MONASH University

Clinical and Economic Evaluation of Anticoagulant Interventions for Stroke Prevention in Patients with Atrial Fibrillation

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Notice 1

Abstract

Background:

Novel oral anticoagulants (NOACs) have emerged as promising alternatives to warfarin, for stroke prevention in atrial fibrillation (SPAF) although there are challenges to their adoption in low- and middle-income countries due to their high costs. Thus, warfarin may remain widely used, especially if the quality of anticoagulation control is improved through warfarin care bundles. Warfarin care bundles such as genotype-guided warfarin dosing, patient's self-testing (PST) or self-management (PSM) and left atrial appendage closure (LAAC) are based on the concept of combining warfarin with another intervention. Although NOACs and warfarin care bundles deliver on the promise of convenience, there remain uncertainties regarding their emerging place in therapy as little is still known about the overall efficacy and cost-effectiveness of warfarin regimens under optimal quality control through warfarin care bundles in comparison with NOACs.

Overall aim:

This dissertation aims to explore the clinical and economic outcomes of anticoagulant interventions in patients with atrial fibrillation.

Methods:

This dissertation included three interrelated studies. In the first study, an overview of review was performed to summarize and appraise previous reviews in this field. Based on the clinical gap identified from the earlier study, a comprehensive systematic review with network meta-analysis was then commissioned. This study simultaneously compared the efficacy and safety of usual warfarin care, warfarin care bundles and NOACs in a single network based on the data extracted from randomized trials via a systematic review process. The final study is a cost-effectiveness analysis which provided an example of presenting evidence in the form of a decision-analytical model. This modelling approach demonstrated an analytic framework for decision-making from the societal and

healthcare perspective of a middle-income country over a lifetime horizon, under the circumstances of uncertainty as in the introduction of new anticoagulant interventions for SPAF patients aged 65 years old and above.

Results:

Based on the overview of review, it was identified that existing evidence in the anticoagulant field is based on the comparison between NOACs with usual warfarin care only, without addressing warfarin care bundles and thereby, present evidence may have favoured NOACs. Our systematic review addressed the above limitation and demonstrated that NOACs and warfarin care bundles performed better than usual warfarin care for SPAF. In fact, the benefits of NOACs were reduced in the presence of warfarin care bundles. Warfarin care bundles improved the quality of anticoagulation control by achieving higher time-in-therapeutic range value than usual warfarin care. In the cost-effectiveness study, NOACs were not cost-effective for SPAF in a resource-limited setting. Conversely, PSM was considered as a cost-effective intervention for SPAF compared to usual warfarin care in a lifetime societal perspective.

Conclusions:

This dissertation demonstrates the value of evidence obtained systematically in facilitating decision-making regarding the choice of anticoagulant interventions for SPAF, consistent with the axioms of evidence-based practice. The synthesized body of evidence from randomized trials provides a better understanding of the comparative efficacy and safety of the old and new anticoagulant interventions. The subsequent economic evaluation in the case of a middle-income country can contribute to a better understanding on how the introduction of these new interventions may affect the current treatment practice and influence resource allocation. This understanding is crucial to help charting the coming course of anticoagulant care for SPAF, especially in low- and middle-income countries which are constantly burdened by increasing budget constraints and pervasive resources scarcity.

Declaration

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

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Publications related to thesis during enrolment

Ng SS, Lai NM, Nathisuwan S, Chaiyakunpruk N. Interventions and strategies to improve oral anticoagulant use in patients with atrial fibrillation: a systematic review of systematic review. Clin Drug Investig. 2018; 38(7):579-591.

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Lai NM, Chang SMW, **Ng SS**, Stanaway F, Tan SL, Chaiyakunapruk N. Animal-assisted therapy for dementia (protocol). Cochrane Database Syst Rev. 2019; 1:CD013243.

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 one original paper published in peer-reviewed journals and two submitted publications. The core theme of the thesis is clinical and economic evidence of anticoagulant interventions for stroke prevention in patients with atrial fibrillation. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia under the supervision of Professor Nathorn Chaiyakunapruk, Dr. Nowrozy Kamar Jahan and Professor Nai Ming Lai. 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 Chapter 5 to 7, my contribution to the work involved the following:

(Table in the next page)

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
Chapter 5	Interventions and strategies to improve oral anticoagulant use in patients with atrial fibrillation: a systematic review of systematic review	Published	60% Concept, data screening, data analysis, writing first draft	1) Nai Ming Lai, data screening, data analysis, input into manuscript 20% 2) Surakit Nathisuwan, concept, input into manuscript 10% 3) Nathorn Chaiyakunapruk, concept, input into manuscript 10%	No No No
Chapter 6	Comparative efficacy and safety of warfarin care bundles and novel oral anticoagulants in patients with atrial fibrillation: a systematic review and network meta-analysis	Submitted	55% Concept, data screening, data analysis, writing first draft	1) Nai Ming Lai, input into manuscript 5% 2) Surakit Nathisuwan, concept, input into manuscript 10% 3) Nowrozy Kamar Jahan, input into manuscript 5% 4) Piyameth Dilokthornsakul, data screening and extraction, 5% 5) Khachen Kongpakwattana, data screening and extraction, 5% 6) William Hollingworth, input into manuscript, 5%	No No No No Yes No

				7) Nathorn Chaiyakunapruk, concept, input into manuscript, 10%	No
Chapter 7	Cost-effectiveness of warfarin care bundles and novel oral anticoagulants in patients with atrial fibrillation in Thailand	Submitted	60% Data acquisition, data analysis, writing first draft	1) Surakit Nathisuwan, concept, data acquisition, input into manuscript, 15% 2) Arintaya Phromminitikul, input into manuscript 5% 3) William Hollingworth, input into manuscript 5% 4) Nathorn Chaiyakunparuk, concept, data acquisition, input into manuscript, 15%	No No No No

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: [redacted] **Date:** 17th June 2019

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

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"We are like dwarfs on the shoulders of giants, so that we can see more than they, and things at a great distance, not by virtue of any sight on our part, or any physical distinction, but because we are carried high and raised up by their giant size."-Bernard of Charters

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List of Abbreviations

AC	Anticoagulation clinics
AF	Atrial Fibrillation
BARC	Bleeding Academic Research Consortium
BIA	Budget Impact Analysis
CEA	Cost-effectiveness Analyses
CEAC	Cost-effectiveness Acceptability Curve
CI	Confidence Interval
CPI	Consumer Price Index
ECH	Extracranial Haemorrhage
FDA	Food and Drug Administration
HTA	Health Technology Assessment
ICER	Incremental Cost-effectiveness Ratio
ICH	Intracranial Haemorrhage
INR	International Normalized Ratio
IS	Ischemic Stroke
ISTH	International Society of Thrombosis and Haemostasis
LAAC	Left Atrial Appendage Closure
MI	Myocardial Infarction
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net Monetary Benefit
NTT	Number Needed to Treat
NOACs	Novel Oral Anticoagulants
PICO	Population, intervention, comparator, outcome

POC	Point-of-care
PRSIMA	Preferred Reporting Items for Systematic Reviews
PROSPERO	The International Prospective Register of Systematic Reviews
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
RCTs	Randomized Controlled Trials
ROB	Risk of Bias
ROBIS	Risk of Bias in the Systematic Reviews
RR	Risk Ratios
RWE	Real-world Evidence
SPAF	Stroke prevention in atrial fibrillation
SUCRA	Surface under the Cumulative Ranking Curve
TIA	Transient Ischemic Attack
TTR	Time in Therapeutic Range
US	United States
VKA	Vitamin K Antagonist
VKORC1	Vitamin K Epoxide Reductase Complex
VTE	Venous Thromboembolism
WTP	Willingness to Pay

CHAPTER 1: Introduction

"Medicine is a science of uncertainty and an art of probability" – Sir William Osler

"Policymakers have to make judgement based on the best intelligence they get" – Frank Carlucci

Stroke prevention is an essential part of managing patients with atrial fibrillation (AF). Effective stroke prevention corresponds to the appropriate use of oral anticoagulants, regardless of symptoms, severity and whether a rhythm or a rate control approach is used to treat these patients. For the past 60 years, warfarin, a Vitamin K antagonist (VKA) has been the standard oral anticoagulant for stroke prevention in atrial fibrillation (SPAF) and remains widely used worldwide. However, the landscape of SPAF in clinical practice has changed markedly in recent years, with the emergence of new anticoagulant interventions such as warfarin care bundles and novel oral anticoagulants (NOACs). Warfarin care bundles such as genotype-guided warfarin dosing, patient's self-testing (PST) or self-management of warfarin (PSM) and left atrial appendage closure (LAAC-Watchman Device), are based on the concept of combining warfarin with another intervention to improve anticoagulation control with warfarin. Conversely, NOACs (e.g. dabigatran, rivaroxaban, apixaban and edoxaban) are alternatives to warfarin, that have fixed dosing and predictable pharmacokinetics to eliminate the need for constant monitoring. The introduction of these new interventions has brought remarkable improvements in the anticoagulant care as many of these interventions address limitations associated with conventional warfarin use by improving health outcomes, enhancing quality of life and reducing adverse or side effects.

This growing anticoagulant armamentarium has presented clinicians and healthcare providers with unprecedented challenges to provide high quality anticoagulant care to the AF population within the healthcare budget while maintaining the basic principles of equity, access and choice. The potential of these new anticoagulant interventions is often questioned with an ongoing debate regarding their emerging place in therapy. However, healthcare decision-making is a complex task as stated by Sir

William Osler's quote in the beginning of the chapter, *'Medicine is a science of uncertainty and an art of probability'*. Clinicians and policymakers must have a clear understanding of the new anticoagulant interventions to aid the selection of the most optimal intervention for SPAF within their healthcare setting. NOACs and warfarin care bundles may offer potential benefits to patients and healthcare system, but their adoption can be problematic in resource-constrained healthcare environment by increasing overall healthcare expenditure. Thus, synthesizing qualitative and quantitative evidence of these anticoagulant interventions for SPAF from both clinical and economic aspect, is important to inform practice and to promulgate evidence-based decision-making in healthcare.

From the clinical aspect, the comparative efficacy of NOAC and warfarin care bundles is unknown as direct comparison among these interventions have not been conducted in randomized clinical trials (RCTs) yet due to regulatory, financial and time constraints. The absence of such comparative clinical evidence may result in clinical decisions being made under conditions of uncertainty or influenced by personal intuition of the stakeholders. Such premature decision-making can compromise evidence-base practice and result in patient harm. Additionally, little is still known about the overall cost-effectiveness of warfarin regimens under optimal quality control through warfarin care bundles in comparison with NOACs. It is also unclear whether NOACs or warfarin care bundles are potentially viable anticoagulant intervention to be considered as part of the healthcare continuum especially in low- and middle-income countries as the cost of these interventions are substantially higher than that of conventional warfarin use.

Based on the gap of current evidence, there is a pressing need to demonstrate the value of each anticoagulant intervention for SPAF, encompassing aspects such as clinical efficacy and economic efficiency. The level of incremental absolute benefits and costs of each intervention should be considered thoroughly and to be compared with the best available practice prior adoption into the

healthcare system. The availability of such information may inform decision-makers about the efficient allocation of scare healthcare resources for the listing pricing and reimbursement of new anticoagulant interventions. Therefore, this dissertation aims to generate clinical and economic evidence of anticoagulant interventions in patients with AF to fully understand the value of these intervention for SPAF and its potential for adoption into the healthcare system.

CHAPTER 2: Literature Review

2.1. Atrial Fibrillation and Stroke: Prevalence and Epidemiology

AF is the most common sustained cardiac arrythmia and is often characterized by rapid irregular heartbeats. In 2010, the Global Burden Disease study estimated that there were 33.5 million patients with AF worldwide, constituting approximately 0.5% of the total population. However, the actual prevalence could be considerably higher as many asymptomatic individuals and those having transient symptoms remain undiagnosed. This prevalence also increased significantly with age from approximately 0.1% in adult less than 55 years old to 9.0% in those aged 80 years or older.[1]

Generally, the prevalence and burden of AF tends to be lower in middle-income countries compared with high-income nations.[2] However, these geographical differences should be interpreted with caution as the lower detection rates of AF in low- and middle-income countries can be due to under reporting, poorer awareness among the community, poorer surveillance and limited access to healthcare services.[2-4] Although the current prevalence of AF is lower in middle-income countries, the rise of cardiovascular disease burden such as ischemic heart disease and hypertension in these countries merit careful consideration as these diseases are risk factors for AF. Moreover, with the global aging of the population and the rapidly evolving demographic changes of population in these regions, the prevalence of AF is expected to rise even more in the next couple of decades. [5]

The growing epidemic of AF creates a huge burden on healthcare systems and economies throughout the world. AF patients are associated with a five-fold increased risk of stroke and thromboembolism, resulting in significant morbidity, mortality and health-related expenditures.[6] AF-related strokes tend to be more severe, debilitating, frequently fatal and recurring when compared to stroke in the absence of AF. [7] Specifically, AF-related stroke often results in up to 20% high risk of mortality and nearly 60% of them are left with disability.[8] Moreover, approximately 50% to 70% of the financial burden of AF is attributable to hospitalization costs.[9] Apart from stroke, AF has also been shown to increase the risk of myocardial infarction, heart failure, dementia and chronic kidney disease, which eventually

increases the risk of mortality and morbidity too.[10] Therefore, the growing epidemic of AF warrants urgent attention from the healthcare system around the world as it conveys a substantial clinical and public health burden.

2.2. Oral Anticoagulants for Stroke Prevention in Patients with AF

Stroke prevention using oral anticoagulants are one of the cornerstones in managing patients with AF. Nonetheless, the decision to initiate oral anticoagulants in AF patients is usually tailored based on individuals and the presence of additional stroke risk factors, as measured by the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75, diabetes, prior stroke or transient ischemic attack, vascular disease, age 65-74 and sex category [female]). Based on the 2014 National Institute for Health and Care Excellence (NICE) guidelines[11] and 2016 European Society of Cardiology guidelines[12], the low-risk patients identified through the CHA_2DS_2-VASc scoring system (score 0 in males and 1 in females) do not require anticoagulation therapy while stroke prevention with oral anticoagulants should be offered to those with at least one additional risk factors (score ≥1 in males and ≥2 in females).

Despite guidelines' recommendations, a substantial percentage of patients who are eligible did not received anticoagulation therapy, due to perceived risks and concerns.[10] The multinational GARFIELD-AF (Global Anticoagulant Registry in the Field) registry reported 39.1% of patients with CHA_2DS_2-VASc score ≥2 were not anticoagulated.[13] The GARFIELD-AF registry included more than 50 countries including low and middle-income nations such as Argentina, Brazil, South Africa, East Asia and Mexico. In REALISE-AF survey, oral anticoagulants were not prescribed in 47.4% in patients with $CHADS_2$ score ≥2.[14] The PINNACLE (Practice Innovation and Clinical Excellence) registry also reported that among 429,417 outpatients with AF, oral anticoagulants were not used in 55.1% of the study cohort.[15] Similarly, in the United States (US) Veterans Administration records,

nearly 56.9% of patients with new onset AF were not initiated with oral anticoagulants.[16] Therefore, it is evident that there is still an underutilization of oral anticoagulants in both developed and developing nations despite the established benefits of oral anticoagulants in patients with AF. Undertreatment with oral anticoagulants on the longer term may result in severe and costly complications such as stroke and thromboembolic events.

2.3. The Classic Oral Anticoagulant: Warfarin

Warfarin, an oral VKA was the only orally effective anticoagulant for a period of almost 60 years.[17] It has been shown to be clinically effective in reducing the risk of stroke in patients with AF. Previous meta-analysis, involving an aggregate of more than 4,600 patients with AF demonstrated that the use of warfarin reduced the risk of stroke by 62% compared with placebo.[18] Several observational studies have also demonstrated similar results whereby warfarin was found to be significantly more effective than either placebo or aspirin for secondary stroke prevention in patients with AF.[19-22]

In patients with AF who were treated with warfarin, the target range of international normalized ratio (INR) monitoring for warfarin effect is 2.0 to 3.0. However, previous study has demonstrated that only approximately one third of those who received warfarin achieved therapeutic INR of 2.0 to 3.0.[23] The high proportion of out-of-range INR (<2.0 or >3.0) is unfavourable as the risk of stroke and bleeding are closely related to the INR range, with the risk of stroke increasing rapidly below an INR of 2.0 while the bleeding risk increasing after an INR of 3.0.[24] In fact, the risk of stroke doubled in those with INR 1.7, tripled in those with INR 1.5 and was seven-fold higher in those with INR 1.3, as compared to patients with an INR of 2.0.[24]

Although inexpensive and effective, long-term use of warfarin in clinical practice is often hampered by the delayed onset of action, highly variable dose-response effects, narrow therapeutic index, drug-drug, drug-food (e.g. dietary vitamin K, excessive alcohol) and disease-state interactions. These

inherent limitations of warfarin prompted the need for frequent INR monitoring and vigilant dosage titration, which resulted in poor patient adherence and decreased quality of life.[25] Moreover, the anticoagulation control as measured by percentage of time in therapeutic range (TTR), is also generally suboptimal especially in low- and middle-income countries. Based on the RE-LY trial[26], there is a marked variation in TTR values across regions. In high-income countries such as Australia, US, UK, and Canada, the TTR value ranged between 65% to 75%. Meanwhile, low- and middle-income countries such as Mexico, Brazil, India, China, Malaysia and Thailand reported lower TTR values, ranging from 45% to 60% only.[26] As the anticoagulation control in majority low- and middle-income countries remain suboptimal, the warfarin care management in these regions should be further optimized.

2.4. Warfarin Care Bundles

The effectiveness of warfarin is contingent on patient adherence and the quality of anticoagulation control. Therefore, warfarin care bundles such as genotype-guided warfarin dosing, PST or PSM and LAAC with temporary warfarin use, have been proposed to improve the quality of anticoagulation control with warfarin. Warfarin care bundles are based on the concept of combining warfarin with another interventions.[27] These pragmatic warfarin care bundles have the potential in improving patient's convenience and the overall quality of warfarin care by resulting in fewer stroke and bleeding complications. [28, 29]

One of the proposed warfarin care bundles to improve anticoagulation control is through the inclusion of genetic information into warfarin dosing algorithm. Polymorphisms of VKORC1 (Vitamin K epoxide reductase complex) and CYP2C9 genes have been found to influence warfarin dosing, accounting for approximately 35% of the variability in warfarin daily-dose requirements. [30-32] The benefits of utilizing this genetic information to guide warfarin dosing was evaluated in two prospective randomized controlled trials (RCTs) published by Pirmohamed et al. [24] and Kimmel et

al.[33] However, there is no final consensus yet on the benefits of genotype-guided warfarin dosing in clinical practice.

Point-of care (POC) testing is an emerging alternative of warfarin management. The use of POC testing provides immediate results and allows same-day warfarin dosage adjustment, which subsequently leads to the introduction of another warfarin care bundle, known as patient's self-monitoring of warfarin. The INR results obtained from self-monitoring could be managed either by healthcare professionals or by patient themselves, addressed as "Patient Self-testing (PST)" or "Patient Self-management (PSM)" respectively. In PSM, patients conduct monitoring test and adjust their warfarin dose independently according to the provided algorithm while in PST, patients conduct the test but obtain dosage recommendations from healthcare professionals instead.[34] It is postulated that the use of POC coagulometers for self-monitoring eliminates the unnecessary visit to hospital or anticoagulation clinics while retaining the need for frequent monitoring and timely warfarin dosage adjustment to achieve high quality anticoagulation control.[35]

2.5. Novel Oral Anticoagulants (NOACs)

Besides warfarin care bundles, recent years have also seen the introduction of NOACs as alternatives to warfarin for SPAF. These agents have fixed dosing and predictable pharmacokinetics, which eliminates the need for routine monitoring.[36] As such, it is possible that NOACs may eventually provide better means of closing the clinical gaps of suboptimal anticoagulation with warfarin than any further investments in the current warfarin care.

To date, there are four NOACs available for the indication of SPAF: dabigatran, rivaroxaban, apixaban and edoxaban. These NOACs have demonstrated superiority or at least non-inferiority to warfarin for prevention of stroke and systemic embolism in patients with AF.[37-40]

In 2015, Food and Drug Administration (FDA) approved the first NOAC reversal agent, idarucizumab which specifically and rapidly reverse the anticoagulation effects of dabigatran.[41] Therefore, the recent approval of idarucizumab is a major step toward the achievement of safer anticoagulation therapy with NOACs and may further shift the paradigm of anticoagulation care for patients with AF

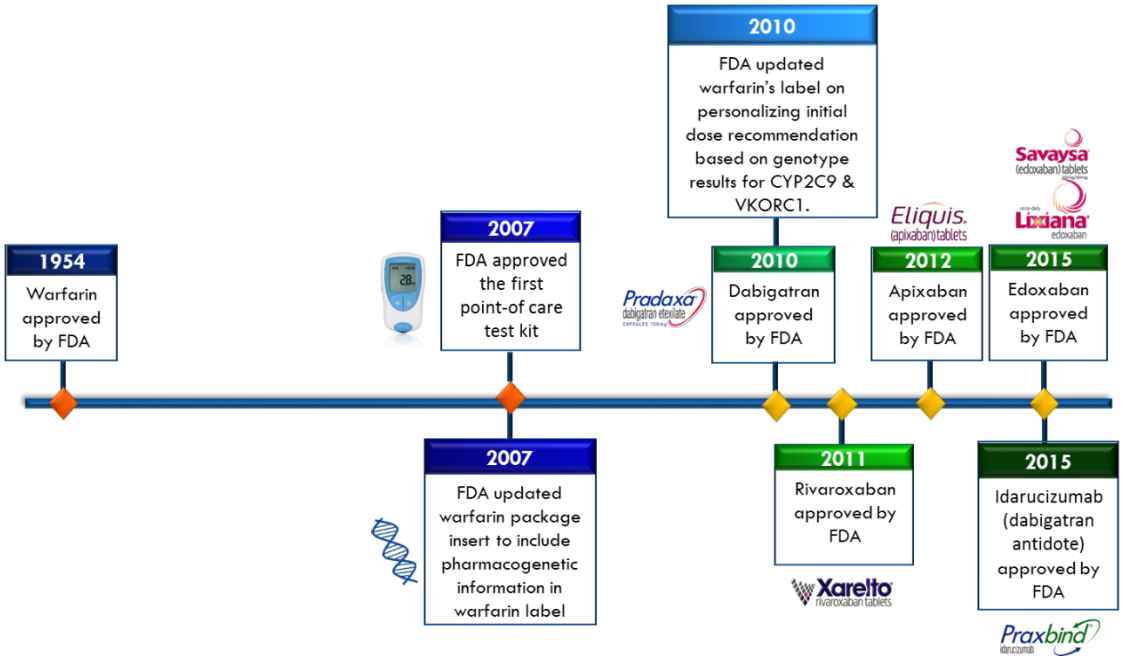

Figure 2.5.1. The Evolution Timeline of Oral Anticoagulants for Stroke Prevention in Patients with Atrial Fibrillation

2.6. Challenges and Barriers Associated with The Paradigm Shift of Oral Anticoagulants

With the growing anticoagulant armamentarium such as warfarin care bundles and NOACs, both clinicians and policymakers are faced with uncertainties in selecting the most optimal intervention for patients with AF. Challenges in adopting these newer interventions can be categorized into two parts: (i) scientific or clinical barriers and (ii) economic barriers.

Clinical Challenges

From the clinical perspective, the degree of benefit of NOACs compared with warfarin is highly dependent on the quality of anticoagulation control with warfarin. However, at current, there is no evidence to support the superiority of NOACs over well-controlled warfarin therapy at TTR $\geq$ 65%.[37, 38, 40, 42] Ironically, the overall quality of anticoagulation control in many low- and middle-income countries is still suboptimal, with a TTR approximately 55% and less than 50% in some resource-limited settings. [26] Thus, the poor anticoagulation control with warfarin can be further optimized through warfarin care bundles and it is plausible that warfarin performance can be as good as NOACs if higher TTR is achieved or the quality of anticoagulation control is good through care bundles. However, most of the previous RCTs [37-40] and meta-analyses[43-46] compared NOACs with usual warfarin care only, without addressing warfarin care bundles and this may have favoured NOACs. Moreover, there are no head-to-head trials yet, comparing NOACs with each other or with warfarin care bundles and thus, the comparative effectiveness between these interventions for SPAF is still unknown.

Additionally, although NOACs deliver on the promise of convenience, uncertainties remain surrounding their uses in clinical practice.[47] Without routine monitoring testing, patient's adherence could not be assessed. The degree of anticoagulation may need to be assessed in some situations such as during severe bleeding or emergency surgery. Furthermore, safety data of NOACs in certain populations are still limited such as those with severe renal insufficiency.

Economic Challenges

Despite the possible clinical benefits of NOACs and warfarin care bundles, their impact on the healthcare is often hampered by the poorly aligned stakeholder incentives with differing economic benefits to efficiency incentives. From the economic standpoint, it remains unclear whether both NOACs and warfarin care bundles are potentially viable interventions to be considered as part of the

healthcare continuum especially in low- and middle-income countries as the cost of these interventions are substantially higher than that of conventional warfarin care. Previous economic studies[48-50] have compared NOACs with usual warfarin care only and as such, little is still known about the overall efficacy and cost-effectiveness of warfarin regimens under optimal quality control through warfarin care bundles in comparison with NOACs. As mentioned previously, the outcomes of warfarin therapy are highly dependent on the adequacy of its therapy and thus, the quality of anticoagulation control is an important factor in determining the cost-effectiveness of NOACs in countries with limited healthcare resources. However, economic studies in these countries are still scarce due to the lack of technical capacity, funding and database to conduct their own economic evaluations. Findings from economic studies conducted in developed countries such as US, Europe and Canada may not be fully relevant to the healthcare context of countries with restricted healthcare resources due to different feasibility, drug pricing, cost-effectiveness threshold and patient's demographics. The unavailability of both comparative clinical and economic evidence further complicates the decision-making process in choosing the most optimal oral anticoagulant for SPAF within the budget availability.

2.7. Summary

Due to the high burden of AF and that new anticoagulant interventions may avert stroke more effectively than usual warfarin care but at higher costs, there is an overbearing need for the clinical and economic evaluations of these interventions. As these interventions often require long-term use, the efficacy and cost of these interventions should be placed into substantial consideration when formulating recommendations and in allocating scare resources efficiently especially in low- and middle-income countries. Each anticoagulant intervention has different clinical and economic implications for patients, clinicians and policymakers to consider.

References for Chapter 2

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. Jama. 2001;285(18):2370-5.
2. Chugh SS, Roth GA, Gillum RF, Mensah GA. Global Burden of Atrial Fibrillation in Developed and Developing Nations. Global Heart. 2014;9(1):113-9.
3. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129(8):837-47.
4. Lim CW, Kasim S, Ismail JR, Chua NY, Najme Khir R, Zainal Abidin HA, et al. Prevalence of atrial fibrillation in the Malaysian communities. Heart Asia. 2016;8(2):62-6.
5. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). European heart journal. 2010;31(19):2369-429.
6. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Archives of internal medicine. 1987;147(9):1561-4.
7. Gladstone DJ, Bui E, Fang J, Laupacis A, Lindsay MP, Tu JV, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. Stroke. 2009;40(1):235-40.
8. Perera KS, Vanassche T, Bosch J, Swaminathan B, Mundl H, Giruparajah M, et al. Global Survey of the Frequency of Atrial Fibrillation-Associated Stroke: Embolic Stroke of Undetermined Source Global Registry. Stroke. 2016;47(9):2197-202.
9. Patel NJ, Atti V, Mitrani RD, Viles-Gonzalez JF, Goldberger JJ. Global rising trends of atrial fibrillation: a major public health concern. Heart (British Cardiac Society). 2018;104(24):1989-90.
10. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nature reviews Cardiology. 2014;11(11):639-54.
11. National Institute for Heatlh and Care Excellence. Atrial Fibrllation: Management (NICE Guideline CG180) [Internet]. 2014. Available from: https://www.nice.org.uk/guidance/cg180.
12. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2016;50(5):e1-e88.
13. Bassand JP, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KA, et al. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. European heart journal. 2016;37(38):2882-9.
14. Gamra H, Murin J, Chiang CE, Naditch-Brule L, Brette S, Steg PG. Use of antithrombotics in atrial fibrillation in Africa, Europe, Asia and South America: insights from the International RealiseAF Survey. Archives of cardiovascular diseases. 2014;107(2):77-87.
15. Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, et al. Oral Anticoagulant Therapy Prescription in Patients With Atrial Fibrillation Across the Spectrum of Stroke Risk: Insights From the NCDR PINNACLE Registry. JAMA cardiology. 2016;1(1):55-62.
16. Buck J, Kaboli P, Gage BF, Cram P, Vaughan Sarrazin MS. Trends in antithrombotic therapy for atrial fibrillation: Data from the Veterans Health Administration Health System. American heart journal. 2016;179:186-91.
17. Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Manag. 2015;11:967-77.
18. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med. 1994;154(13):1449-57.

19. Go AS. Efficacy of anticoagulation for stroke prevention and risk stratification in atrial fibrillation: translating trials into clinical practice. Am J Manag Care. 2004;10(3 Suppl):S58-65.
20. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Ann Intern Med. 1999;131(12):927-34.
21. Frost L, Johnsen SP, Pedersen L, Toft E, Husted S, Sorensen HT. Atrial fibrillation or flutter and stroke: a Danish population-based study of the effectiveness of oral anticoagulation in clinical practice. J Intern Med. 2002;252(1):64-9.
22. Evans A, Perez I, Yu G, Kalra L. Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? Stroke. 2001;32(12):2828-32.
23. Bungard TJ, Ackman ML, Ho G, Tsuyuki RT. Adequacy of anticoagulation in patients with atrial fibrillation coming to a hospital. Pharmacotherapy. 2000;20(9):1060-5.
24. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med. 1996;335(8):540-6.
25. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A randomized trial of genotype-guided dosing of warfarin. N Engl J Med. 2013;369(24):2294-303.
26. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet (London, England). 2010;376(9745):975-83.
27. Resar. R, Griffin. FA, Haraden. C, Nolan. TW. Using Care Bundles to Improve Health Care Quality Cambridge, Massachusetts: Institute for Healthcare Improvement; 2012 [Available from: www.IHI.org.
28. Taborski U, Muller-Berghaus G. State-of-the-art patient self-management for control of oral anticoagulation. Seminars in thrombosis and hemostasis. 1999;25(1):43-7.
29. Gadisseur AP, Kaptein AA, Breukink-Engbers WG, van der Meer FJ, Rosendaal FR. Patient self-management of oral anticoagulant care vs. management by specialized anticoagulation clinics: positive effects on quality of life. Journal of thrombosis and haemostasis : JTH. 2004;2(4):584-91.
30. Carlquist JF, Horne BD, Muhlestein JB, Lappe DL, Whiting BM, Kolek MJ, et al. Genotypes of the cytochrome p450 isoform, CYP2C9, and the vitamin K epoxide reductase complex subunit 1 conjointly determine stable warfarin dose: a prospective study. J Thromb Thrombolysis. 2006;22(3):191-7.
31. Sconce EA, Khan TI, Wynne HA, Avery P, Monkhouse L, King BP, et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood. 2005;106(7):2329-33.
32. Aquilante CL, Langaee TY, Lopez LM, Yarandi HN, Tromberg JS, Mohuczy D, et al. Influence of coagulation factor, vitamin K epoxide reductase complex subunit 1, and cytochrome P450 2C9 gene polymorphisms on warfarin dose requirements. Clin Pharmacol Ther. 2006;79(4):291-302.
33. Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. The New England journal of medicine. 2013;369(24):2283-93.
34. Sharma P, Scotland G, Cruickshank M, Tassie E, Fraser C, Burton C, et al. Is self-monitoring an effective option for people receiving long-term vitamin K antagonist therapy? A systematic review and economic evaluation. BMJ Open. 2015;5(6):e007758.
35. Jones S, Monagle P, Manias E, Bruce AA, Newall F. Quality of life assessment in children commencing home INR self-testing. Thromb Res. 2013;132(1):37-43.
36. Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Therapeutics and clinical risk management. 2015;11:967-77.

37. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2009;361(12):1139-51.
38. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2013;369(22):2093-104.
39. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-92.
40. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. The New England journal of medicine. 2011;365(10):883-91.
41. FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa. U.S Food and Drug Administration 2015.
42. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. The New England journal of medicine. 2011;364(9):806-17.
43. Cameron C, Coyle D, Richter T, Kelly S, Gauthier K, Steiner S, et al. Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation. BMJ open. 2014;4(6):e004301.
44. Lopez-Lopez JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ (Clinical research ed). 2017;359:j5058.
45. Tawfik A, Bielecki JM, Krahn M, Dorian P, Hoch JS, Boon H, et al. Systematic review and network meta-analysis of stroke prevention treatments in patients with atrial fibrillation. Clinical pharmacology : advances and applications. 2016;8:93-107.
46. Tereshchenko LG, Henrikson CA, Cigarroa J, Steinberg JS. Comparative Effectiveness of Interventions for Stroke Prevention in Atrial Fibrillation: A Network Meta-Analysis. Journal of the American Heart Association. 2016;5(5).
47. Gulseth MP, Wittkowsky AK, Fanikos J, Spinler SA, Dager WE, Nutescu EA. Dabigatran etexilate in clinical practice: confronting challenges to improve safety and effectiveness. Pharmacotherapy. 2011;31(12):1232-49.
48. Canestaro WJ, Patrick AR, Avorn J, Ito K, Matlin OS, Brennan TA, et al. Cost-effectiveness of oral anticoagulants for treatment of atrial fibrillation. Circulation Cardiovascular quality and outcomes. 2013;6(6):724-31.
49. Dorian P, Kongnakorn T, Phatak H, Rublee DA, Kuznik A, Lanitis T, et al. Cost-effectiveness of apixaban vs. current standard of care for stroke prevention in patients with atrial fibrillation. European heart journal. 2014;35(28):1897-906.
50. Harrington AR, Armstrong EP, Nolan PE, Jr., Malone DC. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. Stroke. 2013;44(6):1676-81.

CHAPTER 3: Research Questions, Aim and Objectives

3.1. Research Questions

Based on the previous background within this research field, the main research question for this thesis is, "*What are the clinical and economic evidence of anticoagulant interventions for SPAF and how relevant are these evidences for a middle-income country with limited healthcare resources?".* Specific research questions for corresponding chapters are designed to address the main research question around the topic of anticoagulants for SPAF as shown in Figure 3.1.1.

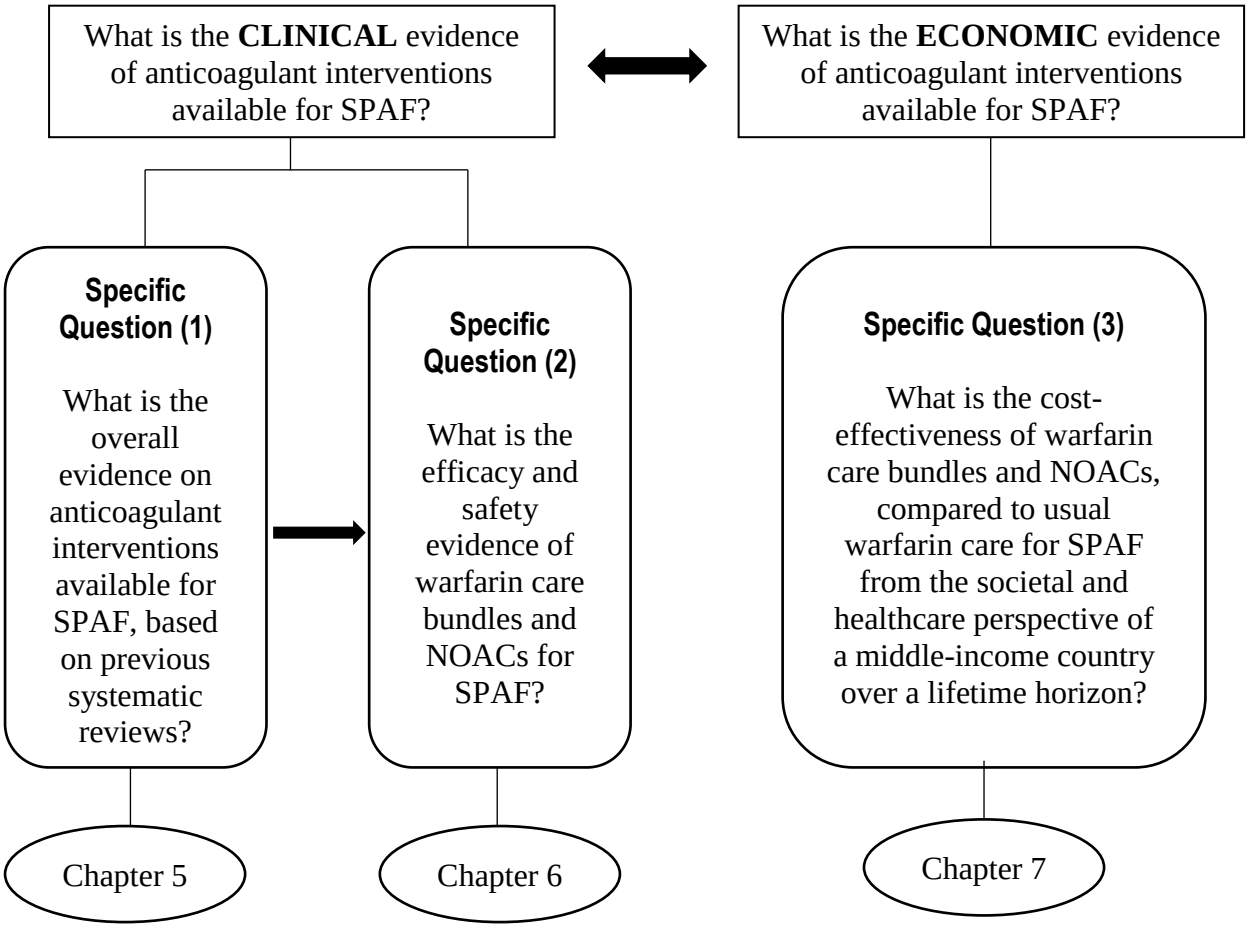

Figure 3.1.1. Overview of outline of the thesis by research questions

These research questions provided the basis for establishing the initial direction of this thesis, thereby leading to the articulation of the dissertation aim and objectives.

3.2. Overall Aim

The overall aim of this dissertation was to explore the clinical and economic outcomes of anticoagulant interventions for stroke prevention in patients with AF. This was covered in three studies, with the first two studies addressing clinical evidence while the third study evaluated the economic implications of the interventions for SPAF.

3.3. Specific Objectives

i) To summarize and evaluate existing evidence from multiple systematic reviews and/or meta-analyses on anticoagulant interventions available for SPAF

ii) To compare the efficacy and safety of warfarin care bundles and NOACs for SPAF, by performing network meta-analysis

iii) To assess the cost-effectiveness of warfarin care bundles and NOACs, compared to usual warfarin care for SPAF patients aged 65 years old and above, from the societal and healthcare perspective of a middle-income country over a lifetime horizon.

CHAPTER 4: Thesis Outline

4.1. Structure of Thesis

The table below listed the chapters included in this thesis and provided a brief description for each corresponding chapter.

Table 4.1.1. Chapter Outline and Description

Chapter	Brief Description
2	A literature review addressing the following topics is presented: • Atrial Fibrillation and Stroke: Prevalence and Epidemiology • Oral Anticoagulants for Stroke Preventions in Patients with AF • The Classic Oral Anticoagulants: Warfarin • Warfarin Care Bundles • Novel Oral Anticoagulants (NOACs) • Challenges and Barriers Associated with The Paradigm Shift of Oral Anticoagulants
5	A study that aimed to summarize and compare existing systematic reviews and/or meta-analyses on anticoagulant interventions available for SPAF. This study presented the big picture and the summary of evidence tables on anticoagulant interventions available for SPAF. It provided a ready means for healthcare decision-makers to gain a clearer understanding on these interventions, based on the highest level of evidence available. It also highlighted the limitations of current reviews in this research field.
6	A study that meta-analysed the efficacy and safety evidence of usual warfarin care, warfarin care bundles and NOACs for SPAF based on randomized controlled trials identified from the literature via a systematic review process. This study filled the gap in current evidence as it provided a clearer representation on the benefits and risks of each anticoagulant intervention for SPAF, especially for NOACs in the presence of warfarin care bundles.

7	A study that intended to assess the cost-effectiveness of newer anticoagulant interventions (e.g. warfarin care bundles and NOACs), compared to usual warfarin care for SPAF patients aged 65 years old and above, from the societal and healthcare perspective of a middle-income country over a lifetime horizon. This study illustrated the potential changes in economic outcomes of NOACs versus investing additional resources to improve the quality of anticoagulation control through care bundles within a resource-limited healthcare setting.
8	Concluding chapter – a discussion on the practicality of the overall findings, the salient contributions of this thesis, as wells as the recap of its limitations. Areas for future research are also discussed.

The figure below illustrates the narrative flow of this thesis and highlighted the relationships between the listed chapters.

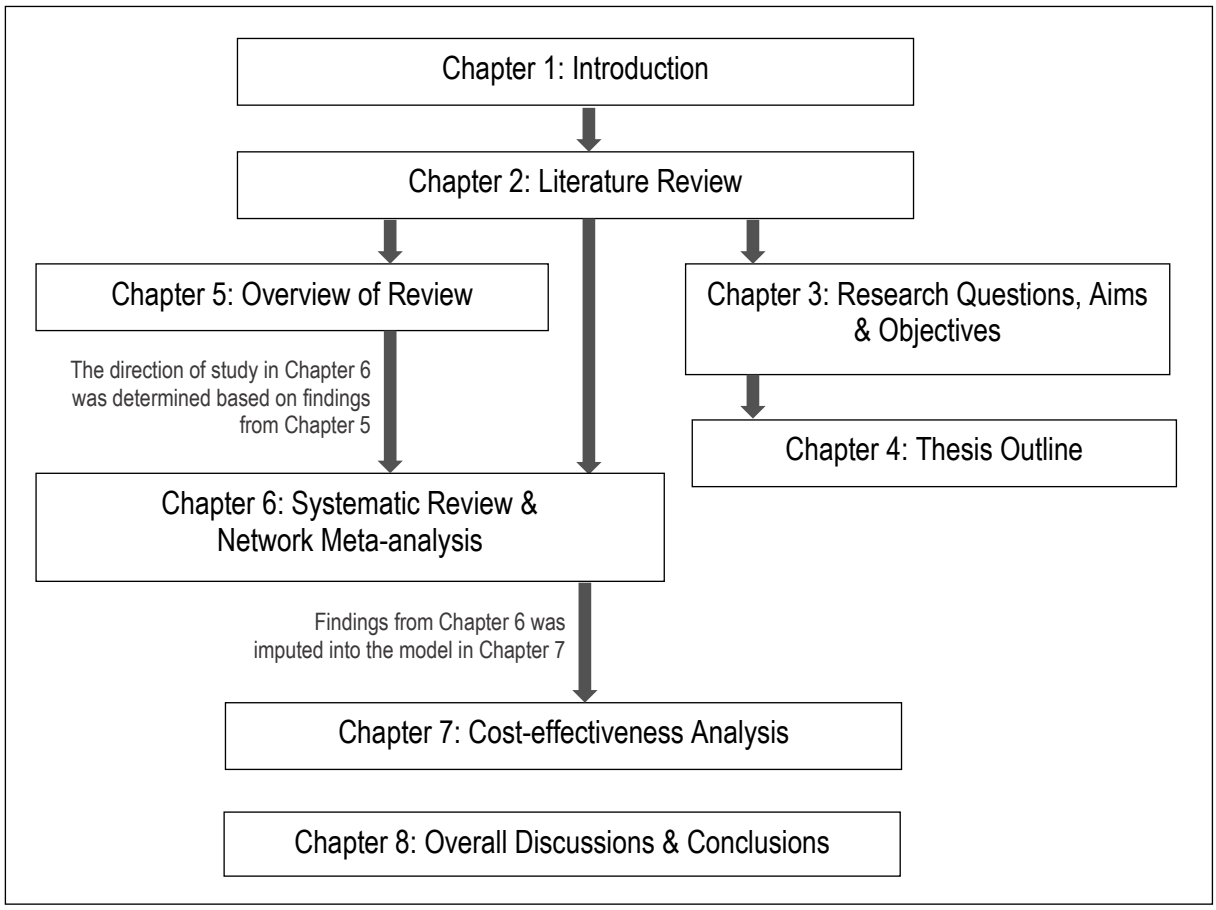

Figure 4.1.1. Graphical illustration of thesis structure

4.2. Overview of materials and methods used in the three studies

Table 4.2.1. Overview of materials and methods used in the three included studies in this thesis

	Study 1 (Chapter 5)	**Study 2 (Chapter 6)**	**Study 3 (Chapter 7)**
Title	Interventions and strategies to improve oral anticoagulant use in patients with atrial fibrillation: a systematic review of systematic review	Comparative efficacy and safety of warfarin care bundles and novel oral anticoagulants in patients with atrial fibrillation: a systematic review and network meta-analysis	Cost-effectiveness of warfarin care bundles and novel oral anticoagulants in patients with atrial fibrillation in Thailand
Study Design	Overview of Review	Systematic Review & Network Meta-analysis	Cost-effectiveness Modelling
Overall Study Aim	To summarize and compare published systematic reviews and/or meta-analyses on anticoagulant interventions available for SPAF	To meta-analyse the efficacy and safety evidence of usual warfarin care, warfarin care bundles and NOACs for SPAF based on randomized controlled trials	To assess the cost-effectiveness of warfarin care bundles and NOACs compared to usual warfarin care for SPAF patients aged 65 years old and above, from the societal and healthcare perspective in a middle-income country over a lifetime horizon.
Data Source	Systematic literature search	Systematic literature search	Several sources (e.g. published literature, meta-analysis, local data)
Approach	Qualitative	Qualitative & Quantitative	Quantitative
Data Analysis/ Results	Compilation of results in a summary of evidence table	Network meta-analysis	Cost-effectiveness analysis using Markov modelling approach

CHAPTER 5: Interventions and strategies to improve oral anticoagulant use in patients with atrial fibrillation: a systematic review of systematic review

Siok Shen Ng
Nai Ming Lai
Surakit Nathisuwan
Nathorn Chaiyakunpauk

Clinical Drug Investigation. 2018; 38:579-591.

5.1. Brief Summary

This chapter reposts an overview of review (a systematic review of systematic review) published in Clinical Drug Investigation journal. Considering the large number of systematic reviews available in this anticoagulant field, a systematic search was performed in PubMed, EMBASE and Cochrane library from inception to Feb 24$^{th,\ 2017}$, to identify systematic reviews and/or meta-analyses of randomized controlled trials that assessed interventions or strategies to improve oral anticoagulant use in AF patients. Overall, there was insufficient evidence to support the efficacy of genotype-guided dosing and pharmacist-managed anticoagulation clinics for stroke prevention in AF patients. Conversely, patient's self-management (PSM) and NOACs, in general were superior to warfarin for preventing stroke and reducing mortality. All interventions showed comparable risk of major bleeding with warfarin.

Findings from this overview of review showed the superiority of NOACs and patient's self-management for preventing stroke in AF patients. However, uncertainties remain on the benefits of genotype-guided dosing and pharmacist-managed anticoagulation clinics due to the poor quality of evidence, and as such, future research on these interventions is warranted.

5.2. Introduction

Atrial fibrillation (AF) is associated with a five-fold increased risk of stroke[1] which leads to substantial morbidity and mortality.[2] Therefore, anticoagulation therapy is the standard care for stroke prevention in patients with AF. Vitamin K antagonists (VKAs), most commonly warfarin, have been the mainstay of oral anticoagulant therapy. However, the recent availability of novel oral anticoagulants (NOACs) has shifted the paradigm of anticoagulation care for stroke prevention in AF patients. NOACs are categorized in two drug classes: oral direct thrombin inhibitors (e.g. dabigatran) and oral Factor Xa inhibitors (e.g. rivaroxaban, apixaban, edoxaban).

Concurrently, various strategies that aim to improve the existing anticoagulation care or to optimize warfarin use are also implemented such as patient's self-monitoring, genotype-guided warfarin dosing and establishment of pharmacist-managed anticoagulation clinics. As more interventions and strategies to improve the use of oral anticoagulants were made available, numerous systematic reviews and meta-analyses comparing the efficacy and safety of these strategies have emerged. However, there has been a lack of an overview summarizing the evidence on these strategies from previously published systematic reviews. Hence, we aim to summarize the evidence across existing systematic reviews and meta-analyses, to provide an overview on interventions and strategies available to improve oral anticoagulant use in AF patients.

5.3. Materials and Methods

Search Strategy

We searched PubMed, Embase and the Cochrane library from inception to Feb 24th, 2017 and restricted search to English language only due to the overwhelming number of systematic reviews published in English language. Search strategy was performed using keywords "atrial fibrillation",

"stroke", "anticoagulants", "systematic review" and "metaanalysis" (See S-5-1 for full search strategy).

Eligibility Criteria

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for reporting systematic reviews and meta-analyses of randomized controlled trials (RCTs) was used in this analysis.[3] We included systematic reviews with meta-analyses of RCTs that compared interventions or anticoagulation strategies in adult patients with AF, whether administered alone or in combination with adjunctive antithrombotic therapy, against other intervention, a placebo, or no treatment. Systematic reviews on other patients in addition to AF patients (e.g. adults with venous thromboembolism [VTE] or adults with previous stroke) were also included, but we highlighted when data were reported from a mixed population. We only considered the four NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) that are currently licensed in the market and excluded reviews with ximelagatran which had been withdrawn from market[4] and darexaban which was no longer in development.[5] Details of the included interventions were described in S-5-2. Systematic reviews that examined patients with renal or liver impairment, pregnant women or patients undergoing percutaneous catheter ablation or cardio-diversion were excluded. We also excluded systematic reviews with indirect network meta-analyses as their actual value and methodological quality are still unclear.[6]

From these eligible systematic reviews, we then identified unique meta-analyses that addressed specific questions based on PICO criteria: (i) population; (ii) intervention; (iii) comparator and (4) outcomes of interest. When more than one meta-analysis addressed a similar question, or had overlapping primary studies, meta-analysis with the largest number of component studies was

selected. Additionally, if two meta-analyses with overlapping primary studies but reported different outcomes, both meta-analyses were included.

Data Extraction and Synthesis

Two reviewers (SSN and NML) independently screened the title and abstract of retrieved citations to identify potentially relevant papers. In the case of discrepancies, these were resolved by consensus with a third reviewer (NC). The full articles were evaluated if a decision could not be made based on the title and abstract. Relevant data were abstracted by the same two reviewers (SSN and NML) using a standardized data extraction form. Data extraction were performed in two stages: (i) systematic review and (ii) meta-analysis level.

In the first stage, data extracted from eligible systematic reviews included the total number of primary studies, population, interventions, and outcomes reported. The 'Risk of Bias in the Systematic Review' (ROBIS) assessment tool[7] was used to assess the methodological quality of the eligible systematic reviews. In the second stage, additional data extracted from each unique meta-analysis included the relative risk estimates (risk ratio, odds ratio, and hazard ratio), along with the corresponding 95% confidence interval, number of patients in each analysis, follow-up period and heterogeneity (I^2 value).

The primary efficacy endpoint was composite of stroke and systemic embolism. The secondary efficacy endpoint was all-cause mortality. The safety endpoint was major bleeding defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria as fatal bleeding or bleeding in critical sites or bleeding with a fall in haemoglobin levels of at least 2g/dL or bleeding leading to transfusion of two or more units of whole blood or red cells.[8] As this is a descriptive

overview of systematic reviews and meta-analyses, no additional statistical analyses were performed. Results were tabulated and summarized narratively.

5.4. Results

Study Selection

We identified 359 records, in which 79 potentially eligible reviews were assessed in full text. Of these, 45 reviews were excluded as most of them were either indirect network meta-analyses (n=18), narrative reviews (n=3), letter to editors (n=2), systematic reviews without meta-analyses (n=3), systematic reviews without inclusion of pre-specified outcomes of interest (n=6), systematic reviews of non-relevant population (n=5), full-text articles not available (n=5) and duplicates (n=3), leaving 34 systematic reviews eligible for inclusion in our overview (see S-5-3, S-5-4, S-5-5 for full details on the 34 reviews). However, only eleven systematic reviews[9-19] were included in our qualitative analysis, corresponding to 40 unique meta-analyses as 23 of the 34 eligible systematic reviews addressed similar PICO questions and had overlapping primary studies. The process of electronic searching is presented in the PRISMA flow diagram in Figure 5.4.1.

Characteristics of the Included Reviews

Table 5.4.1 summarized characteristics of the included eleven systematic reviews, published between 2012 and 2016. Seven systematic reviews[10-12, 14-17] focused on the evaluation of NOACs and the remaining systematic reviews evaluated other anticoagulation strategies: genotype-guided warfarin dosing (n=1)[9], pharmacist-managed anticoagulation clinics (n=1)[19], patient's self-monitoring (n=1)[13] and combination of anticoagulation clinics and self-monitoring (n=1)[18]. Six systematic reviews[10-12, 15-17] examined patients with AF and one of them[17] focused specifically on elderly patients aged 75 years and older. The remaining five systematic reviews reported data from a mixed population, one of which[14] included patients with both AF and previous stroke or transient ischemia attack (TIA) and

the remaining systematic reviews[9, 13, 18, 19] evaluated patients with a range of conditions for whom anticoagulation was indicated (e.g. VTE, AF or valvular heart disease) (n=4). Stroke or systemic embolism and major bleeding were reported in ten systematic reviews[9, 11-19] while all-cause mortality outcome was reported in nine systematic reviews[9-14, 18-20].

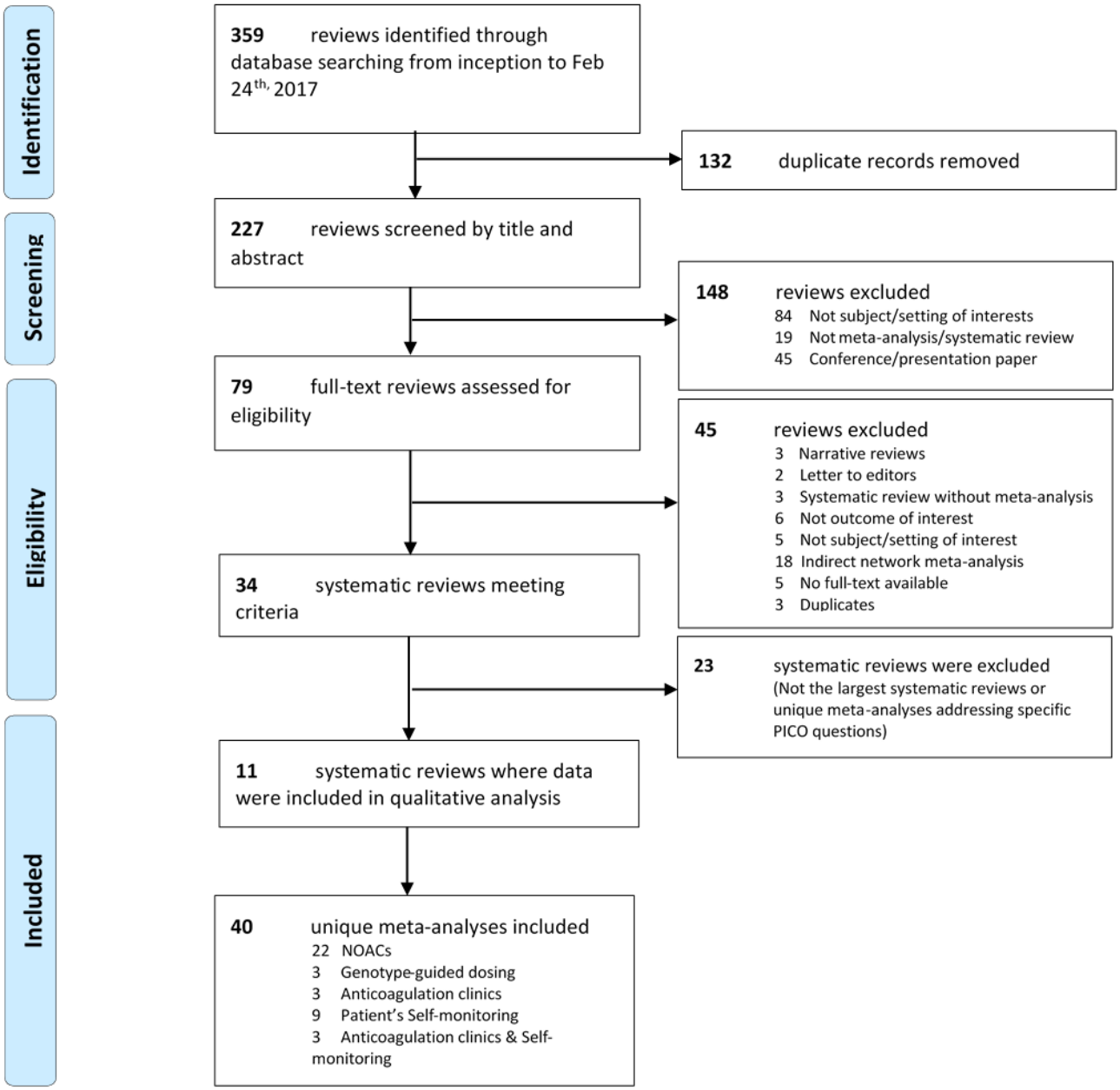

Figure 5.4.1. Flow diagram of selection process of unique meta-analyses on interventions for stroke preventions

Table 5.4.1. Characteristics of the included eleven reviews

First author	Year	No of RCTs	Population	Intervention	Comparator	ROB Assessment of RCTs	ROB of reviews (ROBIS)
Dentali F[11]	2012	12	AF patients	NOACs*	VKAs	JADAD score Allocation treatment concealment	Low
Ruff CT[16]	2014	5	AF patients	NOACs* (High dose & Low dose)	VKAs	Tools used were not specified	Low
Sadlon AH[17]	2016	8	AF Patients aged ≥75 years old	NOACs* (High dose & Low dose)	VKAs or consecutive regimen of LMWH with VKAs	Cochrane ROB	Low
Katsanos AH[14]	2016	4	AF Patients with previous stroke/TIA	NOACs**	VKAs	Cochrane ROB	Low
Garg J[12]	2016	11	AF patients	Factor Xa inhibitors	VKAs	None	High
Bloom BJ[10]	2014	2	AF patients	Direct thrombin inhibitors	VKAs	Cochrane ROB	High
Morilla MA[15]	2012	2	AF patients	Direct thrombin inhibitors	VKAs	Developed their own tool	High
Belley-Cote EP[9]	2015	12	Patients indicated for anticoagulants	Genotype-guided warfarin dosing	Standard VKA dosing algorithms	Modified Cochrane ROB	Low
Zhou S [19]	2016	8	Patients indicated for anticoagulants	Pharmacist-managed AC	Usual care	Cochrane ROB	High
Heneghan CL [13]	2016	28	Patients indicated for anticoagulants	Patient's self-monitoring (PSM + PST) PST alone PSM alone	Usual Care	Cochrane ROB	Low
Wells PS [18]	2013	16	Patients indicated for anticoagulants	AC PST	Usual Care	JADAD score Schulz Criteria	Low

NOACS: dabigatran, rivaroxaban, apixaban & edoxaban; NOACS**: dabigatran, rivaroxaban, apixaban Abbreviations: AC, anticoagulation clinics; AF, atrial fibrillation; PST, patient's self-testing of warfarin; PSM, patient's self-management of warfarin; RCTs, randomized controlled trials; ROB, risk of bias; TIA, transient ischemic attack; VKAs, vitamin K antagonists*

Quality Assessment of the Included Reviews

Figure 5.4.2 and Table 5.4.2 summarized the methodological quality of each review, based on ROBIS tool. Seven systematic reviews[9, 11, 13, 14, 16-18] were considered to have low risk of bias and the remaining four systematic reviews were considered to have high risk of bias[10, 12, 15, 19]. Most of the systematic reviews were generally rated as having low risk of bias across ROBIS domains except for domain 2 on the identification and selection of studies, as six (54.5%)[10, 12, 15-17, 19] of them were rated as high risk of bias. Three systematic reviews[12, 15, 19] performed only major database searches without including additional searches such as citation searches, contacting experts, reference checking or hand-searching, one[16] searched in a single database only while the other two systematic reviews[10, 19] restricted search to English language only.

The quality of primary studies was assessed in all except one systematic review[12]. Six systematic reviews[9, 10, 13, 14, 17, 19] used the Cochrane Collaboration Risk of Bias tool and in one systematic review[15], the authors developed their own ad-hoc tool which was not previously validated. One systematic review[16] did not specify the tool used for quality assessment and the remaining two systematic reviews[11, 18] used other existing instruments such as JADAD scoring or Schulz criteria, either in their original formats or with modifications.

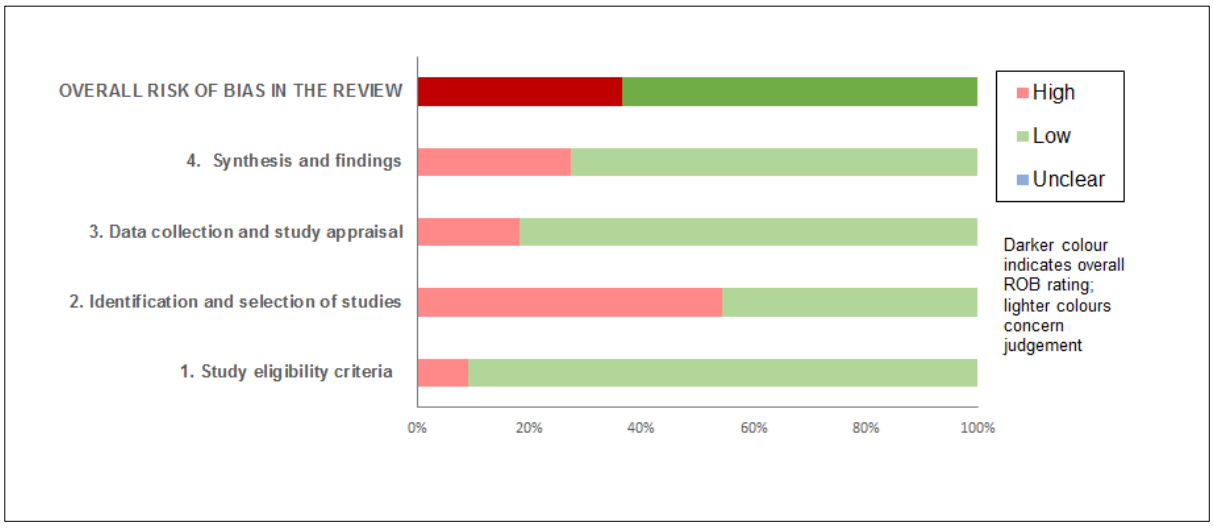

Figure 5.4.2. Graphical Representation for ROBIS Evaluations of 11 Systematic Reviews

Table 5.4.2. Summary Results from ROBIS Evaluation of the Eleven Systematic Reviews

	Phase 2*				Phase 3**
	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	**Risk of Bias in The Review**
Belley-Cote EP, 2015 [9]	Low	Low	Low	Low	Low
Bloom BJ, 2014 [10]	High	High	Low	Low	High
Dentali F, 2012 [11]	Low	Low	Low	Low	Low
Garg J, 2016 [12]	Low	High	High	High	High
Ruff CF, 2014 [16]	Low	High	High	Low	Low
Heneghan CJ, 2016 [13]	Low	Low	Low	Low	Low
Katsanos AH, 2016 [14]	Low	Low	Low	Low	Low
Morilla MA, 2012 [15]	Low	High	Low	High	High
Sadlon AH 2016 [17]	Low	High	Low	Low	Low
Wells PS, 2007 [18]	Low	Low	Low	Low	Low
Zhou S, 2016 [19]	Low	High	Low	High	High

**Phase 2: identifying concerns or areas where bias may be introduced in the review; **Phase 3: overall judgement risk of bias*

Characteristics of the Unique Meta-analyses

The eleven systematic reviews[9-19] comprised of forty unique meta-analyses of RCTs on interventions and strategies to improve oral anticoagulant use. Table 5.4.3 summarized the characteristics of included meta-analyses, stratified based on interventions. The median follow-up period was between 3 months to 2.8 years. 22 meta-analyses examined NOACs, nine meta-analyses on patient's self-monitoring and three meta-analyses each on genotype-guided warfarin dosing, pharmacist-managed anticoagulation clinics, and combination of anticoagulation clinics with self-monitoring intervention. These meta-analyses reported three different outcomes: stroke or systemic embolism (n=14), all-cause mortality (n=12) and major bleeding (n=14). The median number of studies included was seven (range 4-11) and the median number of patients was 15,671 (range 3,980-26,107). Five (12.5%) meta-analyses had moderate-to-substantial heterogeneity (I^2>50%) and five (12.5%) had substantial heterogeneity (I^2>75%). Substantial heterogeneity was observed mostly in meta-analyses reporting major bleeding outcome. Overall, 19 (47.5%) of the 40 meta-analyses of RCTs reported a statistically significant summary result.

Table 5.4.3. Characteristics and Summary Effects of 40 Unique Meta-analyses, stratified according to interventions

First Author, Year	Outcome	Population	Intervention	Comparator	No of RCTs	No of patients	Follow-up period	Summary Effect Size (95% CI)	I^2
NOVEL ORAL ANTICOAGLANTS (NOACs)									
Dentali F, 2012 [11]	Stroke & SE	AF patients	NOACs*	VKAs	12	54143	1.8 – 2.8 yrs	RR[i]: 0.77 (0.70-0.86)	0%
Ruff CT, 2014 [16]	Stroke & SE	AF patients	NOACs* (High-Dose)	VKAs	4	58541	1.8 – 2.8 yrs	RR: 0.81 0.73-0.91)	47%
Ruff CT, 2014 [16]	Stroke & SE	AF patients	NOACs* (Low-Dose)	VKAs	2	26107	1.8 – 2.8 yrs	RR: 1.03 (0.84-1.27)	70%
Sadlon AH, 2016 [17]	Stroke & SE	AF Patients aged ≥75 years	NOACs* (High-Dose)	VKAs or a consecutive regimen of LMWH[g] with VKAs	4	22381	3 mo – 2.8 yrs	OR[j]: 0.71 (0.62-0.82)	0%
Sadlon AH, 2016 [17]	Stroke & SE	AF Patients aged ≥75 years	NOACs* (Low-Dose)	VKAs or a consecutive regimen of LMWH[g] with VKAs	4	22215	3 mo – 2.8 yrs	OR: 0.84 (0.73-0.96)	0%
Katsanos AH, 2016 [14]	Stroke & SE	AF Patients with previous stroke/TIA	NOACs**	VKAs	4	16497	1.8 – 2.5 yrs	RR: 0.85 (0.74-0.97)	0%
Garg J, 2016 [12]	Stroke & SE	AF patients	Factor Xa inhibitors[d]	VKAs	8	57108	3 mo – 2.8 yrs	OR: 0.82 (0.68-0.99)	47%
Morilla MA, 2012 [15]	Stroke & SE	AF patients	Direct thrombin inhibitors[e]	VKAs	2	12268	3 mo	OR: 0.77 (0.62-0.99)	NA[k]
Dentali F, 2012 [11]	All-cause mortality	AF patients	NOACs*	VKAs	12	54115	28 days – 2 yrs	RR: 0.89 (0.83-0.96)	0%
Ruff CT, 2014 [16]	All-cause mortality	AF patients	NOACs* (High-Dose)	VKAs	4	58513	1.8 – 2.8 yrs	RR: 0.90 (0.85-0.95)	0%
Ruff CT, 2014 [16]	All-cause mortality	AF patients	NOACs* (Low-Dose)	VKAs	2	26107	1.8 – 2.8 yrs	RR: 0.89 (0.83-0.96)	0%
Katsanos AH, 2016 [14]	All-cause mortality	AF Patients with previous stroke/TIA	NOACs**	VKAs	4	15685	1.8 – 2.5 yrs	RR: 0.91 (0.80-1.02)	0%
Garg J, 2016 [12]	All-cause mortality	AF patients	Factor Xa inhibitors	VKAs	11	59164	3 mo – 2.8 yrs	OR: 0.88 (0.83-0.94)	0%
Bloom BJ, 2014 [10]	All-cause mortality	AF patients	Direct thrombin inhibitors	VKAs	1	12098	3 mo – 2.8 yrs	RR: 0.89 (0.79-1.01)	0%
Dentali F, 2012 [11]	Major bleeding	AF patients	NOACs*	VKAs	12	54147	28 days – 2 yrs	RR: 0.86 (0.72-1.02)	57%
Ruff CT, 2014 [16]	Major bleeding	AF patients	NOACs* (High-Dose)	VKAs	4	58498	1.8 – 2.8 yrs	RR: 0.86 (0.73-1.00)	85%
Ruff CT, 2014 [16]	Major bleeding	AF patients	NOACs* (Low-Dose)	VKAs	2	26051	1.8 – 2.8 yrs	RR: 0.65 (0.43-1.00)	95%
Sadlon AH, 2016 [17]	Major bleeding	AF Patients aged ≥75 years	NOACs* (High-Dose)	VKA or a consecutive regimen of	4	20921	3 mo – 2.8 yrs	OR: 0.98 (0.90-1.06)	89%

First Author, Year	Outcome	Population	Intervention	Comparator	No of RCTs	No of patients	Follow-up period	Summary Effect Size (95% CI)	I^2
				LMWH with VKA					
Sadlon AH, 2016 [17]	Major bleeding	AF Patients aged ≥75 years	NOACs* (Low-Dose)	VKA or a consecutive regimen of LMWH with VKA	4	20753	3 mo – 2.8 yrs	OR: 0.88 (0.80-0.96)	94.9 %
Katsanos AH, 2016 [14]	Major bleeding	AF Patients with previous stroke/TIA	NOACs**	VKAs	4	15671	1.8 - 2.5 yrs	RR: 0.85 (0.71-1.03)	52%
Garg J, 2016 [12]	Major bleeding	AF patients	Factor Xa inhibitors	VKAs	6	56438	3 mo – 2.8 yrs	OR: 0.74 (0-58-0.96)	74%
Bloom BJ, 2014 [10]	Major bleeding	AF patients	Direct thrombin inhibitors	VKAs	2	12334	3 mo – 2 yrs	RR: 0.94 (0.82-1.07)	0%
GENOTYPE-GUIDED WARFARIN DOSING									
Belley-Cote EP, 2015 [9]	Stroke & SE	Patients indicated for anticoagula-nt	Genotype-guided warfarin dosing	Standard VKA dosing algorithms	7	2261	28 days – 6 mo	RR: 0.74 (0.37-1.49)	0%
Belley-Cote EP, 2015 [9]	All-cause mortality	Patients indicated for anticoagula-nt	Genotype-guided warfarin dosing	Standard VKA dosing algorithms	8	2449	28 days – 6 mo	RR: 1.12 (0.46-2.74)	0%
Belley-Cote EP, 2015 [9]	Major bleeding	Patients indicated for anticoagula-nt	Genotype-guided warfarin dosing	Standard VKA dosing algorithms	9	2567	28 days – 6 mo	RR: 0.71 (0.38-1.29)	0%
PHARMACIST-MANAGED AC									
Zhou S, 2016 [19]	Stroke & SE	Patients indicated for anticoagula-nt	Pharmacist-managed AC	Usual care	7	1406	3 mo – 2 yrs	OR: 0.81 (0.34-1.92)	0%
Zhou S, 2016 [19]	All-cause mortality	Patients indicated for anticoagula-nt	Pharmacist-managed AC	Usual care	4	709	3 mo – 2 yrs	OR: 0.97 (0.44-2.11)	0%
Zhou S, 2016 [19]	Major bleeding	Patients indicated for anticoagula-nt	Pharmacist-managed AC	Usual care	6	1302	3 mo – 2 yrs	OR: 0.90 (0.37-2.19)	0%
PATIENT'S SELF-MONITORING									
Heneghan CL, 2016 [13]	Stroke & SE	Patients indicated for anticoagula-nt	Patient's self-monitoring (PST & PSM)	Usual care	18	7594	3 mo – 4.8 yrs	RR 0.58 (0.45-0.75)	53%
Heneghan CL, 2016 [13]	Stroke & SE	Patients indicated for anticoagula-nt	PST	Usual care	7	4097	3 mo – 4.8 yrs	RR: 0.69 (0.49-0.97)	0%

First Author, Year	Outcome	Population	Intervention	Comparator	No of RCTs	No of patients	Follow-up period	Summary Effect Size (95% CI)	I^2
Heneghan CL, 2016 [13]	Stroke & SE	Patients indicated for anticoagulant	PSM	Usual care	11	3497	3 mo – 4.8 yrs	RR: 0.47 (0.31-0.70)	0%
Heneghan CL, 2016 [13] [13]	All-cause mortality	Patients indicated for anticoagulant	Patient's self-monitoring (PST & PSM)	Usual care	11	6358	3 mo – 4.8 yrs	RR: 0.85 (0.71-1.01)	80%
Heneghan CL, 2016 [13]	All-cause mortality	Patients indicated for anticoagulant	PST	Usual care	3	3300	3 mo – 4.8 yrs	RR: 0.94 (0.78-1.15)	0%
Heneghan CL, 2016 [13]	All-cause mortality	Patients indicated for anticoagulant	PS,	Usual care	8	3058	3 mo – 4.8 yrs	RR: 0.55 (0.36-0.84)	0%
Heneghan CL, 2016 [13]	Major bleeding	Patients indicated for anticoagulant	Patient's self-monitoring (PST & PSM)	Usual care	20	8018	3 mo – 4.8 yrs	RR: 0.95 (0.80-1.12)	0%
Heneghan CL, 2016 [13]	Major bleeding	Patients indicated for anticoagulant	PST	Usual care	7	4038	3 mo – 4.8 yrs	RR: 0.90 (0.74-1.09)	29%
Heneghan CL, 2016 [13]	Major bleeding	Patients indicated for anticoagulant	PS,	Usual care	13	3980	3 mo – 4.8 yrs	RR: 1.08 (0.79-1.47)	0%
AC CLINICS & SELF-MONITORING									
Wells PS, 2013 [18]	Stroke & SE	Patients indicated for anticoagulant	AC & self-monitoring	Usual care	16	NA	3 mo – 4.2 yrs	OR: 0.51 (0.35-0.74)	0%
Wells PS, 2013 [18]	All-cause mortality	Patients indicated for anticoagulant	AC & self-monitoring	Usual care	16	NA	3 mo – 4.2 yrs	OR: 0.58 0.38-0.89)	0%
Wells PS, 2013 [18]	Major bleeding	Patients indicated for anticoagulant	AC & self-monitoring	Usual care	16	NA	3 mo – 4.2 yrs	OR: 0.78 (0.53-1.14)	0%

NOACs: dabigatran, rivaroxaban, apixaban, edoxaban; NOACs**: dabigatran, rivaroxaban, apixaban Abbreviations: AC, anticoagulation clinics; AF, atrial fibrillation; CI, confidence interval; Factor Xa inhibitors, rivarxoaban, apixaban and edoxaban; Direct thrombin inhibitors, dabigatran; LMWH, low molecular weight heparin; mo, months; NA, not available; RCTs, randomized controlled trials; PSM, patient's self-management of warfarin; PST, patient's self-testing of warfarin; RR, risk ratios; OR, odds ratios; SE, systemic embolism; TIA, transient ischemimc attack; yrs, years.*

Effects of Interventions

Novel Oral Anticoagulants (NOACs)

Overall, NOACs were superior to warfarin with respect to the prevention of stroke or systemic embolism (23% risk reduction) and all-cause mortality events (11% risk reduction) (meta-analysis[11] of12 RCTs). However, no significant differences in the risk of major bleeding between NOACs and warfarin were demonstrated in the meta-analysis[11] of 12 RCTs. In AF patients with previous stroke or TIA, NOACs still retained its superiority to warfarin in preventing stroke or emboli events but no significant differences were reported for all-cause mortality and major bleeding outcomes[14].

When NOACs were analysed separately based on dosing regimen, the high-dose regimen was found to be superior to warfarin with respect to stroke or systemic embolism (19% risk reduction) and all-cause mortality (10% risk reduction) events[16]. Similar superiority of the high-dose NOACs to warfarin were also observed in elderly patients aged 75 years and older (meta-analysis[17] of 4 RCTs, 22,381 patients). The meta-analyses of low-dose NOACs[16] showed a similar 11% reduction in mortality but were no longer superior (non-inferiority) to warfarin for the prevention of stroke or systemic embolism For safety outcome, both high-dose and low-dose regimen demonstrated a non-significant 14% and 35% reduction in the risk of major bleeding, compared to warfarin[16]. Additionally, in elderly patients aged 75 years and older, the analysis of low-dose regimen (meta-analysis[17] of 4 RCTs, 20,753 patients) consistently showed a lower risk of major bleeding than warfarin too.

When NOACs were stratified according to mode of actions, both Factor Xa inhibitors and direct thrombin inhibitors showed significant reduction in stroke or emboli events (meta-analysis[12] of 8 RCTs, 57,108 patients and meta-analysis[15] of 2 RCTs, 12,268 patients). However, only Factor Xa inhibitors showed a significant reduction for all-cause mortality (meta-analysis[12] of 11 RCTs, 59,164 patients) and major bleeding outcome (meta-analysis[12] of 6 RCTs (56,438 patients) while direct

thrombin inhibitors showed no clear differences for both outcomes, compared to warfarin (meta-analysis[10] of 2 RCTs).

Genotype-guided Warfarin Dosing

Three meta-analyses showed no significant differences between genotype-guided warfarin dosing and conventional warfarin dosing, for stroke or systemic embolism (meta-analysis[9] of 7 RCTs, 2,261 patients), all-cause mortality (meta-analysis[9] of 8 RCTs, 2,449 patients) and major bleeding outcomes (meta-analysis of 9 RCTs, 2,567 patients).

Pharmacists-managed Anticoagulation Clinics

Three meta-analyses reported no significant differences between pharmacist-managed anticoagulation clinics and usual warfarin care, for stroke or systemic embolism (meta-analysis[19] of 7 RCTs, 1,406 patients), all-cause mortality (meta-analysis[19] of four RCTs, 709 patients) and major bleeding events (meta-analysis[19] of 11 RCTs, 3,497 patients).

Patient's Self-monitoring

Nine unique meta-analyses evaluated patient's self-monitoring. When self-monitoring was compared to usual warfarin care, it significantly reduced stroke or emboli events (42% risk reduction) (meta-analysis[13] of 18 RCTs, 7,594 patients). However, no significant differences were reported for all-cause mortality and major bleeding outcomes between patient's self-monitoring and usual warfarin care, as shown in both meta-analyses[13] of 11 RCTs (6,358 patients) and 20 RCTs (8,018 patients) respectively.

When patient's self-monitoring is stratified into self-management or self-testing approach, both approaches reported significant reduction for stroke when compared to usual warfarin care, based on

the meta-analyses[13] of 7 RCTs (4,097 patients) for self-testing approach and 11 RCTs (3,497 patients) for self-management approach. However, conflicting results were reported for all-cause mortality outcome. The self-management approach was superior to warfarin (45% risk reduction) in reducing mortality (meta-analysis[13] of 8 RCTs, 3,058 patients) while self-monitoring approach was non-inferior to warfarin instead (meta-analysis[13] of 3 RCTS, 3,300 patients). Both strategies demonstrated no clear differences in major bleeding outcome compared to usual warfarin care, as reported in the meta-analyses[13] of 7 RCTs (4,038 patients) for self-testing and 13 RCTs (3,980 patients) for self-management approach.

Combination of Anticoagulation Clinics and Patient's Self-monitoring

Three unique meta-analyses evaluated the clinical outcomes of anticoagulation monitoring by point-of care devices (POCD), including POCD testing at anticoagulation clinics and POCD self-testing by patients. Compared to usual warfarin care, this POC testing strategy led to a significant reduction of stroke and all-cause mortality events without significant differences in the risk of major bleeding.[18]

Time in Therapeutic Range

Since the efficacy and safety of warfarin depends upon the quality of anticoagulation control as expressed by percentage of time in therapeutic range (TTR), TTR may influence the rates of patient outcomes. Among available interventions, patient's self-management was associated with the highest TTR while genotype-guided warfarin dosing had the lowest TTR (Table 5.4.4). For NOACs studies, mean TTR for patients using warfarin ranged from 55 to 64.9%.

Table 5.4.4: Percentage of Time in Therapeutic Range of Different Interventions

Interventions	**Mean TTR**	**Median TTR**	**References**
Anticoagulation control in NOACs studies	55-64.9%	58-68%	[16, 21-24]
Genotype-guided warfarin dosing	57.4%	58.9%	[9]
Pharmacists-managed anticoagulation clinics	73.5%	75.4%	[19]
Patient's self-monitoring *(Combination PST + PSM)*	67.7%	70%	[13]
PST	60.2%	61%	[13]
PSM	75.1%	74.7%	[13]
AC + self-monitoring	73%	NA	[18]

Abbreviations: AC, anticoagulation clinics; NOACs, novel oral anticoagulants; NA, not available; PST, patient's self-testing of warfarin; PSM, patient's self-management of warfarin; TTR, time in therapeutic range;

5.6. Discussion

This overview shows that NOACs were superior to warfarin in preventing stroke or emboli events. NOACs also displayed a clinically relevant reduction in all-cause mortality events with favourable safety profile in terms of major bleeding, compared to warfarin. However, the mortality reduction by NOACs were not evident for secondary stroke prevention, which might relate to the fact that this group of patients with previous stroke are often associated with poorer prognosis.[25, 26]

The separate meta-analyses of high-dose (dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, edoxaban 60 mg once daily) and low-dose NOACs (dabigatran 110 mg twice daily, edoxaban 30 mg once daily) demonstrated that the high-dose regimen has better performance than the low-dose regimen in preventing stroke or emboli events. However, the low-dose regimen has a safer profile than warfarin while retaining the mortality benefits observed with high-dose regimen. Therefore, the low-dose regimen might be a reasonable alternative in elderly patients or in those with high risk of bleeding at full-dose anticoagulation.

Both Dentali et al.[11] and Ruff et al.[16] systematic reviews were conducted in general AF patients but comprised of different number of primary studies (12 vs 4 RCTs respectively). Dentali et al review[11]

included both Phase II and Phase III RCTs while Ruff et al. review[16] included Phase III RCTs only. However, both systematic reviews reported yet similar treatment effect estimates despite different number and type of studies included. Such findings are attributed by the well-conducted Phase II trials of NOACs which incorporated control arm, randomization, and blinding. Hence, the inclusion of these Phase II trials in meta-analyses would not have deviated the results regardless of small patient numbers or events.

When NOACs were analysed based on their mode of actions, direct thrombin inhibitors were not beneficial in reducing mortality, based on the limited evidence from two RCTs only. For safety outcome, Factor Xa inhibitors significantly reduced the risk of major bleeding compared to warfarin but this significant effect should be interpreted cautiously due to the presence of substantial heterogeneity. The presence of large heterogeneity for major bleeding outcome does not provide conclusive evidence for a possible class-effect of direct thrombin inhibitors or Factor Xa inhibitors. In fact, this heterogeneity could be explained by the results of individual trials which were not reproduced by other NOACs of the same class.[27] For example, the two largest trials (ROCKET AF[24] and ARISTITOLE[23]) included in the meta-analysis of Factor Xa inhibitors alone, enrolled study population with different baseline in the risk of bleeding. As such, the choice of NOAC for stroke prevention in AF patients should be individualized based on advantages and disadvantages of individual drugs, rather than its pharmacologic class.

Despite advances in personalized medicines using genotype-guided dosing algorithm, there is a lack of evidence to support the benefits of this strategy for stroke prevention in AF patients. This may partly be explained by the fact that genotype-guided dosing is generally helpful during the initiation therapy only.[28] As a result, such strategy may have a limited impact in improving overall TTR and on clinical outcomes such as stroke, death or major bleeding which reflect long-term control.

Similarly, the clinical benefits of pharmacist-managed anticoagulation clinics are also unclear despite significant improvement on TTR. Reasons for these discrepancies may lie with small sample sizes, relatively short follow-up period, along with low event rates of individual RCTs.

The summarized evidence suggests that patient's self-monitoring appears to reduce the rates of stroke, without increasing the overall risk of major bleeding. When this intervention was further stratified into self-testing or self-management approach, self-management was superior to self-testing alone in reducing the rates of thromboembolism and all-cause mortality. The superiority of self-management is reflected by the higher TTR level achieved (>70%) due to ease in obtaining INR results which allows more frequent INR testing and dose adjustment. Additionally, patients who self-managed their coagulation status may be more motivated in managing their own therapy due to self-empowerment which subsequently improve their adherence and compliance to treatment.[13, 29]

As the efficacy of warfarin depends upon the ability to control international normalized ratio (INR) within therapeutic range, TTR can be utilized as surrogate marker to assess the quality of anticoagulation control. A TTR above 65% is recommended[30] as lower TTR values are associated with increased mortality, bleeding, and thromboembolism risks.[31] In this overview, genotype-guided warfarin dosing has the least improvement on TTR levels as majority RCTs compared genotype-guided dosing with clinically established dosing regimen, instead of the standard care which may underestimate the true benefits of this intervention.[32] Besides, the quality of anticoagulation control is also a major factor in potentially switching from warfarin to NOACs. RCTs of NOACs demonstrated non-inferiority to warfarin at and below the following TTR level: 64% for both dabigatran in RE-LY trial[21] and edoxaban in ENGAGE-TIMI 48 trial[22], 55% for rivaroxaban in Rocket-AF trial[24] and 62% for apixaban in ARISTOTLE trial[23]. There is no evidence to support the non-inferiority of NOACs over well-controlled warfarin therapy at a mean TTR greater than 64%.

Therefore, if strategies that aim to improve anticoagulation control can achieve TTR greater than 70%, it does not necessitate the switch to NOACs as comparable benefits can be achieved at a lower cost. By retaining the use of warfarin, physicians can easily monitor the degree of anticoagulation and compliance based on INR results and affordably reverse warfarin in the event of bleeding.[33]

Previous overview conducted by Raschi et al.[34], focused on the risk and benefit profile of NOACs only. In comparison, our overview summarizes the evidence on all interventions available to improve oral anticoagulant use instead of focusing on NOACs alone. Moreover, our overview adopted the ROBIS tool[7] for quality assessment of the included systematic reviews. The ROBIS tool addresses limitations observed in AMSTAR tool, a tool that has been widely used to-date, as the AMSTAR tool lacks the items to assess subgroup or sensitivity analyses. Additionally, the pooled estimate effects of each intervention for each outcome were also extracted in our overview and therefore, readers can easily quantify the direction and magnitude of these effects.

We acknowledge the following limitations in this overview. Firstly, our searching was restricted to English-language publications only which may result in relevant systematic reviews not included in our overview. Besides, our overview also relied on the findings of previously published systematic reviews only without retrieving information from primary studies. Therefore, missing studies were inevitable, and findings of this overview were restricted by the information reported in the previous systematic reviews only.

Nonetheless, we identified several issues in the conduct and report of systematic reviews while undertaking this overview. We found many systematic reviews with overlapping primary studies that addressed similar question, whereby some systematic reviews had conflicting results and different conclusions due to different methodological approaches and lack of standardization in conducting

systematic reviews. Such conflicts produce difficulties among researchers and stakeholders in making choices among alternative interventions. Hence, we propose a formal evaluation of the proportion of duplicates and possibly discordant systematic reviews in this field, especially those that included exactly or almost the same set of primary studies addressing the same question. The protocol registration for systematic reviews (e.g. in Cochrane Database for Systematic Review, Campbell Collaboration, PROSPERO) should be encouraged to reduce duplication and publications bias. The PRISMA-P checklist could be used as a guidance for the documentation of protocol, to enhance the completeness of protocol reporting and to strengthen the methodological quality and reliability of the completed systematic reviews.[35] Moreover, future systematic reviews should also be reported by reconciling findings from previous systematic reviews. Specifically, each systematic review should provide a summary table of the included primary studies to ease future research in identifying redundancy and in updating the same research question. Such robust methodological approaches are paramount to produce higher quality of evidence without duplication and to generate a well-organized field of literature to facilitate interpretation by stakeholders and to reduce research waste.

5.7. Conclusions

This overview provides a comprehensive and up-to-date evidence on interventions and strategies available to improve oral anticoagulant use in AF patients. Both NOACs and patient's self-management were superior to warfarin for preventing stroke and systemic embolism in AF patients. However, areas of uncertainty remain especially on genotype-guided warfarin dosing and pharmacist-managed anticoagulation clinics due to poor quality evidences. Therefore, the benefits of these interventions warrant further evaluations via higher quality of RCTs with larger sample sizes.

References for Chapter 5

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22(8):983-8.
2. Lip GY. Stroke and bleeding risk assessment in atrial fibrillation: when, how, and why? European heart journal. 2013;34(14):1041-9.
3. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264-9, w64.
4. Keisu M, Andersson TB. Drug-induced liver injury in humans: the case of ximelagatran. Handbook of experimental pharmacology. 2010(196):407-18.
5. Apostolakis S, Lip GY. Novel oral anticoagulants: focus on the direct factor Xa inhibitor darexaban. Expert opinion on investigational drugs. 2012;21(7):1057-64.
6. Bafeta A, Trinquart L, Seror R, Ravaud P. Analysis of the systematic reviews process in reports of network meta-analyses: methodological systematic review. BMJ (Clinical research ed). 2013;347:f3675.
7. Whiting P, Savovic J, Higgins JP, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. Journal of clinical epidemiology. 2016;69:225-34.
8. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of thrombosis and haemostasis : JTH. 2005;3(4):692-4.
9. Belley-Cote EP, Hanif H, D'Aragon F, Eikelboom JW, Anderson JL, Borgman M, et al. Genotype-guided versus standard vitamin K antagonist dosing algorithms in patients initiating anticoagulation. A systematic review and meta-analysis. Thrombosis and haemostasis. 2015;114(4):768-77.
10. Bloom BJ, Filion KB, Atallah R, Eisenberg MJ. Meta-analysis of randomized controlled trials on the risk of bleeding with dabigatran. The American journal of cardiology. 2014;113(6):1066-74.
11. Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation. 2012;126(20):2381-91.
12. Garg J, Chaudhary R, Krishnamoorthy P, Palaniswamy C, Shah N, Bozorgnia B, et al. Safety and efficacy of oral factor-Xa inhibitors versus Vitamin K antagonist in patients with non-valvular atrial fibrillation: Meta-analysis of phase II and III randomized controlled trials. International journal of cardiology. 2016;218:235-9.
13. Heneghan CJ, Garcia-Alamino JM, Spencer EA, Ward AM, Perera R, Bankhead C, et al. Self-monitoring and self-management of oral anticoagulation. The Cochrane database of systematic reviews. 2016;7:Cd003839.
14. Katsanos AH, Mavridis D, Parissis J, Deftereos S, Frogoudaki A, Vrettou AR, et al. Novel oral anticoagulants for the secondary prevention of cerebral ischemia: a network meta-analysis. Therapeutic advances in neurological disorders. 2016;9(5):359-68.
15. Morilla MA, Tumulak CD, Gulay CB, Dioquino CP, DD M. A meta-analysis on the efficacy of dabigatran versus warfarin among patients with atrial fibrillation. Philipp J Intern Med. 2012;50(4):1-4.
16. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet (London, England). 2014;383(9921):955-62.
17. Sadlon AH, Tsakiris DA. Direct oral anticoagulants in the elderly: systematic review and meta-analysis of evidence, current and future directions. Swiss medical weekly. 2016;146:w14356.

18. Wells PS, Brown A, Jaffey J, McGahan L, Poon MC, Cimon K. Safety and effectiveness of point-of-care monitoring devices in patients on oral anticoagulant therapy: a meta-analysis. Open medicine : a peer-reviewed, independent, open-access journal. 2007;1(3):e131-46.
19. Zhou S, Sheng XY, Xiang Q, Wang ZN, Zhou Y, Cui YM. Comparing the effectiveness of pharmacist-managed warfarin anticoagulation with other models: a systematic review and meta-analysis. Journal of clinical pharmacy and therapeutics. 2016;41(6):602-11.
20. Jia B, Lynn HS, Rong F, Zhang W. Meta-analysis of efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation. Journal of cardiovascular pharmacology. 2014;64(4):368-74.
21. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2009;361(12):1139-51.
22. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2013;369(22):2093-104.
23. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2011;365(11):981-92.
24. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. The New England journal of medicine. 2011;365(10):883-91.
25. Saposnik G, Hill MD, O'Donnell M, Fang J, Hachinski V, Kapral MK. Variables associated with 7-day, 30-day, and 1-year fatality after ischemic stroke. Stroke. 2008;39(8):2318-24.
26. Steger C, Pratter A, Martinek-Bregel M, Avanzini M, Valentin A, Slany J, et al. Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian Stroke registry. European heart journal. 2004;25(19):1734-40.
27. Providencia R, Grove EL, Husted S, Barra S, Boveda S, Morais J. A meta-analysis of phase III randomized controlled trials with novel oral anticoagulants in atrial fibrillation: comparisons between direct thrombin inhibitors vs. factor Xa inhibitors and different dosing regimens. Thrombosis research. 2014;134(6):1253-64.
28. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A randomized trial of genotype-guided dosing of warfarin. The New England journal of medicine. 2013;369(24):2294-303.
29. Sharma P, Scotland G, Cruickshank M, Tassie E, Fraser C, Burton C, et al. Is self-monitoring an effective option for people receiving long-term vitamin K antagonist therapy? A systematic review and economic evaluation. BMJ open. 2015;5(6):e007758.
30. National Institute for Health and Care Excellence. Atrial fibrillation: management (CG180) [Internet] London NICE; 2014 [Available from: https://www.nice.org.uk/guidance/cg180.
31. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Archives of internal medicine. 2007;167(3):239-45.
32. Stergiopoulos K, Brown DL. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA internal medicine. 2014;174(8):1330-8.
33. Trusler M. Well-managed warfarin is superior to NOACs. Canadian Family Physician. 2015;61(1):23-4.
34. Raschi E, Bianchin M, Ageno W, De Ponti R, De Ponti F. Risk-Benefit Profile of Direct-Acting Oral Anticoagulants in Established Therapeutic Indications: An Overview of Systematic Reviews and Observational Studies. Drug safety. 2016;39(12):1175-87.

35. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4:1.

CHAPTER 6: Comparative efficacy and safety of warfarin care bundles and novel oral anticoagulants (NOACs) for stroke prevention in patients with atrial fibrillation: a systematic review and network meta-analysis

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6.1. Brief Summary

In the previous chapter, the current landscape of anticoagulant interventions for SPAF were evaluated by summarizing evidence and appraising published reviews in this field. Several limitations within the existing body of evidence were noted. One of the most notable flaws was that previous reviews in this field focused on the comparison between NOACs and usual warfarin care only, without addressing warfarin care bundles and this may have favoured NOACs.

Given the limitations of the available evidence and that new data on these interventions have emerged over the recent years, a more comprehensive and updated systematic review was commissioned. The aim of this chapter is to report a study that simultaneously meta-analyse the efficacy and safety evidence of usual warfarin care, warfarin care bundles and NOACs for SPAF in a single network model, based on data extracted from the literature via a systematic review process. This study was divided in two parts: (i) a comprehensive systematic review of RCTs comparing these anticoagulant interventions in patients with AF followed by (ii) a network meta-analysis to generate quantitative data.

Based on the study findings, both NOACs and warfarin care bundles were found to perform better than usual warfarin care. In fact, the benefits of NOACs were reduced in the presence of warfarin care bundles. Warfarin care bundles achieved a higher TTR than that of usual warfarin care and thus, the improvement of anticoagulation control is achievable through care bundles. By performing simultaneous comparison, this study provided a clearer representation on the benefits and risks of each anticoagulant intervention for SPAF and are useful for clinical practice, guideline development as well as in determining the direction of future research.

Currently, a manuscript reporting this study has been submitted to a peer-review journal for consideration of publication. Given the constraints of publication space, the submitted manuscript reported the detailed methods and results within its supplementary appendix.

6.2. Introduction

For many years, warfarin has been the only effective oral anticoagulant for stroke prevention in patients with atrial fibrillation (SPAF).[1] Due to its complex pharmacodynamic and pharmacokinetic profile, constant monitoring of anticoagulation effect through international normalized ratio (INR) is required to ensure optimal level of anticoagulation. The need for frequent monitoring may result in physical, psychological, social and financial consequences for the patient and the healthcare team.[2] Due to the perceived risks and inconvenience, warfarin remains underused.[3]

The concept of using more than one intervention together to improve patient care is called "a care bundle".[4] This care bundle concept has been shown to be effective in improving patient outcomes in various disease models. Since several interventions have been shown to improve quality of anticoagulation control and outcomes, it is therefore logical to apply this care bundle concept to warfarin therapy. Examples of warfarin care bundles are the employment of genotype guidance into warfarin dosing, patient's self-monitoring using point-of-care devices and left atrial appendage closure (LAAC). These pragmatic warfarin care bundles have the potential in improving patient's convenience and the overall quality of warfarin care by resulting in fewer stroke and bleeding complications.[2, 5]

Recently, novel oral anticoagulants (NOACs) have been introduced. These agents have fixed dosing and predictable pharmacokinetics, which eliminates the need for routine monitoring.[6] Although NOACs deliver on the promise of convenience, uncertainties remain surrounding their uses.[7] Without routine anticoagulation test, patient's adherence could not be assessed. In some circumstances, the degree of anticoagulation may need to be assessed such as during severe haemorrhages or emergent surgery. Furthermore, safety data of NOACs in certain populations are still limited such as those with

severe renal insufficiency. NOACs and their reversal agents have high acquisition costs, which can limit their accesses especially in low-income countries.

With the growing anticoagulant armamentarium, it is becoming more challenging to compare the efficacy and safety of these interventions for SPAF. Unfortunately, there are no head-to-head trials yet, comparing NOACs with each other or with warfarin care bundles. The degree of benefit of NOACs compared with warfarin depends on the patient-time in therapeutic range (TTR).[8] To date, there is no evidence to support the superiority of NOACs over well-controlled warfarin therapy (TTR $\geq$ 65%).[9-12] Therefore, for anticoagulation centres with TTR < 65%, the possible choices are either switching to NOACs or investing additional resources to adopt warfarin care bundles. Each intervention has different clinical implications for patients, clinicians and decision-makers to consider. Hence, this study aimed to compare anticoagulant interventions including warfarin care bundles and NOACs for SPAF, by performing a comprehensive systematic review and network meta-analysis.

6.3. Methods

This study was registered with PROSPERO (CRD42018100321) and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13]

Data Sources and Searches

We searched Embase (S-6-1), Medline, Cochrane Library and ClinicalTrials.gov from inception to November 23rd, 2017. We included RCTs that compared anticoagulant interventions for SPAF in adults, whether administered alone or as care bundles. No language restriction was applied.

Study Selection

Trials with mixed population (e.g. AF, venous thromboembolism and etc) were included in this review if more than 50% of AF patients were represented. This is to ensure that all interventions were incorporated into our network since most trials investigating warfarin care bundles were conducted in a mixed population. Only trials investigating interventions with approved dosing regimen or indication for SPAF were included. Trials with participants only eligible for parenteral anticoagulation or with an INR target outside 2-3 range were excluded. Furthermore, trials assessing patients undergoing catheter ablation, cardioversion, or recent surgery such as hip or knee arthroplasty were excluded. Reference lists of relevant studies were also screened.

Data Extraction and Quality Assessment

Three investigators (SSN, PD and KK) independently screened the titles and abstracts of retrieved citations to identify potentially relevant studies. Full articles were evaluated if a decision could not be made based on the titles and abstracts. When studies have compared more than two interventions, only interventions meeting the pre-specified criteria were included in the review if at least two interventions remained in the study.

The following data was extracted: study characteristics, patients' characteristics, outcomes, and other relevant findings. The Cochrane Collaboration's risk of bias (ROB) tool[14] was used to assess risk of bias. Data extraction and risk of bias assessments were carried out by one reviewer (SSN) and cross-checked by two other reviewers (PD and KK). Any discrepancies were resolved by consensus or by arbitration to a third reviewer (NC) where necessary.

Types of Interventions

Interventions included were antiplatelet (e.g. aspirin of any doses, clopidogrel) and anticoagulant therapy (e.g. warfarin and NOACs). Warfarin was further categorized, either as usual warfarin care or as care bundles. Usual warfarin care consisted of warfarin therapy alone and may have been delivered either in hospitals, primary care or anticoagulation clinics. Anticoagulation clinics were included in the usual warfarin care because most RCTs were multicentre trials, whereby some patients in the warfarin arms may have been monitored in anticoagulation clinics while some in primary care by general physician. As a result, categorizing anticoagulation clinics as a standalone intervention is not feasible and was included as part of the usual warfarin care. Warfarin care bundles were the combination of several interventions performed collectively to improve the quality of warfarin care such as genotype-guided warfarin dosing, patient's self-testing (PST) or patient's self-management (PSM) of warfarin or LAAC procedure (e.g. insertion of Watchman device) with temporary warfarin use. These anticoagulant interventions are described in detail in S-6-2.

This review focused on four NOACs; one direct thrombin inhibitor; dabigatran and three factor Xa inhibitors; apixaban, rivaroxaban and edoxaban. Other NOACs were excluded and reasons for exclusions are listed in S-6-2. Dabigatran and edoxaban were analysed as two separate doses (150mg or 110mg for dabigatran; 60mg or 30mg for edoxaban) as patients were equally randomized to both doses in the main trials[10, 11]. However, rivaroxaban and apixaban were not studied as separate doses due to the absence of equal randomization to respective doses. Patients were predominantly treated with either rivaroxaban 20mg or apixaban 5mg in the respective trials[12, 15] and were only adjusted to the lower dose if old age, low body weight or deterioration of renal function.

Outcomes

The primary efficacy outcomes were stroke or systemic embolism and all-cause mortality while the primary safety outcome was major bleeding. Major bleeding was defined according to Bleeding Academic Research Consortium (BARC) type 3-5[16] and "compatible definitions" if they could be standardized based on BARC type 3-5 criteria (details of compatibility criteria in S-6-4).

Secondary outcomes were ischemic stroke, clinically relevant non-major bleeding (CRNMB), intracranial bleeding (including haemorrhagic stroke, intraparenchymal, subdural, epidural and subarachnoid haemorrhages), gastrointestinal bleeding and myocardial infarction. The risk-benefit balance of anticoagulant interventions was also investigated by incorporating efficacy and safety outcomes using two-dimensional plot and clustering methods to rank these interventions.

Quality of Evidence

The quality of evidence from direct and indirect comparisons were assessed by using GRADEpro GDT software online version (GRADE Working Group, McMaster University, Hamilton, ON, Canada).[17] There were four levels of quality of evidence: high, moderate, low and very low.[18, 19]

Data Synthesis and Statistical Analysis

The relative intervention effects (risk ratio [RR]) along with 95% confidence interval (CI) were estimated for individual studies. Pairwise meta-analysis was used to pool RRs using random-effects model.[20] Heterogeneity was assessed using Cochrane Q test and I^2 statistics.[21] A network meta-analysis with consistency model was conducted to compare all interventions using direct and indirect evidence.[22, 23] Usual warfarin care was used as the common comparator in the network model. Network inconsistency was evaluated using global inconsistency test by fitting design-by-treatment in the inconsistency model.[24] If inconsistency was detected, we then used loop-specific and node-splitting methods to identify the source of inconsistency. The comparison-adjusted funnel plots were

used to analyse publication bias.[25] To rank the intervention hierarchy in the network meta-analysis, surface under the cumulative ranking curves (SUCRA) were estimated.[26]

Sensitivity analysis was performed on different major bleeding definitions. Additionally, we also performed sensitivity analyses by excluding studies conducted prior to year 2006. This is to reduce the heterogeneity in usual warfarin care definition, by assuming that most countries have adopted anticoagulation clinics as part of their warfarin care management from year 2006 onwards.[27] Other sensitivity analyses were the omission of trials with mixed population, small trials (<25th percentile), trials with serious-to-critical risk of bias. All analyses were done in Stata Version 14.0 using self-programmed Stata routines for network meta-analysis.[25] A p-value of less than 0.05 was considered statistically significant.

6.4. Results

Characteristics of Included Studies

We identified 3,008 records, of which 189 potentially eligible articles were reviewed in full text. Of these articles, 152 were excluded, due to the lack of reporting on the outcomes of interest (n=19), compared irrelevant interventions (n=31) or population not of interest (n=49), being non-RCTs or unrelated subgroup analyses (n=14), and other reasons (n=21), leaving 37 studies for inclusion in our review. The PRISMA flow diagram demonstrating process of electronic searching is presented in S-6-1.

A total of 37 studies, involving 100,142 patients[9-12, 15, 28-68] were assessed in our network meta-analysis. The mean age of patients was 69.9 ± 5.7 years. Mean TTR for usual warfarin care was 61.1 ± 8.9% while the mean TTR for warfarin care bundles was 68.9 ± 5.8%.

Eight studies examined warfarin care bundles: two studies[48, 67] on PST, three studies[49, 51, 52] on PSM, two studies[65, 66] on the insertion of Watchman device and one study[33] on genotype-guided warfarin

dosing. Fifteen studies[9-12, 15, 34-43] explored one of the following NOACs: dabigatran[10, 34, 36], rivaroxaban[12, 37-39, 41], apixaban[9, 15, 40] and edoxaban[11, 35, 42, 43]. The remaining 14 studies[47, 50, 53-64] compared warfarin with either antiplatelet therapy or placebo/control. Twenty-three studies[9-12, 15, 34-38, 40, 42, 43, 47, 49, 51, 52, 54, 57, 62, 64-66] were industry-sponsored, including all those that examined NOACs except one study[39]. Sponsor details were not reported in two studies[41, 50]. Other characteristics of the included studies are summarized in S-6-3.

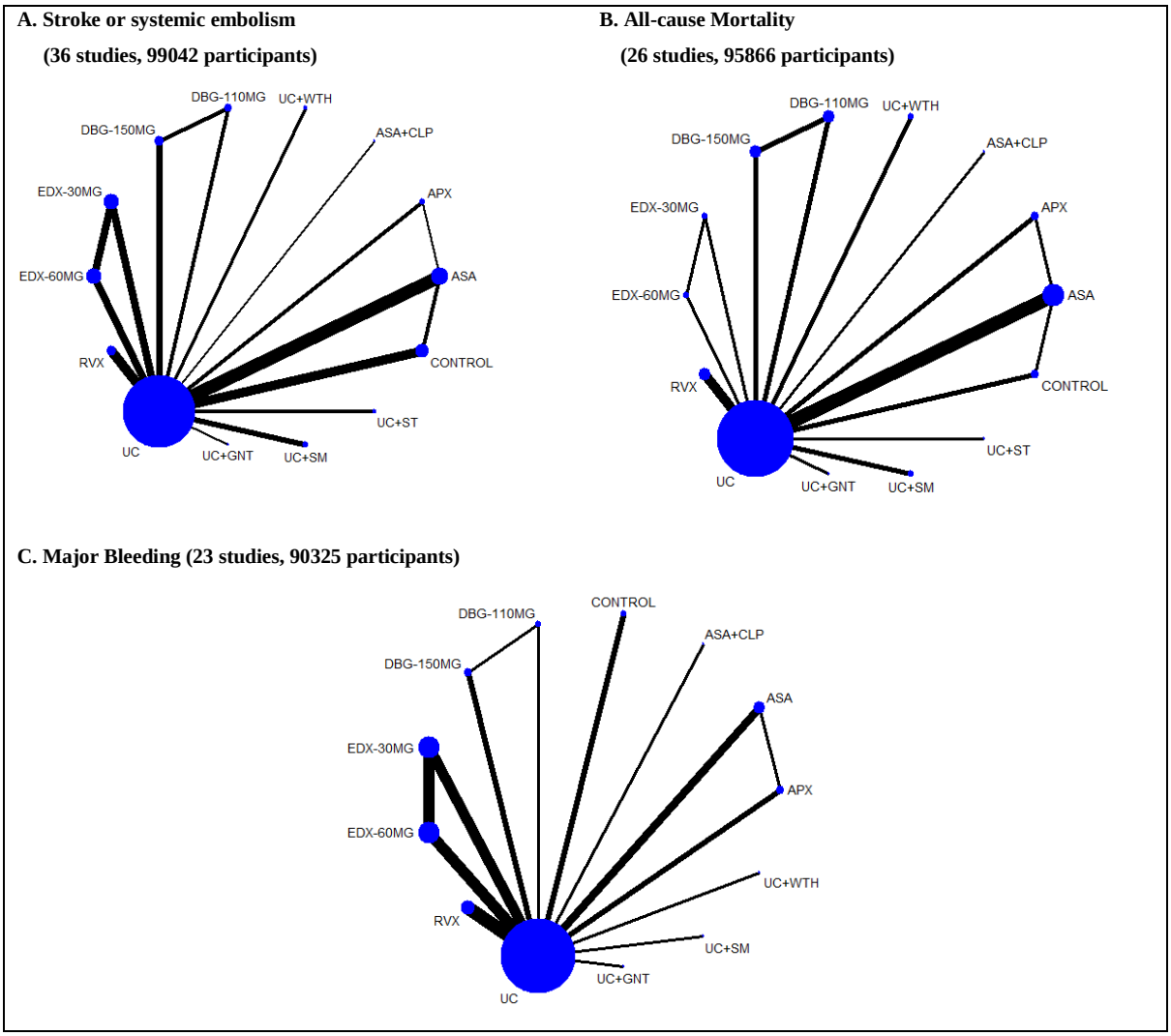

Figure 6.4.1 Network plots of eligible comparisons for primary efficacy and safety outcomes.

(A) Stroke or systemic embolism. (B) All-cause mortality. (C) Major bleeding. Line thickness is proportional to the number of patients that contributed to the comparisons. Abbreviations: APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device

Risk of Bias of Included Studies

The risks of bias among included studies are presented in S-6-5. Most studies were judged to be at low or unclear risk of bias for sequence generation and allocation concealment. However, high risk of bias was found in the blinding of participants and staffs in 26 studies[10, 33, 34, 36, 37, 40-43, 49-64, 67] as most studies were conducted as open-label. Majority of studies were judged to be at low or unclear risk of bias for blinding of outcome assessment, incomplete outcome data and selective reporting.

Efficacy and Safety Results

A total of 14 interventions were included in the network: the direct comparisons for primary outcomes are shown in Figure 6.4.1. Network maps for secondary outcomes are presented in S-6-6. Treatment effects estimated using direct meta-analysis are presented in S-6-8, without evidence of statistical heterogeneity, except in two pairwise comparisons (usual warfarin care vs. aspirin for stroke or systemic embolism outcome and usual warfarin care vs rivaroxaban for gastrointestinal bleeding outcome). Comparisons among all interventions, with usual warfarin care as the reference treatment for all outcomes are presented in S-6-9.

Warfarin care bundles and NOACs except edoxaban 30mg reduced the risk of stroke or systemic embolism when compared with usual warfarin care, as shown in Table 6.4.1. However, only PSM warfarin care bundle showed significant reduction, with 76% risk reduction in stroke or systemic embolism (RR: 0.24, 95% CI 0.08-0.68). Conversely, antiplatelet therapy was associated with a significant increase in risk of stroke; RR 1.72 (95% CI 1.29-2.29) for single and 1.85 (1.07-3.21) for dual antiplatelet therapy, compared with usual warfarin care. Comparing among NOACS, the risk of stroke was higher with apixaban, rivaroxaban and edoxaban 60mg when compared with dabigatran 150mg, although these differences did not reach statistical significance.

Three interventions significantly reduced the risk of all-cause mortality when compared with usual warfarin care: insertion of Watchman device (0.49, 0.28-0.86); apixaban (0.89, 0.80-0.98 and edoxaban 30mg (0.88, 0.80-0.96). There was little evidence that the risk of all-cause mortality differed among NOACs. The risk of myocardial infarction significantly increased with dabigatran 150mg (1.40, 1.01-1.92) when compared with usual warfarin care.

For safety outcomes (Table 6.4.2), apixaban (0.70, 0.61-0.81), dabigatran 110mg (0.81, 0.71-0.94), edoxaban 30mg (0.48, 0.42-0.56), and edoxaban 60mg (0.80, 0.71-0.90) significantly reduced the risk of major bleeding compared with usual warfarin care. The evidence for warfarin care bundles, especially genotype-guided warfarin dosing and PSM intervention in major bleeding outcome is generally weak due to the wide confidence intervals, corresponding to the small sample sizes of included trials. Among NOACs, the major bleeding risk with dabigatran 150mg (1.34, 1.10-1.62) and rivaroxaban (1.44, 1.91-1.74) were significantly higher than apixaban.

The risk of intracranial bleeding was significantly lower, with more than 50% relative risk reduction for all NOACs except rivaroxaban when compared with usual warfarin care. For gastrointestinal bleeding, the risk was higher with dabigatran 110mg (1.11, 0.21-5.87), dabigatran 150mg (1.50, 0.29-7.93), edoxaban 60mg (1.22, 0.23-6.41) and rivaroxaban (1.37, 0.42-4.43) compared with usual warfarin care. On the contrary, the risk of CRNMB for single antiplatelet therapy (0.60, 0.44-0.83), apixaban (0.68, 0.59-0.79), edoxaban 30mg (0.70, 0.65-0.75) and edoxaban 60mg (0.87, 0.82-0.94) was significantly lower than usual warfarin care. ‘

The cluster rank plot (Figure 6.4.3) shows that warfarin care bundles except for PSM were clustered in the same quadrant (lower risk of stroke and major bleeding) as NOACs when balancing both the efficacy and safety outcomes. A global inconsistency test was performed and suggested no evidence

of inconsistency for all outcomes (S-6-7). Therefore, the pooled estimates of all outcomes were based on consistency model. Comparison-adjusted funnel plots show no evidence of asymmetry (S-6-13). In our sensitivity analysis (S-6-12), when studies conducted before year 2006 were excluded, only the RR of PSM intervention for stroke and all-cause mortality outcome increased while the findings for other interventions remain the same. The findings were also generally robust when studies with mixed population were excluded. Moreover, findings for major bleeding outcomes were also robust without significant changes in the treatment hierarchies when major bleeding definition was matched against ISTH definition instead of BARC 3-5 criteria.

The quality of direct evidence for all outcomes was generally rated as very low to moderate in most comparisons. When GRADE was applied to our network meta-analysis evidence, mortality and major bleeding outcome showed better rating on quality of evidence than for direct evidence in several comparisons. More details of the quality of evidence are presented in the S-6-15.

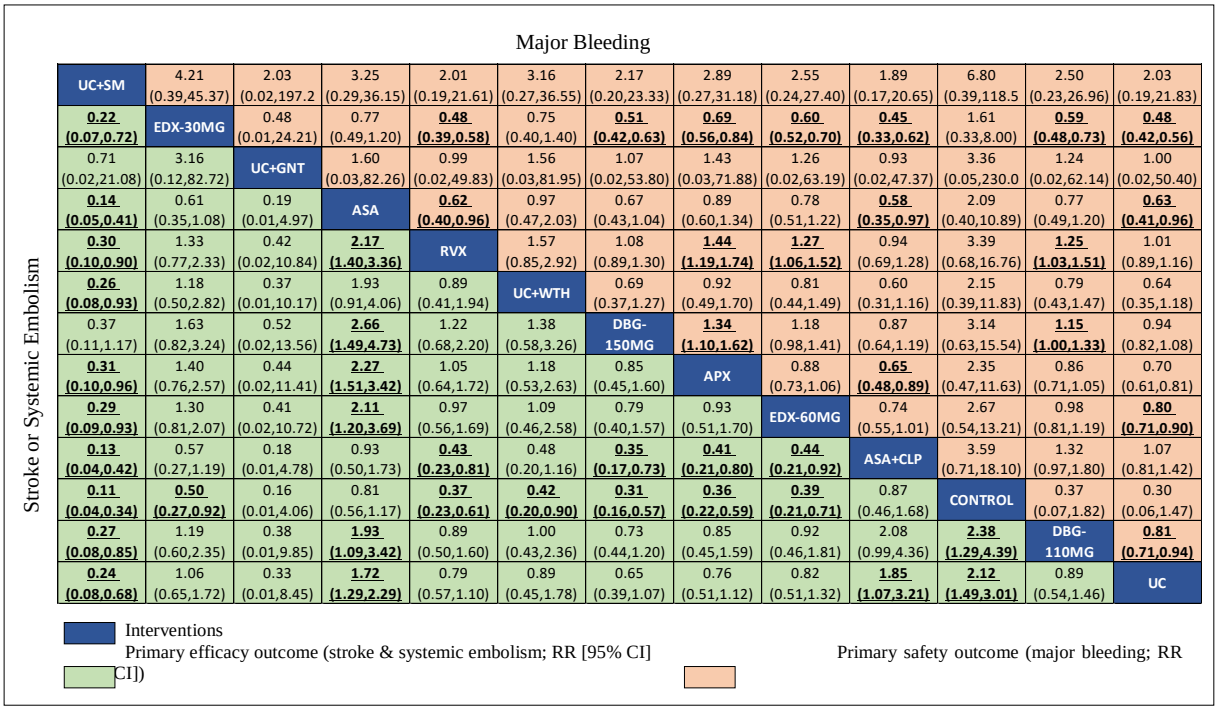

Figure 6.4.2 Network meta-analysis of primary efficacy (stroke or systemic embolism) and safety (major bleeding) outcomes. Interventions are ordered by ranking for stroke or systemic embolism. Results are the RRs (95% CI) from the network meta-analysis between the column-defining interventions and row-defining interventions. Comparisons should be read from left to right. Numbers in bold represent statistically significant results. UC+ST intervention was omitted as major bleeding outcome was not reported by the studies included in the analysis. Abbreviations: APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; WTH: Watchman device.

Table 6.4.1. Network meta-analysis results of stroke, mortality, ischemic stroke and myocardial infarction outcomes in patients with AF

	Primary Efficacy Outcomes		**Secondary Outcomes**	
	Stroke or SE	**All-cause Mortality**	**Ischemic Stroke**	**Myocardial Infarction**
Comparisons with usual warfarin care				
Antiplatelet				
Aspirin	**1.72 (1.29,2.29)**	1.07 (0.92,1.24)	**2.65 (1.89,3.71)**	1.04 (0.68,1.59)
Aspirin + Clopidogrel	**1.85 (1.07,3.21)**	1.00 (0.80,1.23)	**2.12 (1.47,3.05)**	1.55 (0.92,2.61)
Warfarin Care Bundles				
Genotype-guided warfarin dosing	0.33 (0.01,8.45)	2.51 (0.49,12.81)	N/A	N/A
PST	0.99 (0.51,1.93)	0.96 (0.78,1.19)	N/A	1.49 (0.83,2.70)
PSM	**0.24 (0.08,0.68)**	0.42 (0.17,1.04)	N/A	N/A
LAAC procedure (Watchman Device)	0.89 (0.45,1.78)	**0.49 (0.28,0.86)**	1.36 (0.69,2.69)	N/A
NOACs				
Apixaban	0.76 (0.51,1.12)	**0.89 (0.80,0.98)**	0.93 (0.76,1.14)	0.88 (0.67,1.15)
Dabigatran 110mg	0.89 (0.54,1.46)	0.92 (0.81,1.04)	1.12 (0.90,1.40)	1.36 (0.99,1.88)
Dabigatran 150mg	0.65 (0.39,1.07)	0.89 (0.79,1.01)	**0.77 (0.61,0.99)**	**1.40 (1.01,1.92)**
Edoxaban 30mg	1.06 (0.65,1.72)	**0.88 (0.80,0.96)**	**1.42 (1.20,1.67)**	1.21 (0.97,1.50)
Edoxaban 60mg	0.82 (0.51,1.32)	0.92 (0.84,1.01)	1.00 (0.84,1.20)	0.95 (0.75,1.20)
Rivaroxaban	0.79 (0.57,1.10)	0.85 (0.71,1.01)	0.87 (0.72,1.05)	0.82 (0.63,1.06)
Placebo (Control)	**2.12 (1.49,3.01)**	1.11 (0.80,1.56)	**2.86 (1.83,4.49)**	1.00 (0.14,7.00)
Comparisons among recommended doses of NOACs				
Dabigatran 150mg vs. Apixaban	0.85 (0.45,1.60)	1.00 (0.86,1.18)	0.83 (0.61,1.14)	**1.59 (1.05,2.41)**
Edoxaban 60mg vs. Apixaban	1.08 (0.59,1.98)	1.04 (0.91,1.19)	1.08 (0.83,1.41)	1.08 (0.76,1.54)
Rivaroxaban vs. Apixaban	1.05 (0.64,1.72)	0.95 (0.78,1.17)	0.94 (0.71,1.24)	0.93 (0.64,1.35)
Edoxaban 60mg vs. Dabigatran 150mg	1.26 (0.64,2.50)	1.03 (0.89,1.21)	1.30 (0.96,1.76)	0.68 (0.46,1.01)
Rivaroxaban vs. Dabigatran 150mg	1.22 (0.68,2.20)	0.95 (0.76,1.18)	1.13 (0.83,1.53)	**0.59 (0.39,0.88)**
Rivaroxaban vs. Edoxaban 60mg	0.97 (0.56,1.69)	0.92 (0.75,1.12)	0.87 (0.67,1.13)	0.86 (0.61,1.22)
Comparisons between NOACs with Warfarin Care Bundles				
Apixaban vs. Genotype-guided warfarin dosing	2.27 (0.09,58.54)	0.35 (0.07,1.81)	N/A	N/A
Dabigatran 150mg vs. Genotype-guided warfarin dosing	1.93 (0.07,50.71)	0.35 (0.07,1.82)	N/A	N/A
Edoxaban 60mg vs. Genotype-guided warfarin dosing	2.27 (0.09,58.54)	0.37 (0.07,1.88)	N/A	N/A

Rivaroxaban vs. Genotype-guided warfarin dosing	2.37 (0.09,60.75)	0.34 (0.07,1.73)	N/A	N/A
Apixaban vs. PST	0.76 (0.35,1.65)	0.92 (0.73,1.16)	N/A	0.59 (0.31,1.13)
Dabigatran 150mg vs. PST	0.65 (0.28,1.50)	0.93 (0.72,1.18)	N/A	0.94 (0.48,1.83)
Edoxaban 60mg vs. PST	0.82 (0.36,1.87)	0.96 (0.76,1.20)	N/A	0.64 (0.34,1.21)
Rivaroxaban vs. PST	0.80 (0.38,1.67)	0.88 (0.67,1.16)	N/A	0.55 (0.29,1.05)
Apixaban vs. PSM	**3.20 (1.04,9.88)**	2.12 (0.85,5.28)	N/A	N/A
Dabigatran 150mg vs. PSM	2.74 (0.85,8.79)	2.12 (0.85,5.32)	N/A	N/A
Edoxaban 60mg vs. PSM	**3.45 (1.08,11.03)**	2.20 (0.88,5.48)	N/A	N/A
Rivaroxaban vs. PSM	**3.35 (1.11,10.14)**	2.01 (0.80,5.09)	N/A	N/A
Apixaban vs. LAAC procedure	0.85 (0.38,1.90)	**1.81 (1.03,3.19)**	0.68 (0.34,1.39)	N/A
Dabigatran 150mg vs. LAAC procedure	0.72 (0.31,1.71)	**1.81 (1.02,3.21)**	0.57 (0.28,1.18)	N/A
Edoxaban 60mg vs. LAAC procedure	0.91 (0.39,2.16)	**1.88 (1.07,3.30)**	0.74 (0.36,1.50)	N/A
Rivaroxaban vs. LAAC procedure	0.89 (0.41,1.94)	1.72 (0.96,3.09)	0.64 (0.32,1.30)	N/A

PST: patient's self-testing of warfarin; PSM: patient's self-management of warfarin; SE: systemic embolism CRNMB: clinically relevant non-major bleeding; PST: patient's self-testing of warfarin; PSM: patient's self-management of warfarin; WTH: Watchman device.

** Numbers in bold represent statistically significant results*

Table 6.4.2. Network meta-analysis results of bleeding outcomes in patients with atrial fibrillation

	Primary Safety Outcomes		**Secondary Outcomes**	
	Major Bleeding	**Intracranial Bleeding**	**CRNMB**	**GI Bleeding**
Comparison with usual warfarin care				
Antiplatelet				
Aspirin	**0.63 (0.41,0.96)**	0.65 (0.34,1.25)	**0.60 (0.44,0.83)**	0.48 (0.07,3.28)
Aspirin + Clopidogrel	1.07 (0.81,1.42)	0.52 (0.23,1.17)	N/A	N/A
Warfarin Care Bundles				
Genotype-guided warfarin dosing	1.00 (0.02,50.40)	N/A	N/A	0.74 (0.12,4.51)
PST	N/A	1.37 (0.51,3.64)	N/A	N/A
PSM	2.03 (0.19,21.83)	1.00 (0.14,7.29)	N/A	N/A
Watchman Device	0.64 (0.35,1.18)	0.22 (0.06,0.76)	N/A	N/A
NOACs				
Apixaban	**0.70 (0.61,0.81)**	**0.44 (0.28,0.70)**	**0.68 (0.59,0.79)**	0.62 (0.13,2.86)
Dabigatran 110mg	**0.81 (0.71,0.94)**	**0.31 (0.18,0.55)**	0.51 (0.11,2.34)	1.11 (0.21,5.87)
Dabigatran 150mg	0.94 (0.82,1.08)	**0.41 (0.24,0.70)**	1.13 (0.51,2.51)	1.50 (0.29,7.93)
Edoxaban 30mg	**0.48 (0.42,0.56)**	**0.31 (0.19,0.52)**	**0.70 (0.65,0.75)**	0.68 (0.13,3.58)
Edoxaban 60mg	**0.80 (0.71,0.90)**	**0.48 (0.30,0.78)**	**0.87 (0.82,0.94)**	1.22 (0.23,6.41)
Rivaroxaban	1.01 (0.89,1.16)	0.76 (0.53,1.08)	1.04 (0.97,1.11)	1.37 (0.42,4.43)
Placebo (Control)	0.30 (0.06,1.47)	0.57 (0.19,1.71)	0.33 (0.03,3.16)	0.23 (0.02,2.20)
Comparisons among recommended doses of NOACs				
Dabigatran 150mg vs. Apixaban	**1.34 (1.10,1.62)**	0.93 (0.46,1.86)	1.65 (0.73,3.72)	2.42 (0.25,23.12)
Edoxaban 60mg vs. Apixaban	1.14 (0.94,1.37)	1.09 (0.57,2.08)	**1.28 (1.09,1.51)**	1.97 (0.21,18.72)
Rivaroxaban vs. Apixaban	**1.44 (1.19,1.74)**	1.72 (0.96,3.07)	**1.52 (1.29,1.79)**	2.20 (0.30,16.04)
Edoxaban 60mg vs. Dabigatran 150mg	0.85 (0.71,1.02)	1.17 (0.57,2.40)	0.77 (0.35,1.73)	0.81 (0.08,8.50)
Rivaroxaban vs. Dabigatran 150mg	1.08 (0.89,1.30)	1.85 (0.98,3.52)	0.92 (0.41,2.05)	0.91 (0.12,6.97)
Rivaroxaban vs. Edoxaban 60mg	**1.27 (1.06,1.52)**	1.58 (0.86,2.89)	**1.19 (1.08,1.31)**	1.12 (0.15,8.55)
Comparisons between NOACs with warfarin care bundles				
Apixaban vs. Genotype-guided warfarin dosing	0.70 (0.01,35.20)	N/A	N/A	0.84 (0.08,9.02)
Dabigatran 150mg vs. Genotype-guided warfarin dosing	0.93 (0.02,47.03)	N/A	N/A	2.04 (0.17,23.88)
Edoxaban 60mg vs. Genotype-guided warfarin dosing	0.80 (0.02,40.01)	N/A	N/A	1.66 (0.14,19.33)

Rivaroxaban vs. Genotype-guided warfarin dosing	1.01 (0.02,50.75)	N/A	N/A	1.86 (0.21,16.10)
Apixaban vs. PST	N/A	**0.32 (0.11,0.95)**	N/A	N/A
Dabigatran 150mg vs. PST	N/A	**0.30 (0.10,0.91)**	N/A	N/A
Edoxaban 60mg vs. PST	N/A	0.35 (0.12,1.05)	N/A	N/A
Rivaroxaban vs. PST	N/A	0.56 (0.20,1.58)	N/A	N/A
Apixaban vs. PSM	0.35 (0.03,3.72)	0.44 (0.06,3.42)	N/A	N/A
Dabigatran 150mg vs. PSM	0.46 (0.04,4.97)	0.41 (0.05,3.22)	N/A	N/A
Edoxaban 60mg vs. PSM	0.39 (0.04,4.23)	0.48 (0.06,3.73)	N/A	N/A
Rivaroxaban vs. PSM	0.50 (0.05,5.36)	0.76 (0.10,5.75)	N/A	N/A
Apixaban vs. Watchman Device	1.09 (0.59,2.03)	2.01 (0.54,7.44)	N/A	N/A
Dabigatran 150mg vs. Watchman Device	1.46 (0.79,2.71)	1.86 (0.48,7.11)	N/A	N/A
Edoxaban 60mg vs. Watchman Device	1.24 (0.67,2.30)	2.18 (0.58,8.14)	N/A	N/A
Rivaroxaban vs. Watchman Device	1.57 (0.85,2.92)	3.45 (0.95,12.46)	N/A	N/A

PST: patient's self-testing of warfarin; PSM: patient's self-management of warfarin; SE: systemic embolism CRNMB: clinically relevant non-major bleeding; PST: patient's self-testing of warfarin; PSM: patient's self-management of warfarin; WTH: Watchman device.

** Numbers in bold represent statistically significant results*

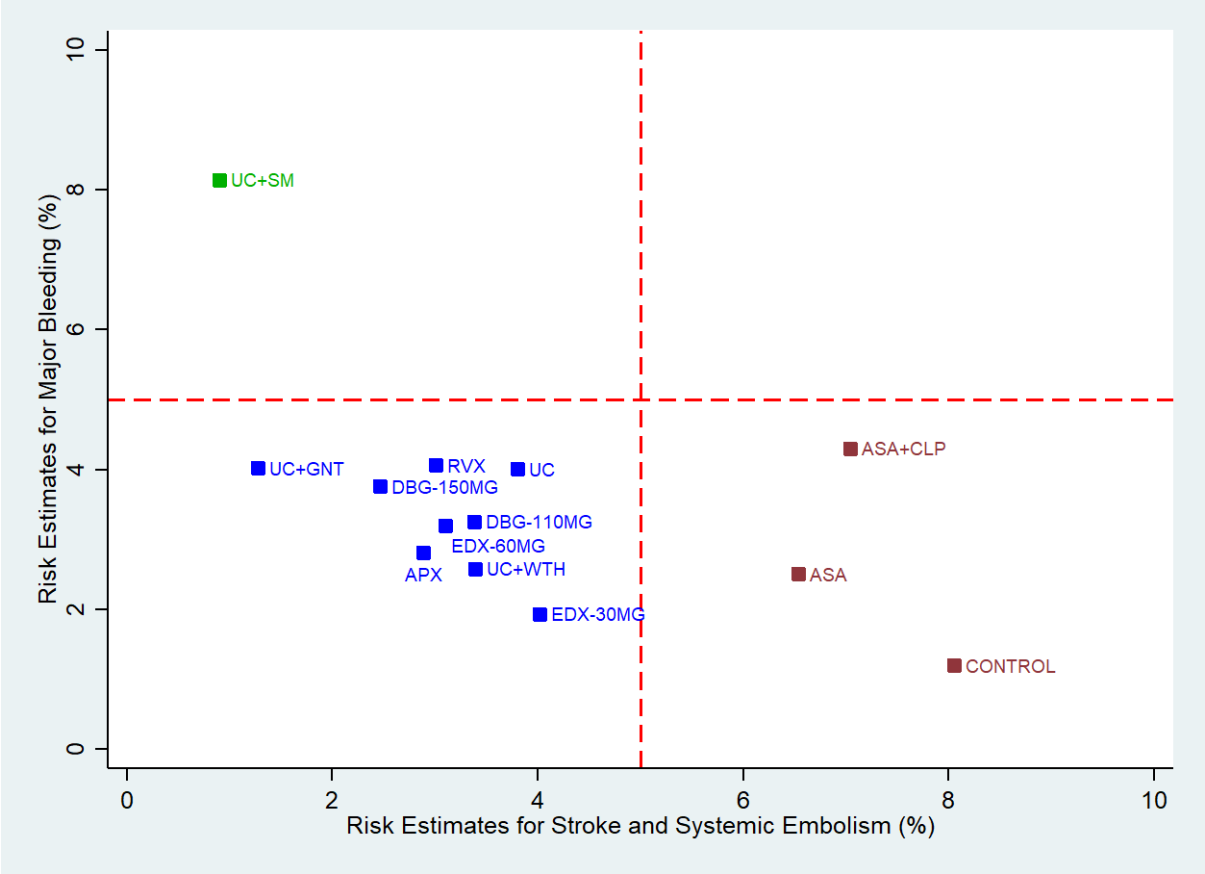

Figure 6.4.3 Cluster rank plot of risk estimates for stroke or systemic embolism and major bleeding.

The risk estimates plot of patient's INR self-testing intervention is omitted because the included studies for this intervention in network meta-analyses did not report on major bleeding outcome. The dashed line represents the different quadrants of the risk estimates. Abbreviations: APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; WTH: Watchman device

6.5. Discussion

To our knowledge, this is the first study that comprehensively compared efficacy and safety of all available anticoagulant interventions. Our analysis help provide new important information by evaluating all interventions in one single network model. This information therefore provides clinicians and policy makers with a broad view of the whole landscape of SPAF interventions.

Our results confirm that NOACs have similar efficacy to usual warfarin for stroke prevention but offer some advantages through reduction in bleeding risk. Nevertheless, some of warfarin care bundles including genotype-guided warfarin dosing, and insertion of Watchman device, performed

well in comparison to NOACs based on the cluster rank plot, which incorporate both efficacy and safety into one aggregate. PSM performed extremely well in stroke risk reduction but with increased risk of major bleeding. The risk of bleeding seen with PSM may need to be interpreted with caution since most trials of PSM were performed in mixed population where bleeding rates may be higher than that of AF patients. For PST, there appears to be no additional benefit on stroke reduction while most trials did not report on the rates of major bleeding. Therefore, we were unable to evaluate PST using cluster rank plot.

It is important to highlight that our findings show that warfarin care bundles are associated with improved quality of anticoagulation control compared with usual warfarin care (TTR of 68.9% vs. 61.1%, respectively). Since the efficacy and safety of warfarin is dependent on the quality of anticoagulation control, it is therefore plausible that warfarin performance can be as good as NOACs if TTR is high. Our study showed that warfarin care bundles achieved a mean TTR of 68.9%. As a result, this bundle care may offer a promising alternative instead of switching to NOACs since comparable benefits can be achieved at a possible lower cost. Nevertheless, we caution readers to consider this result definitive. The quality of evidence for majority warfarin care bundles except for the insertion of Watchman device, was generally rated as very low to low quality due to imprecision, presence of mixed population and wide confidence interval of pooled risk estimates. If possible, this finding should be confirmed in a large, randomized, controlled trial and other types of high-quality researches in the future.

Despite not being definitive, this finding may be an important information for low-income countries where there is still limited accessibility to NOACs in healthcare reimbursement scheme. Nonetheless, additional information such as cost-effectiveness and technical implementation considerations (e.g.

expertise, training, laboratory, facilities) need to be taken into consideration when formulating national or institutional policy decisions.

Our findings also strengthen current recommendation that oral anticoagulants, such as warfarin or NOACs, are far superior to single or dual antiplatelet therapy in preventing stroke in AF patients. Thus, antiplatelet therapy may no longer have a role for stroke prevention in AF patients as risks without considerable benefits is a poor trade-off.

6.6. Strength and Weakness of This Study

The strength of our study includes a comprehensive analysis of NOACs and warfarin care bundles in a single network. Previous meta-analyses[69-72] compared NOACs with usual warfarin care only, without addressing warfarin care bundles and this may have favoured NOACs. The main results in our NMA are also presented by simultaneous clustered ranking of efficacy and safety outcomes, allowing us to explore the intervention that has the best balance of both benefits and risks.

Our review has several limitations. Our analyses were restricted by the modest amount of data in the included studies. Only a few studies reported outcomes such as gastrointestinal bleeding, intracranial bleeding and myocardial infarction and most had few or zero events. Such missing information may encumber a through comparison of all interventions for each individual outcome. Therefore, results for these outcomes should be interpreted with caution. Second, there is a notable heterogeneity in patient's characteristics, especially on the types of AF (e.g. persistent, paroxysmal or permanent). However, the number of studies that addressed the types of AF were small and hence, subgroup analyses could not be conducted to account for this heterogeneity. Third, the heterogeneity of major bleeding is another concern due to diverse classification of bleeding events (e.g. major, life-threatening and minor) among trials in this research field. To minimize heterogeneity in our study,

the definition of major bleeding reported in each study was matched against standardized bleeding end-point definition adopted by BARC.[16] BARC definition was selected because it is the most updated bleeding definition and has been validated against other bleeding definitions.[73, 74] We included studies with reported bleeding definition that was compatible to BARC bleeding type 3-5 criteria into our quantitative analysis. We also performed sensitivity analysis on different major bleeding definition (e.g. ISTH) to assess the robustness of our conclusions. Fourth, we did not analyse apixaban and rivaroxaban separately as high or low doses due to lack of randomization of both doses in the main trials.[9, 12] Finally, follow-up duration in several studies, especially those investigating warfarin care bundles were relatively too short to draw definitive conclusion for long-term mortality outcome.

6.7. Conclusions

In summary, our analysis suggests that NOACs appear to be at least equivalent to usual warfarin care for SPAF and some NOACs carry a reduced risk of bleeding. However, the favourable benefits of NOACs decreases when compared to warfarin care bundles. Warfarin care bundles improve the quality of anticoagulation control as expressed by high TTR value ($\geq$65%). Warfarin care bundles such as PSM and insertion of Watchman device offer the highest level of efficacy in terms of stroke and mortality reduction, respectively. These findings should be considered during the decision-making process, on either adoption of NOACs into the healthcare system or investment in improving warfarin therapy by adopting care bundles. However, more trials comparing these care bundles with NOACs are needed in the future to overcome the need for indirect comparisons and to better understand the role of these interventions in clinical setting.

References for Chapter 6

1. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Archives of internal medicine. 1994;154(13):1449-57.
2. Gadisseur AP, Kaptein AA, Breukink-Engbers WG, van der Meer FJ, Rosendaal FR. Patient self-management of oral anticoagulant care vs. management by specialized anticoagulation clinics: positive effects on quality of life. Journal of thrombosis and haemostasis : JTH. 2004;2(4):584-91.
3. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. The American journal of medicine. 2010;123(7):638-45.e4.
4. Resar R, Griffin FA, Haraden C, Nolan TW. Using Care Bundles to Improve Health Care Quality. Cambridge, Massachusetts: Institute for Healthcare Improvement; 2012 [Available from: www.IHI.org.
5. Taborski U, Muller-Berghaus G. State-of-the-art patient self-management for control of oral anticoagulation. Seminars in thrombosis and hemostasis. 1999;25(1):43-7.
6. Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Therapeutics and clinical risk management. 2015;11:967-77.
7. Gulseth MP, Wittkowsky AK, Fanikos J, Spinler SA, Dager WE, Nutescu EA. Dabigatran etexilate in clinical practice: confronting challenges to improve safety and effectiveness. Pharmacotherapy. 2011;31(12):1232-49.
8. National Insitute for Health and Clinical Excellence. Atrial fibrillation: the management of atrial fibrillation (CG180)2014. Available from: https://www.nice.org.uk/guidance/cg180.
9. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. The New England journal of medicine. 2011;364(9):806-17.
10. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2009;361(12):1139-51.
11. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2013;369(22):2093-104.
12. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. The New England journal of medicine. 2011;365(10):883-91.
13. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Annals of internal medicine. 2015;162(11):777-84.
14. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2011;343:d5928.
15. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2011;365(11):981-92.
16. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736-47.
17. Patel NJ, Atti V, Mitrani RD, Viles-Gonzalez JF, Goldberger JJ. Global rising trends of atrial fibrillation: a major public health concern. Heart (British Cardiac Society). 2018;104(24):1989-90.

18. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of clinical epidemiology. 2011;64(4):401-6.
19. Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ (Clinical research ed). 2014;349:g5630.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003;327(7414):557-60.
22. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ (Clinical research ed). 2005;331(7521):897-900.
23. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Statistics in medicine. 2004;23(20):3105-24.
24. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Statistics in medicine. 2010;29(7-8):932-44.
25. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PloS one. 2013;8(10):e76654.
26. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology. 2011;64(2):163-71.
27. Pengo V, Pegoraro C, Cucchini U, Iliceto S. Worldwide management of oral anticoagulant therapy: the ISAM study. Journal of thrombosis and thrombolysis. 2006;21(1):73-7.
28. Burmester JK, Berg RL, Yale SH, Rottscheit CM, Glurich IE, Schmelzer JR, et al. A randomized controlled trial of genotype-based Coumadin initiation. Genetics in medicine : official journal of the American College of Medical Genetics. 2011;13(6):509-18.
29. Caraco Y, Blotnick S, Muszkat M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. Clinical pharmacology and therapeutics. 2008;83(3):460-70.
30. Hillman MA, Wilke RA, Yale SH, Vidaillet HJ, Caldwell MD, Glurich I, et al. A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. Clinical medicine & research. 2005;3(3):137-45.
31. Jonas DE, Evans JP, McLeod HL, Brode S, Lange LA, Young ML, et al. Impact of genotype-guided dosing on anticoagulation visits for adults starting warfarin: a randomized controlled trial. Pharmacogenomics. 2013;14(13):1593-603.
32. Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. The New England journal of medicine. 2013;369(24):2283-93.
33. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A randomized trial of genotype-guided dosing of warfarin. The New England journal of medicine. 2013;369(24):2294-303.
34. Livingstone-Banks J, Norris E, Hartmann-Boyce J, West R, Jarvis M, Hajek P. Relapse prevention interventions for smoking cessation. Cochrane Database of Systematic Reviews. 2019(2).
35. Chung N, Jeon HK, Lien LM, Lai WT, Tse HF, Chung WS, et al. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. Thrombosis and haemostasis. 2011;105(3):535-44.
36. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). The American journal of cardiology. 2007;100(9):1419-26.

37. Hong KS, Kwon SU, Lee SH, Lee JS, Kim YJ, Song TJ, et al. Rivaroxaban vs Warfarin Sodium in the Ultra-Early Period After Atrial Fibrillation-Related Mild Ischemic Stroke: A Randomized Clinical Trial. JAMA neurology. 2017;74(10):1206-15.
38. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. Circulation journal : official journal of the Japanese Circulation Society. 2012;76(9):2104-11.
39. Mao L, Li C, Li T, Yuan K. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in Chinese patients with atrial fibrillation. Vascular. 2014;22(4):252-8.
40. Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. -The ARISTOTLE-J study. Circulation journal : official journal of the Japanese Circulation Society. 2011;75(8):1852-9.
41. Shosa RI, Ibrahim OM, Setiha ME, Abdelwahab AA. The Efficacy and Safety of Rivaroxaban as an Alternative to Warfarin for the Prevention of Thromboembolism in Patients with Atrial Fibrillation. Int J Pharm Sci Rev Res. 2017;43(2):38-48.
42. Weitz JI, Connolly SJ, Patel I, Salazar D, Rohatagi S, Mendell J, et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thrombosis and haemostasis. 2010;104(3):633-41.
43. Yamashita T, Koretsune Y, Yasaka M, Inoue H, Kawai Y, Yamaguchi T, et al. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. Circulation journal : official journal of the Japanese Circulation Society. 2012;76(8):1840-7.
44. Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. Annals of internal medicine. 2000;133(9):687-95.
45. Cromheecke ME, Levi M, Colly LP, de Mol BJ, Prins MH, Hutten BA, et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. Lancet (London, England). 2000;356(9224):97-102.
46. Dignan R, Keech AC, Gebski VJ, Mann KP, Hughes CF. Is home warfarin self-management effective? Results of the randomised Self-Management of Anticoagulation Research Trial. International journal of cardiology. 2013;168(6):5378-84.
47. Lavitola Pde L, Sampaio RO, Oliveira WA, Boer BN, Tarasoutchi F, Spina GS, et al. Warfarin or aspirin in embolism prevention in patients with mitral valvulopathy and atrial fibrillation. Arquivos brasileiros de cardiologia. 2010;95(6):749-55.
48. Matchar DB, Jacobson A, Dolor R, Edson R, Uyeda L, Phibbs CS, et al. Effect of home testing of international normalized ratio on clinical events. The New England journal of medicine. 2010;363(17):1608-20.
49. Menendez-Jandula B, Souto JC, Oliver A, Montserrat I, Quintana M, Gich I, et al. Comparing self-management of oral anticoagulant therapy with clinic management: a randomized trial. Annals of internal medicine. 2005;142(1):1-10.
50. Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). Age and ageing. 2007;36(2):151-6.
51. Verret L, Couturier J, Rozon A, Saudrais-Janecek S, St-Onge A, Nguyen A, et al. Impact of a pharmacist-led warfarin self-management program on quality of life and anticoagulation control: a randomized trial. Pharmacotherapy. 2012;32(10):871-9.
52. Voller H, Glatz J, Taborski U, Bernardo A, Dovifat C, Heidinger K. Self-management of oral anticoagulation in nonvalvular atrial fibrillation (SMAAF study). Zeitschrift fur Kardiologie. 2005;94(3):182-6.
53. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation. 1991;84(2):527-39.

54. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet (London, England). 1993;342(8882):1255-62.
55. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. Lancet (London, England). 1994;343(8899):687-91.
56. Chen KP, Huang CX, Huang DJ, Cao KJ, Ma CS, Wang FZ, et al. Anticoagulation therapy in Chinese patients with non-valvular atrial fibrillation: a prospective, multi-center, randomized, controlled study. Chinese medical journal. 2012;125(24):4355-60.
57. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet (London, England). 2006;367(9526):1903-12.
58. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. Journal of the American College of Cardiology. 1991;18(2):349-55.
59. Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. Archives of internal medicine. 1998;158(14):1513-21.
60. Liu X, Huang H, Yu J, Cao G, Feng L, Xu Q, et al. Warfarin compared with aspirin for older Chinese patients with stable coronary heart diseases and atrial fibrillation complications. International journal of clinical pharmacology and therapeutics. 2014;52(6):454-9.
61. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet (London, England). 2007;370(9586):493-503.
62. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet (London, England). 1989;1(8631):175-9.
63. Sato H, Ishikawa K, Kitabatake A, Ogawa S, Maruyama Y, Yokota Y, et al. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan Atrial Fibrillation Stroke Trial. Stroke. 2006;37(2):447-51.
64. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SW, et al. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The New England journal of medicine. 1990;323(22):1505-11.
65. Holmes DR, Jr., Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. Journal of the American College of Cardiology. 2014;64(1):1-12.
66. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. Jama. 2014;312(19):1988-98.
67. Khan TI, Kamali F, Kesteven P, Avery P, Wynne H. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. British journal of haematology. 2004;126(4):557-64.
68. Watzke HH, Forberg E, Svolba G, Jimenez-Boj E, Krinninger B. A prospective controlled trial comparing weekly self-testing and self-dosing with the standard management of patients on stable oral anticoagulation. Thrombosis and haemostasis. 2000;83(5):661-5.

69. Cameron C, Coyle D, Richter T, Kelly S, Gauthier K, Steiner S, et al. Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation. BMJ open. 2014;4(6):e004301.
70. Lopez-Lopez JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ (Clinical research ed). 2017;359:j5058.
71. Tawfik A, Bielecki JM, Krahn M, Dorian P, Hoch JS, Boon H, et al. Systematic review and network meta-analysis of stroke prevention treatments in patients with atrial fibrillation. Clinical pharmacology : advances and applications. 2016;8:93-107.
72. Tereshchenko LG, Henrikson CA, Cigarroa J, Steinberg JS. Comparative Effectiveness of Interventions for Stroke Prevention in Atrial Fibrillation: A Network Meta-Analysis. Journal of the American Heart Association. 2016;5(5).
73. Kikkert WJ, van Geloven N, van der Laan MH, Vis MM, Baan J, Jr., Koch KT, et al. The prognostic value of bleeding academic research consortium (BARC)-defined bleeding complications in ST-segment elevation myocardial infarction: a comparison with the TIMI (Thrombolysis In Myocardial Infarction), GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), and ISTH (International Society on Thrombosis and Haemostasis) bleeding classifications. Journal of the American College of Cardiology. 2014;63(18):1866-75.
74. Vranckx P, Leonardi S, Tebaldi M, Biscaglia S, Parrinello G, Rao SV, et al. Prospective validation of the Bleeding Academic Research Consortium classification in the all-comer PRODIGY trial. European heart journal. 2014;35(37):2524-9.

CHAPTER 7: Cost-effectiveness of warfarin care bundles and novel oral anticoagulants (NOACs) for stroke prevention in patients with atrial fibrillation in Thailand

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7.1. Brief Summary

As newer but more expensive anticoagulant interventions such as warfarin care bundles and NOACs have emerged for SPAF, decision-making process in this field is more complicated than ever especially in the presence of budget constraints. Therefore, both clinical and economic evidence should be used to inform decision-makers about the efficient allocation of scare healthcare resources. Previous Chapter 5 and Chapter 6 have addressed the clinical evidence of anticoagulant interventions available for SPAF.

This chapter instead explore the economic aspect of these interventions. The aim of this chapter is to report a study that evaluated whether warfarin care bundles and NOACs are cost-effective alternatives to usual warfarin care for patients with AF from the societal and healthcare perspective, within the healthcare context of a middle-income country. This study focused on a middle-income country because access to newer effective intervention is a major healthcare challenge in such region due to insufficient healthcare resources. Thailand was therefore selected as our study setting to represent the healthcare context of a middle-income country. Additionally, Thailand also has a rather similar healthcare context as other countries within the Southeast Asia region. As such, it is plausible that findings from our study may be transferable to these countries. As our study evaluated all interventions including warfarin care bundles and NOACs simultaneously in a single model, it was able to illustrate the potential changes in economic outcomes of NOACs versus investing more resources to improve the quality of anticoagulation control through warfarin care bundles.

Based on our findings, all NOACs (e.g. dabigatran, rivaroxaban, apixaban and edoxaban) were not cost-effective interventions for the Thailand AF population. Contrarily, PSM has the highest potential to be a cost-effective strategy in Thailand. As NOACs are not fully reimbursed yet in many low- and

middle-income countries, findings from this study will be beneficial in helping to chart their future anticoagulant care.

Currently, a manuscript reporting this study has been submitted to a peer-review journal for consideration of publication. Due to the constraints of word limits and publication space, the submitted manuscript reported the comprehensive methods and results within its supplementary appendix.

7.2. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and affects 1.9% of the Thai population aged more than 65 years.[1] Patients with AF are associated with five-fold increased risk of stroke, resulting in significant morbidity and mortality.[2] Stroke prevention is therefore an essential component of AF management. For decades, warfarin has been the only effective oral anticoagulant for stroke prevention in AF (SPAF).[3] Although inexpensive and effective, it is often associated with increased risk of bleeding and poor quality of life due to the need for frequent monitoring. oreover, the warfarin control in many countries warfarin control is suboptimal; in Thailand the time in therapeutic range (TTR) is less than 50%.[4, 5]

Due to the perceived inconvenience associated with usual warfarin care, warfarin care bundles have been introduced and are based on the concept of combining warfarin with another intervention such as genotyping, patient' self-testing (PST) or self-management of warfarin (PSM) and left atrial appendage closure (LAAC).[6] Warfarin care bundles might optimize anticoagulation control by either achieving higher TTR value or reduce the dependency for long-term warfarin therapy.

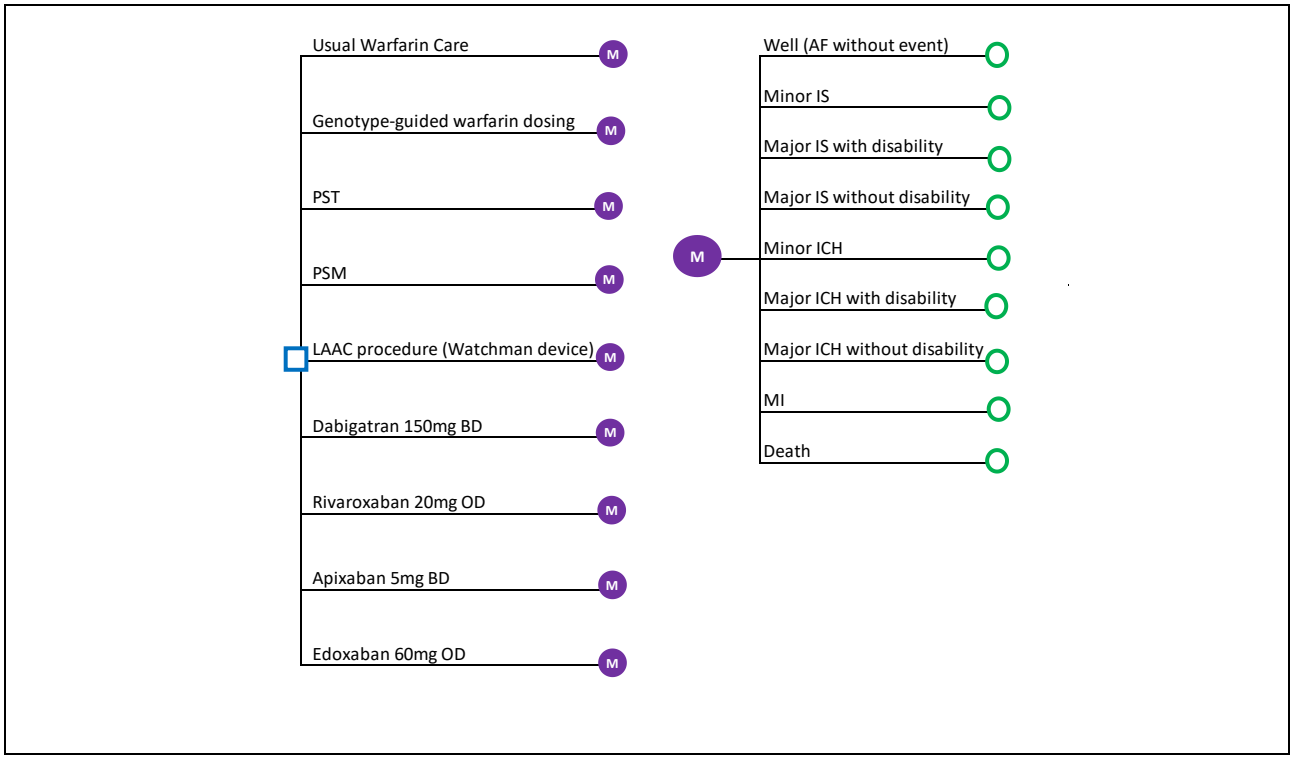
Polymorphisms of VKORC1 and CYP2C9 genes have been found to influence warfarin dosing, accounting for approximately 30% to 50% of the variability in warfarin daily-dose requirements.[7, 8] Therefore, VKORC1 and CYP2C9 pharmacogenetic testing can be used to guide warfarin dosing and the benefits of genotype-guided warfarin dosing have been previously assessed in two randomized trials.[9, 10] However, there is no final consensus yet on the benefits of genotype-guided dosing in clinical practice. In PSM, patients conduct their own monitoring test and adjust their warfarin dosage independently according to the provided algorithm while in PST, patients conduct the test and obtain dosage recommendations from healthcare professionals instead. Previous studies have shown that PST/PSM resulted in fewer thromboembolic events and death.[11, 12] In addition, percutaneous LAAC

is also introduced as a device-based alternative.[13] The Watchman device, the first FDA-approved LAAC device, has demonstrated to be non-inferior to warfarin for SPAF.[13, 14] LAAC-treated patients may discontinue lifelong anticoagulation following device implantation.[14]

Recent years have also seen the introduction of novel oral anticoagulants (NOACs) as alternatives to warfarin for SPAF. These agents have fixed dosing and predictable pharmacokinetics, which eliminates the need for routine monitoring.[15] However, the costs of NOACs and care bundles are substantially higher than that of usual warfarin care. Hence, there remains uncertainty regarding their emerging place in therapy. The objective of this study was to evaluate whether warfarin care bundles and NOACs are cost-effective alternative to usual care for patients with AF within a Thai healthcare context.

7.3. Methods

Description of Model



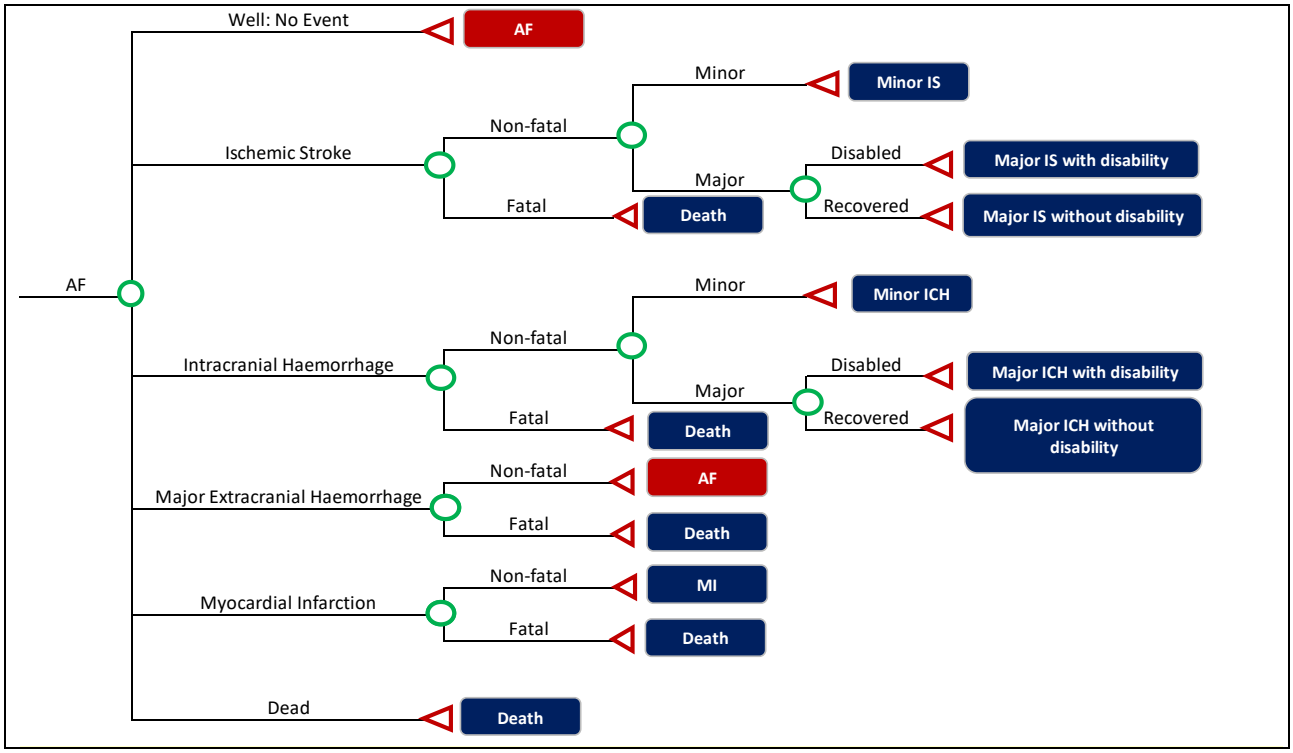


Figure 7.3.1. Schematic of the Markov Model. M represented a Markov process with 10 health states. Health states coloured in blue are permanent health states, with the remainder being transient health states occurring for a maximum period of 3 months before returning to prior health state. Abbreviations: AF, atrial fibrillation; AC, anticoagulation clinics; ECH, extracranial haemorrhage; ICH, intracranial haemorrhage; IS, ischemic stroke; LAAC, left atrial appendage closure; MI, myocardial infarction; PST, patient's self-testing of warfarin; PSM, patient's self-management of warfarin

A Markov model (Figure 7.3.1) was adopted from Rattanachotphanit et al.[16] to evaluate the cost and outcomes of anticoagulant interventions: usual warfarin care, genotype-guided warfarin dosing, PST, PSM, LAAC with Watchman device, dabigatran 150mg, rivaroxaban 20mg, apixaban 5mg and edoxaban 60mg. A detailed description of the interventions can be found in S-7-1.

The baseline patient population was a hypothetical cohort of 65-year old patients with AF who had no contraindications to anticoagulation. All patients entered the model at the well AF health state. In each cycle, patients can either remain in their current health state, experience a clinical event or die. The following clinical events were modelled: ischemic stroke (IS), myocardial infarction (MI), intracranial haemorrhage (ICH), major extracranial haemorrhage (ECH) and death. ICH included haemorrhagic stroke. IS and ICH were further divided with respect to disease severity: minor or major. One third of patients experiencing stroke at the major severity level became disabled.

Consistent with other models[17, 18], IS, ICH and MI were modelled as closed health states, such that after experiencing the first event, patients could only experience recurrent events or die. If patients experienced recurrent IS or ICH in the model, they would transition to IS or ICH of the same or greater severity. Major ECH was modelled as transient health state, such that patients who survived an event would return to the AF "well" state without any residual deficits. A lifetime horizon was adopted in the base-case analysis, which was divided into 3-month cycles and performed from societal perspective. All costs and outcomes were discounted at a rate of 3% in line with the recommendations of Thai Health Technology Assessment (HTA) guideline.[19] The analyses were performed using Microsoft Excel® (Microsoft Corp., Redmond, WA).

The following assumptions were set into the model as: (1) the effects of interventions occurred immediately after initiation and remained constant over time, (2) the adherence to each intervention was similar, (3) NOACs were used in fixed doses without further adjustment in patients with renal impairment, (4) patients who experienced any clinical events remained on the same treatment without switching to other intervention or stopping the anticoagulant. Although these assumptions may overestimate the clinical benefits of the interventions, these assumptions were consistent with previous economic evaluations in this field [20-22].

Risks of Clinical Events

Usual warfarin care served as the reference treatment in the Markov model. Thus, the baseline clinical events for this intervention were derived from Thai patients whenever possible (S-7-3).[4] To represent the comparative risks of clinical events for other interventions, relative risks (RRs) were applied to the rates of usual warfarin care. These RRs were obtained from a network meta-analysis. As head-to-head trials between NOACs and warfarin care bundles are not available yet, their comparative

effectiveness in AF can only be estimated through indirect treatment comparison using a common comparator, in this case usual warfarin care.[23] The model incorporated the same risks of MI for all warfarin care bundles. Additionally, we also assumed that the benefits in reducing the risk of IS and bleedings for genotype-guided dosing occurred in the first 3 months of warfarin initiation only. This is because the maintenance dose is reached in most patients within the induction phase.[24]

Rates of IS, bleedings and MI were adjusted over time to account for the increased risk associated by ageing by a factor of 1.46, 1.97 and 1.30 per decade of life, respectively.[3, 25, 26] Risks of recurrence after any clinical events were assumed to be independent of treatment and were estimated to be 2.2 for IS, 2.72 for bleedings and 2.04 for MI.[16-18] The distribution of diseases severity levels in each health state and the 3-month case-fatality rates were based on previous literature.[16]

Mortality

All clinical events were subjected to case-fatality within 3 months (Table 7.3.1). Allowance was also made in the model for patients to die from other causes, which was modelled based on age-specific general Thai life table[27] and inflated by an excess risk of 1.5 for patients in AF state.[28, 29] Additionally, a higher mortality, depending on disease severity levels, was also applied to patients who survived clinical events, using mortality-risk multipliers obtained from previous literature.[16-18]

Costs

The cost included (i) direct medical costs and (ii) direct non-medical costs. In accordance with Thai HTA guideline[19], indirect cost was excluded to prevent double counting as the health-related quality of life of patients with morbid conditions has been captured by QALY.[30] All costs were adjusted to 2019 Thai Baht (THB) values using the Medical Care consumer price index (CPI).[31] For inter-country comparisons, costs were then converted to US dollars (USD1=31.35 THB).

The cost of acute clinical events selected by the ICD-10 was calculated using the cost-to-charge ratio method based on the number of admissions, length of hospital stay and Diagnosis-related Group relative weight adopted from Rattanachotphanit et al.[16] Maintenance costs for IS, ICH and MI were derived from published Thai study.[32]

The total costs for each intervention were the sum of various cost components that were required for the delivery of the intervention such as the cost of AC visits multiplied by the frequency of visits in 3 months, cost of point-of-care (POC) coagulometers, cost of pharmacogenetic testing, cost of the drug or device, cost of INR strips, cost of lancets and cost of training. Each intervention had different cost components which were summarized in in S-7-5.

Direct non-medical costs included transportation, food and informal care costs. The transportation and food costs were based on the standard cost list for Thai HTA.[33] These costs were counted for the patient and an accompanying person as previous study have shown that a stroke survivor on average came to a hospital with a caretaker.[34] For patients with disabling stroke, additional informal care costs were obtained from a study of 101 Thai patients for at least 6 months.[35]

Utilities

The baseline utility was 0.84, based on the analysis of Thai patients reported with cardiovascular diseases in the 2015 Health and Welfare Survey.[16] We then adjusted the baseline utility to reflect the disutility associated with aging and occurrence of clinical events. Utility decrements associated with permanent clinical events were applied for the remainder of patient's lifetime. Analysis assumed no difference in utility values on interventions.

Table 7.3.1. Input parameters, values and data sources used in the model

Parameters	Base case	Range/SE	Source(s)
Proportion of severity per clinical events			
Ischemic stroke			
Minor	0.313	-	[16]
Major	0.283	-	[16]
Disabled	0.316	0.138 – 0.745	[36]
Fatal	0.404	-	[16]
Intracranial haemorrhage			
Minor	0.210	-	[16]
Major	0.114	-	[16]
Disabled	0.316	0.138 – 0.745	[36]
Fatal	0.676	-	[16]
Myocardial infarction, fatal	0.327	-	[16]
Major extracranial haemorrhage, fatal	0.346	-	[16]
Event-rate adjustments			
Increased risk of recurrence given an event			
Ischemic stroke	2.2	-	[16]
Major bleeding	2.72	-	[17, 18]
Myocardial infarction	2.04	-	[16]
Increased risk of death given an event			
Atrial fibrillation	1.5	-	[16]
Ischemic stroke			
Minor	5.84	4.08 – 7.60	[17, 18]
Major	15.75	13.99 – 17.51	[17, 18]
Intracranial haemorrhage			
Minor	5.84	4.08 – 7.60	[17, 18]
Major	15.75	13.99 – 17.51	[17, 18]
Myocardial infarction	3.36	2.27 – 5.03	[17, 18]
Increased risk of event per 10-year age increment			
Ischemic stroke	1.46	-	[3]
Major bleeding	1.97	-	[25]
Myocardial infarction	1.30	-	[26]
Relative risks of ischemic stroke			
Genotype-guided warfarin dosing	0.33	0.01 – 8.45	[23]
Patient's self-testing of warfarin	0.99	0.51 – 0.93	[23]
Patient's self-management of warfarin	0.24	0.08 – 0.68	[23]

Parameters	Base case	Range/SE	Source(s)
LAAC procedure (Watchman device)	0.89	0.45 – 1.78	[23]
Dabigatran 150mg	0.89	0.54 – 1.46	[23]
Rivaroxaban 20mg	0.79	0.57 – 1.1	[23]
Apixaban 5mg	0.76	0.51 – 1.12	[23]
Edoxaban 60mg	0.82	0.51 – 1.32	[23]
Relative risks of intracranial haemorrhage			
Genotype-guided warfarin dosing	1.00	0.02 – 50.4	[23]
Patient's self-testing of warfarin	1.37	0.51 – 3.64	[23]
Patient's self-management of warfarin	1.00	0.14 – 7.29	[23]
LAAC procedure (Watchman device)	0.22	0.06 – 0.76	[23]
Dabigatran 150mg	0.41	0.24 – 0.70	[23]
Rivaroxaban 20mg	0.76	0.53 – 1.08	[23]
Apixaban 5mg	0.44	0.28 – 0.70	[23]
Edoxaban 60mg	0.48	0.30 – 0.78	[23]
Relative risks of myocardial infarction			
Dabigatran 150mg	1.40	1.01 – 1.92	[23]
Rivaroxaban 20mg	0.82	0.63 – 1.06	[23]
Apixaban 5mg	0.88	0.67 – 1.15	[23]
Edoxaban 60mg	0.95	0.75 – 1.20	[23]
Relative risks of major extracranial haemorrhage			
Genotype-guided warfarin dosing	1.00	0.02 – 50.4	[23]
Patient's self-testing of warfarin	1.37	0.51 – 3.64	[23]
Patient's self-management of warfarin	1.00	0.14 – 7.29	[23]
LAAC procedure (Watchman device)	0.22	0.06 – 0.76	[23]
Dabigatran 150mg	0.41	0.24 – 0.70	[23]
Rivaroxaban 20mg	0.76	0.53 – 1.08	[23]
Apixaban 5mg	0.44	0.28 – 0.70	[23]
Edoxaban 60mg	0.48	0.30 – 0.78	[23]
Utility Values			
Long-term Utility			
Atrial Fibrillation	0.84	0.010	[16]
Utility decrement associated with events			
Ischemic Stroke			
Minor	0.13	-	[16]
Major	0.32	-	[16]

Parameters	Base case	Range/SE	Source(s)
Major with disability	0.48	-	[16]
Intracranial Haemorrhage			
Minor	0.13	-	[16]
Major	0.32	-	[16]
Major with disability	0.48	-	[16]
Myocardial Infarction	0.12	0.10 – 0.14	[16]
Major Extracranial Haemorrhage	0.15	0.040	**[16]**
Decrement per one-year increase of age	0.005	0.002	[16]
Costs (USD 2019)			
Direct Medical Costs			
Drug Acquisition Costs (per cycle)			
Warfarin	10.39	8.31 – 12.47	[37]
Dabigatran 150mg	290.18	232.15 -348.22	[37]
Rivaroxaban 20mg	263.45	210.76 – 316.15	[37]
Apixaban 5mg	271.07	216.85 – 325.28	[37]
Edoxaban 60mg	273.39	218.71 – 328.07	[37]
Aspirin, per tab	0.009	0.007 – 0.011	[37]
Clopidogrel 75mg, per tab	0.12	0.09 – 0.14	[37]
Watchman Device, Boston Scientific (per device)	7,974.48	6,379.59 – 9569.38	Thai Abott
Intervention Component Costs			
Pharmacogenetic Test (first time)	101.53	81.22 – 121.83	[24]
LAAC Procedure plus 2 follow-up TEE (first time)	887.40	709.92 – 1,064.88	[38]
PST Training Session (first time)	22.20	17.76 – 26.64	[39]
PSM Training Session (first time)	44.40	22.20 – 66.60	[39]
Point-of-care device, Coagucheck XS	882.44	705.96 – 1,058.93	[39]
INR strip (per item)	5.15	4.12 – 6.18	[39]
Lancet (per strip)	0.13	0.11 – 0.16	[39]
PST Phone Service Cost (per service)	4.82	3.85 – 5.78	[39]
Anticoagulant Service Cost (per visit)	8.15	6.52 – 9.78	[39]
Laboratory INR test (per test)	2.80	2.24 – 3.36	[39]
Acute Clinical Event Costs (per episode)			
Ischemic Stroke			
Minor	704.31	563.44 – 845.17	[16]
Major	1,622.97	1,298.37 – 1,947.56	[16]
Fatal	1,071.77	857.42 – 1,286.12	[16]
Intracranial Haemorrhage			
Minor	1,408.61	1,126.89 – 1,690.33	[16]
Major	3,184.69	2,547.75 – 3,821.63	[16]

Parameters	Base case	Range/SE	Source(s)
Fatal	918.66	734.93 – 1,102.39	[16]
Myocardial Infarction			
Non-fatal	2,449.76	1,959.81 – 2,939.71	[16]
Fatal	1,133.01	906.41 – 1,359.62	[16]
Major Extracranial Haemorrhage			
Non-fatal	520.57	416.46 – 624.69	[16]
Fatal	857.42	685.93 – 1,028.90	[16]
Maintenance Clinical Event Costs (per cycle)			
Ischemic Stroke	277.81	222.25 – 333.37	[40]
Intracranial Haemorrhage	277.81	222.25 – 333.37	[32]
Myocardial Infarction	101.32	81.05 – 121.58	[40]
Direct Non-Medical Costs			
Transportation (per visit)	4.89	3.91 – 5.87	[33]
Additional food (per visit)	1.80	1.44 – 2.16	[33]
Informal Care for Disabled Stroke Patient (per cycle)	1,244.80	995.84 – 1,493.76	[35]

Abbreviations: SE, standard error

Analyses

The cost-effectiveness of anticoagulant interventions compared to usual warfarin care were assessed using incremental cost-effectiveness ratio (ICER), which was calculated as incremental cost per QALY gained. According to Thai HTA recommendation, any interventions with an ICER less than 160,000 THB (USD5,104) was considered 'cost-effective'.[19] One-way sensitivity analyses were performed to explore uncertainty in the model parameters. Scenario analyses assuming lower costs of NOACs, Watchman device, pharmacogenetic testing and point-of-care device were undertaken to explore the uncertainty surrounding the most important component cost of each intervention.

Probabilistic sensitivity analysis (PSA) was performed to assess the robustness of parameter values and their impact on ICERs. The input parameters were varied using their 95% confidence intervals (CI) of the point estimates or on ±20%. Additionally, net monetary benefit (NMB) was calculated for

the sensitivity in the resultant cost and outcomes, whereby the monetary values of willingness to pay (WTP) for QALY gained were compared with total costs incurred by each intervention. The intervention that yielded the highest NMB was considered cost-effective. The probabilities of being cost-effective across all interventions were plotted against varying WTP threshold to generate the cost-effectiveness acceptability curves (CEAC).

7.4. Results

Base-case Analysis

Table 7.4.1. shows the estimated number needed to treat (NNT) or harm against usual warfarin care and the cumulative events over a lifetime for each intervention in a cohort of 100,000 patients. All interventions demonstrated improved outcomes for IS, with PSM resulted in the smallest NNT. LAAC and each NOACs were associated with improved clinical outcomes for ICH and major ECH. Among NOACs, only dabigatran was associated with poorer outcomes in MI. The cumulative events for Thai patients who used usual warfarin care were approximately 5305 events for IS and 1418 events for ICH. PSM was able to reduce IS to 1317 events while increasing ICH slightly to 1468 events. LAAC reduced IS to 4927 events and ICH to 326 events only. All NOACs reduced IS and ICH to less than 5000 and 1000 events, respectively.

From the base-case analysis (Table 7.4.2), usual warfarin care resulted in 15.87 QALYs to effectiveness, while the estimated lifetime costs from societal and healthcare perspective were USD1,421 and USD868, respectively. All interventions demonstrated higher QALY than usual warfarin care except for PST.

Table 7.4.1. Cumulative events for each intervention per 100 000 patients, number needed to treat, and number needed to harm over a lifetime, base-case analysis results

	Usual Warfarin Care	Genotype-guided warfarin	PST	PSM	LAAC Watchman	Dabigatran 150mg	Rivaroxaban 20mg	Apixaban 5mg	Edoxaban 60mg
Number needed to treat (or to harm): usual AC warfarin as the reference									
IS		648	708	25	264	220	98	90	124
ICH		42191	204	1675	92	122	319	130	140
ECH		14559	70	578	32	42	110	45	48
MI		33655	3441	1471	1308	127	349	662	3206
Cumulative events (total population)									
IS	5305	5151	5164	1317	4927	4850	4287	4192	4499
ICH	1418	1420	1909	1478	326	600	1105	651	706
ECH	4109	4116	5529	4282	947	1740	3204	1888	2047
MI	1779	1782	1750	1847	1855	2566	1492	1628	1748

Abbreviations: ECH, major extracranial haemorrhage; IS, ischemic stroke; ICH, intracranial haemorrhage; LAAC, left atrial appendage closure; MI, myocardial infarction; PST, patient's self-testing; PSM, patient's self-management

Underlining indicates number needed to harm

From both societal and healthcare perspective, PSM is a cost-effective intervention when compared to usual warfarin care, with an incremental cost-effectiveness ratio (ICER) of USD1,395/QALY and USD1,951/QALY respectively. In the base case analysis, no NOACs yielded an ICER below the threshold of USD5,104. When compared to the next most effective intervention, PST, rivaroxaban, edoxaban and dabigatran were strictly dominated (e.g. lower QALYs and higher costs). Genotype-guided dosing and apixaban were extendedly dominated (e.g. higher ICER in comparison to the next most effective intervention). Thus, from the societal perspective, only usual warfarin care, PSM and LAAC remained on the efficient frontier of SPAF with an ICER of USD1,395 for usual warfarin care vs. PSM and USD93,830 for PSM vs. LAAC (Figure 7.4.1). The efficient frontier from the healthcare perspective was provided in S-7-6.

Table 7.4.2. Effectiveness, costs, and incremental cost-effectiveness ratios (ICERs)

Interventions	Life Years	QALY	Costs (USD)	ΔQALY	ΔCost	ICER[c] (USD/QALY)	ICER[d] (USD/QALY)
SOCIETAL PERSPECTIVE [a] (Base case)							
Usual AC warfarin	21.24	15.87	1,421				
Genotype-guided dosing	21.27	15.89	1,498	0.03	77	3,025	Dominated[§]
PSM	21.96	16.36	2,109	0.49	688	1,395	1,395
PST	20.91	15.65	2,427	-0.22	1,006	-4,575*	Dominated
Rivaroxaban	21.69	16.18	5,806	0.31	4,385	14,247	Dominated
Apixaban	22.02	16.40	6,006	0.53	4,586	8,678	Dominated[§]
Edoxaban	21.91	16.32	6,039	0.45	4,619	10,186	Dominated
Dabigatran	21.83	16.27	6,375	0.40	4,954	12,454	Dominated
LAAC (Watchman)	22.09	16.44	9,404	0.57	7,983	13,982	93,830
HEATHCARE PERPSECTIVE [b]							
Usual AC warfarin	21.24	15.87	868				
Genotype-guided dosing	21.27	15.89	958	0.03	90	3,533	Dominated[§]
PSM	21.96	16.36	1,831	0.49	962	1,951	1,952
PST	20.91	15.65	2,148	-0.22	1,279	-5,815*	Dominated
Rivaroxaban 20mg	21.69	16.18	5,525	0.31	4,656	15,126	Dominated
Apixaban 5mg	22.02	16.40	5,724	0.53	4,855	9,188	Dominated[§]
Edoxaban 60mg	21.91	16.32	5,757	0.45	4,888	10,780	Dominated
Dabigatran 150mg	21.83	16.27	6,092	0.40	5,224	13,131	Dominated
LAAC (Watchman)	22.09	16.44	9,185	0.57	8,316	14,564	94,585

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; AC, anticoagulation clinic; PST, patient's self-testing warfarin; PSM, patient's self-management warfarin; LAAC: left atrial appendage closure

[a]*For societal perspective, direct medical and non-medical costs were included.*

[b]*For the payer perspective, only direct medical costs were included.*

[c]*Relative to usual AC warfarin. Values have been rounded*

[d]*Relative to the next less costly nondominated strategy. Values have been rounded*

[§]*Dominated through extension*

**Negative ICER due to higher costs and lower effectiveness of PST compared with usual AC warfarin.*

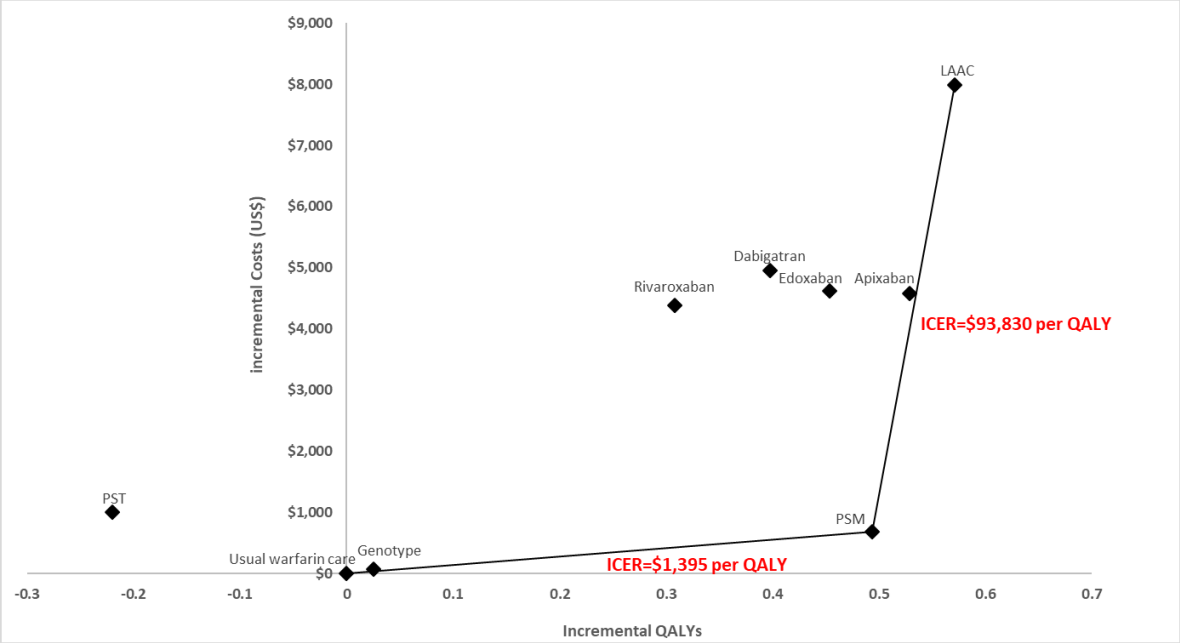


Figure 7.4.1. Incremental costs and effects (measured in QALYs) relative to usual warfarin care (societal perspective). The connecting line represent the efficient frontier; the slope of each segment corresponds to the ICER between the points defining the segment. Interventions with fewer incremental QALYs are to the left and those with greater incremental costs are higher. Points to the left of the life are dominated by interventions that are more effective than at the frontier. Efficiency frontier from the healthcare payer perspective is available in S-7-6.

Abbreviations: ICER, incremental cost-effectiveness ratio; PST: patient's self-testing; LAAC, left atrial appendage closure; PSM: patient's self-management; QALY, quality-adjusted life years.

Sensitivity Analysis

Tornado diagrams illustrating the 10 most influential variables in descending order of influence are depicted at S-7-8. Inputs that had a universal impact on the ICERs of all interventions were the relative risks of IS and ICH. The cost of NOACs also influenced the ICERs of NOACs with lower costs resulting in more favourable cost-effectiveness. Scenario analyses demonstrated that, a 50% reduction in the prices of apixaban and edoxaban yielded ICER below the Thailand's WTP threshold, thereby rendering these NOACs cost-effective at lower drug prices. (S-7-9).

PSA results are shown graphically in S-7-7. In CEAC (Figure 7.4.2), the probability of usual warfarin care being cost-effective was initially 100% and plummeted to 50% at the WTP of USD700 and disappeared once the WTP reached USD7,000. At WTP threshold of USD 5,104, the probability of PSM being cost-effective was 78% while the probabilities of NOACs and LAAC being cost-effective

were negligible. When the WTP increased to the commonly used USD50,000 threshold, the probability of being cost-effective for LAAC increased to 27% while the probabilities of NOACs being cost-effective remain less than 10%.

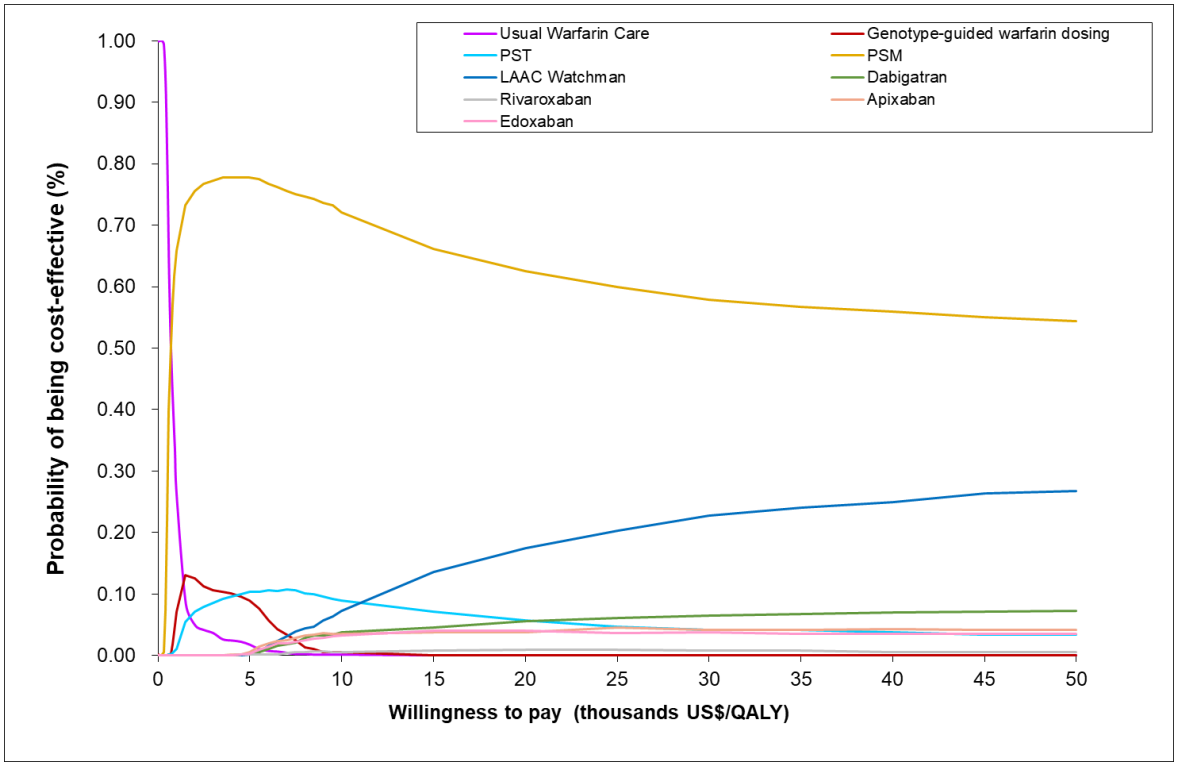


Figure 7.4.2. Cost-effectiveness acceptability curves from societal perspective. The curves show the probability of each intervention being cost-effective at any willingness to pay value for an additional QALY.

Abbreviations: LAAC, left atrial appendage closure; QALY, quality adjusted life year; PSM, patient's self-management; PST: patient's self-testing

7.5. Discussion

The present study is unique because it is the first published economic evaluation comparing warfarin care bundles and NOACs simultaneously in Thailand in terms of costs, QALYs and subsequent efficiency. Several cost-effectiveness analyses (CEA) have been conducted in Thailand[16, 22, 24, 39, 41] but none of them evaluated all interventions simultaneously, with majority of them focusing on NOACs only. Thus, little is known about the potential changes in economic outcomes of NOACs versus investing more resources in improving anticoagulant control through warfarin care bundles. This drawback was addressed in our study which simultaneously compared all interventions in a

single model using efficiency frontier approach. The adoption of such methodology ensures that only interventions that are cost-effective are analysed against each other and thus, interventions with the most value for money can be identified.

In our study, NOACs were not cost-effective in Thailand and were dominated by PSM. Among the NOACs, only apixaban and edoxaban had the potential to be cost-effective when their prices were halved. Our findings contradict with previous CEA[17, 18, 20, 21], whereby NOACs were found to be cost-effective instead in their healthcare settings. Previous studies were mostly conducted in high-income countries which have different drug pricing and a higher cost-effectiveness threshold (≥USD50,000/QALY) than in low- or middle-income countries. Thus, in our study, NOACs were not cost-effective for SPAF at their current prices and such findings are expected to be similar in other low- and middle- income countries too. LAAC was also not cost-effective in Thailand as it offers slight societal gain at a significantly high cost, demonstrated by the very high ICER exceeding the threshold level in Thailand.

Our study showed that PSM has the highest potential to be a cost-effective strategy, with 78% chance of being considered cost-effective in Thailand which suggests that PSM might be cost-effective too in wealthier countries. The key driver for this model was the estimate of the impact of PSM on ischemic stroke. However, based on our Study 2 where the comparative risks were derived from, the quality of evidence of PSM for this outcome was generally rated as low quality due to low number of events and wide confidence interval. [23]. Therefore, these findings need to be interpreted with caution. Additionally, although PSM may be the most optimal intervention, it has several implementation challenges. The inaccuracy of point-of-care (POC) coagulometers, inadequate physician-patient engagement and incomplete follow-up care may serve as possible barriers for PSM adoption. Patient's adherence to optimal pattern of self-management is also another possible barrier

in ensuring good PSM performance and timely anticoagulation control. Therefore, the selection of patients for PSM requires careful consideration, in the context of their cognitive, physical abilities, dexterity and confidence level.[42] Nonetheless, the continual advances in technology and healthcare innovation have greatly expands the practicality of PSM in healthcare settings. It is worth acknowledging that coagulometers is constantly improving and modern coagulometers have improved in their ease of use, accuracy and cost, which in theory, could widen possible candidate pool for PSM and the magnitude of economic evaluation.[42] The telehealth concept can also be integrated within PSM to support the feasibility of PSM adoption. Telehealth may include a variety of telecommunication technologies such as wireless applications, videoconferencing and e-health patient portals which allows physicians to monitor patient's adherence pattern of optimal self-management and to access PSM data remotely in timely manner, thereby improving the physician-patient communication and ensuring good anticoagulation control.

Several limitations apply to our analysis. Firstly, the data used in our model were mostly from clinical trials with restrictive enrolment and short follow-up periods, which may not reflect the effectiveness of these interventions in the long run. Second, we assumed no treatment switching or discontinuation of anticoagulants due to clinical events. We also assumed that the clinical events in our model were mutually exclusive and this may not reflect the real-world setting where patients may experience more than one event at the same time. Although these assumptions may overestimate the clinical benefits of the interventions, such assumptions were consistent with previous.[20, 21] Fourth, our findings might have limited generalizability to other countries. Nonetheless, it is plausible that our findings may still be beneficial in low- or middle-income countries with comparable healthcare context to those adopted in our analysis.

7.6. Conclusion

Our study indicates that NOACs, at their current pricing are unlikely to be cost-effective in a resource-limited setting such as Thailand from both societal and healthcare perspective unless their drug prices are further reduced. Contrarily, PSM has the highest potential to be a cost-effective strategy and appears to be the most economically justifiable intervention offering additional health benefits over other interventions for SPAF, at an acceptable cost based on Thailand's WTP threshold. Nonetheless, apart from economic standpoint, the affordability and feasibility of PSM adoption into the healthcare setting should be considered too.

References for Chapter 7

1. Phrommintikul A, Detnuntarat P, Prasertwitayakij N, Wongcharoen W. Prevalence of atrial fibrillation in Thai elderly. Journal of geriatric cardiology : JGC. 2016;13(3):270-3.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Archives of internal medicine. 1987;147(9):1561-4.
3. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Archives of internal medicine. 1994;154(13):1449-57.
4. Methavigul K Fau - Boonyapisit W, Boonyapisit W. Optimal INR level in Thai atrial fibrillation patients who were receiving warfarin for stroke prevention in Thailand. (0125-2208 (Print)).
5. Saokaew S, Sapoo U, Nathisuwan S, Chaiyakunapruk N, Permsuwan U. Anticoagulation control of pharmacist-managed collaborative care versus usual care in Thailand. International journal of clinical pharmacy. 2012;34(1):105-12.
6. Resar. R, Griffin. FA, Haraden. C, Nolan. TW. Using Care Bundles to Improve Health Care Quality Cambridge, Massachusetts: Institute for Healthcare Improvement; 2012 [Available from: www.IHI.org.
7. Tan GM, Wu E, Lam YY, Yan BP. Role of warfarin pharmacogenetic testing in clinical practice. Pharmacogenomics. 2010;11(3):439-48.
8. Wadelius M, Chen LY, Eriksson N, Bumpstead S, Ghori J, Wadelius C, et al. Association of warfarin dose with genes involved in its action and metabolism. Human genetics. 2007;121(1):23-34.
9. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A randomized trial of genotype-guided dosing of warfarin. The New England journal of medicine. 2013;369(24):2294-303.
10. Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. The New England journal of medicine. 2013;369(24):2283-93.
11. Heneghan CJ, Garcia-Alamino JM, Spencer EA, Ward AM, Perera R, Bankhead C, et al. Self-monitoring and self-management of oral anticoagulation. The Cochrane database of systematic reviews. 2016;7:Cd003839.
12. Sharma P, Scotland G, Cruickshank M, Tassie E, Fraser C, Burton C, et al. The clinical effectiveness and cost-effectiveness of point-of-care tests (CoaguChek system, INRatio2 PT/INR monitor and ProTime Microcoagulation system) for the self-monitoring of the coagulation status of people receiving long-term vitamin K antagonist therapy, compared with standard UK practice: systematic review and economic evaluation. Health technology assessment (Winchester, England). 2015;19(48):1-172.
13. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet (London, England). 2009;374(9689):534-42.
14. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. Jama. 2014;312(19):1988-98.
15. Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Therapeutics and clinical risk management. 2015;11:967-77.
16. Rattanachotphanit T, Limwattananon C, Waleekhachonloet O, Limwattananon P, Sawanyawisuth K. Cost-Effectiveness Analysis of Direct-Acting Oral Anticoagulants for Stroke

Prevention in Thai Patients with Non-Valvular Atrial Fibrillation and a High Risk of Bleeding. PharmacoEconomics. 2019;37(2):279-89.
17. Dorian P, Kongnakorn T, Phatak H, Rublee DA, Kuznik A, Lanitis T, et al. Cost-effectiveness of apixaban vs. current standard of care for stroke prevention in patients with atrial fibrillation. European heart journal. 2014;35(28):1897-906.
18. Lip GY, Kongnakorn T, Phatak H, Kuznik A, Lanitis T, Liu LZ, et al. Cost-effectiveness of apixaban versus other new oral anticoagulants for stroke prevention in atrial fibrillation. Clinical therapeutics. 2014;36(2):192-210.e20.
19. Chaikledkaew U, Kittrongsiri K. Guidelines for health technology assessment in Thailand (second edition)--the development process. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2014;97 Suppl 5:S4-9.
20. Canestaro WJ, Patrick AR, Avorn J, Ito K, Matlin OS, Brennan TA, et al. Cost-effectiveness of oral anticoagulants for treatment of atrial fibrillation. Circulation Cardiovascular quality and outcomes. 2013;6(6):724-31.
21. Harrington AR, Armstrong EP, Nolan PE, Jr., Malone DC. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. Stroke. 2013;44(6):1676-81.
22. Dilokthornsakul P, Nathisuwan S, Krittayaphong R, Chutinet A, Permsuwan U. Cost-Effectiveness Analysis of Non-Vitamin K Antagonist Oral Anticoagulant Versus Warfarin in Thai Patients with Non-Valvular Atrial Fibrillation. Heart Lung Circ. 2019:1-11.
23. Ng SS, Lai NM, Nathisuwan S, Jahan NK, Dilokthornsakul P, Kongpakwattana K, et al. Comparative efficacy and safety of warfarin care bundles and novel oral anticoagulants in patients with atrial fibrillaation: a systematic review and network meta-analysis. 2019.
24. Chong HY, Saokaew S, Dumrongprat K, Permsuwan U, Wu DB-C, Sritara P, et al. Cost-effectiveness analysis of pharmacogenetic-guided warfarin dosing in Thailand. Thrombosis Research. 2014;134(6):1278-84.
25. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke. 2003;34(8):2060-5.
26. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Jama. 2001;285(19):2486-97.
27. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nature reviews Cardiology. 2014;11(11):639-54.
28. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998;98(10):946-52.
29. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ (Clinical research ed). 2016;354:i4482.
30. Riewpaiboon A. Measurement of costs. Journal of the Medical Thailand Association. 2008;91(Suppl 2):S28-S37.
31. Bureau of Trade and Economic Indicies Ministry of Commerce Thailand. Report of consumer price index of Thailand 2019 [
32. Anukoolsawat P, Sritara P, Teerawattananon Y. Costs of Lifetime Treatment of Acute Coronary Syndrome at Ramathibodi Hospital. Thai Heart Journal. 2006;19:132-43.
33. Riewpaiboon A. Standard cost lists for health economic evaluation in Thailand. Journal of the Medical Thailand Association. 2014;97(Suppl 5):S127-S34.
34. Singhpoo K, Tiamkao S, Kuchaisit C, Ariyanuchitkul S, Sangpongsanon S, Kaamsa-ard S, et al. The quality of life of stroke outpatients at Srinagarind Hospital. Journal of the Medical Thailand Association. 2009;92(12):1602-9.

35. Riewpaiboon A, Riewpaiboon W, Ponsoongnern K, Van den Berg B. Economic valuation of informal care in Asia: a case study of care for disabled stroke survivors in Thailand. Social science & medicine (1982). 2009;69(4):648-53.
36. Kuptniratsaikul V, Kovindha A, Piravej K, Dajpratham P. First-Year Outcomes after Stroke Rehabilitation: A Multicenter Study in Thailand. ISRN Rehabilitation. 2013;2013:6.
37. Drug and Medical Supply Information Center, Ministry of Public Health 2019 [Available from: https://dmsic.moph.go.th/dmsic/index.php?p=1&id=1.
38. Standard Cost List for Health Technology Assessment, Health Intervention and Technology Assessment Ministry of Public Health 2019 [Available from: http://www.hitap.net/costingmenu/.
39. Kantito S, Saokaew S, Yamwong S, Vathesatogkit P, Katekao W, Sritara P, et al. Cost-effectiveness analysis of patient self-testing therapy of oral anticoagulation. Journal of thrombosis and thrombolysis. 2018;45(2):281-90.
40. Archongka Y, Manimmanakorn N, Kuptniratsaikul V, Solunda S, Yee-heng P. Unit Cost of Stroke Rehabilitation. Journal of the Medical Thailand Association. 2008;91(8):1257-62.
41. Jarungsuccess S, Taerakun S. Cost-utility analysis of oral anticoagulants for nonvalvular atrial fibrillation patients at the police general hospital, Bangkok, Thailand. Clinical therapeutics. 2014;36(10):1389-94.e4.
42. Sharma P, Scotland G, Cruickshank M, Tassie E, Fraser C, Burton C, et al. Is self-monitoring an effective option for people receiving long-term vitamin K antagonist therapy? A systematic review and economic evaluation. BMJ open. 2015;5(6):e007758.

CHAPTER 8: Overall Discussion and Conclusions

This dissertation presented three interrelated studies on anticoagulant interventions for SPAF. In this concluding chapter, the principal findings and limitations of each study are summarized. The overall implications of this dissertation, beyond each study are also discussed. Lastly, several suggestions on the future directions for this anticoagulant field will be provided.

8.1. Summary of Principal Findings

In Chapter 5 and Chapter 6, clinical evidence on anticoagulant interventions for SPAF, were synthesized from both primary and secondary research studies. Based on our overview of review (Chapter 5), existing evidence in this field is generally based on the comparison between NOACs with usual warfarin care only, without addressing warfarin care bundles and thus, present evidence may have favoured NOACs. Since the time NOACs are introduced into the market, there has been ongoing recommendations on the use of NOACs for SPAF especially in developed countries. As such, warfarin care bundles such as genotype-guided warfarin dosing, PST and PSM have been overshadowed by NOACs and the use of these care bundles has not been prioritized. Such circumstances are unfavourable as it may drive to the wrong conclusion on the benefits of NOACs without doing justice to more easily accessible management strategies that are exercised optimally. Furthermore, the degree of benefits of NOACs is highly dependent on the quality of anticoagulation control with warfarin, as measured by TTR. There is no evidence showing the superiority of NOACs over well-controlled warfarin therapy at TTR ≥65%. Therefore, if warfarin care bundles can improve TTR values, it is possible that warfarin performance may be as good as or even better than NOACs and thus, the switch to NOACs may not be necessary.

Motivated by this gap in clinical evidence, we conducted the second study (Chapter 6-systematic review) by performing indirect comparisons of usual warfarin care, warfarin care bundles and NOACs simultaneously in a single network. To our knowledge, our network meta-analysis is among

the first to perform simultaneous clustered ranking of the efficacy and safety outcomes of anticoagulant interventions, which allowed us to identify intervention that has the best balance of both benefits and risks. Findings from this study shows that warfarin care bundles achieved higher TTR than that of usual warfarin care (68.9% vs. 61.1%). NOACs and warfarin care bundles were also found to perform better than usual warfarin care. In fact, the warfarin care bundle of PSM and LAAC appeared to perform well in reducing the risk of stroke and bleeding respectively.

Economic evaluations in the healthcare has become more important in the recent years due to the pervasive scarcity of resources, driven by various factors such as the ageing population, the development of expensive newer interventions and the heightened knowledge, demands and expectations from the healthcare consumers with increased challenges in the allocation of economic resources. Therefore, economic evaluations can provide useful 'value-for-money' information to inform decision-makers about the efficient allocation of scare resources. In Chapter 7, we performed an economic evaluation in the setting of a middle-income country to characterize the cost-effectiveness of anticoagulant interventions in a resource-limited healthcare context. Our study demonstrates that NOACs were unlikely to be cost-effective in such setting unless NOACs pricing is further reduced by half.

Chapter 7 also identifies that PSM of warfarin is likely to be the most optimal anticoagulant intervention for SPAF in a resource-limited setting, with an approximately 78% chance of being considered cost-effective. Therefore, warfarin therapy is generally preferred for SPAF in middle-income countries and perhaps, improving anticoagulation control of warfarin through care bundles such as PSM should be considered instead of switching to NOACs completely. Although PSM may be the most optimal intervention in such setting, PSM raises several technical, operational and social challenges that should be considered prior adoption. A major barrier – effective implementation

strategies of PSM should be addressed to optimize the benefits of PSM and to prolong the sustainability of PSM in clinical practice. Nonetheless, with the rapid urbanization and technological advancement, the healthcare industry is becoming more reliant on digital technologies and therefore, existing barriers of PSM are not insurmountable. Telehealth can be integrated within PSM to improve the feasibility of PSM for adoption into healthcare system. Telehealth may include a variety of telecommunication technologies such as texting, mobile applications, videoconferencing and e-health patient portals, which allows the delivery of healthcare remotely without compromising the communication between physicians and patients. The integration of telehealth within PSM may also inadvertently increase access to PSM data. As such, clinicians can intervene in a timely manner with appropriate feedback and treatment plan modification without seeing the patient face-to-face. Although PSM may currently remain distant for feasible healthcare system, it is a promising intervention with favourable benefits for SPAF that ought to be explored in further depth and to be considered for future integration with modern healthcare technology.

8.2. Implications of Findings

This dissertation provides a learning model on which to base decision-making for stakeholders especially in middle-income countries on the importance of combining clinical and economic evidence to inform decisions on efficiency and allocation of scare resources. Over the years, several expensive newer anticoagulant interventions such as NOACs and warfarin care bundles have been introduced for SPAF. This growing anticoagulant armamentarium presents a challenge to existing funding deployment and intensifies the discussion on the affordability of these interventions at different healthcare decision-making levels. The costs of anticoagulant interventions should be balanced against the health outcomes estimated for each intervention based on two rationales.[1] Firstly, at a micro level, the absence of comparative clinical evidence may lead to patients receiving interventions that they might have otherwise rejected, had they been fully informed. Secondly, at the

macro level of healthcare system, failure for policymakers to consider the costs and efficiency of these interventions given the available resources may lower the quality of anticoagulant care and escalate healthcare spending.

Our findings suggest that despite the apparent advantages of NOACs for SPAF which eliminates the need for frequent monitoring, NOACs may not be cost-effective in a resource-limited setting. Thus, interventions that are clinically effective, are not necessarily cost-effective in a healthcare setting.

Such findings reiterate the importance of incorporating economic information into evidence-based decision-making. Without economic considerations, clinical evidence alone is an inadequate framework for policy decision-making. Clinical evidence obtained from systematic reviews and RCTs can provide clinicians and stakeholders with relevant information on the efficacy of interventions. However, it focuses on the clinical benefits and harms of interventions only and could not provide a complete evaluation on the efficiency of these interventions. Therefore, economic evaluation presented alongside clinical evidence can provide more valuable information in identifying interventions that result in the highest health gain per monetary unit spend.[2] Our dissertation shows that NOACs were not cost-effective in a middle-income country such as Thailand while warfarin care bundle of PSM is highly cost-effective for SPAF. These findings may provide useful information to policymakers in Thailand and in other low- or middle-income countries with similar healthcare context regarding NOACs affordability, reimbursement and listing in their national drug formulary. By identifying interventions that are most cost-effective in the local setting, policymakers can precisely chart their coming course of anticoagulant care for SPAF and prioritize investment in interventions that are worth investing while optimizing population health gain from a given budget. Besides that, by knowing that NOACs are unlikely to be cost-effective, stakeholders may consider renegotiating NOACs pricing with pharmaceutical industries to allow affordable reimbursement and access of these agents in their healthcare setting.

Nonetheless, integration of economic information into evidence-based decision-making is still lacking especially in low- and middle-income countries. These countries often face with cultural, ethical or institutional barriers in assessing economic evaluations, coupled with a lack of funding and research capacities to coordinate its own economic studies.[3] In addition, the absence of standard guidelines for conducting economic evaluation in most low- and middle-income countries is also one of the major barriers that hamper the use of economic results in healthcare policy decision-making.[3] Findings from this dissertation also highlight that economic evaluation conducted in developed countries like US, Europe or Canada have limited values to inform decisions in the setting of low- and middle-income countries due to constraints related to the context of each healthcare system. These include differences in disease prevalence, population demographics (e.g. age, socioeconomic status and comorbidities) and variations of healthcare system or public reimbursement scheme.[3] The great diversity on methodological requirements for conducting economic evaluations also greatly affects the transferability of economic results into lower income countries. Thus, it is necessary for these countries to develop their own capacity to conduct high-quality economic evaluations if economic evidence is to be used in healthcare policy decision-making.

8.3. Key Limitations

In Chapter 5 and Chapter 6, some of the limitations were the uncertainties on the effect sizes of anticoagulant interventions especially on secondary outcomes due to the presence of heterogeneity among primary studies and the threat of external validity. Thus, the overall findings on the efficacy and safety of these interventions need to be interpreted with caution. These findings are not definitive yet and should be confirmed in larger and higher quality studies especially for warfarin care bundles. Further research evaluating the performance of warfarin care bundles should not be disregarded despite the emergence of NOACs as these care bundles have their own advantages that are not

achievable by NOACs such as the ability to precisely measure anticoagulation effect and easy access to affordable antidote. In addition, head-to-head RCTs comparing NOACs with warfarin care bundles are still the preferred source of evidence to overcome the need for indirect comparison as adopted in our dissertation. Nevertheless, the reviews in our dissertation still serve as important piece of information for clinicians and healthcare providers to better understand the gap in current evidence and to plan future research in the anticoagulant field.

In Chapter 7, one of the limitations of our economic evaluation is the imputation of efficacy data from RCT instead of effectiveness data. Interventions being evaluated in RCTs are targeted at selected population, ideal circumstances and short time horizon in perfect conditions, which may not closely reflect the population encountered in routine clinical practice.[4] As such, future research using effectiveness data (real-world evidence) from large cohort studies or registry analyses for economic evaluations can be considered to improve the relevancy of the outcomes in the population. Even so, economic evaluations using RCT data are still the gold standard and can be supplemented with evaluations using effectiveness data to project real-world clinical situations to a degree capable of providing treatment guidelines in a daily clinical setting.

8.4. Recommendations for Future Research

Several gaps in knowledge and drawbacks are identified in the anticoagulant field that followed from our dissertation findings. Therefore, this field would benefit from further research by extending and further evaluating the conceptual framework developed in our dissertation:

1. Evidence remains sparse especially for warfarin care bundles in terms of stroke prevention and reduction in the risk of bleeding. Therefore, further higher quality studies (RCTs) needs to be conducted in patients with AF who receive these interventions to robustly capture their

potentials for SPAF and to determine how anticoagulant care should be adjusted in patients receiving these interventions.

2. It is important to conduct new studies with head-to-head comparisons of NOACs with each other and NOACs with warfarin care bundles. Due to the variability in patient populations, comorbidities, concomitant therapies and underlying patient care, indirect comparisons across RCTs (e.g. through network meta-analysis) in this anticoagulant field are subjected to heterogeneity and may have limited relevancy in clinical setting.

3. Additional studies utilizing prospectively constructed databases, registries or electronic health records with longer term outcomes data would be beneficial in bringing other insights of these anticoagulant interventions, especially with respect to safety. This real-world evidence (RWE) data can also evaluate the durability of benefits of anticoagulant interventions over a longer period than studied in RCTs. The imputation of RWE data into economic evaluations will also generate a more accurate and realistic prediction of therapeutic benefits of each intervention in a target population. Although it would be challenging to conduct RWE investigation in low- and middle-income countries that lack of registries, databases or proper recording, the future development and incorporation of RWE to supplement existing evidence and to support policy decision-making should be put into consideration.

4. It would be useful to conduct budget impact analysis (BIA) in addition to cost-effectiveness study, to provide policymakers with additional information on the financial consequences of covering and reimbursing new anticoagulant interventions for SPAF.[5] Given the need for financial sustainability in healthcare, BIA has a compelling role in assessing the affordability of an intervention by calculating the potential impact of the new interventions on the existing warfarin therapy used by stakeholders. As such, the benefits and harms of these intervention

can be valued more accurately alongside with cost-effectiveness findings to inform decision in the local setting.

5. The exploration of patients' values and preferences on oral anticoagulant for SPAF and how they would influence healthcare policy decision-making would be highly valuable in this field. Patient-related factors such as patient's adherence to treatment, patient's burden due to disease or treatment and patient's satisfaction with treatment, determined through patient preferences are increasingly considered important factors in influencing clinicians' adherence and uptake of healthcare interventions.[4, 6] Thus, such patients' preferences can be embedded alongside empirical studies and economic evaluations. By including patients' preferences in healthcare decision-making, a more complete picture that accounts for the preferences and characteristics of the target population can be determined, thereby improving the uptake or real-world efficiency of these interventions in a broader sense and enhancing healthcare consumer empowerment.

6. An area worth for further study is the use of NOACs in specific population patients such as those with renal impairment, those with liver diseases, elderly or patients with multiple comorbidities.

8.5. Conclusions

This disseration included a series of original works surrounding the topic of anticoagulant interventions for SPAF. Overall, this dissertation demonstrates the value of evidence obtained systematically in making clinical decisions regarding anticoagulant interventions for SPAF, consistent with the axioms of evidence-based decision-making. The addition of economic evaluations per se translates this evidence into estimates of costs and effects that allows the identification of most optimal anticoagulant intervention for SPAF based on given resource allocation. Based on our

dissertation, PSM may be the most optimal and resource-efficient intervention for SPAF in terms of benefits and costs in a resource-limited setting. Therefore, optimizing anticoagulation control through warfarin care bundles such as PSM might be more suitable for AF patients in middle-income countries with limited healthcare resources. These findings show how the integration of clinical and economic evidence in informing decision can increase their relevance in a local healthcare setting, balance the different levels of healthcare policy decision-making and help charting the future course of anticoagulant care for SPAF.

References for Chapter 8

1. Mason J, Eccles M, Freemantle N, Drummond M. Nicely Does It: Economic Analysis Within Evidence-based Clinical Practice Guidelines. University of York, York.1998.
2. Knies S, Severens JL, Brouwer WBF. Integrating clinical and economic evidence in clinical guidelines: More needed than ever! Journal of evaluation in clinical practice. 2018.
3. Yothasamut J, Tantivess S, Teerawattananon Y. Using economic evaluation in policy decision-making in Asian countries: mission impossible or mission probable? Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2009;12 Suppl 3:S26-30.
4. Callahan KP, Bridges JF. Using comparative effectiveness research to inform decision-making: is there a role of economic evaluation? Journal of comparative effectiveness research. 2012;1(4):299-301.
5. Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins CD, Nuijten M, et al. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices--budget impact analysis. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2007;10(5):336-47.
6. Brazier JE, Dixon S, Ratcliffe J. The role of patient preferences in cost-effectiveness analysis: a conflict of values? PharmacoEconomics. 2009;27(9):705-12.

Supplementary Materials for Chapter 5

S-5-1. Search Strategies

Database searched: MEDLINE, EMBASE & Cochrane Library
#1 Atrial fibrillation OR afib OR atrial arrhythmias AND stroke OR cerebrovascular accident OR transient ischemic attack
#2 Systematic review OR meta-analysis OR systematic literature review OR Cochrane database systematic review OR evidence based OR evidence-based medicine OR best practice OR evidence synthesis
#3 anticoagulants OR vitamin K antagonist OR coumarin OR anti-coagulant OR phenprocoumon OR acenocoumarol
#4 novel anticoagulants OR new oral anticoagulants OR oral thrombin inhibitors OR oral factor Xa inhibitors OR dabigatran OR rivaroxaban OR apixaban OR edoxaban
#5 self-care OR self-administration OR consumer-participation OR self-medication OR home monitoring or self-evaluation OR patient education
#6 pharmacogenetics OR polymorphism OR pharmacogenomics OR genomics OR alleles OR genes OR genotypes OR genetic test OR genetic guide OR algorithm OR nomogram OR genetic variation OR gene variant OR gene variability OR genotype guided OR CYP2C9 or CYP450 or VKORC1 or vitamin K epoxide reductase
#7 anticoagulation clinic OR routine clinic OR pharmacist OR management model OR adherence clinic
#8 1 AND 2
#9 3 OR 4 OR 5 OR 6 OR 7
#10 8 AND 9

S-5-2. Types of Interventions

Novel oral anticoagulants (NOACs) have been developed and offer potential advantages such as rapid onset and offset of action, predictable pharmacokinetics which allows the administration of fixed doses without the need for routine anticoagulation monitoring, fewer drug and food interactions.

Apart from NOACs, various efforts to optimize warfarin use and improve anticoagulation control have been introduced. Anticoagulation clinics may use point-of-care devices to generate immediate international normalized ratio (INR) results and involve the participation of trained healthcare professionals such as pharmacists to monitor patient's INR and warfarin dosing.[1, 2] Genotype-guided warfarin dosing instead utilized CYP2C9 and VKORC1 genotype results to adopt a more individualized dosing regimen with the aim of achieving the correct maintenance dose more rapidly than conventional warfarin therapy.[3] The intervention of self-monitoring may consist either of self-management approach whereby patients conduct their own INR tests using approved portable coagulometers and adjust their dosage according to the provided algorithm or self-testing approach, in which patients perform the test at home but seek treatment recommendations from clinicians through telephone conversations or clinic visits.[4]

S-5-3. Characteristics of 34 Eligible Systematic Reviews

Authors, Year	Population	Comparator	No of RCTs	No of patients	Method assessment of RCTs	Method assessment of reviews (ROBIS)	Summary Effects (95% CI)		
							Stroke & SE	All-cause mortality	Major Bleeding
NOACS[a]									
Dabigatran only									
Bloom BJ, 2014[5]	AF patients	VKA	2	18615	Cochrane ROB	High	NS	RR: 0.89 (0.79-1.01)	RR: 0.94 (0.82-1.07)
Morilla MA, 2012[6]	AF patients	Warfarin	2	12268	Developed their own tool	High	OR: 0.77 (0.62-0.99)	NS	OR: 0.93 (0.81-1.08)
Combination of Dabigatran, Rivaroxaban and Apixaban									
Adam SS, 2012[7]	AF patients	Warfarin	3	50578	Cochrane ROB	High	*Ischemic stroke* RR: 0.89 (0.78-1.02) *Hemorrhagic stroke* RR: 0.48 (0.36-0.62)	RR: 0.88 (0.82-0.96)	RR: 0.80 (0.63-1.01)
Baker WL, 2012[8]	AF patients	Warfarin	4	44733	Based on the Methods Guide for Comparative Effectiveness Reviews	Low	RR: 0.80 (0.70-0.91)	RR: 0.87 (0.80-0.97)	RR: 0.88 (0.66-1.16)
Capodanno D, 2013[9]	AF patients	Warfarin	3	50578	No formal scoring system	Unclear	OR: 0.82 (0.74-0.91)	OR: 0.88 (0.82-0.95)	OR: 0.85 (0.69-1.05)
Gómez-Outes A, 2013[10]	AF patients	Warfarin	3	50578	Cochrane ROB JADDAD score	Low	*Non-hemorrhagic stroke & SE* RR: 0.93 (0.83-1.04)	RR: 0.91 (0.85-0.97)	RR: 0.86 (0.70-1.05)
Katsanos AH, 2016[11]	AF patients with previous stroke/TIA	Warfarin	4	15240	Cochrane ROB	Low	RR: 0.85 (0.74-0.97)	RR: 0.91 (0.80-1.02)	RR: 0.85 (0.71-1.03)
Miller CS, 2012[12]	AF patients	Warfarin	3	44563	Cochrane R0B	Low	RR:0.78 (0.67-0.92)	RR: 0.88 (0.82-0.95)	RR 0.88 (0.71-1.09)
Ntaios G, 2012[13]	AF patients with previous stroke/TIA	VKAs	3	14527	None	High	OR: 0.85 (074-0.99)	OR: 0.90 (0.81-1.01)	OR: 0.86 (0.75-0.99)
Sardar P, 2014[14]	AF/VTE Patients aged ≥ 75 years	Conventional therapy (VKA, LMWH, Aspirin, placebo)	10	25031	Cochrane ROB	Low	OR: 0.65 (0.48-0.87)	NS	OR: 1.02 (0.73-1.43)
Sardar P, 2013[15]	AF Patients with previous stroke/TIA	Warfarin	3	14527	Cochrane ROB	High	OR 0.85 (0.74-0.99)	OR: 0.90 (0.79-1.02)	OR: 0.84 (0.69-1.03)
Senoo K, 2015[16]	Japanese AF patients	Warfarin	3	1940	Cochrane ROB	Low	RR: 0.45 (0.24-0.85)	NS	RR: 0.66 (0.29-1.47)
Testa L, 2012[17]	AF patients	Warfarin	3	50578	Cochrane ROB	Low	OR: 0.92 (0.83-1.02)	OR: 0.90 (0.84-0.96)	OR: 0.98 (0.91-1.07)
Combination of Dabigatran, Rivaroxaban, Apixaban and Edoxaban									
Biondi-Zoccai G, 2013[18]	AF patients	Warfarin	7	52701	Cochrane ROB	Low	OR: 0.81 (0.71-0.92)	OR: 0.88 (0.82-0.95)	OR: 0.83 (0.68-1.02)
Briceno DF, 2015[19]	AF patients	Warfarin	5	72963	None	Unclear	OR: 0.84 (0.72-0.97)	OR: 0.89	OR: 0.79

								(0.84-0.94)	(0.65-0.97)
Dentali F, 2012[20]	AF patients	VKAs	12	54875	JADAD score Allocation treatment concealment	Low	RR: 0.77 (0.70-0.86)	RR: 0.89 (0.83-0.96)	RR: 0.86 (0.72-1.02)
Jia B, 2014[21]	AF patients	Warfarin	5	72911	Cochrane ROB	Low	RR: 0.80 (0.71-0.91)	RR: 0.90 (0.85-0.95)	RR: 0.86 (0.74-0.99)
Liew A, 2014[22]	AF patients	Warfarin	4	71683	Cochrane ROB	High	NS	RR: 0.89 (0.85-0.94)	NS
Ruff CT, 2014[23]	AF patients	Warfarin	4	71683	Tools used were not specified	Low	RR: 0·81 (0.73-0.91)	RR: 0·90 (0.85-0.95)	RR: 0.86 (0.73-1.00)
Sadlon AH, 2016[24]	AF Patients aged ≥75 years	VKA or a consecutive regimen of LMWH with VKA	8	27557	Cochrane ROB	Low	OR: 0.71 (0.62-0.82)	NS	OR: 0.98 (0.90-1.06)
Combination of Rivaroxaban, Apixaban and Edoxaban (Factor Xa Inhibitors)									
Gandara V, 2016[25]	AF patients	VKAs	3	53570	Cochrane ROB	Low	OR: 1.01 (0.81-1.24)	NS	NS
Garg J, 2016[26]	AF patients	VKAs	11	59164	None	High	OR: 0.82 (0.68-0.99)	OR: 0.88 (0.83-0.94)	OR: 0.74 (0.58-0.96)
Nunes JPL, 2014[27]	AF patients	Warfarin	3	53570	None	High	RR: 0.901 (0.78-1.03)	RR: 0.892 (0.84-0.94)	RR: 0.773 (0.58-1.02)
GENOTYPE-GUIDED WARFARIN DOSING									
Belley-Cote EP, 2015[28]	Patients indicated for anticoagulants	Standard VKA dosing algorithms	12	3217	Modified Cochrane ROB	Low	RR: 0.74 (0.37-1.49)	RR: 1.12 (0.46-2.74)	RR: 0.71 (0.38-1.29)
Shi C, 2015[29]	Patients indicated for anticoagulants	Conventional dosing of warfarin	11	2678	Cochrane ROB	Low	RR: 0.52 (0.21-1.24)	RR: 1.38 (0.54-3.49)	RR: 0.36 (95% CI: 0.15-0.89)
Tang HL, 2015[30]	Patients indicated for anticoagulants	Conventional dosing of warfarin	11	2677	Cochrane ROB	Low	OR: 0.83 (0.30-2.27)	OR: 1.18 (0.42-3.28)	OR: 0.44 (0.18-1.10)
Tang T, 2015[31]	Patients indicated for anticoagulants	VKA standard dosing	8	1805	Modified JADAD score with allocation treatment concealment	High	*Secondary outcome (INR ≥ 4, Thromboembolic events & major bleeding events)* RR: 0.89 (0.79-1.0)		
ANTICOAGULATION CLINICS									
Zhou S, 2016[32]	Patients indicated for anticoagulants	Usual care (a control group of physicians, nurses & other healthcare professionals in providing management	8	1493	Cochrane ROB	High	OR: 0.89 (0.56-1.44)	OR: 0.97 (0.44-2.11)	OR: 0.90 (0.37-2.19)
PATIENT'S SELF-MONITORING									
Alonso-Coello P, 2015[33]	Patients indicated for anticoagulants	Usual management of oral anticoagulation	23	8725	None	High	RR: 0.59 (0.46-0.77) *PST* RR: 0.83 (0.57-1.21) *PSM* RR: 0.45 (0.32-0.64)	RR: 0.76 (0.58-0.99) *PST* RR: 0.95 (0.78-1.15) *PS,* RR: 0.62	RR: 0.96 (0.81-1.13)

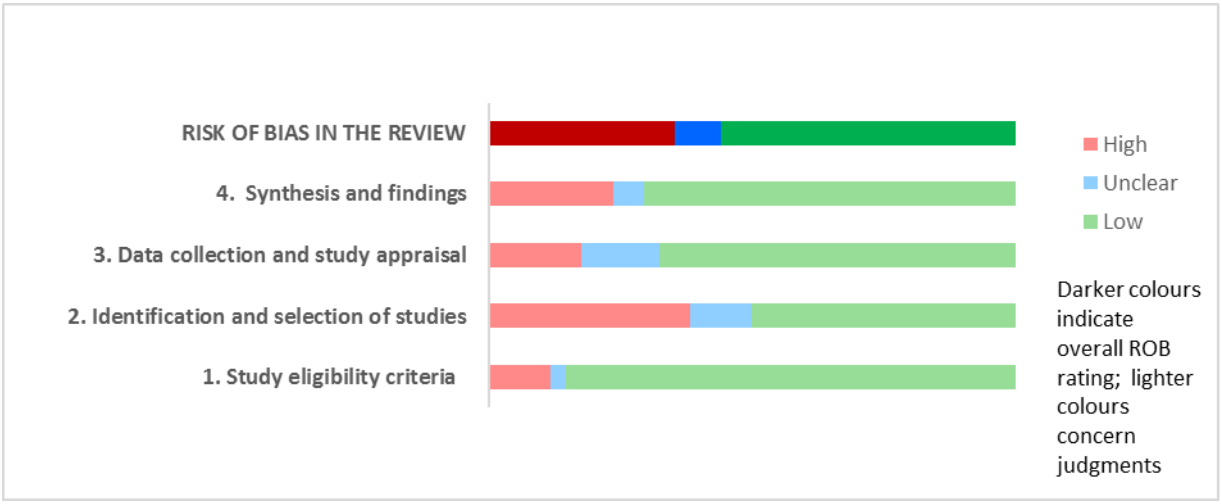
								(0.49-0.78)	
Bloomfield HE, 2011[34]	Patients indicated for anticoagulants	Usual care (received anticoagulation management in anticoagulation clinics or in a primary care of physician office	22	8413	Schulz Criteria	High	OR: 0.58 (0.45-0.75)	OR: 0.74 (0.63-0.87)	OR: 0.89 (0.75-1.05)
Christensen TD, 2007[35]	Patients indicated for anticoagulants	Usual care provided by general practitioner	10	2636	Cochrane ROB	Low	NS	RR: 0.48 (0.29-0.79)	NS
Heneghan CL, 2016[36]	Patients indicated for anticoagulants	Usual care	28	8950	Cochrane ROB	Low	RR 0.58 (0.45-0.75) *PST* RR: 0.69 (0.49-0.97) *PSM* RR: 0.47 (0.31-0.70)	RR: 0.85 (0.71-1.01) *PST* RR: 0.94 (0.78-1.15) *PSM* RR: 0.55 (0.36-0.84)	RR: 0.95 (0.80-1.12) *PST* RR: 0.90 (0.74-1.09) *PS,* RR: 1.08 (0.79-1.47)
Sharma P, 2015[4]	Patients indicated for anticoagulants	Standard clinic care (consisted of INR monitoring managed by healthcare professionals)	26	8763	Cochrane ROB	Low	RR: 0.58 (0.40-0.84) *PST* RR: 0.99 (0.75-1.31) *PSM* RR: 0.51 (0.37-0.69)	RR: 0.83 (0.63-1.10) *PST* RR: 0.97 (0.78-1.19) *PSM* RR: 0.68 (0.46-1.01)	RR: 1.02 (0.86-1.21) *PST* RR: 0.99 (0.80-1.23) *PSM* RR: 1.08 (0.81-1.45)
ANTICOAGULATION CLINICS AND PATIENT'S SELF-MONITORING									
Wells PS, 2013[37]	Patients indicated for anticoagulants	Usual care (venipuncture blood drawn for INR test with management provided by anticoagulation clinic or individual practitioner)	16	NS	JADAD score Schulz criteria	Low	OR: 0.51 (0.35-0.74)	OR: 0.58 (0.38-0.89)	OR: 0.78 (0.53-1.14)

Abbreviations: AF, atrial fibrillation; CI, confidence interval; NS, not specified; RCT, randomized controlled trial; RR, risk ratios; ROB, risk of bias; OR, odds ratio; PSM, patient's self-management; PST, patient's self-testing; SE, systemic embolism; VKA, vitamin K antagonists

S-5-4. Summary Results from ROBIS Evaluation of 34 Systematic Reviews

	Phase 2				Phase 3
	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	**RISK OF BIAS IN THE REVIEW**
Adam SS, 2012	Low	High	High	High	High
Baker W, 2012	Low	Low	Low	Low	Low
Biondi-Zoccai G, 2013	Low	Low	Low	Low	Low
Bloom BJ, 2014	High	High	Low	Low	High
Briceno DF, 2015	Low	Low	Unclear	Low	Unclear
Capodanno D, 2013	Low	Unclear	Unclear	Unclear	Unclear
Dentali F, 2012	Low	Low	Low	Low	Low
Gandara V, 2016	Low	Low	Low	Unclear	Low
Garg J, 2016	Low	High	High	High	High
Gómez-Outes A, 2013	Low	Low	Low	Low	Low
Jia B, 2014	Low	Low	Unclear	High	Unclear
Katsanos AH, 2016	Low	Low	Low	Low	Low
Liew A, 2014	Low	High	Unclear	Low	High
Miller CS, 2012	Low	Low	Low	Low	Low
Morilla MA, 2012	Low	High	Low	High	High
Ntaios G, 2012	Low	High	High	High	High
Nunes JPL, 2014	Unclear	Unclear	Unclear	High	High
Ruff CT, 2014	Low	High	High	Low	Low
Sadlon AH 2016	Low	High	Low	Low	Low
Sardar P, 2013.	Low	High	Low	Low	High
Sardar P, 2014	Low	Low	Low	Low	Low
Senoo K, 2015	Low	Low	Low	Low	Low
Testa L, 2012	Low	Unclear	Low	Low	Low
Belley-Cote EP, 2015	Low	Low	Low	Low	Low
Shi C, 2015	Low	Low	Low	Low	Low
Tang HL, 2015	Low	Low	Low	Low	Low
Tang T, 2015	High	High	Low	High	High
Bloomfield HE, 2011	Low	High	High	Low	High
Zhou S, 2016	Low	High	Low	High	High
Alonso-Coello P, 2015	High	Unclear	High	Low	High
Christensen TD, 2007	Low	Low	Low	Low	Low
Heneghan CJ, 2016	Low	Low	Low	Low	Low
Sharma P, 2015	High	High	Low	Low	Low
Wells PS, 2007	Low	Low	Low	Low	Low

S-5-5. Graphical Representation for ROBIS Evaluation of 34 Systematic Reviews



Supplementary References for Chapter 5

1. Lafata JE, Martin SA, Kaatz S, Ward RE. Anticoagulation clinics and patient self-testing for patients on chronic warfarin therapy: A cost-effectiveness analysis. J Thromb Thrombolysis. 2000;9 Suppl 1:S13-9.
2. Sullivan PW, Arant TW, Ellis SL, Ulrich H. The cost effectiveness of anticoagulation management services for patients with atrial fibrillation and at high risk of stroke in the US. PharmacoEconomics. 2006;24(10):1021-33.
3. Pink J, Pirmohamed M, Lane S, Hughes DA. Cost-effectiveness of pharmacogenetics-guided warfarin therapy vs. alternative anticoagulation in atrial fibrillation. Clinical pharmacology and therapeutics. 2014;95(2):199-207.
4. Sharma P, Scotland G, Cruickshank M, Tassie E, Fraser C, Burton C, et al. Is self-monitoring an effective option for people receiving long-term vitamin K antagonist therapy? A systematic review and economic evaluation. BMJ open. 2015;5(6):e007758.
5. Bloom BJ, Filion KB, Atallah R, Eisenberg MJ. Meta-analysis of randomized controlled trials on the risk of bleeding with dabigatran. The American journal of cardiology. 2014;113(6):1066-74.
6. Morilla MA, Tumulak CD, Gulay CB, Dioquino CP, DD M. A meta-analysis on the efficacy of dabigatran versus warfarin among patients with atrial fibrillation. Philipp J Intern Med. 2012;50(4):1-4.
7. Adam SS, McDuffie JR, Ortel TL, Williams JW, Jr. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review. Annals of internal medicine. 2012;157(11):796-807.
8. Baker WL, Phung OJ. Systematic review and adjusted indirect comparison meta-analysis of oral anticoagulants in atrial fibrillation. Circulation Cardiovascular quality and outcomes. 2012;5(5):711-9.
9. Capodanno D, Capranzano P, Giacchi G, Calvi V, Tamburino C. Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: a meta-analysis of 50,578 patients. International journal of cardiology. 2013;167(4):1237-41.
10. Gomez-Outes A, Terleira-Fernandez AI, Calvo-Rojas G, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, Rivaroxaban, or Apixaban versus Warfarin in Patients with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Subgroups. Thrombosis. 2013;2013:640723.
11. Katsanos AH, Mavridis D, Parissis J, Deftereos S, Frogoudaki A, Vrettou AR, et al. Novel oral anticoagulants for the secondary prevention of cerebral ischemia: a network meta-analysis. Therapeutic advances in neurological disorders. 2016;9(5):359-68.
12. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. The American journal of cardiology. 2012;110(3):453-60.
13. Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials. Stroke. 2012;43(12):3298-304.
14. Sardar P, Chatterjee S, Chaudhari S, Lip GY. New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomized trials. Journal of the American Geriatrics Society. 2014;62(5):857-64.
15. Sardar P, Chatterjee S, Wu WC, Lichstein E, Ghosh J, Aikat S, et al. New oral anticoagulants are not superior to warfarin in secondary prevention of stroke or transient ischemic attacks, but lower the risk of intracranial bleeding: insights from a meta-analysis and indirect treatment comparisons. PloS one. 2013;8(10):e77694.

16. Senoo K, Lau YC, Dzeshka M, Lane D, Okumura K, Lip GY. Efficacy and safety of non-vitamin K antagonist oral anticoagulants vs. warfarin in Japanese patients with atrial fibrillation - meta-analysis. Circulation journal : official journal of the Japanese Circulation Society. 2015;79(2):339-45.
17. Testa L, Agnifili M, Latini RA, Mattioli R, Lanotte S, De Marco F, et al. Adjusted indirect comparison of new oral anticoagulants for stroke prevention in atrial fibrillation. QJM : monthly journal of the Association of Physicians. 2012;105(10):949-57.
18. Biondi-Zoccai G, Malavasi V, D'Ascenzo F, Abbate A, Agostoni P, Lotrionte M, et al. Comparative effectiveness of novel oral anticoagulants for atrial fibrillation: evidence from pair-wise and warfarin-controlled network meta-analyses. HSR proceedings in intensive care & cardiovascular anesthesia. 2013;5(1):40-54.
19. Briceno DF, Villablanca P, Cyrille N, Massera D, Bader E, Manheimer E, et al. Left Atrial Appendage Occlusion Device and Novel Oral Anticoagulants Versus Warfarin for Stroke Prevention in Nonvalvular Atrial Fibrillation: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Circulation Arrhythmia and electrophysiology. 2015;8(5):1057-64.
20. Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation. 2012;126(20):2381-91.
21. Jia B, Lynn HS, Rong F, Zhang W. Meta-analysis of efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation. Journal of cardiovascular pharmacology. 2014;64(4):368-74.
22. Liew A, O'Donnell M, Douketis J. Comparing mortality in patients with atrial fibrillation who are receiving a direct-acting oral anticoagulant or warfarin: a meta-analysis of randomized trials. Journal of thrombosis and haemostasis : JTH. 2014;12(9):1419-24.
23. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet (London, England). 2014;383(9921):955-62.
24. Sadlon AH, Tsakiris DA. Direct oral anticoagulants in the elderly: systematic review and meta-analysis of evidence, current and future directions. Swiss medical weekly. 2016;146:w14356.
25. Gandara V, Vazquez F, Gandara E. Direct oral factor Xa inhibitors for the prevention of non-central nervous systemic embolism patients with non-valvular atrial fibrillation - a systematic review and meta-analysis. VASA Zeitschrift fur Gefasskrankheiten. 2016;45(4):293-8.
26. Garg J, Chaudhary R, Krishnamoorthy P, Palaniswamy C, Shah N, Bozorgnia B, et al. Safety and efficacy of oral factor-Xa inhibitors versus Vitamin K antagonist in patients with non-valvular atrial fibrillation: Meta-analysis of phase II and III randomized controlled trials. International journal of cardiology. 2016;218:235-9.
27. Nunes JP, Rodrigues RP, Goncalves FR. Comparative analysis and meta-analysis of major clinical trials with oral factor Xa inhibitors versus warfarin in atrial fibrillation. Open heart. 2014;1(1):e000080.
28. Belley-Cote EP, Hanif H, D'Aragon F, Eikelboom JW, Anderson JL, Borgman M, et al. Genotype-guided versus standard vitamin K antagonist dosing algorithms in patients initiating anticoagulation. A systematic review and meta-analysis. Thrombosis and haemostasis. 2015;114(4):768-77.
29. Shi C, Yan W, Wang G, Wang F, Li Q, Lin N. Pharmacogenetics-Based versus Conventional Dosing of Warfarin: A Meta-Analysis of Randomized Controlled Trials. PloS one. 2015;10(12):e0144511.
30. Tang HL, Shi WL, Li XG, Zhang T, Zhai SD, Xie HG. Limited clinical utility of genotype-guided warfarin initiation dosing algorithms versus standard therapy: a meta-analysis and trial

sequential analysis of 11 randomized controlled trials. The pharmacogenomics journal. 2015;15(6):496-504.
31. Tang T, Liu J, Zuo K, Cheng J, Chen L, Lu C, et al. Genotype-Guided Dosing of Coumarin Anticoagulants: A Meta-analysis of Randomized Controlled Trials. Journal of cardiovascular pharmacology and therapeutics. 2015;20(4):387-94.
32. Zhou S, Sheng XY, Xiang Q, Wang ZN, Zhou Y, Cui YM. Comparing the effectiveness of pharmacist-managed warfarin anticoagulation with other models: a systematic review and meta-analysis. Journal of clinical pharmacy and therapeutics. 2016;41(6):602-11.
33. Alonso-Coello P, Zhou Q, Guyatt G. Home-monitoring of oral anticoagulation vs. dabigatran. An indirect comparison. Thrombosis and haemostasis. 2012;108(4):647-53.
34. Bloomfield HE, Krause A, Greer N, Taylor BC, MacDonald R, Rutks I, et al. Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. Annals of internal medicine. 2011;154(7):472-82.
35. Christensen TD, Johnsen SP, Hjortdal VE, Hasenkam JM. Self-management of oral anticoagulant therapy: a systematic review and meta-analysis. International journal of cardiology. 2007;118(1):54-61.
36. Heneghan CJ, Garcia-Alamino JM, Spencer EA, Ward AM, Perera R, Bankhead C, et al. Self-monitoring and self-management of oral anticoagulation. The Cochrane database of systematic reviews. 2016;7:Cd003839.
37. Wells PS, Brown A, Jaffey J, McGahan L, Poon MC, Cimon K. Safety and effectiveness of point-of-care monitoring devices in patients on oral anticoagulant therapy: a meta-analysis. Open medicine : a peer-reviewed, independent, open-access journal. 2007;1(3):e131-46.

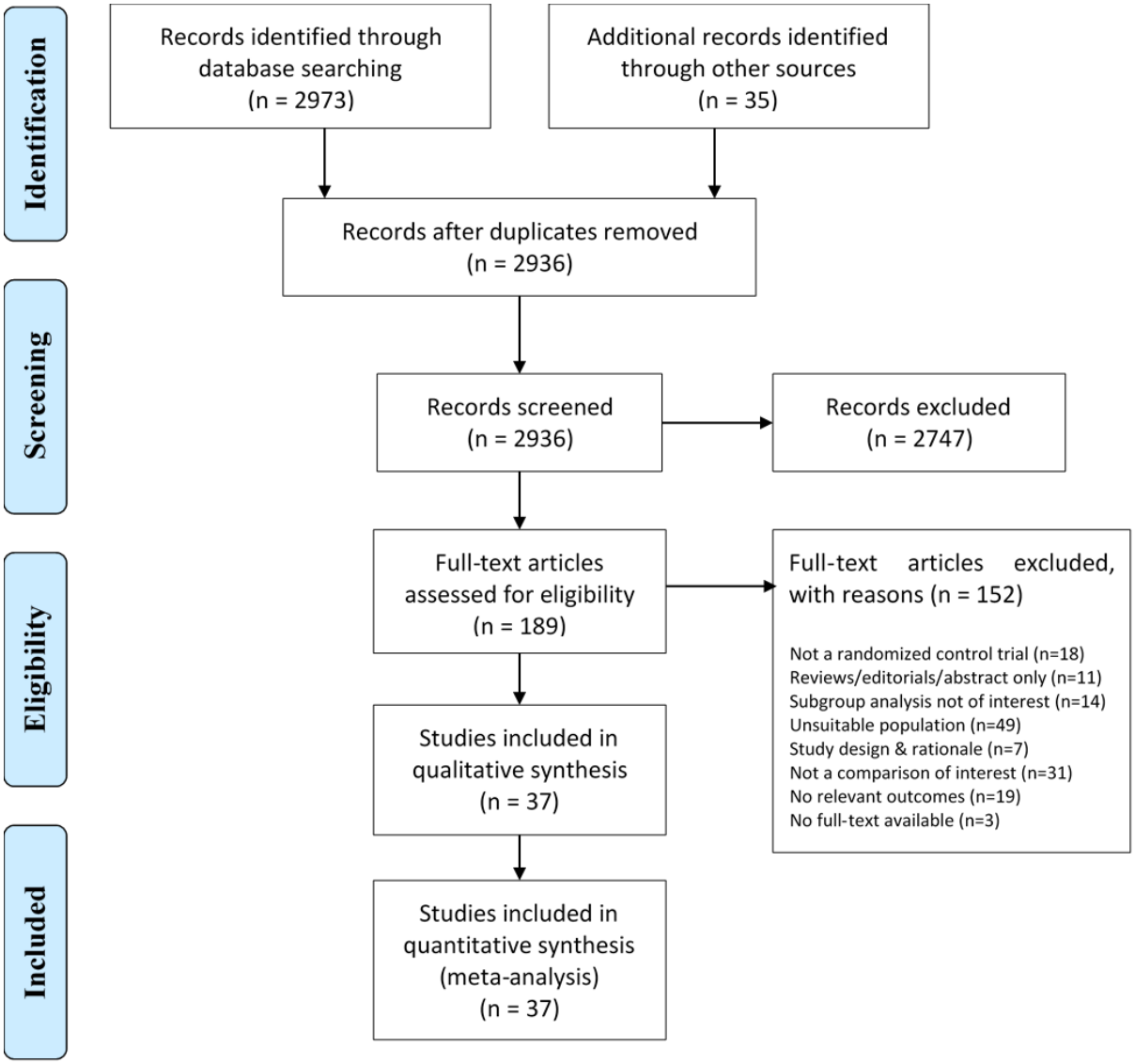
Supplementary Materials for Chapter 6

S-6-1. Search Strategy and PRISMA Flow

EMBASE Search Strategy

#1	atrial fibrillation (121926)
#2	Anticoagulant (80605)
#3	Warfarin (80605)
#4	'self-care'/exp OR 'self-evaluation'/exp OR 'self-monitoring'/exp OR 'point of care testing'/exp (106392)
#5	Pharmacogenetic OR 'vkorc1 gene'/exp OR 'cytochrome p450 2c9'/exp OR 'vitamin K epoxide reductase'/exp (14302)
#6	'ambulatory care'/exp OR 'international normalized ratio'/exp OR 'clinics'/exp OR 'pharmacist'/exp OR 'nurse'/exp (277186)
#7	#4 OR #5 OR #6 (389724)
#8	#3 AND #7 (13765)
#9	'dabigatran'/de OR 'apixaban'/de OR 'edoxaban'/de OR 'rivaroxaban'/de (9477)
#10	'left atrial appendage closure device'/exp OR 'heart atrium appendage'/exp OR 'prostheses and orthoses'/exp (332818)
#11	#8 OR #9 OR #10 (352953)
#12	#1 AND #11 (15202)
#13	#13 AND ('clinical trials'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'randomized controlled trial'/de) (1627)

PRISMA Flow Diagram



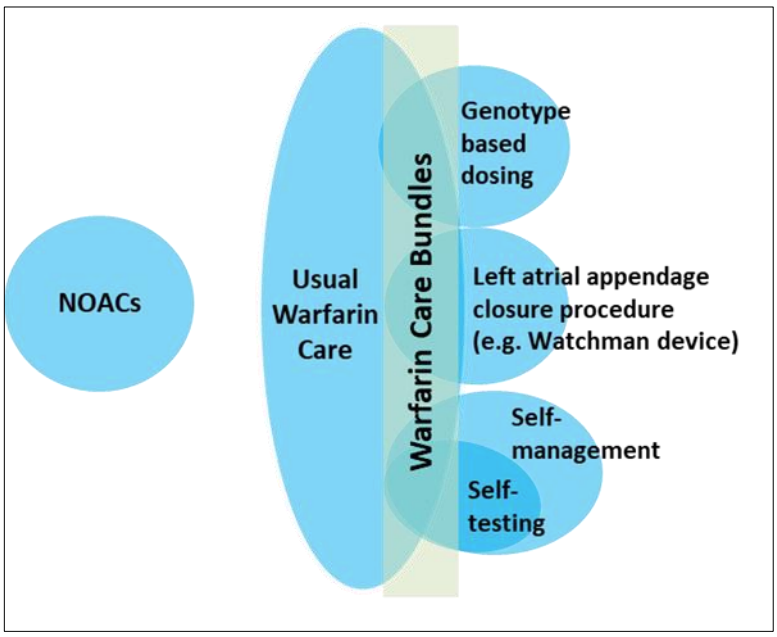
S-6-2. Interventions

General Abbreviations of Interventions

Intervention Abbreviations	General characteristics
APX	Apixaban 5mg BD or 2.5mg BD
ASA	Aspirin of any doses
CONTROL	Placebo/Control/No treatment
CLP	Clopidogrel 75mg OD
DBG-110MG	Dabigatran 110mg BD
DBG-150MG	Dabigatran 150mg BD
EDX-30MG	Edoxaban 30mg OD
EDX-60MG	Edoxaban 60mg OD
GNT	Genotype-guided warfarin dosing
RVX	Rivaroxaban 20mg OD or 15mg OD
SM	Patient's self-management of warfarin
ST	Patient's self-testing of warfarin
WTH	Watchman Device insertion with temporary warfarin use

Abbreviations: APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; INR, international normalized ratio; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device; BD, twice daily; OD, once daily

Graphic Representation of Anticoagulant Interventions for Stroke Prevention in Patients with Atrial Fibrillation



- **Usual warfarin care:** Warfarin therapy alone without any supplementary interventions but may have been delivered either in hospitals, primary care or anticoagulation clinics.

- **Warfarin Care Bundles** **:** A structured way of improving the process of warfarin care by performing several interventions (up to five) collectively to have aggregated beneficial effects on patient's outcomes

- **NOACs:** novel oral anticoagulants (direct thrombin inhibitors: dabigatran and factor Xa inhibitors: rivaroxaban, apixaban and edoxaban). Other NOACs were excluded: betrixaban because the indication for stroke prevention is still not approved; darexaban (YM50) and AZD0837 because they were discontinued, otamixaban (INN) due to its parenteral administration; letaxaban (TAK-442), LY517717 and eribaxaban (PD0348292) as no further information was available on clinical development; and ximelagatran as it was withdrawn from the market due to hepatoxicity

S-6-3. Characteristics of Included Studies

Description of Included Studies

Study name/ First author	Year	Type of study	Country	Sponsor	n	Types of AF	Follow-up Period (mo)	Age Eligibility (yrs)	% AF pts	Time of outcome assessment (mo)	Reporting Pattern*
Matchar DB[1]	2010	Multicentre	North America	Non-ISR	2922	NS	24 - 57	NA	82	24 - 57	1
Khan TI[2]	2004	Single centre	Europe	Non-ISR	79	NS	6	≥65	100	6	2
SMAAF[3]	2005	Single centre	Europe	ISR	202	NVAF	448 - 483	NA	100	448 - 483	3
Menendez-Jandula B[4]	2005	Single centre	Europe	ISR	737	NS	11.8 (median)	≥18	50	11.8 (median)	2
Verret L [5]	2012	Single centre	North America	ISR	117	NS	4	18-75	51	4	3
Pirmohamed M[6]	2013	Multicentre	Europe	Non-ISR	455	NS	3	≥18	72.1	3	3
ACTIVE-W[7]	2006	Multicentre	North America South America Europe Asia Oceania Africa	ISR	6706	NVAF	15.4 (median)	≥55	100	15.4 (median)	1
Liu X[8]	2014	Single centre	Asia	Non-ISR	101	Persistent or Permanent NVAF	24	≥80	100	1, 3, 6, 12, 18, 24	2
SPAF II[9]	1994	Multicentre	North America	Non-ISR	1100	NVAF	37.2 (age ≤ 75)	≥60	100	27.6 (mean)	3
EAFT[10]	1993	Multicentre	Europe Asia	ISR	439	Chronic or paroxysmal NVAF	27.6 (mean)	≥25	100	27.6 (mean)	1
WASPO[11]	2007	Single centre	Europe	NA	75	Permanent NVAF	12	80-90	100	12	2
Lavitola PL[12]	2010	Single centre	South America	ISR	229	NS	57 (mean)	≥18	100	57 (mean)	3
BAFTA[13]	2007	Multicentre	Europe	Non-ISR	973	NVAF or atrial flutter	32.4 (mean)	≥75	100	32.4 (mean)	1
AFASAK[14]	1989	Multicentre	Europe	ISR	1007	Chronic NVAF	24	≥18	100	24	3
AFASAK 2[15]	1998	Single centre	Europe	Non-ISR	339	Chronic NVAF	42	≥18	100	42	3
BAATAF[16]	1990	Multicentre	North America	ISR	420	Persistent or permanent NVAF	27.6 (mean)	NA	100	27.6 (mean)	3
CAFA[17]	1991	Multicentre	North America	Non-ISR	378	Chronic or paroxysmal NVAF	15.2 (mean)	≥19	100	15.2 (mean)	1
JAST[18]	2006	Multicentre	Asia	Non-ISR	871	NVAF	25.6 (mean)	NA	100	25.6 (mean)	3
Chen KP[19]	2012	Multicentre	Asia	Non-ISR	440	NVAF	15 (mean)	50-80	100	15 (mean)	2
SPAF I[20]	1991	Multicentre	North America	Non-ISR	421	NVAF	15.6 (mean)	NA	100	15.6 (mean)	3
PREVAIL[21]	2014	Multicentre	North America	ISR	407	NVAF	11.8 (mean)	NA	100	11.8 (mean)	3
PROTECT AF[22]	2014	Multicentre	North America	ISR	707	NVAF	45.6 (mean)	≥18	100	45.6 (mean)	3

			Europe								
RELY[23]	2009	Multicentre	North America South America Europe Asia Oceania Africa	ISR	18113	NVAF	24 (mean)	≥18	100	24 (mean)	2
ROCKET[24]	2011	Multicentre	North America South America Europe Asia Oceania Africa	ISR	14264	NVAF	23.6 (median)	≥18	100	23.6 (median)	2
ARISTOTLE J[25]	2011	Multicentre	Asia	ISR	222	NVAF	3	≥20	100	3	2
ENGAGE TIMI-48[26]	2013	Multicentre	North America South America Europe Asia Oceania Africa	ISR	21105	NVAF	34,1 (median)	≥21	100	34.1 (median)	2
ARISTOTLE[27]	2011	Multicentre	North America South America Europe Asia Oceania Africa	ISR	18201	NVAF or atrial flutter	21.6 (median)	NA	100	21.6 (median)	3
Weitz JI[28]	2010	Multicentre	North America South America Europe	ISR	719	Persistent NVAF	3	18-85	100	3	2
J-ROCKET[29]	2012	Multicentre	Asia	ISR	1278	NVAF	30	≥20	100	30	2
TRIPLE AXEL[30]	2017	Multicentre	Asia	ISR	183	NVAF	1	≥19	100	1	2
Chung N[31]	2011	Multicentre	Asia	ISR	234	NVAF	3	18-80	100	3	2
PETRO[32]	2007	Multicentre	North America Europe	ISR	236	Paroxysmal, persistent or permanent NVAF	3	NA	100	3	2
Mao L[33]	2014	Single centre	Asia	Non-ISR	353	NVAF	NA	NA	100	NA	2
Yamashita T[34]	2012	Multicentre	Asia	ISR	391	NVAF	3	≥20	100	3	2
AVERROES[35]	2011	Multicentre	North America South America Europe Asia Africa	ISR	5599	NVAF	13.2 (mean)	≥50	100	13.2 (median)	2
Shosha RI[36]	2017	Single centre	Africa	NA	60	NVAF	3	18-60	100	3	2
Boehringer Ingelheim[37]	2014	Multicentre	Japan	ISR	156	Paroxysmal, persistent or permanent NVAF	3	≥20	100	3	2

*ISR=industry-sponsored research, mo = months, NA= not available, NS = not specified, NVAF = non-valvular atrial fibrillation, pt = patients, yrs = years, *1=Number of patients whose first event is of a given type, patients censored thereafter; 2=Number of patients experiencing at least one event of each given type; 3=Total number of events of each type*

Description of Participants of Included Studies

Study name/ First author	Treatment (n)	Age (year)		Male %	HTN %	DM %	HF %	Previous stroke or TIA %	DLP %	MI %	Smoker %	TTR %	Average $CHADS_2$ Score	$CHADS_2$ Score ≥2 %
Matchar DB[1]	UC+ST	66.6	Mean	98	71	9	28	9	NA	NA	NA	66.2	1.94	59.4
	UC	67.4	Mean	98	69	34	30	10	NA	NA	NA	62.4	1.95	61
Khan TI[2]	UC+ST	75	Median	65	NA	NA	NA	NA	NA	NA	7	71.1	NA	NA
	UC	73	Median	48.7	NA	NA	NA	NA	NA	NA	5	63.2	NA	NA
SMAAF[3]	UC+SM	64.6	Mean	71.4	NA	NA	NA	NA	NA	NA	NA	67.8	NA	NA
	UC	64.1	Mean	61.4	NA	NA	NA	NA	NA	NA	NA	58.5	NA	NA
Menendez-Jandula B[4]	UC+SM	65.5	Mean	52	48.6	15.4	NA	NA	NA	NA	NA	60.8	NA	NA
	UC	64.5	Mean	54	42.8	13.6	NA	NA	NA	NA	NA	58.4	NA	NA
Verret L [5]	UC+SM	58.4	Mean	67.2	NA	NA	NA	NA	NA	NA	NA	80	NA	NA
	UC	57	Mean	69.6	NA	NA	NA	NA	NA	NA	NA	75.5	NA	NA
Pirmohamed M[6]	UC+GNT	67.8	Mean	64.2	NA	NA	NA	NA	NA	NA	10.3	67.4	NA	NA
	UC	66.9	Mean	57.9	NA	NA	NA	NA	NA	NA	12.8	60.3	NA	NA
ACTIVE-W[7]	UC	70.4	Mean	66	82	21	31	15	NA	18	NA	63.8	2.0	NA
	ASA+CLP	70,2	Mean	67	83	21	30	15	NA	17	NA	NA	2.0	NA
Liu X[8]	UC	84.8	Median	60.8	39.2	21.6	21.6	NA	NA	15	25.5	NA	2.9*	NA
	ASA	84.4	Median	60	38	22.	20.0	NA	NA	14	24	NA	2.8*	NA
SPAF II[9]	UC	70	Mean	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ASA	70	Mean	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EAFT[10]	UC	71	Mean	55	19.1	5.3	3.6	12	5.3	7	NA	NA	NA	NA
	CONTROL	70	Mean	58	19.1	6.5	4.7	14.9	3.3	10	NA	NA	NA	NA
WASPO[11]	UC	83.5	Median	55	49	3	NA	NA	NA	NA	NA	69.2	NA	NA
	ASA	82.6	Median	54	46	5	NA	NA	NA	NA	NA	NA	NA	NA
Lavitola PL[12]	UC	NS	NS	20.2	NA	12.6	NA	NA	11.8	NA	NA	51.3	NA	NA
	ASA	NS	NS	22.7	NA	12.7	NA	NA	9.1	NA	NA	NA	NA	NA
BAFTA[13]	UC	81.5	Mean	55	53	14	20	13	NA	10	NA	67	NA	NA
	ASA	81.5	Mean	54	55	13	19	12	NA	12	NA	NA	NA	NA
AFASAK[14]	UC	72.8	Median	53	32	7	50	6	NA	8	40	73	NA	NA
	ASA	75.1	Median	55	33	8	54	5.1	NA	7	37	NA	NA	NA
	CONTROL	74.6	Median	54	31	10	51	6.3	NA	8	35	NA	NA	NA
AFASAK 2[15]	UC	73.2	Mean	57	47	14	70	8	NA	8	31	73	NA	NA
	ASA	73.1	Mean	65	43	10	70	8	NA	7	38	NA	NA	NA
BAATAF[16]	UC	68.5	Mean	75	51	14	24	3	NA	10	7	NA	NA	NA
	CONTROL	67.5	Mean	70	51	16	28	3	NA	16	10	NA	NA	NA
CAFA[17]	UC	68	Mean	75.9	43.3	13.9	23.5	3.2	NA	15	NA	43.7	NA	NA
	CONTROL	67.4	Mean	73.3	34	10	20.4	4.2	NA	12	NA	NA	NA	NA
JAST[18]	ASA	65.5	Mean	36.6	36.6	12.7	8.3	2.6	23.9	NA	32.8	NA	NA	NA
	CONTROL	64.8	Mean	40.4	40.4	15.3	10.1	2.5	21.2	NA	27.9	NA	NA	NA
Chen KP[19]	UC	66.8	Mean	59	59	12.1	61.5	20.9	15.9	5.4	NA	51.2	NA	NA
	ASA	67.6	Mean	66.2	66.2	14.9	65.6	15.4	17.4	3	NA	NA	NA	NA
SPAF I[20]	UC	65	Mean	74	49	12	14	8.0	NA	10	13	NA	NA	NA
	CONTROL	66	Mean	70	55	19	19	8.0	NA	6	13	NA	NA	NA
PREVAIL[21]	UC+WTH	74	Mean	67.7	88.5	33.8	23.4	27.5	NA	NA	NA	NA	2.6	92.2
	UC	74.9	Mean	74.6	97.1	29.7	23.2	28.3	NA	NA	NA	68	2.6	91.3
PROTECT AF[22]	UC+WTH	71.7	Mean	70.4	89.6	24.4	26.8	17.7	NA	NA	NA	NA	2.2	66.3
	UC	72.7	Mean	70.1	90.2	29.5	27	20.1	NA	NA	NA	70	2.3	73
RELY[23]	DBG-150MG	71.5	Mean	63.2	78.9	23.1	31.8	20.3	NA	16.9	NA	NA	2.2	67.8
	DBG-110MG	71.4	Mean	64.3	78.8	23.4	32.2	19.9	NA	16.8	NA	NA	2.1	67.4
	UC	71.6	Mean	63.3	78.9	23.4	31.9	19.8	NA	16.1	NA	64	2.1	69.1

ROCKET [24]	RVX	73	Median	60.3	90.3	40.4	62.6	54.9	NA	16.6	NA	NA	3.48	100
	UC	73	Median	60.3	90.8	39.5	62.3	54.6	NA	18	NA	55	3.46	100
ARISTOTLE J[25]	APX	69.7	Mean	83.8	82.4	25	0.7	28.4	NA	NA	NA	NA	1.9	60.1
	UC	71.7	Mean	81.1	85.1	20.3	2.7	27	NA	NA	NA	NA	1.9	50
ENGAGE TIMI-48[26]	EDX-60MG	72	Median	62.1	93.7	36.4	58.2	28.1	NA	NA	NA	NA	2.8	NA
	EDX-30MG	72	Median	61.2	93.5	36.2	56.6	28.5	NA	NA	NA	NA	2.8	NA
	UC	72	Median	62.5	93.6	35.8	57.5	28.3	NA	NA	NA	64.9	2.8	NA
ARISTOTLE[27]	APX	70	Median	64.5	87.3	25.0	35.5	19.2	NA	14.5	NA	NA	2.1	66
	UC	70	Median	65	87.6	24.9	35.4	19.7	NA	13.9	NA	62.2	2.1	66
Weitz JI[28]	EDX-60MG	64.9	Mean	66.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	100
	EDX-30MG	65.2	Mean	59.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	100
	UC	66	Mean	60.4	NA	NA	NA	NA	NA	NA	NA	49.7	NA	100
J-ROCKET [29]	RVX	71	Mean	82.9	79.5	39	41.3	63.8	NA	7	NA	NA	3.27	100
	UC	71.2	Mean	78.2	79.5	37.1	40.2	63.4	NA	8.3	NA	65	3.22	100
TRIPLE AXEL[30]	RVX	70.2	Mean	57.9	68.4	25.3	NA	100	16.8	NA	NA	NA	2.7	71.6
	UC	70.6	Mean	59.1	59.1	11.4	NA	100	20.5	NA	NA	46.6	2.3	71.6
Chung N[31]	EDX-60MG	65.9	Mean	68.8	73.8	27.5	31.3	23.8	NA	NA	NA	NA	1.9	53.8
	EDX-30MG	64.9	Mean	64.6	70.9	38	22.8	26.6	NA	NA	NA	NA	2.0	58.2
	UC	64.5	Mean	62.7	69.3	22.7	32.0	22.7	NA	NA	NA	45.1	1.8	46.7
PETRO[32]	DBG-150MG	70	Mean	81.3	71	27	31.3	17.5	NA	NA	72.3	NA	NA	NA
	UC	69	Mean	84.3	70	21.4	34.3	18.6	NA	NA	75.7	57.2	NA	NA
Mao L[33]	RVX	75	Median	61	90.4	41.8	60.5	49.7	NA	16.9	NA	NA	3.39	100
	UC	75	Median	62.5	91.5	39.8	61.4	48.9	NA	17.6	NA	NA	3.41	100
Yamashita T[34]	EDX-60MG	68.4	Mean	81	74	21	24	30	NA	NA	18	NA	2.1	NA
	EDX-30MG	68.8	Mean	81.7	75	18	24	23	NA	NA	18	NA	1.9	NA
	UC	70	Mean	82.9	71	31	33	30	NA	NA	16	75.7	2.2	NA
AVERROES[35]	APX	70	Mean	59	86	19	40	14	NA	NA	NA	NA	2.0	64.2
	ASA	54	Mean	58	87	20	38	13	NA	NA	NA	NA	2.1	63.3
Shoshari[36]	RVX	55	Mean	60	53.3	13.3	36.6	26.6	NA	NA	NA	NA	NA	40
	UC	68.3	Mean	30	40	26.6	30	10	NA	NA	NA	55	NA	33.3
Boehringer Ingelheim [37]	DBG-150MG	68.3	Mean	91.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	DBG-110MG	69.9	Mean	78.3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	UC	67.4	Mean	91.9	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

APX= apixaban; ASA = aspirin; ASA+CLP = aspirin + clopidogrel; DBG-110mg=dabigatran 110mg; DBG-150MG=dabigatran 150mg; EDX-30MG=edoxaban 30mg; EDX-60MG=edoxaban 60mg; RVX=rivaroxaban; UC=usual care warfarin; GNT = genotype-guided warfarin dosing; SM=patient's self-management of warfarin; ST=patient's self-testing of warfarin; WTH=watchman device; HTN=hypertension; DM=diabetes melitus; HF=heart failure; TIA=transient ischemic attack; MI=myocardial infarction; TTR=time in therapeutic range; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes and previous stroke; NA=not available

Details of Reported Concurrent Medications Received in the Included Studies

Study name/ First author	Treatment (n)	ACEi/ARBs (%)	Beta-blockers (%)	Amiodarone (%)	Statins (%)	Digoxin or digitalis preparations (%)	Verapamil or diltiazem (%)
Matchar DB[1]	UC+ST	NA	NA	8	NA	NA	NA
	UC	NA	NA	8	NA	NA	NA
Khan TI[2]	UC+ST	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
SMAAF[3]	UC+SM	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
Menendez-Jandula B[4]	UC+SM	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
Verret L [5]	UC+SM	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
Pirmohamed M[6]	UC+GNT	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
ACTIVE-W[7]	UC	15	56	NA	37	37	NA
	ASA+CLP	15	58	NA	38	37	NA
Liu X[8]	UC	78.4	72.5	15.7	58.9	13.8	NA
	ASA	84	70	14	62	16	NA
SPAF II[9]	UC	NA	NA	NA	NA	NA	NA
	ASA	NA	NA	NA	NA	NA	NA
EAFT[10]	UC	NA	NA	NA	NA	NA	NA
	CONTROL	NA	NA	NA	NA	NA	NA
WASPO[11]	UC	NA	NA	NA	NA	NA	NA
	ASA	NA	NA	NA	NA	NA	NA
Lavitola PL[12]	UC	NA	NA	NA	NA	NA	NA
	ASA	NA	NA	NA	NA	NA	NA
BAFTA[13]	UC	NA	NA	NA	NA	NA	NA
	ASA	NA	NA	NA	NA	NA	NA
AFASAK[14]	UC	NA	NA	NA	NA	NA	NA
	ASA	NA	NA	NA	NA	NA	NA
	CONTROL	NA	NA	NA	NA	NA	NA
AFASAK 2[15]	UC	NA	NA	NA	NA	NA	NA
	ASA	NA	NA	NA	NA	NA	NA
BAATAF[16]	UC	NA	NA	NA	NA	NA	NA
	CONTROL	NA	NA	NA	NA	NA	NA
CAFA[17]	UC	NA	NA	NA	NA	NA	NA
	CONTROL	NA	NA	NA	NA	NA	NA
JAST[18]	ASA	NA	NA	NA	NA	NA	NA
	CONTROL	NA	NA	NA	NA	NA	NA
Chen KP[19]	UC	NA	NA	NA	NA	NA	NA
	ASA	NA	NA	NA4	NA	NA	NA
SPAF I[20]	UC	NA	NA	NA	NA	NA	NA
	CONTROL	NA	NA	NA	NA	NA	NA
PREVAIL[21]	UC+WTH	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
PROTECT AF[22]	UC+WTH	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
RELY[23]	DBG-150MG	66.7	63.7	10.9	43.9	NA	NA
	DBG-110MG	66.3	62.9	10.4	44.9	NA	NA
	UC	65.5	61.8	10.7	44.4	NA	NA
ROCKET[24]	RVX	NA	65.1	NA	42.96	38.78	NA
	UC	NA	65.7	NA	43.19	38.85	NA

ARISTOTLE J[25]	APX	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
ENGAGE TIMI-48[26]	EDX-60MG	NA	NA	12.3	NA	29.5	NA
	EDX-30MG	NA	NA	11.4	NA	29.5	NA
	UC	NA	NA	11.8	NA	30.9	NA
ARISTOTLE[27]	APX	70.9	63.6	11.1	45	32	30.1
	UC	70.1	62.6	11.5	45.1	32.1	31.1
Weitz JI[28]	EDX-60MG	NA	NA	NA	NA	NA	NA
	EDX-30MG	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
J-ROCKET[29]	RVX	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
TRIPLE AXEL[30]	RVX	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
Chung N[31]	EDX-60MG	NA	NA	NA	NA	NA	NA
	EDX-30MG	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
PETRO[32]	DBG-150MG	69.8	73	5.4	60	45	18.7
	UC	81.4	70	8.5	53	45.7	20
Mao L[33]	RVX	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
Yamashita T[34]	EDX-60MG	NA	NA	NA	NA	NA	NA
	EDX-30MG	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
AVERROES[35]	APX	64	56	11	31	29	9
	ASA	64	55	12	31	27	9
Shosha RI[36]	RVX	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA
Boehringer Ingelheim[37]	DBG-150MG	NA	NA	NA	NA	NA	NA
	DBG-110MG	NA	NA	NA	NA	NA	NA
	UC	NA	NA	NA	NA	NA	NA

APX= apixaban; ASA = aspirin; ASA+CLP = aspirin + clopidogrel; DBG-110mg=dabigatran 110mg; DBG-150MG=dabigatran 150mg; EDX-30MG=edoxaban 30mg; EDX-60MG=edoxaban 60mg; RVX=rivaroxaban; UC=usual care warfarin; GNT = genotype-guided warfarin dosing; SM=patient's self-management of warfarin; ST=patient's self-testing of warfarin; WTH=watchman device; ACEi/ARBs=angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

S-6-4. Matching of Major Bleeding Definitions

In order to minimize the heterogeneity on the definitions of major bleeding across the included studies, major bleeding events were matched against the standardized bleeding end-point definitions adopted by the Bleeding Academic Research Consortium (BARC).[38] Major bleeding outcome was collected based on BARC3-5 criteria because this bleeding definition was standardized to include both clinical and laboratory information. Furthermore, BARC definition was the most updated bleeding definition.

We directly collected major bleeding outcome from any studies reported outcome as BARC definition. If not, the compatibility criteria were considered. The compatible definitions must be standardized based on BARC 3-5 criteria and they must not contain any lower severity of bleeding. For instance, ISTH major bleeding definition (fatal bleeding, symptomatic bleeding in a critical area or organ such as intracranial, reduction of haemoglobin ≥2g/dL or transfusion of two or more units of whole blood) could be categorized into BARC type 3A (reduction of haemoglobin 3 to <5g/Dl or transfusion with overt bleeding), type 3B (reduction of haemoglobin ≥5g/dL), type 3c (intracranial haemorrhage), and type 5 (fatal bleeding). Therefore, ISTH major bleeding was a compatible definition and ISTH major bleeding outcomes could be collected into our analysis. In contrast, a non-official definition such as 'intracranial bleeding and/or requiring blood transfusion or surgical intervention and/or hospitalization' could not be categorized as compatible definition due to the inclusion of hospitalization criteria which was unclear in severity and might not be compatible with BARC 3-5.

Major Bleeding Definitions of Each Study and Compatibility with BARC 3-5, TIMI Major, GUSTO severe and ISTH Major Bleeding Definitions

Study name/First Author	Definition of major bleeding	Details in case of non-official bleeding definition	Compatible with BARC 3-5	Compatible with TIMI major	Compatible with GUSTO severe	Compatible with ISTH major
ACTIVE-W[7]	Non-official definition	Any bleeding requiring transfusion of at least two units of red blood cells or equivalent of whole blood, or which was severe	BARC 3A, 3B	Incompatible due to transfusion criteria	Incompatible due to transfusion criteria	Reported as ISTH
AFASAK[14]	Non-official definition	Bleeding requiring medical intervention	Incompatible due to medical intervention criteria	Incompatible due to medical intervention criteria	Incompatible due to medical intervention criteria	Incompatible due to medical intervention criteria
AFASAK 2[15]	Non-official definition	Fatal, life-threatening or potentially life-threatening, requiring surgical treatment or blood transfusion	Incompatible due to surgical treatment criteria	Incompatible due transfusion and surgical treatment criteria	Incompatible due transfusion and surgical treatment criteria	Incompatible due to surgical treatment criteria
ARISTOTLE[27]	ISTH		BARC 3A, 3B, 3C, 5	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Reported as ISTH
ARISTOTLE J[25]	ISTH		BARC 3A, 3B, 3C, 5	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Reported as ISTH
AVERROES[35]	Non-official definition	Clinically overt bleeding accompanied by one or more of the following: a decrease in the hemoglobin level of 2 g/dL or more over a 24-hour period, transfusion of 2 or more units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding	BARC 3A, 3B, 3C, 5	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Compatible
BAATAF[16]	Non-official definition	Intracranial bleeding, fatal bleeding, or bleeding leading to the transfusions of 4 units of blood within 48 hours	BARC 3A, 3C, 5	Incompatible due to transfusion criteria	Incompatible due to transfusion criteria	Incompatible due to transfusion criteria
BAFTA[13]	Non-official definition	Intracranial hemorrhage or fatal hemorrhage, or one that resulted in the need for transfusion or surgery	Incompatible due to surgery criteria	Incompatible due to transfusion criteria	Incompatible due transfusion criteria	Incompatible due surgery criteria
Boehringer Ingelheim[37]	Non-official definition	Any bleed fulfilling one of the following conditions: Fatal or life-threatening, retroperitoneal, intracranial, intraocular, or intraspinal bleeding (verified by objective testing, bleeding requiring surgical treatment, clinically overt bleeding leading to a transfusion of 4.5 units (equal to 2 units in EU/US) or more, clinically overt bleeding leading to a fall in hemoglobin of at least 2 g/dL	Incompatible due to surgical treatment criteria	Incompatible due to hemoglobin, transfusion and surgical treatment criteria	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to surgical treatment criteria
CAFA[17]	Non-official definition	Any bleeding episode associated with a 2g/dL decrease in serum hemoglobin or requiring a blood transfusion or bleeding into a sensitive location such as the pericardium or retina	BARC 3A, 3B, 3C	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Compatible

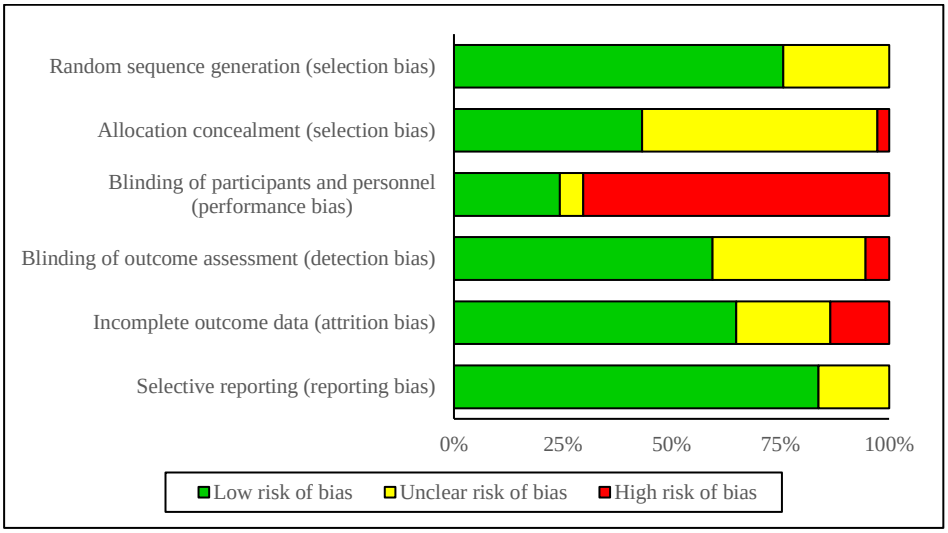
Chen KP[19]	Non-official definition	Intracranial bleeding, fatal bleeding, or bleeding leading to the transfusion of four or more units of blood	BARC 3A, 3C, 5	Incompatible due to transfusion criteria	Incompatible due to transfusion criteria	Incompatible due to transfusion criteria
Chung N[31]	Non-official definition	Fatal, bleeding associated with ≥2 g/dl drop in hemoglobin, transfusion ≥800 ml of packed red blood cells or whole blood, and bleeding into a critical area or organ (retroperitoneal, intracranial, intraocular, intraspinal, intra-articular or pericardial or intramuscular with compartment syndrome)	BARC 3A, 3B, 3C	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Compatible
EAFT[10]	Non-official definition	Bleeding that required hospital admission, blood transfusion or surgery, or when they caused a permanent increase in disability	Incompatible due to hospitalization and permanent disability criteria	Incompatible due to hospitalization and permanent disability criteria	Incompatible due to hospitalization and permanent disability criteria	Incompatible due to hospitalization and permanent disability criteria
ENGAGE TIMI 48[26]	ISTH		BARC 3A, 3B, 3C, 5	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Reported as ISTH
JAST[18]	Non-official definition	Fatal bleeding, bleeding needed for hospital admission for treatment, blood transfusion, or a decrease of hemoglobin concentration 4 g/dL	Incompatible due hospitalization criteria	Incompatible due to hemoglobin, transfusion and hospitalization criteria	Incompatible due to hemoglobin, transfusion and hospitalization criteria	Incompatible due to hospitalization criteria
J-ROCKET[29]	Non-official definition	Clinically overt bleeding that was associated with a fall in hemoglobin ≥20g/L, transfusion of ≥2 units of packed red blood cells or whole blood, or involved a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal hemorrhage), or had a fatal outcome	BARC 3A, 3B, 3C, 5	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Compatible
Khan TI[2]	Non-official definition	Bleeding that was fatal, or was life-threatening, or was potentially life-threatening, or led to severe blood loss, or led to surgical treatment, or led to moderate blood loss that was acute or subacute, and was not explained by trauma or surgery or bleeding that led directly to hospitalization	Incompatible due to surgical treatment and hospitalization criteria	Incompatible due to surgical treatment and hospitalization criteria	Incompatible due to surgical treatment and hospitalization criteria	Incompatible due to surgical treatment and hospitalization criteria
Lavitola PL[12]	X		X	X	X	X
Liu X[8]	Non-official definition	A Hb decrease of at least 2g/dL, a need for at least 2-unit whole blood transfusion, or symptomatic hemorrhage in major locations or organs	BARC 3A, 3B, 3C	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Compatible
Mao L[33]	Non-official definition	Fatal bleeding, decreased in hemoglobin ≥ 2g/dL, bleeding requiring transfusion or bleeding into a critical area or organ (intracranial, intraocular)	BARC 3A, 3B, 3C	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Compatible
Matchar DB[1]	Non-official definition	Severe: Retroperitoneal, intracranial, intraspinal, intra-ocular, or pericardial bleeding or any other source of bleeding that results in hemodynamic compromise Moderate: Bleeding requiring transfusion of red blood cells or whole blood but does not result in hemodynamic compromise or bleeding associated with a drop in hemoglobin of ≥ 2 g/dL (rather than a drop ≥ 5g/dL) from baseline	Incompatible due to surgical bleeding criteria	Incompatible due to hemoglobin, transfusion, and surgical bleeding criteria	Incompatible due to hemoglobin, transfusion, and surgical bleeding criteria	Incompatible due to surgical bleeding criteria

		Surgical Bleeding: Patient had surgical procedure, was transfused with blood, and any of the following occurred: (i) during intra operative period, number of units transfused was more than number specified in OR schedule sent to blood bank prior to surgery, (ii) during post-operative period, number of units transfused was higher than expected by operating physician and met other criteria for major bleed				
Menéndez-Jándula B[4]	Non-official definition	Life-threatening bleeding or bleeding requiring transfusion or hospital admission	Incompatible due to hospitalization criteria	Incompatible due to transfusion and hospitalization criteria	Incompatible due to transfusion and hospitalization criteria	Incompatible due to hospitalization criteria
PETRO[32]	Non-official definition	Fatal or life-threatening retroperitoneal, intracranial, intraocular, or intraspinal bleeding; or bleeding requiring surgery or transfusion of 2 U or associated with a decrease in hemoglobin of 2.0 g/Dl	BARC 3A, 3B, 3C	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Compatible
Pirmohamed M[6]	ISTH		BARC 3A, 3B, 3C, 5	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Reported as ISTH
PREVAIL[21]	X		X	X	X	X
PROTECT AF[22]	Non-official definition	Intracranial or bleeding requiring transfusion	BARC 3A, 3C	Incompatible due to transfusion criteria	Incompatible due to transfusion criteria	Compatible
RELY[23]	Non-official definition	A reduction in the hemoglobin level of at least 20 g/L, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ	BARC 3A, 3B, 3C	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Compatible
ROCKET[24]	Non-official definition	Clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), fall in hemoglobin concentration >2 g/dL, transfusion of >2 units of whole blood or packed red blood cells, or permanent disability	BARC 3A, 3B, 3C, 5	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Compatible
Shosha RI[36]	Non-official definition	Clinically overt and associated with any of the following: fatal outcome; involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, and retroperitoneal, intraparenchymal, intraventricular, and subdural subarachnoid); fall in hemoglobin concentration>2 g/dl; transfusion of>2 U of whole blood; or packed red blood cells.	BARC 3A, 3B, 3C, 5	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Compatible
SMAAF[3]	Non-official definition	Intracerebral or fatal hemorrhages which required transfusions or inpatient admission for more than 24 hours with or without surgical operation.	Incompatible due to hospitalization criteria	Incompatible due to transfusion and hospitalization criteria	Incompatible due to transfusion and hospitalization criteria	Incompatible due to hospitalization criteria
SPAF I[20]	Non-official definition	Any bleeding that Involved the central nervous system, management requiring hospitalization with transfusion and/or surgery, or permanent residual impairment.	Incompatible due to hospitalization and permanent	Incompatible due to transfusion, hospitalization and permanent	Incompatible due to transfusion, hospitalization and permanent	Incompatible due to hospitalization and permanent

			disability criteria	disability criteria	disability criteria	disability criteria
SPAF II[9]	Non-official definition	Overt bleeding that was (1) fatal, (2) life-threatening, (3) potentially life threatening, or (4) acute or subacute and led to reoperation or moderate or severe blood loss	BARC 5	Compatible	Compatible	Compatible
Triple AXEL[30]	ISTH		BARC 3A, 3B, 3C, 5	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Reported as ISTH
Verret L[5]	Non-official definition	Bleeding that required treatment or medical evaluation or life-threatening or fatal	BARC 3A, 3B, 5	Incompatible due to treatment or medical evaluation criteria	Incompatible due to fatal criteria	Compatible
WASPO[11]	Non-official definition	Intracranial hemorrhage, fall in hemoglobin by >2 g/dl, need for blood transfusion	BARC 3A, 3B, 3C	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Compatible
Weitz JI[28]	ISTH		BARC 3A, 3B, 3C, 5	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Reported as ISTH
Yamashita T[34]	Non-official definition	Life-threatening bleeding; intracranial, intraspinal, intraocular (excluding subconjunctival), retroperitoneal, intraarticular, or intrapericardial bleeding; clinically overt bleeding accompanied by a decrease in hemoglobin of ≥20 g/L; or bleeding requiring transfusion of ≥4 units of blood (1 unit= approximately 200 ml)	BARC 3A, 3B, 3C	Incompatible due to hemoglobin and transfusion criteria	Incompatible due to hemoglobin and transfusion criteria	Compatible

S-6-5. Risk of Bias Assessment

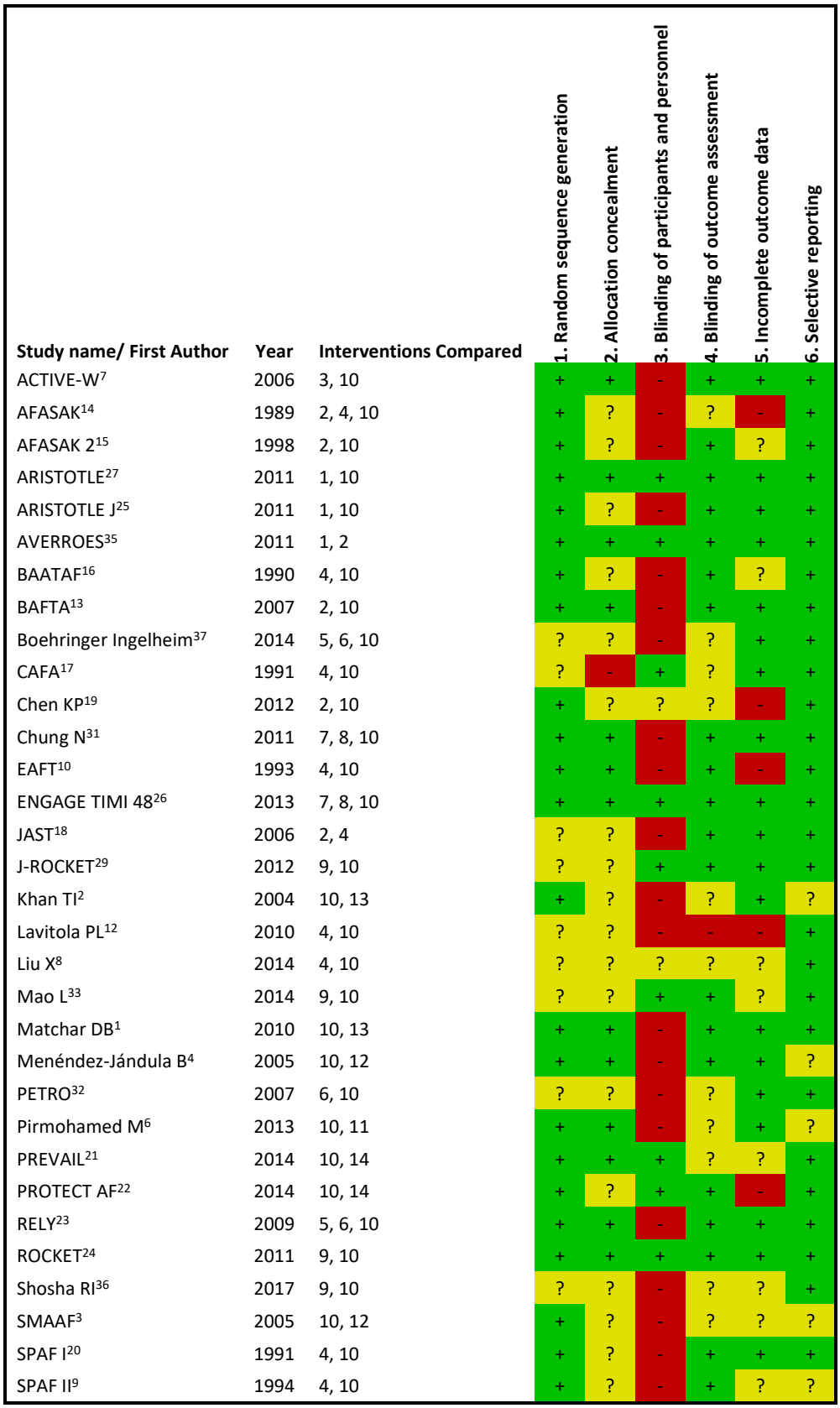
Risk of Bias Graph: review authors' judgements about each risk of bias item presented as percentages for studies including in network analyses (37 studies)



List of interventions examined by included studies for stroke prevention in AF patients

Number	Interventions
1	Apixaban
2	Aspirin
3	Aspirin + Clopidogrel
4	Control/Placebo
5	Dabigatran 110mg BD
6	Dabigatran 150mg BD
7	Edoxaban 30mg OD
8	Edoxaban 60mg OD
9	Rivaroxaban OD
10	Usual Warfarin Care
11	Genotype-guided Warfarin Dosing
12	Patient's Self-management of Warfarin
13	Patient's Self-testing of Warfarin
14	Watchman Device Insertion with Temporary Warfarin Use

Risk of Bias Summary: review authors' judgements about each risk of bias item for each included study

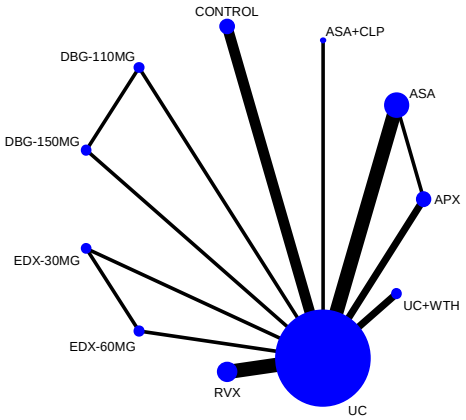


Study name/ First Author	Year	Interventions Compared	1. Random sequence generation	2. Allocation concealment	3. Blinding of participants and personnel	4. Blinding of outcome assessment	5. Incomplete outcome data	6. Selective reporting
ACTIVE-W[7]	2006	3, 10	+	+	-	+	+	+
AFASAK[14]	1989	2, 4, 10	+	?	-	?	-	+
AFASAK 2[15]	1998	2, 10	+	?	-	+	?	+
ARISTOTLE[27]	2011	1, 10	+	+	+	+	+	+
ARISTOTLE J[25]	2011	1, 10	+	?	-	+	+	+
AVERROES[35]	2011	1, 2	+	+	+	+	+	+
BAATAF[16]	1990	4, 10	+	?	-	+	?	+
BAFTA[13]	2007	2, 10	+	+	-	+	+	+
Boehringer Ingelheim[37]	2014	5, 6, 10	?	?	-	?	+	+
CAFA[17]	1991	4, 10	?	-	+	?	+	+
Chen KP[19]	2012	2, 10	+	?	?	?	-	+
Chung N[31]	2011	7, 8, 10	+	+	-	+	+	+
EAFT[10]	1993	4, 10	+	+	-	+	-	+
ENGAGE TIMI 48[26]	2013	7, 8, 10	+	+	+	+	+	+
JAST[18]	2006	2, 4	?	?	-	+	+	+
J-ROCKET[29]	2012	9, 10	?	?	+	+	+	+
Khan TI[2]	2004	10, 13	+	?	-	?	+	?
Lavitola PL[12]	2010	4, 10	?	?	-	-	-	+
Liu X[8]	2014	4, 10	?	?	?	?	?	+
Mao L[33]	2014	9, 10	?	?	+	+	?	+
Matchar DB[1]	2010	10, 13	+	+	-	+	+	+
Menéndez-Jándula B[4]	2005	10, 12	+	+	-	+	+	?
PETRO[32]	2007	6, 10	?	?	-	?	+	+
Pirmohamed M[6]	2013	10, 11	+	+	-	?	+	?
PREVAIL[21]	2014	10, 14	+	+	+	?	?	+
PROTECT AF[22]	2014	10, 14	+	?	+	+	-	+
RELY[23]	2009	5, 6, 10	+	+	-	+	+	+
ROCKET[24]	2011	9, 10	+	+	+	+	+	+
Shosha RI[36]	2017	9, 10	?	?	-	?	?	+
SMAAF[3]	2005	10, 12	+	?	-	?	?	?
SPAF I[20]	1991	4, 10	+	?	-	+	+	+
SPAF II[9]	1994	4, 10	+	?	-	+	?	?

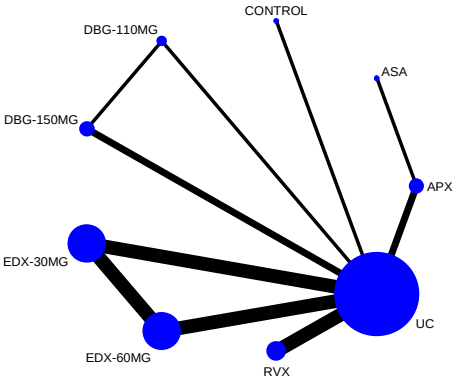
TRIPLE AXEL[30]	2017	9, 10	+	+	-	+	+	+
Verret L[5]	2012	10, 12	+	?	-	?	+	?
WASPO[11]	2007	4, 10	+	+	-	-	+	+
Weitz JI[28]	2010	7, 8, 10	+	+	-	?	+	+
Yamashita T[34]	2012	7, 8, 10	+	?	-	+	+	+

+ Low risk of bias ? Unclear risk of bias - High risk of bias

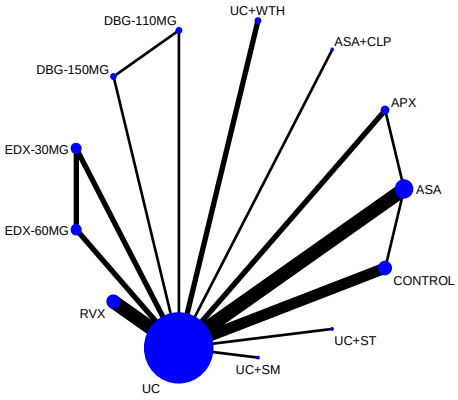
S-6-6. Network Map of Treatment Comparisons for Secondary Outcomes



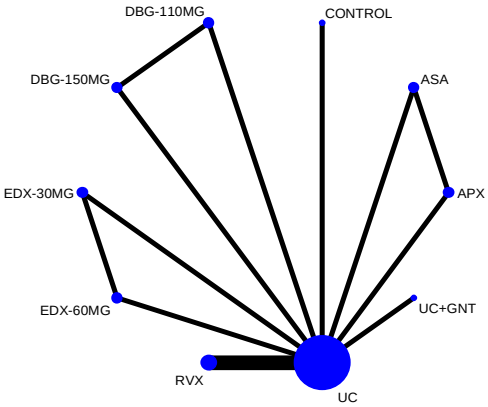
Ischemic Stroke



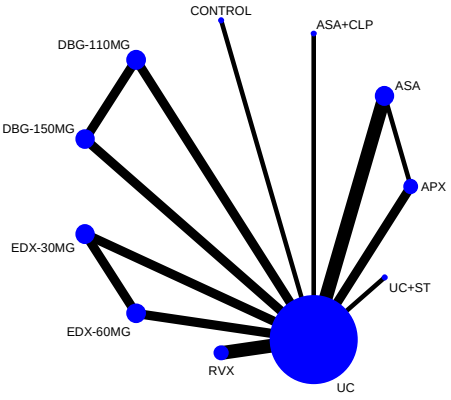
Clinically Relevant Non-Major Bleeding



Intracranial Bleeding



Gastrointestinal Bleeding



Myocardial Infarction

S-6-7. Assessment of Inconsistency

Evaluation of the global inconsistency in network using the 'design-by-treatment' interaction model for each outcome.

Network outcome	Chi-square	P-value test for global inconsistency
Primary Outcome		
• Stroke or Systemic Embolism	4.23	0.5169
• All-cause Mortality	0.60	0.7407
• Major Bleeding	0.90	0.6382
Secondary Outcome		
• Ischemic stroke	0.34	0.5598
• Clinically relevant non-major bleeding (CRNMB)	0.27	0.6042
• Intracranial bleeding	1.03	0.5956
• Gastrointestinal bleeding	1.10	0.2936
• Myocardial infarction	0	0.9562

S-6-8. Pairwise Meta-analyses Risk Ratios (95% Confidence interval) for All Dichotomous Outcomes

Comparisons	vs.	Intervention	No. studies	No. of patients	Pairwise meta-analysis risk ratio (95% CI)		Heterogeneity I_2 (variation in RR attributable to heterogeneity)
					Fixed Effect	Random Effect	
Stroke or Systemic Embolism							
ASA	vs.	APX	1	5599	0.45 (0.32,0.62)	0.45 (0.32,0.62)	.
UC	vs.	APX	2	18419	0.78 (0.66,0.94)	0.40 (0.05,3.27)	59.20%
CONTROL	vs.	ASA	2	1543	1.05 (0.74,1.47)	1.05 (0.74,1.47)	0.00%
UC	vs.	ASA	7	2828	1.64 (1.27,2.12)	1.69 (1.00,2.83)	65.20%
UC	vs.	ASA+CLP	1	6706	1.85 (1.37,2.51)	1.85 (1.37,2.51)	.
UC	vs.	CONTROL	5	2329	2.69 (1.94,3.74)	2.61 (1.80,3.80)	14.00%
DBG-150MG	vs.	DBG-110MG	1	12195	1.37 (1.10,1.71)	1.37 (1.10,1.71)	.
UC	vs.	DBG-110MG	2	12135	0.91 (0.75,1.11)	0.91 (0.75,1.11)	0.00%
UC	vs.	DBG-150MG	2	12444	0.66 (0.54,0.82)	0.67 (0.54,0.83)	0.00%
EDX-60MG	vs.	EDX-30MG	2	14959	1.31 (1.13,1.52)	1.31 (1.13,1.52)	0.00%
UC	vs.	EDX-30MG	2	14969	1.14 (0.99,1.31)	0.84 (0.26,2.70)	41.50%
UC	vs.	EDX-60MG	2	14970	0.86 (0.74,1.01)	0.81 (0.47,1.40)	10.70%
UC	vs.	RVX	5	16045	0.85 (0.74,0.98)	0.86 (0.75,0.99)	0.00%
UC+GNT	vs.	UC	1	455	2.99 (0.12,72.94)	2.99 (0.12,72.94)	.
UC+SM	vs.	UC	2	1056	4.79 (1.75,13.11)	4.76 (1.74,13.06)	0.00%
UC+ST	vs.	UC	1	3001	1.01 (0.61,1.65)	1.01 (0.61,1.65)	.
UC+WTH	vs.	UC	2	1114	1.11 (0.66,1.87)	0.84 (0.21,3.37)	50.80%
All-cause Mortality							
ASA	vs.	APX	1	5599	0.79 (0.62,1.01)	0.79 (0.62,1.01)	.
UC	vs.	APX	1	18419	0.90 (0.81,1.00)	0.90 (0.81,1.00)	.
CONTROL	vs.	ASA	1	871	1.16 (0.48,2.83)	1.16 (0.48,2.83)	.
UC	vs.	ASA	6	3028	1.03 (0.86,1.23)	1.03 (0.86,1.23)	0.00%
UC	vs.	ASA+CLP	1	6706	1.00 (0.80,1.23)	1.00 (0.80,1.23)	.
UC	vs.	CONTROL	2	860	1.15 (0.81,1.65)	1.15 (0.80,1.65)	0.00%
DBG-150MG	vs.	DBG-110MG	1	12195	1.03 (0.91,1.17)	1.03 (0.91,1.17)	.
UC	vs.	DBG-110MG	1	12135	0.92 (0.81,1.04)	0.92 (0.81,1.04)	.
UC	vs.	DBG-150MG	1	12208	0.89 (0.79,1.01)	0.89 (0.79,1.01)	.
EDX-60MG	vs.	EDX-30MG	1	14069	0.95 (0.87,1.05)	0.95 (0.87,1.05)	.
UC	vs.	EDX-30MG	1	14070	0.88 (0.80,0.97)	0.88 (0.80,0.97)	.
UC	vs.	EDX-60MG	1	14071	0.92 (0.84,1.01)	0.92 (0.84,1.01)	.
UC	vs.	RVX	2	15664	0.85 (0.71,1.01)	0.85 (0.71,1.01)	0.00%
UC+GNT	vs.	UC	1	455	0.40 (0.08,2.03)	0.40 (0.08,2.03)	.
UC+SM	vs.	UC	1	854	2.51 (0.98,6.39)	2.51 (0.98,6.39)	.
UC+ST	vs.	UC	1	2922	1.04 (0.84,1.28)	1.04 (0.84,1.28)	.
UC+WTH	vs.	UC	2	1114	1.99 (1.15,3.43)	1.70 (0.62,4.63)	51.70%
Major Bleeding							
ASA	vs.	APX	1	5599	1.12 (0.73,1.72)	1.12 (0.73,1.72)	.
UC	vs.	APX	2	18419	0.70 (0.61,0.81)	0.70 (0.61,0.81)	0.00%
UC	vs.	ASA	3	616	0.65 (0.24,1.77)	0.72 (0.12,4.26)	49.50%

UC	vs.	ASA+CLP	1	6706	1.07 (0.81,1.42)	1.07 (0.81,1.42)	.
UC	vs.	CONTROL	2	798	0.28 (0.06,1.36)	0.30 (0.06,1.47)	0.00%
DBG-150MG	vs.	DBG-110MG	1	12091	0.87 (0.75,1.00)	0.87 (0.75,1.00)	.
UC	vs.	DBG-110MG	1	12037	0.81 (0.70,0.94)	0.81 (0.70,0.94)	.
UC	vs.	DBG-150MG	2	12334	0.94 (0.82,1.08)	0.94 (0.82,1.08)	0.00%
EDX-60MG	vs.	EDX-30MG	3	14959	0.60 (0.52,0.70)	0.61 (0.52,0.71)	0.00%
UC	vs.	EDX-30MG	3	14969	0.48 (0.42,0.56)	0.48 (0.42,0.56)	0.00%
UC	vs.	EDX-60MG	4	14970	0.80 (0.71,0.91)	0.80 (0.71,0.90)	0.00%
UC	vs.	RVX	5	16110	1.00 (0.88,1.14)	0.96 (0.67,1.38)	29.60%
UC+GNT	vs.	UC	N/A	455	N/A	N/A	.
UC+SM	vs.	UC	1	117	0.49 (0.05,5.27)	0.49 (0.05,5.27)	.
UC+WTH	vs.	UC	1	707	1.55 (0.85,2.84)	1.55 (0.85,2.84)	.
Clinically Relevant Non-Major Bleeding							
ASA	vs.	APX	1	5599	1.14 (0.85,1.52)	1.14 (0.85,1.52)	.
UC	vs.	APX	2	18419	0.68 (0.59,0.79)	0.68 (0.59,0.79)	0.00%
UC	vs.	CONTROL	1	421	0.33 (0.04,3.16)	0.33 (0.04,3.16)	.
DBG-150MG	vs.	DBG-110MG	1	104	0.50 (0.10,2.48)	0.50 (0.10,2.48)	.
UC	vs.	DBG-110MG	1	98	0.45 (0.09,2.22)	0.45 (0.09,2.22)	.
UC	vs.	DBG-150MG	2	346	1.14 (0.52,2.53)	1.13 (0.51,2.51)	0.00%
EDX-60MG	vs.	EDX-30MG	4	14959	0.79 (0.73,0.86)	0.77 (0.57,1.03)	8.40%
UC	vs.	EDX-30MG	4	14969	0.69 (0.64,0.75)	0.70 (0.65,0.75)	0.00%
UC	vs.	EDX-60MG	4	14970	0.88 (0.82,0.94)	0.87 (0.82,0.94)	0.00%
UC	vs.	RVX	4	15927	1.04 (0.97,1.12)	1.04 (0.97,1.11)	0.00%
Ischemic Stroke							
ASA	vs.	APX	1	5599	0.37 (0.26,0.55)	0.37 (0.26,0.55)	.
UC	vs.	APX	2	18419	0.91 (0.74,1.12)	0.54 (0.09,3.38)	49.10%
UC	vs.	ASA	4	1853	3.14 (1.87,5.27)	2.99 (1.77,5.06)	0.00%
UC	vs.	ASA+CLP	1	6706	2.12 (1.47,3.05)	2.12 (1.47,3.05)	.
UC	vs.	CONTROL	3	1280	2.97 (1.90,4.64)	2.86 (1.83,4.49)	0.00%
DBG-150MG	vs.	DBG-110MG	1	12091	1.45 (1.14,1.84)	1.45 (1.14,1.84)	.
UC	vs.	DBG-110MG	1	12037	1.12 (0.90,1.40)	1.12 (0.90,1.40)	.
UC	vs.	DBG-150MG	1	12098	0.78 (0.61,0.99)	0.78 (0.61,0.99)	.
EDX-60MG	vs.	EDX-30MG	1	14069	1.41 (1.20,1.66)	1.41 (1.20,1.66)	.
UC	vs.	EDX-30MG	1	14070	1.42 (1.20,1.67)	1.42 (1.20,1.67)	.
UC	vs.	EDX-60MG	1	14071	1.00 (0.84,1.20)	1.00 (0.84,1.20)	.
UC	vs.	RVX	4	15957	0.87 (0.72,1.05)	0.86 (0.69,1.07)	7.00%
UC+WTH	vs.	UC	2	1114	0.72 (0.37,1.43)	0.74 (0.37,1.46)	0.00%
Intracranial Bleeding							
ASA	vs.	APX	1	5599	0.84 (0.38,1.87)	0.84 (0.38,1.87)	.
UC	vs.	APX	2	18419	0.42 (0.31,0.58)	0.42 (0.31,0.58)	0.00%
CONTROL	vs.	ASA	1	871	2.09 (0.39,11.35)	2.09 (0.39,11.35)	.
UC	vs.	ASA	4	2082	0.67 (0.27,1.67)	0.68 (0.27,1.70)	0.00%
UC	vs.	ASA+CLP	1	6706	0.52 (0.25,1.07)	0.52 (0.25,1.07)	.
UC	vs.	CONTROL	4	1658	0.83 (0.24,2.85)	0.83 (0.22,3.17)	0.00%
DBG-150MG	vs.	DBG-110MG	1	12091	0.76 (0.46,1.25)	0.76 (0.46,1.25)	.
UC	vs.	DBG-110MG	1	12037	0.31 (0.20,0.48)	0.31 (0.20,0.48)	.

UC	vs.	DBG-150MG	1	12098	0.41 (0.28,0.60)	0.41 (0.28,0.60)	.
EDX-60MG	vs.	EDX-30MG	2	14331	0.66 (0.45,0.98)	0.67 (0.45,0.98)	0.00%
UC	vs.	EDX-30MG	1	14330	0.31 (0.22,0.44)	0.31 (0.22,0.44)	.
UC	vs.	EDX-60MG	2	14331	0.47 (0.35,0.64)	0.58 (0.18,1.87)	22.30%
UC	vs.	RVX	5	16110	0.73 (0.56,0.94)	0.76 (0.53,1.08)	22.20%
UC+SM	vs.	UC	1	737	1.00 (0.14,7.08)	1.00 (0.14,7.08)	.
UC+ST	vs.	UC	1	2922	0.73 (0.30,1.81)	0.73 (0.30,1.81)	.
UC+WTH	vs.	UC	2	1114	4.45 (1.48,13.36)	3.30 (0.44,24.86)	40.80%
Gastrointestinal Bleeding							
ASA	vs.	APX	1	5599	0.85 (0.40,1.84)	0.85 (0.40,1.84)	.
UC	vs.	APX	1	18201	0.88 (0.68,1.14)	0.88 (0.68,1.14)	.
UC	vs.	ASA	1	440	0.20 (0.02,1.63)	0.20 (0.02,1.63)	.
UC	vs.	CONTROL	1	439	0.23 (0.05,1.07)	0.23 (0.05,1.07)	.
DBG-150MG	vs.	DBG-110MG	1	12091	0.74 (0.59,0.92)	0.74 (0.59,0.92)	.
UC	vs.	DBG-110MG	1	12037	1.11 (0.87,1.42)	1.11 (0.87,1.42)	.
UC	vs.	DBG-150MG	1	12098	1.50 (1.20,1.89)	1.50 (1.20,1.89)	.
EDX-60MG	vs.	EDX-30MG	1	14069	0.56 (0.45,0.69)	0.56 (0.45,0.69)	.
UC	vs.	EDX-30MG	1	14070	0.68 (0.54,0.85)	0.68 (0.54,0.85)	.
UC	vs.	EDX-60MG	1	14071	1.22 (1.01,1.48)	1.22 (1.01,1.48)	.
UC	vs.	RVX	3	15867	1.43 (1.17,1.74)	1.33 (0.48,3.70)	72.00%
UC+GNT	vs.	UC	1	455	1.36 (0.64,2.89)	1.36 (0.64,2.89)	.
Myocardial Infarction							
ASA	vs.	APX	1	5599	0.85 (0.50,1.47)	0.85 (0.50,1.47)	.
UC	vs.	APX	1	18419	0.88 (0.66,1.17)	0.88 (0.66,1.17)	.
UC	vs.	ASA	3	1413	1.06 (0.59,1.90)	1.06 (0.59,1.90)	0.00%
UC	vs.	ASA+CLP	1	6706	1.55 (0.92,2.61)	1.55 (0.92,2.61)	.
UC	vs.	CONTROL	1	421	1.00 (0.14,7.00)	1.00 (0.14,7.00)	.
DBG-150MG	vs.	DBG-110MG	1	12195	0.98 (0.73,1.31)	0.98 (0.73,1.31)	.
UC	vs.	DBG-110MG	1	12135	1.37 (0.99,1.89)	1.37 (0.99,1.89)	.
UC	vs.	DBG-150MG	1	12208	1.40 (1.02,1.93)	1.40 (1.02,1.93)	.
EDX-60MG	vs.	EDX-30MG	2	14538	1.27 (1.01,1.58)	1.27 (1.01,1.58)	0.00%
UC	vs.	EDX-30MG	2	14555	1.21 (0.97,1.51)	1.21 (0.97,1.51)	0.00%
UC	vs.	EDX-60MG	2	14555	0.96 (0.76,1.21)	1.13 (0.40,3.21)	20.10%
UC	vs.	RVX	3	15481	0.82 (0.64,1.06)	0.82 (0.63,1.06)	0.00%
UC+ST	vs.	UC	1	2922	0.67 (0.37,1.21)	0.67 (0.37,1.21)	.

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

S-6-9. Results of Network Meta-Analyses

Intervention options are in order of their efficacy or safety ranking. Estimates are presented as risk ratios (RR) and 95% confidence intervals. Treatments are ordered by rankings for each outcome. Comparisons between interventions should be read from column to row for each outcome (row intervention is reference). Risk ratios less than 1 favour the column-defining treatment. To obtain risks ratios for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underlined. Blue-colour box represents that unfavourable outcome was decreased. In contrast, red-colour box represents that unfavourable outcome was increased.

Results of network meta-analysis of interventions options on stroke or systemic embolism

Interventions	Risk ratio	95% Confidence interval	p-value	SUCRA rank
UC+SM	**0.24**	**(0.08, 0.68)**	**0.007**	1
EDX-30MG	1.06	(0.65, 1.72)	0.820	2
UC+GNT	0.33	(0.13, 8.45)	0.506	3
ASA	**1.72**	**(1.29, 2.29)**	**0.000**	4
UC	reference			5
RVX	0.79	(0.57, 1.10)	0.166	6
UC+WTH	0.89	(0.45, 1.78)	0.748	7
DBG-150MG	0.65	(0.39, 1.07)	0.089	8
UC+ST	0.99	(0.51, 1.93)	0.986	9
APX	0.76	(0.51, 1.12)	0.169	10
EDX-60MG	0.82	(0.51, 1.32)	0.410	11
ASA+CLP	**1.85**	**(1.07, 3.21)**	**0.028**	12
CONTROL	**2.12**	**(1.49, 3.01)**	**0.000**	13
DBG-110MG	0.89	(0.54, 1.46)	0.647	14
Number of RCTs	**36**			

UC+SM													
0.22 (0.07,0.72)	EDX-30MG												
0.71 (0.02,21.08)	3.16 (0.12,82.72)	UC+GNT											
0.14 (0.05,0.41)	0.61 (0.35,1.08)	0.19 (0.01,4.97)	ASA										
0.24 (0.08,0.68)	1.06 (0.65,1.72)	0.33 (0.01,8.45)	1.72 (1.29,2.29)	UC									
0.30 (0.10,0.90)	1.33 (0.77,2.33)	0.42 (0.02,10.84)	2.17 (1.40,3.36)	1.26 (0.91,1.75)	RVX								
0.26 (0.08,0.93)	1.18 (0.50,2.82)	0.37 (0.01,10.17)	1.93 (0.91,4.06)	1.12 (0.56,2.23)	0.89 (0.41,1.94)	UC+WTH							
0.37 (0.11,1.17)	1.63 (0.82,3.24)	0.52 (0.02,13.56)	2.66 (1.49,4.73)	1.54 (0.94,2.55)	1.22 (0.68,2.20)	1.38 (0.58,3.26)	DBG-150MG						
0.24 (0.07,0.83)	1.06 (0.47,2.42)	0.34 (0.01,9.09)	1.73 (0.84,3.57)	1.01 (0.52,1.95)	0.80 (0.38,1.67)	0.90 (0.35,2.34)	0.65 (0.28,1.50)	UC+ST					
0.31 (0.10,0.96)	1.40 (0.76,2.57)	0.44 (0.02,11.41)	2.27 (1.51,3.42)	1.32 (0.89,1.95)	1.05 (0.64,1.72)	1.18 (0.53,2.63)	0.85 (0.45,1.60)	1.31 (0.61,2.84)	APX				
0.29 (0.09,0.93)	1.30 (0.81,2.07)	0.41 (0.02,10.72)	2.11 (1.20,3.69)	1.22 (0.76,1.98)	0.97 (0.56,1.69)	1.09 (0.46,2.58)	0.79 (0.40,1.57)	1.22 (0.54,2.76)	0.93 (0.51,1.70)	EDX-60MG			
0.13 (0.04,0.42)	0.57 (0.27,1.19)	0.18 (0.01,4.78)	0.93 (0.50,1.73)	0.54 (0.31,0.94)	0.43 (0.23,0.81)	0.48 (0.20,1.16)	0.35 (0.17,0.73)	0.54 (0.23,1.27)	0.41 (0.21,0.80)	0.44 (0.21,0.92)	ASA+CLP		
0.11 (0.04,0.34)	0.50 (0.27,0.92)	0.16 (0.01,4.06)	0.81 (0.56,1.17)	0.47 (0.33,0.67)	0.37 (0.23,0.61)	0.42 (0.20,0.90)	0.31 (0.16,0.57)	0.47 (0.22,0.99)	0.36 (0.22,0.59)	0.39 (0.21,0.71)	0.87 (0.46,1.68)	CONTROL	
0.27 (0.08,0.85)	1.19 (0.60,2.35)	0.38 (0.01,9.85)	1.93 (1.09,3.42)	1.12 (0.68,1.84)	0.89 (0.50,1.60)	1.00 (0.43,2.36)	0.73 (0.44,1.20)	1.12 (0.49,2.56)	0.85 (0.45,1.59)	0.92 (0.46,1.81)	2.08 (0.99,4.36)	2.38 (1.29,4.39)	DBG-110MG

* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Results of network meta-analysis of interventions options on major bleeding

Interventions	Risk ratio	95% Confidence interval	p-value	SUCRA rank
EDX-60MG	**0.80**	**(0.71, 0.90)**	**0.000**	1
DBG-110MG	**0.81**	**(0.71, 0.94)**	**0.004**	2
ASA+CLP	1.07	(0.81, 1.42)	0.612	3
ASA	**0.63**	**(0.41, 0.96)**	**0.030**	4
UC+WTH	0.64	(0.35, 1.18)	0.153	5
RVX	1.01	(0.89, 1.16)	0.840	6
DBG-150MG	0.94	(0.82, 1.08)	0.367	7
UC+GNT	1.00	(0.02, 50.40)	0.998	8
EDX-30MG	**0.48**	**(0.42, 0.56)**	**0.000**	9
APX	**0.70**	**(0.61, 0.81)**	**0.000**	10
UC+SM	2.03	(0.19, 21.83)	0.557	11
UC	reference			12
CONTROL	0.30	(0.06, 1.47)	0.138	13
Number of RCTs	**23**			

EDX-60MG												
0.98 (0.81,1.19)	DBG-110MG											
0.74 (0.55,1.01)	0.76 (0.55,1.03)	ASA+CLP										
1.28 (0.82,1.98)	1.30 (0.83,2.03)	1.71 (1.03,2.84)	ASA									
1.24 (0.67,2.30)	1.26 (0.68,2.35)	1.67 (0.86,3.24)	0.97 (0.47,2.03)	UC+WTH								
0.79 (0.66,0.94)	0.80 (0.66,0.97)	1.06 (0.78,1.44)	0.62 (0.40,0.96)	0.64 (0.34,1.18)	RVX							
0.85 (0.71,1.02)	0.87 (0.75,1.00)	1.14 (0.84,1.56)	0.67 (0.43,1.04)	0.69 (0.37,1.27)	1.08 (0.89,1.30)	DBG-150MG						
0.80 (0.02,40.01)	0.81 (0.02,40.74)	1.07 (0.02,54.21)	0.62 (0.01,32.03)	0.64 (0.01,33.70)	1.01 (0.02,50.75)	0.93 (0.02,47.03)	UC+GNT					
1.65 (1.42,1.92)	1.68 (1.37,2.06)	2.22 (1.62,3.04)	1.30 (0.83,2.03)	1.33 (0.72,2.48)	2.10 (1.72,2.55)	1.94 (1.59,2.37)	2.08 (0.04,104.57)	EDX-30MG				
1.14 (0.94,1.37)	1.16 (0.95,1.41)	1.53 (1.12,2.08)	0.89 (0.60,1.34)	0.92 (0.49,1.70)	1.44 (1.19,1.74)	1.34 (1.10,1.62)	1.43 (0.03,71.88)	0.69 (0.56,0.84)	APX			
0.39 (0.04,4.23)	0.40 (0.04,4.31)	0.53 (0.05,5.76)	0.31 (0.03,3.43)	0.32 (0.03,3.66)	0.50 (0.05,5.36)	0.46 (0.04,4.97)	0.49 (0.01,48.07)	0.24 (0.02,2.56)	0.35 (0.03,3.72)	UC+SM		
0.80 (0.71,0.90)	0.81 (0.71,0.94)	1.07 (0.81,1.42)	0.63 (0.41,0.96)	0.64 (0.35,1.18)	1.01 (0.89,1.16)	0.94 (0.82,1.08)	1.00 (0.02,50.40)	0.48 (0.42,0.56)	0.70 (0.61,0.81)	2.03 (0.19,21.83)	UC	
2.67 (0.54,13.21)	2.72 (0.55,13.46)	3.59 (0.71,18.10)	2.09 (0.40,10.89)	2.15 (0.39,11.83)	3.39 (0.68,16.76)	3.14 (0.63,15.54)	3.36 (0.05,230.02)	1.61 (0.33,8.00)	2.35 (0.47,11.63)	6.80 (0.39,118.51)	3.34 (0.68,16.45)	CONTROL

* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Results of network meta-analysis of interventions options on all-cause mortality

Interventions	Risk ratio	95% Confidence interval	p-value	SUCRA rank
UC+WTH	**0.49**	**(0.28, 0.86)**	**0.012**	1
UC+SM	0.42	(0.17, 1.04)	0.061	2
UC				3
EDX-60MG	0.92	(0.84, 1.01)	0.081	4
ASA	1.07	(0.92, 1.24)	0.386	5
EDX-30MG	**0.88**	**(0.80, 0.96)**	**0.007**	6
DBG-150MG	0.89	(0.79, 1.01)	0.069	7
RVX	0.85	(0.71, 1.01)	0.065	8
UC+ST	0.96	(0.78, 1.19)	0.725	9
CONTROL	1.11	(0.80, 1.56)	0.522	10
APX	**0.89**	**(0.80, 0.98)**	**0.020**	11
DBG-110MG	0.92	(0.81, 1.04)	0.169	12
ASA+CLP	1.00	(0.80, 1.23)	0.968	13
UC+GNT	2.51	(0.49, 12.81)	0.268	14
Number of RCTs	**26**			

UC+WTH													
1.17 (0.40,3.40)	UC+SM												
0.49 (0.28,0.86)	0.42 (0.17,1.04)	UC											
0.53 (0.30,0.94)	0.46 (0.18,1.14)	1.09 (0.99,1.19)	EDX-60MG										
0.46 (0.26,0.82)	**0.39 (0.16,0.99)**	0.94 (0.81,1.09)	0.86 (0.73,1.03)	ASA									
0.56 (0.32,0.98)	0.48 (0.19,1.19)	1.14 (1.04,1.25)	1.05 (0.95,1.15)	**1.21 (1.02,1.45)**	EDX-30MG								
0.55 (0.31,0.98)	0.47 (0.19,1.18)	1.12 (0.99,1.27)	1.03 (0.89,1.21)	1.20 (0.99,1.45)	0.99 (0.84,1.15)	DBG-150MG							
0.58 (0.32,1.04)	0.50 (0.20,1.25)	1.18 (0.99,1.41)	1.09 (0.89,1.33)	**1.26 (1.00,1.59)**	1.04 (0.85,1.27)	1.05 (0.85,1.31)	RVX						
0.51 (0.28,0.93)	0.44 (0.17,1.11)	1.04 (0.84,1.28)	0.96 (0.76,1.20)	1.11 (0.86,1.43)	0.91 (0.72,1.15)	0.93 (0.72,1.18)	0.88 (0.67,1.16)	UC+ST					
0.44 (0.23,0.84)	**0.38 (0.14,0.99)**	0.90 (0.64,1.25)	0.83 (0.58,1.17)	0.96 (0.67,1.37)	0.79 (0.56,1.11)	0.80 (0.56,1.14)	0.76 (0.52,1.11)	0.86 (0.58,1.28)	CONTROL				
0.55 (0.31,0.97)	0.47 (0.19,1.18)	**1.13 (1.02,1.24)**	1.04 (0.91,1.19)	1.20 (1.03,1.41)	0.99 (0.86,1.13)	1.00 (0.86,1.18)	0.95 (0.78,1.17)	1.08 (0.86,1.37)	1.26 (0.89,1.78)	APX			
0.54 (0.30,0.95)	0.46 (0.18,1.15)	1.09 (0.96,1.23)	1.00 (0.86,1.17)	1.16 (0.96,1.41)	0.96 (0.82,1.12)	0.97 (0.86,1.10)	0.92 (0.74,1.15)	1.05 (0.82,1.34)	1.22 (0.85,1.73)	0.97 (0.83,1.13)	DBG-110MG		
0.49 (0.27,0.90)	0.42 (0.17,1.07)	1.00 (0.81,1.25)	0.93 (0.73,1.17)	1.07 (0.83,1.39)	0.88 (0.70,1.12)	0.90 (0.70,1.15)	0.85 (0.64,1.12)	0.97 (0.72,1.31)	1.12 (0.75,1.67)	0.89 (0.70,1.13)	0.92 (0.72,1.18)	ASA+CLP	
0.20 (0.03,1.10)	0.17 (0.03,1.08)	0.40 (0.08,2.03)	0.37 (0.07,1.88)	0.43 (0.08,2.18)	0.35 (0.07,1.79)	0.35 (0.07,1.82)	0.34 (0.07,1.73)	0.38 (0.07,1.98)	0.44 (0.08,2.34)	0.35 (0.07,1.81)	0.37 (0.07,1.87)	0.40 (0.08,2.05)	UC+GNT

* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Results of network meta-analysis of interventions options on ischemic stroke

Interventions	Risk ratio	95% Confidence interval	p-value	SUCRA rank
EDX-30MG	**1.42**	**(1.20, 1.67)**	**0.000**	1
UC	reference			2
ASA	**2.65**	**(1.89, 3.71)**	**0.000**	3
RVX	0.87	(0.72, 1.05)	0.155	4
APX	0.93	(0.76, 1.14)	0.478	5
DBG-150MG	**0.77**	**(0.61, 0.99)**	**0.042**	6
UC+WTH	1.36	(0.69, 2.63)	0.378	7
EDX-60MG	1.00	(0.84, 1.20)	0.961	8
CONTROL	**2.86**	**(1.83, 4.49)**	**0.000**	9
ASA+CLP	**2.12**	**(1.47, 3.05)**	**0.000**	10
DBG-110MG	1.12	(0.90, 1.40)	0.316	11
Number of RCTs	**19**			

EDX-30MG										
1.42 (1.20,1.67)	UC									
0.53 (0.37,0.78)	0.38 (0.27,0.53)	ASA								
1.63 (1.27,2.09)	1.15 (0.95,1.39)	3.04 (2.07,4.47)	RVX							
1.52 (1.18,1.98)	1.08 (0.88,1.31)	2.85 (2.07,3.92)	0.94 (0.71,1.24)	APX						
1.83 (1.36,2.46)	1.29 (1.01,1.65)	3.42 (2.26,5.19)	1.13 (0.83,1.53)	1.20 (0.87,1.65)	DBG-150MG					
1.04 (0.52,2.11)	0.74 (0.37,1.46)	1.95 (0.91,4.18)	0.64 (0.32,1.30)	0.68 (0.34,1.39)	0.57 (0.28,1.18)	UC+WTH				
1.41 (1.20,1.66)	1.00 (0.83,1.19)	2.64 (1.80,3.86)	0.87 (0.67,1.13)	0.93 (0.71,1.21)	0.77 (0.57,1.04)	1.35 (0.67,2.74)	EDX-60MG			
0.49 (0.31,0.80)	0.35 (0.22,0.55)	0.93 (0.53,1.62)	0.30 (0.19,0.50)	0.32 (0.20,0.53)	0.27 (0.16,0.45)	0.47 (0.21,1.08)	0.35 (0.22,0.57)	CONTROL		
0.67 (0.45,1.00)	0.47 (0.33,0.68)	1.25 (0.76,2.05)	0.41 (0.27,0.62)	0.44 (0.29,0.66)	0.37 (0.24,0.57)	0.64 (0.30,1.39)	0.47 (0.32,0.71)	1.35 (0.76,2.41)	ASA+CLP	
1.26 (0.96,1.67)	0.89 (0.71,1.12)	2.37 (1.58,3.54)	0.78 (0.58,1.04)	0.83 (0.61,1.12)	0.69 (0.54,0.88)	1.21 (0.59,2.49)	0.90 (0.67,1.19)	2.55 (1.55,4.22)	1.89 (1.23,2.90)	DBG-110MG

* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Results of network meta-analysis of interventions options on clinically relevant non-major bleeding

Interventions	Risk ratio	95% Confidence interval	p-value	SUCRA rank
CONTROL	0.33	(0.03, 3.16)	0.338	1
DBG-110MG	0.51	(0.11, 2.34)	0.385	2
DBG-150MG	1.13	(0.51, 2.51)	0.767	3
ASA	**0.60**	**(0.44, 0.83)**	**0.002**	4
EDX-60MG	**0.87**	**(0.82, 0.94)**	**0.000**	5
RVX	1.04	(0.97, 1.11)	0.295	6
APX	**0.68**	**(0.59, 0.79)**	**0.000**	7
EDX-30MG	**0.70**	**(0.65, 0.75)**	**0.000**	8
UC	reference			9
Number of RCTs	**14**			

CONTROL								
0.65 (0.04,9.99)	**DBG-110MG**							
0.29 (0.03,3.22)	0.45 (0.10,2.08)	**DBG-150MG**						
0.55 (0.06,5.38)	0.84 (0.18,4.03)	1.88 (0.79,4.45)	**ASA**					
0.38 (0.04,3.62)	0.58 (0.13,2.69)	1.29 (0.58,2.88)	0.69 (0.49,0.96)	**EDX-60MG**				
0.32 (0.03,3.05)	0.49 (0.11,2.26)	1.09 (0.49,2.42)	0.58 (0.42,0.81)	0.84 (0.76,0.93)	**RVX**			
0.49 (0.05,4.65)	0.74 (0.16,3.46)	1.65 (0.73,3.72)	0.88 (0.66,1.17)	1.28 (1.09,1.51)	1.52 (1.29,1.79)	**APX**		
0.48 (0.05,4.56)	0.73 (0.16,3.38)	1.62 (0.73,3.62)	0.86 (0.62,1.21)	1.26 (1.16,1.36)	1.49 (1.35,1.66)	0.98 (0.83,1.16)	**EDX-30MG**	
0.33 (0.03,3.16)	0.51 (0.11,2.34)	1.13 (0.51,2.51)	0.60 (0.44,0.83)	0.87 (0.82,0.94)	1.04 (0.97,1.11)	0.68 (0.59,0.79)	0.70 (0.65,0.75)	**UC**

* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Results of network meta-analysis of interventions options on intracranial bleeding

Interventions	Risk ratio	95% Confidence interval	p-value	SUCRA rank
UC+WTH	**0.22**	**0.22 (0.06, 0.76)**	**0.016**	1
EDX-60MG	**0.48**	**0.48 (0.30, 0.78)**	**0.003**	2
DBG-150MG	**0.41**	**0.41 (0.24, 0.70)**	**0.001**	3
EDX-30MG	**0.31**	**0.31 (0.19, 0.52)**	**0.000**	4
ASA	0.65	0.65 (0.34, 1.24)	0.199	5
RVX	0.76	0.76 (0.53, 1.08)	0.131	6
CONTROL	0.57	0.57 (0.19, 1.71)	0.316	7
DBG-110MG	**0.31**	**0.31 (0.18, 0.55)**	**0.000**	8
ASA+CLP	0.52	0.52 (0.23, 1.17)	0.114	9
UC+SM	1.00	(0.14, 7.29)	0.998	10
UC	reference			11
APX	**0.44**	**0.44 (0.28, 0.70)**	**0.000**	12
UC+ST	1.37	1.37 (0.51, 3.64)	0.531	13
Number of RCTs	**26**			

UC+WTH												
0.46 (0.12,1.71)	EDX-60MG											
0.54 (0.14,2.06)	1.17 (0.57,2.40)	DBG-150MG										
0.70 (0.19,2.65)	1.53 (0.90,2.61)	1.30 (0.63,2.71)	EDX-30MG									
0.34 (0.08,1.37)	0.74 (0.33,1.65)	0.63 (0.27,1.47)	0.48 (0.21,1.10)	ASA								
0.29 (0.08,1.05)	0.63 (0.35,1.16)	0.54 (0.28,1.02)	0.41 (0.22,0.77)	0.86 (0.40,1.81)	RVX							
0.39 (0.07,2.01)	0.84 (0.26,2.78)	0.72 (0.21,2.43)	0.55 (0.17,1.84)	1.14 (0.36,3.57)	1.33 (0.42,4.23)	CONTROL						
0.71 (0.18,2.76)	1.55 (0.74,3.25)	1.32 (0.71,2.45)	1.01 (0.48,2.16)	2.09 (0.88,4.98)	**2.45 (1.26,4.77)**	1.84 (0.53,6.31)	DBG-110MG					
0.43 (0.10,1.87)	0.93 (0.36,2.39)	0.79 (0.30,2.09)	0.61 (0.23,1.58)	1.26 (0.44,3.57)	1.47 (0.60,3.57)	1.10 (0.28,4.32)	0.60 (0.22,1.62)	ASA+CLP				
0.22 (0.02,2.30)	0.48 (0.06,3.73)	0.41 (0.05,3.22)	0.32 (0.04,2.45)	0.65 (0.08,5.29)	0.76 (0.10,5.75)	0.57 (0.06,5.55)	0.31 (0.04,2.46)	0.52 (0.06,4.46)	UC+SM			
0.22 (0.06,0.76)	**0.48 (0.30,0.78)**	**0.41 (0.24,0.70)**	**0.31 (0.19,0.52)**	0.65 (0.34,1.25)	0.76 (0.53,1.08)	0.57 (0.19,1.71)	**0.31 (0.18,0.55)**	0.52 (0.23,1.17)	1.00 (0.14,7.29)	UC		
0.50 (0.13,1.85)	1.09 (0.57,2.08)	0.93 (0.46,1.86)	0.71 (0.36,1.39)	1.47 (0.76,2.83)	1.72 (0.96,3.07)	1.29 (0.41,4.08)	0.70 (0.34,1.45)	1.17 (0.46,2.97)	2.25 (0.29,17.30)	**2.26 (1.43,3.55)**	APX	
0.16 (0.03,0.78)	0.35 (0.12,1.05)	**0.30 (0.10,0.91)**	**0.23 (0.08,0.69)**	0.48 (0.15,1.55)	0.56 (0.20,1.58)	0.42 (0.10,1.82)	**0.23 (0.07,0.70)**	0.38 (0.11,1.35)	0.73 (0.08,6.69)	0.73 (0.27,1.95)	0.32 (0.11,0.95)	UC+ST

* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Results of network meta-analysis of interventions options on gastrointestinal bleeding

Interventions	Risk ratio	95% Confidence interval	p-value	SUCRA rank
DBG-110MG	1.11	(0.21, 5.87)	0.903	1
CONTROL	0.23	(0.02, 2.20)	0.204	2
ASA	0.48	(0.07, 3.28)	0.457	3
EDX-60MG	1.22	(0.23, 6.41)	0.813	4
UC+GNT	0.74	(0.12, 4.51)	0.741	5
APX	0.62	(0.13, 2.86)	0.541	6
DBG-150MG	1.50	(0.29, 7.93)	0.631	7
RVX	1.37	(0.42, 4.43)	0.601	8
UC	reference			9
EDX-30MG	0.68	(0.13, 3.58)	0.648	10
Number of RCTs	**10**			

DBG-110MG									
4.75 (0.29,77.51)	**CONTROL**								
2.30 (0.18,29.06)	0.48 (0.03,9.22)	**ASA**							
0.91 (0.09,9.52)	0.19 (0.01,3.11)	0.40 (0.03,4.99)	**EDX-60MG**						
1.51 (0.13,17.65)	0.32 (0.02,5.67)	0.66 (0.05,9.17)	1.66 (0.14,19.33)	**UC+GNT**					
1.79 (0.19,17.10)	0.38 (0.02,5.66)	0.78 (0.16,3.83)	1.97 (0.21,18.72)	1.19 (0.11,12.68)	**APX**				
0.74 (0.14,3.89)	0.16 (0.01,2.53)	0.32 (0.03,4.06)	0.81 (0.08,8.50)	0.49 (0.04,5.73)	0.41 (0.04,3.95)	**DBG-150MG**			
0.81 (0.11,6.23)	0.17 (0.01,2.15)	0.35 (0.03,3.64)	0.89 (0.12,6.81)	0.54 (0.06,4.67)	0.45 (0.06,3.31)	1.10 (0.14,8.42)	**RVX**		
1.11 (0.21,5.87)	0.23 (0.02,2.20)	0.48 (0.07,3.28)	1.22 (0.23,6.41)	0.74 (0.12,4.51)	0.62 (0.13,2.86)	1.50 (0.29,7.93)	1.37 (0.42,4.43)	**UC**	
1.63 (0.16,17.17)	0.34 (0.02,5.60)	0.71 (0.06,8.99)	1.80 (0.34,9.46)	1.08 (0.09,12.68)	0.92 (0.10,8.74)	2.21 (0.21,23.23)	2.01 (0.26,15.42)	1.47 (0.28,7.76)	**EDX-30MG**

* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Results of network meta-analysis of interventions options on myocardial infarction

Interventions	Risk ratio	95% Confidence interval	p-value	SUCRA rank
UC	reference			1
ASA	1.04	(0.68, 1.59)	0.848	2
RVX	0.82	(0.63, 1.06)	0.128	3
APX	0.88	(0.67, 1.15)	0.340	4
ASA+CLP	1.55	(0.92, 2.61)	0.100	5
DBG-110MG	1.36	(0.99, 1.88)	0.058	6
EDX-60MG	0.95	(0.75, 1.20)	0.686	7
DBG-150MG	1.40	(1.01, 1.92)	0.041	8
EDX-30MG	1.21	(0.97, 1.50)	0.096	9
UC+ST	1.49	(0.83, 2.70)	0.185	10
CONTROL	1.00	(0.14, 7.00)	0.996	11
Number of RCTs	**16**			

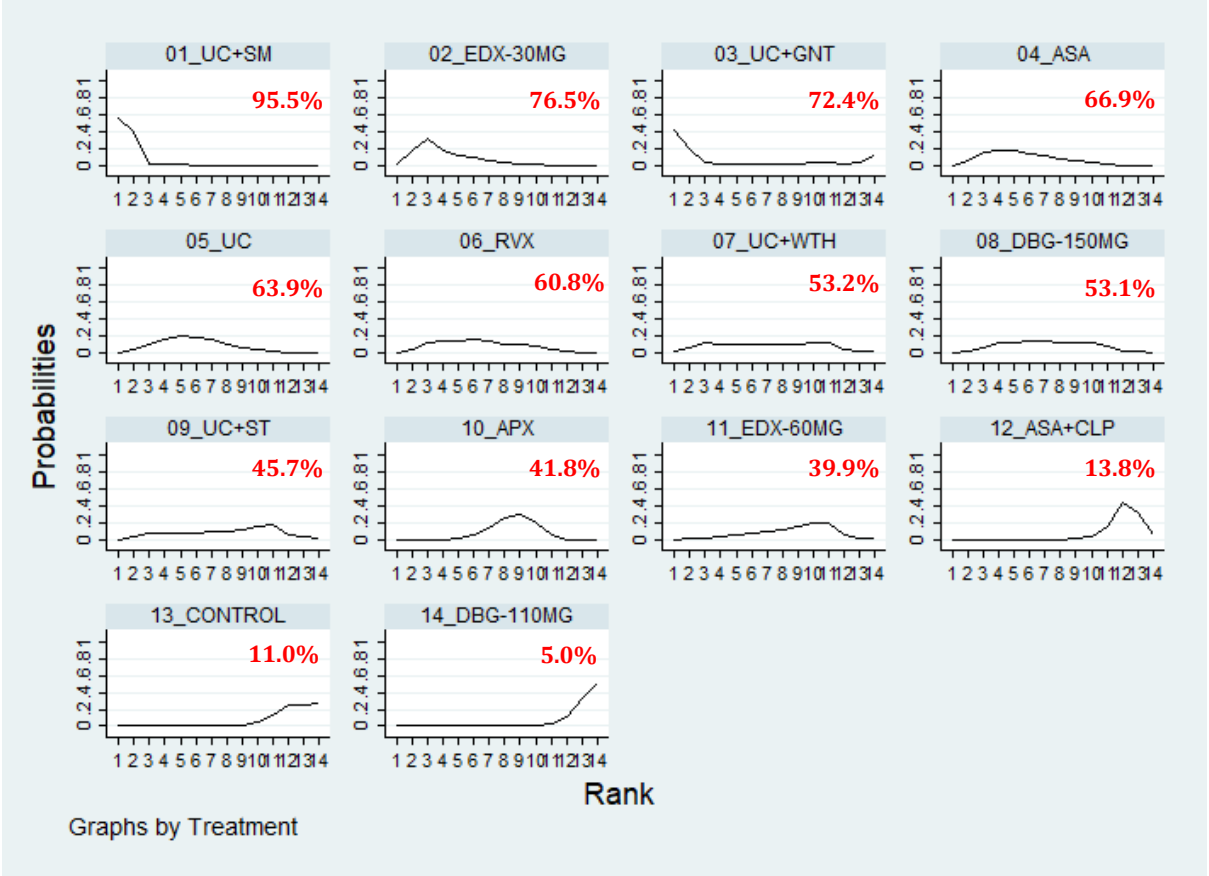
UC										
0.96 (0.63,1.47)	ASA									
1.22 (0.94,1.58)	1.27 (0.77,2.09)	RVX								
1.14 (0.87,1.48)	1.19 (0.78,1.80)	0.93 (0.64,1.35)	APX							
0.65 (0.38,1.09)	0.67 (0.34,1.32)	0.53 (0.30,0.95)	0.57 (0.32,1.02)	ASA+CLP						
0.73 (0.53,1.01)	0.76 (0.45,1.30)	0.60 (0.40,0.91)	0.64 (0.42,0.98)	1.13 (0.62,2.09)	DBG-110MG					
1.05 (0.83,1.33)	1.09 (0.67,1.78)	0.86 (0.61,1.22)	0.92 (0.65,1.31)	1.63 (0.92,2.88)	1.43 (0.96,2.13)	EDX-60MG				
0.72 (0.52,0.99)	0.75 (0.44,1.27)	0.59 (0.39,0.88)	0.63 (0.42,0.95)	1.11 (0.60,2.04)	0.98 (0.73,1.31)	0.68 (0.46,1.01)	DBG-150MG			
0.83 (0.67,1.03)	0.86 (0.54,1.39)	0.68 (0.48,0.95)	0.73 (0.52,1.03)	1.28 (0.73,2.26)	1.13 (0.77,1.67)	0.79 (0.63,0.99)	1.16 (0.79,1.71)	EDX-30MG		
0.67 (0.37,1.21)	0.70 (0.34,1.45)	0.55 (0.29,1.05)	0.59 (0.31,1.13)	1.04 (0.47,2.28)	0.91 (0.47,1.79)	0.64 (0.34,1.21)	0.94 (0.48,1.83)	0.81 (0.43,1.52)	UC+ST	
1.00 (0.14,7.07)	1.05 (0.14,7.71)	0.82 (0.12,5.89)	0.88 (0.12,6.32)	1.56 (0.21,11.72)	1.37 (0.19,9.90)	0.96 (0.13,6.83)	1.40 (0.19,10.13)	1.21 (0.17,8.62)	1.50 (0.20,11.51)	CONTROL

* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

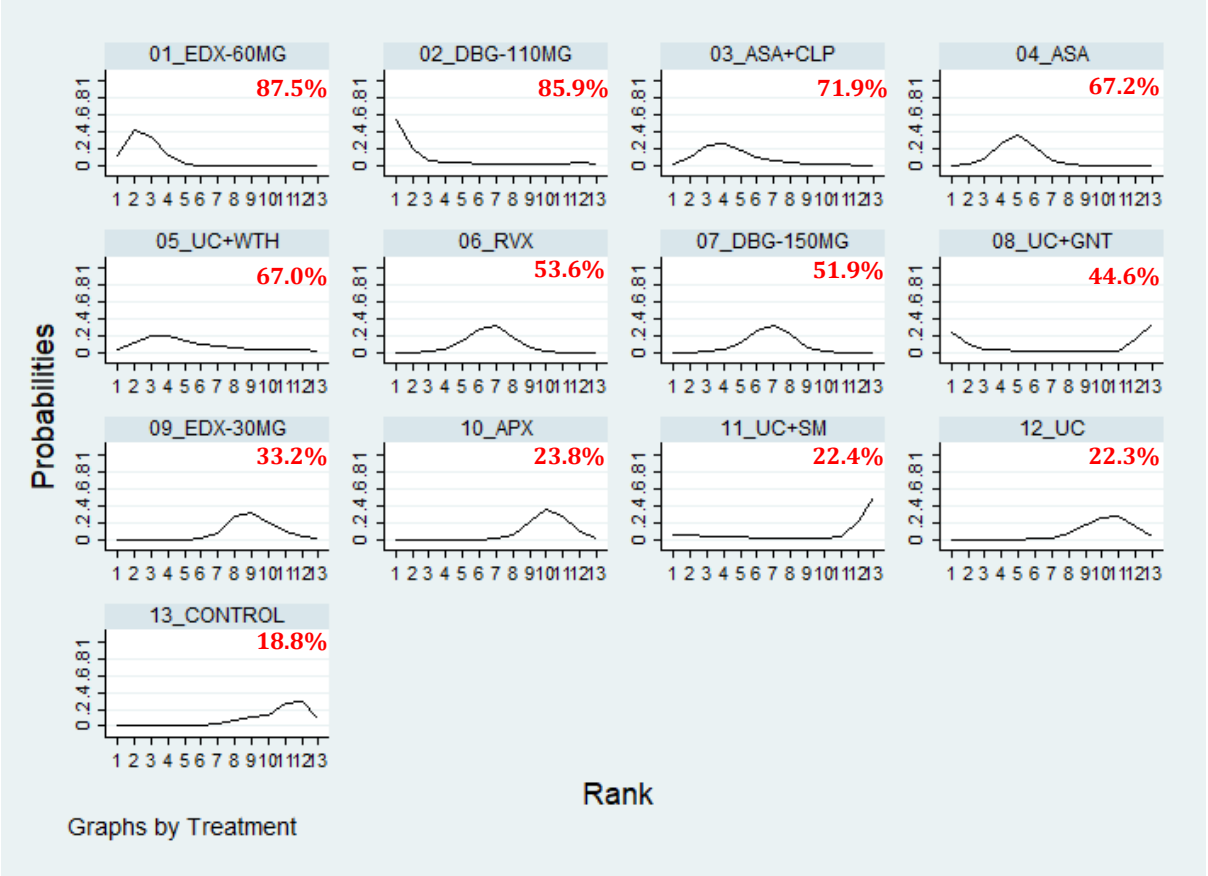
S-6-10. Treatment Ranking and Surface Under the Cumulative Ranking Curves (SUCRA)

SUCRA ranking curve for stroke or systemic embolism



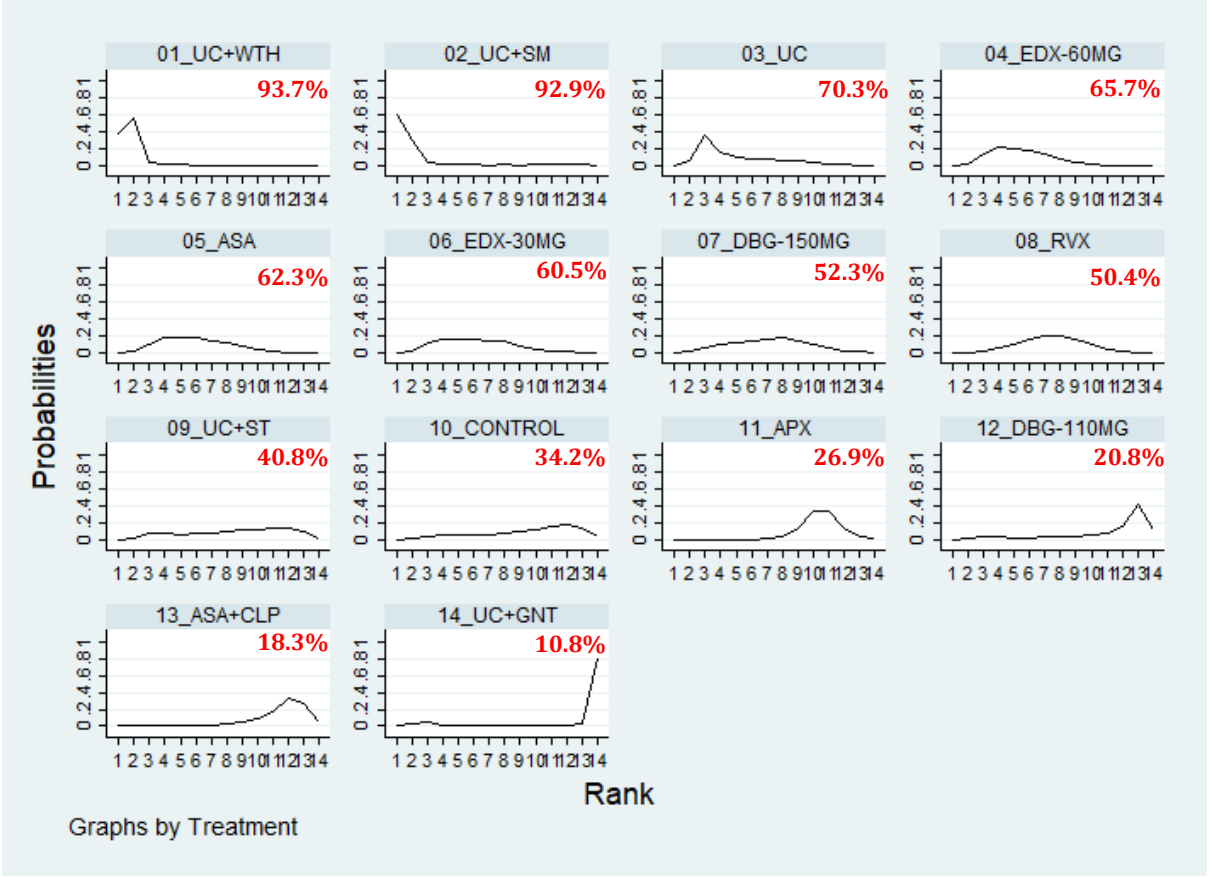
Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

SUCRA ranking curve for major bleeding



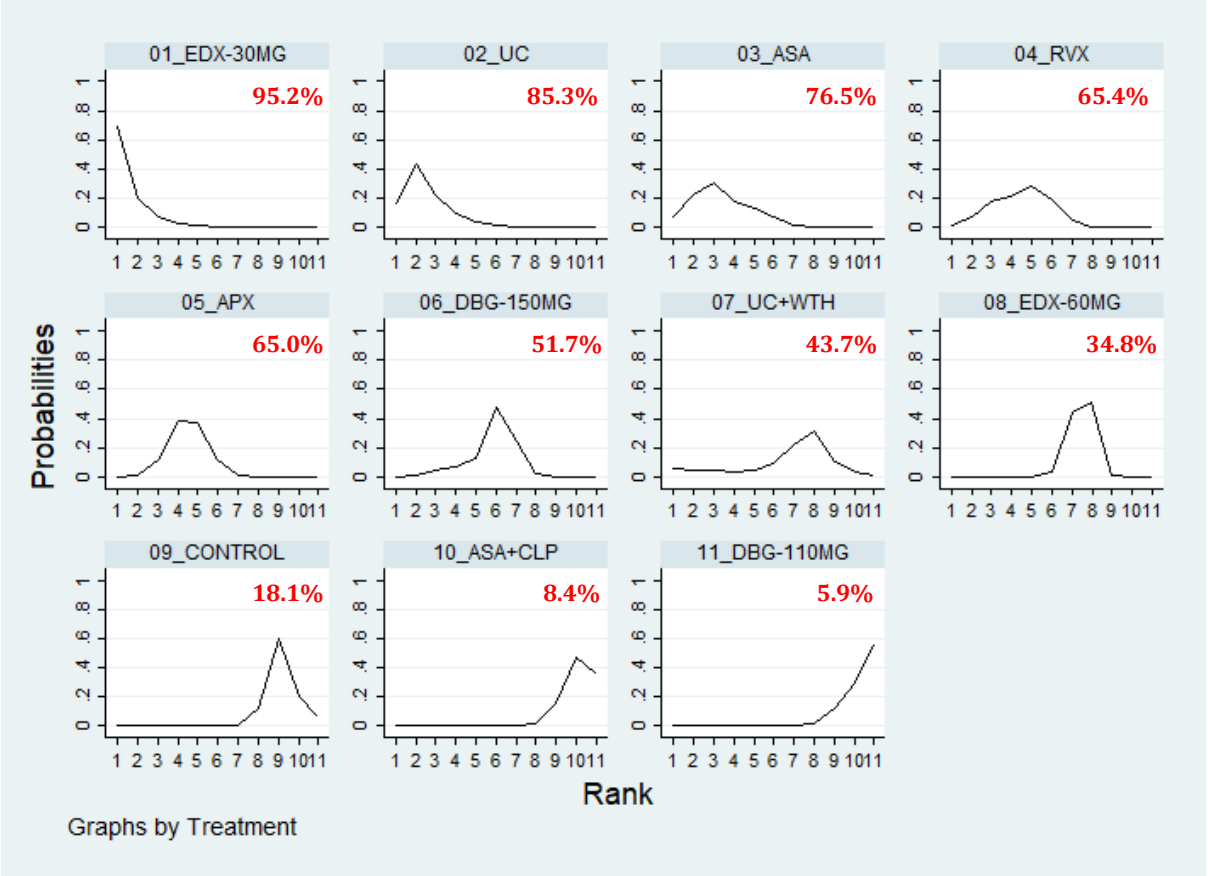
Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

SUCRA ranking curve for all-cause mortality



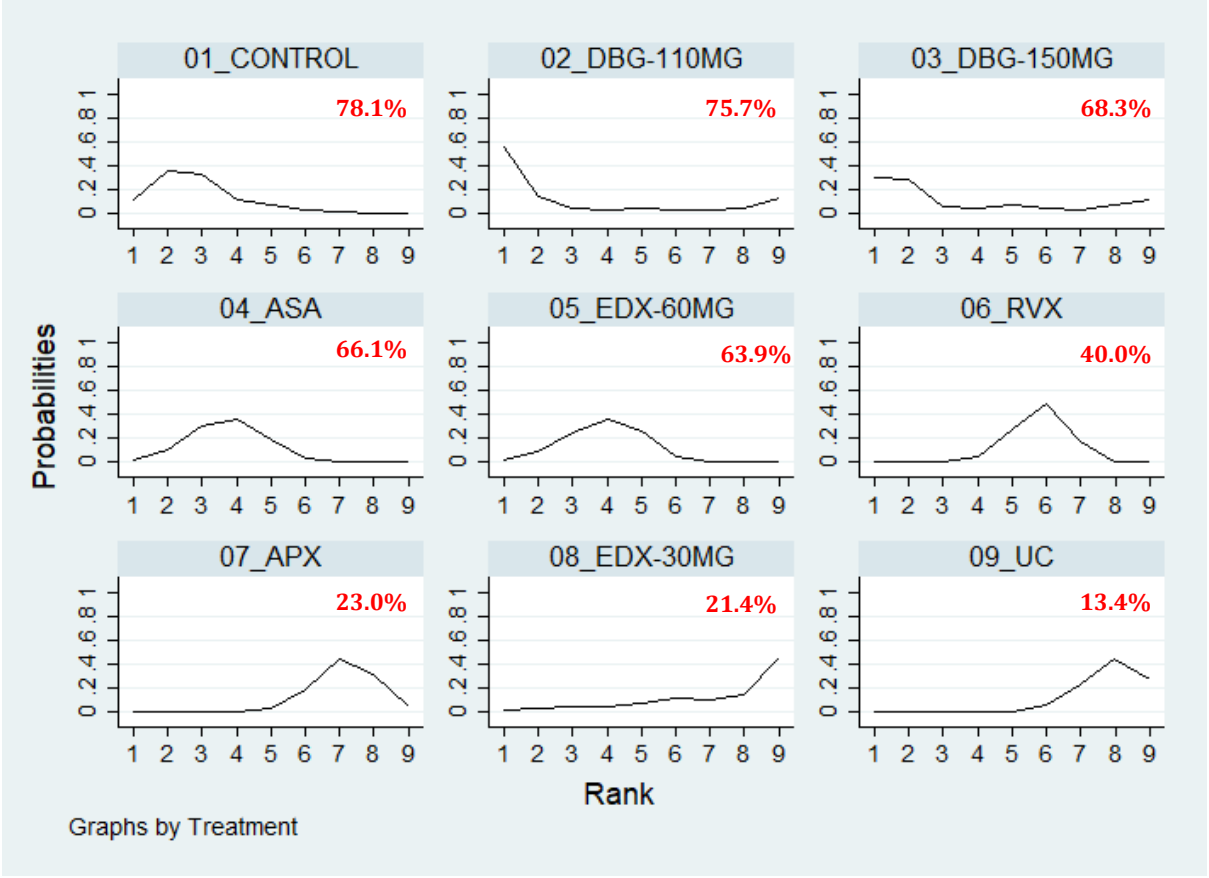
Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

SUCRA ranking curve for ischemic stroke



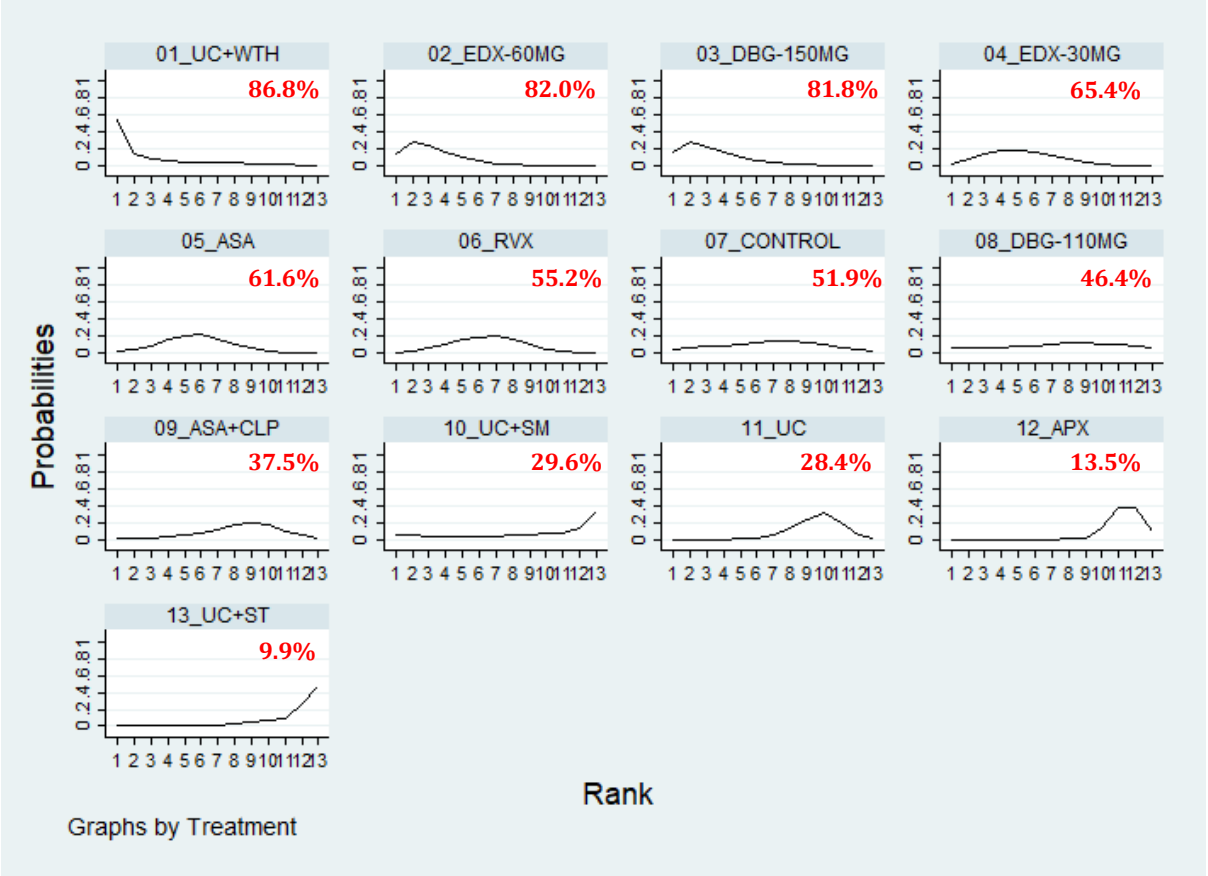
Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

SUCRA ranking curve for clinically relevant non-major bleeding



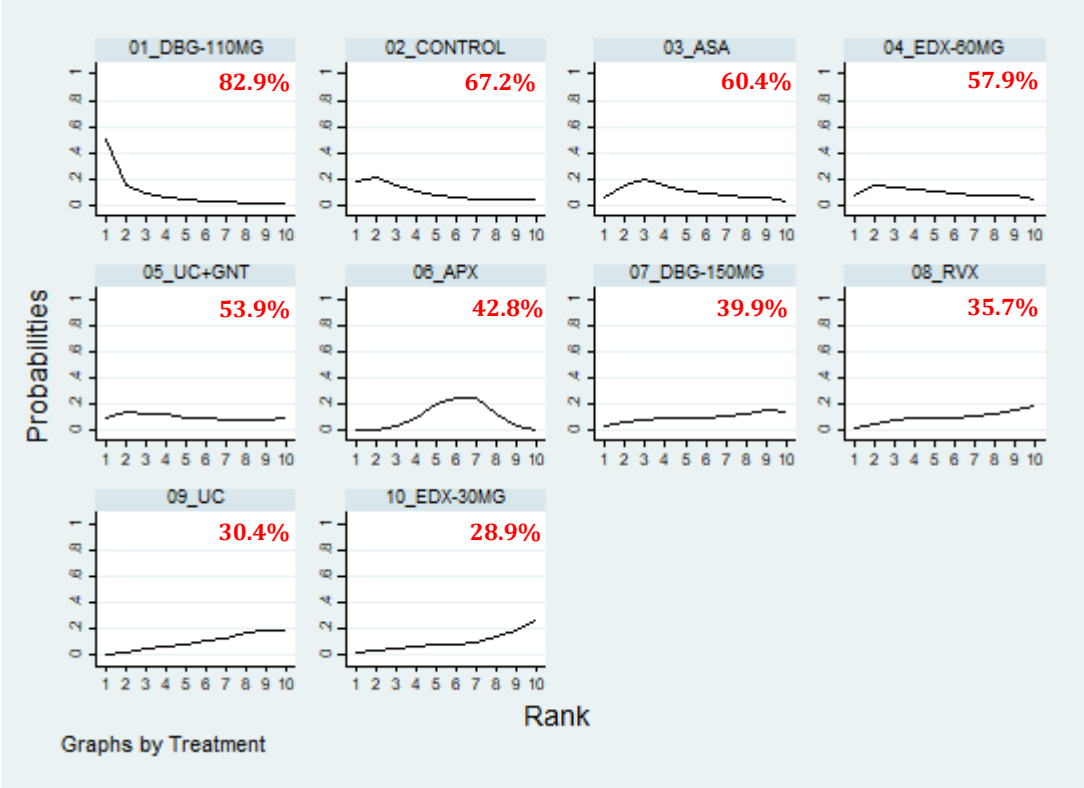
Abbreviations: APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device

SUCRA ranking curve for intracranial bleeding



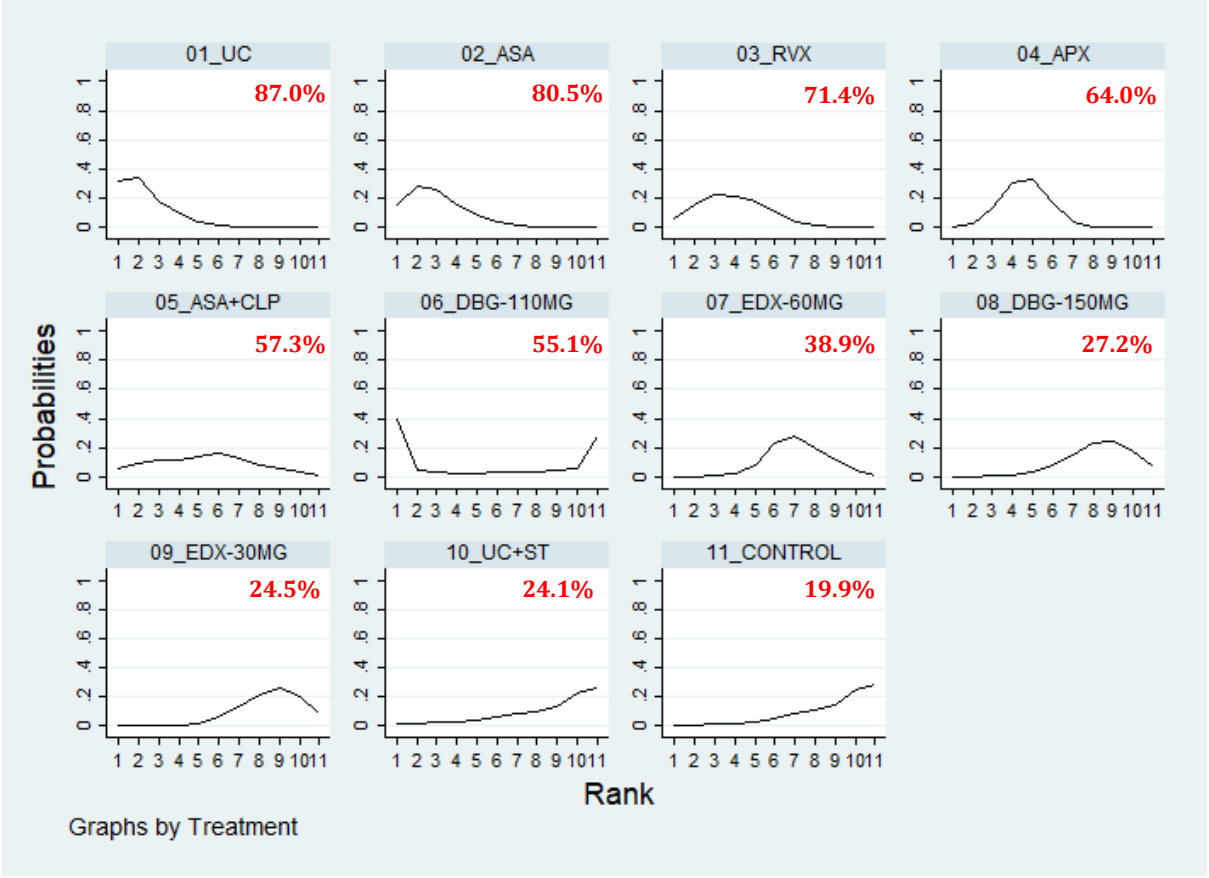
Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

SUCRA ranking curve for gastrointestinal bleeding



Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

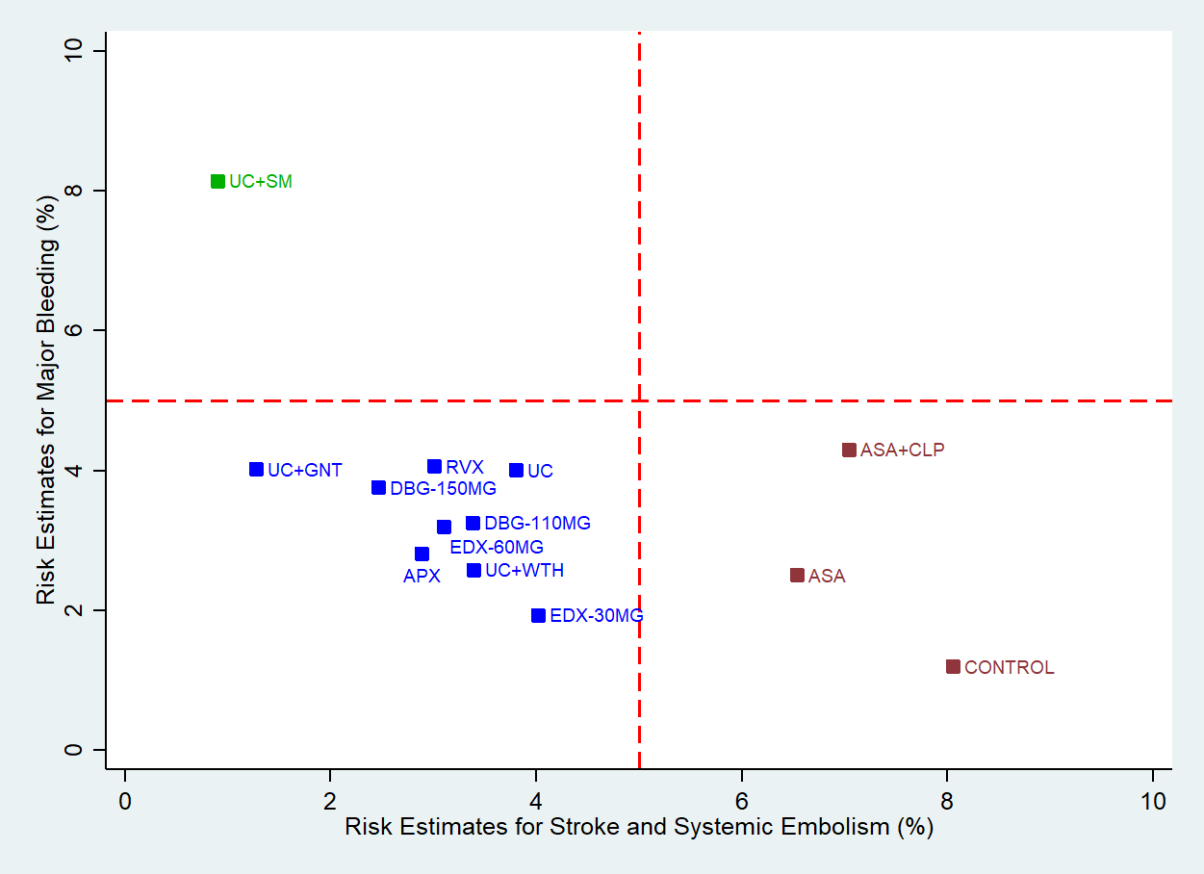
SUCRA ranking curve for myocardial infarction



Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

S-6-11. Cluster Rank Plot

Cluster rank incorporating risk estimates of stroke or systemic embolism (efficacy) vs. major bleeding (safety)



Abbreviations: APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device

S-6-12. Sensitivity Analyses

Sensitivity analyses for the risk of stroke or systemic embolism with intervention options of different study characteristics

Intervention	Standard analysis	SUCRA rank	Trials with AF participants only	SUCRA rank	Inclusion of studies from Year 2006 onwards*	SUCRA rank	Omitting small sample size studies (<25th percentile)	SUCRA rank	Omitting studies with high overall risk of bias	SUCRA rank
UC+SM	**0.24 (0.08, 0.68)**	1	0.33 (0.01, 8.37)	2	1.02 (0.02, 51.78)	8	**0.28 (0.11, 0.69)**	1	**0.23 (0.09, 0.62)**	1
EDX-30MG	1.06 (0.65, 1.72)	2	1.05 (0.64, 1.73)	1	1.06 (0.64, 1.75)	1	1.01 (0.55, 1.87)	3	1.14 (0.99, 1.31)	2
UC+GNT	0.33 (0.13, 8.45)	3	-	-	0.33 (0.01, 8.45)	2	0.33 (0.01, 8.67)	2	0.33 (0.01, 8.18)	3
ASA	**1.72 (1.29, 2.29)**	4	**1.72 (1.29, 2.30)**	3	**1.60 (1.13, 2.26)**	3	**1.65 (1.17, 2.33)**	4	**1.85 (1.48, 2.32)**	4
UC	Reference	5	Reference	4	Reference	4	Reference	5	Reference	5
RVX	0.79 (0.57, 1.10)	6	0.79 (0.57, 1.10)	5	0.79 (0.56, 1.12)	5	0.73 (0.45, 1.21)	6	**0.86 (0.75, 0.98)**	7
UC+WTH	0.89 (0.45, 1.78)	7	0.90 (0.45, 1.80)	6	0.89 (0.45, 1.79)	7	0.93 (0.42, 2.03)	8	0.84 (0.50, 1.44)	6
DBG-150MG	0.65 (0.39, 1.07)	8	0.65 (0.39, 1.08)	7	0.65 (0.39, 1.07)	6	0.66 (0.35, 1.25)	7	**0.66 (0.54, 0.82)**	8
UC+ST	0.99 (0.51, 1.93)	9	0.98 (0.02, 49.37)	8	0.99 (0.51, 1.95)	9	0.99 (0.45, 2.19)	9	0.99 (0.61, 1.62)	9
APX	0.76 (0.51, 1.12)	10	0.76 (0.51, 1.13)	9	0.73 (0.49, 1.11)	10	0.73 (0.44, 1.20)	11	**0.80 (0.68, 0.94)**	10
EDX-60MG	0.82 (0.51, 1.32)	11	0.81 (0.50, 1.33)	10	0.82 (0.50, 1.33)	11	0.79 (0.43, 1.45)	10	0.86 (0.74, 1.01)	11
ASA+CLP	**1.85 (1.07, 3.21)**	12	**1.85 (1.06, 3.24)**	11	**1.85 (1.07, 3.21)**	13	1.85 (0.93, 3.68)	12	**1.85 (1.37, 2.51)**	13
CONTROL	**2.12 (1.49, 3.01)**	13	**2.12 (1.49, 3.03)**	12	1.46 (0.72, 2.96)	14	**2.12 (1.43, 3.16)**	13	**1.88 (1.32, 2.67)**	12
DBG-110MG	0.89 (0.54, 1.46)	14	0.89 (0.54, 1.48)	13	0.89 (0.54, 1.46)	12	0.91 (0.48, 1.73)	14	0.91 (0.75, 1.11)	14
Overall inconsistency chi2 (P value)	4.23 (p-0.5169)		4.14 (p=0.5291)		0.04 (p=0.9799)		4.16 (p=0.5265)		0.80 (p=0.8483)	
Number of studies	36		32		27		30		32	

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Sensitivity analyses for the risk of major bleeding with interventions options with different major bleeding definitions

Interventions	Main analysis (BARC 3-5 based definition)	SUCRA rank	ISTH (major)-based definition	SUCRA rank
EDX-60MG	**0.80 (0.71, 0.90)**	1	**0.81 (0.71, 0.94)**	1
DBG-110MG	**0.81 (0.71, 0.94)**	2	**0.80 (0.71, 0.90)**	2
ASA+CLP	1.07 (0.81, 1.42)	3	1.07 (0.81, 1.42)	3
ASA	**0.63 (0.41, 0.96)**	4	0.66 (0.43, 1.02)	4
UC+WTH	0.64 (0.35, 1.18)	5	0.64 (0.35, 1.18)	5
RVX	1.01 (0.89, 1.16)	6	1.01 (0.89, 1.16)	6
DBG-150MG	0.94 (0.82, 1.08)	7	0.94 (0.82, 1.08)	7
UC+GNT	1.00 (0.02, 50.40)	8	1.00 (0.02, 50.40)	8
EDX-30MG	**0.48 (0.42, 0.56)**	9	**0.48 (0.42, 0.56)**	9
APX	**0.70 (0.61, 0.81)**	10	**0.71 (0.62, 0.81)**	10
UC+SM	2.03 (0.19, 21.83)	11	2.03 (0.19, 21.83)	11
UC	Reference	12	Reference	12
CONTROL	0.30 (0.06, 1.47)	13	0.20 (0.02, 1.66)	13
Overall inconsistency chi2 (P value)	0.90 (p=0.6382)		1.61 (p=0.4480)	
Number of studies	23		21	

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Sensitivity analyses for the risk of major bleeding with intervention options of different study characteristics

Interventions	Standard analysis	SUCRA rank	Trials with AF participants only	SUCRA rank	Inclusion of studies from Year 2006 onwards*	SUCRA rank	Omitting small sample size studies (<25th percentile)	SUCRA rank	Omitting studies with high overall risk of bias	SUCRA rank
EDX-60MG	**0.80 (0.71, 0.90)**	1	**0.80 (0.71, 0.90)**	**1**	**0.80 (0.71, 0.90)**	1	**0.80 (0.71, 0.90)**	1	**0.80 (0.71, 0.90)**	1
DBG-110MG	**0.81 (0.71, 0.94)**	2	**0.81 (0.71, 0.94)**	**2**	**0.81 (0.71, 0.94)**	12	**0.81 (0.71, 0.94)**	2	**0.81 (0.71, 0.94)**	2
ASA+CLP	1.07 (0.81, 1.42)	3	1.07 (0.81, 1.42)	3	1.07 (0.81, 1.42)	2	1.07 (0.81, 1.42)	3	1.07 (0.81, 1.42)	3
ASA	**0.63 (0.41, 0.96)**	4	**0.63 (0.41, 0.96)**	**4**	**0.63 (0.41, 0.96)**	4	**0.59 (0.38, 0.92)**	4	**0.60 (0.39, 0.91)**	4
UC+WTH	0.64 (0.35, 1.18)	5	0.64 (0.35, 1.18)	5	0.64 (0.35, 1.18)	3	0.64 (0.35, 1.18)	5	0.64 (0.35, 1.18)	5
RVX	1.01 (0.89, 1.16)	6	1.01 (0.89, 1.16)	6	1.01 (0.89, 1.16)	5	1.02 (0.89, 1.16)	6	1.01 (0.89, 1.16)	6
DBG-150MG	0.94 (0.82, 1.08)	7	0.94 (0.82, 1.08)	7	0.94 (0.82, 1.08)	6	0.94 (0.82, 1.08)	7	0.94 (0.82, 1.08)	7
UC+GNT	1.00 (0.02, 50.40)	8	-	-	1.00 (0.02, 50.40)	7	1.00 (0.02, 50.40)	8	1.00 (0.02, 50.40)	8
EDX-30MG	**0.48 (0.42, 0.56)**	9	**0.48 (0.42, 0.56)**	**8**	**0.48 (0.42, 0.56)**	8	**0.48 (0.42, 0.56)**	9	**0.48 (0.42, 0.56)**	9
APX	**0.70 (0.61, 0.81)**	10	**0.70 (0.61, 0.81)**	**9**	**0.70 (0.61, 0.81)**	9	**0.70 (0.61, 0.80)**	10	**0.70 (0.61, 0.80)**	10
UC+SM	2.03 (0.19, 21.83)	11	-	-	2.03 (0.19, 21.83)	11	-	-	2.03 (0.19, 21.83)	11
UC	Reference	12	Reference	10	Reference	10	Reference	11	Reference	12
CONTROL	0.30 (0.06, 1.47)	13	0.30 (0.06, 1.47)	11	-	-	0.30 (0.06, 1.47)	12	0.30 (0.01, 1.47)	13
UC+ST	-	-	0.90 (p=0.6382)		0.90 (p=0.6382)		-	-	-	-
Overall inconsistency chi2 (P value)	0.90 (p=0.6382)		21		21		2.34 (p=0.3111)		1.36 (p=0.5066)	
Number of studies	23						18		22	

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

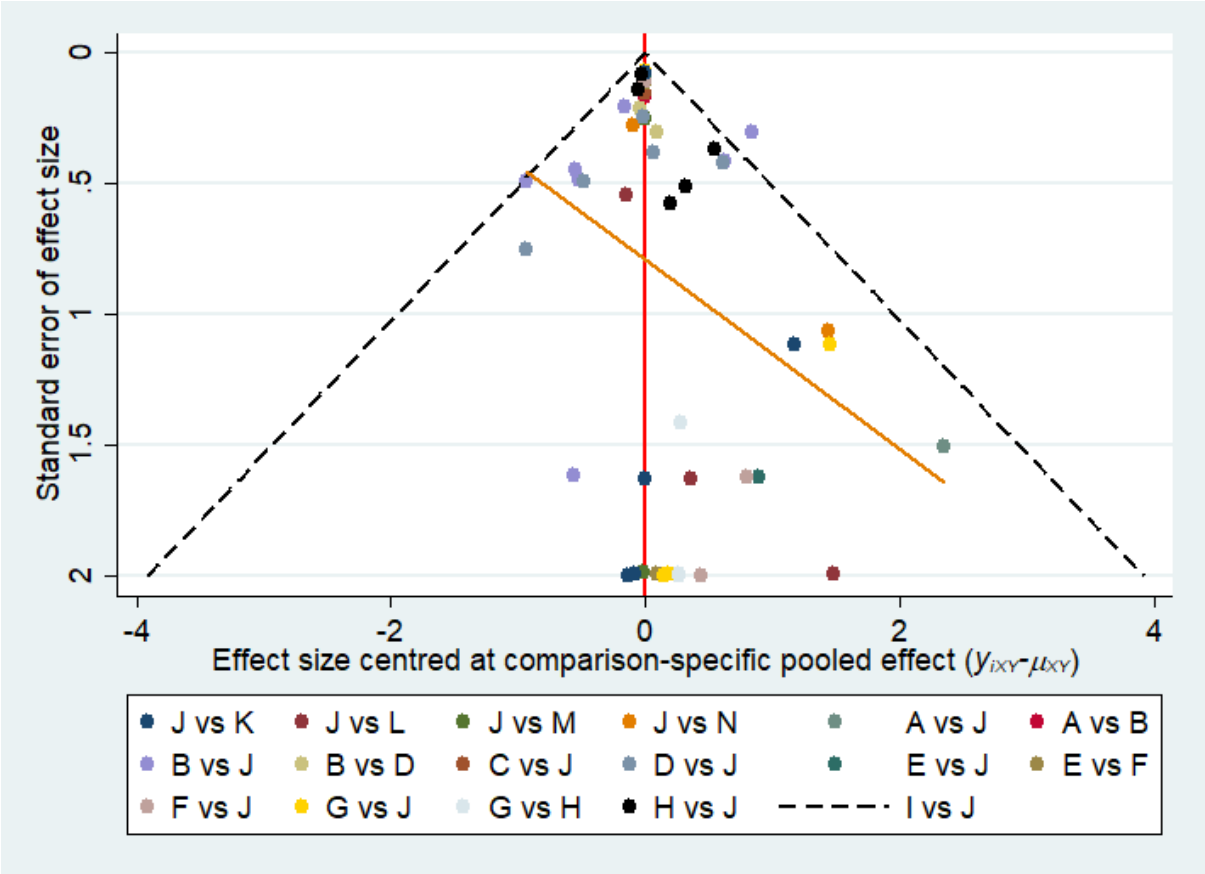
Sensitivity analyses for the risk of all-cause mortality with intervention options of different study characteristics

Interventions	Standard analysis	SUCRA rank	Trials with AF participants only	SUCRA rank	Inclusion of studies from Year 2006 onwards*	SUCRA rank	Omitting small sample size studies (<25th percentile)	SUCRA rank	Omitting studies with high overall risk of bias	SUCRA rank
UC+WTH	**0.49 (0.28, 0.86)**	**1**	**0.49 (0.28, 0.86)**	**1**	**0.49 (0.28, 0.86)**	1	**0.49 (0.81, 0.86)**	2	**0.49 (0.28, 0.86)**	1
UC+SM	0.42 (0.17, 1.04)	**2**	-	-	1.02 (0.02, 50.41)	9	0.40 (0.16, 1.02)	1	0.42 (0.17, 1.04)	2
UC	Reference	**3**	Reference	2	Reference	2	Reference	3	Reference	3
EDX-60MG	0.92 (0.84, 1.01)	**4**	0.92 (0.84, 1.01)	3	0.88 (0.84, 1.01)	3	0.92 (0.84, 1.01)	4	0.92 (0.84, 1.01)	4
ASA	1.07 (0.92, 1.24)	**5**	1.07 (0.92, 1.24)	4	1.08 (0.91, 1.28)	4	1.07 (0.92, 1.24)	5	1.06 (0.92, 1.23)	5
EDX-30MG	**0.88 (0.80, 0.96)**	**6**	**0.88 (0.80, 0.96)**	**5**	**0.89 (0.80, 0.96)**	5	**0.88 (0.80, 0.96)**	6	**0.88 (0.80, 0.96)**	6
DBG-150MG	0.89 (0.79, 1.01)	**7**	0.89 (0.79, 1.01)	6	0.92 (0.79, 1.01)	6	0.89 (0.79, 1.01)	7	0.89 (0.79, 1.01)	7
RVX	0.85 (0.71, 1.01)	**8**	0.85 (0.71, 1.01)	7	0.92 (0.71, 1.01)	7	0.85 (0.71, 1.01)	8	0.85 (0.71, 1.01)	8
UC+ST	0.96 (0.78, 1.19)	**9**	-	-	0.96 (0.78, 1.19)	10	0.96 (0.78, 1.19)	9	0.96 (0.78, 1.19)	9
CONTROL	1.11 (0.80, 1.56)	**10**	1.11 (0.80, 1.56)	8	0.93 (0.37, 2.30)	11	1.11 (0.80, 1.56)	10	1.07 (0.54, 2.12)	11
APX	**0.89 (0.80, 0.98)**	**11**	**0.89 (0.80, 0.98)**	**9**	**0.89 (0.80, 0.98)**	12	**0.89 (0.80, 0.98)**	11	**0.89 (0.80, 0.98)**	12
DBG-110MG	0.92 (0.81, 1.04)	**12**	0.92 (0.81, 1.04)	10	0.92 (0.81, 1.04)	8	0.92 (0.81, 1.04)	12	0.92 (0.81, 1.04)	10
ASA+CLP	1.00 (0.80, 1.23)	**13**	1.00 (0.80, 1.23)	11	1.00 (0.80, 1.23)	13	1.00 (0.80, 1.23)	13	1.00 (0.80, 1.23)	13
UC+GNT	2.51 (0.49, 12.81)	**14**	-	-	2.51 (0.49, 12.81)	14	2.51 (0.49, 12.81)	14	2.51 (0.49, 12.81)	14
Overall inconsistency chi2 (P value)	0.60 (p=0.7407)		0.60 (p=0.7407)		0.29 (p=0.5930)		0.63 (p=0.7303)		0.70 (p=0.7061)	
Number of studies	26		22		21		20		24	

Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

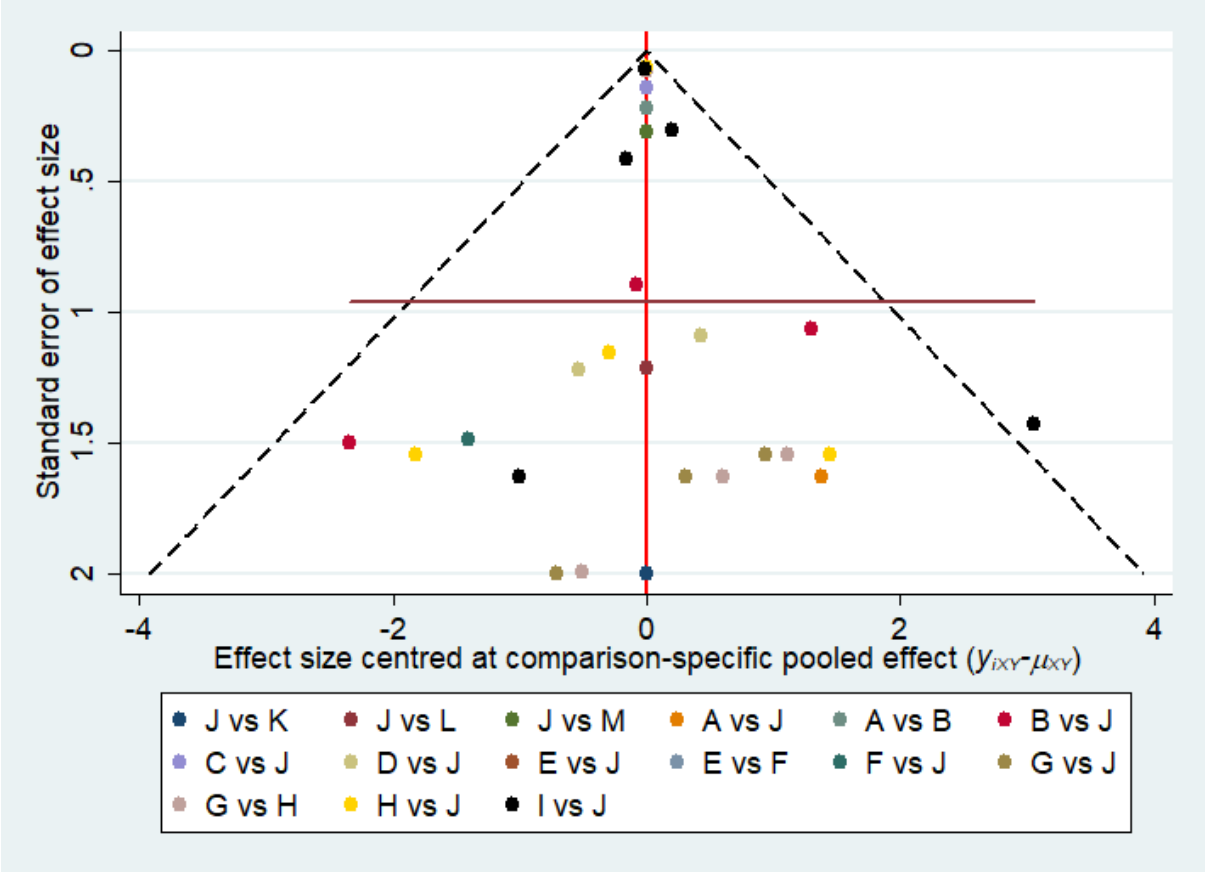
S-6-13. Adjusted Funnel Plots

Comparison-adjusted funnel plot for the network of stroke or systemic embolism in all comparisons



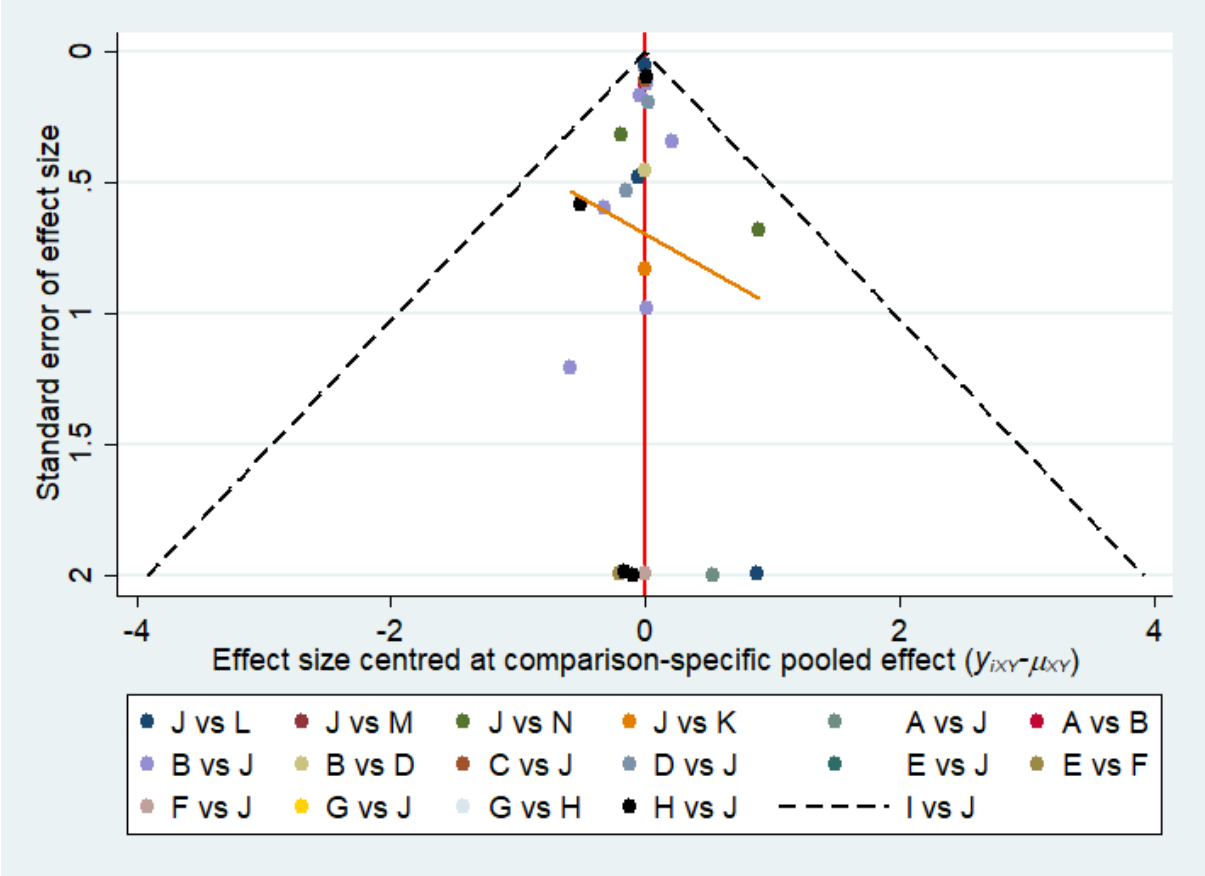
Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Comparison-adjusted funnel plot for the network of major bleeding in all comparisons



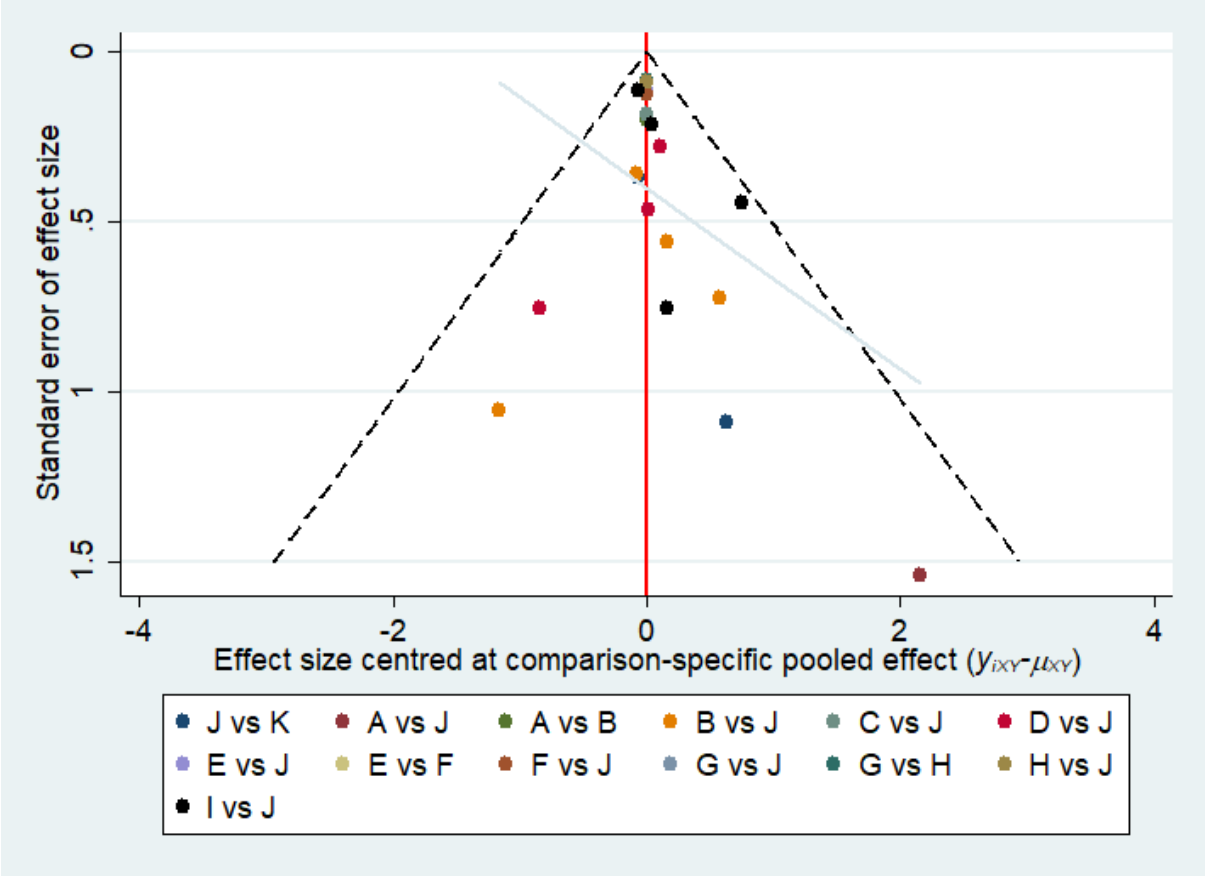
Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Comparison-adjusted funnel plot for the network of all-cause mortality in all comparisons



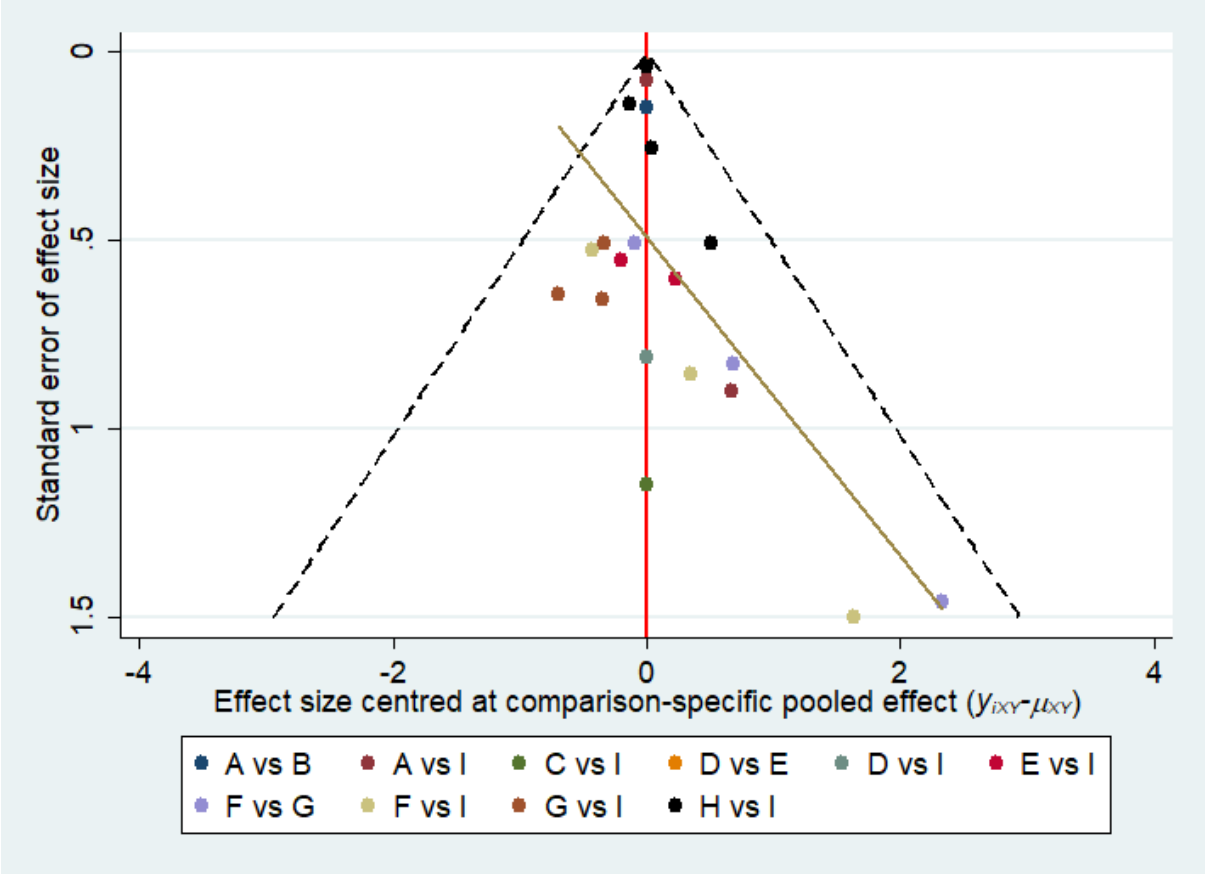
Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Comparison-adjusted funnel plot for the network of ischemic stroke in all comparisons



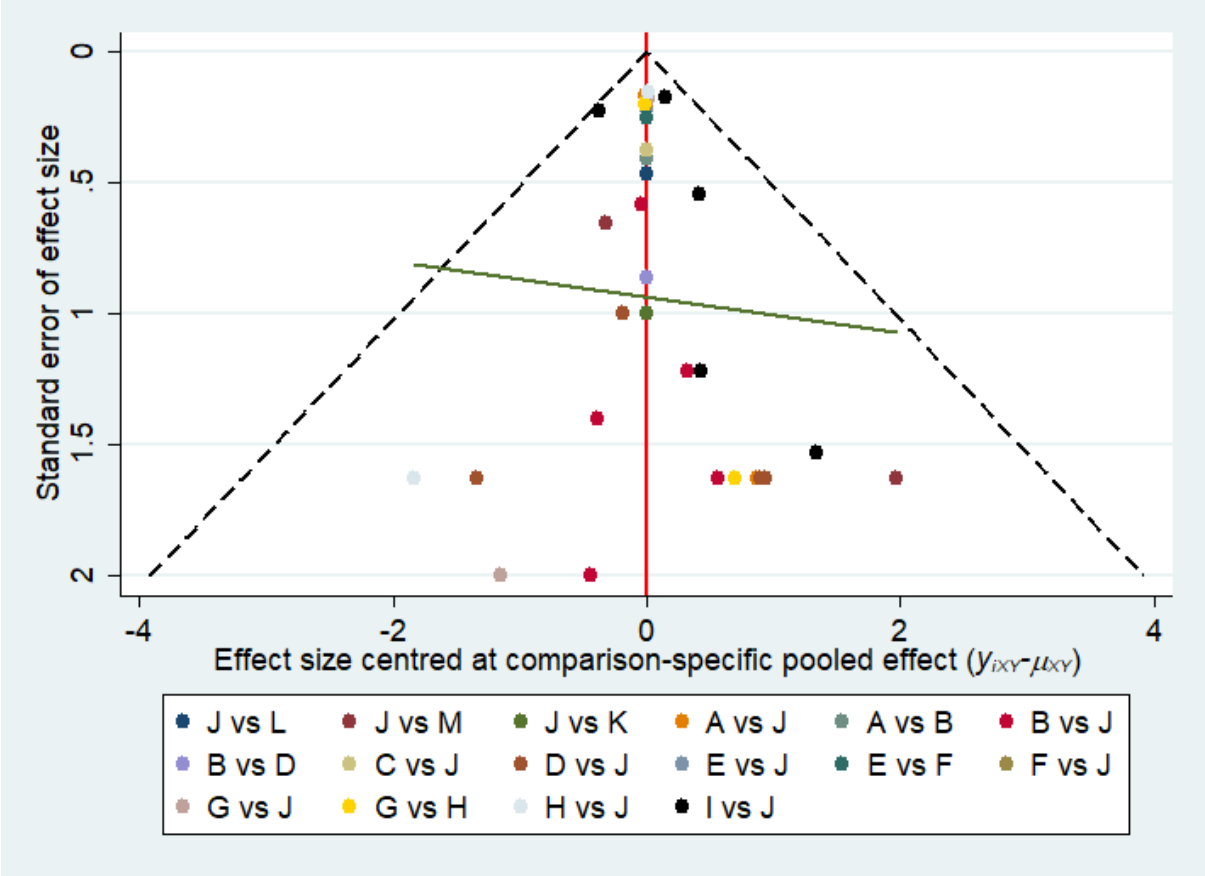
Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Comparison-adjusted funnel plot for the network of clinically relevant non-major bleeding in all comparisons



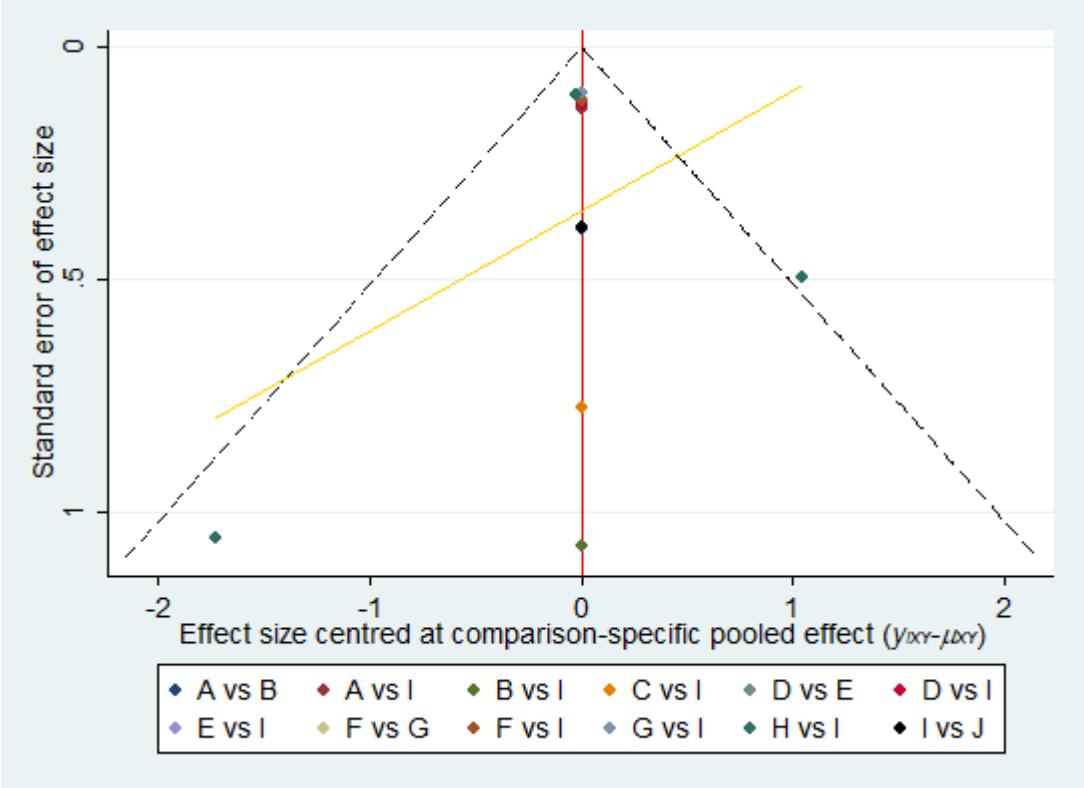
Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Comparison-adjusted funnel plot for the network of intracranial bleeding in all comparisons



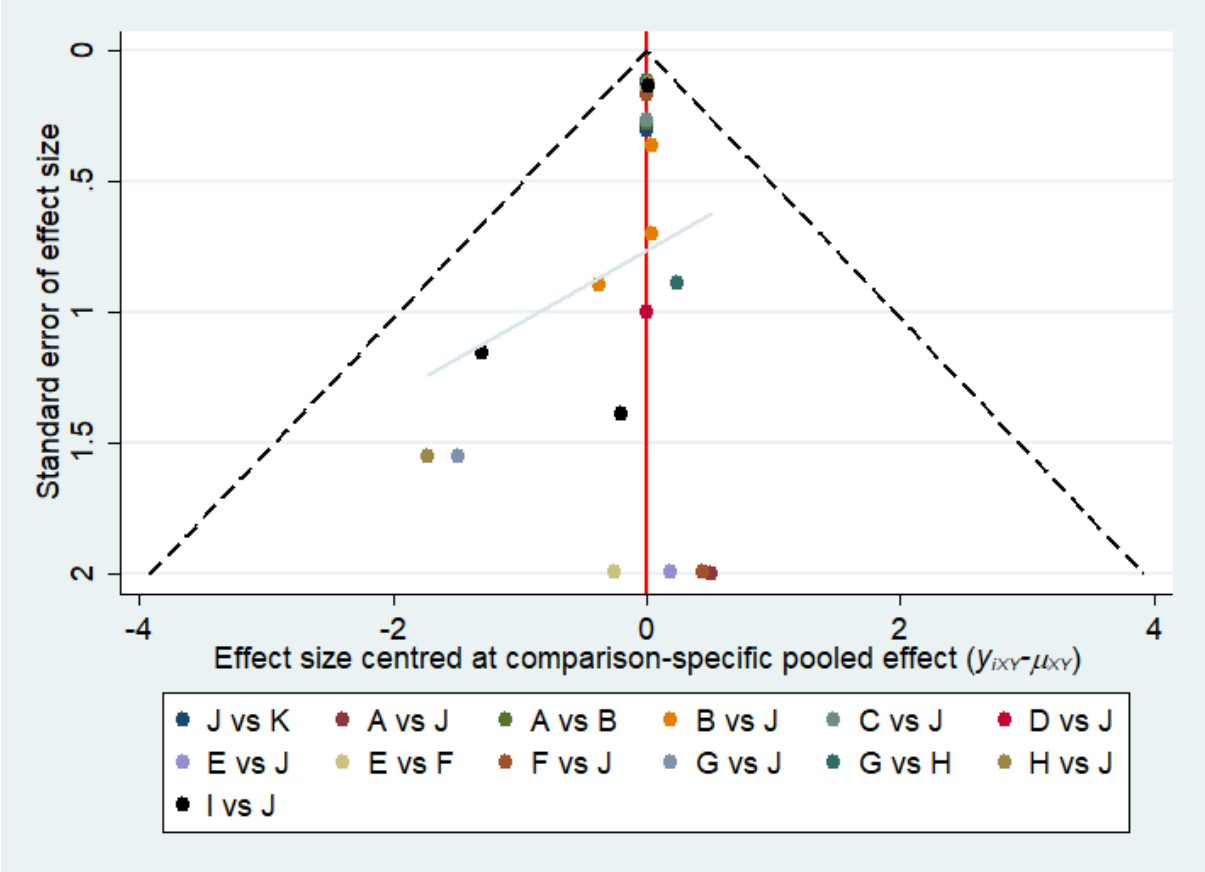
Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Comparison-adjusted funnel plot for the network of gastrointestinal bleeding in all comparisons



Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

Comparison-adjusted funnel plot for the network of myocardial infarction in all comparisons



Abbreviations: *APX, apixaban; ASA, aspirin; CLP, clopidogrel; DBG-110MG, dabigatran 110mg; DBG-150MG, dabigatran 150mg; EDX-30MG, edoxaban 30mg; EDX-60MG, edoxaban 60mg; GNT, genotype-guided warfarin dosing; RVX, rivaroxaban; SM: self-management of warfarin; ST: self-testing of warfarin; WTH: Watchman device*

S-6-14. Assessment of Small Study Effects by Egger's Test for Each Pairwise in Each Outcome

Outcome	Comparison				Number of studies	P-value
Stroke or Systemic Embolism	B - A	ASA	vs.	APX	1	
	D - B	CONTROL	vs.	ASA	2	
	F - E	DBG-150MG	vs.	DBG-110MG	1	
	H - G	EDX-60MG	vs.	EDX-30MG	2	
	J - A	UC	vs.	APX	2	
	J - B	UC	vs.	ASA	7	0.639
	J - C	UC	vs.	ASA+CLP	1	
	J - D	UC	vs.	CONTROL	5	0.495
	J - E	UC	vs.	DBG-110MG	2	
	J - F	UC	vs.	DBG-150MG	2	
	J - G	UC	vs.	EDX-30MG	2	
	J - H	UC	vs.	EDX-60MG	2	
	J - I	UC	vs.	RVX	5	0.129
	K - J	UC+GNT	vs.	UC	1	
	L - J	UC+SM	vs.	UC	2	
	M - J	UC+ST	vs.	UC	1	
	N - J	UC+WTH	vs.	UC	2	
All-cause Mortality	B - A	ASA	vs.	APX	1	
	D - B	CONTROL	vs.	ASA	1	
	F - E	DBG-150MG	vs.	DBG-110MG	1	
	J - B	UC	vs.	ASA	6	
	H - G	EDX-60MG	vs.	EDX-30MG	1	
	J - A	UC	vs.	APX	1	
	J - B	UC	vs.	ASA	6	0.506
	J - C	UC	vs.	ASA+CLP	1	
	J - D	UC	vs.	CONTROL	2	
	J - E	UC	vs.	DBG-110MG	1	
	J - F	UC	vs.	DBG-150MG	1	
	J - G	UC	vs.	EDX-30MG	1	
	J - H	UC	vs.	EDX-60MG	1	
	J - I	UC	vs.	RVX	2	
	K - J	UC+GNT	vs.	UC	1	
	M - J	UC+ST	vs.	UC	1	
	N - J	UC+WTH	vs.	UC	2	
Major Bleeding	B - A	ASA	vs.	APX	1	
	F - E	DBG-150MG	vs.	DBG-110MG	1	
	H - G	EDX-60MG	vs.	EDX-30MG	3	0.198
	J - A	UC	vs.	APX	2	
	J - B	UC	vs.	ASA	3	0.570
	J - C	UC	vs.	ASA+CLP	1	
	J - D	UC	vs.	CONTROL	2	
	J - E	UC	vs.	DBG-110MG	1	

	J - F	UC	vs.	DBG-150MG	2	
	J - G	UC	vs.	EDX-30MG	3	0.307
	J - H	UC	vs.	EDX-60MG	4	0.831
	J - I	UC	vs.	RVX	5	0.503
	K - J	UC+GNT	vs.	UC	N/A	
	M - J	UC+WTH	vs.	UC	1	
Clinically Relevant Non-Major Bleeding (CRNMB)	B - A	ASA	vs.	APX	1	
	I - A	UC	vs.	APX	2	
	I - C	UC	vs.	CONTROL	1	0.264
	E - D	DBG-150MG	vs.	DBG-110MG	1	
	I - D	UC	vs.	DBG-110MG	1	
	I - E	UC	vs.	DBG-150MG	2	
	G - F	EDX-60MG	vs.	EDX-30MG	4	
	I - F	UC	vs.	EDX-30MG	4	0.702
	I - G	UC	vs.	EDX-60MG	4	**0.049**
	I - H	UC	vs.	RVX	4	0.831
Ischemic Stroke	B - A	ASA	vs.	APX	1	
	F - E	DBG-150MG	vs.	DBG-110MG	1	
	H - G	EDX-60MG	vs.	EDX-30MG	1	
	J - A	UC	vs.	APX	2	
	J - B	UC	vs.	ASA	4	0.790
	J - C	UC	vs.	ASA+CLP	1	
	J - D	UC	vs.	CONTROL	3	0.264
	J - E	UC	vs.	DBG-110MG	1	
	J - F	UC	vs.	DBG-150MG	1	
	J - G	UC	vs.	EDX-30MG	1	
	J - H	UC	vs.	EDX-60MG	1	
	J - I	UC	vs.	RVX	4	0.247
	K - J	UC+WTH	vs.	UC	2	
Intracranial Bleeding	B - A	ASA	vs.	APX	1	
	J - A	UC	vs.	APX	2	
	D - B	CONTROL	vs.	ASA	1	
	J - B	UC	vs.	ASA	4	
	J - C	UC	vs.	ASA+CLP	1	
	J - D	UC	vs.	CONTROL	4	0.616
	F - E	DBG-150MG	vs.	DBG-110MG	1	
	J - E	UC	vs.	DBG-110MG	1	0.782
	J - F	UC	vs.	DBG-150MG	1	
	H - G	EDX-60MG	vs.	EDX-30MG	2	
	J - G	UC	vs.	EDX-30MG	1	
	J - H	UC	vs.	EDX-60MG	2	
	J - I	UC	vs.	RVX	5	0.504
	K - J	UC+SM	vs.	UC	1	
	L - J	UC+ST	vs.	UC	1	
	M - J	UC+WTH	vs.	UC	2	

Gastrointestinal Bleeding	B - A	ASA	vs.	APX	1	
	I - A	UC	vs.	APX	1	
	I - B	UC	vs.	ASA	1	
	I - C	UC	vs.	CONTROL	1	
	E - D	DBG-150MG	vs.	DBG-110MG	1	
	I - D	UC	vs.	DBG-110MG	1	
	I - E	UC	vs.	DBG-150MG	1	
	G - F	EDX-60MG	vs.	EDX-30MG	1	
	I - F	UC	vs.	EDX-30MG	1	
	I - G	UC	vs.	EDX-60MG	1	
	I - H	UC	vs.	RVX	3	0.962
	J - I	UC+GNT	vs.	UC	1	0.927
Myocardial Infarction	B - A	ASA	vs.	APX	1	
	J - A	UC	vs.	APX	1	
	J - B	UC	vs.	ASA	3	
	J - C	UC	vs.	ASA+CLP	1	
	J - D	UC	vs.	CONTROL	1	0.463
	F - E	DBG-150MG	vs.	DBG-110MG	1	
	J - E	UC	vs.	DBG-110MG	1	
	J - F	UC	vs.	DBG-150MG	1	
	H - G	EDX-60MG	vs.	EDX-30MG	2	
	J - G	UC	vs.	EDX-30MG	2	
	J - H	UC	vs.	EDX-60MG	2	
	J - I	UC	vs.	RVX	3	0.424
	K - J	UC+ST	vs.	UC	1	

S-6-15. Evaluation of the Quality of Evidence using GRADE Framework for All Outcomes

Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
	Risk ratio (95% confidence interval)	Quality of evidence	Risk ratio (95% confidence interval)	Quality of evidence	Risk ratio (95% confidence interval)	Quality of evidence
Stroke or systemic embolism						
ASA vs. APX	2.22 (1.61,3.13)	⊕⊕⊕⊕ HIGH	2.39 (1.19,4.79)	⊕⊕◯◯ LOW §	2.27 (1.51,3.42)	⊕⊕⊕⊕ HIGH
ASA+CLP vs. APX			2.44 (1.24,4.80)	⊕⊕◯◯ LOW ++	2.44 (1.24,4.80)	⊕⊕◯◯ LOW
CONTROL vs. APX			2.80 (1.68,4.64)	⊕◯◯◯ VERY LOW ++	2.80 (1.68,4.64)	⊕◯◯◯ VERY LOW
DBG-110MG vs. APX			1.17 (0.63,2.20)	⊕⊕◯◯ LOW ++	1.17 (0.63,2.20)	⊕⊕◯◯ LOW
DBG-150MG vs. APX			0.85 (0.45,1.60)	⊕⊕◯◯ LOW ++	0.85 (0.45,1.60)	⊕⊕◯◯ LOW
EDX-30MG vs. APX			1.40 (0.76,2.57)	⊕⊕◯◯ LOW ++	1.40 (0.76,2.57)	⊕⊕◯◯ LOW
EDX-60MG vs. APX			1.08 (0.59,1.98)	⊕⊕◯◯ LOW ++	1.08 (0.59,1.98)	⊕⊕◯◯ LOW
RVX vs. APX			1.05 (0.64,1.72)	⊕⊕◯◯ LOW ++	1.05 (0.64,1.72)	⊕⊕◯◯ LOW
UC vs. APX	1.28 (1.06,1.52)	⊕⊕◯◯ LOW a, e	1.28 (0.61,2.69)	⊕◯◯◯ VERY LOW §	1.32 (0.89,1.95)	⊕⊕◯◯ LOW
UC+GNT vs. APX			0.44 (0.02,11.41)	⊕◯◯◯ VERY LOW ++	0.44 (0.02,11.41)	⊕◯◯◯ VERY LOW
UC+SM vs. APX			0.31 (0.10,0.96)	⊕◯◯◯ VERY LOW ++	0.31 (0.10,0.96)	⊕◯◯◯ VERY LOW
UC+ST vs. APX			1.31 (0.61,2.84)	⊕◯◯◯ VERY LOW ++	1.31 (0.61,2.84)	⊕◯◯◯ VERY LOW
UC+WTH vs. APX			1.18 (0.53,2.63)	⊕⊕◯◯ LOW ++	1.18 (0.53,2.63)	⊕⊕◯◯ LOW
ASA+CLP vs. ASA			1.08 (0.58,2.00)	⊕◯◯◯ VERY LOW ++	1.08 (0.58,2.00)	⊕◯◯◯ VERY LOW
CONTROL vs. ASA	0.95 (0.68,1.35)	⊕⊕◯◯ LOW a,b	1.68 (1.00,2.80)	⊕◯◯◯ VERY LOW j	1.23 (0.85,1.78)	⊕⊕◯◯ LOW
DBG-110MG vs. ASA			0.52 (0.29,0.92)	⊕◯◯◯ VERY LOW ++	0.52 (0.29,0.92)	⊕◯◯◯ VERY LOW
DBG-150MG vs. ASA			0.38 (0.21,0.67)	⊕◯◯◯ VERY LOW ++	0.38 (0.21,0.67)	⊕◯◯◯ VERY LOW
EDX-30MG vs. ASA			0.61 (0.35,1.08)	⊕◯◯◯ VERY LOW ++	0.61 (0.35,1.08)	⊕◯◯◯ VERY LOW
EDX-60MG vs. ASA			0.47 (0.27,0.83)	⊕◯◯◯ VERY LOW ++	0.47 (0.27,0.83)	⊕◯◯◯ VERY LOW
RVX vs. ASA			0.46 (0.30,0.71)	⊕◯◯◯ VERY LOW ++	0.46 (0.30,0.71)	⊕◯◯◯ VERY LOW
UC vs. ASA	0.61 (0.47,0.79)	⊕◯◯◯ VERY LOW a,e,f,g	0.48 (0.28,0.82)	⊕⊕◯◯ LOW §	0.58 (0.44,0.77)	⊕⊕◯◯ LOW
UC+GNT vs. ASA			0.19 (0.01,4.97)	⊕◯◯◯ VERY LOW ++	0.19 (0.01,4.97)	⊕◯◯◯ VERY LOW
UC+SM vs. ASA			0.14 (0.05,0.41)	⊕◯◯◯ VERY LOW ++	0.14 (0.05,0.41)	⊕◯◯◯ VERY LOW
UC+ST vs. ASA			0.58 (0.28,1.19)	⊕◯◯◯ VERY LOW ++	0.58 (0.28,1.19)	⊕◯◯◯ VERY LOW
UC+WTH vs. ASA			0.52 (0.25,1.09)	⊕◯◯◯ VERY LOW ++	0.52 (0.25,1.09)	⊕◯◯◯ VERY LOW
CONTROL vs. ASA+CLP			1.14 (0.60,2.19)	⊕⊕⊕◯ MODERATE ++	1.14 (0.60,2.19)	⊕⊕⊕◯ MODERATE
DBG-110MG vs. ASA+CLP			0.48 (0.23,1.01)	⊕⊕◯◯ LOW ++	0.48 (0.23,1.01)	⊕⊕◯◯ LOW

DBG-150MG vs. ASA+CLP			0.35 (0.17,0.73)	⊕⊕⊕◯ MODERATE ↔	0.35 (0.17,0.73)	⊕⊕⊕◯ MODERATE
EDX-30MG vs. ASA+CLP			0.57 (0.27,1.19)	⊕⊕◯◯ LOW ↔	0.57 (0.27,1.19)	⊕⊕◯◯ LOW
EDX-60MG vs. ASA+CLP			0.44 (0.21,0.92)	⊕⊕◯◯ LOW ↔	0.44 (0.21,0.92)	⊕⊕◯◯ LOW
RVX vs. ASA+CLP			0.43 (0.23,0.81)	⊕⊕⊕◯ MODERATE ↔	0.43 (0.23,0.81)	⊕⊕⊕◯ MODERATE
UC vs. ASA+CLP	0.54 (0.40,0.73)	⊕⊕⊕◯ MODERATE [a]	Not estimable	Not estimable *	0.54 (0.31,0.94)	⊕⊕⊕◯ MODERATE
UC+GNT vs. ASA+CLP			0.18 (0.01,4.78)	⊕◯◯◯ VERY LOW ↔	0.18 (0.01,4.78)	⊕◯◯◯ VERY LOW
UC+SM vs. ASA+CLP			0.13 (0.04,0.42)	⊕◯◯◯ VERY LOW ↔	0.13 (0.04,0.42)	⊕◯◯◯ VERY LOW
UC+ST vs. ASA+CLP			0.54 (0.23,1.27)	⊕◯◯◯ VERY LOW ↔	0.54 (0.23,1.27)	⊕◯◯◯ VERY LOW
UC+WTH vs. ASA+CLP			0.48 (0.20,1.16)	⊕⊕⊕◯ MODERATE ↔	0.48 (0.20,1.16)	⊕⊕⊕◯ MODERATE
DBG-110MG vs. CONTROL			0.42 (0.23,0.77)	⊕⊕◯◯ LOW ↔	0.42 (0.23,0.77)	⊕⊕◯◯ LOW
DBG-150MG vs. CONTROL			0.31 (0.16,0.57)	⊕⊕⊕◯ MODERATE ↔	0.31 (0.16,0.57)	⊕⊕⊕◯ MODERATE
EDX-30MG vs. CONTROL			0.50 (0.27,0.92)	⊕⊕◯◯ LOW ↔	0.50 (0.27,0.92)	⊕⊕◯◯ LOW
EDX-60MG vs. CONTROL			0.39 (0.21,0.71)	⊕⊕◯◯ LOW ↔	0.39 (0.21,0.71)	⊕⊕◯◯ LOW
RVX vs. CONTROL			0.37 (0.23,0.61)	⊕⊕⊕◯ MODERATE ↔	0.37 (0.23,0.61)	⊕⊕⊕◯ MODERATE
UC vs. CONTROL	0.37 (0.27,0.52)	⊕⊕⊕◯ MODERATE [a]	0.78 (0.42,1.45)	⊕◯◯◯ VERY LOW [§]	0.47 (0.33,0.67)	⊕⊕⊕◯ MODERATE
UC+GNT vs. CONTROL			0.16 (0.01,4.06)	⊕◯◯◯ VERY LOW ↔	0.16 (0.01,4.06)	⊕◯◯◯ VERY LOW
UC+SM vs. CONTROL			0.11 (0.04,0.34)	⊕◯◯◯ VERY LOW ↔	0.11 (0.04,0.34)	⊕◯◯◯ VERY LOW
UC+ST vs. CONTROL			0.47 (0.22,0.99)	⊕◯◯◯ VERY LOW ↔	0.47 (0.22,0.99)	⊕◯◯◯ VERY LOW
UC+WTH vs. CONTROL			0.42 (0.20,0.90)	⊕⊕⊕◯ MODERATE ↔	0.42 (0.20,0.90)	⊕⊕⊕◯ MODERATE
DBG-150MG vs. DBG-110MG	0.73 (0.58,0.91)	⊕⊕⊕◯ MODERATE [a]	0.31 (0.00,856.89)	⊕⊕◯◯ LOW [§]	0.73 (0.44,1.20)	⊕⊕⊕◯ MODERATE
EDX-30MG vs. DBG-110MG			1.19 (0.60,2.35)	⊕⊕◯◯ LOW ↔	1.19 (0.60,2.35)	⊕⊕◯◯ LOW
EDX-60MG vs. DBG-110MG			0.92 (0.46,1.81)	⊕⊕◯◯ LOW ↔	0.92 (0.46,1.81)	⊕⊕◯◯ LOW
RVX vs. DBG-110MG			0.89 (0.50,1.60)	⊕⊕◯◯ LOW ↔	0.89 (0.50,1.60)	⊕⊕◯◯ LOW
UC vs. DBG-110MG	1.10 (0.91,1.33)	⊕⊕◯◯ LOW [a,b]	2.63 (0.00,7,270.20)	⊕⊕⊕◯ MODERATE [¶]	1.12 (0.68,1.84)	⊕⊕⊕◯ MODERATE
UC+GNT vs. DBG-110MG			0.38 (0.01,9.85)	⊕◯◯◯ VERY LOW ↔	0.38 (0.01,9.85)	⊕◯◯◯ VERY LOW
UC+SM vs. DBG-110MG			0.27 (0.08,0.85)	⊕◯◯◯ VERY LOW ↔	0.27 (0.08,0.85)	⊕◯◯◯ VERY LOW
UC+ST vs. DBG-110MG			1.12 (0.49,2.56)	⊕◯◯◯ VERY LOW ↔	1.12 (0.49,2.56)	⊕◯◯◯ VERY LOW
UC+WTH vs. DBG-110MG			1.00 (0.43,2.36)	⊕⊕◯◯ LOW ↔	1.00 (0.43,2.36)	⊕⊕◯◯ LOW
EDX-30MG vs. DBG-150MG			1.63 (0.82,3.24)	⊕⊕◯◯ LOW ↔	1.63 (0.82,3.24)	⊕⊕◯◯ LOW
EDX-60MG vs. DBG-150MG			1.26 (0.64,2.50)	⊕⊕◯◯ LOW ↔	1.26 (0.64,2.50)	⊕⊕◯◯ LOW
RVX vs. DBG-150MG			1.22 (0.68,2.20)	⊕⊕⊕◯ MODERATE ↔	1.22 (0.68,2.20)	⊕⊕⊕◯ MODERATE

UC vs. DBG-150MG	1.52 (1.22,1.85)	⨁⨁⨁◯ MODERATE [a]	1.54 (0.94,2.55)	⨁⨁◯◯ LOW [§]	1.54 (0.94,2.55)	⨁⨁⨁◯ MODERATE
UC+GNT vs. DBG-150MG			0.52 (0.02,13.56)	⨁◯◯◯ VERY LOW [++]	0.52 (0.02,13.56)	⨁◯◯◯ VERY LOW
UC+SM vs. DBG-150MG			0.37 (0.11,1.17)	⨁◯◯◯ VERY LOW [++]	0.37 (0.11,1.17)	⨁◯◯◯ VERY LOW
UC+ST vs. DBG-150MG			1.54 (0.67,3.53)	⨁◯◯◯ VERY LOW [++]	1.54 (0.67,3.53)	⨁◯◯◯ VERY LOW
UC+WTH vs. DBG-150MG			1.38 (0.58,3.26)	⨁⨁⨁◯ MODERATE [++]	1.38 (0.58,3.26)	⨁⨁⨁◯ MODERATE
EDX-30MG vs. DBG-150MG			1.63 (0.82,3.24)	⨁⨁◯◯ LOW [++]	1.63 (0.82,3.24)	⨁⨁◯◯ LOW
EDX-60MG vs. DBG-150MG			1.26 (0.64,2.50)	⨁⨁◯◯ LOW [++]	1.26 (0.64,2.50)	⨁⨁◯◯ LOW
RVX vs. DBG-150MG			1.22 (0.68,2.20)	⨁⨁⨁◯ MODERATE [++]	1.22 (0.68,2.20)	⨁⨁⨁◯ MODERATE
UC+GNT vs. DBG-150MG			0.52 (0.02,13.56)	⨁◯◯◯ VERY LOW [++]	0.52 (0.02,13.56)	⨁◯◯◯ VERY LOW
UC+SM vs. DBG-150MG			0.37 (0.11,1.17)	⨁◯◯◯ VERY LOW [++]	0.37 (0.11,1.17)	⨁◯◯◯ VERY LOW
UC+ST vs. DBG-150MG			1.54 (0.67,3.53)	⨁◯◯◯ VERY LOW [++]	1.54 (0.67,3.53)	⨁◯◯◯ VERY LOW
UC+WTH vs. DBG-150MG			1.38 (0.58,3.26)	⨁⨁⨁◯ MODERATE [++]	1.38 (0.58,3.26)	⨁⨁⨁◯ MODERATE
EDX-60MG vs. EDX-30MG	0.76 (0.66,0.88)	⨁⨁⨁◯ MODERATE [a]	0.77 (0.48,1.24)	⨁⨁◯◯ LOW [j]	0.77 (0.48,1.24)	⨁⨁⨁◯ MODERATE
RVX vs. EDX-30MG			0.75 (0.43,1.31)	⨁⨁◯◯ LOW [++]	0.75 (0.43,1.31)	⨁⨁◯◯ LOW
UC vs. EDX-30MG	0.88 (0.76,1.01)	⨁⨁◯◯ LOW [a,b]	0.95 (0.58,1.54)	⨁⨁◯◯ LOW [§]	0.95 (0.58,1.54)	⨁⨁◯◯ LOW
UC+GNT vs. EDX-30MG			0.32 (0.01,8.28)	⨁◯◯◯ VERY LOW [++]	0.32 (0.01,8.28)	⨁◯◯◯ VERY LOW
UC+SM vs. EDX-30MG			0.22 (0.07,0.72)	⨁◯◯◯ VERY LOW [++]	0.22 (0.07,0.72)	⨁◯◯◯ VERY LOW
UC+ST vs. EDX-30MG			0.94 (0.41,2.14)	⨁◯◯◯ VERY LOW [++]	0.94 (0.41,2.14)	⨁◯◯◯ VERY LOW
UC+WTH vs. EDX-30MG			0.84 (0.35,2.01)	⨁⨁◯◯ LOW [++]	0.84 (0.35,2.01)	⨁⨁◯◯ LOW
RVX vs. EDX-60MG			0.97 (0.56,1.69)	⨁⨁◯◯ LOW [++]	0.97 (0.56,1.69)	⨁⨁◯◯ LOW
UC vs. EDX-60MG	1.16 (0.99,1.35)	⨁⨁◯◯ LOW [a,b]	1.22 (0.76,1.98)	⨁⨁◯◯ LOW [§]	1.22 (0.76,1.98)	⨁⨁◯◯ LOW
UC+GNT vs. EDX-60MG			0.41 (0.02,10.72)	⨁◯◯◯ VERY LOW [++]	0.41 (0.02,10.72)	⨁◯◯◯ VERY LOW
UC+SM vs. EDX-60MG			0.29 (0.09,0.93)	⨁◯◯◯ VERY LOW [++]	0.29 (0.09,0.93)	⨁◯◯◯ VERY LOW
UC+ST vs. EDX-60MG			1.22 (0.54,2.76)	⨁◯◯◯ VERY LOW [++]	1.22 (0.54,2.76)	⨁◯◯◯ VERY LOW
UC+WTH vs. EDX-60MG			1.09 (0.46,2.58)	⨁⨁◯◯ LOW [++]	1.09 (0.46,2.58)	⨁⨁◯◯ LOW
UC vs. RVX	1.18 (1.02,1.35)	⨁⨁⨁◯ MODERATE [a]	Not estimable	Not estimable *	1.26 (0.91,1.75)	⨁⨁⨁◯ MODERATE
UC+GNT vs. RVX			0.42 (0.02,10.84)	⨁◯◯◯ VERY LOW [++]	0.42 (0.02,10.84)	⨁◯◯◯ VERY LOW
UC+SM vs. RVX			0.30 (0.10,0.90)	⨁◯◯◯ VERY LOW [++]	0.30 (0.10,0.90)	⨁◯◯◯ VERY LOW
UC+ST vs. RVX			1.25 (0.60,2.63)	⨁◯◯◯ VERY LOW [++]	1.25 (0.60,2.63)	⨁◯◯◯ VERY LOW
UC+WTH vs. RVX			1.13 (0.51,2.47)	⨁⨁⨁◯ MODERATE [++]	1.13 (0.51,2.47)	⨁⨁⨁◯ MODERATE
UC+GNT vs. UC	0.33 (0.01,8.33)	⨁◯◯◯ VERY LOW [a,b,c,d,h]	Not estimable	Not estimable *	0.33 (0.01,8.45)	⨁◯◯◯ VERY LOW

UC+SM vs. UC	0.21 (0.08,0.57)	⨁◯◯◯ VERY LOW [a,c,d,h]	Not estimable	Not estimable *	0.24 (0.08,0.68)	⨁◯◯◯ VERY LOW
UC+ST vs. UC	0.99 (0.61,1.64)	⨁◯◯◯ VERY LOW [a,b,h]	Not estimable	Not estimable *	0.99 (0.51,1.93)	⨁◯◯◯ VERY LOW
UC+WTH vs. UC	0.90 (0.53,1.52)	⨁⨁⨁◯ MODERATE [a]	Not estimable	Not estimable *	0.89 (0.45,1.78)	⨁⨁⨁◯ MODERATE
UC+SM vs. UC+GNT			0.71 (0.02,21.08)	⨁◯◯◯ VERY LOW [++]	0.71 (0.02,21.08)	⨁◯◯◯ VERY LOW
UC+ST vs. UC+GNT			2.97 (0.11,80.15)	⨁◯◯◯ VERY LOW [++]	2.97 (0.11,80.15)	⨁◯◯◯ VERY LOW
UC+WTH vs. UC+GNT			2.67 (0.10,72.41)	⨁◯◯◯ VERY LOW [++]	2.67 (0.10,72.41)	⨁◯◯◯ VERY LOW
UC+ST vs. UC+SM			4.20 (1.21,14.57)	⨁◯◯◯ VERY LOW [++]	4.20 (1.21,14.57)	⨁◯◯◯ VERY LOW
UC+WTH vs. UC+SM			3.77 (1.08,13.21)	⨁◯◯◯ VERY LOW [++]	3.77 (1.08,13.21)	⨁◯◯◯ VERY LOW
All-cause mortality						
ASA vs. APX	1.27 (0.99,1.61)	⨁⨁⨁◯ MODERATE [b]	1.16 (0.94,1.42)	⨁◯◯◯ VERY LOW [§]	1.20 (1.03,1.41)	⨁⨁⨁◯ MODERATE
ASA+CLP vs. APX			1.12 (0.88,1.42)	⨁⨁◯◯ LOW [++]	1.12 (0.88,1.42)	⨁⨁◯◯ LOW
CONTROL vs. APX			1.26 (0.89,1.78)	⨁⨁◯◯ LOW [++]	1.26 (0.89,1.78)	⨁⨁◯◯ LOW
DBG-110MG vs. APX			1.03 (0.88,1.21)	⨁⨁◯◯ LOW [++]	1.03 (0.88,1.21)	⨁⨁◯◯ LOW
DBG-150MG vs. APX			1.00 (0.86,1.18)	⨁⨁◯◯ LOW [++]	1.00 (0.86,1.18)	⨁⨁◯◯ LOW
EDX-30MG vs. APX			0.99 (0.86,1.13)	⨁⨁⨁◯ MODERATE [++]	0.99 (0.86,1.13)	⨁⨁⨁◯ MODERATE
EDX-60MG vs. APX			1.04 (0.91,1.19)	⨁⨁⨁◯ MODERATE [++]	1.04 (0.91,1.19)	⨁⨁⨁◯ MODERATE
RVX vs. APX			0.95 (0.78,1.17)	⨁⨁⨁◯ MODERATE [++]	0.95 (0.78,1.17)	⨁⨁⨁◯ MODERATE
UC vs. APX	1.11 (1.00,1.23)	⨁⨁⨁◯ MODERATE [b]	1.22 (0.91,1.65)	⨁◯◯◯ VERY LOW [§]	1.13 (1.02,1.24)	⨁⨁⨁◯ MODERATE
UC+GNT vs. APX			2.83 (0.55,14.47)	⨁◯◯◯ VERY LOW [++]	2.83 (0.55,14.47)	⨁◯◯◯ VERY LOW
UC+SM vs. APX			0.47 (0.19,1.18)	⨁◯◯◯ VERY LOW [++]	0.47 (0.19,1.18)	⨁◯◯◯ VERY LOW
UC+ST vs. APX			1.08 (0.86,1.37)	⨁◯◯◯ VERY LOW [++]	1.08 (0.86,1.37)	⨁◯◯◯ VERY LOW
UC+WTH vs. APX			0.55 (0.31,0.97)	⨁⨁⨁◯ MODERATE [++]	0.55 (0.31,0.97)	⨁⨁⨁◯ MODERATE
ASA+CLP vs. ASA			0.93 (0.72,1.21)	⨁◯◯◯ VERY LOW [++]	0.93 (0.72,1.21)	⨁◯◯◯ VERY LOW
CONTROL vs. ASA	0.86 (0.35,2.10)	⨁⨁◯◯ LOW [a,b]	1.08 (0.73,1.60)	⨁◯◯◯ VERY LOW [§]	1.04 (0.73,1.49)	⨁⨁◯◯ LOW
DBG-110MG vs. ASA			0.86 (0.71,1.04)	⨁◯◯◯ VERY LOW [++]	0.86 (0.71,1.04)	⨁◯◯◯ VERY LOW
DBG-150MG vs. ASA			0.84 (0.69,1.01)	⨁◯◯◯ VERY LOW [++]	0.84 (0.69,1.01)	⨁◯◯◯ VERY LOW
EDX-30MG vs. ASA			0.82 (0.69,0.98)	⨁◯◯◯ VERY LOW [++]	0.82 (0.69,0.98)	⨁◯◯◯ VERY LOW
EDX-60MG vs. ASA			0.86 (0.73,1.03)	⨁◯◯◯ VERY LOW [++]	0.86 (0.73,1.03)	⨁◯◯◯ VERY LOW
RVX vs. ASA			0.79 (0.63,1.00)	⨁◯◯◯ VERY LOW [++]	0.79 (0.63,1.00)	⨁◯◯◯ VERY LOW
UC vs. ASA	0.97 (0.81,1.16)	⨁◯◯◯ VERY LOW [a,b,f,g]	0.87 (0.67,1.12)	⨁⨁⨁◯ MODERATE [b]	0.94 (0.81,1.09)	⨁⨁⨁◯ MODERATE
UC+GNT vs. ASA			2.35 (0.46,12.08)	⨁◯◯◯ VERY LOW [++]	2.35 (0.46,12.08)	⨁◯◯◯ VERY LOW

UC+SM vs. ASA			0.39 (0.16,0.99)	⨁◯◯◯ VERY LOW ++	0.39 (0.16,0.99)	⨁◯◯◯ VERY LOW
UC+ST vs. ASA			0.90 (0.70,1.17)	⨁◯◯◯ VERY LOW ++	0.90 (0.70,1.17)	⨁◯◯◯ VERY LOW
UC+WTH vs. ASA			0.46 (0.26,0.82)	⨁◯◯◯ VERY LOW ++	0.46 (0.26,0.82)	⨁◯◯◯ VERY LOW
CONTROL vs. ASA+CLP			1.12 (0.75,1.67)	⨁⨁◯◯ LOW ++	1.12 (0.75,1.67)	⨁⨁◯◯ LOW
DBG-110MG vs. ASA+CLP			0.92 (0.72,1.18)	⨁⨁◯◯ LOW ++	0.92 (0.72,1.18)	⨁⨁◯◯ LOW
DBG-150MG vs. ASA+CLP			0.90 (0.70,1.15)	⨁⨁◯◯ LOW ++	0.90 (0.70,1.15)	⨁⨁◯◯ LOW
EDX-30MG vs. ASA+CLP			0.88 (0.70,1.12)	⨁⨁◯◯ LOW ++	0.88 (0.70,1.12)	⨁⨁◯◯ LOW
EDX-60MG vs. ASA+CLP			0.93 (0.73,1.17)	⨁⨁◯◯ LOW ++	0.93 (0.73,1.17)	⨁⨁◯◯ LOW
RVX vs. ASA+CLP			0.85 (0.64,1.12)	⨁⨁◯◯ LOW ++	0.85 (0.64,1.12)	⨁⨁◯◯ LOW
UC vs. ASA+CLP	1.00 (0.81,1.25)	⨁⨁◯◯ LOW a,b	Not estimable	Not estimable *	1.00 (0.81,1.25)	⨁⨁◯◯ LOW
UC+GNT vs. ASA+CLP			2.52 (0.49,13.05)	⨁◯◯◯ VERY LOW ++	2.52 (0.49,13.05)	⨁◯◯◯ VERY LOW
UC+SM vs. ASA+CLP			0.42 (0.17,1.07)	⨁◯◯◯ VERY LOW ++	0.42 (0.17,1.07)	⨁◯◯◯ VERY LOW
UC+ST vs. ASA+CLP			0.97 (0.72,1.31)	⨁◯◯◯ VERY LOW ++	0.97 (0.72,1.31)	⨁◯◯◯ VERY LOW
UC+WTH vs. ASA+CLP			0.49 (0.27,0.90)	⨁⨁◯◯ LOW ++	0.49 (0.27,0.90)	⨁⨁◯◯ LOW
DBG-110MG vs. CONTROL			0.82 (0.58,1.17)	⨁⨁◯◯ LOW ++	0.82 (0.58,1.17)	⨁⨁◯◯ LOW
DBG-150MG vs. CONTROL			0.80 (0.56,1.14)	⨁⨁◯◯ LOW ++	0.80 (0.56,1.14)	⨁⨁◯◯ LOW
EDX-30MG vs. CONTROL			0.79 (0.56,1.11)	⨁⨁◯◯ LOW ++	0.79 (0.56,1.11)	⨁⨁◯◯ LOW
EDX-60MG vs. CONTROL			0.83 (0.58,1.17)	⨁⨁◯◯ LOW ++	0.83 (0.58,1.17)	⨁⨁◯◯ LOW
RVX vs. CONTROL			0.76 (0.52,1.11)	⨁⨁◯◯ LOW ++	0.76 (0.52,1.11)	⨁⨁◯◯ LOW
UC vs. CONTROL	0.87 (0.61,1.23)	⨁⨁◯◯ LOW a,b	1.09 (0.44,2.70)	⨁◯◯◯ VERY LOW §	0.90 (0.64,1.25)	⨁⨁◯◯ LOW
UC+GNT vs. CONTROL			2.25 (0.43,11.88)	⨁◯◯◯ VERY LOW ++	2.25 (0.43,11.88)	⨁◯◯◯ VERY LOW
UC+SM vs. CONTROL			0.38 (0.14,0.99)	⨁◯◯◯ VERY LOW ++	0.38 (0.14,0.99)	⨁◯◯◯ VERY LOW
UC+ST vs. CONTROL			0.86 (0.58,1.28)	⨁◯◯◯ VERY LOW ++	0.86 (0.58,1.28)	⨁◯◯◯ VERY LOW
UC+WTH vs. CONTROL			0.44 (0.23,0.84)	⨁⨁◯◯ LOW ++	0.44 (0.23,0.84)	⨁⨁◯◯ LOW
DBG-150MG vs. DBG-110MG	0.97 (0.85,1.10)	⨁⨁◯◯ LOW a,b	0.97 (0.86,1.10)	⨁⨁◯◯ LOW §	0.97 (0.86,1.10)	⨁⨁◯◯ LOW
EDX-30MG vs. DBG-110MG			0.96 (0.82,1.12)	⨁⨁◯◯ LOW ++	0.96 (0.82,1.12)	⨁⨁◯◯ LOW
EDX-60MG vs. DBG-110MG			1.00 (0.86,1.17)	⨁⨁◯◯ LOW ++	1.00 (0.86,1.17)	⨁⨁◯◯ LOW
RVX vs. DBG-110MG			0.92 (0.74,1.15)	⨁⨁◯◯ LOW ++	0.92 (0.74,1.15)	⨁⨁◯◯ LOW
UC vs. DBG-110MG	1.09 (0.96,1.23)	⨁⨁◯◯ LOW a,b	1.09 (0.96,1.23)	⨁⨁◯◯ LOW §	1.09 (0.96,1.23)	⨁⨁◯◯ LOW
UC+GNT vs. DBG-110MG			2.74 (0.53,14.03)	⨁◯◯◯ VERY LOW ++	2.74 (0.53,14.03)	⨁◯◯◯ VERY LOW
UC+SM vs. DBG-110MG			0.46 (0.18,1.15)	⨁◯◯◯ VERY LOW ++	0.46 (0.18,1.15)	⨁◯◯◯ VERY LOW

UC+ST vs. DBG-110MG			1.05 (0.82,1.34)	⨁◯◯◯ VERY LOW ++	1.05 (0.82,1.34)	⨁◯◯◯ VERY LOW
UC+WTH vs. DBG-110MG			0.54 (0.30,0.95)	⨁⨁◯◯ LOW ++	0.54 (0.30,0.95)	⨁⨁◯◯ LOW
EDX-30MG vs. DBG-150MG			0.99 (0.84,1.15)	⨁⨁◯◯ LOW ++	0.99 (0.84,1.15)	⨁⨁◯◯ LOW
EDX-60MG vs. DBG-150MG			1.03 (0.89,1.21)	⨁⨁◯◯ LOW ++	1.03 (0.89,1.21)	⨁⨁◯◯ LOW
RVX vs. DBG-150MG			0.95 (0.76,1.18)	⨁⨁◯◯ LOW ++	0.95 (0.76,1.18)	⨁⨁◯◯ LOW
UC vs. DBG-150MG	1.12 (0.99,1.26)	⨁⨁◯◯ LOW a,b	1.12 (0.99,1.27)	⨁⨁◯◯ LOW §	1.12 (0.99,1.27)	⨁⨁◯◯ LOW
UC+GNT vs. DBG-150MG			2.82 (0.55,14.44)	⨁◯◯◯ VERY LOW ++	2.82 (0.55,14.44)	⨁◯◯◯ VERY LOW
UC+SM vs. DBG-150MG			0.47 (0.19,1.18)	⨁◯◯◯ VERY LOW ++	0.47 (0.19,1.18)	⨁◯◯◯ VERY LOW
UC+ST vs. DBG-150MG			1.08 (0.85,1.38)	⨁◯◯◯ VERY LOW ++	1.08 (0.85,1.38)	⨁◯◯◯ VERY LOW
UC+WTH vs. DBG-150MG			0.55 (0.31,0.98)	⨁⨁◯◯ LOW ++	0.55 (0.31,0.98)	⨁⨁◯◯ LOW
EDX-30MG vs. DBG-150MG			0.99 (0.84,1.15)	⨁⨁◯◯ LOW ++	0.99 (0.84,1.15)	⨁⨁◯◯ LOW
EDX-60MG vs. DBG-150MG			1.03 (0.89,1.21)	⨁⨁◯◯ LOW ++	1.03 (0.89,1.21)	⨁⨁◯◯ LOW
RVX vs. DBG-150MG			0.95 (0.76,1.18)	⨁⨁◯◯ LOW ++	0.95 (0.76,1.18)	⨁⨁◯◯ LOW
UC+GNT vs. DBG-150MG			2.82 (0.55,14.44)	⨁◯◯◯ VERY LOW ++	2.82 (0.55,14.44)	⨁◯◯◯ VERY LOW
UC+SM vs. DBG-150MG			0.47 (0.19,1.18)	⨁◯◯◯ VERY LOW ++	0.47 (0.19,1.18)	⨁◯◯◯ VERY LOW
UC+ST vs. DBG-150MG			1.08 (0.85,1.38)	⨁◯◯◯ VERY LOW ++	1.08 (0.85,1.38)	⨁◯◯◯ VERY LOW
UC+WTH vs. DBG-150MG			0.55 (0.31,0.98)	⨁⨁◯◯ LOW ++	0.55 (0.31,0.98)	⨁⨁◯◯ LOW
EDX-60MG vs. EDX-30MG	1.05 (0.95,1.15)	⨁⨁⨁◯ MODERATE b	1.05 (0.95,1.15)	⨁⨁⨁◯ MODERATE ¶	1.05 (0.95,1.15)	⨁⨁⨁◯ MODERATE
RVX vs. EDX-30MG			0.96 (0.79,1.18)	⨁⨁⨁◯ MODERATE ++	0.96 (0.79,1.18)	⨁⨁⨁◯ MODERATE
UC vs. EDX-30MG	1.14 (1.03,1.25)	⨁⨁⨁⨁ HIGH	1.14 (1.04,1.25)	⨁⨁⨁◯ MODERATE ¶	1.14 (1.04,1.25)	⨁⨁⨁⨁ HIGH
UC+GNT vs. EDX-30MG			2.86 (0.56,14.62)	⨁◯◯◯ VERY LOW ++	2.86 (0.56,14.62)	⨁◯◯◯ VERY LOW
UC+SM vs. EDX-30MG			0.48 (0.19,1.19)	⨁◯◯◯ VERY LOW ++	0.48 (0.19,1.19)	⨁◯◯◯ VERY LOW
UC+ST vs. EDX-30MG			1.10 (0.87,1.38)	⨁◯◯◯ VERY LOW ++	1.10 (0.87,1.38)	⨁◯◯◯ VERY LOW
UC+WTH vs. EDX-30MG			0.56 (0.32,0.98)	⨁⨁⨁◯ MODERATE ++	0.56 (0.32,0.98)	⨁⨁⨁◯ MODERATE
RVX vs. EDX-60MG			0.92 (0.75,1.12)	⨁⨁⨁◯ MODERATE ++	0.92 (0.75,1.12)	⨁⨁⨁◯ MODERATE
UC vs. EDX-60MG	1.09 (0.99,1.19)	⨁⨁⨁◯ MODERATE b	1.09 (0.99,1.19)	⨁⨁⨁◯ MODERATE ¶	1.09 (0.99,1.19)	⨁⨁⨁◯ MODERATE
UC+GNT vs. EDX-60MG			2.73 (0.53,13.94)	⨁◯◯◯ VERY LOW ++	2.73 (0.53,13.94)	⨁◯◯◯ VERY LOW
UC+SM vs. EDX-60MG			0.46 (0.18,1.14)	⨁◯◯◯ VERY LOW ++	0.46 (0.18,1.14)	⨁◯◯◯ VERY LOW
UC+ST vs. EDX-60MG			1.04 (0.83,1.32)	⨁◯◯◯ VERY LOW ++	1.04 (0.83,1.32)	⨁◯◯◯ VERY LOW
UC+WTH vs. EDX-60MG			0.53 (0.30,0.94)	⨁⨁⨁◯ MODERATE ++	0.53 (0.30,0.94)	⨁⨁⨁◯ MODERATE
UC vs. RVX	1.18 (0.99,1.41)	⨁⨁⨁◯ MODERATE b	Not estimable	Not estimable *	1.18 (0.99,1.41)	⨁⨁⨁◯ MODERATE

UC+GNT vs. RVX			2.97 (0.58,15.30)	⨁◯◯◯ VERY LOW ++	2.97 (0.58,15.30)	⨁◯◯◯ VERY LOW
UC+SM vs. RVX			0.50 (0.20,1.25)	⨁◯◯◯ VERY LOW ++	0.50 (0.20,1.25)	⨁◯◯◯ VERY LOW
UC+ST vs. RVX			1.14 (0.86,1.50)	⨁◯◯◯ VERY LOW ++	1.14 (0.86,1.50)	⨁◯◯◯ VERY LOW
UC+WTH vs. RVX			0.58 (0.32,1.04)	⨁⨁⨁◯ MODERATE ++	0.58 (0.32,1.04)	⨁⨁⨁◯ MODERATE
UC+GNT vs. UC	2.50 (0.49,12.50)	⨁◯◯◯ VERY LOW a,b,c,d,h	Not estimable	Not estimable *	2.51 (0.49,12.81)	⨁◯◯◯ VERY LOW
UC+SM vs. UC	0.40 (0.16,1.02)	⨁◯◯◯ VERY LOW a,b,h	Not estimable	Not estimable *	0.42 (0.17,1.04)	⨁◯◯◯ VERY LOW
UC+ST vs. UC	0.96 (0.78,1.19)	⨁◯◯◯ VERY LOW a,b,h	Not estimable	Not estimable *	0.96 (0.78,1.19)	⨁◯◯◯ VERY LOW
UC+WTH vs. UC	0.50 (0.29,0.87)	⨁⨁⨁◯ MODERATE e	Not estimable	Not estimable *	0.49 (0.28,0.86)	⨁⨁⨁◯ MODERATE
UC+SM vs. UC+GNT			0.17 (0.03,1.08)	⨁◯◯◯ VERY LOW ++	0.17 (0.03,1.08)	⨁◯◯◯ VERY LOW
UC+ST vs. UC+GNT			0.38 (0.07,1.98)	⨁◯◯◯ VERY LOW ++	0.38 (0.07,1.98)	⨁◯◯◯ VERY LOW
UC+WTH vs. UC+GNT			0.20 (0.03,1.10)	⨁◯◯◯ VERY LOW ++	0.20 (0.03,1.10)	⨁◯◯◯ VERY LOW
UC+ST vs. UC+SM			2.29 (0.90,5.84)	⨁◯◯◯ VERY LOW ++	2.29 (0.90,5.84)	⨁◯◯◯ VERY LOW
UC+WTH vs. UC+SM			1.17 (0.40,3.40)	⨁◯◯◯ VERY LOW ++	1.17 (0.40,3.40)	⨁◯◯◯ VERY LOW
Major Bleeding						
ASA vs. APX	0.89 (0.58,1.37)	⨁⨁⨁◯ MODERATE b	0.89 (0.26,3.03)	⨁◯◯◯ VERY LOW §	0.89 (0.60,1.34)	⨁⨁⨁◯ MODERATE
ASA+CLP vs. APX			1.53 (1.12,2.08)	⨁⨁◯◯ LOW ++	1.53 (1.12,2.08)	⨁⨁◯◯ LOW
CONTROL vs. APX			0.43 (0.09,2.11)	⨁◯◯◯ VERY LOW ++	0.43 (0.09,2.11)	⨁◯◯◯ VERY LOW
DBG-110MG vs. APX			1.16 (0.95,1.41)	⨁⨁⨁◯ MODERATE ++	1.16 (0.95,1.41)	⨁⨁⨁◯ MODERATE
DBG-150MG vs. APX			1.34 (1.10,1.62)	⨁⨁◯◯ LOW ++	1.34 (1.10,1.62)	⨁⨁◯◯ LOW
EDX-30MG vs. APX			0.69 (0.56,0.84)	⨁⨁⨁◯ MODERATE ++	0.69 (0.56,0.84)	⨁⨁⨁◯ MODERATE
EDX-60MG vs. APX			1.14 (0.94,1.37)	⨁⨁⨁◯ MODERATE ++	1.14 (0.94,1.37)	⨁⨁⨁◯ MODERATE
RVX vs. APX			1.44 (1.19,1.74)	⨁⨁◯◯ LOW ++	1.44 (1.19,1.74)	⨁⨁◯◯ LOW
UC vs. APX	1.43 (1.23,1.64)	⨁⨁⨁◯ MODERATE a	1.42 (0.39,5.18)	⨁◯◯◯ VERY LOW §	1.42 (1.24,1.63)	⨁⨁⨁◯ MODERATE
UC+GNT vs. APX			1.43 (0.03,71.88)	⨁⨁⨁◯ MODERATE ++	1.43 (0.03,71.88)	⨁⨁⨁◯ MODERATE
UC+SM vs. APX			2.89 (0.27,31.18)	⨁⨁◯◯ LOW ++	2.89 (0.27,31.18)	⨁⨁◯◯ LOW
UC+WTH vs. APX			0.92 (0.49,1.70)	⨁⨁⨁◯ MODERATE ++	0.92 (0.49,1.70)	⨁⨁⨁◯ MODERATE
ASA+CLP vs. ASA			1.71 (1.03,2.84)	⨁◯◯◯ VERY LOW ++	1.71 (1.03,2.84)	⨁◯◯◯ VERY LOW
CONTROL vs. ASA			0.48 (0.09,2.48)	⨁◯◯◯ VERY LOW ++	0.48 (0.09,2.48)	⨁◯◯◯ VERY LOW
DBG-110MG vs. ASA			1.30 (0.83,2.03)	⨁◯◯◯ VERY LOW ++	1.30 (0.83,2.03)	⨁◯◯◯ VERY LOW
DBG-150MG vs. ASA			1.50 (0.96,2.33)	⨁◯◯◯ VERY LOW ++	1.50 (0.96,2.33)	⨁◯◯◯ VERY LOW
EDX-30MG vs. ASA			0.77 (0.49,1.20)	⨁◯◯◯ VERY LOW ++	0.77 (0.49,1.20)	⨁◯◯◯ VERY LOW
EDX-60MG vs. ASA			1.28	⨁◯◯◯	1.28 (0.82,1.98)	⨁◯◯◯

			(0.82,1.98)	VERY LOW ++		VERY LOW
RVX vs. ASA			1.62 (1.04,2.52)	⨁◯◯◯ VERY LOW ++	1.62 (1.04,2.52)	⨁◯◯◯ VERY LOW
UC vs. ASA	1.54 (0.56,4.20)	⨁◯◯◯ VERY LOW a,b,d,f,g	1.60 (1.02,2.50)	⨁⨁⨁◯ MODERATE ¶	1.60 (1.05,2.43)	⨁⨁⨁◯ MODERATE
UC+GNT vs. ASA			1.60 (0.03,82.26)	⨁◯◯◯ VERY LOW ++	1.60 (0.03,82.26)	⨁◯◯◯ VERY LOW
UC+SM vs. ASA			3.25 (0.29,36.15)	⨁◯◯◯ VERY LOW ++	3.25 (0.29,36.15)	⨁◯◯◯ VERY LOW
UC+WTH vs. ASA			1.03 (0.49,2.15)	⨁◯◯◯ VERY LOW ++	1.03 (0.49,2.15)	⨁◯◯◯ VERY LOW
CONTROL vs. ASA+CLP			0.28 (0.06,1.41)	⨁◯◯◯ VERY LOW ++	0.28 (0.06,1.41)	⨁◯◯◯ VERY LOW
DBG-110MG vs. ASA+CLP			0.76 (0.55,1.03)	⨁⨁◯◯ LOW ++	0.76 (0.55,1.03)	⨁⨁◯◯ LOW
DBG-150MG vs. ASA+CLP			0.87 (0.64,1.19)	⨁⨁◯◯ LOW ++	0.87 (0.64,1.19)	⨁⨁◯◯ LOW
EDX-30MG vs. ASA+CLP			0.45 (0.33,0.62)	⨁⨁◯◯ LOW ++	0.45 (0.33,0.62)	⨁⨁◯◯ LOW
EDX-60MG vs. ASA+CLP			0.74 (0.55,1.01)	⨁⨁◯◯ LOW ++	0.74 (0.55,1.01)	⨁⨁◯◯ LOW
RVX vs. ASA+CLP			0.94 (0.69,1.28)	⨁⨁◯◯ LOW ++	0.94 (0.69,1.28)	⨁⨁◯◯ LOW
UC vs. ASA+CLP	0.93 (0.70,1.23)	⨁⨁◯◯ LOW a,b	Not estimable	Not estimable *	0.93 (0.71,1.23)	⨁⨁◯◯ LOW
UC+GNT vs. ASA+CLP			0.93 (0.02,47.37)	⨁⨁◯◯ LOW ++	0.93 (0.02,47.37)	⨁⨁◯◯ LOW
UC+SM vs. ASA+CLP			1.89 (0.17,20.65)	⨁⨁◯◯ LOW ++	1.89 (0.17,20.65)	⨁⨁◯◯ LOW
UC+WTH vs. ASA+CLP			0.60 (0.31,1.16)	⨁⨁◯◯ LOW ++	0.60 (0.31,1.16)	⨁⨁◯◯ LOW
DBG-110MG vs. CONTROL			2.72 (0.55,13.46)	⨁◯◯◯ VERY LOW ++	2.72 (0.55,13.46)	⨁◯◯◯ VERY LOW
DBG-150MG vs. CONTROL			3.14 (0.63,15.54)	⨁◯◯◯ VERY LOW ++	3.14 (0.63,15.54)	⨁◯◯◯ VERY LOW
EDX-30MG vs. CONTROL			1.61 (0.33,8.00)	⨁◯◯◯ VERY LOW ++	1.61 (0.33,8.00)	⨁◯◯◯ VERY LOW
EDX-60MG vs. CONTROL			2.67 (0.54,13.21)	⨁◯◯◯ VERY LOW ++	2.67 (0.54,13.21)	⨁◯◯◯ VERY LOW
RVX vs. CONTROL			3.39 (0.68,16.76)	⨁◯◯◯ VERY LOW ++	3.39 (0.68,16.76)	⨁◯◯◯ VERY LOW
UC vs. CONTROL	3.34 (0.68,16.45)	⨁◯◯◯ VERY LOW a,b,c,d	Not estimable	Not estimable *	3.34 (0.68,16.45)	⨁◯◯◯ VERY LOW
UC+GNT vs. CONTROL			3.36 (0.05,230.02)	⨁◯◯◯ VERY LOW ++	3.36 (0.05,230.02)	⨁◯◯◯ VERY LOW
UC+SM vs. CONTROL			6.80 (0.39,118.51)	⨁◯◯◯ VERY LOW ++	6.80 (0.39,118.51)	⨁◯◯◯ VERY LOW
UC+WTH vs. CONTROL			2.15 (0.39,11.83)	⨁◯◯◯ VERY LOW ++	2.15 (0.39,11.83)	⨁◯◯◯ VERY LOW
DBG-150MG vs. DBG-110MG	1.15 (1.00,1.33)	⨁⨁◯◯ LOW a,b	0.05 (0.00,17.53)	⨁⨁◯◯ LOW §	1.15 (1.00,1.33)	⨁⨁◯◯ LOW
EDX-30MG vs. DBG-110MG			0.59 (0.48,0.73)	⨁⨁⨁◯ MODERATE ++	0.59 (0.48,0.73)	⨁⨁⨁◯ MODERATE
EDX-60MG vs. DBG-110MG			0.98 (0.81,1.19)	⨁⨁⨁◯ MODERATE ++	0.98 (0.81,1.19)	⨁⨁⨁◯ MODERATE
RVX vs. DBG-110MG			1.25 (1.03,1.51)	⨁⨁◯◯ LOW ++	1.25 (1.03,1.51)	⨁⨁◯◯ LOW
UC vs. DBG-110MG	1.23 (1.06,1.43)	⨁⨁⨁◯ MODERATE a	0.07 (0.00,24.90)	⨁⨁◯◯ LOW §	1.23 (1.07,1.42)	⨁⨁⨁◯ MODERATE
UC+GNT vs. DBG-110MG			1.24 (0.02,62.14)	⨁⨁⨁◯ MODERATE ++	1.24 (0.02,62.14)	⨁⨁⨁◯ MODERATE

UC+SM vs. DBG-110MG			2.50 (0.23,26.96)	⨁⨁◯◯ LOW ++	2.50 (0.23,26.96)	⨁⨁◯◯ LOW
UC+WTH vs. DBG-110MG			0.79 (0.43,1.47)	⨁⨁⨁◯ MODERATE ++	0.79 (0.43,1.47)	⨁⨁⨁◯ MODERATE
EDX-30MG vs. DBG-150MG			0.51 (0.42,0.63)	⨁⨁◯◯ LOW ++	0.51 (0.42,0.63)	⨁⨁◯◯ LOW
EDX-60MG vs. DBG-150MG			0.85 (0.71,1.02)	⨁⨁◯◯ LOW ++	0.85 (0.71,1.02)	⨁⨁◯◯ LOW
RVX vs. DBG-150MG			1.08 (0.89,1.30)	⨁⨁◯◯ LOW ++	1.08 (0.89,1.30)	⨁⨁◯◯ LOW
UC vs. DBG-150MG	1.06 (0.93,1.22)	⨁⨁◯◯ LOW a,b	1.06 (0.93,1.22)	⨁⨁◯◯ LOW §	1.06 (0.93,1.22)	⨁⨁◯◯ LOW
UC+GNT vs. DBG-150MG			1.07 (0.02,53.80)	⨁⨁◯◯ LOW ++	1.07 (0.02,53.80)	⨁⨁◯◯ LOW
UC+SM vs. DBG-150MG			2.17 (0.20,23.33)	⨁⨁◯◯ LOW ++	2.17 (0.20,23.33)	⨁⨁◯◯ LOW
UC+WTH vs. DBG-150MG			0.69 (0.37,1.27)	⨁⨁◯◯ LOW ++	0.69 (0.37,1.27)	⨁⨁◯◯ LOW
EDX-60MG vs. EDX-30MG	1.67 (1.43,1.92)	⨁⨁⨁◯ MODERATE a	1.65 (1.42,1.92)	⨁⨁⨁◯ MODERATE ¶	1.65 (1.42,1.92)	⨁⨁⨁◯ MODERATE
RVX vs. EDX-30MG			2.10 (1.72,2.55)	⨁⨁◯◯ LOW ++	2.10 (1.72,2.55)	⨁⨁◯◯ LOW
UC vs. EDX-30MG	2.08 (1.79,2.38)	⨁⨁⨁◯ MODERATE a	2.07 (1.79,2.39)	⨁⨁⨁◯ MODERATE ¶	2.07 (1.79,2.39)	⨁⨁⨁◯ MODERATE
UC+GNT vs. EDX-30MG			2.08 (0.04,104.57)	⨁⨁⨁◯ MODERATE ++	2.08 (0.04,104.57)	⨁⨁⨁◯ MODERATE
UC+SM vs. EDX-30MG			4.21 (0.39,45.37)	⨁⨁◯◯ LOW ++	4.21 (0.39,45.37)	⨁⨁◯◯ LOW
UC+WTH vs. EDX-30MG			1.33 (0.72,2.48)	⨁⨁⨁◯ MODERATE ++	1.33 (0.72,2.48)	⨁⨁⨁◯ MODERATE
RVX vs. EDX-60MG			1.27 (1.06,1.52)	⨁⨁◯◯ LOW ++	1.27 (1.06,1.52)	⨁⨁◯◯ LOW
UC vs. EDX-60MG	1.25 (1.10,1.41)	⨁⨁⨁◯ MODERATE a	1.25 (1.11,1.42)	⨁⨁⨁◯ MODERATE ¶	1.25 (1.11,1.42)	⨁⨁⨁◯ MODERATE
UC+GNT vs. EDX-60MG			1.26 (0.02,63.19)	⨁⨁⨁◯ MODERATE ++	1.26 (0.02,63.19)	⨁⨁⨁◯ MODERATE
UC+SM vs. EDX-60MG			2.55 (0.24,27.40)	⨁⨁◯◯ LOW ++	2.55 (0.24,27.40)	⨁⨁◯◯ LOW
UC+WTH vs. EDX-60MG			0.81 (0.44,1.49)	⨁⨁⨁◯ MODERATE ++	0.81 (0.44,1.49)	⨁⨁⨁◯ MODERATE
UC vs. RVX	1.00 (0.88,1.14)	⨁⨁◯◯ LOW a,b	Not estimable	Not estimable *	0.99 (0.87,1.12)	⨁⨁◯◯ LOW
UC+GNT vs. RVX			0.99 (0.02,49.83)	⨁⨁◯◯ LOW ++	0.99 (0.02,49.83)	⨁⨁◯◯ LOW
UC+SM vs. RVX			2.01 (0.19,21.61)	⨁⨁◯◯ LOW ++	2.01 (0.19,21.61)	⨁⨁◯◯ LOW
UC+WTH vs. RVX			0.64 (0.34,1.18)	⨁⨁◯◯ LOW ++	0.64 (0.34,1.18)	⨁⨁◯◯ LOW
UC+SM vs. UC	2.04 (0.19,1.18)	⨁⨁◯◯ LOW a,b,d	Not estimable	Not estimable *	2.03 (0.19,21.83)	⨁⨁◯◯ LOW
UC+WTH vs. UC	0.65 (0.35,1.18)	⨁⨁⨁◯ MODERATE a	Not estimable	Not estimable *	0.64 (0.35,1.18)	⨁⨁⨁◯ MODERATE
UC+SM vs. UC+GNT			2.03 (0.02,197.24)	⨁⨁◯◯ LOW ++	2.03 (0.02,197.24)	⨁⨁◯◯ LOW
UC+WTH vs. UC+GNT			0.64 (0.01,33.70)	⨁⨁⨁◯ MODERATE ++	0.64 (0.01,33.70)	⨁⨁⨁◯ MODERATE
UC+WTH vs. UC+SM			0.32 (0.03,3.66)	⨁⨁◯◯ LOW ++	0.32 (0.03,3.66)	⨁⨁◯◯ LOW
Ischemic Stroke						
ASA vs. APX	2.70 (1.82,3.85)	⨁⨁⨁⨁ HIGH	3.28 (1.86,5.78)	⨁⨁◯◯ LOW §	2.85 (2.07,3.92)	⨁⨁⨁⨁ HIGH
ASA+CLP vs. APX			2.28	⨁⨁◯◯	2.28 (1.51,3.45)	⨁⨁◯◯

			(1.51,3.45)	LOW ↔		LOW
CONTROL vs. APX			3.08 (1.88,5.04)	⨁⨁◯◯ LOW ↔	3.08 (1.88,5.04)	⨁⨁◯◯ LOW
DBG-110MG vs. APX			1.21 (0.89,1.63)	⨁⨁◯◯ LOW ↔	1.21 (0.89,1.63)	⨁⨁◯◯ LOW
DBG-150MG vs. APX			0.83 (0.61,1.14)	⨁⨁◯◯ LOW ↔	0.83 (0.61,1.14)	⨁⨁◯◯ LOW
EDX-30MG vs. APX			1.52 (1.18,1.98)	⨁⨁◯◯ LOW ↔	1.52 (1.18,1.98)	⨁⨁◯◯ LOW
EDX-60MG vs. APX			1.08 (0.83,1.41)	⨁⨁◯◯ LOW ↔	1.08 (0.83,1.41)	⨁⨁◯◯ LOW
RVX vs. APX			0.94 (0.71,1.24)	⨁⨁◯◯ LOW ↔	0.94 (0.71,1.24)	⨁⨁◯◯ LOW
UC vs. APX	1.10 (0.89,1.35)	⨁⨁◯◯ LOW [a,b]	0.89 (0.47,1.72)	⨁⨁◯◯ LOW §	1.08 (0.88,1.31)	⨁⨁◯◯ LOW
UC+WTH vs. APX			1.46 (0.72,2.98)	⨁⨁◯◯ LOW ↔	1.46 (0.72,2.98)	⨁⨁◯◯ LOW
ASA+CLP vs. ASA			0.80 (0.49,1.31)	⨁⨁◯◯ LOW ↔	0.80 (0.49,1.31)	⨁⨁◯◯ LOW
CONTROL vs. ASA			1.08 (0.62,1.89)	⨁⨁◯◯ LOW ↔	1.08 (0.62,1.89)	⨁⨁◯◯ LOW
DBG-110MG vs. ASA			0.42 (0.28,0.63)	⨁⨁◯◯ LOW ↔	0.42 (0.28,0.63)	⨁⨁◯◯ LOW
DBG-150MG vs. ASA			0.29 (0.19,0.44)	⨁⨁◯◯ LOW ↔	0.29 (0.19,0.44)	⨁⨁◯◯ LOW
EDX-30MG vs. ASA			0.53 (0.37,0.78)	⨁⨁◯◯ LOW ↔	0.53 (0.37,0.78)	⨁⨁◯◯ LOW
EDX-60MG vs. ASA			0.38 (0.26,0.55)	⨁⨁◯◯ LOW ↔	0.38 (0.26,0.55)	⨁⨁◯◯ LOW
RVX vs. ASA			0.33 (0.22,0.48)	⨁⨁◯◯ LOW ↔	0.33 (0.22,0.48)	⨁⨁◯◯ LOW
UC vs. ASA	0.32 (0.19,0.53)	⨁⨁◯◯ LOW [a,e,f]	0.41 (0.26,0.64)	⨁⨁◯◯ LOW §	0.38 (0.27,0.53)	⨁⨁◯◯ LOW
UC+WTH vs. ASA			0.51 (0.24,1.10)	⨁⨁◯◯ LOW ↔	0.51 (0.24,1.10)	⨁⨁◯◯ LOW
CONTROL vs. ASA+CLP			1.35 (0.76,2.41)	⨁⨁⨁◯ MODERATE ↔	1.35 (0.76,2.41)	⨁⨁⨁◯ MODERATE
DBG-110MG vs. ASA+CLP			0.53 (0.35,0.81)	⨁⨁◯◯ LOW ↔	0.53 (0.35,0.81)	⨁⨁◯◯ LOW
DBG-150MG vs. ASA+CLP			0.37 (0.24,0.57)	⨁⨁⨁◯ MODERATE ↔	0.37 (0.24,0.57)	⨁⨁⨁◯ MODERATE
EDX-30MG vs. ASA+CLP			0.67 (0.45,1.00)	⨁⨁⨁◯ MODERATE ↔	0.67 (0.45,1.00)	⨁⨁⨁◯ MODERATE
EDX-60MG vs. ASA+CLP			0.47 (0.32,0.71)	⨁⨁⨁◯ MODERATE ↔	0.47 (0.32,0.71)	⨁⨁⨁◯ MODERATE
RVX vs. ASA+CLP			0.41 (0.27,0.62)	⨁⨁◯◯ LOW ↔	0.41 (0.27,0.62)	⨁⨁◯◯ LOW
UC vs. ASA+CLP	0.47 (0.33,0.68)	⨁⨁⨁◯ MODERATE [a]	Not estimable	Not estimable *	0.47 (0.33,0.68)	⨁⨁⨁◯ MODERATE
UC+WTH vs. ASA+CLP			0.64 (0.30,1.39)	⨁⨁⨁◯ MODERATE ↔	0.64 (0.30,1.39)	⨁⨁⨁◯ MODERATE
DBG-110MG vs. CONTROL			0.39 (0.24,0.65)	⨁⨁◯◯ LOW ↔	0.39 (0.24,0.65)	⨁⨁◯◯ LOW
DBG-150MG vs. CONTROL			0.27 (0.16,0.45)	⨁⨁⨁◯ MODERATE ↔	0.27 (0.16,0.45)	⨁⨁⨁◯ MODERATE
EDX-30MG vs. CONTROL			0.49 (0.31,0.80)	⨁⨁⨁◯ MODERATE ↔	0.49 (0.31,0.80)	⨁⨁⨁◯ MODERATE
EDX-60MG vs. CONTROL			0.35 (0.22,0.57)	⨁⨁⨁◯ MODERATE ↔	0.35 (0.22,0.57)	⨁⨁⨁◯ MODERATE
RVX vs. CONTROL			0.30 (0.19,0.50)	⨁⨁◯◯ LOW ↔	0.30 (0.19,0.50)	⨁⨁◯◯ LOW
UC vs. CONTROL	0.35	⨁⨁⨁◯	Not estimable	Not estimable *	0.35 (0.22,0.55)	⨁⨁⨁◯

	(0.22,0.55)	MODERATE [a]				MODERATE
UC+WTH vs. CONTROL			0.47 (0.21,1.08)	⊕⊕⊕◯ MODERATE [++]	0.47 (0.21,1.08)	⊕⊕⊕◯ MODERATE
DBG-150MG vs. DBG-110MG	0.69 (0.54,0.88)	⊕⊕⊕◯ MODERATE [a]	0.69 (0.54,0.88)	⊕⊕◯◯ LOW [§]	0.69 (0.54,0.88)	⊕⊕⊕◯ MODERATE
EDX-30MG vs. DBG-110MG			1.26 (0.96,1.67)	⊕⊕◯◯ LOW [++]	1.26 (0.96,1.67)	⊕⊕◯◯ LOW
EDX-60MG vs. DBG-110MG			0.90 (0.67,1.19)	⊕⊕◯◯ LOW [++]	0.90 (0.67,1.19)	⊕⊕◯◯ LOW
RVX vs. DBG-110MG			0.78 (0.58,1.04)	⊕⊕◯◯ LOW [++]	0.78 (0.58,1.04)	⊕⊕◯◯ LOW
UC vs. DBG-110MG	0.89 (0.71,1.11)	⊕⊕◯◯ LOW [a,b]	0.89 (0.71,1.12)	⊕⊕⊕◯ MODERATE [¶]	0.89 (0.71,1.12)	⊕⊕⊕◯ MODERATE
UC+WTH vs. DBG-110MG			1.21 (0.59,2.49)	⊕⊕◯◯ LOW [++]	1.21 (0.59,2.49)	⊕⊕◯◯ LOW
EDX-30MG vs. DBG-150MG			1.83 (1.36,2.46)	⊕⊕⊕◯ MODERATE [++]	1.83 (1.36,2.46)	⊕⊕⊕◯ MODERATE
EDX-60MG vs. DBG-150MG			1.30 (0.96,1.76)	⊕⊕⊕◯ MODERATE [++]	1.30 (0.96,1.76)	⊕⊕⊕◯ MODERATE
RVX vs. DBG-150MG			1.13 (0.83,1.53)	⊕⊕◯◯ LOW [++]	1.13 (0.83,1.53)	⊕⊕◯◯ LOW
UC vs. DBG-150MG	1.28 (1.01,1.64)	⊕⊕⊕◯ MODERATE [a]	1.29 (1.01,1.65)	⊕⊕◯◯ LOW [§]	1.29 (1.01,1.65)	⊕⊕⊕◯ MODERATE
UC+WTH vs. DBG-150MG			1.75 (0.85,3.63)	⊕⊕⊕◯ MODERATE [++]	1.75 (0.85,3.63)	⊕⊕⊕◯ MODERATE
EDX-60MG vs. EDX-30MG	0.71 (0.60,0.83)	⊕⊕⊕⊕ HIGH	0.71 (0.60,0.83)	⊕⊕⊕◯ MODERATE [¶]	0.71 (0.60,0.83)	⊕⊕⊕⊕ HIGH
RVX vs. EDX-30MG			0.62 (0.48,0.79)	⊕⊕◯◯ LOW [++]	0.62 (0.48,0.79)	⊕⊕◯◯ LOW
UC vs. EDX-30MG	0.70 (0.60,0.83)	⊕⊕⊕⊕ HIGH	0.71 (0.60,0.83)	⊕⊕⊕◯ MODERATE [¶]	0.71 (0.60,0.83)	⊕⊕⊕⊕ HIGH
UC+WTH vs. EDX-30MG			0.96 (0.48,1.94)	⊕⊕⊕◯ MODERATE [++]	0.96 (0.48,1.94)	⊕⊕⊕◯ MODERATE
RVX vs. EDX-60MG			0.87 (0.67,1.13)	⊕⊕◯◯ LOW [++]	0.87 (0.67,1.13)	⊕⊕◯◯ LOW
UC vs. EDX-60MG	1.00 (0.83,1.19)	⊕⊕⊕◯ MODERATE [b]	1.00 (0.83,1.19)	⊕⊕⊕⊕ HIGH [¶]	1.00 (0.83,1.19)	⊕⊕⊕⊕ HIGH
UC+WTH vs. EDX-60MG			1.35 (0.67,2.74)	⊕⊕⊕◯ MODERATE [++]	1.35 (0.67,2.74)	⊕⊕⊕◯ MODERATE
UC vs. RVX	1.15 (0.95,1.39)	⊕⊕◯◯ LOW [a,b]	Not estimable	Not estimable *	1.15 (0.95,1.39)	⊕⊕◯◯ LOW
UC+WTH vs. RVX			1.56 (0.77,3.17)	⊕⊕◯◯ LOW [++]	1.56 (0.77,3.17)	⊕⊕◯◯ LOW
UC+WTH vs. UC	1.39 (0.70,2.70)	⊕⊕⊕◯ MODERATE [a]	Not estimable	Not estimable *	1.36 (0.69,2.69)	⊕⊕⊕◯ MODERATE
Clinically relevant non-major bleeding						
ASA vs. APX	0.88 (0.66,1.18)	⊕⊕⊕⊕ HIGH	Not estimable	Not estimable *	0.88 (0.66,1.17)	⊕⊕⊕⊕ HIGH
CONTROL vs. APX			0.49 (0.05,4.65)	⊕⊕◯◯ LOW [++]	0.49 (0.05,4.65)	⊕⊕◯◯ LOW
DBG-110MG vs. APX			0.74 (0.16,3.46)	⊕⊕◯◯ LOW [++]	0.74 (0.16,3.46)	⊕⊕◯◯ LOW
DBG-150MG vs. APX			1.65 (0.73,3.72)	⊕⊕⊕◯ MODERATE [++]	1.65 (0.73,3.72)	⊕⊕⊕◯ MODERATE
EDX-30MG vs. APX			1.02 (0.86,1.20)	⊕⊕⊕◯ MODERATE [++]	1.02 (0.86,1.20)	⊕⊕⊕◯ MODERATE
EDX-60MG vs. APX			1.28 (1.09,1.51)	⊕⊕⊕◯ MODERATE [++]	1.28 (1.09,1.51)	⊕⊕⊕◯ MODERATE
RVX vs. APX			1.52 (1.29,1.79)	⊕⊕⊕◯ MODERATE [++]	1.52 (1.29,1.79)	⊕⊕⊕◯ MODERATE
UC vs. APX	1.47 (1.27,1.69)	⊕⊕⊕◯ MODERATE [a]	Not estimable	Not estimable *	1.46 (1.26,1.70)	⊕⊕⊕◯ MODERATE

CONTROL vs. ASA			0.55 (0.06,5.38)	⨁⨁◯◯ LOW ↔	0.55 (0.06,5.38)	⨁⨁◯◯ LOW
DBG-110MG vs. ASA			0.84 (0.18,4.03)	⨁⨁◯◯ LOW ↔	0.84 (0.18,4.03)	⨁⨁◯◯ LOW
DBG-150MG vs. ASA			1.88 (0.79,4.45)	⨁⨁⨁◯ MODERATE ↔	1.88 (0.79,4.45)	⨁⨁⨁◯ MODERATE
EDX-30MG vs. ASA			1.16 (0.83,1.61)	⨁⨁⨁◯ MODERATE ↔	1.16 (0.83,1.61)	⨁⨁⨁◯ MODERATE
EDX-60MG vs. ASA			1.45 (1.04,2.02)	⨁⨁⨁◯ MODERATE ↔	1.45 (1.04,2.02)	⨁⨁⨁◯ MODERATE
RVX vs. ASA			1.73 (1.24,2.41)	⨁⨁⨁◯ MODERATE ↔	1.73 (1.24,2.41)	⨁⨁⨁◯ MODERATE
UC vs. ASA			1.66 (1.20,2.30)	⨁⨁⨁◯ MODERATE ↔	1.66 (1.20,2.30)	⨁⨁⨁◯ MODERATE
DBG-110MG vs. CONTROL			1.53 (0.10,23.33)	⨁⨁◯◯ LOW ↔	1.53 (0.10,23.33)	⨁⨁◯◯ LOW
DBG-150MG vs. CONTROL			3.40 (0.31,37.22)	⨁⨁◯◯ LOW ↔	3.40 (0.31,37.22)	⨁⨁◯◯ LOW
EDX-30MG vs. CONTROL			2.10 (0.22,20.01)	⨁⨁◯◯ LOW ↔	2.10 (0.22,20.01)	⨁⨁◯◯ LOW
EDX-60MG vs. CONTROL			2.63 (0.28,25.15)	⨁⨁◯◯ LOW ↔	2.63 (0.28,25.15)	⨁⨁◯◯ LOW
RVX vs. CONTROL			3.13 (0.33,29.88)	⨁⨁◯◯ LOW ↔	3.13 (0.33,29.88)	⨁⨁◯◯ LOW
UC vs. CONTROL	3.03 (0.32,25.00)	⨁⨁◯◯ LOW [a,c,d]	Not estimable	Not estimable *	3.01 (0.32,28.74)	⨁⨁◯◯ LOW
DBG-150MG vs. DBG-110MG	2.00 (0.4,10.0)	⨁⨁◯◯ LOW [a,d]	4.63 (0.20,109.95)	⨁⨁◯◯ LOW §	2.23 (0.48,10.30)	⨁⨁◯◯ LOW
EDX-30MG vs. DBG-110MG			1.37 (0.30,6.35)	⨁⨁◯◯ LOW ↔	1.37 (0.30,6.35)	⨁⨁◯◯ LOW
EDX-60MG vs. DBG-110MG			1.72 (0.37,7.98)	⨁⨁◯◯ LOW ↔	1.72 (0.37,7.98)	⨁⨁◯◯ LOW
RVX vs. DBG-110MG			2.05 (0.44,9.48)	⨁⨁◯◯ LOW ↔	2.05 (0.44,9.48)	⨁⨁◯◯ LOW
UC vs. DBG-110MG	2.22 (0.45,11.10)	⨁⨁◯◯ LOW [a,d]	0.95 (0.04,22.54)	⨁⨁◯◯ LOW §	1.97 (0.43,9.12)	⨁⨁◯◯ LOW
EDX-30MG vs. DBG-150MG			0.62 (0.28,1.37)	⨁⨁⨁◯ MODERATE ↔	0.62 (0.28,1.37)	⨁⨁⨁◯ MODERATE
EDX-60MG vs. DBG-150MG			0.77 (0.35,1.73)	⨁⨁⨁◯ MODERATE ↔	0.77 (0.35,1.73)	⨁⨁⨁◯ MODERATE
RVX vs. DBG-150MG			0.92 (0.41,2.05)	⨁⨁⨁◯ MODERATE ↔	0.92 (0.41,2.05)	⨁⨁⨁◯ MODERATE
UC vs. DBG-150MG	0.88 (0.40,1.92)	⨁⨁⨁◯ MODERATE [a]	0.89 (0.40,1.97)	⨁⨁◯◯ LOW §	0.89 (0.40,1.97)	⨁⨁⨁◯ MODERATE
EDX-60MG vs. EDX-30MG	1.27 (1.16,1.37)	⨁⨁⨁◯ MODERATE [a]	1.26 (1.16,1.36)	⨁⨁⨁◯ MODERATE ¶	1.26 (1.16,1.36)	⨁⨁⨁◯ MODERATE
RVX vs. EDX-30MG			1.49 (1.35,1.66)	⨁⨁⨁◯ MODERATE ↔	1.49 (1.35,1.66)	⨁⨁⨁◯ MODERATE
UC vs. EDX-30MG	1.45 (1.33,1.56)	⨁⨁⨁◯ MODERATE [a]	1.44 (1.33,1.55)	⨁⨁⨁◯ MODERATE ¶	1.44 (1.33,1.55)	⨁⨁⨁◯ MODERATE
RVX vs. EDX-60MG			1.19 (1.08,1.31)	⨁⨁⨁◯ MODERATE ↔	1.19 (1.08,1.31)	⨁⨁⨁◯ MODERATE
UC vs. EDX-60MG	1.14 (1.06,1.22)	⨁⨁⨁◯ MODERATE [a]	1.14 (1.07,1.23)	⨁⨁⨁◯ MODERATE ¶	1.14 (1.07,1.23)	⨁⨁⨁◯ MODERATE
UC vs. RVX	0.96 (0.89,1.03)	⨁⨁⨁◯ MODERATE [a]	Not estimable	Not estimable *	0.96 (0.90,1.03)	⨁⨁⨁◯ MODERATE
Intracranial bleeding						
ASA vs. APX	1.19 (0.53,2.63)	⨁⨁⨁◯ MODERATE [b,c]	1.91 (0.70,5.24)	⨁◯◯◯ VERY LOW §	1.47 (0.76,2.83)	⨁⨁⨁◯ MODERATE
ASA+CLP vs. APX			1.17 (0.46,2.97)	⨁⨁◯◯ LOW ↔	1.17 (0.46,2.97)	⨁⨁◯◯ LOW

CONTROL vs. APX			1.29 (0.41,4.08)	⨁⨁◯◯ LOW ++	1.29 (0.41,4.08)	⨁⨁◯◯ LOW
DBG-110MG vs. APX			0.70 (0.34,1.45)	⨁⨁◯◯ LOW ++	0.70 (0.34,1.45)	⨁⨁◯◯ LOW
DBG-150MG vs. APX			0.93 (0.46,1.86)	⨁⨁◯◯ LOW ++	0.93 (0.46,1.86)	⨁⨁◯◯ LOW
EDX-30MG vs. APX			0.71 (0.36,1.39)	⨁⨁◯◯ LOW ++	0.71 (0.36,1.39)	⨁⨁◯◯ LOW
EDX-60MG vs. APX			1.09 (0.57,2.08)	⨁⨁◯◯ LOW ++	1.09 (0.57,2.08)	⨁⨁◯◯ LOW
RVX vs. APX			1.72 (0.96,3.07)	⨁⨁◯◯ LOW ++	1.72 (0.96,3.07)	⨁⨁◯◯ LOW
UC vs. APX	2.38 (1.72,3.23)	⨁⨁◯◯ LOW a,c	1.50 (0.43,5.22)	⨁◯◯◯ VERY LOW §	2.26 (1.43,3.55)	⨁⨁◯◯ LOW
UC+SM vs. APX			2.25 (0.29,17.30)	⨁◯◯◯ VERY LOW ++	2.25 (0.29,17.30)	⨁◯◯◯ VERY LOW
UC+ST vs. APX			3.09 (1.05,9.07)	⨁◯◯◯ VERY LOW ++	3.09 (1.05,9.07)	⨁◯◯◯ VERY LOW
UC+WTH vs. APX			0.50 (0.13,1.85)	⨁⨁◯◯ LOW ++	0.50 (0.13,1.85)	⨁⨁◯◯ LOW
ASA+CLP vs. ASA			0.80 (0.28,2.27)	⨁⨁◯◯ LOW ++	0.80 (0.28,2.27)	⨁⨁◯◯ LOW
CONTROL vs. ASA	0.48 (0.09,2.60)	⨁⨁◯◯ LOW a,b,d	1.40 (0.31,6.38)	⨁◯◯◯ VERY LOW §	0.88 (0.28,2.75)	⨁⨁◯◯ LOW
DBG-110MG vs. ASA			0.48 (0.20,1.14)	⨁◯◯◯ VERY LOW ++	0.48 (0.20,1.14)	⨁◯◯◯ VERY LOW
DBG-150MG vs. ASA			0.63 (0.27,1.47)	⨁◯◯◯ VERY LOW ++	0.63 (0.27,1.47)	⨁◯◯◯ VERY LOW
EDX-30MG vs. ASA			0.48 (0.21,1.10)	⨁◯◯◯ VERY LOW ++	0.48 (0.21,1.10)	⨁◯◯◯ VERY LOW
EDX-60MG vs. ASA			0.74 (0.33,1.65)	⨁◯◯◯ VERY LOW ++	0.74 (0.33,1.65)	⨁◯◯◯ VERY LOW
RVX vs. ASA			1.17 (0.55,2.48)	⨁◯◯◯ VERY LOW ++	1.17 (0.55,2.48)	⨁◯◯◯ VERY LOW
UC vs. ASA	1.49 (0.60,3.70)	⨁◯◯◯ VERY LOW a,b,c,f,g	1.61 (0.62,4.19)	⨁⨁◯◯ LOW §	1.54 (0.80,2.96)	⨁⨁◯◯ LOW
UC+SM vs. ASA			1.53 (0.19,12.45)	⨁◯◯◯ VERY LOW ++	1.53 (0.19,12.45)	⨁◯◯◯ VERY LOW
UC+ST vs. ASA			2.10 (0.65,6.83)	⨁◯◯◯ VERY LOW ++	2.10 (0.65,6.83)	⨁◯◯◯ VERY LOW
UC+WTH vs. ASA			0.34 (0.08,1.37)	⨁◯◯◯ VERY LOW ++	0.34 (0.08,1.37)	⨁◯◯◯ VERY LOW
CONTROL vs. ASA+CLP			1.10 (0.28,4.32)	⨁⨁◯◯ LOW ++	1.10 (0.28,4.32)	⨁⨁◯◯ LOW
DBG-110MG vs. ASA+CLP			0.60 (0.22,1.62)	⨁⨁◯◯ LOW ++	0.60 (0.22,1.62)	⨁⨁◯◯ LOW
DBG-150MG vs. ASA+CLP			0.79 (0.30,2.09)	⨁⨁◯◯ LOW ++	0.79 (0.30,2.09)	⨁⨁◯◯ LOW
EDX-30MG vs. ASA+CLP			0.61 (0.23,1.58)	⨁⨁◯◯ LOW ++	0.61 (0.23,1.58)	⨁⨁◯◯ LOW
EDX-60MG vs. ASA+CLP			0.93 (0.36,2.39)	⨁⨁◯◯ LOW ++	0.93 (0.36,2.39)	⨁⨁◯◯ LOW
RVX vs. ASA+CLP			1.47 (0.60,3.57)	⨁⨁◯◯ LOW ++	1.47 (0.60,3.57)	⨁⨁◯◯ LOW
UC vs. ASA+CLP	1.92 (0.93,4.00)	⨁⨁◯◯ LOW a,b,c	1.93 (0.85,4.36)	⨁◯◯◯ VERY LOW §	1.93 (0.85,4.36)	⨁⨁◯◯ LOW
UC+SM vs. ASA+CLP			1.92 (0.22,16.51)	⨁◯◯◯ VERY LOW ++	1.92 (0.22,16.51)	⨁◯◯◯ VERY LOW
UC+ST vs. ASA+CLP			2.64 (0.74,9.43)	⨁◯◯◯ VERY LOW ++	2.64 (0.74,9.43)	⨁◯◯◯ VERY LOW
UC+WTH vs. ASA+CLP			0.43 (0.10,1.87)	⨁⨁◯◯ LOW ++	0.43 (0.10,1.87)	⨁⨁◯◯ LOW

DBG-110MG vs. CONTROL			0.54 (0.16,1.87)	⊕⊕◯◯ LOW ++	0.54 (0.16,1.87)	⊕⊕◯◯ LOW
DBG-150MG vs. CONTROL			0.72 (0.21,2.43)	⊕⊕◯◯ LOW ++	0.72 (0.21,2.43)	⊕⊕◯◯ LOW
EDX-30MG vs. CONTROL			0.55 (0.17,1.84)	⊕⊕◯◯ LOW ++	0.55 (0.17,1.84)	⊕⊕◯◯ LOW
EDX-60MG vs. CONTROL			0.84 (0.26,2.78)	⊕⊕◯◯ LOW ++	0.84 (0.26,2.78)	⊕⊕◯◯ LOW
RVX vs. CONTROL			1.33 (0.42,4.23)	⊕⊕◯◯ LOW ++	1.33 (0.42,4.23)	⊕⊕◯◯ LOW
UC vs. CONTROL	1.20 (0.38,4.20)	⊕⊕◯◯ LOW a,b,c	3.53 (0.55,22.67)	⊕◯◯◯ VERY LOW §	1.75 (0.59,5.25)	⊕⊕◯◯ LOW
UC+SM vs. CONTROL			1.75 (0.18,16.93)	⊕◯◯◯ VERY LOW ++	1.75 (0.18,16.93)	⊕◯◯◯ VERY LOW
UC+ST vs. CONTROL			2.40 (0.55,10.42)	⊕◯◯◯ VERY LOW ++	2.40 (0.55,10.42)	⊕◯◯◯ VERY LOW
UC+WTH vs. CONTROL			0.39 (0.07,2.01)	⊕⊕◯◯ LOW ++	0.39 (0.07,2.01)	⊕⊕◯◯ LOW
DBG-150MG vs. DBG-110MG	1.32 (0.80,2.17)	⊕⊕◯◯ LOW a,b,c	1.32 (0.71,2.45)	⊕⊕◯◯ LOW §	1.32 (0.71,2.45)	⊕⊕◯◯ LOW
EDX-30MG vs. DBG-110MG			1.01 (0.48,2.16)	⊕⊕◯◯ LOW ++	1.01 (0.48,2.16)	⊕⊕◯◯ LOW
EDX-60MG vs. DBG-110MG			1.55 (0.74,3.25)	⊕⊕◯◯ LOW ++	1.55 (0.74,3.25)	⊕⊕◯◯ LOW
RVX vs. DBG-110MG			2.45 (1.26,4.77)	⊕⊕◯◯ LOW ++	2.45 (1.26,4.77)	⊕⊕◯◯ LOW
UC vs. DBG-110MG	3.23 (2.08,5.00)	⊕⊕◯◯ LOW a,c	3.22 (1.83,5.66)	⊕⊕◯◯ LOW §	3.22 (1.83,5.66)	⊕⊕◯◯ LOW
UC+SM vs. DBG-110MG			3.21 (0.41,25.37)	⊕◯◯◯ VERY LOW ++	3.21 (0.41,25.37)	⊕◯◯◯ VERY LOW
UC+ST vs. DBG-110MG			4.40 (1.42,13.63)	⊕◯◯◯ VERY LOW ++	4.40 (1.42,13.63)	⊕◯◯◯ VERY LOW
UC+WTH vs. DBG-110MG			0.71 (0.18,2.76)	⊕⊕◯◯ LOW ++	0.71 (0.18,2.76)	⊕⊕◯◯ LOW
EDX-30MG vs. DBG-150MG			0.77 (0.37,1.60)	⊕⊕◯◯ LOW ++	0.77 (0.37,1.60)	⊕⊕◯◯ LOW
EDX-60MG vs. DBG-150MG			1.17 (0.57,2.40)	⊕⊕⊕◯ MODERATE ++	1.17 (0.57,2.40)	⊕⊕⊕◯ MODERATE
RVX vs. DBG-150MG			1.85 (0.98,3.52)	⊕⊕⊕◯ MODERATE ++	1.85 (0.98,3.52)	⊕⊕⊕◯ MODERATE
UC vs. DBG-150MG	2.43 (1.67,3.57)	⊕⊕⊕◯ MODERATE a	2.44 (1.43,4.15)	⊕⊕◯◯ LOW §	2.44 (1.43,4.15)	⊕⊕⊕◯ MODERATE
UC+SM vs. DBG-150MG			2.43 (0.31,19.06)	⊕◯◯◯ VERY LOW ++	2.43 (0.31,19.06)	⊕◯◯◯ VERY LOW
UC+ST vs. DBG-150MG			3.33 (1.09,10.16)	⊕◯◯◯ VERY LOW ++	3.33 (1.09,10.16)	⊕◯◯◯ VERY LOW
UC+WTH vs. DBG-150MG			0.54 (0.14,2.06)	⊕⊕⊕◯ MODERATE ++	0.54 (0.14,2.06)	⊕⊕⊕◯ MODERATE
EDX-60MG vs. EDX-30MG	1.52 (1.02,2.22)	⊕⊕⊕◯ MODERATE a	1.53 (0.90,2.61)	⊕⊕◯◯ LOW §	1.53 (0.90,2.61)	⊕⊕⊕◯ MODERATE
RVX vs. EDX-30MG			2.42 (1.30,4.49)	⊕⊕◯◯ LOW ++	2.42 (1.30,4.49)	⊕⊕◯◯ LOW
UC vs. EDX-30MG	3.23 (2.27,4.54)	⊕⊕◯◯ LOW a,c	3.18 (1.92,5.26)	⊕⊕⊕◯ MODERATE ¶	3.18 (1.92,5.26)	⊕⊕⊕◯ MODERATE
UC+SM vs. EDX-30MG			3.17 (0.41,24.65)	⊕◯◯◯ VERY LOW ++	3.17 (0.41,24.65)	⊕◯◯◯ VERY LOW
UC+ST vs. EDX-30MG			4.35 (1.45,13.06)	⊕◯◯◯ VERY LOW ++	4.35 (1.45,13.06)	⊕◯◯◯ VERY LOW
UC+WTH vs. EDX-30MG			0.70 (0.19,2.65)	⊕⊕◯◯ LOW ++	0.70 (0.19,2.65)	⊕⊕◯◯ LOW

RVX vs. EDX-60MG			1.58 (0.86,2.89)	⊕⊕⊕◯ MODERATE ++	1.58 (0.86,2.89)	⊕⊕⊕◯ MODERATE
UC vs. EDX-60MG	2.13 (1.56,2.86)	⊕⊕⊕◯ MODERATE [a]	2.08 (1.29,3.35)	⊕⊕◯◯ LOW §	2.08 (1.29,3.35)	⊕⊕◯◯ LOW
UC+SM vs. EDX-60MG			2.07 (0.27,16.01)	⊕◯◯◯ VERY LOW ++	2.07 (0.27,16.01)	⊕◯◯◯ VERY LOW
UC+ST vs. EDX-60MG			2.84 (0.96,8.44)	⊕◯◯◯ VERY LOW ++	2.84 (0.96,8.44)	⊕◯◯◯ VERY LOW
UC+WTH vs. EDX-60MG			0.46 (0.12,1.71)	⊕⊕⊕◯ MODERATE ++	0.46 (0.12,1.71)	⊕⊕⊕◯ MODERATE
UC vs. RVX	1.37 (1.06,1.79)	⊕⊕⊕◯ MODERATE [a]	Not estimable	Not estimable *	1.31 (0.92,1.87)	⊕⊕⊕◯ MODERATE
UC+SM vs. RVX			1.31 (0.17,9.88)	⊕◯◯◯ VERY LOW ++	1.31 (0.17,9.88)	⊕◯◯◯ VERY LOW
UC+ST vs. RVX			1.80 (0.63,5.09)	⊕◯◯◯ VERY LOW ++	1.80 (0.63,5.09)	⊕◯◯◯ VERY LOW
UC+WTH vs. RVX			0.29 (0.08,1.05)	⊕⊕⊕◯ MODERATE ++	0.29 (0.08,1.05)	⊕⊕⊕◯ MODERATE
UC+SM vs. UC	1.00 (0.14,7.14)	⊕◯◯◯ VERY LOW [a,b,c,d,h]	Not estimable	Not estimable *	1.00 (0.14,7.29)	⊕◯◯◯ VERY LOW
UC+ST vs. UC	1.37 (0.55,3.33)	⊕◯◯◯ VERY LOW [a,b,c,h]	Not estimable	Not estimable *	1.37 (0.51,3.64)	⊕◯◯◯ VERY LOW
UC+WTH vs. UC	0.22 (0.07,0.68)	⊕⊕⊕◯ MODERATE [c]	Not estimable	Not estimable *	0.22 (0.06,0.76)	⊕⊕⊕◯ MODERATE
UC+ST vs. UC+SM			1.37 (0.15,12.58)	⊕◯◯◯ VERY LOW ++	1.37 (0.15,12.58)	⊕◯◯◯ VERY LOW
UC+WTH vs. UC+SM			0.22 (0.02,2.30)	⊕◯◯◯ VERY LOW ++	0.22 (0.02,2.30)	⊕◯◯◯ VERY LOW
UC+WTH vs. UC+ST			0.16 (0.03,0.78)	⊕◯◯◯ VERY LOW ++	0.16 (0.03,0.78)	⊕◯◯◯ VERY LOW
Gastrointestinal bleeding						
ASA vs. APX	1.18 (0.54,2.50)	⊕⊕◯◯ LOW [c,d]	5.55 (0.11,275.93)	⊕⊕⊕◯ MODERATE ¶	0.78 (0.16,3.83)	⊕⊕⊕◯ MODERATE
CONTROL vs. APX			0.38 (0.02,5.66)	⊕⊕◯◯ LOW ++	0.38 (0.02,5.66)	⊕⊕◯◯ LOW
DBG-110MG vs. APX			1.79 (0.19,17.10)	⊕⊕⊕◯ MODERATE ++	1.79 (0.19,17.10)	⊕⊕⊕◯ MODERATE
DBG-150MG vs. APX			2.42 (0.25,23.12)	⊕⊕⊕◯ MODERATE ++	2.42 (0.25,23.12)	⊕⊕⊕◯ MODERATE
EDX-30MG vs. APX			1.09 (0.11,10.44)	⊕⊕⊕◯ MODERATE ++	1.09 (0.11,10.44)	⊕⊕⊕◯ MODERATE
EDX-60MG vs. APX			1.97 (0.21,18.72)	⊕⊕⊕◯ MODERATE ++	1.97 (0.21,18.72)	⊕⊕⊕◯ MODERATE
RVX vs. APX			2.20 (0.30,16.04)	⊕⊕◯◯ LOW ++	2.20 (0.30,16.04)	⊕⊕◯◯ LOW
UC vs. APX	1.14 (0.88,1.47)	⊕⊕⊕◯ MODERATE [d]	5.77 (0.12,286.98)	⊕⊕◯◯ LOW §	1.61 (0.35,7.41)	⊕⊕⊕◯ MODERATE
UC+GNT vs. APX			1.19 (0.11,12.68)	⊕⊕◯◯ LOW ++	1.19 (0.11,12.68)	⊕⊕◯◯ LOW
CONTROL vs. ASA			0.48 (0.03,9.22)	⊕⊕◯◯ LOW ++	0.48 (0.03,9.22)	⊕⊕◯◯ LOW
DBG-110MG vs. ASA			2.30 (0.18,29.06)	⊕⊕⊕◯ MODERATE ++	2.30 (0.18,29.06)	⊕⊕⊕◯ MODERATE
DBG-150MG vs. ASA			3.11 (0.25,39.30)	⊕⊕⊕◯ MODERATE ++	3.11 (0.25,39.30)	⊕⊕⊕◯ MODERATE
EDX-30MG vs. ASA			1.41 (0.11,17.75)	⊕⊕⊕◯ MODERATE ++	1.41 (0.11,17.75)	⊕⊕⊕◯ MODERATE
EDX-60MG vs. ASA			2.53 (0.20,31.83)	⊕⊕⊕◯ MODERATE ++	2.53 (0.20,31.83)	⊕⊕⊕◯ MODERATE
RVX vs. ASA			2.83 (0.27,29.15)	⊕⊕◯◯ LOW ++	2.83 (0.27,29.15)	⊕⊕◯◯ LOW
UC vs. ASA	5.00	⊕⊕⊕◯	0.97 (0.02,48.21)	⊕⊕◯◯	2.07 (0.30,14.05)	⊕⊕⊕◯

	(0.61,50.00)	MODERATE [c,d]		LOW [§]		MODERATE
UC+GNT vs. ASA			1.52 (0.11,21.29)	⊕⊕◯◯ LOW [++]	1.52 (0.11,21.29)	⊕⊕◯◯ LOW
DBG-110MG vs. CONTROL			4.75 (0.29,77.51)	⊕⊕◯◯ LOW [++]	4.75 (0.29,77.51)	⊕⊕◯◯ LOW
DBG-150MG vs. CONTROL			6.43 (0.39,104.86)	⊕⊕◯◯ LOW [++]	6.43 (0.39,104.86)	⊕⊕◯◯ LOW
EDX-30MG vs. CONTROL			2.91 (0.18,47.35)	⊕⊕◯◯ LOW [++]	2.91 (0.18,47.35)	⊕⊕◯◯ LOW
EDX-60MG vs. CONTROL			5.23 (0.32,84.94)	⊕⊕◯◯ LOW [++]	5.23 (0.32,84.94)	⊕⊕◯◯ LOW
RVX vs. CONTROL			5.85 (0.47,73.58)	⊕⊕◯◯ LOW [++]	5.85 (0.47,73.58)	⊕⊕◯◯ LOW
UC vs. CONTROL	4.35 (0.93,20.00)	⊕⊕◯◯ LOW [b,c,d]	Not Estimable	Not estimable *	4.28 (0.45,40.27)	⊕⊕◯◯ LOW
UC+GNT vs. CONTROL			3.15 (0.18,56.31)	⊕⊕◯◯ LOW [++]	3.15 (0.18,56.31)	⊕⊕◯◯ LOW
DBG-150MG vs. DBG-110MG	1.35 (1.09,1.69)	⊕⊕⊕◯ MODERATE [a]	1.35 (0.26,7.14)	⊕⊕⊕◯ MODERATE [¶]	1.35 (0.26,7.14)	⊕⊕⊕◯ MODERATE
EDX-30MG vs. DBG-110MG			0.61 (0.06,6.43)	⊕⊕⊕◯ MODERATE [++]	0.61 (0.06,6.43)	⊕⊕⊕◯ MODERATE
EDX-60MG vs. DBG-110MG			1.10 (0.10,11.54)	⊕⊕⊕◯ MODERATE [++]	1.10 (0.10,11.54)	⊕⊕⊕◯ MODERATE
RVX vs. DBG-110MG			1.23 (0.16,9.46)	⊕⊕◯◯ LOW [++]	1.23 (0.16,9.46)	⊕⊕◯◯ LOW
UC vs. DBG-110MG	0.90 (0.70,1.15)	⊕⊕⊕◯ MODERATE [a]	0.90 (0.17,4.76)	⊕⊕⊕◯ MODERATE [¶]	0.90 (0.17,4.76)	⊕⊕⊕◯ MODERATE
UC+GNT vs. DBG-110MG			0.66 (0.06,7.78)	⊕⊕◯◯ LOW [++]	0.66 (0.06,7.78)	⊕⊕◯◯ LOW
EDX-30MG vs. DBG-150MG			0.45 (0.04,4.74)	⊕⊕⊕◯ MODERATE [++]	0.45 (0.04,4.74)	⊕⊕⊕◯ MODERATE
EDX-60MG vs. DBG-150MG			0.81 (0.08,8.50)	⊕⊕⊕◯ MODERATE [++]	0.81 (0.08,8.50)	⊕⊕⊕◯ MODERATE
RVX vs. DBG-150MG			0.91 (0.12,6.97)	⊕⊕◯◯ LOW [++]	0.91 (0.12,6.97)	⊕⊕◯◯ LOW
UC vs. DBG-150MG	0.67 (0.53,0.83)	⊕⊕⊕◯ MODERATE [a]	0.67 (0.13,3.51)	⊕⊕⊕◯ MODERATE [¶]	0.67 (0.13,3.51)	⊕⊕⊕◯ MODERATE
UC+GNT vs. DBG-150MG			0.49 (0.04,5.73)	⊕⊕◯◯ LOW [++]	0.49 (0.04,5.73)	⊕⊕◯◯ LOW
EDX-60MG vs. EDX-30MG	1.79 (1.45,2.22)	⊕⊕⊕⊕ HIGH	1.80 (0.34,9.46)	⊕⊕⊕⊕ HIGH [¶]	1.80 (0.34,9.46)	⊕⊕⊕⊕ HIGH
RVX vs. EDX-30MG			2.01 (0.26,15.42)	⊕⊕◯◯ LOW [++]	2.01 (0.26,15.42)	⊕⊕◯◯ LOW
UC vs. EDX-30MG	1.47 (1.18,1.85)	⊕⊕⊕⊕ HIGH	1.47 (0.28,7.76)	⊕⊕⊕⊕ HIGH [¶]	1.47 (0.28,7.76)	⊕⊕⊕⊕ HIGH
UC+GNT vs. EDX-30MG			1.08 (0.09,12.68)	⊕⊕◯◯ LOW [++]	1.08 (0.09,12.68)	⊕⊕◯◯ LOW
RVX vs. EDX-60MG			1.12 (0.15,8.55)	⊕⊕◯◯ LOW [++]	1.12 (0.15,8.55)	⊕⊕◯◯ LOW
UC vs. EDX-60MG	0.82 (0.68,0.99)	⊕⊕⊕⊕ HIGH	0.82 (0.16,4.30)	⊕⊕⊕⊕ HIGH [¶]	0.82 (0.16,4.30)	⊕⊕⊕⊕ HIGH
UC+GNT vs. EDX-60MG			0.60 (0.05,7.03)	⊕⊕◯◯ LOW [++]	0.60 (0.05,7.03)	⊕⊕◯◯ LOW
UC vs. RVX	0.70 (0.57,0.85)	⊕⊕◯◯ LOW [a,e]	Not estimable	Not estimable *	0.73 (0.23,2.37)	⊕⊕◯◯ LOW
UC+GNT vs. RVX			0.54 (0.06,4.67)	⊕⊕◯◯ LOW [++]	0.54 (0.06,4.67)	⊕⊕◯◯ LOW
UC+GNT vs. UC	0.74 (0.35,1.56)	⊕⊕◯◯ LOW [a,h]	Not estimable	Not estimable *	0.74 (0.12,4.51)	⊕⊕◯◯ LOW
Myocardial Infarction						
ASA vs. APX	1.18 (0.68,2.00)	⊕⊕⊕◯ MODERATE [c]	1.20 (0.63,2.31)	⊕⊕◯◯ LOW [§]	1.19 (0.78,1.80)	⊕⊕⊕◯ MODERATE

ASA+CLP vs. APX			1.76 (0.98,3.16)	⨁⨁◯◯ LOW ↔	1.76 (0.98,3.16)	⨁⨁◯◯ LOW
CONTROL vs. APX			1.13 (0.16,8.11)	⨁⨁◯◯ LOW ↔	1.13 (0.16,8.11)	⨁⨁◯◯ LOW
DBG-110MG vs. APX			1.55 (1.02,2.36)	⨁⨁⨁◯ MODERATE ↔	1.55 (1.02,2.36)	⨁⨁⨁◯ MODERATE
DBG-150MG vs. APX			1.59 (1.05,2.41)	⨁⨁⨁◯ MODERATE ↔	1.59 (1.05,2.41)	⨁⨁⨁◯ MODERATE
EDX-30MG vs. APX			1.37 (0.97,1.94)	⨁⨁⨁◯ MODERATE ↔	1.37 (0.97,1.94)	⨁⨁⨁◯ MODERATE
EDX-60MG vs. APX			1.08 (0.76,1.54)	⨁⨁⨁◯ MODERATE ↔	1.08 (0.76,1.54)	⨁⨁⨁◯ MODERATE
RVX vs. APX			0.93 (0.64,1.35)	⨁⨁⨁◯ MODERATE ↔	0.93 (0.64,1.35)	⨁⨁⨁◯ MODERATE
UC vs. APX	1.14 (0.85,1.51)	⨁⨁⨁⨁ HIGH [b]	1.11 (0.50,2.48)	⨁⨁◯◯ LOW [§]	1.14 (0.87,1.48)	⨁⨁⨁⨁ HIGH
UC+ST vs. APX			1.70 (0.89,3.25)	⨁⨁◯◯ LOW ↔	1.70 (0.89,3.25)	⨁⨁◯◯ LOW
ASA+CLP vs. ASA			1.49 (0.76,2.91)	⨁⨁◯◯ LOW ↔	1.49 (0.76,2.91)	⨁⨁◯◯ LOW
CONTROL vs. ASA			0.95 (0.13,7.03)	⨁⨁◯◯ LOW ↔	0.95 (0.13,7.03)	⨁⨁◯◯ LOW
DBG-110MG vs. ASA			1.31 (0.77,2.23)	⨁⨁◯◯ LOW ↔	1.31 (0.77,2.23)	⨁⨁◯◯ LOW
DBG-150MG vs. ASA			1.34 (0.79,2.28)	⨁⨁◯◯ LOW ↔	1.34 (0.79,2.28)	⨁⨁◯◯ LOW
EDX-30MG vs. ASA			1.16 (0.72,1.87)	⨁⨁◯◯ LOW ↔	1.16 (0.72,1.87)	⨁⨁◯◯ LOW
EDX-60MG vs. ASA			0.91 (0.56,1.48)	⨁⨁◯◯ LOW ↔	0.91 (0.56,1.48)	⨁⨁◯◯ LOW
RVX vs. ASA			0.79 (0.48,1.29)	⨁⨁◯◯ LOW ↔	0.79 (0.48,1.29)	⨁⨁◯◯ LOW
UC vs. ASA	0.94 (0.53,1.69)	⨁⨁◯◯ LOW [a,f,g]	0.97 (0.53,1.79)	⨁⨁⨁◯ MODERATE [¶]	0.96 (0.63,1.47)	⨁⨁⨁◯ MODERATE
UC+ST vs. ASA			1.43 (0.69,2.97)	⨁⨁◯◯ LOW ↔	1.43 (0.69,2.97)	⨁⨁◯◯ LOW
CONTROL vs. ASA+CLP			0.64 (0.09,4.84)	⨁⨁◯◯ LOW ↔	0.64 (0.09,4.84)	⨁⨁◯◯ LOW
DBG-110MG vs. ASA+CLP			0.88 (0.48,1.63)	⨁⨁◯◯ LOW ↔	0.88 (0.48,1.63)	⨁⨁◯◯ LOW
DBG-150MG vs. ASA+CLP			0.90 (0.49,1.66)	⨁⨁◯◯ LOW ↔	0.90 (0.49,1.66)	⨁⨁◯◯ LOW
EDX-30MG vs. ASA+CLP			0.78 (0.44,1.37)	⨁⨁◯◯ LOW ↔	0.78 (0.44,1.37)	⨁⨁◯◯ LOW
EDX-60MG vs. ASA+CLP			0.62 (0.35,1.09)	⨁⨁◯◯ LOW ↔	0.62 (0.35,1.09)	⨁⨁◯◯ LOW
RVX vs. ASA+CLP			0.53 (0.30,0.95)	⨁⨁◯◯ LOW ↔	0.53 (0.30,0.95)	⨁⨁◯◯ LOW
UC vs. ASA+CLP	0.65 (0.38,1.09)	⨁⨁◯◯ LOW [a,c]	Not estimable	Not estimable *	0.65 (0.38,1.09)	⨁⨁◯◯ LOW
UC+ST vs. ASA+CLP			0.96 (0.44,2.12)	⨁⨁◯◯ LOW ↔	0.96 (0.44,2.12)	⨁⨁◯◯ LOW
DBG-110MG vs. CONTROL			1.37 (0.19,9.90)	⨁⨁◯◯ LOW ↔	1.37 (0.19,9.90)	⨁⨁◯◯ LOW
DBG-150MG vs. CONTROL			1.40 (0.19,10.13)	⨁⨁◯◯ LOW ↔	1.40 (0.19,10.13)	⨁⨁◯◯ LOW
EDX-30MG vs. CONTROL			1.21 (0.17,8.62)	⨁⨁◯◯ LOW ↔	1.21 (0.17,8.62)	⨁⨁◯◯ LOW
EDX-60MG vs. CONTROL			0.96 (0.13,6.83)	⨁⨁◯◯ LOW ↔	0.96 (0.13,6.83)	⨁⨁◯◯ LOW
RVX vs. CONTROL			0.82 (0.12,5.89)	⨁⨁◯◯ LOW ↔	0.82 (0.12,5.89)	⨁⨁◯◯ LOW

UC vs. CONTROL	1.00 (0.14, 7.14)	⊕⊕◯◯ LOW [a,d]	Not estimable	Not estimable *	1.00 (0.14,7.07)	⊕⊕◯◯ LOW
UC+ST vs. CONTROL			1.50 (0.20,11.51)	⊕⊕◯◯ LOW ++	1.50 (0.20,11.51)	⊕⊕◯◯ LOW
DBG-150MG vs. DBG-110MG	1.02 (0.76,1.37)	⊕⊕⊕◯ MODERATE [a]	1.02 (0.76,1.37)	⊕⊕⊕◯ MODERATE ¶	1.02 (0.76,1.37)	⊕⊕⊕◯ MODERATE
EDX-30MG vs. DBG-110MG			0.88 (0.60,1.30)	⊕⊕⊕◯ MODERATE ++	0.88 (0.60,1.30)	⊕⊕⊕◯ MODERATE
EDX-60MG vs. DBG-110MG			0.70 (0.47,1.04)	⊕⊕⊕◯ MODERATE ++	0.70 (0.47,1.04)	⊕⊕⊕◯ MODERATE
RVX vs. DBG-110MG			0.60 (0.40,0.91)	⊕⊕⊕◯ MODERATE ++	0.60 (0.40,0.91)	⊕⊕⊕◯ MODERATE
UC vs. DBG-110MG	0.73 (0.53,1.01)	⊕⊕⊕◯ MODERATE [a]	0.73 (0.53,1.01)	⊕⊕⊕◯ MODERATE ¶	0.73 (0.53,1.01)	⊕⊕⊕◯ MODERATE
UC+ST vs. DBG-110MG			1.09 (0.56,2.14)	⊕⊕◯◯ LOW ++	1.09 (0.56,2.14)	⊕⊕◯◯ LOW
EDX-30MG vs. DBG-150MG			0.86 (0.59,1.27)	⊕⊕⊕◯ MODERATE ++	0.86 (0.59,1.27)	⊕⊕⊕◯ MODERATE
EDX-60MG vs. DBG-150MG			0.68 (0.46,1.01)	⊕⊕⊕◯ MODERATE ++	0.68 (0.46,1.01)	⊕⊕⊕◯ MODERATE
RVX vs. DBG-150MG			0.59 (0.39,0.88)	⊕⊕⊕◯ MODERATE ++	0.59 (0.39,0.88)	⊕⊕⊕◯ MODERATE
UC vs. DBG-150MG	0.71 (0.52,0.98)	⊕⊕⊕◯ MODERATE [a]	0.72 (0.52,0.99)	⊕⊕⊕◯ MODERATE ¶	0.72 (0.52,0.99)	⊕⊕⊕◯ MODERATE
UC+ST vs. DBG-150MG			1.07 (0.55,2.09)	⊕⊕◯◯ LOW ++	1.07 (0.55,2.09)	⊕⊕◯◯ LOW
EDX-60MG vs. EDX-30MG	0.78 (0.63,0.99)	⊕⊕⊕◯ MODERATE [a]	0.79 (0.63,0.99)	⊕⊕⊕◯ MODERATE ¶	0.79 (0.63,0.99)	⊕⊕⊕◯ MODERATE
RVX vs. EDX-30MG			0.68 (0.48,0.95)	⊕⊕⊕◯ MODERATE ++	0.68 (0.48,0.95)	⊕⊕⊕◯ MODERATE
UC vs. EDX-30MG	0.83 (0.66,1.03)	⊕⊕⊕◯ MODERATE [a]	0.83 (0.67,1.03)	⊕⊕⊕◯ MODERATE [a]	0.83 (0.67,1.03)	⊕⊕⊕◯ MODERATE
UC+ST vs. EDX-30MG			1.24 (0.66,2.33)	⊕⊕◯◯ LOW ++	1.24 (0.66,2.33)	⊕⊕◯◯ LOW
RVX vs. EDX-60MG			0.86 (0.61,1.22)	⊕⊕⊕◯ MODERATE ++	0.86 (0.61,1.22)	⊕⊕⊕◯ MODERATE
UC vs. EDX-60MG	1.04 (0.83,1.32)	⊕⊕⊕◯ MODERATE [a]	1.05 (0.83,1.33)	⊕⊕⊕◯ MODERATE [a]	1.05 (0.83,1.33)	⊕⊕⊕◯ MODERATE
UC+ST vs. EDX-60MG			1.57 (0.83,2.96)	⊕⊕◯◯ LOW ++	=1.57 (0.83,2.96)	⊕⊕◯◯ LOW
UC vs. RVX	1.22 (0.94,1.56)	⊕⊕⊕◯ MODERATE [a]	Not estimable	Not estimable *	1.22 (0.94,1.58)	⊕⊕⊕◯ MODERATE
UC+ST vs. RVX			1.82 (0.95,3.47)	⊕⊕◯◯ LOW ++	1.82 (0.95,3.47)	⊕⊕◯◯ LOW
UC+ST vs. UC	1.49 (0.83,2.70)	⊕⊕◯◯ LOW [a,h]	Not estimable	Not estimable *	1.49 (0.83,2.70)	⊕⊕◯◯ LOW

[a] Unblinded participants and personnel
[b] Confidence interval included potential for important harm or benefits
[c] Imprecise due to low number of events
[d] Wide confidence interval
[e] Large I_2 (≥50%)
[f] Unblinded outcome assessment
[g] Heterogeneity on the age eligibility among trials
[h] Mixed population (inclusive of AF, DVT, PE, etc)
§Contributing direct evidence of low/very low quality
¶Contributing direct evidence of moderate quality
++Indirect estimate from order loops higher than first order
*Cannot be estimated because drug was not connected in a loop in the evidence network

Supplementary References for Chapter 6

1. Matchar DB, Jacobson A, Dolor R, Edson R, Uyeda L, Phibbs CS, et al. Effect of home testing of international normalized ratio on clinical events. The New England journal of medicine. 2010;363(17):1608-20.
2. Khan TI, Kamali F, Kesteven P, Avery P, Wynne H. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. British journal of haematology. 2004;126(4):557-64.
3. Voller H, Glatz J, Taborski U, Bernardo A, Dovifat C, Heidinger K. Self-management of oral anticoagulation in nonvalvular atrial fibrillation (SMAAF study). Zeitschrift fur Kardiologie. 2005;94(3):182-6.
4. Menendez-Jandula B, Souto JC, Oliver A, Montserrat I, Quintana M, Gich I, et al. Comparing self-management of oral anticoagulant therapy with clinic management: a randomized trial. Annals of internal medicine. 2005;142(1):1-10.
5. Verret L, Couturier J, Rozon A, Saudrais-Janecek S, St-Onge A, Nguyen A, et al. Impact of a pharmacist-led warfarin self-management program on quality of life and anticoagulation control: a randomized trial. Pharmacotherapy. 2012;32(10):871-9.
6. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A randomized trial of genotype-guided dosing of warfarin. The New England journal of medicine. 2013;369(24):2294-303.
7. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet (London, England). 2006;367(9526):1903-12.
8. Liu X, Huang H, Yu J, Cao G, Feng L, Xu Q, et al. Warfarin compared with aspirin for older Chinese patients with stable coronary heart diseases and atrial fibrillation complications. International journal of clinical pharmacology and therapeutics. 2014;52(6):454-9.
9. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. Lancet (London, England). 1994;343(8899):687-91.
10. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet (London, England). 1993;342(8882):1255-62.
11. Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). Age and ageing. 2007;36(2):151-6.
12. Lavitola Pde L, Sampaio RO, Oliveira WA, Boer BN, Tarasoutchi F, Spina GS, et al. Warfarin or aspirin in embolism prevention in patients with mitral valvulopathy and atrial fibrillation. Arquivos brasileiros de cardiologia. 2010;95(6):749-55.
13. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet (London, England). 2007;370(9586):493-503.
14. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet (London, England). 1989;1(8631):175-9.
15. Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke

prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. Archives of internal medicine. 1998;158(14):1513-21.
16. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SW, et al. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The New England journal of medicine. 1990;323(22):1505-11.
17. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. Journal of the American College of Cardiology. 1991;18(2):349-55.
18. Sato H, Ishikawa K, Kitabatake A, Ogawa S, Maruyama Y, Yokota Y, et al. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan Atrial Fibrillation Stroke Trial. Stroke. 2006;37(2):447-51.
19. Chen KP, Huang CX, Huang DJ, Cao KJ, Ma CS, Wang FZ, et al. Anticoagulation therapy in Chinese patients with non-valvular atrial fibrillation: a prospective, multi-center, randomized, controlled study. Chinese medical journal. 2012;125(24):4355-60.
20. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation. 1991;84(2):527-39.
21. Holmes DR, Jr., Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. Journal of the American College of Cardiology. 2014;64(1):1-12.
22. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. Jama. 2014;312(19):1988-98.
23. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2009;361(12):1139-51.
24. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. The New England journal of medicine. 2011;365(10):883-91.
25. Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. -The ARISTOTLE-J study. Circulation journal : official journal of the Japanese Circulation Society. 2011;75(8):1852-9.
26. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2013;369(22):2093-104.
27. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2011;365(11):981-92.
28. Weitz JI, Connolly SJ, Patel I, Salazar D, Rohatagi S, Mendell J, et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thrombosis and haemostasis. 2010;104(3):633-41.
29. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. Circulation journal : official journal of the Japanese Circulation Society. 2012;76(9):2104-11.
30. Hong KS, Kwon SU, Lee SH, Lee JS, Kim YJ, Song TJ, et al. Rivaroxaban vs Warfarin Sodium in the Ultra-Early Period After Atrial Fibrillation-Related Mild Ischemic Stroke: A Randomized Clinical Trial. JAMA neurology. 2017;74(10):1206-15.
31. Chung N, Jeon HK, Lien LM, Lai WT, Tse HF, Chung WS, et al. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. Thrombosis and haemostasis. 2011;105(3):535-44.

32. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). The American journal of cardiology. 2007;100(9):1419-26.
33. Mao L, Li C, Li T, Yuan K. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in Chinese patients with atrial fibrillation. Vascular. 2014;22(4):252-8.
34. Yamashita T, Koretsune Y, Yasaka M, Inoue H, Kawai Y, Yamaguchi T, et al. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. Circulation journal : official journal of the Japanese Circulation Society. 2012;76(8):1840-7.
35. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. The New England journal of medicine. 2011;364(9):806-17.
36. Shosha RI, Ibrahim OM, Setiha ME, Abdelwahab AA. The Efficacy and Safety of Rivaroxaban as an Alternative to Warfarin for the Prevention of Thromboembolism in Patients with Atrial Fibrillation. Int J Pharm Sci Rev Res. 2017;43(2):38-48.
37. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. Circulation. 2013;127(6):720-9.
38. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736-47.

Supplementary Materials for Chapter 7

S-7-1. Details of Interventions

	Anticoagulant Interventions	Descriptions
Reference Therapy	Usual warfarin care	Patients are routinely managed either in the hospitals, primary care or in anticoagulation clinics by a range of healthcare professionals including physicians, nurses and clinical pharmacists.
Warfarin bundled care*	Genotype-guided warfarin dosing	Patients received CYP2C9 and VKORC1 genotyping. Based on their genotype status, they were then initiated on a warfarin dose as calculated by the pharmacogenetic-based algorithm using demographic, clinical and genetic data. Based on previous study [1], we assumed that patients who received warfarin therapy will reach their maintenance dose within the induction phase. Therefore, the benefits of genotype-guided dosing in reducing stroke and bleedings occurred in the first 3 months only. We also assumed that the monitoring frequency in the first 3 months of genotype-guided dosing setting was lesser than in the usual warfarin care, as the median time to reach a stable dose was shorter in the former group [2].
	Patient's self-testing of warfarin	Patients were trained to be capable in using the point-of care device. Point-of-care tests were performed by patients themselves at the comfort of their own home with their test results managed by clinical pharmacists in the anticoagulation clinics through trans-telephonic. The anticoagulation clinic visits for this strategy would be less frequent than usual warfarin care[3].
	Patient's self-management of warfarin	Patients were trained to be capable in using the point-of-care device and in self-adjusting their own warfarin dosage based on their INR results. Point-of-care tests were performed by patients themselves in the comfort of their own home, followed by the interpretation of test results by patients themselves and self-adjustment of warfarin dosage according to the predefined protocol. The anticoagulation clinic visits for this strategy would be less frequent than usual warfarin care [3].
	LAAC procedure (Watchman device)	The Watchman device was implanted into the patient's left atrial appendage. Following the successful device implantation, patients

	with temporary warfarin use	received warfarin and aspirin for 45 days, aspirin plus clopidogrel from 46 days to 6 months and aspirin alone thereafter. Transoesophageal echocardiogram was performed twice within the first year after device implantation. LAAC-treated patients were monitored under the anticoagulation clinics every 2 weeks for the first 45 days. After 45 days, follow-up visits occurred every 3 months for the first year, followed by twice annually visits thereafter.
NOACs	Dabigatran, 150mg twice daily	Patients were initiated with respective NOACs in THE anticoagulation clinics and follow-up visits occurred every 3 months.
	Rivaroxaban, 20mg once daily	
	Apixaban, 5mg twice daily	
	Edoxaban, 60mg once daily	

**Warfarin care bundles were the combination of several interventions performed collectively to improve the quality of conventional warfarin care.*

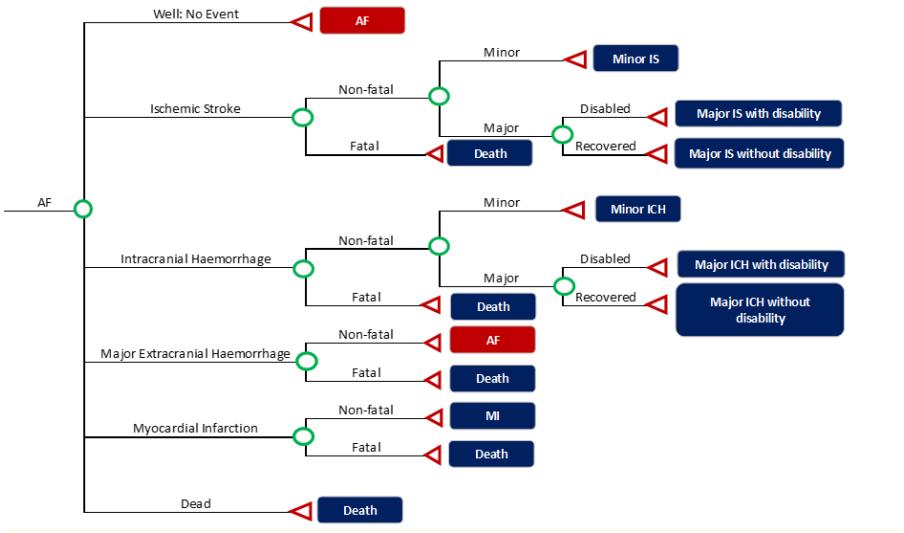
Abbreviations: LAAC, left atrial appendage closure; INR, international normalized ratio; NOACs, novel oral anticoagulants;

S-7-2. Model Structure

All patients started with atrial fibrillation (AF) well state, defined as patients with AF on anticoagulation who have not experienced any events within the model. Patients with AF may either remained in the same health state at baseline, experienced a clinical event or died. The following clinical events were modelled: ischemic stroke (IS), myocardial infarction (MI), intracranial haemorrhage (ICH), major extracranial haemorrhage (ECH) and death. ICH included haemorrhagic stroke.

All clinical events were subjected to case-fatality within 3 months and were transferred to the death state in the next cycle. Patients who survived an IS or ICH transitioned to three IS or ICH health states (minor, major with disability, major without disability) independently of prior treatment. IS, ICH and MI were modelled as closed health states, such that after experiencing the first event, patients would only experience recurrent events or die. If patients experience recurrent IS or ICH in the model, they would transition to IS or ICH of the same or greater severity. Major ECH was modelled as transient health state, whereby patients who survived an event would return to the AF "well" state without any residual deficits.

Decision Sub-tree for AF



S-7-3. Event Rates of Usual Warfarin Care for Model Input Parameters

Clinical Events	Point Estimates (per 100 person-years) *	Sources
Ischemic Stroke	1.63	[4]
Major Bleeding	1.9	[4]
Intracranial Haemorrhage	0.78	Pooled analysis, warfarin arms in East Asian subgroups from ARISTOTLE [5], RE-LY [6], ENGAGE AF-TIMI [7], and ROCKET-AF [8] in Appendix 4.
Extracranial Haemorrhage	1.12	
Myocardial Infarction	0.49	

**Limits in the parameter variation were based on ±20% in the sensitivity analysis.*

S-7-4. Calculation of Clinical Event Rates of Usual Warfarin Care that were Unavailable in Thailand studies

Our analysis used findings reported from the Methavigul et al. study[4] for clinical events ischemic stroke (IS) and major bleedings of usual warfarin care in Thai patients with atrial fibrillation. Therefore, other clinical events such as myocardial infarction were estimated. The calculation methods for the rate of other clinical event rates of usual AC warfarin that were unavailable in Thailand were adopted from Rattanachotphanit et al.[9]

Myocardial infarction

As local data for Thai patients was unavailable, the rates of MI were estimated from the pooling of four pivotal NOAC trials [5-8], using Stata's metaprop, the command for meta-analysis of binomial data.

Pooled estimates for MI in East Asian Patients

		Myocardial Infarction	
	Uusal Warfarin Care)Number of patients(	**Number of events)rate per 100 person-years(**	**Person-years ***
ARISTOTLE [5]	1,005	7)0.39(	1,795
ENGAGE-TIMI [7]	641	8)0.45(	1,778
RE-LY [6]	926	10 (0.58)	1724
ROCKET-AF [8]	462	8)0.99(	808
Pooled estimates			
Rate per 100 person-years		0.49	
I^2		0%	

** Based on number of event and event rate*

Types of Major Bleedings

Methavigul et al. study reported major bleedings in total and did not stratified based on specific bleeding types which may not fit our analysis. Contrarily, the pivotal NOAC trials [5-8] reported outcomes on both total major bleedings and ICH. As such, the rates per 100 person-years for ICH and total major bleedings were pooled across these trials using Stata's metaprop command. The rate of major extracranial bleeding instead was calculated as the pooled total major bleedings subtracted by that of pooled ICH. The fractions obtained for each specific bleeding types were then calculated as the proportion of the overall rates across the two major bleeding types.

Pooled event rates and fractions of major bleeding types in East Asian patients

	Usual Warfarin Care arm)Number of patients(	ICH		Major ECH		Total major bleedings	
		Number of events)rate per 100 person-years(	Person-years *	Number of events)rate per 100 person-years(	Person-years *	Number of events)rate per 100 person-years(	Person-years *
ARISTOTLE [5]	1,005	31)1.88(	1,649	-	-	63)3.84(	1,641
ENGAGE TIMI	641	28)1.92(	1,458	-	-	68)4.80(	1,417
RE-LY	926	19)1.10(	1,727	-	-	66)3.82(	1,728
ROCKET-AF	462	17)2.46(	691	-	-	35)5.14(	681
Pooled estimates							
Rate per 100 person-years		1.73		N/A		4.21	
I^2		60.45%		N/A		16.71%	
Fraction		0.41		0.59		1.00	

** Based on number of event and event rate*

Abbreviations: ICH, intracranial haemorrhage; ECH, extracranial haemorrhage

S-7-5. Cost Calculation Lists for Each Anticoagulant Interventions

The total costs for each intervention were the sum of various cost components that were required for the delivery of the intervention such as the cost of anticoagulation clinic (AC) visits multiplied by the frequency of visits in 3 months, cost of point-of-care (POC) coagulometers, cost of pharmacogenetic testing, cost of Watchman device, cost of INR strips, cost of lancets or cost of training. The cost components for each intervention were summarized in table Page 225.

A. Usual Warfarin Care

The total costs for usual warfarin care were the sum of warfarin cost and anticoagulation clinic visit cost multiplied by the frequency of visit in 3 months. Cost of AC visit included laboratory INR testing and anticoagulant service cost, which was derived from previous Thai study [3].

B. Genotype-guided Warfarin Dosing

For genotype-guided dosing intervention, the total costs included were the cost of pharmacogenetic testing (included in the first cycle only), cost of warfarin and cost of AC visit multiplied by the frequency of visits in 3 months.

C. Patient's Self-Testing of Warfarin (PST)

The total cost for PST included cost of warfarin, cost of point-of-care device, cost of training and cost for follow-up. The device and training costs were applied in the model in the first cycle only. The follow-up cost was calculated from both self-testing and AC visits, which was then multiplied by the frequency of self-testing and AC visit in 3 months. Cost of self-testing included the strips used and PST telephone service cost provided by AC.

D. Patient's Self-Management of Warfarin (PSM)

The total cost for PSM was calculated in similar fashion as the total cost of PST with the exclusion of PST telephone service cost as patients under PSM intervention self-adjusted their warfarin dosing.

E. Left Atrial Appendage Closure (LAAC)

For LAAC, the total costs included the cost of Watchman device, cost of LAAC procedure plus the cost for 2 transoesophageal echocardiograms and cost for follow-up AC visit. Cost of other medications were also applied for LAAC-treated patients as concomitant antithrombotic were required post-surgery to facilitate device endothelization: warfarin and aspirin for 45 days, followed by aspirin and clopidogrel until the 6th month and then the continuation of aspirin only [10, 11]. For LAAC-treated patients, INR monitoring under the AC visits was performed every 2 weeks for the first 45 days on warfarin, targeting an INR between 2 and 3. After 45 days, warfarin was stopped and follow-up AC visits occurred every 3 months for the first year followed by twice annually visits thereafter.

F. Novel Oral Anticoagulants (NOACs)

The total cost for NOAC interventions were based on the cost of NOAC and cost of AC visit only, multiplied by the frequency of visits within 3 months.

		Usual Warfarin Care	PST	PSM	Genotype-guided dosing**	NOACS	LAAC***
Direct Medical Costs	**Self-testing at home** -INR strip -Lancet -PST Service (Telephone) -Self training session -Point of care INR device		 Monthly Monthly Monthly Once Once	 Monthly Monthly - Once Once			
	Pharmacogenetic Testing				Once		
	LAAC -Watchman Device - LAAC procedure (including 2 TEE)						 Once Once
	Anticoagulation clinic outpatient visit						
	-Anticoagulation service cost (Visit duration x physician and pharmacists salary)	Monthly for first 3 months, then every 1.5 mo	Every 3 mo	Every 3 mo	Every 1.5 mo	Every 3 mo	Every 2 weeks for first 45 days, then at the 3rd, 6th, 9th and 12th month then every 6 months thereafter
	-Laboratory INR	Monthly for first 3 months, then every 1.5 mo	Every 3 mo	Every 3 mo	Every 1.5 mo	-	Every 2 weeks for the first 45 days
Direct Non-medical Costs*	Transportation	Monthly for first 3 months, then every 1.5 mo	Every 3 mo	Every 3 mo	Every 1.5 mo	Every 3 mo	Every 2 weeks for first 45 days, then at the 3rd, 6th, 9th and 12th month then

	Usual Warfarin Care	PST	PSM	Genotype-guided dosing**	NOACS	LAAC***
						every 6 months thereafter
Food	Monthly for first 3 months, then every 1.5 mo	Every 3 mo	Every 3 mo	Every 1.5 mo	Every 3 mo	Every 2 weeks for first 45 days, then at the 3rd, 6th, 9th and 12th month then every 6 months thereafter

**The direct non-medical costs were calculated for the patient and one caregiver as previous study showed that a stroke survivor on average come to hospital with one caretaker [12].*

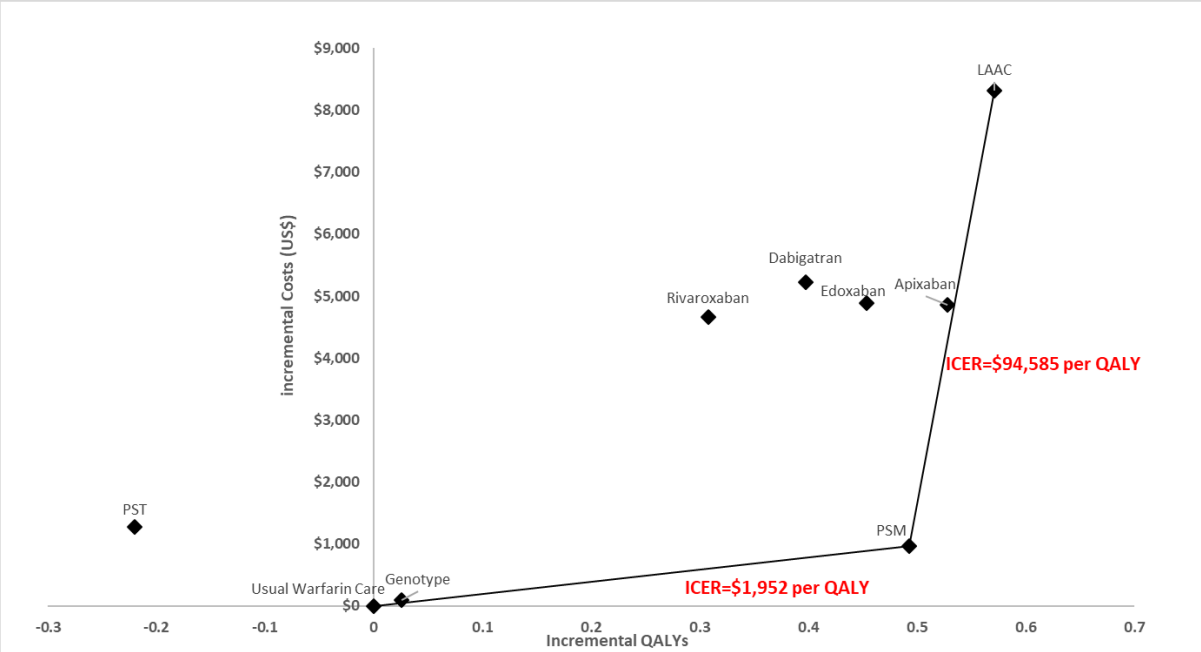
***Monitoring frequency in the first 3 months in genotype-guided dosing group was assumed to be less frequent than in the usual AC warfarin group, as median time to reach a stable dose was shorter in genotype-guided group [2].*

****For LAAC-treated patients, INR monitoring under the AC visit was performed every 2 weeks for the first 45 days on warfarin, targeting an INR between 2 and 3. After 45 days, warfarin was stopped and follow-up AC visits occurred every 3 months for the 1st year followed by twice annually visits thereafter.*

Abbreviations: INR, international normalized ratio; LAAC, left atrial appendage closure; NOACs, novel oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaba); PST, patient's self-testing of warfarin; PSM, patient's self-management of warfarin; TEE, transoesophageal echocardiogram

S-7-6. Efficacy Frontier from The Healthcare Payer Perspective

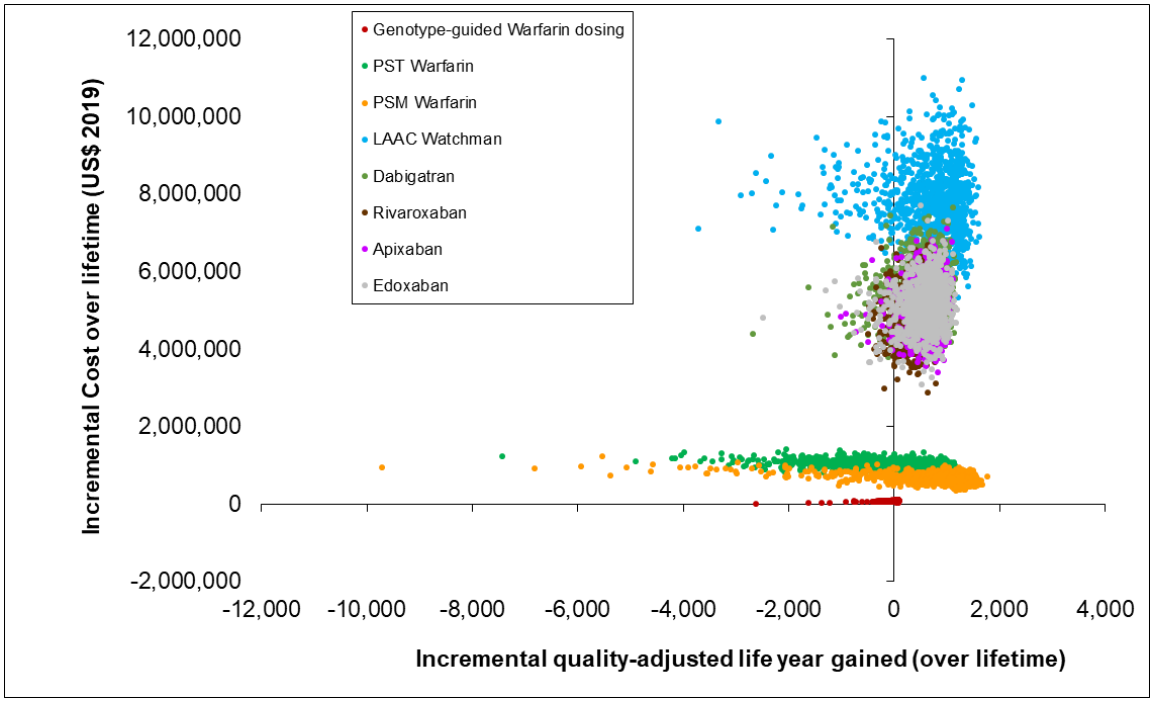
Incremental costs and effects (measured in QALYs) relative to usual warfarin care from the healthcare payer perspective



The connecting line represent the efficient frontier; the slope of each segment corresponds to the ICER between the points defining the segment. Interventions with fewer incremental QALYs are to the left and those with greater incremental costs are higher. Points to the left of the life are dominated by interventions that are more effective than at the frontier. In the healthcare payer perspective, only direct medical costs were considered.

Abbreviations: ICER, incremental cost-effectiveness ratio; PST: patient's self-testing; LAAC, left atrial appendage closure; PSM: patient's self-management; QALY, quality-adjusted life years

S-7-7. Probabilistic Sensitivity Analysis from 1000 Monte Carlo Simulations

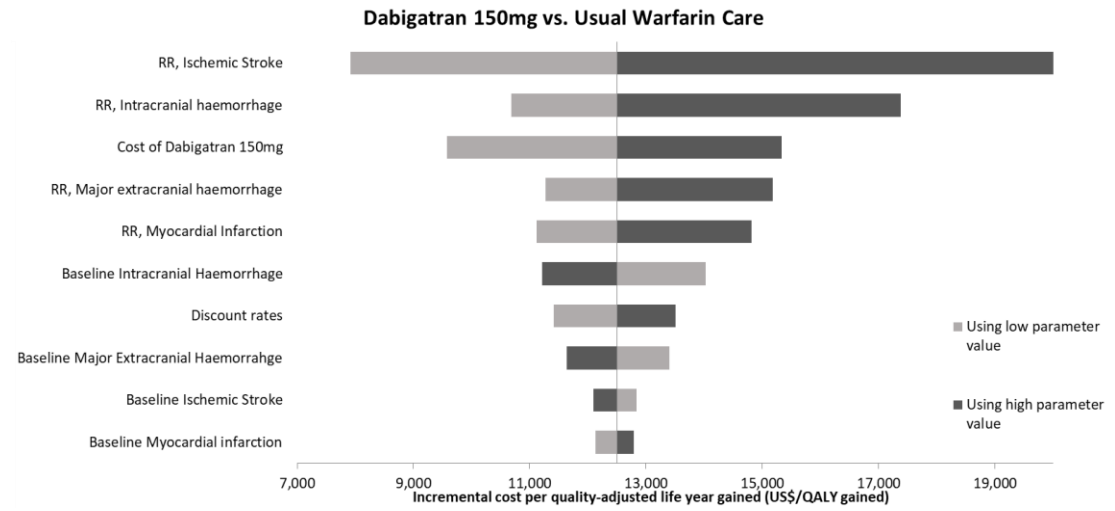


***A**bbreviations: LAAC, left atrial appendage closure; PST, patient's self-testing of warfarin; PSM, patient's self-management of warfarin*

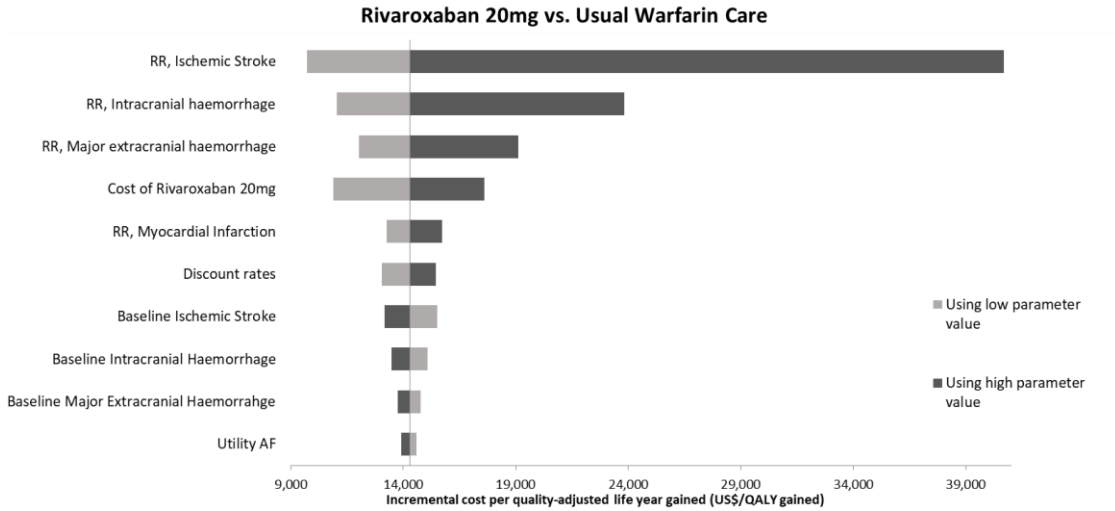
S-7-8. Sensitivity Analyses

Tornado diagram showing a series of one-way sensitivity analyses comparing each anticoagulant intervention in the model with usual warfarin care. The 10 most infleuntial parameters are presented in descending order of influence. The horizon bars represent the range of the incremental cost-effectiveness ratio (ICER) for one-way sensitivity over the range of parameters in parenthesis. All were varied, in standard fashion, as published 95% confidence intervals or ±20%. The wider the horizon bar, the more uncertainty that parameter introduces. The vertical line represents the base-case ICER.

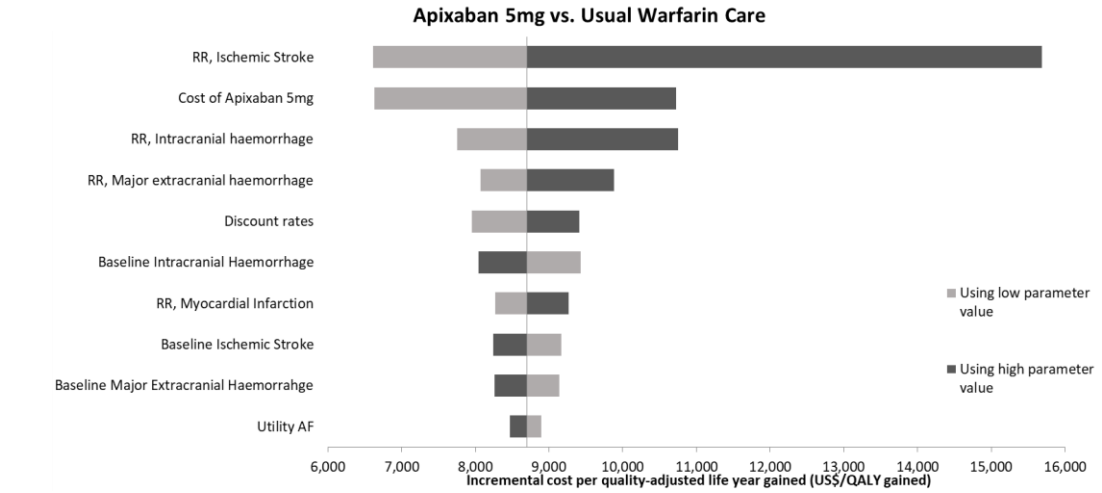
A.



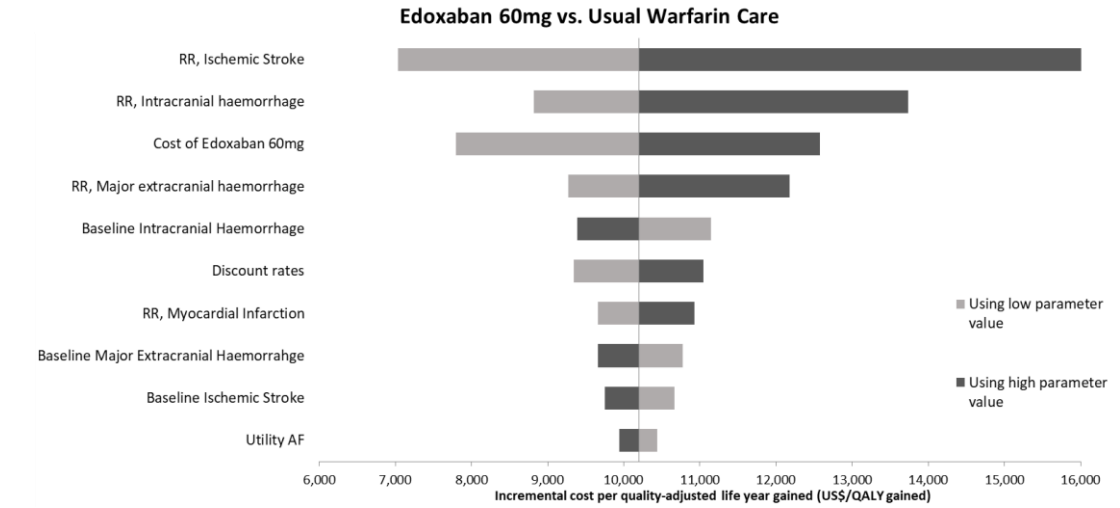
B.



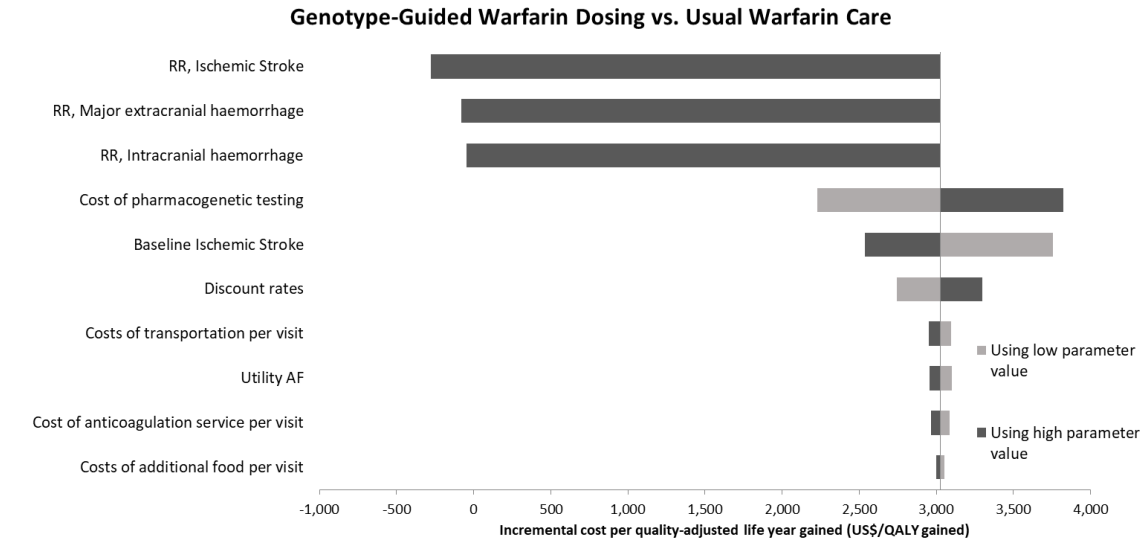
C.


Apixaban 5mg vs. Usual Warfarin Care
RR, Ischemic Stroke
Cost of Apixaban 5mg
RR, Intracranial haemorrhage
RR, Major extracranial haemorrhage
Discount rates
Baseline Intracranial Haemorrhage
RR, Myocardial Infarction
Baseline Ischemic Stroke
Baseline Major Extracranial Haemorrahge
Utility AF
Using low parameter value
Using high parameter value
6,000 7,000 8,000 9,000 10,000 11,000 12,000 13,000 14,000 15,000 16,000
Incremental cost per quality-adjusted life year gained (US$/QALY gained)

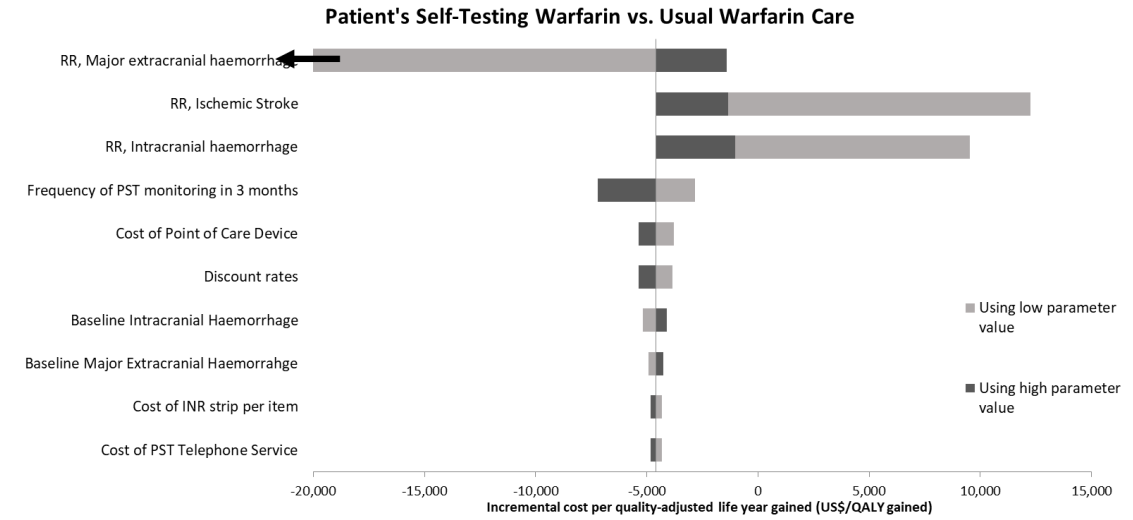
D.


Edoxaban 60mg vs. Usual Warfarin Care
RR, Ischemic Stroke
RR, Intracranial haemorrhage
Cost of Edoxaban 60mg
RR, Major extracranial haemorrhage
Baseline Intracranial Haemorrhage
Discount rates
RR, Myocardial Infarction
Baseline Major Extracranial Haemorrahge
Baseline Ischemic Stroke
Utility AF
Using low parameter value
Using high parameter value
6,000 7,000 8,000 9,000 10,000 11,000 12,000 13,000 14,000 15,000 16,000
Incremental cost per quality-adjusted life year gained (US$/QALY gained)

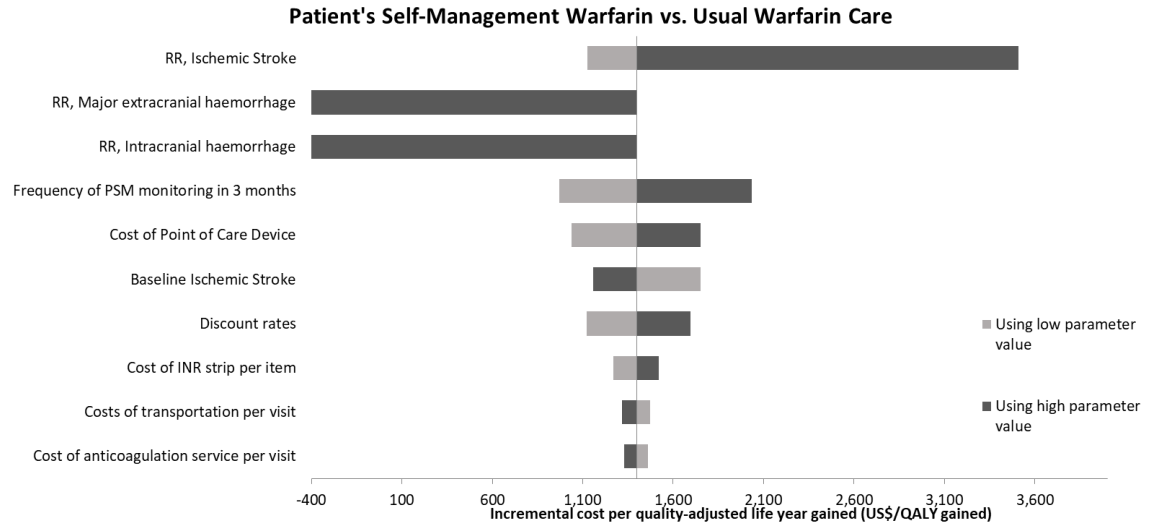
E.


Genotype-Guided Warfarin Dosing vs. Usual Warfarin Care
RR, Ischemic Stroke
RR, Major extracranial haemorrhage
RR, Intracranial haemorrhage
Cost of pharmacogenetic testing
Baseline Ischemic Stroke
Discount rates
Costs of transportation per visit
Utility AF
Cost of anticoagulation service per visit
Costs of additional food per visit
Using low parameter value
Using high parameter value
-1,000 -500 0 500 1,000 1,500 2,000 2,500 3,000 3,500 4,000
Incremental cost per quality-adjusted life year gained (US$/QALY gained)

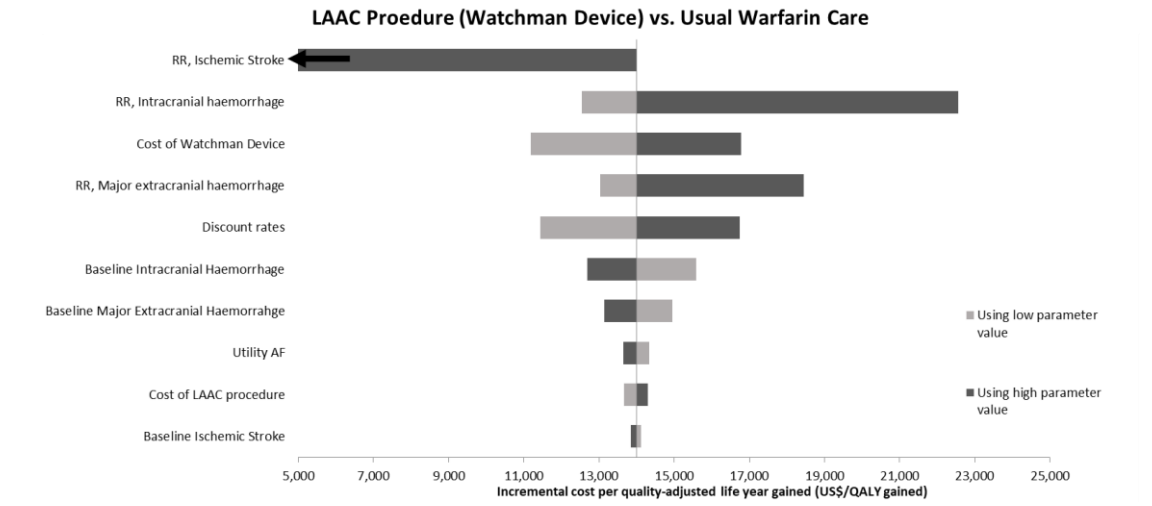
F.



G.



H.



Abbreviations: AF, atrial fibrillation; INR, international normalized ratio; LAAC, left atrial appendage closure; RR, relative risks; PST, patient's self-testing; PSM, patient's self-management

S-7-9. Scenario Analyses

Option	QALYs	Cost ($)	Δ QALYs*	Δ Cost (USD)*	ICER (USD/QALY)*
1. 20% reduced treatment prices [a]					
Usual Warfarin Care	15.87	1,403			
Genotype-guided dosing	15.89	1,477	0.03	57	2,227
PST	15.65	2,251	-0.22	830	-3,773[§]
PSM	16.36	1,932	0.49	512	1,037
Watchman device (LAAC)	16.44	7,809	0.57	6,389	11,188
Dabigatran, 150mg twice daily	16.27	5,228	0.40	3,808	9,572
Rivaroxaban, 20mg once daily	16.18	4,770	0.31	3,350	10,884
Apixaban, 5mg once daily	16.40	4,927	0.53	3,506	6,634
Edoxaban, 60mg once daily	16.32	4,955	0.45	3,535	7,796
2. 50% reduced treatment prices [a]					
Usual Warfarin Care	15.87	1,421			
Genotype-guided dosing	15.89	1,447	0.03	26	1,031
PST	15.65	1,986	-0.22	565	-2,569[§]
PSM	16.36	1,667	0.49	247	500
Watchman Device (LAAC)	16.44	5,417	0.57	3,996	6,999
Dabigatran, 150mg twice daily	16.27	3,508	0.40	2,088	5,248
Rivaroxaban, 20mg once daily	16.18	3,218	0.31	1,797	5,839
Apixaban, 5mg once daily	16.40	3,307	0.53	1,886	3,570
Edoxaban, 60mg once daily	16.32	3,329	0.45	1,909	4,209
3. Replace non-significant efficacy of anticoagulant interventions by null (1.0)					
Usual Warfarin Care	15.87	1,421			
Genotype-guided dosing	15.87	1,497	0.00	77.20	Dominated
PST	15.87	2,416	0.00	995	Dominated
PSM	16.36	2109	0.00	688	1,395
LAAC procedure	16.36	9,415	0.50	7995	16,090

Option	QALYs	Cost ($)	Δ QALYs*	Δ Cost (USD)*	ICER (USD/QALY)*
Dabigatran, 150mg twice daily	16.19	6,359	0.33	4,939	15,181
Rivaroxaban, 20mg once daily	15.87	5,750	0.00	4,329	Dominated
Apixaban, 5mg once daily	16.22	5,977	0.35	4,556	12,875
Edoxaban, 60mg once daily	16.20	6,016	0.33	4,596	14,008

**Compared with that of usual warfarin care*

[a] Reduced prices on individual NOACs, Watchman device, pharmacogenetic testing, and point-of-care devices used in PST/PSM intervention (important component cost of each intervention)

[§] Negative ICER due to higher costs and lower effectiveness of PST compared with usual AC warfarin.

Abbreviations: ICER, incremental cost-effectiveness ratio; LAAC, left atrial appendage closure; PST, patient's self-testing of warfarin; PSM, patient's self-management of warfarin, QALY, quality adjusted life year

Supplementary References for Chapter 7

1. Chong HY, Saokaew S, Dumrongprat K, Permsuwan U, Wu DB-C, Sritara P, et al. Cost-effectiveness analysis of pharmacogenetic-guided warfarin dosing in Thailand. Thrombosis Research. 2014;134(6):1278-84.
2. Janzic A, Kos M. Cost effectiveness of novel oral anticoagulants for stroke prevention in atrial fibrillation depending on the quality of warfarin anticoagulation control. PharmacoEconomics. 2015;33(4):395-408.
3. Kantito S, Saokaew S, Yamwong S, Vathesatogkit P, Katekao W, Sritara P, et al. Cost-effectiveness analysis of patient self-testing therapy of oral anticoagulation. Journal of thrombosis and thrombolysis. 2018;45(2):281-90.
4. Methavigul K Fau - Boonyapisit W, Boonyapisit W. Optimal INR level in Thai atrial fibrillation patients who were receiving warfarin for stroke prevention in Thailand. (0125-2208 (Print)).
5. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2011;365(11):981-92.
6. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2009;361(12):1139-51.
7. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2013;369(22):2093-104.
8. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. The New England journal of medicine. 2011;365(10):883-91.
9. Rattanachotphanit T, Limwattananon C, Waleekhachonloet O, Limwattananon P, Sawanyawisuth K. Cost-Effectiveness Analysis of Direct-Acting Oral Anticoagulants for Stroke Prevention in Thai Patients with Non-Valvular Atrial Fibrillation and a High Risk of Bleeding. PharmacoEconomics. 2019;37(2):279-89.
10. Holmes DR, Jr., Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. Journal of the American College of Cardiology. 2014;64(1):1-12.
11. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. Jama. 2014;312(19):1988-98.
12. Singhpoo K, Tiamkao S, Kuchaisit C, Ariyanuchitkul S, Sangpongsanon S, Kaamsa-ard S, et al. The quality of life of stroke outpatients at Srinagarind Hospital. Journal of the Medical Thailand Association. 2009;92(12):1602-9.

Thesis Amendments (Responses to Examiners' Comments)

Comments by Examiner 1: Emeritus Professor Gary M. Oderda:

No.	Comments	Response to Comments	Amendments Page
1	Page 24, Paragraph 3 'AF patients is associated should be AF patients are associated.'	Following the examiner's comment, the sentence was corrected accordingly" *"AF patients are associated with a five-fold increased risk of stroke and thromboembolism, resulting in significant morbidity, mortality and health-related expenditures.[1]"*	Chapter 2, Page 24, Section 2.1, Paragraph 3
2	Page 26 The statement is made "For the past 60 years, warfarin has been the only effective oral anticoagulant." This reference is from 1994 so it does not support the timeline. The first NOAC was approved in 2008 and warfarin was introduced in 1954. This is a difference of 56 years. I think it would be appropriate to say something like "Warfarin was the only orally effective anticoagulant for a period of almost 60 years" and to include a reference more recent than 1994.	Following the examiner's comment, the sentence was rephrased, and a newer reference (2015) was used to support the timeline of 60 years. *"Warfarin, an oral VKA was the only orally effective anticoagulant for a period of almost 60 years.[17] It has been shown to be clinically effective in reducing the risk of stroke in patients with AF."*	Chapter 2, Page 26, Section 2.3
3	Page 28, Paragraph 1 "Meanwhile, developing countries such as …" is not referenced. I assume this comes from reference 25. If so that reference should be inserted after that sentence.	Following the examiner's comment, reference was added to the corresponding sentence: *"Meanwhile, low- and middle-income countries such as Mexico,*	Chapter 2, Page 27, Paragraph 1

No.	Comments	Response to Comments	Amendments Page
		Brazil, India, China, Malaysia and Thailand reported lower TTR values, ranging from 45% to 60% only.[26]*"*	
4	Page 30, Paragraph 2 "Without routing monitoring test patient's…" should either be Without a routine monitoring test or Without routine monitoring testing.	Based on the examiner's comment, the sentence was rephrased as following: *"Without routine monitoring testing, patient's adherence could not be assessed."*	Chapter 2, Page 30, Paragraph 2
5	Page 31, Paragraph 1 "However, economic studies in these countries are still scare…" Scare should be scarce.	Following the examiner's comment, the spelling error in the sentence was corrected: *"However, economic studies in these countries are still scarce due to the lack of technical capacity, funding and database to conduct their own economic evaluations."*	Chapter 2, Page 31, Paragraph 1
6	Page 39 Should "…summary of evidence table…" be "summary of evidence tables"? "It provided a ready mean…" should be "It provided ready means…"	Following the examiner's advice, the sentences in the Table 4.1.1, Chapter 4 were rephrased accordingly: *"This study presented the big picture and the summary of evidence tables on anticoagulant interventions available for SPAF. It provided ready means for healthcare decision-makers to gain a clearer understanding on these interventions, based on the highest level of evidence available. It also highlighted the*	Chapter 4, Page 39, Table 4.1.1

No.	Comments	Response to Comments	Amendments Page
		limitations of current reviews in this research field."	
7	Page 40 "…a discussion of the practicability". Practicability is an appropriate word, but it is not commonly used. I would consider practicality.	Following the examiner's comment, the phrase 'practicability' was substituted with 'practicality': *"Concluding chapter – a discussion on the practicality of the overall findings, the salient contributions of this thesis, as wells as the recap of its limitations. Areas for future research are also discussed"*	Chapter 4, Page 40, Table 4.1.1
8	Page 41 Heading Data Material. Data Material is awkward. I think that Data Source may be more appropriate.	Following the examiner's advice, the heading 'Data Material' was replaced with 'Data Source' in Table 4.2.1, Chapter 4.	Chapter 4, Page 41, Table 4.2.1
9	Page 44 Search Strategy - Since the focus of the work is in developing countries, it would have been helpful to look at publications in other than English. This is a limitation and it is appropriately included in the limitations section.	The restriction of our searching to English-language publications only was addressed as one of our study limitations and were discussed in Section 5.6, Chapter 5.	Chapter 5, Page 61, Section 5.6, Paragraph 3
10	Page 46, Paragraph 3 The statement is made "When more than one meta-analysis addressed similar question" should either be "questions" or "a similar question". This is not clear. It says that if there are overlapping studies the one with	From the eligible systematic reviews, unique meta-analyses were identified using PICO criteria (population, intervention, comparator and outcome). When more than one meta-analysis addressed a similar outcome or had overlapping primary studies,	Chapter 5, Page 4, Paragraph 3

No.	Comments	Response to Comments	Amendments Page
	the largest number of component studies was selected. The next sentence, however, says that if there are overlapping studies but different outcomes both were included. If there were similar questions, but not overlapping studies was only the one with the largest number of component studies included?	only the meta-analysis with the largest number of component studies was selected to avoid duplication. For instance, in scenario 1 (two meta-analyses addressed similar questions but had no overlapping studies) and in scenario 2 (two meta-analyses addressed similar questions and had overlapping studies), only the one with largest number of component studies were included.	
11	Page 58 "Discussions" should be "Discussion". This error is repeated in other sections. Also in this sections "favourable" is included. Here, and in other areas, the British spelling of English words is included. This is acceptable but depending on where the sections are published these may need to be changed to US spellings. This may not be an issue since all sections have been submitted.	Following the examiner's comment, the error in Page 58 for the heading 'Discussion' was rectified. The spelling 'favourable' was not changed as this was the preferred Australian spelling.	Chapter 5, Page 58, Section 5.6
12	Page 79 Edoxaban Secondary Outcome Ischemic Stroke. This table doesn't include a description of what the meaning of bolding is in the results. I assume that this indicates a statistically significant result. If so, that needs to be included in the footnote. With a CI of 0.84 to 1.20 the	Following the examiner's comments, a description on the meaning of bolding was provided as footnotes of Table 6.4.1, Chapter 6. The bolding in CI 0.84 to 1.20 was removed as it did not represent statistically significant results. **Footnote in Table 6.4.1, Chapter 6:**	Chapter 6, Page 79, Table 6.4.1

No.	Comments	Response to Comments	Amendments Page
	result appears to not be significant but bolded.	*'Numbers in bold represent statistically significant results'*	
13	Page 83 Discussions. "Discussions" should be "Discussion".	Following the examiner's comment, the error in Page 83 was rectified.	Chapter 6, Page 83, Section 6.5
14	Page 103 Costs. At several points in the thesis it is unclear whether costs are being included in US $ or Thai Baht. In this case the heading says that costs are included in US $. Why are drug costs for drugs used in Thailand not included in Thai Baht? They should be available in Thai Baht.	All costs (including direct medical, direct non-medical and clinical event costs) were consistently reported in US dollars (USD) throughout Chapter 7 to enable easier inter-country comparisons. The drug costs for drugs used in Thailand were originally obtained in Thai Baht (THB) values but were then converted to USD, based on the exchange rate of USD1 = 31.35THB. Therefore, the final drug costs presented in Table 7.3.1 were in USD only to ensure consistency with the other costs reported in Chapter 7.	Chapter 7, Page 103, Table 7.3.1
15	Page 104 Analyses. "160,00 THB" should be "160,000 THB".	Following the examiner's comment, the error in Page 104 was rectified: *"According to Thai HTA recommendation, any interventions with an ICER less than 160,000 THB (USD5,104) was considered 'cost-effective'.*[19]"	Chapter 7, Page 104, Paragraph 1
16	Page 105	Following the examiner's comment, the error in Page 105 was rectified:	Chapter 7, Page 105,

No.	Comments	Response to Comments	Amendments Page
	Base Case Analysis. "…t0" should be "to".	*"PSM was able to reduce IS to 1317 events while increasing ICH slightly to 1468 events."*	Section 7.4, Paragraph 2
17	Page 109 Discussions. "Discussions" should be "Discussion".	Following the examiner's comment, the error in Page 109 was rectified.	Chapter 7, Page 105, Section 7.5
18	Page 110 "…single model using efficient frontier approach". Shouldn't this be efficiency frontier approach?	Following the examiner's comment, the phrase efficiency frontier approach was used instead: "This drawback was addressed in our study which simultaneously compared all interventions in a single model using efficiency frontier approach."	Chapter 7, Page 110, Section 7.5, Paragraph 1
19	Page 119, Paragraph 1 Consider changing "Telehealth concept can be integrated …" to "Telehealth can be integrated…"	Following the examiner's comment, the sentence was rephrased accordingly: "Telehealth can be integrated within PSM to improve the feasibility of PSM for adoption into healthcare system"	Chapter 8, Page 119, Paragraph 1
20	Page 119, Paragraph 2 "…combining clinical and economic evidences…" should be "…combining clinical and economic evidence…"	Following the examiner's comment, the spelling error was corrected: "This dissertation provides a learning model on which to base decision-making for stakeholders especially in	Chapter 8, Page 119, Paragraph 2

No.	Comments	Response to Comments	Amendments Page
		developing countries on the importance of combining clinical and economic evidence to inform decisions on efficiency and allocation of scare resources."	
21	Page 126 I have a couple of questions in this section. I think incorporating some of this information would be helpful in providing context. It would be important in the US. I am not sure of the importance in Thailand. What is being done in Thailand? Is only warfarin available? What would you recommend to a patient in Thailand as a result of these results? Should an individual patient consider a NOAC if available and they had sufficient funds to pay for it? What would the cost be in Thailand?	The examiner's concerns were addressed in Section 8.2, Chapter 8, which elaborated the implications and importance of this study findings. The study findings may provide useful information to policymakers in Thailand and in other low- or middle-income countries with similar healthcare context regarding NOACs affordability, reimbursement and listing in their national drug formulary. It was found that NOACs were not cost-effective in Thailand from both societal and healthcare perspective. Thus, such findings may guide decisions for allocation of scarce healthcare resources in Thailand at a population level but may not be useful for individual decisions due to varied individual priorities, attitudes, beliefs and expectations. Therefore, the examiner's question on "Should an individual patient consider a NOAC if available and they had sufficient funds to pay for it?" could not to be answered. Nonetheless, one of the future researches recommended in	Chapter 8, Section 8.2, Page 120

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		this thesis was the exploration of patients' values and preferences on anticoagulants for SPAF, which was aligned with the examiner's concerns. The availability of patients' preferences studies, alongside with clinical evidence and economic evaluations can guide decision-making process in both population and individual level. **Chapter 8, Section 8.2**: *"Our dissertation shows that NOACs were not cost-effective in a middle-income country such as Thailand while warfarin care bundle of PSM is highly cost-effective for SPAF. These findings may provide useful information to policymakers in Thailand and in other low- or middle-income countries with similar healthcare context regarding NOACs affordability, reimbursement and listing in their national drug formulary. By identifying interventions that are most cost-effective in the local setting, policymakers can precisely chart their coming course of anticoagulant care for SPAF and prioritize investment in interventions that are worth investing while optimizing population health gain from a given budget. Besides that, by knowing that*	

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		NOACs are unlikely to be cost-effective, stakeholders may consider renegotiating NOACs pricing with pharmaceutical industries to allow affordable reimbursement and access of these agents in their healthcare setting."	

Comments by Examiner 2: Professor Peter Coyte

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1	The perspective adopted and the time horizon used could have been included in the thesis title and mentioned early in both the abstract and the thesis itself.	The perspective adopted and the time horizon were not included in the thesis title as these components were only employed in Study 3 of the thesis. Inclusions of these components in the title may create confusion to less familiar readers. However, the abstract, Chapter 3 and Chapter 4 of the thesis were edited to introduce both components earlier to the readers, creating an appropriate presumption of the whole thesis. **Abstract**: "*This modelling approach demonstrated an analytic framework for decision-making from the societal and healthcare perspective of a middle-income country over a lifetime horizon, under the circumstances of uncertainty as in the introduction of new anticoagulant interventions for SPAF patients aged 65 years old and above."* **Chapter 3, Figure 3.1.1:** *"What is the cost-effectiveness of warfarin care bundles and NOACs, compared to usual warfarin care for SPAF from the societal and healthcare perspective of a middle-income country over a lifetime horizon?"*	Abstract, Page 3, Chapter 3, Page 36, Figure 3.1.1 Chapter 3, Page 37, Section 3.3. Chapter 4, Page 40, Table 4.1.1 Chapter 4, Page 41, Table 4.2.1

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		Chapter 3, Section 3.3: *"iii) To assess the cost-effectiveness of warfarin care bundles and NOACs, compared to usual warfarin care for SPAF patients aged 65 years old and above, from the societal and healthcare perspective of a middle-income country over a lifetime horizon."* **Chapter 4, Table 4.1.1**: *"A study that intended to assess the cost-effectiveness of newer anticoagulant interventions (e.g. warfarin care bundles and NOACs), compared to usual warfarin care for SPAF patients aged 65 years old and above, from the societal and healthcare perspective of a middle-income country over a lifetime horizon."* **Chapter 4, Table 4.2.1:** *"To assess the cost-effectiveness of warfarin care bundles and NOACs compared to usual warfarin care for SPAF patients aged 65 years old and above, from the societal and healthcare perspective in a middle-income country over a lifetime horizon."*	
2	While the intervention is for stroke prevention in atrial fibrillation, the abstract does not identify the inclusion and exclusion criteria in	Following the examiner's comments, amendments were made and the explicit target population for the cost-effectiveness study was specified in	Abstract, Page 3 Chapter 3,

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	order to identify an explicit target population. This is needed in order to make any statement about the cost-effectiveness of interventions. The literature review chapter talks about the use of the CHA2DS2-VASc scoring system to partition patients into various clinical groups, but clear guidelines are warranted for the economic evaluation to generalize to specific target populations. Only when we get to Chapter 7, is it clear that the target population is initially identified as a "65-year old patients with AF who had no contraindications to anticoagulation". Moreover, only after specific clinical events occur would patients become eligible for receipt of one of the interventions under review. It would be better if this was stated more succinctly and precisely at the outset	the Abstract, Chapter 3 and Chapter 4. **Abstract**: *"This modelling approach demonstrated an analytic framework for decision-making from the societal and healthcare perspective of a middle-income country over a lifetime horizon, under the circumstances of uncertainty as in the introduction of new anticoagulant interventions for SPAF patients aged 65 years old and above."* **Chapter 3, Section 3.3:** *"iii) To assess the cost-effectiveness of warfarin care bundles and NOACs, compared to usual warfarin care for SPAF patients aged 65 years old and above, from the societal and healthcare perspective of a middle-income country over a lifetime horizon."* **Chapter 4, Table 4.1.1:** *"A study that intended to assess the cost-effectiveness of newer anticoagulant interventions (e.g. warfarin care bundles and NOACs), compared to usual warfarin care for SPAF patients aged 65 years old and above, from the societal and healthcare perspective of a middle-income country over a lifetime horizon."*	Page 37, Section 3.3. Chapter 4, Page 40, Table 4.1.1 Chapter 4, Page 41, Table 4.2.1

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		Chapter 4, Table 4.2.1: *"To assess the cost-effectiveness of warfarin care bundles and NOACs compared to usual warfarin care for SPAF patients aged 65 years old and above, from the societal and healthcare perspective in a middle-income country over a lifetime horizon."*	
3	While it has been common in the past literature to say "developed" and "developing" these terms are normative and often considered judgmental. More objective terms, such as low-income or middle-income might better be used to represent decision-making when the resources for consumption and investment are scarcer for some jurisdictions than other places.	Following the examiner's advice, the term 'developing' or 'developed' countries were substituted with low-income or middle-income' countries instead.	Throughout the thesis
3	My main concern with the finding is that how can we be assured that patients will adhere to the optimal pattern of self-management that involves frequent monitoring in order to ensure that there is timely anticoagulation control? This is a crucial assumption and the economic evaluation results are based on this premise.	I agree with the examiner's comments, whereby we cannot be assured that patients will fully adhere to the optimal pattern of self-management and the assumption of 100% adherence may overestimate our findings. Therefore, it was emphasized in the discussion that our findings were not definitive and should be interpreted with caution. The patient's adherence was also addressed as one of the barriers for	Chapter 7, Page 110-111 Section 7.5

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		successful implementation of patient's self-management despite being the most cost-effective intervention for SPAF. However, these barriers were not insurmountable with technology advancements as elaborated in Section 7.5, Chapter 7. **Chapter 7, Section 7.5:** *"Additionally, although PSM may be the most optimal intervention, it has several implementation challenges. The inaccuracy of point-of-care (POC) coagulometers, inadequate physician-patient engagement and incomplete follow-up care may serve as possible barriers for PSM adoption. Patient's adherence to optimal pattern of self-management is also another possible barrier in ensuring good PSM performance and timely anticoagulation control. Therefore, the selection of patients for PSM requires careful consideration, in the context of their cognitive, physical abilities, dexterity and confidence level.*[42]" *"Telehealth may include a variety of telecommunication technologies such as wireless applications, videoconferencing and e-health patient portals which allows*	

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		physicians to monitor patient's adherence pattern of optimal self-management and to access PSM data remotely in timely manner, thereby improving the physician-patient communication and ensuring good anticoagulation control."	
4	My second concern rests on the use of a societal perspective. While this perspective, at a theoretical level, is the approach to adopt for optimal resource usage for society, it offers findings that often deviate from optimal behaviour to be undertaken by individual stakeholders. These stakeholders generally face only a sub-set of the costs (either because of insurance for patients or because the indirect costs associated with lost productivity are not borne by the third-party insurers, such as the Ministry of Health or an insurance company). As such, the evaluation undertaken does not inform decisions taken by most health system participants because it does not estimate the costs and consequences that are relevant to the decisions they make.	Both the societal and healthcare perspective have been addressed in the cost-effectiveness study of Chapter 7, as shown in Table 7.4.2. However, the examiner may not have noticed as findings from the healthcare perspective were not highlighted in the results. Therefore, amendments were made in Chapter 7, Section 7.4: Results, whereby findings from both societal and healthcare perspective were emphasized in text and table form. As both perspectives were addressed in the cost-effectiveness study, the economic evaluation can provide a relatively reasonable estimates of both costs and consequences for various stakeholders in the healthcare setting (e.g. Ministry of Health, patient themselves or insurer companies), which makes the study's findings valuable and relevant in decision-making process.	Chapter 7, Page 105-107, Section 7.4, Table 7.4.2
5	While a societal perspective was adopted, most economic		

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	evaluation guidelines call for sub analyses that offer a health system perspective, so for publicly financed health systems whereby the key stakeholders want information relevant to their perspective. Why was this not offered and how might the findings generalize to this narrower perspective from the one used by in this thesis?	**Chapter 7, Section 7.4:** "From the base-case analysis (Table 7.4.2), usual warfarin care resulted in 15.87 QALYs to effectiveness, while the estimated lifetime costs from societal and healthcare perspective were USD1,421 and USD868, respectively." "From both societal and healthcare perspective, PSM is a cost-effective intervention when compared to usual warfarin care, with an incremental cost-effectiveness ratio (ICER) of USD1,395/QALY and USD1,951/QALY respectively." "Thus, from the societal perspective, only usual warfarin care, PSM and LAAC remained on the efficient frontier of SPAF with an ICER of USD1,395 for usual warfarin care vs. PSM and USD93,830 for PSM vs. LAAC (Figure 7.4.1). The efficient frontier from the healthcare perspective was provided in S-7-6."	