognitive impairment and only 3 with moderate cognitive impairment thus the majority had MCI corresponding to a MoCA score between 18 and 25. Overall, delayed recall and executive function had the highest proportion of deficits (237 (70%) and 145 (43%), respectively (Table 9-2). There were no differences in the proportion of cognitive domain deficits between those with and without subclinical LVD (Table 9-1), except for orientation, although only 2% of participants had deficits in this domain.

9.5.3 Subclinical AF screening and cognitive impairment

Of the 293 screened, there were 10 instances of device malfunction leaving 283 for analysis. Subclinical AF was detected in 11 (3.9%). Subclinical AF was equally incident in those with and without MCI, as was pre-existing AF (Table 9-1). In those with pre-existing AF, only 13 (57%) were taking an anticoagulant. By echocardiographic AF risk stratification, 9 (2.7%) were deemed high risk and again there was no association with MCI (Table 9-1). However, after instances of battery/device malfunction were excluded (n=10), MCI was significantly associated with a reduced number of recordings (<30 recordings), 51 (25%) and 33 (40%) for no MCI and MCI, respectively, p=0.01. Therefore, in those undergoing AF screening with a hand-held device a 12% (33/283) rate of non-adherence, related to MCI, was observed.

9.5.4 Clinical and echocardiographic associations with cognitive impairment.

Those with MCI were less obese and reported significantly fewer years of formal education (Table 9-1). There was a non-significant trend towards higher blood pressure and longer duration of a diagnosis of hypertension and type II diabetes. The proportion with at least moderate anxiety or depression did not differ by presence of MCI, and while on average functional capacity by 6MWT and minutes per week of MVPA were less in those with MCI, neither were statistically significant (Table 9-1). Overall, 155 (46%) had subclinical LVD. Echocardiographic markers of systolic and diastolic LV function did not differ by presence of MCI (Table 9-3). However, LVMI was significantly higher in those with MCI compared to normal cognition (75g/m^2 (60-84) vs. 67g/m^2 (55-79), p=0.04, respectively), although this did not translate into a greater proportion of those with MCI having LVH (7 (7%) vs. 13 (5.5%), p=0.62, respectively). LA function measured by LARS was abnormal (<24%) in 9 (3.6%) with a mean value of 36.2±7%. LARS did not differ by presence of MCI, nor did the proportion of those with abnormal LARS (Table 9-3).

Table 9-1: Clinical, anthropometric, functional, and physical activity measures by presence or absence of mild cognitive impairment (MCI).

	All (n=337)	**No MCI (n=236)**	**MCI (n=101)**	**p-value**
Age, years (IQR)	70 (68-73)	70 (68-73)	70 (67-73)	0.83
Gender, female (%)	194 (58)	140 (59)	54 (54)	0.32
Hypertension (%)	292 (87)	201 (85)	91 (90.1)	0.22
Hypertension duration, years (IQR)	13 (7-20)	12 (7-20)	15 (7-20)	0.56
Type II Diabetes (%)	108 (32)	72 (31)	36 (36)	0.36
Diabetes duration, years (IQR)	8 (5-15)	7 (4.5-12.5)	10 (5-18)	0.1
Obesity (%)	214 (64)	158 (68)	56 (56)	0.04
Dyslipidemia (%)	208 (62)	145 (62)	63 (62)	0.9
Ever smoker (%)	152 (45)	110 (47)	42 (42)	0.34
AF, known (%)	23 (7)	14 (6)	9 (9)	0.32
AF, detected by screening* (%)	11 (4)	8 (4)	3 (4)	0.88
High risk for AF† (%)	9 (3)	8 (3)	1 (1)	0.21
Stroke/TIA	21 (6)	11 (5)	10 (10)	0.07
Alcohol abuse (%)	25 (7)	21 (9)	4 (4)	0.12
ACE-I/ARB (%)	264 (78)	183 (78)	81 (80)	0.59
Beta blocker (%)	37 (11)	22 (9)	15 (15)	0.14
Statin (%)	179 (53)	123 (52)	56 (55)	0.58
Antiplatelet agent (%)	68 (20)	43 (18)	25 (25)	0.17
Anticoagulant (%)	16 (5)	10 (4)	6 (6)	0.5
Education, years (IQR)	12 (10-15)	12 (10-15)	11 (10-14)	0.02
PHQ9 >6 (moderate depression)	27 (8)	20 (8.5)	7 (6.9)	0.63
GAD7 >6 (moderate anxiety)	26 (8)	19 (8)	7 (6.9)	0.72
EQ-5D-L score (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	0.77

Systolic BP, mm Hg (IQR)	138 (131-150)	137 (129-149)	141 (133-151)	0.07
Diastolic BP, mm Hg (IQR)	83 (78-90)	83 (77-89)	85 (79-91)	0.09
BMI, kg/m^2 (IQR)	31 (28-35)	32 (28-36)	30 (27-33)	0.002
Waist-hip ratio (SD)	0.93 (0.09)	0.92 (0.09)	0.94 (0.09)	0.07
Duke activity score index (IQR)	51.7 (46.7-52.7)	52 (49.5-52.7)	50.7 (46-52.7)	0.39
Six-minute walk test, m (IQR)	441 (403-476)	445 (403-477)	438 (405-472)	0.49
MVPA, minutes/week (IQR)	63 (18-144)	65 (18-135)	48 (17-152)	0.89
Sedentary time, % (SD)	66 (10)	67 (10)	64 (9)	0.15
NT-proBNP, pg/ml (IQR)	51 (30-100)	55 (31-101)	49 (24-95)	0.34

* total screened = 293, †echocardiographic criteria

TIA – transient ischemic attack, ACE-I/ARB – angiotensin converting enzyme inhibitor/receptor blocker, BP – blood pressure, BMI – body mass index, MVPA – moderate-vigorous physical activity, NT-proBNP – N terminal pro-brain natriuretic peptide.

Table 9-2: Mild cognitive impairment (MCI) and deficits in individual cognitive domains according to presence or absence of subclinical left ventricular dysfunction (LVD). P-value for comparison of normal LV function vs. subclinical LVD.

	Overall (n=337)	**MCI (n=101)**	**Normal LV function (n=175)**	**Subclinical LVD (n=162)**	**p-value**
MCI (MoCA <26)	101 (30)		52 (29.7)	49 (30.2)	0.9
Moderate CI (MoCA <18)	3 (3)		2 (4)	1 (2)	0.7
Executive and visuospatial (%)	145 (43)	70 (69)	75 (43)	70 (43)	0.9
Naming (%)	15 (4.5)	9 (9)	6 (3.4)	9 (5.6)	0.34
Attention (%)	5 (1.5)	5 (5)	4 (2.3)	1 (0.62)	0.21
Language (%)	124 (37)	69 (68)	70 (40)	54 (33)	0.2
Abstraction (%)	88 (26)	61 (60)	50 (29)	38 (23)	0.29
Delayed recall (%)	237 (70)	94 (93)	121 (69)	116 (72)	0.62
Orientation (%)	7 (2)	6 (6)	7 (4)	0 (0)	0.01

Table 9-3: Echocardiographic variables by presence or absence of mild cognitive impairment (MCI).

	No MCI (n=236)	**MCI (n=101)**	**p-value**
LV ejection fraction, % (SD)	62 (6.8)	62 (5.8)	0.7
GLS, % (IQR)	18.7 (17-20)	18.7 (17-20)	0.87
EA, (IQR)	0.8 (0.68-0.95)	0.82 (0.69-0.99)	0.63
e', cm/s (IQR)	7.5 (6.3-8.9)	7.5 (6.5-8.7)	0.67
E/e' (IQR)	8.2 (6.9-10.2)	8.7 (7.2-11)	0.32
LAVI, ml/m^2 (IQR)	34 (28-40)	33 (29-42)	0.56
LA reservoir strain*, % (SD)	36.2 (7)	36.1 (7)	0.9
LARS <24%* (%)	7 (4)	2 (3)	0.61

Relative wall thickness (IQR)	0.37 (0.34-0.43)	0.39 (0.33-0.43)	0.96
LV mass indexed, g/m^2 (IQR)	67 (55-79)	75 (60-84)	0.04
Subclinical LV dysfunction (%)	113 (48)	49 (48.5)	0.9
Systolic dysfunction (GLS≤16%)	42 (18)	13 (13)	0.26
Diastolic dysfunction (%)	54 (23)	26 (26)	0.54
LV hypertrophy (%)	13 (5.5)	7 (7)	0.62

*available in 248 participants

LV – left ventricular, GLS – global longitudinal strain, LAVI – left atrial volume indexed to body surface area, LARS – left atrial reservoir strain

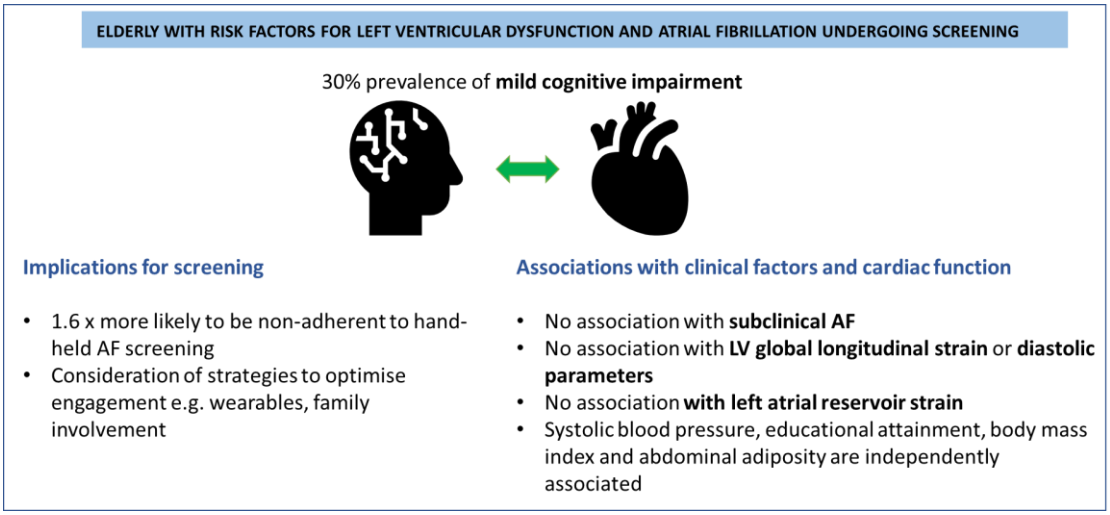
In univariable logistic regression modelling no echocardiographic markers of LV or LA function, nor presence of atrial fibrillation showed an association. Prior cerebrovascular accident (CVA), education duration, SBP, BMI and waist-to-hip ratio (WHR) were associated with MCI, ($p<0.1$) (Table 9-4).. In multivariable analysis, MCI was independently associated with higher SBP (OR 1.02 (1.00-1.04), p=0.03) and WHR (OR 40 (2.3-708), p=0.01), while greater numbers of years in formal education (0.9 (0.86-0.98), p=0.01) and higher BMI (0.9 (0.85-0.95), $p<0.001$) were independently associated with normal cognition.

Table 9-4: Logistic regression modelling for prediction of mild cognitive impairment (abbreviations as per tables 1 and 3).

	Univariable		**Multivariable**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, years	1.00 (0.95-1.06)	0.88		
Female gender	0.8 (0.49-1.26)	0.32		
Hypertension	1.58 (0.75-3.33)	0.23		
Hypertension duration	1.00 (0.97-1.03)	0.76		
Type II diabetes	1.26 (0.77-2.06)	0.36		
Diabetes duration	1.03 (0.98-1.09)	0.22		
Dyslipidemia	1.03 (0.63-1.66)	0.9		
Ever smoker	0.88 (0.23-3.44)	0.86		
Stroke/TIA	2.2 (0.87-5.6)	0.09	2.5 (0.93-6.8)	0.07
AF (known)	1.54 (0.65-3.69)	0.33		
AF (detected or high risk)	0.63 (0.2-1.96)	0.43		
Education, years	0.92 (0.86-0.98)	0.02	0.9 (0.86-0.98)	0.011
Depression (PHQ9 >6), %	0.8 (0.32-2)	0.6		
Anxiety (GAD7 >6), %	0.85 (0.33-2.1)	0.72		
ACE-I/ARB	1.17 (0.65-2)	0.59		
Beta blocker	1.7 (0.84-3.4)	0.14		
Statin	1.14 (0.7-1.8)	0.58		
Antiplatelet	1.47 (0.84-2.59)	0.17		
Anticoagulant	1.43 (0.5-4)	0.5		
Systolic BP, mm Hg	1.02 (0.99-1.03)	0.07	1.02 (1.00-1.04)	0.03
Diastolic BP, mm Hg	1.02 (0.99-1.04)	0.2		
BMI, kg/m^2	0.93 (0.88-0.97)	0.001	0.9 (0.85-0.95)	<0.001
Waist-hip ratio	11 (0.8-161)	0.07	40 (2.3-708)	0.01
NT-proBNP, pg/ml	0.99 (0.99-1.00)	0.7		
MVPA, hr/week	0.99 (0.99-1.00)	0.98		
Sedentary time, %	0.98 (0.94-1.01)	0.15		

Echocardiographic classifications		
Subclinical LV dysfunction	1.03 (0.64-1.63)	0.9
Systolic dysfunction (GLS ≤16%)	0.68 (0.35-1.33)	0.26
Diastolic dysfunction	1.18 (0.69-2)	0.54
LV hypertrophy	1.27 (0.49-3.3)	0.62
Echocardiographic continuous measures		
LV ejection fraction, %	0.99 (0.95-1.03)	0.7
GLS, %	1.01 (0.92-1.11)	0.82
e', cm/s	0.96 (0.84-1.09)	0.57
E/e'	1.03 (0.94-1.12)	0.4
LAVI ml/m^2	1 (0.98-1.03)	0.56
LA reservoir strain, %	0.98 (0.96-1.04)	0.91
LARS <24%	0.66 (0.13-3.27)	0.61
LV mass indexed, g/m^2	1.00 (0.99-1.02)	0.13

Figure 9-1: Summary of cognition study findings.



9.6 Discussion

Up to 30% of individuals included in a screening program for subclinical LVD and AF had MCI, manifest most commonly as executive dysfunction, and poor recall of recently delivered information. This is more prevalent than in unselected people aged >65 years, among whom the prevalence of MCI is 3-19% (280). The higher prevalence in our population supports the notion that MCI can be expected in people at risk of HF and AF. This is consistent with evidence that CV risk factors compromise executive function, which is especially true for hypertension – even at subclinical levels (281).

For the first time, associations were sought between sensitive deformation markers of LV and LA function (strain) and none were found, nor did we find evidence that subclinical AF or high AF risk was associated with MCI, although the number of subjects concerned was low. However, consistent with existing data, lower educational achievement, higher systolic blood pressure and visceral adiposity, but lower BMI were independently associated with MCI (282,283) (Figure 9-1).

9.6.1 Cognition and cardiac disease

There is contemporary focus on cognitive dysfunction in the setting of cardiac diseases, principally HF and AF. Cognitive impairment, specifically vascular cognitive impairment shares well documented risk factors with HF and AF. Exposure to hypertension, diabetes, smoking and abdominal obesity in mid-life is associated with an accelerated decline in executive function a decade later. This is coupled with magnetic resonance imaging (MRI) evidence of cerebral vascular damage and atrophy (283).

Symptomatic heart failure is independently associated cognitive impairment, although data with robust adjustment for shared risk factors is sparse. Nevertheless, the impact is significant, with most recent estimates of incidence being around 30% over 3.5 years (284), with cerebral hypoperfusion and subclinical cardiogenic emboli likely mechanisms (285). Population studies demonstrate conflicting results regarding associations between LV function and cognition. Cross-sectional data from the Framingham Heart Study found a U-shaped relationship between LVEF quintiles and cognition with the extremes displaying worse cognitive performance (memory and executive function) (286). Conversely, longitudinal data from the Netherlands demonstrated that LAVI but not LVEF at baseline was associated with lower performances in attention and executive function at follow-up (287). Furthermore, another cross-sectional population study found lower systolic function, assessed by tissue Doppler early systolic peak velocity, was not associated with poor cognitive performance but was associated with lower total brain volume (288). With regards LA size, several studies have demonstrated an association between greater LA size and cognitive impairment by global assessment or specific domain testing (272,287,288). However, adjustment for atrial fibrillation is inconsistent and recent evidence suggests the association is not independent of known AF (276).

Less is known about the link between cardiac dysfunction and cognition in asymptomatic patients. In patients with chronic heart disease (e.g. coronary disease) but without symptomatic HF, diastolic filling pressure estimated by E/e', was associated with significantly higher odds of MCI after comprehensive adjustment for clinical factors, although effect size was small (OR 1.07, 1.01-1.13, p=0.022) (275). This finding did not extend to LVMI, LAVI or stroke volume index (275). In a population without symptomatic cardiac or cerebrovascular disease, those with silent cerebral infarcts (SCIs) on MRI had significantly lower systolic function, as assessed by GLS (289). Moreover, GLS in those with SCIs was in the abnormal range.

Atrial fibrillation is associated with a 42% increase in risk of dementia, independent of age and cardiovascular risk factors (270,290). Interestingly, this association appears strongest in those <70 years with data suggesting no association > 67 years, presumably due to the influence of neurodegenerative pathophysiology (290,291). This is significant given the median age in our study was 70 years. The most prominent mechanism behind the association between AF and cognitive impairment is SCIs, the presence of which determine cognitive decline associated with AF, and

conversely those with AF without SCIs do not exhibit cognitive decline (292). However, no study has examined the distribution of SCIs preventing inference about the pathophysiologic mechanism i.e. small vessel versus embolic disease. Anticoagulation in AF is associated with up to a 60% reduction in cognitive decline and incident dementia, supporting a cardioembolic mechanism (293). Neuroimaging would have strengthened our study and revealed whether those with AF were free of SCIs thus potentially explaining the lack of association with MCI.

9.6.2 Clinical implications

Clinicians involved in management of patient with CV risk factors must be alert to the significant proportion of patients who will have MCI – affecting their ability to recall medical information and self-manage aspects of their condition. Indeed, those with MCI progress to dementia at a rate of over 50% in 5 years (280). Our data highlight that even in the early stages of cognitive compromise modifiable risk factors i.e. systolic hypertension and abdominal obesity are contributors, and it may be argued that cognitive screening be undertaken routinely in this scenario. We did not find evidence of an association between certain echocardiographic measures, even sensitive markers of LV and LA function. So, based on these data, echocardiographic abnormality alone should not prompt cognitive evaluation.

In terms of HF prevention, while management of subclinical disease largely rests on risk factor control, the onus is on the patient to recognize the often-insidious transition to a symptomatic state. Current ACC/AHA HF management guidelines suggest that patients with subclinical HF undertake self-surveillance for symptoms and our data highlight one of the problems with this approach i.e. the potential for under-recognition due to cognitive impairment. While screening for subclinical LVD is not currently advocated, it is plausible that early institution of therapy may preserve cognition if progression to symptomatic HF is delayed or prevented. Indeed, anticoagulation for AF, whether permanent or paroxysmal, is associated with a significant reduction in cognitive impairment (293), an observation that could extend to subclinical AF detected by screening.

One of the primary objectives of this study was to assess the prevalence of MCI and therefore the consequences to delivery of screening programs for HF and AF. This study population may have been subject to selection bias given they had sufficient cognition to apply for the trial, meaning the true prevalence is likely higher. However,

for those with established dementia, prevention of HF or AF is not their primary care goal. Population-based screening for dementia or MCI is not presently advocated, however a novel proposal may be that HF/AF screening be used as a platform for cognitive screening given the high yield in this cohort. Our data suggest that strategies to optimize engagement and follow-up with a HF/AF screening program should be considered. For example, engagement of services beyond the screening program and consideration given to the impact of reduced cognition and health literacy. When cognition is compromised, close relatives can assist with health literacy to promote use of health services. Our finding of a 12% rate of non-adherence to self-initiated AF screening, that related to MCI, is also of importance in considering the mode of delivery of AF screening. Technologies like monitoring patches or smartwatches may be more effective than devices that participants are required to operate.

9.6.3 Limitations

The study would have been strengthened by a longitudinal design, to additionally assess impact on incident MCI. While our sample size was not based on calculation, it is comparable to other studies in specific populations. As mentioned previously, brain MRI would have provided additional mechanistic insights. Our method of assessment for MCI was chosen both for its speed and validity. However, use of more detailed tests for individual cognitive domains may have added more depth to our results and made comparisons with other studies easier. Indeed, variation in the literature surrounding CV disease and cognition may be largely due to inconsistencies in methods. MoCA is not well suited for inferences regarding deficiencies in individual cognitive domains, although we did describe domain-specific results. Finally, it should be borne in mind that while a significant proportion of subjects exhibited subclinical LVD, the number with reduced atrial function and/or subclinical AF was low, limiting the certainty of our observations.

9.7 Conclusion

Elderly subjects enrolled in a trial screening for subclinical LVD and AF exhibited a 30% prevalence of MCI. There was no association between sensitive measures of LV and LA function nor subclinical AF and presence of MCI.

9.8 Postscript

Both chapters in this part highlight that in the age group of interest the heart cannot be considered an entity to treat in isolation. Interventions must be considered in the context of other organ pathophysiology and effects on quality of life. In Vic-ELF, not only was renal impairment problematic but 7.6% of those taking spironolactone discontinued the drug due to urinary frequency; an imposition on their quality of life that for them outweighed potential benefit. With this in mind, adherence to any future interventions in this space should be expected to fall somewhat short of target as has been observed in symptomatic HF. In a cohort of elderly (mean age 75±6 years), insured Americans with HFrEF, underuse of GDMT prior to planned defibrillator implantation was prevalent – only 61% filled a script for any GDMT in the 3 months prior (294). A strong predictor of this was chronic kidney disease (CKD). In a Korean observational cohort (mean age 76 years) admitted with acute decompensated HFrEF, RAS inhibitors plus beta-blockers were prescribed in 44% of patients on discharge, and this was associated with a significant mortality benefit even in those >80 years (295). Conversely in Dutch octogenarians with chronic HF, prescription rates for RAS inhibitors and beta-blockers were 78% and 73% respectively, although only around half reached ≥50% target dose (296). Reasons for under-prescription were not fully explained by intolerances and contraindications (although there is controversy over the benefit of beta-blockers and reaching target dose of any GDMT in the very elderly), but frailty may be contribute (297).

Interventions in the elderly are a complex undertaking, even in those who are independent, community dwelling and with minimal comorbidities. This highlights why appropriate patient selection is important – so the risk benefit ratio of the intervention and the cost-effectiveness are maximised. The next part addresses the findings on HF risk heterogeneity (Vic-ELF vs. Tas-ELF) and incorporates findings from chapters 2 and 3 to investigate how risk prediction can be practically improved to ensure optimal selection in the future.

PART 4: Addressing variations in heart failure risk

10 Improved heart failure risk prediction using simple clinical and sociodemographic variables

10.1 Preface

This chapter deals with two striking observations made during the thesis. Firstly, the rate of incident HF was 4% in the Vic-ELF trial in contrast to 12% in its predecessor conducted in Tasmania (14). Secondly, the ARIC HF risk score under-estimated observed risk in both trials. The variations in risk both between trial locations and from the predictions of a validated risk score are intriguing. The analysis presented here combines data from the two trials and incorporates an understanding of the risk conferred by socioeconomic status including potential access to healthcare, and functional capacity investigated in Part 1 of the thesis. It aims to provide improved risk prediction with readily available or easily acquired data.

10.2 Abstract

Background. Simple clinical risk scores could direct patient selection for heart failure (HF) prevention. However, existing risk scores are derived from general population cohorts rather than people with HF risk factors (Stage A HF, SAHF). We sought to determine the performance of the atherosclerosis risk in communities (ARIC) HF risk score in an elderly population with SAHF and whether easily acquired variables could improve risk prediction.

Methods. We evaluated the ability of the ARIC HF risk score to predict incident HF in 862 community-dwelling elderly subjects with ≥1 HF risk factors, followed for 2-years. We evaluated 1) association of the ARIC score and additional candidate risk factors with incident HF by Cox regression, 2) incremental discriminative ability of models incorporating additional risk factors by area-under receiver operating characteristic curves (AUC) and 3) changes in risk classification by net reclassification improvement (NRI). A classification and regression tree (CART) analysis, using ARIC score and additional discriminative risk factors, was used to evaluate their optimal, sequential utility.

Results. Of the 862 subjects (47% male, median aged 70 [IQR 67-73] years), median 2-year ARIC score was 2.3% (1.4-4.1) and 78 (9%) developed HF. ARIC risk score, chronic obstructive pulmonary disease (COPD), Duke Activity Status Index (DASI), and remoteness classification were predictive of incident HF, independent of atrial fibrillation (AF), subjective health status (EuroQol), depression and area-level socioeconomic status (SES). AF, COPD, DASI and remoteness classification individually increased the ARIC score AUC by >0.01 and the model incorporating

these variables improved AUC from 0.660 (95% CI 0.597-0.724) to 0.722 (95% CI 0.657-0.789), p=0.03). NRI by the additional variables was 26% (p<0.001) and 46% (p<0.001) depending on risk stratification. CART analysis identified remoteness classification as the initial step in risk assessment, followed by ARIC risk score then other variables.

Conclusions. An existing, validated HF risk score has modest performance in an elderly population with SAHF and addition of 4 clinical and sociodemographic variables significantly improves discrimination and risk classification. Living remotely is a major driver of incident HF risk.

10.3 Introduction

The heart failure (HF) epidemic demands ongoing preventive efforts. Non-pharmacological and pharmacological interventions require risk-guided selection given the attendant cost and side-effects. This is particularly relevant in the elderly, who carry the burden of HF risk (25), but among whom preventive strategies must be balanced against competing comorbidities. Furthermore, over 50% of elderly have HF risk factors (Stage A HF [SAHF]) and half again are likely to have unrecognized subclinical left ventricular dysfunction (LVD) (11). This large and heterogeneous group must therefore be refined for some preventive strategies to be feasible and justifiable.

Clinical risk scores are an attractive tool to guide interventions, particularly when they only require easily attainable information. There have been 29 proposed HF risks scores, primarily derived from population studies in the USA (39,40). Of these, the atherosclerosis risk in communities (ARIC) HF risk score has the best discriminative ability, has been externally validated and requires only basic clinical data, although it has not been validated outside of the USA. Unlike newer risk calculators for atherosclerotic cardiovascular disease (ASCVD), which incorporate SES and some non-traditional risk factors (298,299), the ARIC-HF score does not contain certain traditional and non-traditional risk factors, for example atrial fibrillation (300), socioeconomic status (SES) (301) and functional capacity (302). As this information is easily and cheaply attainable, inclusion would be warranted if these features improved discrimination for future events. Accordingly, we prospectively assessed the performance of the ARIC HF risk score in an Australian cohort of elderly with SAHF and sought whether the addition of clinical and sociodemographic risk factors could improve prediction of incident HF.

10.4 Methods

10.4.1 Participant selection

Participants came from two Australian studies of HF prevention**.** The Tasmanian Study of Echocardiographic Detection of Left Ventricular Dysfunction (Tas-ELF, ACTRN:12614000080628) (14) recruited 618 participants between 2013 and 2015 via community engagement and advertising. The Victorian Study of Echocardiographic Detection of Subclinical Left Ventricular Dysfunction (Vic-ELF; ACTRN:12617000116325) recruited 349 participants between 2017 and 2019 via primary care and community advertising. Individuals aged ≥65 years were included if they had ≥1 HF risk factor –hypertension (self-reported diagnosis including treatment or blood pressure ≥140/90mmHg), type 2 diabetes mellitus, obesity (body mass index ≥ 30kg/m^2). Ineligibility was determined if patient interview, symptom questionnaire or clinical examination identified existing HF, known coronary artery disease (CAD) or life expectancy <1 year, or if at least moderate valve disease and LVEF <40% were identified by echocardiography.

Subjects with missing outcome data were excluded leaving 862 for analysis. All subjects provided written informed consent and the study was approved by the relevant Human Research Ethics Committee (Tas-ELF: University of Tasmania, HREC number H001333; Vic-ELF: Bellberry, HREC number 2016-10-727).

10.4.2 Clinical and socioeconomic data

HF risk factors along with other relevant co-morbidities and medications were documented along with heart rate, resting averaged blood pressures, and body mass index (BMI). This was used to calculate the ARIC HF risk score (2-year risk given follow-up duration) using the publicly available online calculator. A six-minute walk test (6MWT) to assess functional capacity was undertaken in accordance with standard procedure (111). Patient–reported functional capacity was assessed using the Duke activity score index (DASI). Depression and anxiety were evaluated with the patient health questionnaire-9 (PHQ-9) and generalized anxiety disorder 7-item scale (GAD-7), respectively. For both questionnaires, a score of >6 indicated moderate or greater depression or anxiety. The EuroQol visual analog scale was used as a metric of subjective health status (0-100%, 100% = best health) (303). In 417 participants' serum N-terminal pro B-type natriuretic peptide (NT-proBNP) was measured. Individual level SES was evaluated by stratified educational attainment (<12 years schooling, ≥12 years

schooling or trade/diploma/certificate, university degree). Area-level (postcode) SES was determined using the socioeconomic indexes for areas (SEIFA) generated by the Australian Bureau of Statistics from 5-yearly census data. The index of relative socioeconomic disadvantage (IRSD) was used (2016) (304), which is based on 16 indicators e.g. average household income, unemployment, educational level and physical disability. Each geographical area is assigned a decile rank with 1=most disadvantaged and 10=least disadvantaged. Given the influence of living remote from urban centers on health care access, the Australian Statistical Geographical Classification – Remoteness area (305), termed herein the 'remoteness classification' was assessed as a geographic influence on incident HF. This is derived using road distance to the nearest urban center.

10.4.3 Echocardiography

Resting 2D and Doppler echocardiography was performed with standard equipment (ACUSON SC2000, Siemens Healthcare USA, Mountain View, CA) and transducer (4V1c, 1.25 to 4.5 MHz; 4Z1c, 1.5 to 3.5 MHz) in accordance with guidelines (117). A speckle tracking algorithm (Syngo VVI, Siemens Medical Solutions, Siemens Healthcare USA, Mountain View, CA) was used for quantification of global longitudinal strain (GLS) and averaged from apical, 2-, 3- and 4-chamber views. Diastolic function was assessed by measuring mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, septal and lateral mitral annular early diastolic velocities (e') and E/e' ratio. Biplane method of disks (Simpson's modified rule) was used for left atrial volume quantification and indexed to body surface area (BSA) (LAVI). LV mass was calculated from 2D images using the linear method and indexed to BSA (LVMI).

10.4.4 Incident heart failure adjudication

Incident HF was diagnosed by a study physician blinded to echocardiography and randomization using Framingham criteria, as previously described (119). HF diagnosed external to the study was adjudicated by 2 physicians, blinded to randomization, using hospital discharge summaries or primary care notes.

10.4.5 Statistical analysis

Continuous variables are presented as median with interquartile ranges (IQR) or mean ± standard deviation, based on distribution testing using the Shapiro-Wilk test. Categorical variables are presented as frequencies and percentages. Differences

between two independent groups were determined using χ^2 and unpaired Student's t-test for categorical and continuous variables, respectively. Bonferonni adjustment was undertaken in the case of multiple pairwise comparisons. Cox proportional hazard regression was used to assess predictors of incident HF and build a predictive model. Variables with a p-value <0.1 in univariable analysis were selected for inclusion in multivariable modelling. This modeling was used to further guide selection of variables with incremental discriminative value (when added to the ARIC HF risk score). Incremental discriminative value was assessed by comparing the area under the receiver operating characteristic curve (AUC) of logistic regression models. For easily acquired clinical variables an improvement in AUC of at least 0.01 was considered meaningful. Model calibration was assessed using the Hosmer-Lemeshow (H-L) test for goodness of fit in deciles of predicted vs. observed risk. Net reclassification improvement (NRI) assessed impact of the new model on risk classification. Risk was dichotomized into high and low by a 6% 2-year risk of incident HF given evidence for cost-effectiveness of echo-guided therapeutic intervention at this level of risk (306). To provide a more granular risk grouping and to assess effects on very high-risk individuals, a 3-group risk classification was assessed with 6% and 12% cut points to define low, intermediate, and high risk. Classification and regression tree analysis (CART) (in this case *classification* given the binary outcome) was used to define the optimal, sequential use of the explanatory variables with cut-points that maximize discrimination between events and non-events at each 'node' in the 'tree'. This was intended to provide insight into relative importance of the variables, that may inform on larger-scale approaches to identification of high-risk individuals. Statistical significance was defined as a two-tailed p-value <0.05. Analyses were conducted using STATA 15.1 (StataCorp, College Station, TX) and CART analysis was conducted in R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) using the party package.

10.5 Results

10.5.1 Participant characteristics

Of the 862 subjects (median age 70 [67-73] years, 47% male), 78 (9%) developed HF over a median of 65 (48-94) weeks follow-up (Table 10-1). The median 2-year ARIC HF risk score was 2.3% (1.4-4.1%). The most prevalent risk factor was hypertension (82%) and almost half had type 2 diabetes mellitus (45%). On average systolic blood pressure was not within target range (140 ± 16 mm Hg). Functional capacity was in the

normal range for this age group by 6MWT and the moderate range by DASI questionnaire, (461m ± 89, 8.3 METS [7.3-8.9], respectively). There was a gradient of SES by both area level and individual level measures. By remoteness classification, 175 (20%) were classified as 1 (metropolitan), 433 (50%) as 2 (inner regional), 247 (29%) as 3 (outer regional), 6 (0.7%) as 4 (remote) and 1 (0.1%) as 5 (very remote).

10.5.2 Predictors of incident HF

In univariable analysis**,** ARIC HF risk score, atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD) and functional capacity by both 6MWT and DASI were significantly predictive of incident HF (Table 10-2). In addition, subjective health status (EuroQol) and ≥ moderate depression were also significantly predictive of incident HF, but anxiety was not. Of the SES measures, increasing SEIFA decile but not increasing educational attainment was associated with reduced risk of incident HF. For each increase in remoteness class, there was a significant increase in risk of incident HF (Table 10-2).

In multivariable modeling that included all significant univariable predictors except the 6MWT (given a more easily acquired DASI assessment of functional status was available), ARIC score, COPD, functional capacity (DASI) and remoteness index were independently predictive of incident HF (Harrell's C-statistic 0.74). SEIFA decile and remoteness classification were correlated (Spearman's rho 0.42, $p<0.001$) and with remoteness classification excluded, SEIFA decile was independently associated with incident HF (HR 0.91 [95% CI 0.84-0.99], $p=0.025$).

Table 10-1: Baseline characteristics and outcome.

	All participants (n=862)
Age, years (IQR)	70 (67-73)
Gender, male	407 (47)
Hypertension (%)	708 (82)
Diabetes Mellitus, type 2 (%)	387 (45)
Obesity (%)	440 (51)
Atrial Fibrillation (%)	43 (5)
Chronic obstructive pulmonary disease (%)	51 (6)
Ever smoker (%)	412 (48)
Dyslipidemia (%)	472 (55)
ACE-I/ARB (%)	623 (72)
Beta blocker (%)	166 (19)
MRA (%)	30 (3.5)
Thiazide diuretic (%)	160 (20)
Calcium channel blocker (%)	220 (25)
Statin (%)	451 (52)
Antiplatelet (%)	257 (30)
Heart rate, bpm (SD)	68 (11)
Systolic BP, mm Hg (SD)	140 (16)
Diastolic BP, mm Hg (SD)	82 (10)
BMI, kg/m^2 (SD)	30 (6)
ARIC HF risk score (2-year) (IQR)	2.3 (1.4-4.1)
6-minute walk test, m (SD)	461 (89)
Duke activity status index, METS (IQR)	8.3 (7.3-8.9)
EuroQol visual analog scale, % (IQR)	80 (70-90)
PHQ-9 ≥ 6 (%)*	57 (8)
GAD7 ≥ 6 (%)†	44 (6)
SEIFA decile (IQR)	5 (2-7)
Remoteness classification (IQR)	2 (2-3)
Education (%)	
< 12 years school	371 (43)
≥ 12 years school or trade, diploma/certificate, without university degree	304 (35)
University/higher degree	187 (22)
NT-proBNP, pg/ml (IQR)‡	59 (30-110)
LV ejection fraction, % (SD)	62 (6)
Global longitudinal strain, % (SD)	18 (3)
e prime (average) (SD)	7.6 (1.7)
E/e' (IQR)	8.3 (7.0-10.2)
LA volume index, ml/m^2 (IQR)	32 (26-39)
LV mass index, g/m^2 (SD)	79 (20)

Follow-up (weeks) (IQR)	65 (48-94)
Incident HF (%)	78 (9)

ACE-I/ARB – angiotensin converting enzyme inhibitor/receptor blocker, MRA – mineralocorticoid antagonist, BP – blood pressure, BMI – body mass index, ARIC – Atherosclerosis Risk in Communities, HF – heart failure, PHQ – patient health questionnaire, GAD - generalized anxiety disorder, SEIFA – socioeconomic indexes for area, NT-proBNP - N-terminal pro b-type natriuretic peptide, LV - left ventricular, LA – left atrial. *available in 712, † available in 697, ‡ available in 491, § n=836.

10.5.3 Improving HF discrimination

The ARIC HF score alone had modest discrimination for predicting incident HF with an AUC of 0.660 (95% CI 0.597-0.724) (Table 10-3). Of the variables that were included in the multivariable Cox model (Table 10-2), depression, subjective health status (EuroQol) and SES by SEIFA decile failed to improve AUC by ≥0.01 (Table 10-3). The model that contained the remaining variables (ARIC score plus AF, COPD, DASI and remoteness classification [Appendix Table 10-6]) improved the AUC to 0.722 (95% CI 0.657-0.786, p=0.03). This model was internally validated using bootstrapping with 500 repetitions resulting in an AUC of 0.725 ± 0.032. Calibration was good across the range of risk (H-L χ^2 8.68, p=0.56) (Appendix Figure 10-4). A Cox regression model with the same components had a Harrell's c-statistic of 0.734.

10.5.4 Reclassification and CART analysis

The NRI for the final model (ARIC HF risk score, AF, COPD, DASI and remoteness classification) with a single cut-point of 6% HF risk showed that overall, 26% cases (p<0.001) were appropriately reclassified (Table 10-4). However, for those with incident HF, 19% were inappropriately reclassified as low risk, while in those without incident HF, 45% were appropriately reclassified as low risk. Dividing risk into low, intermediate, and high, the new model saw an NRI of 46% (p<0.001) (Table 10-5). For events and non-events there was an overall improvement in reclassification. The largest category in both events and non-events by ARIC score alone, was the intermediate group. For incident HF, 15 cases were inappropriately downgraded in risk but 21 were appropriately upgraded (NRI = 8%). In the non-HF group 354 were appropriately downgraded in risk category and 47 inappropriately upgraded in risk category (NRI 39%). To validate the improvement in risk designation against other risk markers we assessed NT-proBNP across risk groups before and after reclassification. Consistent with the improvement in risk classification with the additional variables,

NT-proBNP level exhibited a clearer dose-response relationship across risk groups (Figure 10-1).

Table 10-2: Cox regression modelling for incident heart failure evaluating the ARIC heart failure risk score and additional clinical and non-traditional risk factors.

	Univariable		**Multivariable**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
ARIC HF risk score (2-yr), %	1.12 (1.06-1.17)	<0.001	1.08 (1.01-1.14)	0.009
Atrial fibrillation	2.36 (1.23-4.6)	0.01	1.34 (0.65-2.78)	0.43
COPD	3.29 (1.8-5.99)	<0.001	2.57 (1.33-4.96)	0.005
6-minute walk test, m	0.996 (0.993-0.998)	0.002		
Duke activity status index, METS	0.71 (0.62-0.82)	<0.001	0.80 (0.68-0.95)	0.009
EuroQol visual analog scale	0.98 (0.97-0.997)	0.017	1 (0.98-1.01)	0.73
Depression (≥moderate)	3.10 (1.54-6.25)	0.002	2.19 (0.98-4.88)	0.06
Anxiety (≥moderate)	1.38 (0.50-3.82)	0.532		
SEIFA decile, per 1 decile increase	0.89 (0.83-0.97)	0.009	0.99 (0.90-1.09)	0.86
Education stratum, per 1 stratum increase	0.82 (0.61-1.11)	0.2		
Remoteness classification				
1	reference			
2	5.15 (1.84-14.41)	0.002	5.68 (2.02-15.89)	0.001
3	10.48 (3.68-29.88)	<0.001	9.43 (3.19-27.84)	<0.001
4	48.6 (5.38-439)	0.001	26.42 (2.69-259)	0.005

ARIC – atherosclerosis risk in communities, HR – hazard ratio, HF – heart failure, COPD – chronic obstructive pulmonary disease, SEIFA – socioeconomic indexes for areas.

Table 10-3: Comparison of discriminative ability of logistic regression models, incorporating additional clinical, functional, and socioeconomic/geographical predictors, for prediction of incident HF.

Variables in model	**AUC (95% CI)**	**Incremental AUC**	**p-value**
ARIC score	0.660 (0.597-0.724)		
ARIC, atrial fibrillation	0.672 (0.607-0.737)	0.012	0.27
ARIC, COPD	0.680 (0.616-0.743)	0.02	0.22
ARIC, Duke activity status index	0.673 (0.60-0.724)	0.013	0.6
ARIC, atrial fibrillation, COPD	0.692 (0.626-0.756)	0.032	0.08
ARIC, atrial fibrillation, COPD, Duke activity status index	0.700 (0.628-0.764)	0.04	0.17
ARIC, depression*	0.658 (0.594-0.723)	-0.002	0.81
ARIC, EuroQol	0.662 (0.595-0.728)	0.002	0.87
ARIC, remoteness classification	0.690 (0.63-0.750)	0.03	0.2
ARIC, SEIFA decile	0.664 (0.602-0.726)	0.004	0.86
ARIC, remoteness classification, SEIFA decile	0.691 (0.631-0.750)	0.031	0.2
ARIC, atrial fibrillation, COPD, Duke activity status index, remoteness classification	0.722 (0.657-0.786)	0.062	0.03

*missing data imputed. ARIC – Atherosclerosis Risk in Communities, COPD – chronic obstructive pulmonary disease, SEIFA – socioeconomic indexes for areas.

Table 10-4: Net reclassification improvement of 2-year heart failure risk with the addition of variables to the ARIC HF risk score. Risk dichotomized as low and high by 6% cut-off.

				+ AF, COPD, Duke activity status index, remoteness classification		
			Risk	<6%	≥6%	Total
ARIC risk score		HF	<6%	2		2
			≥6%	15	61	76
			Total	17	61	78
		Non-HF	<6%	26	8	34
			≥6%	362	388	750
			Total	388	396	784
NRI		26% (p<0.001)				

Table 10-5: Net reclassification improvement of 2-year heart failure risk with the addition of variables to the ARIC HF risk score. Risk classified as low, intermediate, or high by 6% and 12% cut-offs.

				+ AF, COPD, Duke activity status index, remoteness classification			
			Risk	<6%	6-12%	>12%	Total
ARIC risk score		HF	6%	2			2
			6-12%	14	20	23	57
			>12%	1	1	17	19
			Total	17	21	40	78
		Non-HF	<6%	26	8		34
			6-12%	348	234	85	667
			>12%	14	24	45	83
			Total	388	266	130	784
NRI		46% (p<0.001)					

To delineate an optimal sequence for use of the model variables, and their respective cut points for HF prediction, a classification tree was constructed that revealed 5 discriminatory nodes (Figure 10-2). The remoteness classification was the first node, which immediately identified those living the least remotely (i.e. metropolitan) as being low risk (2.3%), without further classification. A higher remoteness classification but sequential evaluation of ARIC HF risk score as ≤3.6%, no COPD and no AF also determined low risk (5.9%). ARIC HF risk score >3.6% but

with higher functional capacity (DASI >6.8 METS) determined a relatively intermediate risk (13%). All other sequential combinations resulted in 29-33% risk. Being in a high to intermediate-risk CART group ('CART +') had a sensitivity of 60% (95% CI 49-71%), specificity of 77% (95% CI 74-80%), negative predictive value (NPV) of 95% (95% CI 94-96%) and positive predictive value (PPV) of 21% (95% CI 17-25%). The addition of CART status (positive/negative) to ARIC HF risk score showed an NRI of 37% (p<0.001) for a single risk cut-off of 6% (2 risk groups) and an NRI of 59% (p<0.001) for cut-offs of 6% and 12% (3 risk groups) (Appendix Table 10-7 and Table 10-8). CART-positive status was associated with significantly higher NT-proBNP, LV mass (indexed to BSA), E/e' and lower GLS (Figure 10-3).

Figure 10-1: Comparison of N-terminal pro B-type natriuretic peptide (NT-proBNP) by risk classification with the ARIC heart failure risk score (a) and with the addition of AF, COPD, functional capacity, and remoteness classification (b).

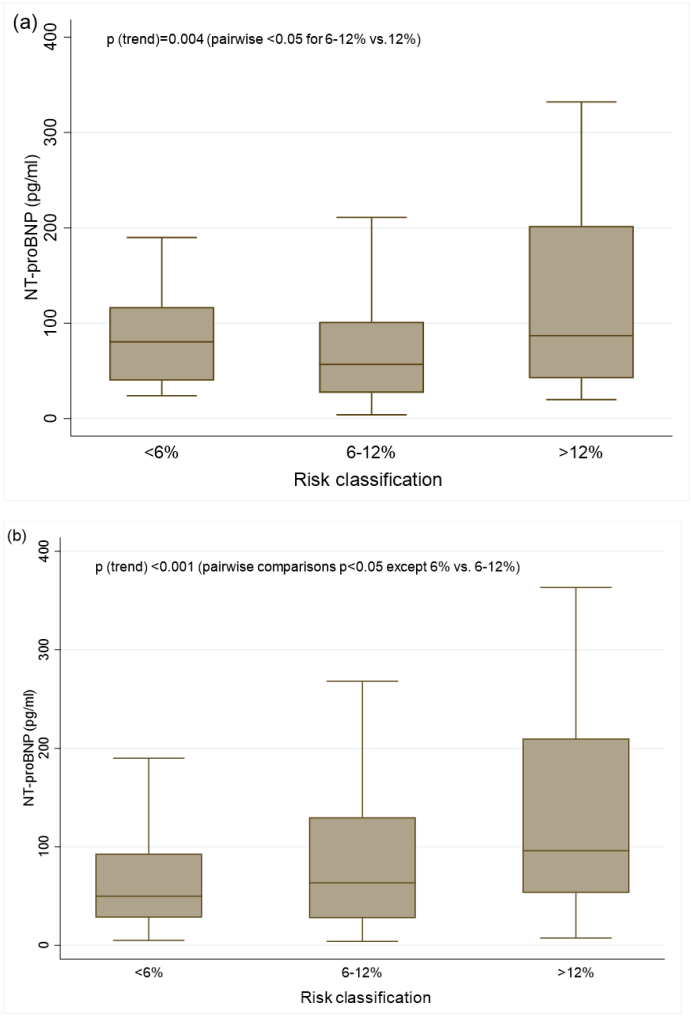


Figure 10-2: Classification and regression tree (CART) analysis. 'CART +' denotes intermediate to high heart failure risk. 'CART-' denotes low heart failure risk.

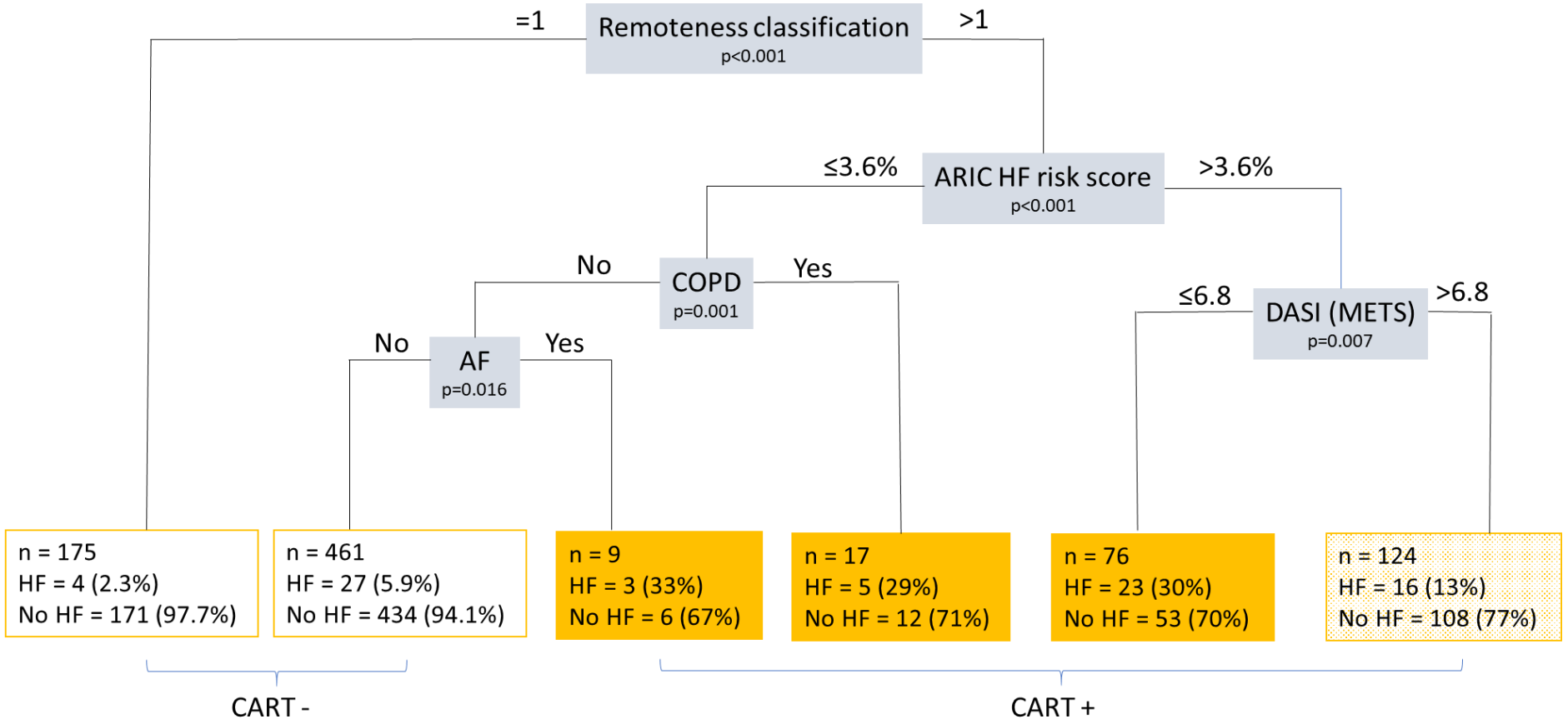
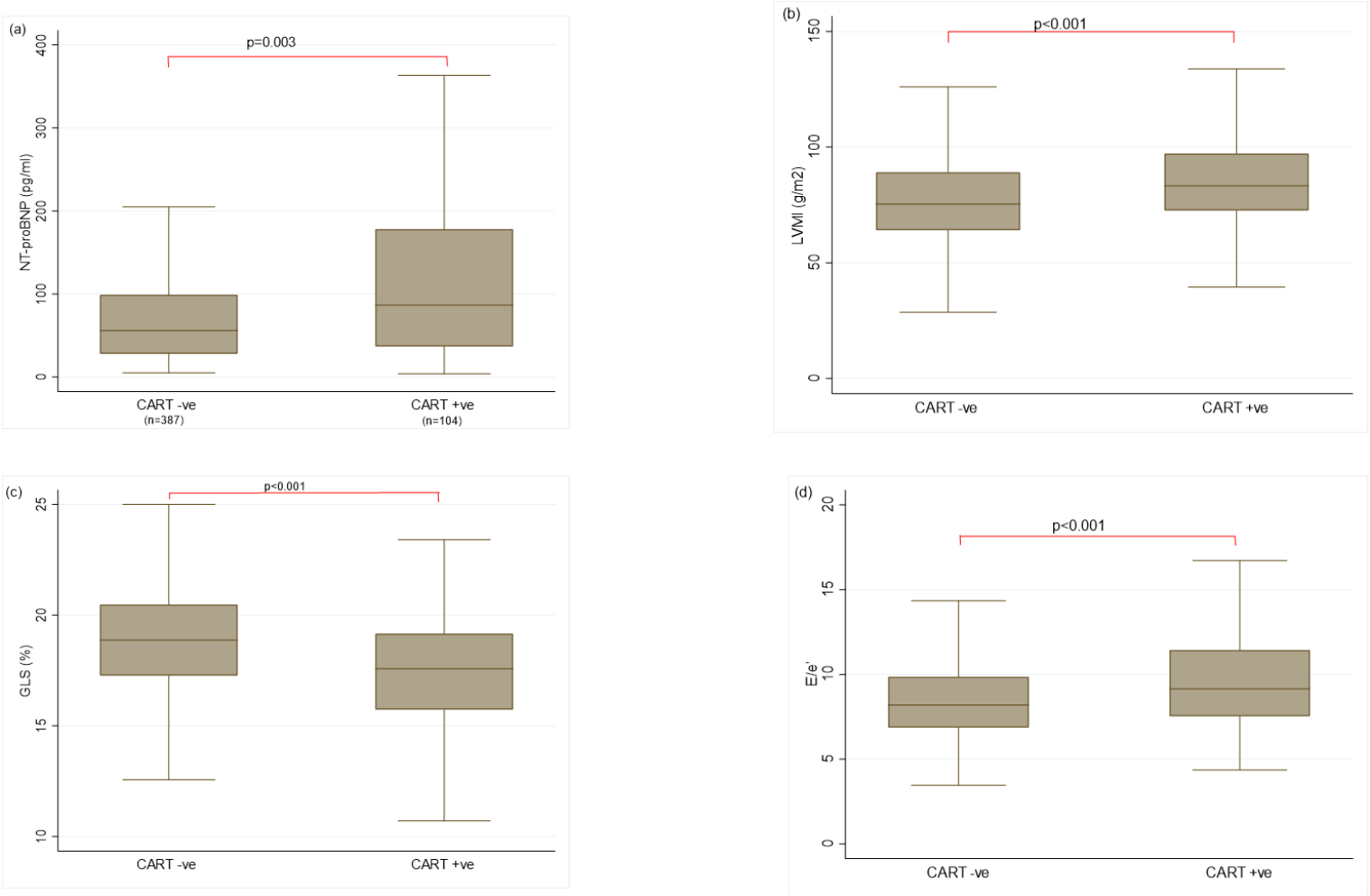


Figure 10-3: Biomarker and echocardiographic measures by CART analysis. NT-proBNP- N-terminal pro B-type natriuretic peptide, LVMI – left ventricular mass index, GLS – global longitudinal strain, E/e' - mitral inflow/mitral annular early diastolic velocity.



10.6 Discussion

We demonstrate that HF risk prediction using a validated risk score is only modestly discriminative, in an elderly Australian population with SAHF, and can be significantly improved with the addition of readily available clinical and sociodemographic variables. The addition of AF, COPD, questionnaire-based functional capacity (DASI) and geographical remoteness, significantly improved discrimination and risk classification for incident HF over the ARIC HF risk score alone. Classification of 2-year risk improved by 23-46%, depending on risk categories. Finally, we offer an algorithm (CART) that could be implemented on a large-scale or population level for the purposes of clinical trial recruitment or to target community prevention. This demonstrated that geographical remoteness was a major influence on incident HF risk, putting it as the primary branching point in risk assessment, and highlighting the need for improvements in healthcare access outside of metropolitan areas. Those with SAHF living outside of metropolitan areas, who are low risk by ARIC score are only truly low risk in the absence of COPD and AF. Alternatively, those at high risk by ARIC score can be further stratified as high or intermediate risk by functional capacity, although we combined the intermediate group with high risk given 2-year risk was 13%. The CART algorithm demonstrated high negative predictive value (95%) and thus a useful tool for confidently assigning low HF risk.

10.6.1 HF prediction scores

In total, 29 HF risk models have been presented with a range of components from clinical data to biomarkers and cardiac imaging (39,40). Six models have been externally validated, although only the Health ABC score has been validated outside it's country of derivation (307). This demonstrated acceptable discrimination (AUC 0.706 [95% CI 0.672-0.739]) and was similar to the internal validation reported (AUC 0.72) (308). While the ARIC HF risk score reported better discrimination in external validation (AUC 0.797), the validation population was part of the ARIC cohort study (41). We found that discrimination of the ARIC HF risk score was significantly lower in our cohort and overall ARIC underestimated true risk. Apart from geography there are potentially important differences between the ARIC derivation cohort and our cohort that could account for this. Firstly, our subjects were significantly older (age range 45-64 in the ARIC cohort) so there is some uncertainty around the extrapolation to older ages. Secondly, the ARIC cohort was a general population rather than those

already at increased HF risk/SAHF, and as calibration of the ARIC score has not been reported, its performance at the higher end of the risk range is unknown. It may be more appropriate to derive a risk score from clinical populations in whom it is intended to be used.

Our study highlighted the importance of risk factors additional to those incorporated in the ARIC score. Atrial fibrillation has a well-recognized association with HF, each being a risk factor for the other. In a large cohort of patients, AF was associated with a two-fold increase in incident HF, independent of age, hypertension, diabetes, CAD and valvular disease (309). Similarly, in around 9000 patients with impaired fasting glucose, COPD was found to have an adjusted HR of 2.46 (95% CI 1.46-4.13) for incident HF hospitalization (310). AF was not evaluated as a candidate variable for the ARIC score, while COPD was found to have an incremental AUC of just 0.008 and was excluded. We found COPD to be a strong, independent predictor of HF and it incremented AUC by 0.02. Although this was not statistically significant this is reasonable improvement for a single predictor that is part of routine medical assessment. To our knowledge, no HF risk models have previously included a measure of functional capacity. We have previously shown that reduced functional capacity in the setting of LV dysfunction confers over a 3-fold increase in risk of incident HF (adjusted for ARIC score, AF, COPD and cardioprotective therapies) and that reduced functional capacity and echocardiographic LVD appear to be risk equivalents (302). In this analysis we used a validated short questionnaire (DASI) rather than a 6MWT as DASI had a large effect size in univariable analysis and has wider patient applicability given the potential for musculoskeletal pathology to influence walk speed. Of note, both COPD and symptom status are part of the HF mortality calculator from the MAGGIC meta-analysis (311), so their importance earlier in the HF continuum is not unexpected.

SES is a recognized risk factor for incident HF by both individual measures e.g. education, as well as area-level measures (301). Interestingly, we did not find an association with educational level, only with area-level SES. SEIFA is similar to other area-level indices including the index of multiple deprivation, that has demonstrated a HR for incident HF of 1.61 (95% CI 1.56–1.65), in a population free of established CVD and adjusted for HF risk factors as per the ARIC score i.e. a similar clinical population to ours (301). However, data has been lacking regarding geographical remoteness and incident HF. Remoteness predicted HF independently of SEIFA decile and conferred superior discriminative ability. As a pure measure of SES (with which it

was associated) geography is too crude, and the main driver of the association may be access to healthcare, especially preventive healthcare. In Australia, the frequency of not attending primary care due to distance needed to travel is 2.5 times higher for regional areas compared with metropolitan areas (312). Furthermore, 26% of people in regional areas report distance to a specialist as a barrier to seeing one, compared with just 6% of metropolitan patients.

10.6.2 Directing preventive strategies with HF risk prediction

The designation of risk categories is somewhat arbitrary as rationale for specific treatment at certain HF risk thresholds is not established. Our thresholds are higher compared to other analyses e.g. the Health ABC HF risk score, which described 4 risk groups with extremes being <5% and >20% 5-year risk (313). However, our population were at higher average risk and we aimed to identify high-risk within the SAHF population. The optimal risk threshold for triggering certain management pathways is yet to be determined.

While a clinical risk score coupled with a preventive intervention has not been tested as a HF preventive strategy, there is evidence that intensification of therapy directed by other risk markers e.g. BNP, improves outcomes (61). Indeed, measurement of natriuretic peptide and specialist cardiovascular care is a class IIa recommendation in patients at risk of developing HF (60). If taking the definition of 'risk of developing HF' as at least 1 HF risk factor (as in the STOP-HF trial that informed the guideline), then this is a heterogeneous group in terms of risk. Whether a natriuretic peptide-directed compared to a foreseeably cheaper clinical risk score-directed strategy would provide equal if not better outcomes is unknown. Adding NT-proBNP to the Health ABC HF risk score (comprising age, CAD, smoking, SBP, heart rate, glucose, creatinine, albumin and LV hypertrophy) incremented AUC for incident HF discrimination by 0.027 ($p<0.01$) and had a NRI of 10% (42). This is inferior to the improvements we demonstrated with clinical and sociodemographic variables, potentially supporting a case for head-to-head comparison.

10.6.3 Clinical implications

The decision tree identified remoteness as the first step in refining risk classification and this has clinical implications. First, recruitment into trials of HF prevention should include at least inner regional areas. Second, risk factor control is

already proven to reduce HF risk, and access to high-quality risk factor control should be a health policy priority outside of metropolitan areas.

10.6.4 Limitations

Compared with other studies that have constructed a risk model or score, our sample size is relatively small. However, the age and risk factor profile are appropriate for the population in which a HF risk score is intended to be used. For example, inclusion of younger subjects with no cardiovascular risk factors, as may have be included in some of the large cohort studies discussed, will contribute little to evaluation of risk discrimination within our population of interest. Finally, the clinical application of our model requires external validation. The role of such a score in directing therapies would require evidence before it could have clinical application and impact.

10.7 Conclusions

The ARIC HF risk score has modest performance in an elderly Australian population with SAHF. However, the addition of 4 clinical and sociodemographic variables significantly improves discrimination and risk classification. If externally validated, this new model could be adopted as a risk scoring method for directing intensive preventive therapies. Our CART analysis showed living remotely to be a major driver of HF risk, which highlights the association between access to healthcare and outcomes and is something potentially modifiable in the effort to stem the HF epidemic.

10.8 Postscript

This chapter highlights the importance of externally validating models in a range of settings and especially in populations in which the model may be clinically implemented. While the ARIC HF model was improved upon, the new model now requires validation. This is planned by using the ASPREE trial data. The ASPREE trial evaluated aspirin in 19,114 community-dwelling, healthy elderly (≥70 years) in Australia and the United States. The primary outcome was disability-free survival but a range of secondary outcomes including incident HF hospitalisation were recorded. Of those included, 14,213 had hypertension and 2057 had diabetes. Although AF was an exclusion criterion, the remainder of the variables used in the model are available. An important strength of using this cohort, apart from the size, will be that model performance will be assessed in two countries.

10.9 Appendix

Figure 10-4: Calibration of the HF prediction model (logistic) incorporating ARIC score plus AF, COPD, DASI and remoteness classification. Circles represent risk deciles.

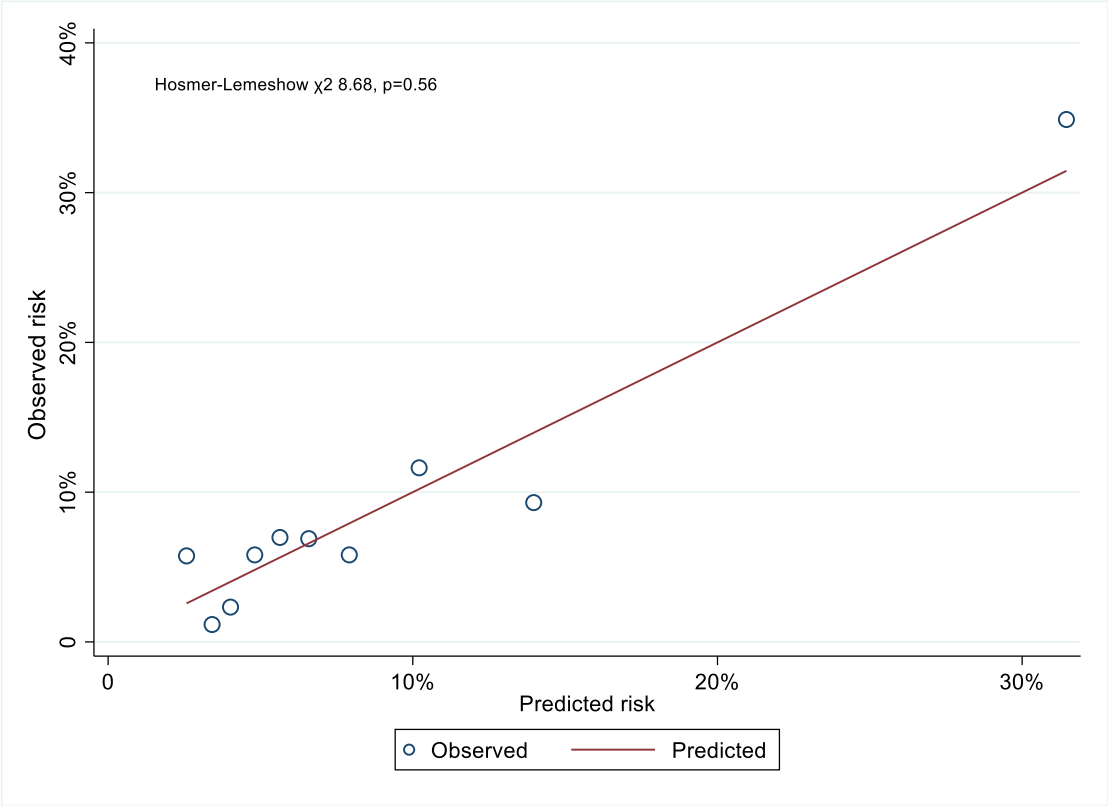


Table 10-6: Final logistic regression model resulting in optimal discrimination of incident HF compared to ARIC HF risk score alone.

	Multivariable	
	OR (95% CI)	**p-value**
ARIC HF risk score (2-yr), %	1.09 (1.02-1.17)	0.008
Atrial fibrillation	2.71 (1.18-6.18)	0.018
Chronic obstructive pulmonary disease	3.17 (1.51-6.69)	0.002
Duke activity status index, METS	0.76 (0.64-0.89)	0.001
Remoteness index, per 1 category of increased remoteness	1.81 (1.28-2.54)	0.014

Table 10-7: Net reclassification improvement of 2-year heart failure risk with the addition of CART analysis to the ARIC HF risk score. Risk dichotomized as low and high by 6% cut-off.

				+ CART		
			Risk	<6%	≥6%	Total
ARIC risk score		HF	<6%	2		2
			≥6%	27	49	76
			Total	29	49	78
		Non-HF	<6%	33	1	34
			≥6%	560	190	750
			Total	593	191	784
NRI		37% (p<0.001)				

Table 10-8: Net reclassification improvement of 2-year heart failure risk with the addition of CART analysis to the ARIC HF risk score. Risk classified as low, intermediate, or high by 6% and 12% cut-offs.

				+ CART			
			Risk	<6%	6-12%	>12%	Total
ARIC risk score		HF	6%	2			2
			6-12%	27		30	57
			>12%		2	17	19
			Total	29	2	47	78
		Non-HF	<6%	33		1	34
			6-12%	547		120	667
			>12%	13	12	58	83
			Total	593	12	179	784
NRI		59% (p<0.001)					

PART 5: Discussion and conclusions

11 Discussion and conclusions

This thesis hypothesised that appropriate screening for, and detection of, early subclinical LV dysfunction with subsequent spironolactone therapy would reduce progression to symptomatic HF. Ultimately this was unproven but valuable lessons were learned. There were 3 key factors in this proposition: appropriate selection for screening, early detection of LVD, and therapy. Selection and therapy were where this process unexpectedly fell down. Selection for screening in those with non-ischemic HF risk factors was determined by risk enrichment – age ≥ 65 years old and fulfilling ARIC HF risk score and 6MWT criteria (13). This proved insufficient as HF incidence was only 3.6% over the observed period, which the trial was not powered for. Secondly the therapy was found to be inappropriate, especially in those taking ACE-I or ARBs.

Due to these problems, the role of GLS in clinical-decision making has not been significantly advanced. However, it was established that GLS does not decline with normal aging between the ages of 65 and 88 years – supporting a single cut-off. Furthermore, the clinical utility of LA strain was advanced by demonstrating abnormal LA strain to be an independent predictor of incident HF. Furthermore, its use in place LA volume improved diagnostic clarity by reducing the proportion of cases with indeterminate diastolic function, without impacting the prognosis associated with the stages of diastolic dysfunction. Whether modifications to the diastolic function guidelines will be made as a result of these, and other findings, remains to be seen. Indeed, the current guidelines are 4 years old and the role of LA strain was then not backed by significant evidence in a broad range of scenarios and there were concerns regarding technical challenges (32).

11.1 Future directions in selection for screening

One of the aims of the thesis was to refine selection for echocardiographic screening. The importance of this was highlighted by the heterogeneity in HF risk seen in the Vic-ELF and Tas-ELF trials. In chapter 10 the ARIC HF risk score was found to be only modestly discriminative, and I proposed this was due to the derivation population being different from the population of interest for screening i.e. SAHF, and uncertainty around calibration. Several variables were found to improve upon the ARIC score – AF, COPD, functional capacity (DASI) and geographical remoteness. Somewhat contrary to the findings of the meta-analysis on SES, individual level SES (education) was not found to be predictive, and although an area-

level measure (SEIFA score) was, this was not independent of other factors including geographical remoteness. This suggests that access to healthcare is an important driver of risk and this was highlighted by the CART analysis. To draw more certain conclusions about the validity of the HF risk prediction models and CART algorithms, validation will be undertaken in a large Australian and United States population.

There are of course risk factors that were not assessed, such as anaemia and CKD, which have been associated with progression from asymptomatic diastolic dysfunction to HFpEF (8,262). However, identification of these biomarkers of risk potentially adds to the complexity and cost of scoring systems that already contain several variables. This thesis therefore additionally investigated a pre-screening test in the form of a signal-processed ECG and found it to be superior to the ARIC score. Furthermore, the addition of the ARIC score to the machine-learning algorithm did not improve discrimination. Interestingly ewECG performed better than NT-proBNP in discriminating LVD. Natriuretic peptide levels in patients at risk of HF are already advocated in guidelines (class IIa, level of evidence B) to direct specialist care and intensification of GDMT (60).

Approaches to selection that detect subclinical disease, like ewECG, applied in a simply defined population (e.g. >65 years with SAHF) could overcome problems of derivation, validation and wide applicability, inherent in risk scores. However, the abnormalities detected by this technology may also be population specific and based on the ewECG study sample size in alone, further work is needed.

11.2 Future directions in therapy for subclinical LVD

Spironolactone was not well tolerated primarily due to compromised renal function that outweighed potential benefit, as well as less serious problems, including urinary frequency that were felt by participants to outweigh potential benefits. Future trials of pharmacological intervention should bear in mind that 1) the risk benefit ratio of treatment in these patients (e.g. as opposed to those with established heart failure) is skewed more heavily towards need for benefit and 2) the potential for side-effects in the elderly with comorbidities is not insignificant. Sample size calculations may therefore need to account for this.

HFpEF is the most frequent HF phenotype among patients considered suitable for screening by the criteria in this thesis - in chapter 3 this proportion was 95%.

Therapeutic options in pre-HFpEF may take the lead from established HFpEF. While most clinical trials have been neutral, the focus on HFpEF phenotyping may lead to more personalised and therefore effective therapies. A similar process may translate to pre-clinical disease. Apart from spironolactone, which has shown some promise in HFpEF (314), exercise training also improves functional capacity and quality of life (315). Indeed, non-pharmacological interventions such as exercise training and weight-loss are likely of benefit in SBHF (316) but maintaining a level of physical activity and a healthy weight are already recommended in SAHF. Applying them in SBHF does not represent a specialised or additive intervention – it should already be happening in the community, much like adequate anti-hypertensive therapy. However, the finding of subclinical LVD may provide the personal motivation and funding for more specialised programs. Ultimately, I envisage the best intervention to be a personalised approach that involves selection from a suite of therapies: initiation/up-titration of ACE-I/ARBs, betablockers or mineralocorticoid antagonism (in those not taking an ACE-I/ARB), exercise training and weight loss. It may be clear in some instances how to match patient with therapy, but cases of uncertainty will have to rely on an evidence base drawn from trials of individual interventions, and this comes back to appropriate patient selection.

11.3 Limitations

Some general limitations that may apply to more than one project on the thesis include:

- The method of recruitment into the Vic-ELF trial involved patients in primary care. While it would be reasonable to think that most individuals have a primary care physician, those who are more engaged are a) more likely to be in good health and b) would have been more likely to respond to an invitation to enrol. This selection bias may have affected our results, particularly in the incidence of HF and in the prevalence of cognitive impairment.
- Sample size was a limitation for several studies including the cognition study and importantly, the machine-learning of the ewECG. The latter is notable given the high dimensionality of the data. However, the feature selection process minimized this problem.
- The definition of heart failure using Framingham criteria has problems inherent in any test that relate to sensitivity and specificity. For HFrEF sensitivity is excellent although specificity moderate (317,318). For HFpEF one report, with a small sample size, found

that sensitivity was lower (89% versus 97%) but I suspect that this may be an over estimation given the complexities of diagnosing HFpEF.

- Follow-up duration was relatively short (2 years), and this influences event rate and therefore certainty of findings.

11.4 Conclusions

- HF risk is heterogeneous and current clinical risk scores are imperfect but are improved with additional clinical, functional, and sociodemographic variables.
- Reduced functional capacity improves risk prediction and may be used to identify an early symptomatic state in the presence of LVD.
- An alternative to clinical risk scores for selection for screening may be a pre-screening step involving signal processing of a standard surface ECG.
- Normal aging does not influence GLS therefore a single cut-off (≤16%) is justified.
- Left atrial strain independently predicts incident HF and may be used in diastolic evaluation in place of LA volume index to reduce intermediate cases.
- Echocardiographic screening for early subclinical LVD, defined by reduced GLS and diastolic abnormalities does not reduce incident HF as spironolactone, the therapeutic intervention trialled, is poorly tolerated. This is primarily due to a decline in renal function that is associated with existing treatment with ACE-Is and ARBs.

References

1. Sahle BW, Owen AJ, Mutowo MP, Krum H, Reid CM. Prevalence of heart failure in Australia: a systematic review. BMC Cardiovas Disord 2016;16:32.
2. Dunstan DW, Zimmet PZ, Welborn TA et al. The Rising Prevalence of Diabetes and Impaired Glucose Tolerance. Diabetes Care 2002;25:829.
3. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: The Cardiovascular Health Study. J Am Coll Cardiol 2001;37:1042-1048.
4. Bluemke DA, Kronmal RA, Lima JAC et al. The Relationship of Left Ventricular Mass and Geometry to Incident Cardiovascular Events: The MESA (Multi-Ethnic Study of Atherosclerosis) Study. J Am Coll Cardiol 2008;52:2148-2155.
5. Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. JAMA 2011;306:856-863.
6. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural History of Asymptomatic Left Ventricular Systolic Dysfunction in the Community. Circulation 2003;108:977.
7. Echouffo-Tcheugui J, Erqou S, Butler J, Yancy C, Fonarow G. Assessing the Risk of Progression From Asymptomatic Left Ventricular Dysfunction to Overt Heart Failure. J Am Coll Cardiol Heart Fail 2016;4:237-248.
8. Lam CS, Lyass A, Kraigher-Krainer E et al. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. Circulation 2011;124:24-30.
9. The SOLVD Investigators. Effect of Enalapril on Mortality and the Development of Heart Failure in Asymptomatic Patients with Reduced Left Ventricular Ejection Fractions. N Engl J Med 1992;327:685-691.
10. Douglas PS, Garcia MJ, Haines DE 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;57:1126-1166.
11. Shah A, Claggett B, Loehr L, Chang P, Matsushita K, Kitzman D. Heart Failure Stages Among Older Adults in the Community. Circulation 2017;135:224-240.
12. Shah A, Claggett B, Sweitzer N, Shah S, Anand I, Liu L. Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. Circulation 2015;132:402-14.
13. Yang H, Wang Y, Nolan M, Negishi K, Okin P, Marwick T. Community Screening for Nonischemic Cardiomyopathy in Asymptomatic Subjects > 65Years With Stage B Heart Failure. Am J Cardiol 2016;117:1959-1965.
14. Yang H, Negishi K, Wang Y, Nolan M, Marwick T. Imaging-Guided Cardioprotective Treatment in a Community Elderly Population of Stage B Heart Failure. J Am Coll Cardiol Imag 2017;10:217-226.
15. Redfield MM, Jacobsen SJ, Burnett JJC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of Systolic and Diastolic Ventricular Dysfunction in the Community Appreciating the Scope of the Heart Failure Epidemic. JAMA 2003;289:194-202.
16. Welfare AIoHa. Cardiovascular disease: Australian facts Canberra: Australian Institute of Health and Welfare 2011. Report No:CVD5310 2016.

17. Chan Y-K, Tuttle C, Ball J et al. Current and projected burden of heart failure in the Australian adult population: a substantive but still ill-defined major health issue. BMC Health Serv Res 2016;16:501.
18. 2014 AIoHaW. Trends in coronary heart disease mortality: age groups and populations. Cardiovascular disease series no. 38. Cat. no CVD 67. . Canberra: AIHW.
19. Ford E, Roger V, Dunlay S, Go A, Rosamond W. Challenges of Ascertaining National Trends in the Incidence of Coronary Heart Disease in the United States. JAHA 2014;3:e001097.
20. 2017-18 ABoSNHSFr. Report number 4364.0.55.001. Feb 2019.
21. Lawson C, Zaccardi F, Squire I et al. 20-year trends in cause-specific heart failure outcomes by sex, socioeconomic status, and place of diagnosis: a population-based study. Lancet Pub Health 2019;4:e406-e420.
22. Levy D, Kenchaiah S, Larson MG et al. Long-Term Trends in the Incidence of and Survival with Heart Failure. N Engl J Med 2002;347:1397-1402.
23. Roger V, Weston S, Redfield M. Trends in heart failure incidence and survival in a community-based population. JAMA 2004;292:344-350.
24. Barker W, Mullooly J, Getchell W. Changing Incidence and Survival for Heart Failure in a Well-Defined Older Population, 1970–1974 and 1990–1994. Circulation 2006;113:799-805.
25. Conrad N, Judge A, Tran J et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. The Lancet 2018;391:572-580.
26. Heidenreich PA, Albert NM, Allen LA et al. Forecasting the Impact of Heart Failure in the United States. Circ Heart Fail 2013;6:606-619.
27. Hawkins NM, Jhund PS, McMurray JJV, Capewell S. Heart failure and socioeconomic status: accumulating evidence of inequality. Eur J Heart Fail 2012;14:138-146.
28. Hunt SA, Abraham WT, Chin MH et al. 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. Circulation 2009;119:e391-e479.
29. Ammar KA, Jacobsen SJ, Mahoney DW et al. Prevalence and Prognostic Significance of Heart Failure Stages. Circulation 2007;115:1563-1570.
30. From A, Scott C, Chen H. The Development of Heart Failure in Patients With Diabetes Mellitus and Pre-Clinical Diastolic Dysfunction. J Am Coll Cardiol 2010;55:300-305.
31. Wan S-H, Vogel MW, Chen HH. Pre-Clinical Diastolic Dysfunction. J Am Coll Cardiol 2014;63:407-416.
32. Nagueh SF, Smiseth OA, Appleton CP 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 Echocardiog 2016;29:277-314.
33. Takemoto Y, Barnes ME, Seward JB et al. Usefulness of Left Atrial Volume in Predicting First Congestive Heart Failure in Patients ≥65 Years of Age With Well-Preserved Left Ventricular Systolic Function. Am J Cardiol 2005;96:832-836.
34. Wang Y, Yang H, Huynh Q, Nolan M, Negishi K, Marwick TH. Diagnosis of Nonischemic Stage B Heart Failure in Type 2 Diabetes Mellitus: Optimal Parameters for Prediction of Heart Failure. J Am Coll Cardiol Cardiovasc Img 2018;11:1390-1400.
35. Farsalinos K, Daraban A, Ünlü S, Thomas J, Badano L, Voigt J-U. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors. J Am Soc Echocardiog 2015;28:1171-81.e2.
36. Yang H, Marwick T, Fukuda N, Oe H, Saito M, Thomas J. Improvement in Strain Concordance between Two Major Vendors after the Strain Standardization Initiative. J Am Soc Echocardiog 2015;28:642-8

37. Potter EL, Marwick TH. Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction. J Am Coll Cardiol Img 2018;11:260-274.
38. Pandhi J, Gottdiener JS, Bartz TM, Kop WJ, Mehra MR. Comparison of characteristics and outcomes of asymptomatic versus symptomatic left ventricular dysfunction in subjects 65 years old or older (from the Cardiovascular Health Study). Am J Cardiol 2011;107:1667-1674.
39. Echouffo-Tcheugui Justin B, Greene Stephen J, Papadimitriou L et al. Population Risk Prediction Models for Incident Heart Failure. Circ Heart Fail 2015;8:438-447.
40. Khan SS, Ning H, Shah SJ et al. 10-Year Risk Equations for Incident Heart Failure in the General Population. J Am Coll Cardiol 2019;73:2388.
41. Agarwal SK, Chambless LE, Ballantyne CM et al. Prediction of Incident Heart Failure in General Practice. Circ Heart Fail 2012;5:422-429.
42. Kalogeropoulos A, Georgiopoulou V, deFilippi C, Gottdiener J, Butler J. Echocardiography, Natriuretic Peptides, and Risk for Incident Heart Failure in Older Adults. J Am Coll Cardiol Imag 2012;5:131-140.
43. Yancy C, Jessup M, Bozkurt B, Butler J, Casey D, Drazner M. 2013 ACCF/AHA Guideline for the Management of Heart Failure. Circulation 2013;128:e240.
44. Pfeffer MA, Braunwald E, Moyé LA et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669-77.
45. Køber L, Torp-Pedersen C, Carlsen JE et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333:1670-6.
46. Vantrimpont P, Rouleau JL, Wun CC et al. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. SAVE Investigators. J Am Coll Cardiol 1997;29:229-36.
47. Exner DV, Dries DL, Waclawiw MA, Shelton B, Domanski MJ. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post hoc analysis of the Studies of Left Ventricular Dysfunction. J Am Coll Cardiol 1999;33:916-23.
48. Moser M, Hebert PR. Prevention of disease progression, left ventricular hypertrophy and congestive heart failure in hypertension treatment trials. J Am Coll Cardiol 1996;27:1214.
49. Soliman Elsayed Z, Ambrosius Walter T, Cushman William C et al. Effect of Intensive Blood Pressure Lowering on Left Ventricular Hypertrophy in Patients With Hypertension. Circulation 2017;136:440-450.
50. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015;373:2103-2116.
51. Staessen JA, Wang J-G, Thijs L. Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003. J Hypertens 2003;21.
52. Sciarretta S, Palano F, Tocci G, Baldini R, Volpe M. Antihypertensive Treatment and Development of Heart Failure in Hypertension. Arch Intern Med 2011;171.
53. Garbi M, Edvardsen T, Bax J et al. EACVI appropriateness criteria for the use of cardiovascular imaging in heart failure derived from European National Imaging Societies voting. Eur Heart J Cardiovasc Img 2016;17:711-721.
54. Wilson J, Junger G. Principles and Practice of Screening for Disease. Geneva World Health Organisation Public Health papers No 34 1968.
55. Hobbs R, Roalfe A, Hare R, Davis R. Midlands Research Practices Consortium. Prognosis of all-cause heart failure and borderline left ventricular systolic

dysfunction: 5 year mortality follow-up of the Echocardiographic Heart of England Screening Study (ECHOES). Eur H J 2007;28:1128-1134.
56. McMurray JJV, Packer M, Desai AS et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med 2014;371:993-1004.
57. Heidenreich PA, Gubens MA, Fonarow GC, Konstam MA, Stevenson LW, Shekelle PG. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. J Am Coll Cardiol 2004;43:1019-1026.
58. Vasan RS, Benjamin EJ, Larson MG et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. Jama 2002;288:1252-9.
59. Heidenreich PA. Should We Start Community Screening for Left Ventricular Dysfunction? J Cardiac Fail 2016;22:24-5.
60. Yancy C, Jessup M, Bozkurt B, Butler J, Casey D, Colvin M. 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. J Am Coll Cardiol 2017;70:776-803.
61. Ledwidge M, Gallagher J, Conlon C et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA 2013;310:66-74.
62. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart 2007;93:172.
63. Brindle PM, McConnachie A, Upton MN, Hart CL, Smith GD, Watt GCM. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. Brit J Gen Pract 2005;55:838-845.
64. Rose G. Sick individuals and sick populations. Int J Epidemiology 2001;30:427-432.
65. Adler NE, Glymour M, Fielding J. Addressing social determinants of health and health inequalities. JAMA 2016;316:1641-1642.
66. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. British Medical Bulletin 2007;81-82:21-37.
67. Havranek EP, Mujahid MS, Barr DA et al. Social Determinants of Risk and Outcomes for Cardiovascular Disease. Circulation 2015;132:873.
68. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015.
69. http://www.isdscotland.org/products-and-Services/GPD-Support/deprivation/carstairs.
70. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
71. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Int Med 2001;161:996-1002.
72. McAlister FA, Murphy NF, Simpson CR et al. Influence of socioeconomic deprivation on the primary care burden and treatment of patients with a diagnosis of heart failure in general practice in Scotland: Population based study. BMJ 2004;328:1110-1112.
73. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a Risk Factor for Dementia and Cognitive Decline: A Meta-Analysis of Prospective Studies. Am J Epidemiol 2007;166:367-378.
74. Fretz A, Schneider ALC, McEvoy JW et al. The Association of Socioeconomic Status With Subclinical Myocardial Damage, Incident Cardiovascular Events, and Mortality in the ARIC Study. Am J Epidemiol 2016;183:452-61.
75. Ramsay SE, Whincup PH, Papacosta O, Morris RW, Lennon LT, Goya Wannamethee S. Inequalities in heart failure in older men: Prospective associations between socioeconomic measures and heart failure incidence in a 10-year follow-up study. Eur Heart J 2014;35:442-447.

76. Pujades-Rodriguez M, Timmis A, Stogiannis D et al. Socioeconomic deprivation and the incidence of 12 cardiovascular diseases in 1.9 million women and men: Implications for risk prediction and prevention. PLoS ONE 2014;9:e104671.
77. Benderly M, Haim M, Boyko V, Goldbourt U. Socioeconomic status indicators and incidence of heart failure among men and women with coronary heart disease. J Card Fail 2013;19:117-24.
78. Christensen S, Mogelvang R, Heitmann M, Prescott E. Level of education and risk of heart failure: a prospective cohort study with echocardiography evaluation. Eur Heart J 2011;32:450-8.
79. Roberts CB, Couper DJ, Chang PP, James SA, Rosamond WD, Heiss G. Influence of life-course socioeconomic position on incident heart failure in blacks and whites. Am J Epidemiol 2010;172:717-727.
80. Schaufelberger M, Rosengren A. Heart failure in different occupational classes in Sweden. Eur Heart J 2007;28:212-8.
81. Stewart S, Murphy NF, McMurray JJV, Jhund P, Hart CL, Hole D. Effect of socioeconomic deprivation on the population risk of incident heart failure hospitalisation: an analysis of the Renfrew/Paisley Study. Eur J Heart Fail 2006;8:856-63.
82. Ingelsson E, Lind L, Arnlov J, Sundstrom J. Socioeconomic factors as predictors of incident heart failure. J Cardiac Fail 2006;12:540-5.
83. Cuthbertson CC, Heiss G, Wright JD et al. Socioeconomic status and access to care and the incidence of a heart failure diagnosis in the inpatient and outpatient settings. Ann Epidemiol 2018;28:350-355.
84. Akwo EA, Kabagambe EK, Harrell FE et al. Neighborhood Deprivation Predicts Heart Failure Risk in a Low-Income Population of Blacks and Whites in the Southeastern United States. Circ Cardiovasc Qual Outcomes 2018;11:e004052.
85. Conrad N, Judge A, Tran J et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. The Lancet 2017;391:572-580.
86. Kubota Y, Heiss G, Maclehose RF, Roetker NS, Folsom AR. Association of educational attainment with lifetime risk of cardiovascular disease the atherosclerosis risk in communities study. JAMA Int Med 2017;177:1165-1172.
87. Laitinen TT, Puolakka E, Ruohonen S et al. Association of Socioeconomic Status in Childhood With Left Ventricular Structure and Diastolic Function in Adulthood: The Cardiovascular Risk in Young Finns Study. JAMA Pediatrics 2017;171:781-787.
88. Medenwald D, Tiller D, Nuding S et al. Educational status and differences in left ventricular mass and ejection fraction - The role of BMI and parameters related to the metabolic syndrome: A longitudinal analysis from the population-based CARLA cohort. Nutri Metab Cardiovasc Dis 2016;26:815-23.
89. Murray ET, Jones R, Thomas C et al. Life Course Socioeconomic Position: Associations with Cardiac Structure and Function at Age 60-64 Years in the 1946 British Birth Cohort. PloS One 2016;11:e0152691.
90. Rodriguez CJ, Sciacca RR, Diez-Roux AV et al. Relation Between Socioeconomic Status, Race–Ethnicity, and Left Ventricular Mass. Hypertension 2004;43:775.
91. Khaing W, Vallibhakara SA, Attia J, McEvoy M, Thakkinstian A. Effects of education and income on cardiovascular outcomes: A systematic review and meta-analysis. Eur J Prev Cardiol 2017;24:1032-1042.
92. Sedgwick P. Meta-analyses: what is heterogeneity? BMJ 2015;350:h1435.
93. Hartling L, Hamm M, Milne A. Validity and Inter-Rater Reliability Testing of Quality Assessment Instruments [Internet]. Agency for Healthcare Research and Quality 2012;https://www.ncbi.nlm.nih.gov/books/NBK92297/.
94. Albert MA, Glynn RJ, Buring J, Ridker PM. Impact of Traditional and Novel Risk Factors on the Relationship Between Socioeconomic Status and Incident Cardiovascular Events. Circulation 2006;114:2619.

95. Rikard RV, Thompson MS, McKinney J, Beauchamp A. Examining health literacy disparities in the United States: a third look at the National Assessment of Adult Literacy (NAAL). BMC Public Health 2016;16:975.
96. Filc D, Davidovich N, Novack L, Balicer RD. Is socioeconomic status associated with utilization of health care services in a single-payer universal health care system? Int J Equity Health 2014;13:115.
97. Steptoe A, Kunz-Ebrecht S, Owen N et al. Socioeconomic Status and Stress-Related Biological Responses Over the Working Day. Psychosomatic Medicine 2003;65.
98. Steptoe A, Feldman PJ, Kunz S, Owen N, Willemsen G, Marmot M. Stress responsivity and socioeconomic status. A mechanism for increased cardiovascular disease risk? Eur Heart J 2002;23:1757-1763.
99. Pilote L, Lynch JW, Richard H, Almeida N, Benjamin EJ, Murabito JM. Life course socioeconomic position is associated with inflammatory markers: the Framingham Offspring Study. Social Sci Med 2010;71:187-195.
100. Steptoe A, Hamer M, O'Donnell K, Venuraju S, Marmot MG, Lahiri A. Socioeconomic Status and Subclinical Coronary Disease in the Whitehall II Epidemiological Study. PLoS ONE 2010;5:e8874.
101. Bergmann N, Gyntelberg F, Faber J. The appraisal of chronic stress and the development of the metabolic syndrome: a systematic review of prospective cohort studies. Endocrine Connections 2014;3:R55-R80.
102. Fiscella K, Tancredi D, Franks P. Adding socioeconomic status to Framingham scoring to reduce disparities in coronary risk assessment. Am Heart J 2009;157:988-994.
103. Boffa U, McGrady M, Reid CM et al. SCReening Evaluation of the Evolution of New Heart Failure Study (SCREEN-HF): early detection of chronic heart failure in the workplace. Aust Health Rev 2017;41:121-126.
104. Adler N, Cutler D, Fielding J. Vital Directions for Health: Addressing Health Disparities and Social Determinants of Health. NAM Perspectives 2016;Discussion Paper, National Academy of Medicine, Washington, DC.
105. Bostock S, Steptoe A. Association between low functional health literacy and mortality in older adults: longitudinal cohort study. BMJ 2012;344.
106. Wu J-R, Moser DK, DeWalt DA, Rayens MK, Dracup K. Health Literacy Mediates the Relationship Between Age and Health Outcomes in Patients With Heart Failure. Circ Heart Fail 2016;9:e002250.
107. De Walque D, Filmer D. Trends and Socioeconomic Gradients in Adult Mortality around the Developing World. Pop Dev Re 2013;39:1-29.
108. Szlachcic J, Masse BM, Kramer BL, Topic N, Tubau J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. Am J Cardiol 1985;55:1037-1042.
109. Willens HJ, Blevins RD, Wrisley D, Antonishen D, Reinstein D, Rubenfire M. The prognostic value of functional capacity in patients with mild to moderate heart failure. Am Heart J 1987;114:377-382.
110. Keteyian S, Patel M, Kraus W, Brawner C, McConnell T, Piña I. HF-Action Investigators. Variables Measured During Cardiopulmonary Exercise Testing as Predictors of Mortality in Chronic Systolic Heart Failure. J Am Coll Cardiol 2016;67:780-789.
111. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-117.
112. Zugck C, Kruger C, Durr S. Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? Eur Heart J 2000;21.
113. Bittner V, Weiner DH, Yusuf S et al. Prediction of Mortality and Morbidity With a 6-Minute Walk Test in Patients With Left Ventricular Dysfunction. JAMA 1993;270:1702-1707.

114. Hlatky MA, Boineau RE, Higginbotham MB et al. A brief self-administered questionnaire to determine functional capacity (The Duke Activity Status Index). Am J Cardiol 1989;64:651-654.
115. Shaw LJ, Olson MB, Kip K et al. The Value of Estimated Functional Capacity in Estimating Outcome: Results From the NHBLI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study. J Am Coll Cardiol 2006;47:S36-S43.
116. Casanova C, Celli BR, Barria P et al. The 6-min walk distance in healthy subjects: reference standards from seven countries. Eur Resp J 2011;37:150-156.
117. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the ASE and the EACVI. J Am Soc Echocardiog 2015;28:1-39.
118. Curtis J, Sokol S, Wang Y, Rathore S, Ko D, Jadbabaie F. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. J Am Coll Cardiol 2003;42:736-42.
119. McKee PA, Castelli WP, McNamara PM, Kannel WB. The Natural History of Congestive Heart Failure: The Framingham Study. N Engl J Med 1971;285:1441-1446.
120. Brindle L, Pope C, Corner J, Leydon G, Banerjee A. Eliciting symptoms interpreted as normal by patients with early-stage lung cancer: could GP elicitation of normalised symptoms reduce delay in diagnosis? Cross-sectional interview study. BMJ open 2012;2:e001977.
121. Corner J, Hopkinson J, Fitzsimmons D, Barclay S, Muers M. Is late diagnosis of lung cancer inevitable? Interview study of patients' recollections of symptoms before diagnosis. Thorax 2005;60:314-319.
122. Robb K, Stubbings S, Ramirez A et al. Public awareness of cancer in Britain: a population-based survey of adults. British J Cancer 2009;101 Suppl 2:S18-S23.
123. Dhakal BP, Malhotra R, Murphy RM et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. Circ Heart Fail 2015;8:286-294.
124. Enright PL, McBurnie MA, Bittner V et al. The 6-min Walk Test: A Quick Measure of Functional Status in Elderly Adults. Chest 2003;123:387-398.
125. Brooks GC, Vittinghoff E, Iyer S et al. Accuracy and Usability of a Self-Administered 6-Minute Walk Test Smartphone Application. Circ Heart Fail 2015;8:905-913.
126. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography. J Am Soc Echocardiogr 2011;24:229-267.
127. Crowe J, Gibson N, Woolfson M, Somekh M. Wavelet transform as a potential tool for ECG analysis and compression. J Biomed Eng 1992;14:268-272.
128. Meste O, Rix H, Caminal P, Thakor N. Ventricular late potentials characterization in time-frequency domain by means of a wavelet transform. IEEE Trans Biomedi Eng 1994;41:625-634.
129. Sengupta P, Kulkarni H, Narula J. Prediction of Abnormal Myocardial Relaxation From Signal Processed Surface ECG. J Am Coll Cardiol 2018;71:1650.
130. Sauer A, Wilcox J, Andrei A, Passman R, Goldberger J, Shah S. Diastolic Electromechanical Coupling. Circ Arrhythm Electrophysiol 2012;5:537-543.
131. Willems J, Abreu-Lima C, Arnaud P et al. The Diagnostic Performance of Computer Programs for the Interpretation of Electrocardiograms. N Engl J Med 1991;325:1767-1773.
132. Clark E, Sejersten M, Clemmensen P, Macfarlane P. Automated Electrocardiogram Interpretation Programs Versus Cardiologists' Triage Decision Making Based on Teletransmitted Data in Patients With Suspected Acute Coronary Syndrome. Am J Cardiol 2010;106:1696-1702.
133. The MathWorks I. Five Easy Steps to a Continuous Wavelet Transform. Retrived from: http://matlabizmiranru/help/toolbox/wavelet/ch01_i15html 1994-2005.

134. Potter E, Marwick T. Detection of Stage B Heart Failure in the Community using Energy Waveform ECG. J Am Coll Cardiol 2019;73:Supplement 1.
135. Pedregosa F, Varoquaux G, Gramfort A et al. Scikit-learn: Machine learning in python. J Machine Learn Res 2011;12:2825-2830.
136. Pencina MJ, D'Agostino RB, Sr., Demler OV. Novel metrics for evaluating improvement in discrimination: net reclassification and integrated discrimination improvement for normal variables and nested models. Statistics in medicine 2012;31:101-113.
137. Pencina MJ, D' Agostino Sr RB, D' Agostino Jr RB, Vasan RS. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. Statistics in Medicine 2008;27:157-172.
138. Administration on Aging (AoA) AfCL, U.S. Department of Health and Human Services. A Profile of Older Americans. 2017.
139. Attia Z, Kapa S, Lopez-Jimenez F et al. Screening for cardiac contractile dysfunction using an artificial intelligence–enabled electrocardiogram. Nature Med 2019;25:70-74.
140. Schlegel T, Kulecz W, Feiveson A, Greco E, DePalma J, Starc V. Accuracy of advanced versus strictly conventional 12-lead ECG for detection and screening of coronary artery disease, left ventricular hypertrophy and left ventricular systolic dysfunction. BMC Cardiovasc Disord 2010;10:28-28.
141. Addison P. Wavelet transforms and the ECG: a review. Physiological Measurement 2005;26:R155.
142. Reinhardt L, Mäkijärvi M, Fetsch T, Montonen J, Sierra G. Predictive value of wavelet correlation functions of signal-averaged electrocardiogram in patients after anterior versus inferior myocardial infarction. J Am Coll Cardiol 1996;27:53-59.
143. Chevalier P, Rodriguez C, Bontemps L et al. Non-invasive testing of acquired long QT syndrome: evidence for multiple arrhythmogenic substrates. Cardiovasc Res 2001;50:386-98.
144. Savoye C, Klug D, Denjoy I et al. Tissue Doppler echocardiography in patients with long QT syndrome. Eur J Echocardiog 2003;4:209-213.
145. Haugaa K, Edvardsen T, Leren T et al. Left ventricular mechanical dispersion by tissue Doppler imaging: a novel approach for identifying high-risk individuals with long QT syndrome. Eur H J 2009;30:330-337.
146. Piacentino V, Weber C, Chen X et al. Cellular Basis of Abnormal Calcium Transients of Failing Human Ventricular Myocytes. Circ Res 2003;92:651-658.
147. Hobai I, O'Rourke B. Decreased Sarcoplasmic Reticulum Calcium Content Is Responsible for Defective Excitation-Contraction Coupling in Canine Heart Failure. Circulation 2001;103:1577-1584.
148. Kagiyama N, Piccirilli M, Yanamala N et al. Machine Learning Assessment of Left Ventricular Diastolic Function Based on Electrocardiographic Features. J Am Coll Cardiol 2020;76:930.
149. Potter E, Wright L, Yang H, Marwick T. Normal Range of Global Longitudinal Strain in the Elderly: The Impact of Subclinical Disease. J Am Coll Cardiol Img 2020;https://doi.org/10.1016/j.jcmg.2020.07.014.
150. Yu C-M, Lin H, Yang H, Kong S-L, Zhang Q, Lee S-L. Progression of Systolic Abnormalities in Patients With "Isolated" Diastolic Heart Failure and Diastolic Dysfunction. Circulation 2002;105:1195-1201.
151. Kraigher-Krainer E, Shah A, Gupta D, Santos A, Claggett B, Pieske B. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014;63:447-56.
152. Biering-Sorensen T, Biering-Sorensen S, Olsen F, Sengelov M, Jorgensen P, Mogelvang R. Global Longitudinal Strain by Echocardiography Predicts Long-Term Risk of Cardiovascular Morbidity and Mortality in a Low-Risk General Population: The Copenhagen City Heart Study. Circ Cardiovasc Imaging 2017;10:e005521.

153. Stanton T, Leano R, Marwick T. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. Circ Cardiovasc Imaging 2009;2:356-64.
154. Dries D, Strong M, Cooper R, Drazner M. Efficacy of angiotensin-converting enzyme inhibition in reducing progression from asymptomatic left ventricular dysfunction to symptomatic heart failure in black and white patients. J Am Coll Cardiol 2002;40:311-317.
155. CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;357:1385-90.
156. Jacobsen K, O'Meara K, Key E, Buist D, Kerlikowske D, Vejborg K. Comparing sensitivity and specificity of screening mammography in the United States and Denmark. Int J Cancer 2015;137:2198-2207.
157. Kavanagh A, Giles G, Mitchell H, Cawson J. The sensitivity, specificity, and positive predictive value of screening mammography and symptomatic status. J Med Screen 2000;7:105-110.
158. Park D, Ryu S, Kim Y. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105:2017-25.
159. Sweeney C, Ryan F, Ledwidge M et al. Natriuretic peptide-guided treatment for the prevention of cardiovascular events in patients without heart failure. Cochrane Database of Systematic Reviews 2019.
160. Senni M, Tribouilloy CM, Rodeheffer RJ et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998;98:2282-9.
161. Nishimura RA, Otto CM, Bonow RO et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the ACC/AHA Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159.
162. Buckberg G, Hoffman J, Mahajan A, Saleh S, Coghlan C. Cardiac Mechanics Revisited. Circulation 2008;118:2571.
163. Esch B, Warburton D. Left ventricular torsion and recoil: implications for exercise performance and cardiovascular disease. J App Physiol 2009;106:326.
164. Collier P, Phelan D, Klein A. A Test in Context: Myocardial Strain Measured by Speckle-Tracking Echocardiography. J Am Coll Cardiol 2017;69:1043-56.
165. Negishi K, Negishi T, Kurosawa K et al. Practical Guidance in Echocardiographic Assessment of Global Longitudinal Strain. J Am Coll Cardiol Cardiovasc Img 2015;8:489-492.
166. Buchalter MB, Weiss JL, Rogers WJ et al. Noninvasive quantification of left ventricular rotational deformation in normal humans using magnetic resonance imaging myocardial tagging. Circulation 1990;81:1236-1244.
167. Maier SE, Fischer SE, McKinnon GC, Hess OM, Krayenbuehl HP, Boesiger P. Evaluation of left ventricular segmental wall motion in hypertrophic cardiomyopathy with myocardial tagging. Circulation 1992;86:1919-1928.
168. Yeon S, Reichek N, Tallant B, Lima J, Calhoun L, Clark N. Validation of in vivo myocardial strain measurement by magnetic resonance tagging with sonomicrometry. J Am Coll Cardiol 2001;38:555-61.
169. MacGowan Guy A, Shapiro Edward P, Azhari H et al. Noninvasive Measurement of Shortening in the Fiber and Cross-Fiber Directions in the Normal Human Left Ventricle and in Idiopathic Dilated Cardiomyopathy. Circulation 1997;96:535-541.
170. Negishi T, Negishi K, Thavendiranathan P, Cho G-Y, Popescu B, D. V. Effect of Experience and Training on the Concordance and Precision of Strain Measurements. J Am Coll Cardiol Cardiovasc Img 2017;10:518-522.

171. Negishi K, Lucas S, Negishi T, Hamilton J, Marwick T. What is the Primary Source of Discordance in Strain Measurement Between Vendors: Imaging or Analysis? Ultrasound Med Biol 2013;39:714-720.
172. Voigt J-U, Pedrizzetti G, Lysyansky P, Marwick T, Houle H, Baumann R. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur H J Cardiovasc Img 2015;16:1-11.
173. Yingchoncharoen T, Agarwal S, Popovic Z, Marwick T. Normal ranges of left ventricular strain: a meta-analysis. J Am Soc Echocardiog 2013;26:185-91.
174. Zghal F, Bougteb H, Réant P, Lafitte S, Roudaut R. Assessing Global and Regional Left Ventricular Myocardial Function in Elderly Patients Using the Bidimensional Strain Method. Echocardiography 2011;28:978-82.
175. Cheng S, Larson M, McCabe E, Osypiuk E, Lehman B, Stanchev P. Age- and sex-based reference limits and clinical correlates of myocardial strain and synchrony: the Framingham Heart Study. Circ Cardiovasc Imaging 2013;6:692-9.
176. Takigiku K, Takeuchi M, Izumi C et al. Normal Range of Left Ventricular 2-Dimensional Strain: Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) Study. Circ J 2012;76:2623-2632.
177. Cohn J, Johnson G, Shabetai R, Loeb H, Tristani F, Rector T. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. Circulation 1993;87:V15-16.
178. Gomes J, Mehta D, Ip J, Winters S, Camunas J, Ergin A. Predictors of Long-Term Survival in Patients With Malignant Ventricular Arrhythmias. Am J Cardiol 1997;79:1054-60.
179. Gottdiener J, McClelland R, Marshall R. Outcome of congestive heart failure in elderly persons: Influence of left ventricular systolic function: the cardiovascular health study. Ann Internal Med 2002;137:631-9.
180. Bhatia R, Tu J, Lee D, Austin P, Fang J, Haouzi A. Outcome of Heart Failure with Preserved Ejection Fraction in a Population-Based Study. N Engl J Med 2006;355:260-9.
181. Zhang K, French B, A. M, Plappert T, Fang J, Sweitzer N. Strain improves risk prediction beyond ejection fraction in chronic systolic heart failure. J Am Heart Assoc 2013;3:e000550.
182. Sengelov M, Jorgensen P, Jensen J, Bruun N, Olsen F, Fritz-Hansen T. Global Longitudinal Strain is a Superior Predictor of All-Cause Mortality in Heart Failure with Reduced Ejection Fraction. J Am Coll Cardiol Cardiovasc Img 2015;8:1351-9.
183. Hung C-L, Verma A, Uno H, Shin S-H, Bourgoun M, Hassanein A. Longitudinal and Circumferential Strain Rate, Left Ventricular Remodeling, and Prognosis After Myocardial Infarction. J Am Coll Cardiol 2010;56:1812-22.
184. Russo C, Jin Z, Elkind M, Rundek T, Homma S, Sacco R. 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.
185. Plana J, Galderisi M, Barac A, Ewer M, Ky B, Scherrer-Crosbie M. Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiog 2014;27:911-39.
186. Chen J, Long J, Hurria A, Owusu C, Steingart R, Gross C. Incidence of Heart Failure or Cardiomyopathy After Adjuvant Trastuzumab Therapy for Breast Cancer. J Am Coll Cardiol 2012;60:2504-12.
187. Thavendiranathan P, Poulin F, Lim K, Plana J, Woo A, TH. M. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: A systematic review. J Am Coll Cardiol 2014;63:2751-68.

188. Weidemann F, Herrmann S, Störk S, Niemann M, Frantz S, Lange V. Impact of Myocardial Fibrosis in Patients With Symptomatic Severe Aortic Stenosis. Circulation 2009;120:577-84.
189. Yingchoncharoen T, Gibby C, Rodriguez L, Grimm R, Marwick T. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. Circ Cardiovasc Imaging 2012;5:719-25.
190. Mascle S SF, Thebault C, Corbineau H, Laurent M, Hamonic S, Veillard D MP, Leguerrier A, Donal E. Predictive Value of Global Longitudinal Strain in a Surgical Population of Organic Mitral Regurgitation. J Am Soc Echocardiogr 2012;25:766-772.
191. Citro RB, C., Lancellotti P, Silverio A, Provenza G, Bellino M. Global longitudinal strain predicts outcome after MitraClip implantation for secondary mitral regurgitation. J Cardiovasc Med 2017;18.
192. Nishimura R, Otto C, Bonow R, Carabello B, Erwin J, Guyton R. AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. Circulation 2014;129:2440-2492.
193. Smedsrud M, Pettersen E, Gjesdal O, Svennevig J, Andersen K, Ihlen H. Detection of left ventricular dysfunction by global longitudinal systolic strain in patients with chronic aortic regurgitation. J Am Soc Echocardiog 2011;24:1253-9.
194. Ewe S, Haeck M, Ng A, Witkowski T, Auger D, Leong D. Detection of subtle left ventricular systolic dysfunction in patients with significant aortic regurgitation and preserved left ventricular ejection fraction: Speckle tracking echocardiographic analysis. Eur H J Cardiovasc Imaging 2015;16:992-9.
195. Singh A, Addetia K, Maffessanti F, Mor-Avi V, Lang RM. LA Strain for Categorization of LV Diastolic Dysfunction. J Am Coll Cardiol Cardiovasc Img 2017;10:735.
196. Russo C, Jin Z, Homma S et al. Subclinical left ventricular dysfunction and silent cerebrovascular disease: The cardiovascular abnormalities and brain lesions (CABL) study. Circulation 2013;128:1105-1111.
197. Lee W, Liu Y, Yang L, Tsai W. Prognostic value of longitudinal strain of subepicardial myocardium in patients with hypertension. J Hypertens 2016;34:1195-200.
198. Holland D, Marwick T, Haluska B, Leano R, Hordern M, Hare J. Subclinical LV dysfunction and 10-year outcomes in type 2 diabetes mellitus. Heart 2015;101:1061-6.
199. Chen Y, Yuen M, Zhen Z, Chan C, Lam K, Tse H. Incremental prognostic value of global longitudinal strain in patients with type 2 diabetes mellitus. Cardiovasc Diabetol 2016;15:doi:10.1186/s12933-016-0333-5.
200. Olsen N, Sogaard P, Larsson H et al. Speckle-tracking echocardiography for predicting outcome in chronic aortic regurgitation during conservative management and after surgery.
201. Witkowski TG, Thomas JD, Debonnaire PJMR et al. Global longitudinal strain predicts left ventricular dysfunction after mitral valve repair. Eur Heart J Cardiovasc Imaging 2012;14:69-76.
202. Liu H, Pozios I, Haileselassie B, Nowbar A, Sorensen L, Phillip S. Role of Global Longitudinal Strain in Predicting Outcomes in Hypertrophic Cardiomyopathy. Am J Cardiol 2017;120:670-5.
203. Ng A, Bertini M, Borleffs C, Delgado V, Boersma E, Piers S. Predictors of Death and Occurrence of Appropriate Implantable Defibrillator Therapies in Patients With Ischemic Cardiomyopathy. Am J Cardiol 2010;106:1566-73.
204. Biering-Sorensen T, Hoffmann S, Mogelvang R, Zeeberg Iversen A, Galatius S, Fritz-Hansen T. Myocardial strain analysis by 2-dimensional speckle tracking echocardiography improves diagnostics of coronary artery stenosis in stable angina pectoris. Circ Cardiovasc Imaging 2014;7:58-65.

205. Choi J-O, Cho S, Song Y, Cho S, Song B, Lee S-C. Longitudinal 2D strain at rest predicts the presence of left main and three vessel coronary artery disease in patients without regional wall motion abnormality. Eur J Echocardiog 2009;10:695-701.
206. Liou K, Negishi K, Ho S, Russell E, Cranney G, Ooi S-Y. Detection of Obstructive Coronary Artery Disease Using Peak Systolic Global Longitudinal Strain Derived by Two-Dimensional Speckle-Tracking: A Systematic Review and Meta-Analysis. J Am Soc Echocardiog 2016;29:724-35.
207. Dahlslett T, Karlsen S, Grenne B, Eek C, Sjoli B, H. K. Early assessment of strain echocardiography can accurately exclude significant coronary artery stenosis in suspected non-ST-segment elevation acute coronary syndrome. J Am Soc Echocardiog 2014;27:512-9.
208. Antoni M, Mollema S, Delgado V, Atary J, Borleffs C, Boersma E. Prognostic importance of strain and strain rate after acute myocardial infarction. Eur Heart J 2010;31:1640-7.
209. Biering-Sørensen T, Knappe D, Pouleur A-C, Claggett B, Wang P, Moss A. Regional Longitudinal Deformation Improves Prediction of Ventricular Tachyarrhythmias in Patients With Heart Failure With Reduced Ejection Fraction. Circ Cardiovasc Imaging 2016;10:e005096.
210. Haugaa K, Grenne B, Eek C, Ersbøll M, Valeur N, Svendsen J. Strain Echocardiography Improves Risk Prediction of Ventricular Arrhythmias After Myocardial Infarction. J Am Coll Cardiol Cardiovasc Img 2013;6:841-50.
211. Kydd A, Khan F, Watson W, Pugh P, Virdee M, Dutka D. Prognostic Benefit of Optimum Left Ventricular Lead Position in Cardiac Resynchronization Therapy: Follow-Up of the TARGET Study Cohort (Targeted Left Ventricular Lead Placement to guide Cardiac Resynchronization Therapy). J Am Coll Cardiol Heart Fail 2014;2:205-212.
212. Saba S, Marek J, Schwartzman D, Jain S, Adelstein E, White P. Echocardiography-Guided Left Ventricular Lead Placement for Cardiac Resynchronization Therapy. Circ Heart Failure 2013;6:427.
213. Gersh B, Maron B, Bonow R, Dearani J, Fifer M, Link M. ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2011;58:e212.
214. Serri K, Reant P, Lafitte M, Berhouet M, Le Bouffos V, Roudaut R. Global and Regional Myocardial Function Quantification by Two-Dimensional Strain. J Am Coll Cardiol 2006;47:1175-81.
215. Popovic Z, Kwon D, Mishra M, Buakhamsri A, Greenberg N, Thamilarasan M. Association Between Regional Ventricular Function and Myocardial Fibrosis in Hypertrophic Cardiomyopathy Assessed by Speckle Tracking Echocardiography and Delayed Hyperenhancement Magnetic Resonance Imaging. J Am Soc Echocardiog 2008;21:1299-305.
216. Saito M, Okayama H, Yoshii T, Higashi H, Morioka H, Hiasa G. Clinical significance of global two-dimensional strain as a surrogate parameter of myocardial fibrosis and cardiac events in patients with hypertrophic cardiomyopathy. Eur H J Cardiovasc Imaging 2012;13:617-23.
217. Paraskevaidis I, Farmakis D, Papadopoulos C, Ikonomidis I, Parissis J, Rigopoulos A. Two-dimensional strain analysis in patients with hypertrophic cardiomyopathy and normal systolic function: A 12-month follow-up study. Am Heart J 2009;158:444-50.
218. Phelan D, Collier P, Thavendiranathan P, Popović Z, Hanna M, Plana J. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart 2012;98:1442-8.
219. Liu D, Hu K, Niemann M, Herrmann S, Cikes M, Störk S. Effect of Combined Systolic and Diastolic Functional Parameter Assessment for Differentiation of Cardiac Amyloidosis From Other Causes of Concentric Left Ventricular Hypertrophy. Circ Cardiovasc Imaging 2013;6:1066-72.

220. Jamal F, Kukulski T, Strotmann J, Szilard M, D'Hooge J, Bijnens B. Quantification of the spectrum of changes in regional myocardial function during acute ischemia in closed chest pigs: An ultrasonic strain rate and strain study. J Am Soc Echocardiog 2002;14:874-84.
221. Sarvari S, Haugaa K, Zahid W, Bendz B, Aakhus S, Aaberge L. Layer-specific quantification of myocardial deformation by strain echocardiography may reveal significant CAD in patients with non-ST-segment elevation acute coronary syndrome. J Am Coll Cardiol Cardiovasc Img 2013;6:535-44.
222. Grenne B, Eek C, Sjøli B, Dahlslett T, Uchto M, Hol P. Acute coronary occlusion in non-ST-elevation acute coronary syndrome: outcome and early identification by strain echocardiography. Heart 2010;96:1550-6.
223. Gjesdal O, Hopp E, Vartdal T, Lunde K, Helle-Valle T, Aakhus S. Global longitudinal strain measured by two-dimensional speckle tracking echocardiography is closely related to myocardial infarct size in chronic ischaemic heart disease. Clin Sci 2007;113:287-96.
224. Kosmala W, Sanders P, Marwick T. Subclinical Myocardial Impairment in Metabolic Diseases. J Am Coll Cardiol Cardiovasc Img 2017;10:692-703.
225. D'Elia N, Caselli S, Kosmala W et al. Normal Global Longitudinal Strain: An Individual Patient Meta-Analysis. J Am Coll Cardiol Cardiovasc Img 2020;13:167-169.
226. Sugimoto T, Dulgheru R, Bernard A et al. Echocardiographic reference ranges for normal left ventricular 2D strain: results from the EACVI NORRE study. Eur Heart J Cardiovasc Imaging 2017;18:833-840.
227. Almeida JG, Fontes-Carvalho R, Sampaio F et al. Impact of the 2016 ASE/EACVI recommendations on the prevalence of diastolic dysfunction in the general population. Eur Heart J Cardiovasc Imag 2018;19:380-386.
228. Boyd A, Schiller N, Leung D, Ross D, Thomas L. Atrial Dilation and Altered Function Are Mediated by Age and Diastolic Function But Not Before the Eighth Decade. J Am Coll Cardiol Cardiovasc Img 2011;4:234-242.
229. Braunauer K, Pieske-Kraigher E, Belyavskiy E et al. Early detection of cardiac alterations by left atrial strain in patients with risk for cardiac abnormalities with preserved left ventricular systolic and diastolic function. Int J Cardiovasc Img 2018;34:701-711.
230. Kojima T, Kawasaki M, Tanaka R et al. Left atrial global and regional function in patients with paroxysmal atrial fibrillation has already been impaired before enlargement of left atrium: velocity vector imaging echocardiography study. Eur H J Cardiovasc Img 2011;13:227-234.
231. Morris D, Belyavskiy E, Aravind-Kumar R et al. Potential Usefulness and Clinical Relevance of Adding Left Atrial Strain to Left Atrial Volume Index in the Detection of Left Ventricular Diastolic Dysfunction. J Am Coll Cardiol Cardiovasc Img 2018;11:1405-1415.
232. Brecht A, Oertelt-Prigione S, Seeland U et al. Left Atrial Function in Preclinical Diastolic Dysfunction: Two-Dimensional Speckle-Tracking Echocardiography Derived Results from the BEFRI Trial. J Am Soc Echocardiogr 2016;29:750-758.
233. Marsan NAMD, Tops LFMD, Holman ERMDP et al. Comparison of Left Atrial Volumes and Function by Real-Time Three-Dimensional Echocardiography in Patients Having Catheter Ablation for Atrial Fibrillation With Persistence of Sinus Rhythm Versus Recurrent Atrial Fibrillation Three Months Later. Am J Cardiol 2008;102:847-853.
234. Kokubu N, Yuda S, Tsuchihashi K, Hashimoto A, Nakata T, Miura T. Noninvasive Assessment of Left Atrial Function by Strain Rate Imaging in Patients with Hypertension: A Possible Beneficial Effect of Renin-Angiotensin System Inhibition on Left Atrial Function. Hypertens Res 2007;30:13-20.

235. Morris DA, Takeuchi M, Krisper M et al. Normal values and clinical relevance of left atrial myocardial function analysed by speckle-tracking echocardiography: multicentre study. Eur Heart J Cardiovasc Img 2015;16:364-372.
236. Santos Angela BS, Roca Gabriela Q, Claggett B et al. Prognostic Relevance of Left Atrial Dysfunction in Heart Failure With Preserved Ejection Fraction. Circ Heart Fail 2016;9:e002763.
237. Freed BH, Daruwalla V, Cheng JY et al. Prognostic Utility and Clinical Significance of Cardiac Mechanics in Heart Failure With Preserved Ejection Fraction: Importance of Left Atrial Strain. Circ Cardiovasc Img 2016;9:10.1161/CIRCIMAGING.115.003754 e003754.
238. Huttin O, Fraser AG, Coiro S et al. Impact of Changes in Consensus Diagnostic Recommendations on the Echocardiographic Prevalence of Diastolic Dysfunction. J Am Coll Cardiol 2017;69:3119-3121.
239. Obokata M, Kane GC, Reddy YNV, Olson TP, Melenovsky V, Borlaug BA. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. Circulation 2017;135:825-838.
240. Lancellotti P, Galderisi M, Edvardsen T et al. Echo-Doppler estimation of left ventricular filling pressure: results of the multicentre EACVI Euro-Filling study. Eur Heart J Cardiovas Img 2017;18:961-968.
241. Mondillo SMD, Cameli MMD, Caputo MLMD et al. Early Detection of Left Atrial Strain Abnormalities by Speckle-Tracking in Hypertensive and Diabetic Patients with Normal Left Atrial Size. J Am Soc Echocardiogr 2011;24:898-908.
242. Thomas L, Abhayaratna WP. Left Atrial Reverse Remodeling. J Am Coll Cardiol Cardiovasc Img 2017;10:65.
243. Degirmenci H, Duman H, Demirelli S et al. Assessment of effect of irbesartan and nebivolol on the left atrium volume and deformation in the patients with mild-moderate hypertension. Eur Rev Med Pharmacol Sci 2014;18:781-789.
244. Cameli M, Sparla S, Losito M et al. Correlation of Left Atrial Strain and Doppler Measurements with Invasive Measurement of Left Ventricular End-Diastolic Pressure in Patients Stratified for Different Values of Ejection Fraction. Echocardiography 2016;33:398-405.
245. Kadappu KK, Boyd A, Eshoo S et al. Changes in left atrial volume in diabetes mellitus: more than diastolic dysfunction? Eur H J Cardiovasc Img 2012;13:1016-1023.
246. Badano LP, Kolias TJ, Muraru D et al. 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 Imag 2018;19:591-600.
247. Haji K, Wong C, Wright L, Ramkumar S, Marwick T. Left Atrial Strain Performance and its Application in Clinical Practice. J Am Coll Cardiol Cardiovasc Img 2019;12:1093-1101.
248. Reddy YNV, Obokata M, Egbe A et al. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. Eur J Heart Fail 2019;21:891-900.
249. Steele JM, Urbina EM, Mazur WM et al. Left atrial strain and diastolic function abnormalities in obese and type 2 diabetic adolescents and young adults. Cardiovasc Diabetology 2020;19:163.
250. McMurray JJV, Solomon SD, Inzucchi SE et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019;381:1995-2008.
251. Packer M, Anker SD, Butler J et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 2020;383:1413-1424.
252. Struthers AD. Why does spironolactone improve mortality over and above an ACE inhibitor in chronic heart failure? British J Clin Pharm 1999;47:479-482.

253. Pitt B, Zannad F, Remme WJ et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. N Engl J Med 1999;341:709-717.
254. Struthers AD. The clinical implications of aldosterone escape in congestive heart failure. Eur J Heart Fail 2004;6:539-545.
255. Sato A, Saruta T. Aldosterone Escape during Angiotensin converting Enzyme Inhibitor Therapy in Essential Hypertensive Patients with Left Ventricular Hypertrophy. J Int Med Res 2001;29:13-21.
256. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
257. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
258. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. Current Med Res Opinion 2009;25:2303-2310.
259. Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. Lancet 2006;367:356-367.
260. Paulus WJ, Tschöpe C. A Novel Paradigm for Heart Failure With Preserved Ejection Fraction: Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation. J Am Coll Cardiol 2013;62:263-271.
261. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL. Inflammation in Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:1324-1340.
262. Vogel MW, Slusser JP, Hodge DO, Chen HH. The Natural History of Preclinical Diastolic Dysfunction: A Population-Based Study. Circ Heart Fail 2012;5:144.
263. Kosmala W, Przewlocka-Kosmala M, Szczepanik-Osadnik H, Mysiak A, O'Moore-Sullivan T, Marwick TH. A Randomized Study of the Beneficial Effects of Aldosterone Antagonism on LV Function, Structure, and Fibrosis Markers in Metabolic Syndrome. J Am Coll Cardiol Cardiovasc Img 2011;4:1239-1249.
264. Kosmala W, Przewlocka-Kosmala M, Szczepanik-Osadnik H, Mysiak A, Marwick TH. Fibrosis and cardiac function in obesity: a randomised controlled trial of aldosterone blockade. Heart 2013;99:320.
265. Edelmann F, Wachter R, Schmidt AG et al. Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients With Heart Failure With Preserved Ejection Fraction: The Aldo-DHF Randomized Controlled Trial. JAMA 2013;309:781-791.
266. Edwards NC, Steeds RP, Chue CD, Stewart PM, Ferro CJ, Townend JN. The safety and tolerability of spironolactone in patients with mild to moderate chronic kidney disease. British J Clin Pharm 2012;73:447-454.
267. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA 2014;312:2551-2561.
268. 2019 AIoHaW. Hospital care for people with dementia 2016–17. Cat no AGE 94 Canberra: AIHW.
269. Vogels RLC, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: A systematic review of the literature. Eur J Heart Fail 2007;9:440-449.
270. Santangeli P, Di Biase L, Bai R et al. Atrial fibrillation and the risk of incident dementia: A meta-analysis. Heart Rhythm 2012;9:1761-1768
271. Leto L, Feola M. Cognitive impairment in heart failure patients. J Geriatric Cardiol 2014;11:316-328.
272. Huynh Quan L, Negishi K, De Pasquale Carmine G et al. Cognitive Domains and Postdischarge Outcomes in Hospitalized Patients With Heart Failure. Circ Heart Fail 2019;12:e006086.

273. Almeida OP, Garrido GJ, Beer C, Lautenschlager NT, Arnolda L, Flicker L. Cognitive and brain changes associated with ischaemic heart disease and heart failure. Eur Heart J 2012;33:1769-1776.
274. Frey A, Sell R, Homola György A et al. Cognitive Deficits and Related Brain Lesions in Patients With Chronic Heart Failure. J Am Coll Cardiol Heart Fail 2018;6:583-592.
275. Sacre JW, Ball J, Wong C et al. Mild cognitive impairment is associated with subclinical diastolic dysfunction in patients with chronic heart disease. Eur Heart J Cardiovasc Imaging 2017;19:285-92.
276. Zhang Michael J, Norby Faye L, Lutsey Pamela L et al. Association of Left Atrial Enlargement and Atrial Fibrillation With Cognitive Function and Decline: The ARIC-NCS. J Am Heart Assoc 2019;8:e013197.
277. https://www.mocatest.org.
278. Abd Razak MA, Ahmad NA, Chan YY et al. Validity of screening tools for dementia and mild cognitive impairment among the elderly in primary health care: a systematic review. Public Health 2019;169:84-92.
279. Ramkumar S, Ochi A, Kawakami H et al. Echocardiographic Risk Assessment to Guide Screening for Atrial Fibrillation. J Am Soc Echocardiogr 2019;32:1259-67.
280. Gauthier S, Reisberg B, Zaudig M et al. Mild cognitive impairment. Lancet 2006;367:1262-1270.
281. Leritz EC, McGlinchey RE, Kellison I, Rudolph JL, Milberg WP. Cardiovascular Disease Risk Factors and Cognition in the Elderly. Current Cardiovasc Risk Reports 2011;5:407-412.
282. Hou Q, Guan Y, Yu W et al. Associations between obesity and cognitive impairment in the Chinese elderly: an observational study. Clinical Interv Aging 2019;14:367-373.
283. Debette S, Seshadri S, Beiser A et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology 2011;77:461-468.
284. Lee TC, Qian M, Liu Y et al. Cognitive Decline Over Time in Patients With Systolic Heart Failure. J Am Coll Cardiol Heart Fail 2019;7:1042-1053.
285. Cannon JA, McMurray JJV, Quinn TJ. 'Hearts and minds': association, causation and implication of cognitive impairment in heart failure. Alzheimers Res Ther 2015;7:22.
286. Jefferson AL, Himali J, Au R et al. Relation of left ventricular ejection fraction to cognitive aging (from the Framingham Heart Study). Am J Cardiol;108:1346-51.
287. van den Hurk K, Reijmer YD, van den Berg E et al. Heart failure and cognitive function in the general population: the Hoorn Study. Eur J Heart Fail 2011;13:1362-1369.
288. Park CM, Williams ED, Chaturvedi N et al. Associations Between Left Ventricular Dysfunction and Brain Structure and Function: Findings From the SABRE (Southall and Brent Revisited) Study. J Am Heart Assoc 2017;6:e004898.
289. Prins ND, van Dijk EJ, den Heijer T, et al. Cerebral white matter lesions and the risk of dementia. Arch Neurol 2004;61:1531-1534.
290. de Bruijn RF, Heeringa J, Wolters FJ et al. Association Between Atrial Fibrillation and Dementia in the General Population. JAMA Neurol 2015;72:1288-94.
291. Marengoni A, Qiu C, Winblad B, Fratiglioni L. Atrial fibrillation, stroke and dementia in the very old: a population-based study. Neurobiol Aging 2011;32:1336-7.
292. Chen LY, Lopez FL, Gottesman RF et al. Atrial fibrillation and cognitive decline-the role of subclinical cerebral infarcts: the atherosclerosis risk in communities study. Stroke 2014;45:2568-2574.
293. Ding M, Fratiglioni L, Johnell K et al. Atrial fibrillation, antithrombotic treatment, and cognitive aging. Neurology 2018;91:e1732-40.
294. Roth GA, Poole JE, Zaha R, Zhou W, Skinner J, Morden NE. Use of Guideline-Directed Medications for Heart Failure Before Cardioverter-Defibrillator Implantation. J Am Coll Cardiol 2016;67:1062-1069.

295. Seo W-W, Park JJ, Park HA et al. Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: a cohort study. BMJ Open 2020;10:e030514-e030514.
296. Linssen GCM, Veenis JF, Kleberger A et al. Medical treatment of octogenarians with chronic heart failure: data from CHECK-HF. Clin Res Cardiol 2020;109:1155-1164.
297. Vidán MT, Blaya-Novakova V, Sánchez E, Ortiz J, Serra-Rexach JA, Bueno H. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. Eur J Heart Fail 2016;18:869-875.
298. Piepoli MF, Hoes AW, Agewall S et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315-2381.
299. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017;357:j2099.
300. Miyasaka Y, Barnes M, Gersh B et al. Incidence and mortality risk of congestive heart failure in atrial fibrillation patients: a community-based study over two decades. Eur Heart J 2006;27:936-41.
301. Potter E, Hopper I, Sen J, Salim A, Marwick T. Impact of socioeconomic status on incident heart failure and left ventricular dysfunction: systematic review and meta-analysis. Eur Heart J Qual Care Clin Outcomes 2019;5:169-179.
302. Potter E, Yang H, Wright L, Wang B, Marwick TH. Measurement of Functional Capacity to Discriminate Clinical from Subclinical Heart Failure in Patients ≥65 Years of Age. Am J Cardiol 2020;127:84-91.
303. EuroQol Research Foundation. EQ-5D-5L User Guide, 2019. Available from: https://euroqol.org/publications/user-guides.
304. 2018 ABoS. Socio-Economic Indexes for Areas (SEIFA) 2016. Table 1: Postal Area (POA) SEIFA summary, 2016, data cube: Excel spreadsheet, cat no 2033055001, viewed 21/8/2020;https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/2033.0.55.001 2016.
305. https://www.health.gov.au/resources/apps-and-tools/health-workforce-locator. Accessed on 21/8/2020.
306. Wang Y, Marwick T. Cost-effectiveness of myocardial imaging to identify subclinical left ventricular dysfunction in elderly patients with asymptomatic type 2 diabetes. J Am Coll Cardiol 2016;67:2033.
307. Wannamethee S, Welsh P, Whincup PH, Lennon L, Papacosta O, Sattar N. N-terminal pro brain natriuretic peptide but not copeptin improves prediction of heart failure over other routine clinical risk parameters in older men with and without cardiovascular disease: population-based study. Eur J Heart Fail 2014;16:25-32.
308. Butler J, Kalogeropoulos A, Georgiopoulou V et al. Incident heart failure prediction in the elderly: the health ABC heart failure score. Circ Heart Fail 2008;1:125-133.
309. Goyal A, Norton CR, Thomas TN et al. Predictors of incident heart failure in a large insured population: a one million person-year follow-up study. Circ Heart Fail 2010;3:698-705.
310. Wong YW, Thomas L, Sun JL et al. Predictors of incident heart failure hospitalizations among patients with impaired glucose tolerance: insight from the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research study. Circ Heart Fail 2013;6:203-10.
311. Pocock SJ, Ariti CA, McMurray JJV et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J 2013;34:1404-1413.

312. Australian Institute of Health and Welfare 2019. Rural & remote health. Cat. no. PHE 255. Canberra: AIHW. https://wwwaihwgovau/reports/rural-remote-australians/rural-remote-health.
313. Butler J, Kalogeropoulos A, Georgiopoulou V et al. Incident heart failure prediction in the elderly: the health ABC heart failure score. Circulation Heart failure 2008;1:125-133.
314. Pfeffer Marc A, Claggett B, Assmann Susan F et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. Circulation 2015;131:34-42.
315. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol 2020;17:559-573.
316. Patel K, Bahnson J, Gaussoin S et al. Association of Baseline and Longitudinal Changes in Body Composition Measures With Risk of Heart Failure and Myocardial Infarction in Type 2 Diabetes: Findings From the Look AHEAD Trial. Circulation 2020;Epub.
317. Jimeno Sainz A, Gil V, Merino J, García M, Jordán A, Guerrero L. Validity of Framingham criteria as a clinical test for systolic heart failure. Rev Clin Esp 2006;206:495-8.
318. Maestre A, Gil V, Gallego J, Aznar J, Mora A, Martín-Hidalgo A. Diagnostic accuracy of clinical criteria for identifying systolic and diastolic heart failure: cross-sectional study. J Eval Clin Pract 2009;15:55-61.