Therapeutic Review

Safety, Effectiveness, and Cost-Effectiveness of New Oral Anticoagulants Compared with Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation

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This report is based on research conducted by the Canadian Collaborative for Drug Safety, Effectiveness and Network Meta – Analysis in collaboration with the Canadian Agency for Drugs and Technologies in Health (CADTH).

This report is being used by CADTH for the purpose of informing formulary listing recommendations for new oral anticoagulant(s) for stroke prevention in patients with atrial fibrillation and for informing policy decisions and potentially optimal use of these agents by the publicly funded federal, provincial and territorial drug plans participating in the Common Drug Review.

The report contains a comprehensive review of the existing public literature, studies, materials, and other information and documentation (collectively, the source documentation) available at the time of report preparation, and was guided by expert input and advice throughout its preparation.

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Abbreviations

AF	atrial fibrillation
CIHR	Canadian Institutes of Health Research
CI	confidence interval
CrI	credibility interval
CRNM	clinically relevant non-major
CV	cardiovascular
DARE	Database of Abstracts of Reviews of Effects
DSEN	Drug Safety and Effectiveness Network
FDA	Food and Drug Administration
FXa	factor Xa
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GLMM	generalized linear mixed models
ICH	intracerebral hemorrhage
INR	international normalized ratio
ISTH	International Society on Thrombosis and Haemostasis
ITT	intention to treat
MCMC	Markov chain Monte Carlo
MI	myocardial infarction
MTC	mixed treatment comparison
λ	maximum willingness to pay
NICE	National Institute for Health and Clinical Excellence
NOAC	new oral anticoagulant
NRS	non-randomized study
NSAID	nonsteroidal antiinflammatory drug
OR	odds ratio
PE	pulmonary embolism
PICO	patient/population, intervention, comparator and outcome
QALY	quality-adjusted life-year
RCT	randomized controlled trial
ROB	risk of bias
SE	systemic embolism
SIGN	Scottish Intercollegiate Guidelines Network
TIA	transient ischemic attack
TTR	time in therapeutic range
VKA	vitamin K antagonist

1 EXECUTIVE SUMMARY

1.1 Background

Approximately 250,000 Canadians are affected by atrial fibrillation (AF).[1] Stroke is a complication of AF, and Canadians with AF are five times more likely to have a stroke and are twice as likely to die than individuals without AF.[1,2] AF and stroke are more common among the elderly.[3,4]

Preventing thromboembolic events such as stroke is an important part of managing AF patients. Antithrombotic strategies for AF patients include anticoagulant drugs, notably the coumadin class of vitamin K antagonists (VKAs), such as warfarin, and antiplatelet agents, such as aspirin. VKAs reduce the risk of stroke in patients with AF by more than 60% when compared with no treatment, and by 30% to 40% when compared with low-dose aspirin.[5,6] However, VKA use is associated with some drawbacks, including a need for laboratory monitoring, an increased risk of bleeding complications, and several food and drug interactions. An improved understanding of how the blood clotting cascade works has led to the development of new oral anticoagulants (NOACs) that exhibit more predictable pharmacokinetics and pharmacodynamics, thereby obviating the need for laboratory monitoring. The NOACs that have either been approved, or are under review by regulators, for the prevention of thromboembolic events in AF patients include dabigatran, a direct thrombin inhibitor, and the direct Factor Xa (FXa) inhibitors, rivaroxaban, apixaban, and edoxaban. Ximelagatran, a direct thrombin inhibitor, was the first NOAC to be approved for use, but was withdrawn from the market in 2006 because of safety concerns.

While dabigatran, apixaban, and rivaroxaban have been demonstrated to be effective in preventing stroke/systemic embolism (SE) in AF patients, the relative effectiveness and associated bleeding risks of these NOACs, both among themselves and in comparison to warfarin, is not clear. Therefore, the aim of this project was to systematically review and analyze the safety and effectiveness of three NOACs – namely dabigatran, rivaroxaban, and apixaban – compared with warfarin in patients with non-valvular AF. In addition, the cost-effectiveness of the NOACs and warfarin was assessed using economic modelling.

1.2 Primary Research Questions

In patients with non-valvular AF:

- What is the clinical effectiveness and safety of new oral anticoagulants compared with warfarin?
- What is the cost-effectiveness of new oral anticoagulants compared to warfarin?
- How do the new oral anticoagulants compare to optimal warfarin therapy when considering the time spent in the time in therapeutic range (TTR)?
- How do the new oral anticoagulants compare to warfarin therapy in specific groups of patients with older age, other medical conditions, or who are taking other drug therapies?
- What are the costs associated with warfarin when patients are stratified according to TTR? How do these compare with estimates for the new oral anticoagulants?
- What is the cost-effectiveness of new oral anticoagulants compared to warfarin when stratified by age and $CHADS_2$ score ($CHADS_2$: C= congestive heart failure, H = hypertension, A = older than age 75 years, D = diabetes mellitus, S_2 = prior stroke or history of transient ischemic attack).?

1.3 Methods

Clinical evidence was selected systematically according to a predefined protocol following accepted guidelines.[7] Trials were selected for inclusion in the systematic review and subsequent analyses if they were carried out in AF patients, included treatment with one or more NOACs and warfarin, and included

the following outcomes: all-cause stroke/SE (stroke/SE), major bleeding, intracranial bleeding, major gastrointestinal (GI) bleeding, all-cause mortality, and myocardial infarction (MI).

Next, randomized controlled trials (RCTs) for the NOAC identified in the systematic review were used for a mixed treatment comparison (MTC) that comprised a network meta-analysis for each of the aforementioned outcomes.

Finally, the results of the MTC were used to evaluate the cost-effectiveness of warfarin and the NOACs following standard procedures.[8] The price of apixaban was assumed because this drug was not approved at the time that this report was prepared.

1.4 Results

1.4.1 Key clinical findings

The systematic review included five unique RCTs that each evaluated the non-inferiority of the three NOACs versus adjusted-dose warfarin.[9-13] Three of these RCTs (ROCKET-AF, RE-LY, ARISTOTLE) were suitable for inclusion in the network meta-analysis.

There was substantial heterogeneity among the three RCTs, including differences in trial design (blinded warfarin use versus open label), populations (specifically in baseline risk of stroke), definitions of major end points (bleeding), and duration and type of follow-up. In addition, data for the ROCKET-AF trial were not reported consistently (intention-to-treat versus as-treated data), with the exception of all-cause stroke/SE and mortality. These limitations should be borne in mind when interpreting the clinical results:

- Dabigatran 150 mg and apixaban, but not rivaroxaban or dabigatran 110 mg, significantly reduced all-cause stroke/systemic embolism compared with adjusted-dose warfarin. The absolute difference in all-cause stroke/SE for the NOACs versus warfarin ranged from two to six fewer events per 1,000 patients treated each year. Except for apixaban (1 less death per 1,000 patients), none of the NOACs significantly reduced all-cause mortality. None of the NOACs reduced the risk of **MI** relative to adjusted-dose warfarin.

- Apixaban and dabigatran 110 mg significantly reduced the risk of major bleeding relative to adjusted-dose warfarin. The absolute difference in major bleeding for all the NOACs versus warfarin ranged from one to eight fewer events per 1,000 patients treated each year. All of the NOACs significantly reduced the risk of intracranial bleeding relative to adjusted-dose warfarin, and the absolute difference versus warfarin ranged from three to five fewer events per 1,000 patients treated each year. By contrast, none of the NOACs significantly reduced the risk of major GI bleeding relative to adjusted-dose warfarin, and dabigatran 150 mg and rivaroxaban were associated with a significant increase in the risk of a major GI bleed versus warfarin. The absolute difference in GI bleeding for all the NOACs versus warfarin ranged from one fewer to eight more events per 1,000 patients treated each year.

Similar subgroup data were reported for all-cause stroke/SE and major bleeding but not consistently reported or available for other outcomes. Results from subgroup analyses are hypothesis-generating and revealed the following:

- For TTR < 66%, 150 mg dabigatran reduced the risk of stroke/SE versus warfarin, whereas 110 mg dabigatran, 150 mg dabigatran, and 150 mg apixaban reduced the risk of major bleeding versus warfarin. For TTR ≥ 66%, none of the NOACs reduced the risk of stroke/SE versus warfarin, whereas apixaban was the only NOAC that reduced the risk of major bleeding versus warfarin.

- For patients younger than 75-years-old, 150 mg dabigatran reduced the risk of stroke/SE versus warfarin, whereas 110 and 150 mg dabigatran and apixaban reduced the risk of major bleeding versus warfarin. For patients 75 years and older, 150 mg dabigatran, apixaban and rivaroxaban reduced the risk of stroke/SE versus warfarin, whereas apixaban was the only NOAC that reduced the risk of major bleeding versus warfarin.

- For lower risk patients ($CHADS_2 < 2$), 150 mg dabigatran was the only NOAC that reduced the risk of stroke/SE versus warfarin, whereas 110 mg dabigatran and apixaban reduced the risk of major bleeding versus warfarin. For high-risk patients ($CHADS_2 \geq 2$), 150 mg dabigatran and apixaban reduced the risk of stroke/SE versus warfarin, whereas apixaban was the only NOAC that reduced the risk of major bleeding versus warfarin.

1.4.2 Key economic findings

In the base-case analysis for the whole patient population, dabigatran 150 mg twice daily was the optimal treatment assuming a decision-maker is willing to pay $17,525 for each quality-adjusted life-year (QALY) gained. Dabigatran 110 mg twice daily, rivaroxaban, and apixaban were more effective and more costly than warfarin. However, they were more costly and less effective than dabigatran 150 mg.

The cost of apixaban was assumed to be the same as that of dabigatran. If the cost of apixaban was 20% less per day than dabigatran, apixaban would be the optimal treatment assuming a willingness to pay of $11,742 per QALY. The base result was very uncertain regarding the relative cost-effectiveness of apixaban and dabigatran 150 mg. The probability that dabigatran 150 mg is optimal given a willingness to pay of $50,000 per QALY was 68.1%, whereas the probability that apixaban is optimal was 29.0%.

The results of the analysis of specific patient subgroups were very sensitive to the patient population under consideration. Dabigatran 150 mg was the most cost-effective treatment option irrespective of risk of stroke ($CHADS_2$ score). Apixaban was most cost-effective in patients 80 years old, while dabigatran 150 mg was the most cost-effective treatment option in younger patients (60 or 70 years old). In centres where the TTR was < 66%, dabigatran 150 mg was the most cost-effective treatment option, whereas apixaban was the most cost-effective treatment option where the TTR was ≥ 66%. None of the NOACs were likely to be considered cost-effective for patients with a previous major stroke.

1.5 Strengths of Review

- Clinical results have been presented using relative and absolute effect measures.
- Attempts were made to adjust for heterogeneity by formally comparing results from subgroups as versus the alternative — an informal comparison.
- Results presented at the study level and using a Bayesian and frequentist network meta-analysis.
- Robustness of the cost-effectiveness results was demonstrated through extensive sensitivity analyses.

1.6 Limitations of Review

- The validity of indirect comparisons is determined by the extent of clinical and methodological trial similarity, so that differences in study populations, interventions, and outcome definitions are potential sources of incomparability.
- Heterogeneity of patient populations in the included RCTs is a key limitation, and the small number of trials available in the published literature limited the ability to adjust for this heterogeneity during analysis.

- The small number of trials in the published literature limited the modelling that could be considered primarily to fixed effects models and, as a result, study variability could not be fully incorporated.
- Not all outcomes were comprehensively or consistently reported across the three RCTs included in the network meta-analysis.
- Trial design is a potential source of bias. The open-label design RE-LY trial may have led to performance, ascertainment, or adjudication bias, when compared with the ROCKET-AF and ARISTOTLE trials, which both employed a double dummy design.
- ROCKET-AF did not report results using ITT data for many outcomes, whereas RE-LY and ARISTOTLE used ITT. As a result, only analyses for stroke/SE and all-cause mortality use for rivaroxaban use ITT data throughout.
- While outcome definitions for efficacy end points are similar across the included trials, definitions of bleeding events, especially minor bleeding, differed substantially.
- All studies included in the network meta-analysis were multinational, which could impact the generalizability to the Canadian health care system.
- The limited follow-up (maximum median of two yrs) from the three RCTs and the sensitivity of the results to the duration of treatment effect leads to uncertainty around whether the included NOACs will be cost-effective in the long term.

1.7 Conclusions

The results of this report highlight the paucity of clinical evidence available to definitively compare the efficacy and safety of the NOACs as a thromboprophylaxis in AF patients. There were three large, well-designed and properly conducted studies available for analysis, each comparing NOACs and warfarin. However, there was heterogeneity across the three RCTs and, with only three studies handling this, heterogeneity was limited. This should be borne in mind when interpreting the results.

Compared with adjusted-dose warfarin, dabigatran 150 mg and apixaban produced statistically significant reductions in stroke/SE, whereas rivaroxaban and dabigatran 110 mg did not. Apixaban and dabigatran 110 mg were associated with significantly less major bleeding versus adjusted-dose warfarin, whereas there was no association with major bleeding with dabigatran 150 mg and rivaroxaban. All treatments were associated with a significant reduction in intracranial bleeding relative to adjusted-dose warfarin, whereas no treatments were associated with a significant reduction in MI relative to adjusted-dose warfarin. No treatments were associated with a significant reduction in GI bleeding relative to adjusted-dose warfarin, but dabigatran 150 mg and rivaroxaban were associated with a significant increase. Apixaban was associated with a significant reduction in all-cause mortality relative to adjusted-dose warfarin. Even though some differences were statistically significant between treatments for some outcomes, the absolute differences for the NOACs versus warfarin where statistical significance was achieved ranged from two to a maximum of eight fewer events per 1,000 patients.

The results of the subgroup analyses were further limited by a paucity of data, but suggested that there may be subpopulations for which the use of NOACs may be more or less beneficial. In patients where warfarin treatment is well-controlled (TTR ≥ 66%), the use of NOAC may be rather less favourable — the absolute risk increase of a major bleed exceeded the absolute risk reduction of stroke/SE. In elderly patients (≥ 75 years old), the NOACs may be more favourable for preventing thromboembolic events than warfarin, but are associated with a greater risk of major bleeding. Indeed, for dabigatran 150 mg and rivaroxaban, the absolute risk of major bleeding exceeded or approached the absolute risk of stroke/SE, respectively, in this population. For low to moderate risk patients ($CHADS_2 < 2$), the NOACs were less favourable than warfarin for preventing stroke/SE, but were preferable to warfarin for reducing the absolute risk of major bleeding.

In addition to the limitations imposed by the clinical data, the results of the analysis of cost-effectiveness of the NOACs and warfarin were limited by the uncertainty regarding the pricing of the NOACs. Analysis

of the base case suggested that either dabigatran 150 mg or apixaban would be the most cost-effective treatment option. Analysis of subpopulations suggested that dabigatran 150 mg was the most cost-effective treatment option in younger patients (< 80 years old), and in centres where the TTR is < 66%, whereas apixaban was the most cost-effective treatment option in older patients (80 years old) and in centres where the TTR was ≥ 66%. None of NOACs were likely to be considered cost-effective for patients with a previous major stroke. However, the results of the cost-effectiveness analysis were highly sensitive to the patient population under consideration, reinforcing the need for tailoring the treatment of individual patients according to individual characteristics that affect treatment outcomes(includes the degree of control of which warfarin therapy (TTR), age, risk of stroke, and history of thromboembolic events).

In conclusion, the limited number of RCTs available for analysis and heterogeneity in several important features of these RCTs means that there is uncertainty regarding the comparative clinical or cost-effectiveness of the NOACs and warfarin. To fully elucidate the comparative effectiveness of these agents and facilitate the identification of subpopulations within which the NOACs might be more beneficial than warfarin, rigorously conducted comparative RCTs or network meta-regression analyses of patient-level data are required.

2 INTRODUCTION

2.1 Background — Atrial Fibrillation and Anticoagulants

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and is associated with high morbidity and mortality, much of which is due to thromboembolism, especially ischemic stroke. AF is characterized by disorganized, rapid, and irregular activity of the upper chambers of the heart (atria), associated with irregular response of the lower chambers of the heart (ventricles). Patients with AF are at a higher risk of clot formation due to the disorganization of regional atrial mechanical function, which favours thrombus formation in zones of blood stasis, especially in the left atrial appendage.[14] AF increases the overall risk of stroke four- to five-fold in all age groups[15,16] and is associated with particularly severe strokes.[17,18] AF represents a common cause of stroke among elderly people, causing approximately 25% of strokes in patients aged 80 years or older, and leads to 10% to 15% of all ischemic strokes. It has been reported to represent the most important cause of ischemic stroke in women 75 years of age and older.[1,4,14,16,17] Thus, AF is a chronic disorder. The management of patients with AF begins with the recognition of the risk and the prevention of thromboembolic complications.

2.2 Impact of the Condition on the Health of the Population

The Heart and Stroke Foundation estimates that approximately 250,000 Canadians are affected by AF.[1] The prevalence of AF increases with age (ranging from 0.1% of the population under 55 years of age to 9% among individuals aged 80 years or older) and is more prevalent in patients with structural heart diseases, hypertension, obesity, diabetes, and other chronic conditions.[19,20] After the age of 55, the incidence of AF doubles with each decade of life. Currently, about 6% of Canadians aged 65 and older have AF.[1] Because the prevalence of AF increases with age, the number of people with the disease will increase dramatically over the next 50 years. In the United States (US), the current prevalence of 3 million to 5 million persons is projected to exceed 10 million by 2050.[1,21]

The clinical and economic implications of AF are considerable given that Canadians with AF are at least five times more at risk of having a stroke and are twice as likely to die.[1,2] Furthermore, because of its high incidence and the potential for adverse outcomes, more disability results from AF than from any other cardiac arrhythmia.

Cardiovascular disease is the most costly disease in Canada, representing 11.6% of the total Canadian cost of illness, with hospitalizations accounting for 61% of direct cardiovascular disease costs. Stroke alone costs the Canadian economy $3.6 billion a year in physician services, hospital costs, lost wages, and decreased productivity (2000 statistic).[22] Canadians spend 3 million days in hospital because of stroke.[23] The rate of hospitalization for AF in Canada is about 583 per 100,000 persons, with 3% readmission within a year due to stroke. (This is noteworthy given that the hospitalization rate for AF has become an important end point in clinical studies.)[23] AF is not only a leading cause of stroke, but it is also associated with higher mortality and costlier hospital stays than stroke patients without AF.[17,24]

In the United States, the direct cost of managing AF is estimated to be over US$6 billion per year, with 50% of the cost of managing AF being directly attributable to in-patient care.[25-27] There are limited data on the cost of managing AF in Canada; however, the recently released results of a study designed to determine the cost of hospitalization for AF and to identify the main determinants of this cost in a Canadian setting revealed that the median cost of an AF hospitalization (excluding physician fees) at a large Canadian teaching hospital was C$3532, 56% of which was attributable to nursing unit care and 20% to overhead costs.[28]

2.3 Interventions Currently Available

Stroke is an established complication of AF and has been associated with greater mortality and morbidity and costlier medical care than in stroke patients without AF.[17,24,29] Hence, the prevention of thromboembolism is an important part of patient management. Current antithrombotic strategies for patients with AF include anticoagulant drugs, notably the coumadin class of vitamin K antagonists (VKAs), such as warfarin, and antiplatelet agents, such as aspirin.[30,31]

The recent Canadian Cardiovascular Society guidelines[32] recommend a risk-based approach to stroke prevention, where the choice of optimum antithrombotic therapy for a given patient depends on the risk of thromboembolism using validated stratification schemes — such as the $CHADS_2$ Score ($CHADS_2$: C= congestive heart failure, H = hypertension, A = older than age 75 years, D = diabetes mellitus, S_2 = prior stroke or history of transient ischemic attack).[33] This is because the risk of stroke is not homogeneous among all patients with AF and can vary 20-fold, depending on clinical features.[34,35] Schematically, VKA treatment is recommended for stroke prevention in patients at moderate-to-high risk (approximately 50% to 70% of patients with AF).[36,37] For patients with AF at lower risk, aspirin is recommended, though this offers only modest protective efficacy compared with warfarin.[14,31,38]

VKAs have been shown to be highly effective under optimal conditions in which a stable level of anticoagulation can be obtained. They have also been shown to reduce the risk of AF-related stroke by as much as 64%.[39-41] However, VKAs have a number of limitations:[30,31]

- They have a slow onset of action, taking several days to reach therapeutic levels.
- They have a narrow therapeutic window: insufficient anticoagulation may result in stroke, whereas over-anticoagulation increases the risk of bleeding.
- Their pharmacokinetics and pharmacodynamics are affected by genetic factors, drug–drug interactions, and consumption of foods containing vitamin K.

Due to these factors, regular coagulation monitoring and dose adjustment of VKAs are needed to ensure that anticoagulant effects remain within the narrow therapeutic range. Even with frequent monitoring and dose adjustments, patients in the United Kingdom are kept within this narrow therapeutic window (international normalized ratio [INR] 2.0-3.0) only 50% to 66% of the time.[38] The rest of the time, the patients may be at risk of bleeding (INR > 3.0) or at risk of thromboembolism (INR< 2.0). The risk of bleeding is likely to be higher in common clinical practice than in the rigorous setting of a clinical trial with a dedicated anticoagulation service.[32] Fear of adverse events and the complexity of dose management are key factors contributing to the widespread underuse of warfarin for patients with AF who are qualified candidates for therapy. Consistently with reports from other countries, in Canada, the frequency of warfarin use has been shown to be below 50% in patients over 75 years of age and in patients with two or more risk factors.[42]

Furthermore, it is worth noting that a recent Canadian study identified in-patient use of warfarin as one of the main determinants of the excessive cost of AF management.[28] This is in part due to the slow onset of action requiring in-hospital “bridging anticoagulation” until therapeutic levels were achieved. Therefore, strategies for reducing AF-related costs should focus on preventing or decreasing the length of hospital stay for patients to reach therapeutic levels by either using warfarin alternatives with quicker onset of action or using outpatient-bridging anticoagulation to facilitate earlier hospital discharge.

To date, several novel agents have been developed to replace VKAs.[30,31,43] In contrast to the latter — which prevent the synthesis of functional forms of vitamin K-dependent coagulation factors II, VII, IX, and X — these novel agents inhibit selectively the active form of a single factor of the coagulation cascade. Out of the numerous classes of new drugs, factor Xa (FXa) blockers and direct thrombin inhibitors have been most successfully studied in various indications.

2.4 New Proposed Treatments

An improved understanding of how the blood clotting cascade works has led to the evolution of NOACs with more predictable pharmacokinetics and pharmacodynamics. The NOACs, with distinctly different mechanisms of action, offer an alternative to the VKAs and have the potential to change the way patients at risk for venous and arterial thromboembolic disease are managed.

The NOACs have been developed to pinpoint a specific target for controlling the clotting cascade with maximum efficacy and minimum inconvenience. In contrast to VKAs, which target an enzyme in the vitamin K pathway that leads to the reduction of the functional levels of factors II, VII, IX, and X, many of the new agents rely on targeting a particular coagulation factor and directly inhibiting it.[30,31,40,43-46] These novel anticoagulant drugs were developed with the aim of an orally available compound that did not require monitoring of the anticoagulant effect but could be applied at a fixed dose. They reach peak maximal effect within a few hours; have predictable dose responses, thus eliminating the need for routine monitoring; and they have few, if any, important food or drug interactions, thus simplifying management.

A small number of new anticoagulants have reached phase III clinical studies for use in AF.[30,31,44-46] Usually, the safety and efficacy of novel anticoagulants are first tested in patients undergoing elective hip or knee replacement surgery, as this patient population has a relatively high rate of thrombotic events and offers a possibility of monitoring bleeding events in a hospital environment. Among the new agents at the most advanced stages of clinical development are a direct thrombin inhibitor, dabigatran, and direct FXa inhibitors, rivaroxaban and apixaban. Dabigatran and rivaroxaban have been approved in more than 70 countries for the prevention of venous thromboembolism in patients undergoing elective hip or knee arthroplasty.[47,48] Apixaban has just been approved in Europe and Canada for this indication. Dabigatran was shown in a large phase III trial to be more effective and safer than warfarin for the prevention of stroke or systemic embolism in patients with AF and has recently been approved in Canada for this indication.[9] Rivaroxaban was recently approved for AF in Canada by Health Canada.[49]

2.5 Possible Benefits and Safety of the Old and New Drugs

From a number of NOACs, several have proven to be at least non-inferior to warfarin in the prevention or treatment of thromboembolism not related to AF.[9,31,44,45] For the prevention of stroke in AF, dabigatran was one the first direct thrombin inhibitors orally available, and one of the first to provide data from a phase III trial, making it an alternative to VKAs. Previously, the first orally available direct thrombin inhibitor, ximelagatran, was studied for AF in two phase III trials, but was subsequently withdrawn from the market in 2006 by AstraZeneca due hepatotoxicity.[50]

As aforementioned, the new anticoagulants have many potential advantages over VKAs, such as rapid onset of action, predictable therapeutic effect, and lower probabilities of drug-drug interactions. This, in turn, may reduce the burden of care for physicians, increase the quality of life for the patient, and result in greater use of anticoagulants, especially for conditions like AF, which, as mentioned earlier, is widely undertreated. The new agents are not without limitations and potential adverse effects.[9,31,44,45] For example, short half-lives of the new agents make the issue of medication adherence extremely important, particularly for conditions likeAF, as missing two to three doses could lead to ineffective anticoagulation. Another issue that warrants some concern is the fact that the new agents are not free from all-drug interactions, either. In the case of dabigatran, for example, the antibiotic rifampicin can reduce its anti-clotting effects, whereas the antiarrhythmic agent amiodarone and the antihypertensive drug verapamil can enhance its anticoagulation effects.[51] Rivaroxaban, and to a lesser extent, apixaban, is metabolized in the liver by enzymes that are influenced by numerous other drugs, including antibiotics, antifungals, and anti-seizure agents.[49,52] Additionally, the Canadian drug monograph for dabigatran recommends dosing adjustment in the elderly.[53] Apixaban does not require age-related dose adjustment, and rivaroxaban, in the product monograph, mentions age only in the context of risk of bleeding.[49,52]

Another potential problem that must be addressed in the future is the reversibility of the new anticoagulants in clinical situations that require immediate reconstitution of the coagulation system (e.g., severe bleeding events). There are currently no antidotes available to reverse the action of direct thrombin inhibitors or direct FXa inhibitors. Finally, the use of novel anticoagulants for stroke prevention or prophylaxis and treatment of venous thromboembolism is likely to be substantially more expensive than VKAs. Dabigatran, for example, is available in Canada and the US[43] at approximately 20 times the cost of warfarin. However, these differences may be reduced by the lack of need for laboratory monitoring, as well as the improvement in clinical benefit for the novel anticoagulant. In fact, a recent economic analysis indicated that dabigatran is a cost-effective alternative to current care for the prevention of stroke among Canadian patients with atrial fibrillation[54] — an effect attributed to a superior prevention of stroke and systemic embolism alongside a reduction in devastating intracranial bleeding compared to well-controlled warfarin.

Although the novel anticoagulants are attractive in theory, data from large clinical trials are critical, as was strikingly demonstrated in the case of ximelagatran (a direct thrombin inhibitor, which was the first of this class to complete phase III clinical trials, including two large stroke-prevention-in-AF trials, but had to be dropped from further development because of hepatotoxicity).[55] Additional studies will show whether other drugs such as the FXa inhibitors can raise similar hopes of replacing the VKAs with stroke prevention in patients with AF. Conclusions on differences in effectiveness and safety between different new compounds will, however, be limited as long as head-to-head comparisons have not been carried out. Safety profiles will play a decisive role in the race for the most successful anticoagulant when efficacy data of most currently developed compounds show non-inferiority to VKA.

2.6 Economic Context

Although a safer, more convenient alternative to warfarin would be clinically desirable given the associated difficulties of maintaining an appropriate INR level, such alternatives must be considered in conjunction with the impact on health care costs. Currently, treatment with warfarin including regular INR monitoring costs less than C$300 per annum. The new anticoagulants examined in this report cost more than C$1,200 per annum. Thus, the cost-effectiveness of these agents will depend on the balance between the increased benefits in terms of stroke prevention, the effect on bleeding rates, and the increased drug costs.[54,56-59]

Four separate analyses of the cost-effectiveness of dabigatran versus warfarin in patients with non-valvular atrial fibrillation have been published — all in 2011, with an additional study published in 2012 relating specifically to AF patients with previous strokes.[56-60] All studies were heavily reliant on clinical data from the RE-LY clinical trial and adopted Markov models of similar format. No studies of the cost-effectiveness of rivaroxaban or apixaban in this population have been published.

In a United Kingdom (UK) study funded by the Medical Research Council, dabigatran was cost-effective compared with warfarin for a $CHADS_2$ score of 2 and for $CHADS_2$ score ≥ 3.[58] However, for centres where patients achieved good therapeutic control (average time in therapeutic range [TTR] > 66%), it was argued that dabigatran would not be cost-effective.

In a Canadian study funded by the manufacturer, dabigatran was found to have an incremental cost of C$10,440 per quality-adjusted life-year (QALY) gained compared to warfarin.[54] This finding is consistent with a US study, which found that the incremental cost per QALY gained from dabigatran versus warfarin based on the RE-LY trial population was US$12,386 when reanalyzed based on actual drug price.[57]

However, an additional US study found differing results in that the incremental cost per QALY gained from dabigatran versus warfarin based on the RE-LY trial population was US$86,000.[59]

In the most recent US study, dabigatran 150 mg was found to be cost-effective when compared to warfarin in patients with previous stroke or transient ischemic attack (TIA), with an incremental cost per

QALY gained of $25,000.[60] This study was published providing only limited details of methodology, and no statement of funding was provided. Thus, a critical review of the study is not possible.

In addition to the published studies, there is a recent UK National Institute for Health and Clinical Excellence (NICE) ERG report relating to the cost- effectiveness of dabigatran in the UK setting.[61] The ERG reanalysis found the incremental cost per QALY gained from dabigatran 150 mg compared to warfarin was £24,173. However, much of the data for this report has been redacted at the request of the manufacturer, limiting the ability to review and critique the study results.

In addition to the inconsistencies in the findings of these studies, differences in the study design and parameter estimates limit the generalizability of these studies to the Canadian context. The analysis contained in this report is the first systematic, independent analysis of the cost-effectiveness of all three NOACs in comparison with warfarin in patients with non-valvular AF.

3 CLINICAL REVIEW

3.1 Primary Research Questions

In patients with non-valvular AF:

- What is the clinical effectiveness and safety of new oral anticoagulants compared with warfarin?
- What is the cost-effectiveness of new oral anticoagulants compared to warfarin?
- How do the new oral anticoagulants compare to optimal warfarin therapy when considering the time spent in the time in therapeutic range (TTR)?
- How do the new oral anticoagulants compare to warfarin therapy in specific groups of patients with older age, other medical conditions, or who are taking other drug therapies?
- What are the costs associated with warfarin when patients are stratified according to TTR? How do these compare with estimates for the new oral anticoagulants?
- What is the cost-effectiveness of new oral anticoagulants compared to warfarin when stratified by age and $CHADS_2$ score ($CHADS_2$: C= congestive heart failure, H = hypertension, A = older than age 75 years, D = diabetes mellitus, S_2 = prior stroke or history of transient ischemic attack).?

3.2 Methods

The strategy for building and analyzing the evidence base for the NOAC consists of three fundamental steps based on a predefined systematic review protocol. First, a broad systematic review of the available randomized and non-randomized evidence in the published literature for the outcomes specified in the protocol was undertaken, following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[7] Second, a network meta-analysis was conducted involving three new oral anticoagulants in a network for each of the outcomes specified a priori. The methods and procedures followed are those developed by the Canadian Collaborative for Methods, Applications, and Capacity Development in Network Meta-Analysis for Drug Safety and Effectiveness, funded by the Drug Safety and Effectiveness Network (DSEN) of the Canadian Institutes of Health Research. Third, an economic evaluation was conducted based on the Canadian Agency for Drugs and Technologies in Health's *Guidelines for the Economic Evaluation of Health Technologies: Canada* and using the results of the network meta-analysis.[8] A summary of the protocol is provided in Appendix 7.2.

The systematic review followed a protocol written a priori and was conducted in line with the *Cochrane Handbook for Systematic Reviews of Interventions*.[7] A systematic review was undertaken to build the evidence base for the three NOAC identified in the protocol. The objective was to present an unbiased summary of all relevant studies of adequate quality in order to evaluate the clinical safety and

efficacy/effectiveness of dabigatran, rivaroxaban, and apixaban compared with adjusted-dose warfarin (and nicoumalone) in preventing morbidity and mortality in patients with non-valvular atrial fibrillation.

The patient/population, intervention, comparator and outcome (PICO) statement is:

- The patient/population of interest consists of individuals with non-valvular atrial fibrillation requiring anticoagulation.
- The interventions include dabigatran, rivaroxaban, and apixaban.
- The comparators include warfarin and other oral coumadin derivatives (i.e., nicoumalone).
- The outcomes include:
    - For the clinical assessment:
        - All-cause stroke or systemic embolism
        - Major bleeding (International Society of Thrombosis and Haemostasis [ISTH] definition)
        - All-cause mortality
        - Intracranial bleeding [including intracerebral hemorrhage(ICH)]
        - Cardiovascular mortality
        - Ischemic/uncertain stroke or systemic embolism
        - Life-threatening bleeds.
    - For the economic modelling, the following additional outcomes will be considered:
        - Primary:
            - Stroke
            - ICH
            - Extracranial hemorrhage
            - Minor bleeds.
        - Secondary:
            - Myocardial infarction (MI)
            - Pulmonary embolism (PE)
            - TIA
            - Non-cardiovascular mortality.

The evidence network will consist of published randomized controlled trials (RCTs) and non-randomized studies (NRS) if they are at least 12 weeks in duration.

3.2.1 Literature search methodology

Studies were included if the PICO criteria were met and the types of studies included published active and non-active controlled RCTs and NRS of at least 12 weeks in duration. A computerized search strategy based on this was created with the help of an information specialist in order to address clinical safety and efficacy/effectiveness simultaneously. The following electronic databases were searched through December, 2011, using an OVID interface: Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews, The Cochrane Library, 2011; Embase, 1980 to 2011; and MEDLINE, 1947 to present and In-Process & Other Non-Indexed Citations. Searches in MEDLINE and Embase used validated filters for systematic reviews, RCTs, cohorts, and case-controlled studies. No language filters were applied. Where possible, retrieval was limited to the human population. The following keywords were used to search the Cochrane Database of Systematic Reviews, DARE, and grey

literature: anticoagulants, atrial fibrillation, rivaroxaban, apixaban, edoxaban, and dabigatran. The literature search strategy is provided in Appendix 7.3.

Grey literature (literature that is not commercially published) was searched December 8, 2011 and again on January 8, 2012. Relevant grey literature was identified by searching the websites of health technology assessment and related agencies, guideline producers, and professional associations that maintain safety information on pharmaceutical products. In addition, bibliographies of included articles and relevant systematic and non-systematic reviews were searched for possible references not otherwise found. In addition, reviews for the advisory committee of the US Food and Drug Administration (FDA), Division of Cardiovascular and Renal Drug Products, on rivaroxaban and dabigatran were used as information sources. There are no FDA review documents for apixaban, as it is currently under review with an estimated date for decision listed as June 28, 2012.[62] At the time of this review, Health Canada had not yet approved apixaban for use in Canada. NICE manufacturer submissions for dabigatran and rivaroxaban were also consulted, as both drugs are currently under review for AF.[63,64]

3.2.2 Selection of studies

Studies were included if the PICO criteria and type of study outlined in the protocol (Section 2.1) were appropriate. Selection eligibility criteria were applied to each title and abstract identified in the literature search by two independent review authors in a standardized manner. Any uncertainties were resolved by discussion and consensus with a third review author. Any RCT and NRS passing the selection criteria were obtained in full-text format. Only NRS with comparative control were eligible for inclusion. The eligibility criteria were then applied and a final decision was made for inclusion. The reviewers were not blinded to study authors or centre of publication prior to study selection, as this complicates the review process and there is only weak evidence to suggest this would improve results.[65]

3.2.3 Data extraction and management

All information was extracted using a standardized data abstraction form (Appendix 7.4), which was based on the Cochrane Consumers and Communication Review Groups' data extraction template. Abstraction included:

- characteristics of trial participants including, inclusion and exclusion criteria
- type of intervention including dose, duration, and co-medication
- results of the clinical safety and efficacy/effectiveness outcomes of the intervention.[7]

All extracted data were checked for accuracy by two independent review authors.

The original, primary publication for each unique study included was used for data extraction, except where multiple publications for a single RCT or NRS were found. Multiple publications for a unique RCT or NRS (e.g., supplemental online appendices, companion publications of specific outcomes, or populations from the original study) were handled by extracting the most recently adjudicated data for each outcome specified in the protocol.

3.2.4 Quality assessment

Two sets of quality assessment instruments were considered. For RCTs, the checklist proposed by the Scottish Intercollegiate Guidelines Network (SIGN 50) for RCTs and the Cochrane Collaboration's tool for assessing risk of bias (ROB) were used.[65,66] Similarly, for NRS, the SIGN 50 checklist for cohort studies[66] and an adaption of the Cochrane Collaboration's tool for assessing ROB applicable for cohort studies were considered.[7,65]

The SIGN 50 assessment form for RCT (Appendix 7.5) consists of 14 checklist questions assessing internal validity, a question identifying the source of funding for the trial, and an overall assessment of the study by rating the methodological quality based on answers to the these questions. Answers from the

checklist are not weighted. The risk of bias is classified as either:

- Low: All or most of the criteria from the assessment of internal validity are satisfied. Study conclusions would not likely be altered if methods were changed.
- Moderate: Some of the criteria from the assessment of internal validity are satisfied. Study conclusions would not likely be altered if methods were changed.
- High: Few or none of the criteria from the assessment of internal validity are satisfied.

The Cochrane Collaboration's ROB tool (Appendix 7.6) is a two-part tool addressing six specific domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and "other issues" which were identified as a source of funding). Each domain includes one or more specific entries in an ROB table, and a form was created in line with the Cochrane Collaboration's ROB template: the first part involves describing what was reported to have happened in the study; and the second part involves assigning a judgment relating to the risk of bias for that entry by answering a pre-specified question about the adequacy of the study in relation to the entry, including a judgment of "LOW" risk of bias, "HIGH"risk of bias, and "UNCLEAR" or unknown risk of bias. Two entries were considered for the domain "blinding" for assessments of outcomes that were subjective or objective.

For each unique RCT or NRS, information for the quality appraisal was first obtained from the original publication, but additional relevant study literature was also used to conduct the assessment, including where available: design and rationale documents, companion study publications, protocols, published comments on the study, and contact with investigators.

3.2.5 Assessment of heterogeneity

We qualitatively assessed clinical and methodological heterogeneity across studies. To adjust for potential sources of heterogeneity, subgroup analyses were performed at the study-level where data was available. Additional details on assessment of heterogeneity are presented in Section 3.3.16.4.

3.2.6 Data synthesis

All outcomes of interest reported in each study were dichotomous and analyzed. For each outcome, the odds ratio (OR) and corresponding 95% confidence interval were calculated for the overall treatment effect. The absolute risk difference per 1,000 patients treated each year for each outcome was also calculated for each outcome using study-level data. Confidence intervals for absolute risk reductions were calculated by multiplying the confidence intervals of the relative risk estimates (see Appendix 7.7) by the annual baseline event rate. Although hazard ratios were reported for each study (see Appendix 7.7), ORs were used because hazard ratios were often not available for certain patient subgroups. Moreover, use of ORs facilitated comparison of study-level results with those from Bayesian MTC meta-analyses where WinBUGS code for dichotomous data is readily available and widely used.[67] Nevertheless, there were negligible differences between study-level ORs, and hazard ratios and relative risks (see Appendix 7.7).

3.2.7 Assessment of publication bias

Reporting bias was assessed by constructing funnel plots for each outcome. An asymmetrical plot would imply publication bias, as in the absence of bias the plot should resemble an inverted funnel.

3.2.8 Subgroup analysis

Subgroups of interest included: TTR, $CHADS_2$ (or $CHADS_2$-VASC) score, age (stratified as < 65 years, 65 years to 74 years, and ≥ 75 years), weight, impaired renal function (including mild, moderate, and severe), prior history of gastrointestinal (GI) bleed, concurrent use of antiplatelet agents, concurrent use of nonsteroidal antiinflammatory drus (NSAIDs).

Rational for subgroup inclusion:

1. **Weight** – Although no dosing modifications are indicated for low or high body weight in the product monographs, low weight is known to increase drug exposure in apixaban.[52] Older age is known to be associated with weight loss. Also, overweight patients are becoming increasingly common in clinical practice. There is limited evidence on novel treatments relating to weight-related safety and whether dosing should be adjusted based on higher or lower renal or hepatic clearance, or variations in other pharmacokinetic areas.

2. **Age –** Prevalence of AF increases with age and the majority of AF patients are elderly; however, this group is often under-represented in clinical trials. Both risk of bleeding and risk of stroke increases with age. Prior studies with different antithrombotic drugs showed significant interactions with age.[68] In addition, older patients have more comorbidities and are on more concomitant drugs, which could influence the efficacy and safety of old and new treatments.

3. **Renal Impairment –** The renal clearance of each new oral anticoagulant varies. According to the individual drug monographs, the renal clearance of dabigatran is 80%, meaning that the drug is mostly eliminated through the kidneys. Rivaroxaban (33%) and apixaban (27%) are less dependent on renal elimination.[49,52,53] The potential for bioaccumulation in patients with renal failure could necessitate dosage adjustments or prevent this cohort of individuals from using novel anticoagulant drugs.[69] No dosage adjustments are required for warfarin use in renally impaired patients.

4. **$CHADS_2$** – $CHADS_2$ score is a validated risk score to predict the risk of stroke in patients with AF. In addition, $CHADS_2$ score is also related to the risk of bleeding. Subgroup analyses according to $CHADS_2$ allow further exploration into the efficacy and safety of novel treatments in low- and high-risk patients.

5. **CHA_2DS_2VASc** – CHA_2DS_2VASc expands on the $CHADS_2$ score by including additional risk categories for age 64 to 75, vascular disease, and gender.

6. **Prior Use of Vitamin K Agonist** – VKA-naïve participants may be more at risk for complications in warfarin arms until the dose has been stabilized, and, therefore, warfarin arms could be subject to higher discontinuation rates. This subgroup could have implications in first- or second-line therapy choice.

7. **History of Gastrointestinal Bleed** – All bleeding complications are of interest for the novel anticoagulants and warfarin, as they can increase the risk of GI bleeding. Although this population of patients is potentially excluded in clinical trials, understanding the role of anticoagulation therapy following GI bleeding is important in the clinical setting.

8. **Concurrent use of NSAID medication** – This subgroup was prioritized through consultation with clinical experts across Canada. There are drug interactions to consider with the novel anticoagulants, and bleeding risk could increase with concurrent NSAID use.

9. **Concurrent use of antiplatelet medication** – This subgroup was prioritized through consultation with clinical experts across Canada. Bleeding risk and other adverse events associated with combining therapy with antiplatelet medications has not been quantified extensively in the novel anticoagulants.

10. **TTR** – TTR is one of the most important determinants of therapeutic effectiveness in VKA therapy, and good INR control is essential to minimizing the risk of hemorrhagic events associated with over-coagulation and stroke associated with under-coagulation. TTR can also be influenced by many factors external to anticoagulation.

3.2.9 Sensitivity Analysis

If relevant heterogeneity was present, sensitivity analysis were conducted based on aspects of the PICO statement and study methodology.

3.2.10 Network Meta-Analysis

3.2.10.1 Methods for Bayesian Mixed Treatment Comparison Meta-analysis

Bayesian mixed treatment comparison (MTC) meta-analyses were conducted for the following outcomes: all-cause stroke or systemic embolism, all-cause stroke, all-cause mortality, cardiovascular mortality, major bleeding, intracranial hemorrhage (including ICH), GI bleeding, and myocardial infarction (MI). WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) was used to conduct Bayesian MTC meta-analysis using a binomial likelihood model which allows for the use of multi-arm trials.[67,70] Both fixed and random-effects network meta-analyses were conducted; assessment of model fit and choice of model was based on assessment of the deviance information criterion (DIC) and comparison of residual deviance to number of unconstrained data points.[67,71] Trials with zero cells in both arms were excluded from evidence networks because they do not contribute information.[67]

Point estimates and 95% credible intervals were modelled for OR using Markov chain Monte Carlo (MCMC) methods. We also assessed the probability that each drug was the most efficacious regimen, the second best, the third best, and so on, by calculating the OR for each drug compared with a warfarin control group, and counting the proportion of iterations of the Markov chain in which each drug had the highest OR, the second highest, and so on. Vague or flat priors, such as $N(0, 100^2)$ were assigned for basic parameters throughout.[67] To ensure convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed.[72] Three chains were fit in WinBUGS for each analysis, with at least 20,000 iterations, and a burn-in of at least 20,000 iterations.

Both MTC and traditional meta-analysis require studies to be sufficiently similar in order to pool their results. Consequently, heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols across trials was carefully assessed.[70,71]

3.2.10.2 Methods for the Frequentist General Linear Mixed Models

A general linear mixed model (GLMM) was also used to conduct the network meta-analysis for the pre-specified outcomes following careful assessment of heterogeneity across trials regarding subject characteristics, trial methodologies, and treatment protocols.

As the outcomes followed a binomial distribution, a mixed log-binomial model was implemented with the logit link function to generate the OR estimates. Point estimates and 95% confidence intervals were provided to summarize findings.

A random effects GLMM model was conducted. The random effects trial accounted for the response variables of patients within a given trial being correlated. The random effects trial X treatment was considered to account for the correlation of responses between any two patients from the same treatment arm within a given study. However, the random effects trial X treatment had to be excluded from the model because of the small number of trials. In cases where the number of observations is lower than the number of model parameters to be estimated, then the model cannot sustain the inclusion of the trial*treatment random effect.

The GLIMMIX procedure in SAS 9.2 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

3.3 Systematic Review Results

In this section, the results of the literature review, critical appraisal of the studies identified, and comparability of the studies are provided.

3.3.1 Literature search results

The initial literature search returned 4,677 database abstracts and 30 grey literature documents. Of the 66 full-text articles assessed for inclusion after duplicates were removed, 51 were excluded for a variety of reasons detailed in the PRISMA flow diagram detailing the literature search screening and selection process (Figure 1).[73]

Five unique RCTs were identified, with a total of 51,302 study participants.[9-13] Ten companion studies, conference abstracts, conference posters, and online supplemental data appendices were also located.[74-83] Two trials had full data results posted online at www.clinicaltrials.gov, as located during the grey literature search. The grey literature search also located supplemental data for dabigatran and rivaroxaban in two reports published by the FDA from its drug approval process. The FDA data were only used where gaps in the published literature data existed; this has been noted where relevant in this report. No FDA report was available for apixaban at the time of this therapeutic review. A complete list of included and excluded studies is available in Appendix 7.8.

3.3.2 Summary of included studies

Study characteristics of the five included trials are summarized in Table 1. The review included five unique RCTs (reported in 13 literature sources and two FDA reports) evaluating the effects of NOAC in patients with non-valvular AF.[9-13,74-83] No NRS were located.

Figure 1: PRISMA Flow Diagram of Study Selection[73]

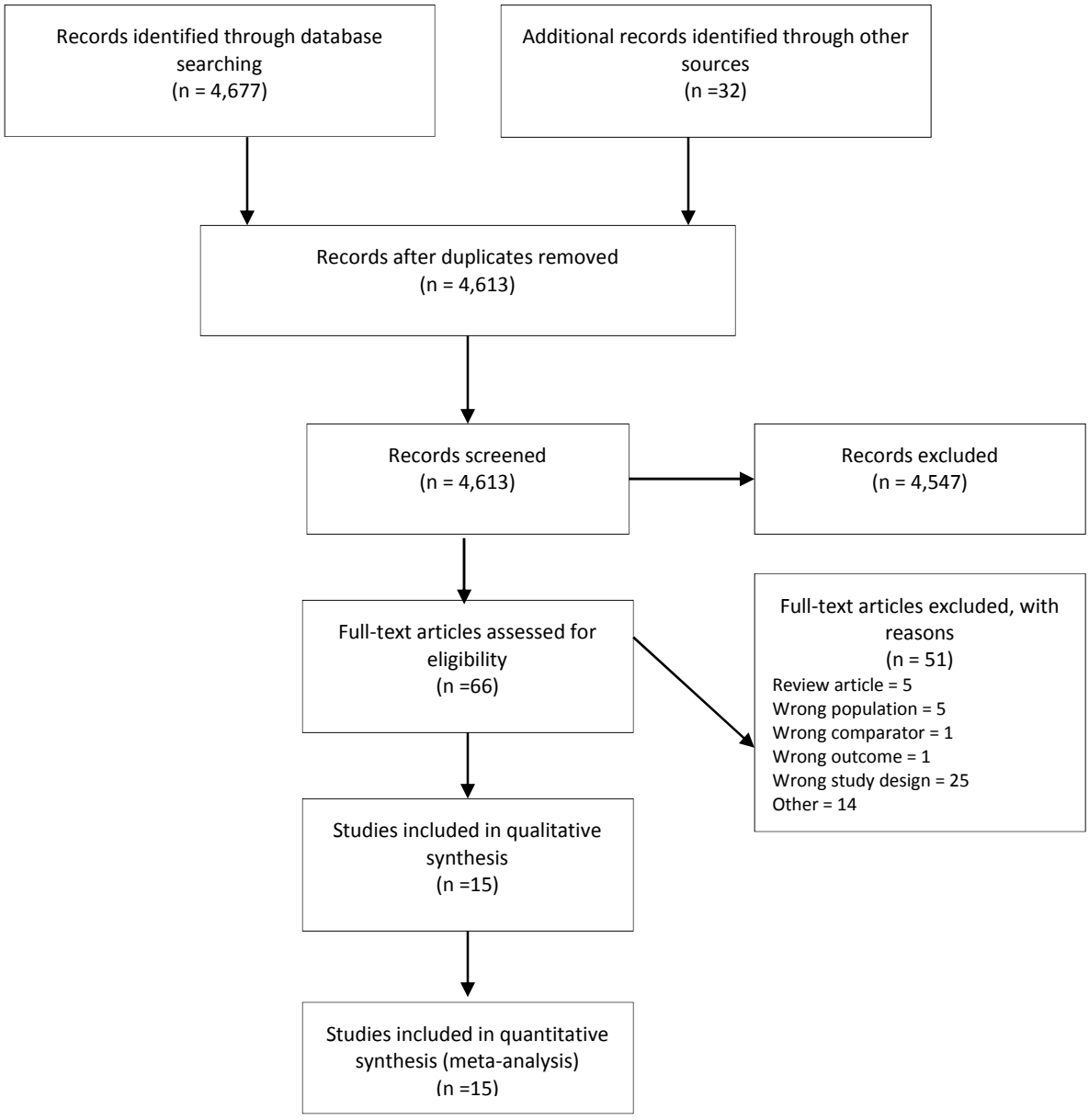


Table 1: Trial Characteristics of Included Studies[9-13,74-83]

Author, Year, Trial Name	Intervention(s) / Comparator	Randomized Sample Size	Study Duration/Exposure	Country	Sponsor	Primary Outcome(s)	TTR	Design
Connolly et al, 2009 **RE-LY**	Dabigatran 110 mg b.i.d. or dabigatran 150 mg b.i.d. VS. warfarin	N = 6,015 N = 6,076 N = 6,022 Total = 18,113	Maximum 3 years Median f/u: 2 years Subjects exposed: > 6 months =16,009 >12 months = 15,068 > 24 months = 7,262	44 countries 951 sites	BI	Combined end point of stroke or systemic embolic event	Mean 64%	PROBE (dose of dabigitran blinded, otherwise open-label)
Patel et al, 2011 **ROCKET-AF**	Rivaroxaban 20 mg q.d. VS. warfarin NOTE: 15 mg q.d. in patients with cClear of 30 to 49 mL/min	N = 7,131 N = 7,133 Total = 14,264	Maximum 4 years Median f/u: 1.9 years Subjects exposed*: > 6 months = 12,111 >12 months = 11,182 >24 months = 5,183	45 countries 1,178 sites	JJ B	Composite of stroke and non-CNS systemic embolism	Mean 55%,	Double-dummy, double-blinded
Granger et al, 2011 **ARISTOTLE**	Apixaban 5 mg b.i.d. or matching placebo VS. warfarin NOTE: (APX 2.5 mg b.i.d. for patients with 2 or more of: ≥ 80 years, body weight < 60 kg or a serum creatinine level of 1.5 mg/dL), N = 428 (4.9%)	N = 9,120 N = 9,081 Total =18,201	Maximum 4 years Median f/u: 1.8 years	39 countries 1,034 sites	BMS P	Combined end point of stroke (ischemic or hemorrhagic) and systemic embolism	Mean 62.2%	Double-dummy, double-blinded
Ogawa et al, 2011 **ARISTOTLE-J**	Apixaban 5 mg b.i.d. or apixaban 2.5 mg b.i.d. VS. warfarin	N = 74 N = 74 N = 74 Total = 222	Maximum 12 weeks Median duration of treatment: 85 days	Single country: Japan 23 sites	BMS P	Combined end point of major and clinically relevant non-major bleeding events	60% of pts had INR within the 2.0 to 3.0 range for 60% of the treatment period	Blinded APX, open label WRF, blinded outcome assessment

Table 1: Trial Characteristics of Included Studies[9-13,74-83]								
Author, Year, Trial Name	**Intervention(s) / Comparator**	**Randomized Sample Size**	**Study Duration/Exposure**	**Country**	**Sponsor**	**Primary Outcome(s)**	**TTR**	**Design**
Ezekowitz et al, 2007 **PETRO**	Dabigatran 150 mg bid[†] VS. warfarin Important to note that this was a dose-finding trial aimed at primary safety end points, not efficacy. NO formal statistical hypothesis was tested.[10]	N = 166 N = 70 Total = 502[‡]	Maximum 12 weeks	4 countries, 53 centres	BI	- Fatal or life-threatening major bleeding events - Minor/relevant bleeding events - Minor/nuisance bleeding events	57.2%	Blinded DBG, open label WRF, blinded outcome assessment (ASA use was not blinded)

APX = apixanban; ASA = acetylsalicylic acid or aspirin; B = Bayer HealthCare, BI = Boehringer Ingelheim, b.i.d. = twice daily; BMS = Bristol-Myers Squibb, cClear = creatinine clearance, CNS = central nervous system DBG = dabigatran; f/u = follow-up, INR = international normalized ratio; JJ = Johnson & Johnson Pharmaceutical Research and Development; min. = minute; PROBE = prospective; q.d. = once daily; P = Pfizer; pts = patients; WRF = warfarin; VS. = versus.

*http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM270797.pdf.

†This was a multi-dose trial. The 50 mg and 300 mg doses of the intervention were excluded from this therapeutic review. Only the 150 mg bid dose was requested for regulatory board approval in North America and Europe.[10]

‡Results from 236 patients used for data extraction due to the exclusion of the 50 and 300 mg dose groups. See section 5.3.1 for additional details.

3.3.3 Trial characteristics

Table 2 provides summaries of the characteristics of the included RCTs.[9-13,74-83] Three of the included studies are large, multinational, multicentre studies that account for 50,578 of the 51,302 randomized patients in this review.[9,11,13] The final number of randomized patients included in this review is 51,066 due to the exclusion of the 50 and 300 mg twice-daily treatment arms from PETRO.[10] One smaller RCT was conducted in four international locations (n = 502, 53 sites), and one small trial (n = 222, 23 sites) was conducted in a single country (Japan).[10,12] All trials published results in 2007 or later, and three of the trials published results in 2011.

Table 2: Summary of Trial Characteristics*

Trial Characteristics	Categories	Number of Included Studies (%)
Publication status	Literature sources	15
	Unique RCTs	5
Country	Multinational (N)	4
	Single country	1
Study design	Parallel	4
	Factorial	1
Sponsors	Industry	5 RCTs (100%)
Publication year		Range: 2007 to 2011
Randomized sample size		Range: 222 to 18,221
Number of sites		Range: 23 to 1,178

RCT = randomized controlled trial.
*9-13,74-83

3.3.4 Treatments evaluated

Evidence was available for the following interventions: apixaban (two unique RCTs),[11,12] dabigatran (two unique RCTs),[9,10] rivaroxaban (one RCT).[13] A total of five distinct treatment strategies were tested in the included studies (Table 3).

In all studies, dose-adjusted warfarin was the comparator. All warfarin arms in the five RCTs adjusted the warfarin dosage based on a target INR range of 2 to 3. One RCT used an alternative INR range of 2 to 2.6 in patients aged 70 or higher (ARISTOTLE-J). The PETRO trial evaluated dose escalation of dabigatran: 50 mg, 150 mg, and 300 mg twice daily. The 50 and 300 mg twice-daily treatment arms from this RCT have been excluded from this therapeutic review. Only the 110 mg and 150 mg twice-daily doses have been approved in Canada and Europe. It is also important to note that PETRO was aimed at evaluating primary end points related to safety and not efficacy.

The ARISTOTLE trial reduced the dose of apixaban (2.5 mg twice daily) for participants with two or more of the following characteristics:

- ≥ 80 years
- body weight ≤ 60 kg
- a serum creatinine level ≥ 1.5mg/dL (N = 428 or 4.9%).

ROCKET-AF allowed for a reduced dose of rivaroxaban (15 mg/day) in patients with reduced renal function, described as creatinine clearance of 30 to 49 mL/min.

ROCKET-AF administered study medication once daily. All other trials administered study drugs twice daily.

Table 3: Summary of Treatments Evaluated		
Treatment Evaluated	**Dose Specification**	**Studies (n)**
Apixaban	2.5 mg b.i.d.	1
	5 mg b.i.d.	2
Rivaroxaban	20 mg q.d.	1
Dabigatran	110 mg b.i.d.	1
	150 mg b.i.d.	2

b.i.d. = twice daily; mg = milligrams; q.d. = once daily.

3.3.5 Study design features

All of the studies included were RCTs with active comparators (warfarin). Placebo studies were excluded from this review. Four of five of the trials were parallel group design, and one trial (PETRO) employed a 3×3 factorial design. In the PETRO trial, randomization was stratified in the ratio 6:9:9:4 (for dabigatran 50 mg , 150 mg, and 300 mg, and warfarin, respectively). The 3×3 factorial design incorporated three different levels of concomitant aspirin (none, high, low dose) with the dabigatran; however, the aspirin dosing was not stratified in the randomization. PETRO was a dose-finding study designed to evaluate safety, and was not designed to look at efficacy.

Warfarin comparison arms were blinded in two RCTs (ROCKET-AF and ARISTOTLE) and remained open-label in the other three trials (PETRO, RE-LY and ARISTOTLE-J). Three trials (ROCKET-AF, ARISTOTLE, and PETRO) employed a placebo pills and/or sham INR adjustment to maintain the blinding of the intervention arms. The RE-LY trial blinded the dose of dabigatran, but otherwise remained open-label. All trials blinded outcome assessment.

3.3.6 Follow-up duration

The five included RCTs ranged from three to 48 months in duration. Both smaller studies (ARISTOTLE-J, PETRO) (n = 724, n = 458 included in this review) followed patients for 84 days (12 weeks), whereas the three large studies (ROCKET-AF, RE-LY, ARISTOTLE) (n = 50,578) had a mean follow-up time of 708.7 days (SD ± 27.5).

3.3.7 Funding

All the studies included were sponsored by the pharmaceutical industry.

3.3.8 Populations

Three large RCTs (ROCKET-AF, ARISTOTLE, and RE-LY) account for 50,578 of the 51,302 randomized participants. The individual trial inclusion and exclusion criteria can be found in Appendix 7.9. The five included studies randomized adults of both genders. Gender balance was relatively similar across the large trials; however, patients in all arms of the two smaller studies were predominantly male (> 81%). Mean age differed slightly among trials. The ROCKET-AF study had a higher median age (73 years) when compared with the other included studies, and differed in a number of other baseline characteristics. Patients enrolled in the ROCKET-AF trial had notably higher patient percentages of congestive heart failure, diabetes mellitus, hypertension, and prior stroke/TIA or MI (although prior MI was not reported for all trials). Specifically, the history of stroke or TIA was 20% or less in the ARISTOTLE and RE-LY studies, but was almost 55% in the ROCKET-AF study. ROCKET-AF was the only trial that allowed newly diagnosed patients with AF to enter the trial. (See Table 4.)

Table 4: Baseline Population Characteristics[9-13,74-83]										
	Age (Mean[1], Median[2])	**Male (%)**	**CHF (%)**	**DM (%)**	**HT (%)**	**Prior TIA/S (%)**	**Prior MI (%)**	**$CHADS_2$ (Mean)**	**ASA at Baseline (%)**	**VKA-Naïve (%)**
RE-LY 110 DBG	71.4[1]	64.3	32.2	23.4	78.8	19.9	16.8	2.1	40.0	49.9
RE-LY 150 DBG	71.5[1]	63.2	31.8	23.1	78.9	20.3	16.9	2.2	38.7	49.8
RE-LY WRF	71.6[1]	63.3	31.9.	23.4	78.9	19.8	16.1	2.1	40.6	51.4
ROCKET-AF RVX*	**73.0[2]**	60.3	**62.6**	**40.4**	**90.3**	**54.9**†	16.6	**3.48**	38.3	37.7
ROCKET-AF WRF*	**73.0[2]**	60.3	**62.3**	**39.5**	**90.8**	**54.6**†	18.0	**3.46**	38.7	37.5
ARISTOTLE APX	70.0[2]	64.5	35.5	25.0	87.3	19.2	14.5	2.1	31.3	42.9
ARISTOTLE WRF	70.0[2]	65.0	35.4	24.9	87.6	19.7	13.9	2.1	30.5	42.8
PETRO 150 DBG	70.0[2]	**81.3**	31.3	27.0	71.0	17.5	NR	NR	NR	0.0‡
PETRO WRF	69.0[2]	**84.3**	34.4	21.4	70.0	18.6	NR	NR	NR	0.0‡
ARISTOTLE-J 2.5 APX	69.3[1]	**85.1**	**0**	28.4	82.4	21.6	NR	1.8	20.8§	**15.3**
ARISTOTLE-J 5 APX	70.0[1]	**82.4**	**1.4**	21.6	82.4	35.1	NR	2.1	28.2§	**12.7**
ARISTOTLE-J WRF	71.7[1]	**81.1**	**2.7**	20.3	85.1	27.0	NR	1.9	25.3§	**16.0**

APX = apixaban; ASA = acetylsalicylic acid or aspirin; CHF = congestive heart failure; DBG = dabigatran; DM = diabetes mellitus; HT = hypertension; MI = myocardial infarction; RVX = rivaroxaban; TIA/S = transient ischemic attack or stroke; VKA = Vitamin K antagonist.
*ROCKET-AF data taken from intention to treat group; not per-protocol or on-treatment.
†ROCKET-AF also includes prior embolism in this category.
‡Reported 100% long-term VKA therapy.
§ARISTOTLE-J only reported concomitant ASA use during study, which has been extracted here.

These baseline differences were reflected in the higher mean $CHADS_2$ score for the ROCKET-AF study (mean 3.58 versus 2.1 for both RE-LY and ARISTOTLE) (Table 5). The RE-LY study had approximately 32% of participants, with a low-risk $CHADS_2$ score of 0 or 1; and ARISTOTLE had 34%, with a $CHADS_2$ score of 1. The ROCKET-AF trial excluded these patients. The ROCKET-AF trial had more than 85% of patients with a $CHADS_2$ score of 3 or higher, which means they were at a higher risk for stroke at baseline. Guidelines recommend that patients with a $CHADS_2$ score of 0 are not indicated for anticoagulation, as their risk of stroke is smallest.[32]

Table 5: Baseline $CHADS_2$ Score				
	0-1 (%)	**2 (%)**	**3-6 (%)**	**Mean $CHADS_2$ Score (study)**
RE-LY 110 DBG	32.6	34.7	32.7	2.13
RE-LY 150 DBG	32.2	35.2	32.6	
RE-LY WRF	30.9	37.0	32.1	
ROCKET-AF 20 RVX	0	13.0	87.0	3.48*
ROCKET-AF WRF	0	13.1	86.9	
ARISTOTLE 5APX	34.0*	35.8	30.2	2.1†
ARISTOTLE WRF	34.0*	35.8	30.2	
PETRO 150 DBG	NR	NR	NR	NR
PETRO WRF				
ARISTOTLE-J 2.5 APX	43.3	33.8	23.0	NR
ARISTOTLE-J 5 APX	36.5	32.4	31.1	
ARISTOTLE-J WRF	50.0	21.6	28.4	

APX = apixaban; DBG = dabigatran; RVX = rivaroxaban.

* The proportion of patients who had not had a previous ischemic stroke, transient ischemic attack, or systemic embolism and who had no more than two risk factors was limited to 10% of the cohort for each region.

† Excluded CHADS2 = 0

ARISTOTLE-J had a very low percentage of patients with CHD (< 1.5%), which could be attributed to the small number of participants (n = 222). It also included patients with a higher baseline level of prior stroke/TIA (21.6 to 35.1%) when compared to all other studies except for ROCKET-AF.

None of the trials reported a history of GI bleed in their baseline characteristics; however, this was an excluded population in many of the trials.

Previous use of VKA therapy also differed significantly across trials, and certain trials aimed to randomize specific proportions of VKA-naïve participants. ARISTOTLE aimed for 40% VKA-naïve, RE-LY required a balanced proportion of VKA-naïve and experienced participants, and ROCKET-AF preferentially sought VKA-naïve participants. ARISTOTLE also had stratified randomization based on participant's VKA experience. This could impact trial results, as VKA-naïve participants may be more at risk for complications in warfarin arms until the dose has been stabilized and, therefore, warfarin arms could be subject to higher discontinuation rates. ROCKET-AF rationalized that VKA-naïve patients may reflect a more realistic experience with anticoagulants as compared with those already successfully taking oral anticoagulant therapy. The PETRO trial had 100% of participants on long-term VKA therapy. Only 12% to 16% of participants in the ARISTOTLE-J trial were VKA-naïve. ROCKET-AF reported 37.5% of participants were VKA-naïve, despite having preferential enrollment for these patients. Approximately 50% of the participants in RE-LY were first-time users of VKA therapy. Numbers for ARISTOTLE fell in between those of the ROCKET-AF and RE-LY trials, with 42% being VKA-naïve at randomization.

The type of AF was reported in all three large trials, but different classification criteria were used. PETRO and ARISTOTLE-J did not report this data (see Table 6). ARISTOTLE and ROCKET-AF did not report permanent and persistent separately. Inclusion of patients with new onset atrial fibrillation was only allowed in ROCKET-AF, but the number of included patients was small (1.4%). Importantly, almost one-third of patients in RE-LY had paroxysmal A, whereas ROCKET-AF and ARISTOTLE included only 17% and 15%, respectively. The AF criteria used for patient enrollment is reported in Table 7.

Table 6: Patient Characteristics by Type of Atrial Fibrillation				
	Persistent (%)	**Permanent (%)**	**Paroxysmal (%)**	**Newly Diagnosed or New Onset (%)**
RE-LY 110 DBG	32.4	35.4	32.1	Excluded
RE-LY 150 DBG	31.4	36.0	32.6	Excluded
RE-LY WRF	32.0	34.1	33.8	Excluded
ROCKET-AF 20 RVX	81.1	NR	17.5	1.4
ROCKET-AF WRF	80.8	NR	17.8	1.4
ARISTOTLE 5 APX	84.9*		15.1	Excluded
ARISTOTLE WRF	84.5*		15.5	Excluded
PETRO 150 DBG	22.9	38.2	38.8	Excluded
PETRO WRF				
ARISTOTLE-J 2.5 APX	NR	NR	NR	NR
ARISTOTLE-J 5 APX	NR	NR	NR	NR
ARISTOTLE-J WRF	NR	NR	NR	NR

APX = apixaban; DBG = dabigatran; NR = not reported; RVX = rivaroxaban.
*Persistent and permanent AF were not reported separately for these trials.

Mean time in TTR (target INR of 2 to 3) ranged from 55% in ROCKET-AF to 64% in RE-LY. In ROCKET-AF, TTR included time on and off the drug (on treatment safety population), whereas in ARISTOTLE and RE-LY, only time on the study drug was included in this statistic. TTR in PETRO and ARISTOTLE-J may be challenging to compare with the three larger trials given their short trial duration (12 weeks) and small sample sizes.

Table 7: Atrial Fibrillation Entry Criteria	
RE-LY	AF documented by ECG in the 30 days before screening/randomization and symptomatic paroxysmal or persistent AF in previous 6 months
ROCKET-AF	AF documented by ECG in the 30 days before randomization and AF within 1 year before and at least one day before the qualifying ECG evidence. Allowed newly diagnosed AF
ARISTOTLE	AF or AFL at enrollment, or > 2 episodes of AF or AFI , > 2 weeks apart in previous 12 months
PETRO	AF – details unclear or unreported
ARISTOTLE-J	AF < 1 minute duration, occurred on 2 separate occasions, at least 2 weeks apart, within 12 months prior of enrollment

AF = atrial fibrillation, AFL = atrial flutter; ECG = electrocardiogram.

3.3.9 Concomitant medications

Trials varied regarding permitted concomitant medications. Table 8 summarizes concomitant medications allowed in the included studies. PETRO allowed high-dose acetylsalicylic acid or aspirin, defining high dose as ≥ 325 mg. Three trials (ARISTOTLE-J, RE-LY, and ROCKET-AF) allowed low-dose aspirin, up to 100 mg/day, whereas ARISTOTLE permitted up to 165 mg/day and PETRO 81 mg/day.

RE-LY permitted dual antiplatelet therapy, whereas ROCKET-AF permitted dual antiplatelet therapy only in patients undergoing appropriate vascular interventions, and at the discretion of trial investigators. ARISTOTLE-J did not permit any thienopyridine use. ARISTOTLE reported the percentage of patients taking clopidogrel at baseline, but was unclear as to whether patients could continue this medication or if it was discontinued when study medications were allotted.

Nonsteroidal antiinflammatory drugs (NSAID) were not permitted in ROCKET-AF, and "discouraged" in the RE-LY trial (no usage statistics were provided). ARISTOTLE reported NSAID use at baseline, but, again, it was unclear if participants were allowed to continue use during the trial.

Table 8: Concomitant Medications Permitted

	Thienopyridine(s)	Low Dose ASA	High Dose ASA	NSAID
RE-LY	Permitted clopidogrel, ticlopidine, dipyridamole, or ASA/dipyridamole	Permitted ≤ 100 mg/d, but did not permit over-the-counter meds containing ASA	Not permitted	"Discouraged"
ROCKET-AF	Not permitted*	Permitted ≤ 100 mg/d	Not permitted	Not permitted
ARISTOTLE	Unclear[†]	Permitted ≤ 165 mg/d	Not permitted	Unclear[‡]
PETRO	Unclear	Permitted 81 mg/d[§]	Permitted 325 mg/d[§]	Unclear
ARISTOTLE - J	Not permitted	Permitted ≤ 100 mg/d	Not permitted	Unclear

ASA = acetylsalicylic acid or aspirin; NSAID = nonsteroidal antiinflammatory medication.
[†]Both arms had 1.9% clopidogrel use at baseline, but unsure if this was discontinued at randomization.
[‡]8.35% on NSAID at baseline, but unsure if this was discontinued at randomization.
*Patients who undergo appropriate vascular interventions can receive dual antiplatelet therapy with ASA and thienopyridine at the investigator's discretion
[§] ASA use stratified by none, low- and high-dose, but not stratified prior to randomization.

3.3.10 Frequency of INR monitoring and outcome assessment

INR monitoring across included studies varied at study outset (Table 9). Participants were generally monitored for INR every 4 weeks in all five trials. ARISTOTLE, ARISTOTLE-J, and PETRO stipulated shorter interval INR assessment in the first month of the trial, and ARISTOTLE had a different initial monitoring frequency based on the participants' VKA-naïve or experienced status. All three large trials permitted individual INR monitoring to be adjusted as clinically indicated to maintain an INR between 2 and 3. PETRO and ARISTOTLE-J did not report if more frequent monitoring was permitted to maintain INR, or whether any increased monitoring occurred. These trials were much shorter in duration and, therefore, less time was available to assess and adjust INR during the trial.

Table 9: Frequency of INR Monitoring

RE-LY	At least once every 4 weeks. Dose adjustments required to maintain INR 2 to 3, were made by the local investigator. A warfarin dose-adjustment algorithm was provided to centres, but the protocol did not mandate its use. (See Appendix 1, available online.)
ROCKET-AF	At least once every 4 weeks or as often as clinically indicated.
ARISTOTLE	*WRF-naïve:* Day 4, 2 × week for 2 weeks, 1 × week for 2 weeks, and then monthly once stable INR attained. *WRF-experienced*: Day 1, week 1, week 2, then monthly. An investigator may increase the frequency of INR monitoring if it is considered clinically indicated.
PETRO	1, 2, 4, 8, and 12 weeks
ARISTOTLE-J	1, 2, 4, 8, and 12 weeks.

INR = international normalized ratio.

Table 10: Frequency of Outcome Assessment	
RE-LY	Study visits at 14 days (via telephone), months 1 and 3 and then: Year 1, every 3 months Year 2+, every 4 months
ROCKET-AF	1, 2, and 4 weeks, and every month thereafter for detection of primary efficacy end point events, TIA, MI, bleeding, procedures, and vital status evaluation. end of study visit within 30 days of event
ARISTOTLE	Event-driven with no designated follow-up except for INR monitoring (sham apixaban titration mentioned but unclear if visits were matched), as reported in table 9above. All subjects will be followed from randomization until the study end-date. Follow-up scheduled until the attainment of at least 448 primary study events
PETRO	1, 2, 4, 8, and 12 weeks
ARISTOTLE-J	1, 2, 4, 8, and 12 weeks.

MI = myocardial infarction; TIA = transient ischemic attack.

Frequency of outcome assessment during the trial and at the end of study varied (Table 10). ARISTOTLE was an event-driven trial, and the only follow-up was sham or real INR monitoring, with no other scheduled visits until 448 primary events occurred, or four years, whichever came first. PETRO and ARISTOTLE-J did not provide detailed outcome or assessment details; however, given the short duration of both trials, it is assumed that follow-up and outcome assessment occurred simultaneously, ending at 12 weeks. RE-LY and ROCKET-AF followed patients up for a maximum of three and four years, respectively. After year one, RE-LY monitored patients every three months, and then every four months during year 2 and 3. ROCKET-AF followed up with patients every month until the end of the study.

3.3.11 Patient disposition

3.3.11.1 Early withdrawals

Study-level detail regarding the proportion of patients who withdrew from each trial is presented in Table 11. There is a potential source of bias due to withdrawals and early discontinuation of study medications in some of the included RCTs. This potential issue with participant retention could be attributed to either the proportion of withdrawals across study arms, or for the trial as a whole, or the reasons cited for discontinuing the study medications (see Table 11).

Reporting of withdrawals and discontinuation was difficult to reconcile across trials. Both PETRO and ARISTOTLE-J reported study medication discontinuation, but zero loss to follow-up. Details on discontinuation and loss to follow-up were well reported for the three large trials; however, each differed in presentation and how final numbers and analysis populations were described.

The trials report low percentages of participants who were lost to follow-up, but have very high numbers of patients who discontinued from the study medications (20% to 35%), with varying rates of follow-up completion. ROCKET-AF and RE-LY report both discontinuations from the study and of study medications (FDA reports). In those who discontinued study medications, many continued follow-up. Tables reporting this data state that subjects may be double-counted; however, it is not possible to differentiate exactly where double-counting occurred.

RE-LY and ARISTOTLE report both loss-to-follow-up, and subjects where they have participants with final vital status unknown at the end of study. Further detail is not provided.

Table 11: Patient Disposition[9-13,74-83]					
Study Arm (n)	**Randomized (n)**	**Loss to Follow-up (n)**	**Discontinued Study Drug (n)**	**Primary Reasons Provided (n or % as stated)**	**Additional Details Provided**
RE-LY 110 DBG	6,015	17	**203**[1] (3.4%) **1,170**[2] (19.6%)	**For [1]:** Sites closed for cause = 25 Withdrew consent = 126 Lost to follow-up = 17 Other = 35	Final vital status unknown = 5
RE-LY 150 DBG	6,076	31	**235**[1] (3.9%) **1,197**[2] (19.8%)	**For [1]:** Sites closed for cause = 27 Withdrew consent = 144 Lost to follow-up =31 Other =33	Final vital status unknown = 8
RE-LY WRF	6,022	40	**242**[1] (4.0%) **907**[2] (15.1%)	**For [1]:** Sites closed for cause = 27 Withdrew consent = 136 Lost to follow-up =40 Other = 39	Final vital status unknown = 11
ROCKET-AF 20 RVX	7,131	18	**1,124**[1] (15.8%) **1,396**[2] (19.6%)	**For [1]:** Died = 599 Consent withdrawn = 406 Lost to follow-up = 18 Other = 101	Total discontinued study medication = 35.44%
ROCKET-AF WRF	7,133	15	**1,151**[1] (16.1%) **1,325**[2] (18.6%)	**For [1]:** Died = 650 Consent withdrawn = 390 Lost to follow-up = 15 Other = 96	Total discontinued study medication = 34.64%
ARISTOTLE 5 APX	9,120	51	2,310 (25.3%)	AE = 679 Death = 331 Subject request = 921 Other = 379	Vital status unknown at EOS = 180, itemized by: Withdrawn consent = 92 Lost to follow-up = 35 Other = 53
ARISTOTLE WRF	9,081	39	2,493 (27.5%)	AE = 738 Death = 349 Subject request = 989 Other = 417	Vital status unknown at EOS = 200, itemized by: Withdrawn consent = 107 Lost to follow-up = 34 Other = 59
PETRO 150 DBG	166	0	11	AE = 9[†]	n/a
PETRO WRF	70	0	2	AE = 0	n/a
ARISTOTLE-J 2.5 APX	74	0	7 (9.5%)	NR	NR
ARISTOTLE-J 5 APX	74	0	5 (6.8%)	NR	NR
ARISTOTLE-J WRF	74	0	9 (12.2%)	NR	NR

APX = apixaban; DBG = dabigatran; EOS = end of study; RVX = rivaroxaban; WRF = warfarin.

ROCKET-AF numbers based on safety population; "other" mostly due to sites that were closed (also taken from FDA report).
[†] PETRO: Some points had more than one event.
[1] Prematurely discontinued, did not complete follow-up.

[2] Stopped study medication prematurely but completed follow-up.

Analysis populations

Analysis populations were assessed for all studies included in this review. PETRO and ARISTOTLE-J reported no formal statistical hypothesis testing. PETRO provided no definitions for study populations used to present outcome data. ARISTOTLE-J reported tghree different populations used to assess bleeding, efficacy, and safety, but no P-values or confidence intervals are presented due to the lack of a formal statistical test. ARISTOTLE and RE-LY analyzed primary outcomes using ITT populations with ARISTOTLE, also reporting a modified ITT analysis for safety. ROCKET-AF presented a minimum of four study populations, reporting primary non-inferiority analysis on per-protocol populations, primary superiority analysis on the "safety/on treatment" population, and post-hoc analysis in ITT "up to site notification" or ITT "up to data cut-off." Definitions, where available, are listed as follows:

ROCKET-AF:

1. Per-Protocol = Received one dose of study drug, no major protocol violations, and were followed for events while receiving a study drug, or within two days after discontinuation.
2. Safety On Treatment = Received at least one dose, were followed for events, regardless of adherence to protocol, while receiving assigned study drug or within two days of discontinuation.

ARISTOTLE:

1. ITT.
2. Modified ITT sensitivity analysis to analyze bleeding that occurred in patients who received at least one study dose.

RE-LY: All analyses ITT.

ARISTOTLE-J: No formal statistical hypothesis tested. No P-values or confidence intervals presented.

1. "Treatment period" analysis for bleeding events = Starting on the day of first dosing and continuing until two days after discontinuation.
2. Efficacy**:** based on "intended treatment period" = Starting on the day of randomization and ending either two days after the last dose of study drug or at the 12-week visit, whichever came last.
3. Safety = All patients who received at least one dose of study medications.

PETRO: Dose-finding study. No formal statistical hypothesis tested.

3.3.12 Outcomes

The relative safety and efficacy of the new oral anticoagulant drugs was assessed for the outcomes listed in section 6. An overview of the RCT evidence available for each outcome of interest is presented in Table 12.

Table 12: Summary of RCT Evidence by Outcome	
Outcome	**RCTs Reporting (n)**
All-cause stroke or systemic embolism	4
Ischemic/uncertain stroke or systemic embolism	0
All-cause mortality	5
Cardiovascular mortality	4*
Major bleeding	5
Intracranial hemorrhage (including ICH)	4
Life-threatening bleeding	2

ICH = intracerebral hemorrhage; RCT = randomized controlled trial.

* Sometimes reported in studies within vascular mortality

3.3.12.1 All-cause stroke or systemic embolism

This composite outcome had similar definitions across trials in which the outcome definition was reported. PETRO did not report this outcome, and ARISTOTLE-J did not provide a definition (Table 13).

Table 13: Composite Definition for All-cause Stroke or SE			
	ARISTOTLE	**RE-LY**	**ROCKET-AF**
Primary	Ischemic or hemorrhagic stroke or systemic embolism	Stroke (including hemorrhagic) or systemic embolism	Composite of stroke (ischemic or hemorrhagic) and SE
Secondary	Stroke was defined as a non-traumatic focal neurologic deficit lasting ≥24 hours. A retinal ischemic event (embolism or thrombosis) was considered a stroke. A cerebral imaging study (CT scan or MRI) was recommended for all suspected strokes.	Defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery and categorized as ischemic, hemorrhagic, or unspecified. Hemorrhagic transformation of ischemic stroke was not considered to be a hemorrhagic stroke.	Stroke was defined as a sudden focal neurologic deficit of presumed cerebrovascular etiology that persisted beyond 24 hours and was not due to another identifiable cause.

CT = computed tomography; MRI = magnetic resonance imaging; SE = systemic embolism.
NOTE: PETRO did not report this outcome; ARISTOTLE-J did not provide a definition for this outcome.

3.3.12.2 Major bleeding (ISTH definition)

The Subcommittee on Control of Anticoagulation, of the Scientific and Standardization Committee of the ISTH, endorses the following criteria for major bleeding in non-surgical patients:

- fatal bleeding, and/or
- symptomatic bleeding in a critical area or organ, such as intracranial, instraspinal, intraocular, retroperitoneal, intraarticular, or pericardial, or intramuscular with compartment syndrome, and/or
- bleeding causing a fall in hemoglobin level of 20g L (-1) (1.24 mmol/L[-1]) or more, or leading to a transfusion of two or more units of whole blood or red cells.

Major bleeding definitions are comparable across trials, and all trials followed the ISTH definition, even where it was not specifically stipulated that this definition was used. ROCKET-AF added permanent disability to its definition of major bleeding, the only departure from the ISTH classification (Table 14).

Table 14: Major Bleeding Definitions					
ISTH Definition Component	**ARISTOTLE**	**RE-LY**	**ROCKET-AF**	**PETRO**	**ARISTOTLE-J**
Fatal Bleeding	ISTH	Matches ISTH "fatal bleeding"	Matches ISTH "fatal outcome"	Matches ISTH "fatal bleeding"	ISTH
Symptomatic bleeding in critical area	ISTH	Similar to ISTH symptomatic bleeding into a critical area or organ. Major bleeding was separated into intracranial (intracerebral, subdural) and extracranial (GI, non-GI) bleeding	Matches ISTH "critical anatomic site," with same examples as ISTH	Life-threatening retroperitoneal, intracranial, intraocular, or intraspinal bleeding; or bleeding requiring surgery	ISTH
Bleeding causing hemoglobin fall or leading to transfusion	ISTH	Fall in hemoglobin at least 20g/L or transfusion of > 2 units of whole blood (packed cells mentioned in life-threatening *bleed definition)	Matches ISTH fall in hemoglobin > 2g/dL or transfusion of > 2 units of whole blood/red cells	Bleeding requiring surgery or transfusion of ≥2 U or associated with a decrease in hemoglobin of ≥ 2.0 g/L. episodes	ISTH
Other criteria included beyond ISTH			Permanent disability		

GI = gastrointestinal; ISTH = International Society on Thrombosis and Haemostasis; U = unit.
*RE-LY definition of life-threatening bleeding: ≥ 1 of the following criteria: (1) fatal, symptomatic intracranial bleed; (2) reduction in hemoglobin level of at least 5.0 g/L; (3) transfusion of at least 4 U of blood or packed cells; (4) associated with hypotension requiring the use of intravenous inotropic agents; or (5) necessitated surgical intervention.

3.3.12.3 All-cause mortality

All-cause mortality was reported in similar fashion in the included studies.

3.3.12.4 Cardiovascular mortality

Cardiovascular (CV) mortality was sometimes reported in studies within vascular mortality.

3.3.12.5 Ischemic/uncertain stroke or systemic embolism

This composite outcome was not reported in any trials and, therefore, no definitions were reported in any of the included studies.

3.3.12.6 Life-threatening bleeds

Regarding RE-LY, life-threatening bleeding was a subset of major bleeding that included fatal or symptomatic intracranial bleeding, bleeding associated with a hemoglobin decrease of 5.0 g/dL, or requiring transfusion of four units of blood or inotropic agents, or bleeding necessitating surgery.

3.3.12.7 Minor bleeding

There is currently no established definition or criteria for minor bleeding similar to the ISTH definition for major bleeding. Definitions for minor bleeding varied significantly in all five included studies, and made across-trial comparisons difficult. ARISTOTLE and ROCKET-AF reported clinically relevant non-major (CRNM) bleeding, whereas RE-LY and PETRO report only minor bleeding. PETRO and ARISTOTLE-J reported both CRNM bleeding and minor bleeding separately, or as subgroups within a broader definition. The primary safety outcome for ROCKET-AF was the composite outcome of CRNM bleeding and major bleeding, and ARISTOTLE also reported this composite outcome (Table 15).

PETRO is specific in its definition of minor bleeding; as this was a primary outcome assessed in the trial; however, the definition also includes a clause where any other relevant bleeding deemed important by investigators could be added. RE-LY reported a truncated definition of minor bleeding that included all other bleeding that was not major or ICH-related. ARISTOTLE-J likewise gave a somewhat open minor bleeding definition that includes all acute, clinically overt bleeding events that do not fit into the CRNM or major bleeding categories. The definitions of CRNM bleeding also vary in those trials that reported this as an outcome. Definitions for CRNM bleeding in ARISTOTLE and ARISTOTLE-J are equivalent; however, the CRNM bleeding definition used by ROCKET-AF differs. For example, the definition used for the ROCKET-AF trial bleeding requiring any medical intervention or unscheduled contact, not only hospitalization as specified in the comparable definitions. It also includes the impairment of any daily activities, with no further instruction on level of impairment or functional limitations. ISTH notes that characteristics for hospitalization on medical contact have been intentionally left out of the major bleeding definition, as they can be influenced by a number of external factors, not limited to community medical access, availability of beds, and presence of comorbidities.

Table 15: Minor Bleeding Definitions

	ARISTOTLE	RE-LY	ROCKET-AF	PETRO	ARISTOTLE-J
Outcome	CRNM bleeding	Minor bleeding	CRNM bleeding	Minor bleeding subdivided into clinically relevant or nuisance bleeding	2 outcomes defined: CRNM bleeding *and* minor bleeding
Defined As	Acute or sub-acute clinically overt bleeding that did not satisfy the criteria for major bleeding and led to hospital admission for bleeding, physician-guided medical or surgical treatment for bleeding, or a change in antithrombotic therapy (including study drugs) for bleeding	All other bleeding (except major and ICH)	Overt bleeding not meeting the criteria for major bleeding but requiring medical intervention, unscheduled contact (visit or telephone) with a physician, temporary interruption of study drug (i.e., delayed dosing), pain, or impairment of daily activities)	Clinically relevant bleeding was defined as skin hematoma > 25 cm^2, spontaneous nosebleed of > 5 minutes duration, macroscopic hematuria, spontaneous rectal bleeding, gingival bleeding for >5 minutes, any bleeding leading to hospitalization, any bleeding leading to transfusion < 2 U, or any other bleeding considered	CRNM defined as acute or subacute, clinically overt, not major, and leading to hospital admission for bleeding, physician- guided medical or surgical treatment for bleeding, or a change in antithrombotic therapy Minor bleeding events defined as acute clinically overt events not meeting the

				relevant by the investigator.	criteria for either major or CRNM bleeding

*CRNM = clinically relevant non-major bleeding; U = units.

3.3.12.8 Gastrointestinal bleeding

GI bleeding was not explicitly defined across all studies included in this therapeutic review. ROCKET-AF included GI bleeding within a category defined as major mucosal bleeding, which included gingival, epistaxis, and upper GI tract bleeding, and further categorized data into life-threatening mucosal bleeding. RE-LY reported data for both major GI bleed and any GI bleed, whereas ARISTOTLE-J reported GI bleeds within the ISTH major bleeding outcome. Life-threatening versus non–life-threatening bleeding was not defined or reported in RE-LY or ARISTOTLE-J. No GI bleeding outcome data has been reported for ARISTOTLE.

3.3.13 Subgroups

The following sub-groups of interest were specified a priori:

- Weight
- Age
- Renal impairment
- $CHADS_2$
- $CHADS_2VASC$
- Prior use of vitamin K Agonist
- History of GI
- Concurrent use of NSAID medication
- Concurrent use of antiplatelet medication
- TTR.

Subgroup analysis was limited by availability of data. Appendix 7.10 contains a comparison table of data available for each subgroup across all included studies. Event numbers were too small to include study-level data from ARISTOTLE-J or PETRO in the subgroup analyses. Availability of data and categorization differed across trials, and it was not possible to conduct analysis for the majority of the pre-specified subgroups.

Where published data were available, subgroup categories were collapsed into comparable sets for ARISTOTLE, RE-LY, and ROCKET-AF. Subgroup analyses were conducted for age (< 75 or ≥ 75), TTR (< 66% or ≥ 66%), and $CHADS_2$ score (< 2 or ≥ 2) for the outcomes of all-cause stroke/SE and major bleeding. The reported data and study subgroups in ARISTOTLE, RE-LY, and ROCKET-AF were not informative or consistent enough to identify across these three studies a common subgroup based on weight, renal impairment, $CHADS_2VASC$, prior use of VKA, history of GI bleed, concurrent use of NSAID medication. and concurrent use of antiplatelet medication (Appendix 7.10).

3.3.13.1 Subgroup credibility assessment

The outcomes of all-cause stroke/SE and major bleeding were assessed with respect to the criteria for the credibility of subgroup analyses (Oxman 1992[84], updated by Sun 2010[85]) (Table 16). Data were analyzed for the subgroups of age, TTR, and $CHADS_2$ for the primary outcomes of all-cause stroke or SE and major bleeding. No other subgroup data was analyzed in this review.

The intention of applying the criteria suggested by Sun et al.[85] is to aid the decision-making process by providing clarity and perspective on whether subgroup analyses can be considered spurious or reliable. Evaluating the difference of effect between study subgroups usually involves some measure

of uncertainty or confidence. Often, theoretical subgroup effects cannot be explicitly accepted or rejected but, rather, placed on a spectrum of likelihood based on whether we believe the subgroup effect to be true (highly plausible) or false (unlikely). In looking at the criteria in Table 16, the greater the number of criteria that are satisfied for each subgroup and outcome, the more plausible is the hypothesized subgroup effect.[84,85]

Table 16: Criteria to Assess the Credibility of S**u**bgro**u**p Analyses

For all-cause stroke or SE				
		RE-LY	**ROCKET-AF**	**ARISTOTLE**
Is the subgroup variable a characteristic measured at baseline or after randomization?	**Age**	Y	Y	Y
	TTR	Y	Y	Y
	$CHADS_2$	Y	Y	Y
Is the effect suggested by comparisons within rather than between studies?	**Age**	Y	Y	Y
	TTR	Y	Y	Y
	$CHADS_2$	Y	Y	Y
Was the hypothesis specified a priori?	**Age**	Y	Y	Y
	TTR	Y	Y	Y
	$CHADS_2$	Y	Y	Y
Was the direction of the subgroup effect specified a priori?	**Age**	N	N	N
	TTR	N	N	N
	$CHADS_2$	N	N	N
Was the subgroup effect one of a small number of hypothesized effects tested?	**Age**	Y	Y	Y
	TTR	Y	Y	Y
	$CHADS_2$	Y	Y	Y
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	**Age**	N	N	N
	TTR	N	N	N
	$CHADS_2$	N	N	N
Is the significant subgroup effect independent?	**Age**	N/A	N/A	N/A
	TTR	N/A	N/A	N/A
	$CHADS_2$	N/A	N/A	N/A
Is the size of the subgroup effect large?	**Age**	N/A	N/A	N/A
	TTR	N/A	N/A	N/A
	$CHADS_2$	N/A	N/A	N/A
Is the interaction consistent across studies?	**Age**	N/A	N/A	N/A
	TTR	N/A	N/A	N/A
	$CHADS_2$	N/A	N/A	N/A
Is the interaction consistent across closely related outcomes within the study?	**Age**	N/A	N/A	N/A
	TTR	N/A	N/A	N/A
	$CHADS_2$	N/A	N/A	N/A
Is there evidence that supports the hypothesized interaction (biological rationale)?	**Age**	N	N	N
	TTR	N	N	N
	$CHADS_2$	Y	N	N
For major bleeding				
		RE-LY	**ROCKET-AF**	**ARISTOTLE**
Is the subgroup variable a characteristic measured at baseline or after randomization?	**Age**	Y	Y	Y
	TTR	Y	Y	Y
	$CHADS_2$	Y	Y	Y
Is the effect suggested by comparisons within rather than between studies?	**Age**	Y	Y	Y
	TTR	Y	Y	Y
	$CHADS_2$	Y	Y	Y
Was the hypothesis specified a priori?	**Age**	Y	Y	Y
	TTR	Y	Y	Y
	$CHADS_2$	Y	Y	Y

Table 16: Criteria to Assess the Credibility of S**u**bgro**u**p Analyses				
Was the direction of the subgroup effect specified a priori?	**Age**	N	N	N
	TTR	N	N	N
	$CHADS_2$	N	N	N
Was the subgroup effect one of a small number of hypothesized effects tested?	**Age**	Y	Y	Y
	TTR	Y	Y	Y
	$CHADS_2$	Y	Y	Y
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	**Age**	Y	N	N
	TTR	Y	N	N
	$CHADS_2$	N	N	N
Is the significant subgroup effect independent?	**Age**	N/A	N/A	N/A
	TTR	N/A	N/A	N/A
	$CHADS_2$	N/A	N/A	N/A
Is the size of the subgroup effect large?	**Age**	N/A	N/A	N/A
	TTR	N/A	N/A	N/A
	$CHADS_2$	N/A	N/A	N/A
Is the interaction consistent across studies?	**Age**	N/A	N/A	N/A
	TTR	N/A	N/A	N/A
	$CHADS_2$	N/A	N/A	N/A
Is the interaction consistent across closely related outcomes within the study?	**Age**	Y	Y	N
	TTR	Y	Y	Y
	$CHADS_2$	Y	Y	N
Is there evidence that supports the hypothesized interaction (biological rationale)?	**Age**	Y	N	N
	TTR	Y	N	N
	$CHADS_2$	N	N	N

SE = systemic embolism; N = no; N/A = not applicable; TTR = time in therapeutic range; Y = yes.

3.3.14 Critical appraisal

The SIGN 50 quality assessment instrument and the Cochrane Collaboration's ROB tool were used to critically appraise the included studies. The details of these assessments are provided in Appendices 7.5.1 and 7.6.1. Summaries of these assessments are given in Table 17.

The overall SIGN 50 assessment of the methodological quality of the study is based on criteria related to the design and conduct of the study using the following coding system:

++ All or most of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter.

+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.

- Few or no criteria have been fulfilled. The conclusions of the study are thought likely or very likely to alter.

All studies had reasonable quality, with the quality of the ARISTOTLE, ROCKET-AK, and PETRO identified as "very good," and RE-LY and ARISTOTLE-J considered "good."

For the ROB, low, unclear, and high risk of bias are identified for different sources of bias in the design of the study. For eight sources of bias, all studies did well with ≥ 5 of the 8 criteria scored low or unclear bias.

Table 17: Critical Appraisal Summary*					
	ARISTOTLE	**RE-LY**	**ROCKET-AF**	**PETRO**	**ARISTOTLE-J**
SIGN 50 (-/+/++)	++	+	++	++	+
Risk of Bias (low/unclear/high)	3/ 2/ 3	2/ 4/ 2	4/ 1/ 3	3/ 4/ 1	4/ 2/ 2

* See explanation of coding system in section 3.3.15.

3.3.15 Sources of Bias

3.3.15.1 Handling of missing data

No bias could be identified for handling missing data. A small number of patients (0% to 0.66%) were lost to follow-up (Table 11).

3.3.15.2 Methodological limitations

The small number of trials limited the applicability of random effects models because vague and weak informative prior distributions of the between-study variance have been shown to exert an unintentionally large degree of influence on any inference. Similarly, the random effects trial treatment had to be excluded from the GLMM model due to the small number of trials. Without including random effects terms, the full variability in the data cannot be included with the results.

Further, not all outcomes of interest were reported, in particular for various predefined subgroups. In particular, life-threatening bleeding and the composite ischemic/uncertain stroke or SE were often not reported in studies and CV-mortality was reported within vascular mortality (Table 12). All-cause mortality, intracranial bleeding, MI, and major GI bleeding were not reported by subgroups of interest TTR, age, and $CHADS_2$ score.

3.3.15.3 External validity

As all major studies were performed as multinational, multicentre trials, generalizability to the Canadian health care system may be limited. Treatment of comorbidities and management of patients who are candidates for warfarin may differ between various countries. Further, TTR of warfarin treatment showed substantial differences between the trials and was also affected by geography. In RE-LY and ARISTOTLE, INR-control rates were substantially better than in ROCKET-AF. Skillful warfarin use as a predictor of treatment success might play a role to transfer trial results to the Canadian setting. In addition, the usual generalizability issues associated with randomized controlled trials need to be considered. In particular, the inclusion and exclusion criteria identifying the patients' eligibility for the study may be different than in clinical practice, where prescribing practices may provide these drugs to patients with contraindications (such as low body weight or impaired renal function) leading to increased bleeding risk.

3.3.15.4 Clinical and methodological heterogeneity

The validity of indirect comparisons is determined by the extent of clinical and methodological trial similarity, so that differences in study populations, interventions, and outcomes definitions are potential sources of biases or errors.

ROCKET-AF included higher-risk patients with a $CHADS_2$ score of at least 2, which limits the comparability of treatment effects to lower risk patients and to results from RE-LY and ARISTOTLE (which included more patients at low risk). In addition, ROCKET-AF also aimed to include a substantially higher number of patients with prior TIA, stroke, or SE (55%) compared to RE-LY (20%, not including prior SE) and ARISTOTLE (20%).

While ROCKET-AF and ARISTOTLE were designed as double-blind trials, warfarin treatment was not blinded in RE-LY, which might be a potential source of bias such as performance bias (i.e., systematic differences between groups in the care provided or exposure to factors other than the interventions of interest).

In ROCKET-AF, non-inferiority of rivaroxaban was achieved for the primary outcome stroke/SE in the safety of treatment population, mostly due to a rather high number of events in the transition phase after stopping the study drug. Thus, the magnitude of treatment effect was smaller in the ITT population. The implication of this observation for drug use in clinical routine is unclear, but does indicate differences in methodology between the trials.

While outcome definitions for efficacy end points are similar throughout the included trials, definitions of bleeding events differed substantially, in particular for minor bleeding (RE-LY) or non-major clinically relevant bleeding (ROCKET-AF and ARISTOTLE). Thus, these bleeding rates were markedly higher in RE-LY and ROCKET-AF compared to ARISTOTLE, limiting the comparability of results in network meta-analysis.

A number of areas were identified where there was clinical and methodological heterogeneity across trials, particularly for the ROCKET-AF trial (Table 18). The differences in the trials are partially reflected in the variation of the event rates in the warfarin control group seen across studies, particularly for the ROCKET-AF study. The small number of data points in our evidence network, however, restricted the ability to assess the impact of heterogeneity using standard approaches such as meta-regression. Heterogeneity was therefore assessed by conducting network meta-analysis using subgroup data reported in the individual RCTs. The methodological limitations with this approach are acknowledged (e.g., lack of information on similarity of patients across subgroups). In most instances, subgroup data was only available for the primary efficacy and safety outcomes in the trials — all-cause stroke/SE and major bleeding outcomes. As a consequence, the ability to explore the impact of heterogeneity between studies regarding patient population and study design for other outcomes considered in the network meta-analyses was limited (Table 18).

Table 18: Approach to Addressing Key Areas of Clinical and Methodological Heterogeneity

Issue	Description of Heterogeneity	Action
TTR (centre TTR)	TTR (target INR of 2 to 3) varied from 55% in ROCKET-AF to 64% in RE-LY	• Subgroup analysis for stroke/SE and major bleeding by TTR < 66%, ≥ 66%
$CHADS_2$ score	Mean $CHADS_2$ score at baseline ranged from 2.1 in RE-LY and ARISTOTLE to 3.48 in ROCKET; ROCKET-AF also only included patients with $CHADS_2 \geq 2$, whereas ARISTOTLE and RE-LY included patients with $CHADS_2 < 2$	• Subgroup analysis for stroke/SE and major bleeding by $CHADS_2$ <2, ≥ 2
Age	Age ranged from a median of 70 years in ARISTOTLE to a median of 73 years in ROCKET-AF	• Subgroup analysis for stroke/SE and major bleeding by age < 75, ≥ 75

Table 18: Approach to Addressing Key Areas of Clinical and Methodological Heterogeneity		
Issue	**Description of Heterogeneity**	**Action**
ITT versus as treated per protocol analysis population	RE-LY and ARISTOTLE used ITT; ROCKET-AF used as-treated per protocol efficacy analysis	• Subgroup analysis where ITT population for ROCKET-AF is used • Due to differences in patient populations across trials (see Section 5.6), subgroup analysis by as-treated per protocol versus ITT were only applied to $CHADS_2 \geq 2$ populations

SE = systemic embolism; TTR = time in therapeutic range.

3.4 Individual Study Results

Four RCTs (N = 50,498) reported data on all-cause stroke/SE, major bleeding, all-cause mortality, intracranial bleeding, MI, and major GI bleeding. However, results for Section 3.4 and 3.5 are limited to data reported in ARISTOTLE, RE-LY, and ROCKET. The ARISTOTLE-J study was much smaller (N = 222) than ARISTOTLE (N = 18,201), RE-LY (N = 18,113), and ROCKET-AF (N = 14,264) and zero events were reported in both arms of ARISTOTLE-J.

A summary of the individual study result ORs for all-cause stroke/SE, major bleeding, all-cause mortality, intracranial bleeding, major GI bleeding, and MI are shown in Table 19. Results using hazard ratios were similar and are reported in Appendix 7.12. A summary of the number needed to treat for all outcomes of interest are shown in Table 20 for:

- **All-cause stroke/SE:** With the exception of dabigatran 110 mg and rivaroxaban, all treatments achieved statistically significant reductions in all-cause stroke/SE relative to adjusted-dose warfarin. The use of dabigatran 150 mg produced the largest effect, with a reduction in odds of all-cause stroke/SE (OR [95% CI]: 0.65 [0.52 to 0.81]. The absolute risk reduction of all-cause stroke/SE ranged from 2 to 6 fewer events per 1,000 patients treated per year.

- **Major bleeding:** Apixaban and dabigatran 110 mg achieved statistically significant reductions in major bleed relative to adjusted-dose warfarin. The use of apixaban produced the largest effects, with a reduction in odds of major bleed (OR [95% CI]: 0.69 [0.60 to 0.80]). The absolute risk reduction of major bleeding ranged from one more to eight fewer events per 1,000 patients treated per year.

- **All-cause mortality:** Apixaban was associated with a statistically significant reduction in all-cause mortality relative to adjusted-dose warfarin (OR [95% CI]: 0.89 (0.79 to 0.997]). Relative to adjusted-dose warfarin, the reduction in odds for dabigatran 150 mg, dabigatran 110 mg, and rivaroxaban 20 mg ranged from 0.88 to 0.92, and all were not statistically significant. The absolute risk reduction of all-cause mortality ranged from three to four fewer events per 1,000 patients treated per year.

- **Intracranial bleeding:** All treatments were associated with a statistically significant reduction in intracranial bleeding, with ORs ranging from 0.30 to 0.65. The use of dabigatran 110 mg produced the largest effect, with a reduction in odds of intracranial bleeding (OR [95% CI]: 0.30 [0.19 to 0.46]). The absolute risk reduction of intracranial bleeding ranged from three to five fewer events per 1,000 patients treated per year.

- **Major GI bleeding:** No treatments were associated with a statistically significant reduction in major GIbleeding relative to adjusted-dose warfarin. However, dabigatran 150 mg (OR [95% CI]: 1.45 [1.13 to 1.85]) and rivaroxaban (OR [95% CI]: 1.60 [1.29 to 1.98]) were associated with a statistically significant increase in major GI bleeding. The absolute risk reduction of major GI bleeding ranged from eight more to one fewer events per 1,000 patients treated per year.

- **Myocardial infarction:** No treatments were associated with a statistically significant reduction in MI relative to adjusted-dose warfarin. Apixaban was associated with the most favourable results (OR [95% CI]: 0.88 [0.66 to 1.17]). The ORs for the other treatments ranged from 0.918 to 1.31. The absolute risk reduction of all-cause mortality ranged from two more to two fewer events per 1,000 patients treated per year.

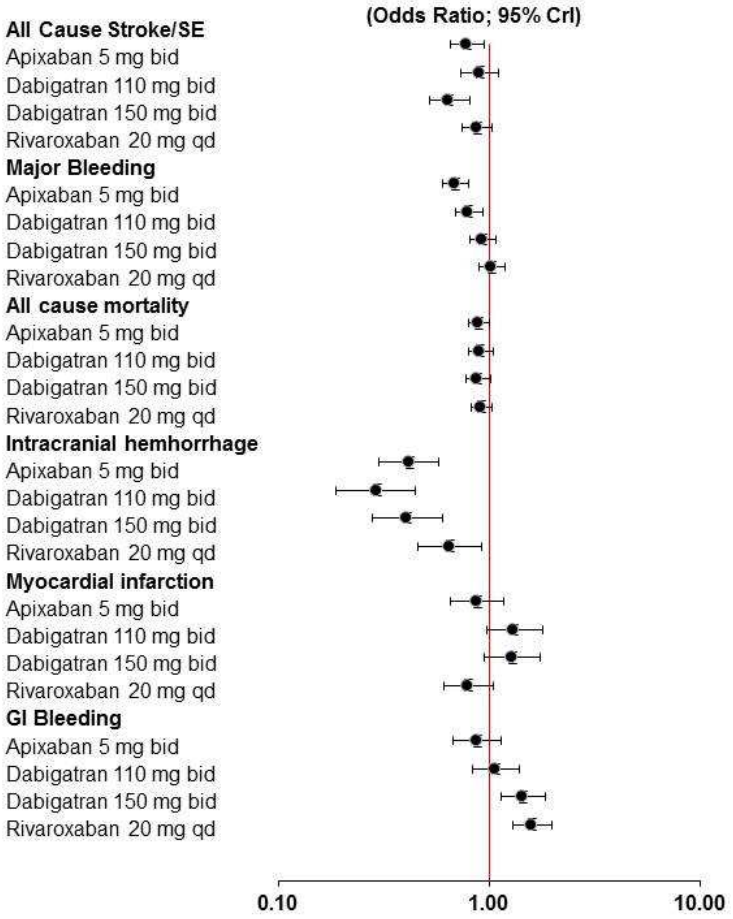
Table 19: Summary of Individual Study Results — Odds Ratio (95% CI) for Each Outcome*

	Stroke/SE	Major Bleeding	All-cause Mortality	Intracranial Bleeding	Major GI Bleeding	MI
Apixaban 5 mg b.i.d.	0.79 (0.66 to 0.95)	0.69 (0.60 to 0.80)	0.89 (0.79 to 0.997)	0.42 (0.30 to 0.58)	0.88 (0.67 to 1.14)	0.88 (0.66 to 1.17)
Dabigatran 110 mg b.i.d.	0.90 (0.74 to 1.11)	0.80 (0.69 to 0.93)	0.91 (0.80 to 1.04)	0.3 (0.19 to 0.46)	1.08 (0.83 to 1.40)	1.31 (0.97 to 1.78)
Dabigatran 150 mg b.i.d.	0.65 (0.52 to 0.81)	0.94 (0.81 to 1.08)	0.88 (0.77 to 1.01)	0.41 (0.28 to 0.61)	1.45 (1.13 to 1.85)	1.29 (0.95 to 1.74)
Rivaroxaban 20 mg q.d.	0.88 (0.74 to1.03)	1.03 (0.89 to 1.19)	0.92 (0.82 to 1.04)	0.65 (0.46 to 0.92)	1.60 (1.29 to 1.98)	0.81‡ (0.63 to 1.06)

b.i.d. = twice daily; CI = confidence interval; GI = gastrointestinal; MI = myocardial infarction; q.d. = once daily; SE = systemic embolism.

* Intention to treat (ITT) population for all treatments for efficacy outcomes (e.g., Stroke/SE, all-cause mortality, MI) unless otherwise stated; ITT for dabigatran, modified-ITT for apixaban, and safety on treatment population for rivaroxaban for safety outcomes (i.e., major bleeding, intracranial bleeding, major GI bleeding).
‡Mahaffey 2010[78] (AHA) reports ITT hazard ratio (HR) in ROCKET-AF for MI as 0.91 (0.72 to 1.16).

Figure 2: Forest Plot of the Individual Study Results — Odds Ratio for Each Outcome



b.i.d. = twice daily; CrI = credibility interval; GI = gastrointestinal; SE = systemic embolism.

Table 20: Summary of Individual Study Results — Absolute Risk Reduction per 1,000 patients Treated Each Year*

	Mean or Median Follow-Up	Stroke/SE	Major Bleeding	All-Cause Mortality	Intra-cranial Bleeding	Major GI Bleeding	Myocardial Infarction
Apixaban 5 mg b.i.d.	1.8y	3 fewer (1 fewer, 5 fewer)	8 fewer (6 fewer, 11 fewer)	4 fewer (0 more, 8 fewer)	4 fewer (3 fewer, 5 fewer)	1 fewer (1 more, 2 fewer)	1 fewer (1 more, 2 fewer)
Dabigatran 110 mg b.i.d.	2y	2 fewer (2 more, 4 fewer)	7 fewer (2 fewer, 11 fewer)	3 fewer (2 more, 8 fewer)	5 fewer (4 fewer, 6 fewer)	1more (4 more, 1 fewer)	2 more (5 more, 0 more)

Table 20: Summary of Individual Study Results — Absolute Risk Reduction per 1,000 patients Treated Each Year*

	Mean or Median Follow-Up	Stroke/SE	Major Bleeding	All-Cause Mortality	Intra-cranial Bleeding	Major GI Bleeding	Myocardial Infarction
Dabigatran 150 mg b.i.d.	2y	6 fewer (3 fewer, 8 fewer)	2 fewer (3 more, 6 fewer)	4 fewer (0 more, 9 fewer)	4 fewer (3 fewer, 5 fewer)	4 more (8 more, 1 more)	2 more (5 more, 0 more)
Rivaroxaban 20 mg q.d.*	1.9y, ITT 1.6y,SOT	3 fewer (1 more, 6 fewer)	1 more (6 more, 3 fewer)	4 fewer (2 more, 8 fewer)	3 fewer (1fewer, 4 fewer)	8 more (13 more, 4 more)	2 fewer (1 more, 4 fewer)

b.i.d. = twice daily; q.d. = once daily; SE = systemic embolism; SOT = safety of treatment; ITT = intention to treat; y = year.
* ITT population for all treatments for efficacy outcomes (i.e., stroke/SE, all-cause mortality); ITT for dabigatran, modified ITT for apixaban, and SOT population for rivaroxaban for safety outcomes (i.e., major bleeding, intracranial bleeding, major GI bleeding); all results rounded up.

A summary of the absolute risk reduction per 1,000 patients treated per year by age for stroke/SE and major bleeding by centre TTR are shown in Table 21. More detailed results are provided in Appendix 7.7 for:

- **TTR < 66%** — the absolute risk reduction of stroke/SE ranged from 2 to 9 per 1,000 patients treated in a year, whereas the absolute risk reduction for major bleed ranged from 2 to 11.
- **TTR ≥ 66%** — the absolute risk reduction of stroke/SE ranged from 1 to 5 per 1,000 patients treated in a year, whereas the absolute risk reduction for major bleed ranged from 11 more to 6 fewer.

Table 21: Summary of Individual Study Results by TTR — Absolute Risk Reduction Per 1,000 Patients Treated Each Year

	Reference Case		TTR < 66%		TTR ≥ 66%	
	Stroke/SE	Major Bleeding	Stroke/SE	Major Bleeding	Stroke/SE	Major Bleeding
Apixaban 5 mg	3 fewer (1 fewer, 5 fewer)	8 fewer (6 fewer, 11 fewer)	4 fewer (0 more, 7 fewer)	11 fewer (8 fewer, 14 fewer)	3 fewer (1 more, 5 fewer)	6 fewer (0 more, 10 fewer)
Dabigatran 110 mg b.i.d.	2 fewer (2 more, 4 fewer)	7 fewer (2fewer, 11 fewer)	2 fewer (4 more, 6 fewer)	9 fewer (3 fewer, 14 fewer)	1 fewer (3 more, 5 fewer)	4 fewer (2 more, 10 fewer)
Dabigatran 150 mg b.i.d.	6 fewer (3 fewer, 8 fewer)	2 fewer (3 more, 6 fewer)	9 fewer (5 fewer, 12 fewer)	9 fewer (2 fewer, 14 fewer)	3 fewer (2 more, 6 fewer)	5 more (13 more, 2 fewer)

Table 21: Summary of Individual Study Results by TTR — Absolute Risk Reduction Per 1,000 Patients Treated Each Year						
Rivaroxaban 20 mg q.d.*	3 fewer (1 more, 6 fewer)	1 more (6 more, 3 fewer)	3 fewer* (0 more, 6 fewer)	2 fewer (3 more, 6 fewer)	5 fewer* (2 more, 10 fewer)	11 more (25 more, 0 more)

b.i.d. = twice daily; q.d. = once daily; SE = systemic embolism; TTR = time in therapeutic range.
* Safety of treatment population for rivaroxaban sub-groups — intention to treat data was not available for TTR subgroups

A summary of the absolute risk reduction per 1,000 patients treated per year by age for stroke/SE and major bleeding are shown in Table 22. More detailed results are provided in Appendix 7.12 for:

- **Age < 75 years** — the absolute risk reduction of stroke/SE ranged from 1 to 5 per 1,000 patients treated in a year, whereas the absolute risk reduction for major bleed ranged from 2 to 11.
- **Age ≥ 75 years** — the absolute risk reduction of stroke/SE ranged from 2 to 7 per 1,000 patients treated in a year, whereas the absolute risk reduction for major bleed ranged from 8 more to 15 fewer.

Table 22: Summary of Individual Study Results by Age — Absolute Risk Reduction Per 1,000 Patients Treated Each Year						
	Reference Case		**Age < 75**		**Age ≥ 75**	
	Stroke/SE	**Major Bleeding**	**Stroke/SE**	**Major Bleeding**	**Stroke/SE**	**Major Bleeding**
Apixaban 5 mg	3 fewer (1 fewer, 5 fewer)	8 fewer (6 fewer, 11 fewer)	2 fewer (1 more, 4 fewer)	6 fewer (2 fewer, 8 fewer)	6 fewer (1 fewer, 10 fewer)	15 fewer (8 fewer, 21 fewer)
Dabigatran 110 mg b.i.d.	2 fewer (2 more, 4 fewer)	7 fewer (2 fewer, 11 fewer)	1 fewer (3 more, 4 fewer)	11 fewer (7 fewer, 15 fewer)	2 fewer (4 more, 7 fewer)	1 more (10 more, 7 fewer)
Dabigatran 150 mg b.i.d.	6 fewer (3 fewer, 8 fewer)	2 fewer (3 more, 6 fewer)	5 fewer (2 fewer, 7 fewer)	9 fewer (4 fewer, 13 fewer)	7 fewer (2 fewer, 11 fewer)	8 more (18 more, 0 more)
Rivaroxaban 20 mg q.d.	3 fewer (1 more, 6 fewer)	1 more (6 more, 3 fewer)	1 fewer (5 more, 6 fewer)	2 fewer (4 more, 8 fewer)	6 fewer (1 more, 11 fewer)	5 more (14 more, 2 fewer)

b.i.d. = twice daily; q.d. = once daily; SE = systemic embolism.

A summary of the absolute risk reduction per 1,000 patients treated per year by $CHADS_2$ for stroke/SE and major bleeding are shown in Table 23. More detailed results are provided in Appendix 7.12 for:

- **$CHADS_2$ < 2** — the absolute risk reduction of stroke/SE ranged from 0 to 4 per 1,000 patients treated over a year, whereas the absolute risk reduction for major bleed ranged from 7 to 9.

- **$CHADS_2$ ≥2** — the absolute risk reduction of stroke/SE ranged from 2 to 6 per 1,000 patients treated over a year, whereas the absolute risk reduction for major bleed ranged from 1 more to 8 fewer.

Table 23: Summary of Individual Study Results by $CHADS_2$ Score — Absolute Risk Reduction Per 1,000 Patients Treated Each Year

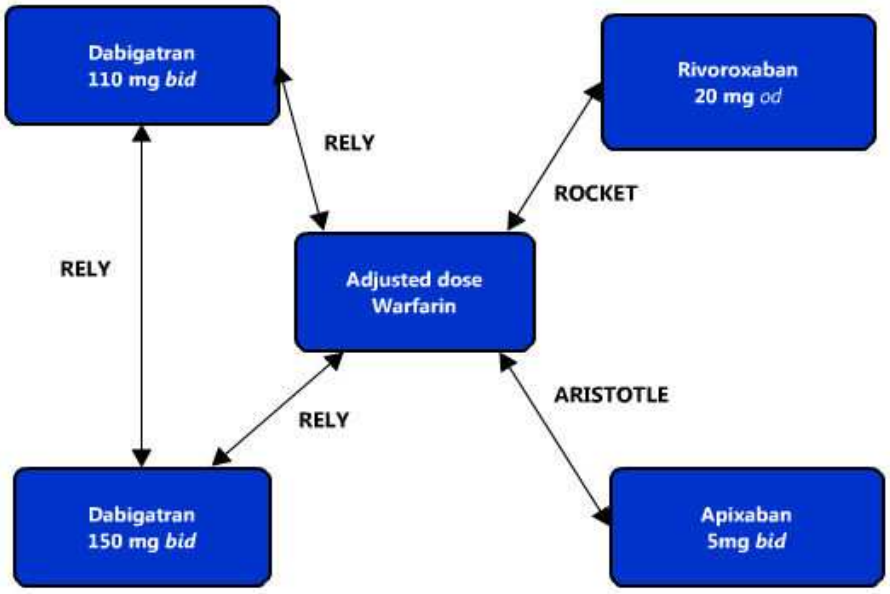
	Reference Case		$CHADS_2$ < 2		$CHADS_2$ ≥ 2	
	Stroke/SE	**Major Bleeding**	**Stroke/SE**	**Major Bleeding**	**Stroke/SE**	**Major Bleeding**
Apixaban 5 mg	3 fewer (1 fewer, 5 fewer)	8 fewer (6 fewer, 11 fewer)	1 fewer (3 more, 4 fewer)	9 fewer (5 fewer, 13 fewer)	4 fewer (1 fewer, 7 fewer)	8 fewer (4 fewer, 12 fewer)
Dabigatran 110 mg b.i.d.	2 fewer (2 more, 4 fewer)	7 fewer (2 fewer, 11 fewer)	0 more (6 more, 4 fewer)	10 fewer (3 fewer, 15 fewer)	2 fewer (2 more, 6 fewer)	5 fewer (1 more, 10 fewer)
Dabigatran 150 mg b.i.d.	6 fewer (3 fewer, 8 fewer)	2 fewer (3 more, 6 fewer)	4 fewer (0 more, 7 fewer)	7 fewer (1 more, 12 fewer)	6 fewer (3 fewer, 9 fewer)	0 more (7 more, 5 fewer)
Rivaroxaban 20 mg q.d.*	3 fewer (1 more, 6 fewer)	1 more (6 more, 3 fewer)	NA	NA	3 fewer (1 more, 7 fewer)	1 more (6 more, 3 fewer)

b.i.d. = twice daily; q.d. = once daily; SE = systemic embolism.
* Safety on treatment population; intention to treat data was not available for time in therapeutic range subgroups.

3.5 Network Meta-Analysis Results

The evidence networks were restricted to three studies — ARISTOTLE, RE-LY, and ROCKET-AF (Figure 3) — as no events were reported in both arms for the many of outcomes in the other studies and trials with zero cells in both arms do not contribute information. Adjusted-dose warfarin was chosen as the reference group.

Figure 3: Schematic of Evidence Network Used for the Network Meta-analysis



b.i.d. = twice daily; od = .once daily

A summary of the ORs of each oral anticoagulant compared with warfarin, based on the Bayesian fixed-effects MTC network meta-analysis, are provided in Table 24 and Figure 4 for stroke/SE, major bleeding, all-cause mortality, intracranial bleeding, major GI bleeding, and MI. For:

- **Stroke/SE —** With the exception of dabigatran 110 mg and rivaroxaban, all treatments achieved statistically significant reductions in the odds of all-cause stroke/SE (range 0.65 to 0.80) relative to adjusted-dose warfarin. The use of dabigatran 150 mg produced the largest effects, with a reduction in odds of stroke/ SE (OR [95% confidence interval {CrI}]: 0.65 [0.52 to 0.81]) relative to adjusted-dose warfarin. There were no statistically significant differences between agents, the exception being dabigatran 150 mg versus 110 mg (OR [95% CrI]: 0.72 [0.58 to 0.91]).

- **Major bleeding —** Apixaban and dabigatran 110 mg achieved statistically significant reductions in the odds of major bleed relative to adjusted-dose warfarin. The use of apixaban produced the largest effects, with a reduction in odds of major bleeding (OR [95% CrI]: 0.70 [0.61, 0.81]) relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for other treatments ranged from 0.81 to 1.03.

- **All-cause mortality:** Except for apixaban, none of the NOACs significantly reduced all-cause mortality (OR [95% CrI]: 0.90 [0.80 to 0.998]).

- **Intracranial bleeding:** All treatments were associated with a statistically significant difference in intracranial bleeding compared with adjusted-dose warfarin with ORs, ranking from 0.30 to 0.66. The use of dabigatran 110 mg produced the largest effects in intracranial bleeding, with a reduction in odds (OR [95% CrI]: 0.29 [0.19 to 0.45]) relative to adjusted-dose warfarin.

- **Major GI bleeding:** No treatments were associated with a statistically significant reduction in major GI bleeding relative to adjusted-dose warfarin. However, dabigatran 150 mg (OR [95% CrI]:

0.1.45 [1.14 to 1.86]) and rivaroxaban (OR [95% CrI]: 1.61 [1.30 to 1.99]) were associated with a statistically significant increase in major GI bleeding.

- **Myocardial infarction:** No treatments were associated with a statistically significant reduction in MI relative to adjusted-dose warfarin. The ORs for other treatments ranged from 0.88 to 1.32.

The estimates of effects derived from fixed-effects Bayesian MTC analyses aligned closely with individual study results and frequentist network meta-analysis results in both direction and magnitude (Appendix 7.13). The point estimates for the Bayesian random-effects MTC analysis were similar to those reported in the Bayesian fixed-effects MTC, although the credible intervals were wider (Appendix 7.11).

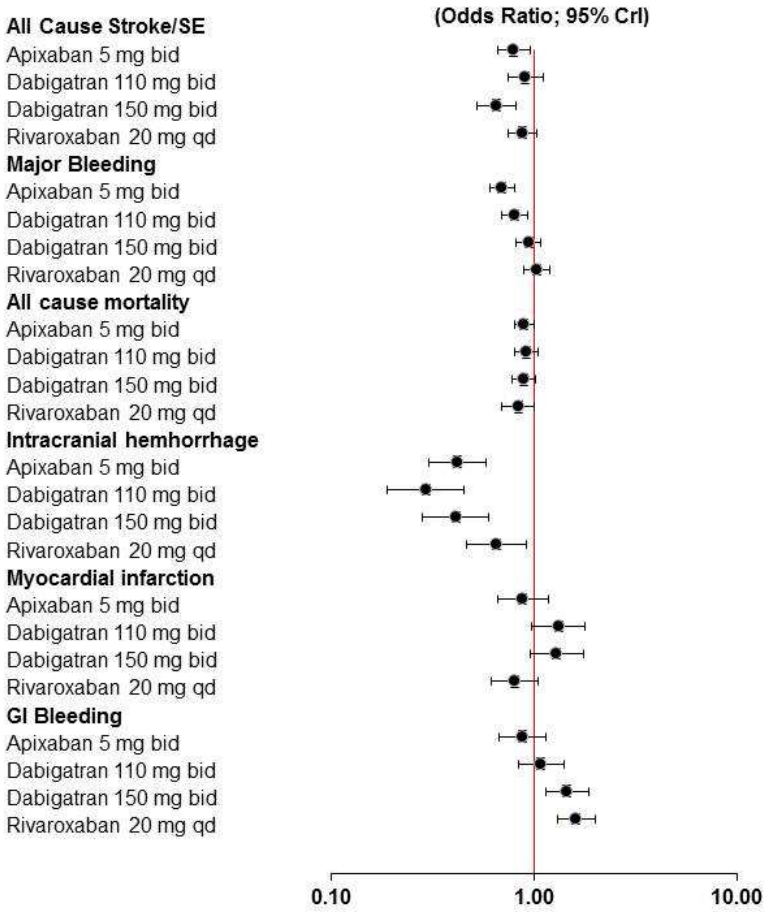
Table 24: Summary of Results from the MTC Network Meta-analyses — Odds Ratio (95%CrI) for Each Outcome*

		Stroke/SE	Major Bleeding	All-Cause Mortality	Intracranial Bleeding	Major GI Bleeding	Myocardial Infarction
Apixaban versus warfarin		0.8 (0.66,0.95)	0.70 (0.61,0.81)	0.90 (0.80,0.998)	0.42 (0.30,0.58)	0.88 (0.68,1.15)	0.88 (0.66,1.17)
Dabigatran 110 mg versus warfarin		0.91 (0.74,1.11)	0.81 (0.7,0.93)	0.91 (0.8,1.05)	0.30 (0.19,0.45)	1.08 (0.84,1.40)	1.32 (0.98,1.79)
Dabigatran 150 mg versus warfarin		0.65 (0.52,0.81)	0.94 (0.82,1.08)	0.89 (0.78,1.01)	0.42 (0.28,0.60)	1.45 (1.14,1.86)	1.29 (0.96,1.75)
Rivaroxaban versus warfarin		0.88 (0.74,1.04)	1.03 (0.89,1.19)	0.93 (0.83,1.04)	0.66 (0.47,0.92)	1.61 (1.30,1.99)	0.80‡ (0.62,1.05)
Dabigatran 110 mg versus apixaban		1.15 (0.87,1.51)	1.16 (0.95,1.43)	1.03 (0.86,1.22)	0.71 (0.41,1.21)	1.23 (0.85,1.78)	1.50 (0.99,2.28)
Dabigatran 150 mg versus apixaban		0.82 (0.62,1.1)	1.35 (1.11,1.66)	1.00 (0.84,1.19)	0.99 (0.60,1.62)	1.65 (1.16,2.38)	1.47 (0.97,2.23)
Rivaroxaban versus apixaban		1.11 (0.87,1.42)	1.48 (1.21,1.82)	1.04 (0.89,1.23)	1.56 (0.97,2.5)	1.83 (1.30,2.57)	0.92 (0.62,1.35)
Dabigatran 150 mg versus dabigatran 110 mg		0.72 (0.58,0.9)	1.17 (1.01,1.36)	0.97 (0.85,1.12)	1.41 (0.86,2.33)	1.35 (1.07,1.72)	0.98 (0.74,1.31)
Rivaroxaban versus dabigatran 110 mg		0.97 (0.75,1.26)	1.28 (1.04,1.58)	1.02 (0.86,1.21)	2.22 (1.29,3.89)	1.49 (1.07,2.09)	0.61 (0.41,0.91)
Rivaroxaban versus dabigatran 150 mg		1.35(1.03, 1.79)	1.10 (0.9,1.35)	1.05 (0.88,1.26)	1.58 (0.95,2.66)	1.11 (0.8,1.53)	0.63 (0.42,0.93)
Model fit statistics	Residual deviance	6.999	6.9920	7.0020	6.9920	6.9910	6.9980
	DIC	64.29	68.175	70.507	68.175	61.044	58.81

CrI = credibility interval; DIC = deviance information criterion; GI = gastrointestinal; MTC = mixed treatment comparison; SE = systemic embolism.

* Intention to treat (ITT) population for all treatments for efficacy outcomes (i.e., Stroke/SE, all-cause mortality) when data available; ITT for dabigatran, modified ITT for apixaban, and safety of population for rivaroxaban for safety outcomes (i.e., major bleeding, intracranial bleeding, major GI bleeding).
‡ Safety on treatment value; Mahaffey 2010[78] (AHA) reports ITT hazard ratio (HR) in ROCKET AF for MI as 0.91 (0.72-1.16)

Figure 4: Forest Plot of the Results from the MTC Network Meta-analysis for Each Outcome — Comparison with Warfarin



b.i.d. = twice daily; q.d. = once daily; SE = systemic embolism.

A summary of the ORs by TTR, derived from a Bayesian fixed-effects MTC analysis, for stroke/SE and major bleeding are shown in Table 25. For:

- **Stroke/SE —**
  - **For TTR < 66%**, dabigatran 150 mg had a strong trend in reducing the odds of all-cause stroke/SE relative to adjusted-dose warfarin (OR [95% CrI]: 0.54 [0.40 to 0.74]). Relative to adjusted-dose warfarin, the reduction in odds for the other treatments ranged from 0.80 to 0.91.
  - **For TTR ≥ 65%**, no treatments had a strong trend in reducing the odds of all-cause stroke/SE relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for all treatments ranged from 0.80 to 0.91.

- **Major Bleeding —**
  - **For TTR < 66%**, apixaban, dabigatran 110 mg, and dabigatran 150 mg were all associated with a strong trend in reducing the odds of major bleeding relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, rivaroxaban was associated with a reduction in odds of 0.92.

- **For TTR ≥ 66%**, apixaban was associated with a strong trend in reducing the odds of major bleeding relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, rivaroxaban had a trend of an increase in the odds of major bleeding (OR [95% CrI]: 1.30 [1.01, 1.69]), and dabigatran 110 mg and 150 mg had an odds of 0.86 and 1.15, respectively.

Table 25: Summary of Results from MTC Analysis by TTR — Odds Ratio (95%CrI) for Each Outcome

	Reference Case		TTR < 66%		TTR ≥ 66%	
	Stroke/SE	**Major Bleeding**	**Stroke/SE**	**Major Bleeding**	**Stroke/SE**	**Major Bleeding**
Apixaban 5 mg	0.80 (0.66,0.95)	0.70 (0.61, 0.81)	0.80 (0.63, 1.01)	0.57 (0.46, 0.71)	0.80 (0.60, 1.06)	0.82 (0.67, 0.99)
Dabigatran 110 mg b.i.d.	0.91 (0.74,1.11)	0.81 (0.70, 0.93)	0.91 (0.70, 1.20)	0.75 (0.61, 0.92)	0.91 (0.66, 1.24)	0.86 (0.70, 1.07)
Dabigatran 150 mg b.i.d.	0.65 (0.52,0.81)	0.94 (0.82, 1.08)	0.54 (0.40, 0.74)	0.77 (0.63, 0.94)	0.81 (0.59, 1.11)	1.15 (0.95, 1.41)
Rivaroxaban 20 mg q.d.	0.88 (0.74,1.04)	1.03 (0.89, 1.19)	0.82 (0.66, 1.01)	0.92 (0.78, 1.10)	0.73 (0.48, 1.11)	1.30 (1.01, 1.69)

b.i.d. = twice daily; CrI = credibility interval; q.d. = once daily; SE = systemic embolism; TTR = time in therapeutic range.
* Safety of treatment data as intention to treat (ITT) data for stroke/SE not available for rivaroxaban by centre TTR(cTTR); ITT for dabigatran, modified ITT for apixaban, and safety of treatment population for rivaroxaban for major bleeding.

A summary of the ORs by age, derived from a Bayesian fixed-effects MTC analysis, for stroke/SE and major bleeding are shown in Table 26. For:

- **Stroke/SE —**
  - **For age < 75 years**, dabigatran 150 mg had a strong trend of reducing the odds of all-cause stroke/SE relative to adjusted-dose warfarin (OR [95% CrI]: 0.64 [0.46, 0.87]). Relative to adjusted-dose warfarin, the reduction in odds for other treatments ranged from 0.85 to 0.94.
  - **For age ≥ 75 years**, apixaban, dabigatran 150 mg and rivaroxaban all had strong trends in reducing the odds of all-cause stroke/SE relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for dabigatran 110 mg was 0.89.

- **Major bleeding:**
  - **For age < 75 years**, apixaban, dabigatran 110 mg and dabigatran 150 mg all were associated with a strong trend in reducing the odds of major bleeding relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for rivaroxaban was 0.93.
  - **For age ≥ 75 years**, apixaban was associated with a strong trend in reducing the odds of major bleeding relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the other treatments were associated with an odds ratio ranging from 1.03 to 1.20.
  - With the exception of apixaban, the benefits diminished for age ≥ 75 years compared to age < 75 years.

Table 26: Summary of Results from MTC Analysis by Age — Odds Ratio (95%CrI) for Each Outcome

	Reference Case		Age < 75		Age ≥ 75	
	Stroke/SE	**Major Bleeding**	**Stroke/SE**	**Major Bleeding**	**Stroke/SE**	**Major Bleeding**
Apixaban 5 mg b.i.d.	0.8 (0.66,0.95)	0.70 (0.61, 0.81)	0.85 (0.67,1.08)	0.73 (0.60, 0.89)	0.72 (0.53,0.96)	0.65 (0.53, 0.81)
Dabigatran 110 mg b.i.d.	0.91 (0.74,1.11)	0.81 (0.70, 0.93)	0.94 (0.71,1.24)	0.62 (0.50, 0.77)	0.89 (0.66,1.19)	1.03 (0.84, 1.26)
Dabigatran 150 mg b.i.d.	0.65 (0.52,0.81)	0.94 (0.82, 1.08)	0.64 (0.46,0.87)	0.70 (0.57, 0.87)	0.67 (0.49,0.90)	1.20 (0.99, 1.45)
Rivaroxaban 20 mg q.d.	0.88 (0.74,1.04)	1.03 (0.89, 1.19)	0.91 (0.70,1.18)	0.93 (0.76, 1.14)	0.66 (0.49,0.87)	1.15 (0.94, 1.42)

b.i.d. = twice daily; CrI = credibility interval; MTC = mixed treatment comparison; q.d. = once daily; SE = systemic embolism.
* Intention to treat (ITT) population for all treatments for stroke/SE; ITT for dabigatran, modified ITT for apixaban, and SOT population for rivaroxaban for major bleeding.

A summary of the ORs by $CHADS_2$ score, derived from a Bayesian fixed-effects MTC analysis, for stroke/SE and major bleeding are shown in Table 27. For:

- **Stroke/SE —**
  - **For $CHADS_2$ < 2**, dabigatran 150 mg was associated with a strong trend to reducing the odds of all-cause stroke/SE relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for apixaban and dabigatran 110 mg was 0.86 and 1.00, respectively. For rivaroxaban, results were not available, as patients with a $CHADS_2 < 2$ were not recruited into the study.
  - **For $CHADS_2 \geq 2$**, apixaban 150 mg and dabigatran 150 mg were associated with strong trends in reducing the odds of all-cause stroke/SE relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for dabigatran 110 mg and rivaroxaban was 0.89 and 0.88, respectively. For rivaroxaban, the reduction in the odds stroke/SE using the published as treated per protocol results was statistically significant, but not so for the results based on the intention-to-treat analysis.

- **Major Bleeding —**
  - **For $CHADS_2$ < 2**, apixaban 110 mg and dabigatran 110 mg had a strong trend in reducing the odds of major bleeding relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for dabigatran 150 mg was 0.77. Results were not available for rivaroxaban, as patients with $CHADS_2 < 2$ were not included in the study.
  - **For $CHADS_2 \geq 2$**, apixaban was associated with a strong trend in reducing the odds of major bleeding relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for all treatments ranged from 0.74 to 1.03.

Table 27: Summary of Results from MTC Analysis by $CHADS_2$ Score — Odds Ratio (95%CI) for Each Outcome

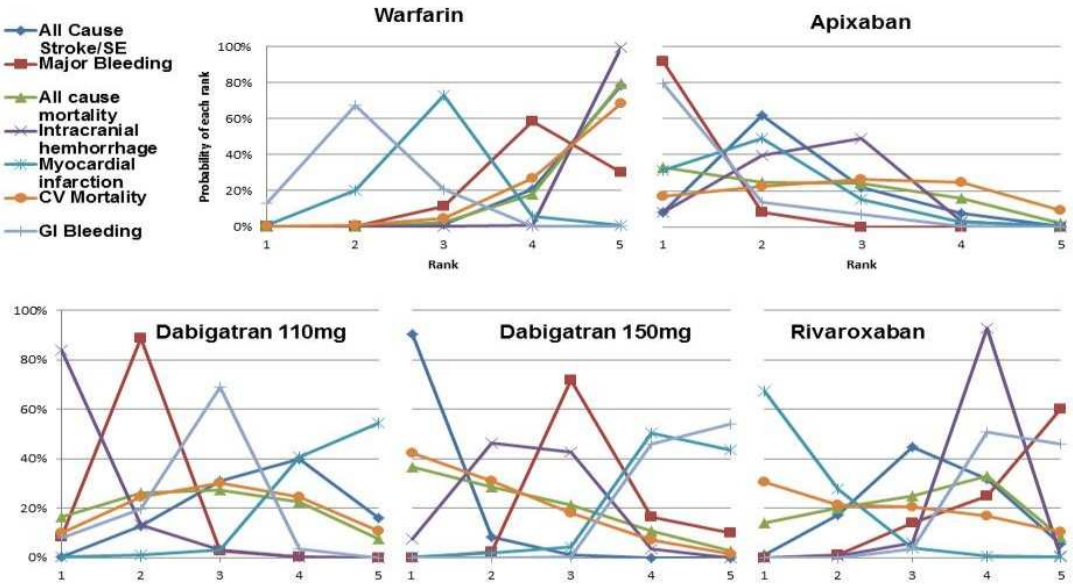
	Reference Case		$CHADS_2$<2		$CHADS_2$≥2	
	Stroke/SE	**Major Bleeding**	**Stroke/SE**	**Major Bleeding**	**Stroke/SE**	**Major Bleeding**
Apixaban 5 mg b.i.d.	0.80 (0.66 to 0.95)	0.70 (0.61 to 0.81)	0.86 (0.57 to 1.29)	0.59 (0.44 to 0.79)	0.78 (0.64 to 0.96)	0.74 (0.62 to 0.87)
Dabigatran 110 mg b.i.d.	0.91 (0.74 to 1.11)	0.81 (0.70 to 0.93)	1.00 (0.65 to 1.56)	0.65 (0.48 to 0.89)	0.89 (0.71 to 1.12)	0.87 (0.73 to 1.02)
Dabigatran 150 mg b.i.d.	0.65 (0.52 to 0.81)	0.94 (0.82 to 1.08)	0.61 (0.37 to 0.997)	0.77 (0.57 to 1.04)	0.67 (0.52 to 0.85)	1.01 (0.86 to 1.19)
Rivaroxaban 20 mg q.d.	0.88 (0.74 to1.04)	1.03 (0.89 to 1.19)	NA	NA	0.88 (0.74 to 1.04)	1.03 (0.89 to 1.19)

b.i.d. = twice daily; CI = confidence interval; MTC = mixed treatment comparison; N/A = not applicable; q.d. = once daily; SE = systemic embolism.
* Intention to treat (ITT) population for all treatments for stroke/SE; ITT for dabigatran, modified ITT for apixaban, and safety of treatment population for rivaroxaban for major bleeding.

For the five treatments — apixaban, dabigatran 110 mg, dabigatran 150 mg, rivaroxaban, and adjusted-dose warfarin — Figure 5 shows the distribution of the probabilities of each of these treatments being ranked first, second, third, fourth, or fifth (the possible five ranking positions) for each of the outcomes of stroke/SE, major bleeding, all-cause mortality, intracranial bleeding, major GI bleeding, and MI. These results — which should be considered from a descriptive and not inferential, statistical perspective — are based on the Bayesian fixed-effects MTC network meta-analysis. Apixaban had a low probability of being ranked fifth for all outcomes considered. Dabigatran had a high probability of being best for some outcomes (e.g., all-cause stroke/SE) and a high probability of being ranked last for others (e.g., MI). In particular:

- **Warfarin** has a high probability of being one of the top treatment options for MI and GI bleeding, but a high probability of being ranked last for intracranial hemorrhage, all-cause mortality and all cause stroke/SE.
- **Apixaban:** Apixaban has a low probability of being ranked last for all outcomes and a high probability of being best for major bleeding and GI bleeding.
- **Dabigatran 110 mg** has a high probability of being one of the top treatment options for intracranial hemorrhage and major bleeding and a high probability of being one of the worst options for MI and all cause stroke/SE.
- **Dabigatran 150 mg** has a high probability of being one of the top treatment options for all cause stroke/ SE and intracranial hemorrhage and a high probability of being one of the worst options for MI and major GI bleeding.
- **Rivaroxaban** has a high probability of being one of the top treatment options for MI and a high probability of being one of the worst options for intracranial hemorrhage and major GI bleeding.

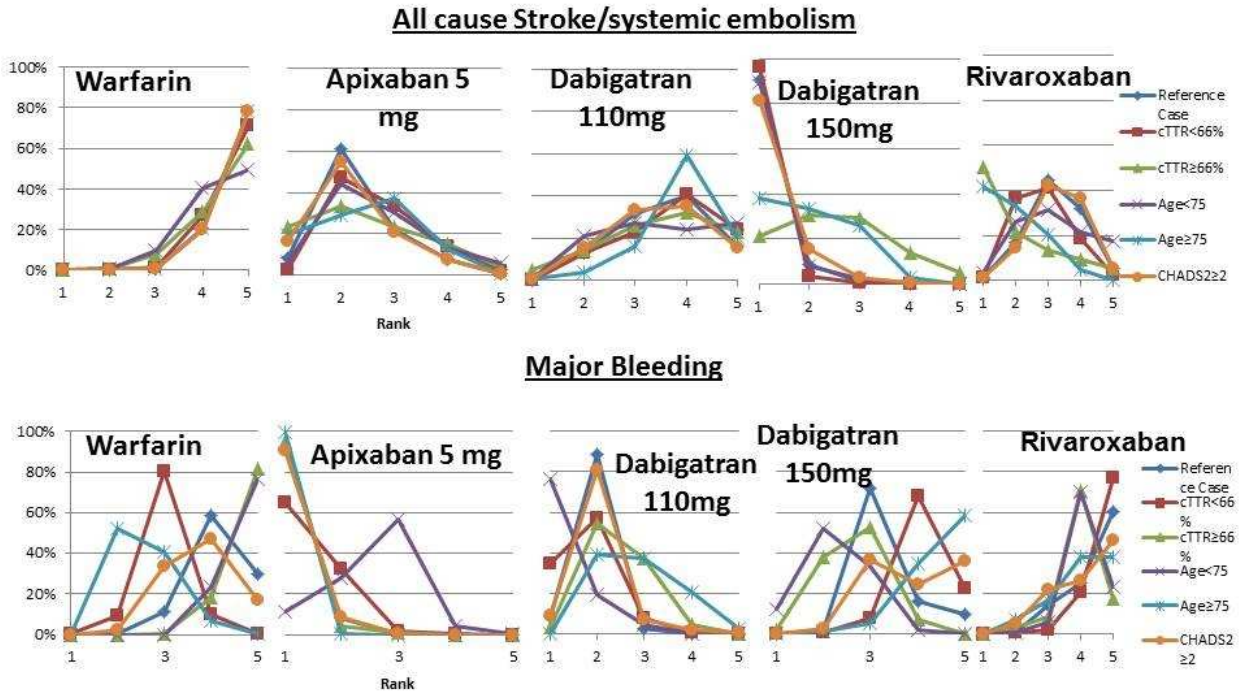
Figure 5: Rankograms for Bayesian MTC Network Meta-analysis — for Each Outcome*



CV =cardiovascular; GI = gastrointestinal; SE = systemic embolism.
* Intention to treat (ITT) population for all treatments for efficacy outcomes (i.e., stroke/SE, all-cause mortality) when data available; ITT for dabigatran, modified ITT for apixaban, and safety of treatment population for rivaroxaban for safety outcomes (i.e., major bleeding, intracranial bleeding, major GI bleeding)

The rankograms in Figure 5 are not adjusted for heterogeneity across trials. In Figure 6, the rankograms from five subgroup analyses are shown: TTR < 66%, TTR ≥ 66%, age < 75 years, age ≥ 75 years, and $CHADS_2$ ≥ 2. For all-cause stroke or SE, the probability of each rank is similar for the various subgroup analyses for warfarin 110 mg, apixaban 110 mg, and dabigatran 110 mg. However, for dabigatran 150 mg and rivaroxaban 110 mg, there are variations in the probability of each rank, depending on subgroup analysis. For example, for age ≥ 75 years and TTR ≥ 66%, the probability that dabigatran 150 mg is best reduces relative to the reference case analysis. There is less consistency across rankograms for major bleeding, particularly for warfarin and dabigatran. For example, the probability that warfarin is second best increases for the age ≥ 75 subgroup analysis relative to the reference case, whereas the probability that dabigatran is ranked fifth increases.

Figure 6: Rankograms for Bayesian MTC Network Meta-analysis by Subgroups — for Stroke/SE and Major Bleeding



4 ECONOMIC REVIEW

4.1 Primary Research Questions

1) What is the cost-effectiveness of new oral anticoagulants compared to warfarin (and nicoumalone) in patients with non-valvular atrial fibrillation?

2) What are the costs associated with warfarin (and nicoumalone) when patients are stratified according to the time spent within the therapeutic range (TTR)? How do these compare with estimates for the new oral anticoagulants?

3) What is the cost-effectiveness of new oral anticoagulants compared to warfarin (and nicoumalone) when stratified by age and $CHADS_2$ (or CHA_2DS_2-VASc) score?

4.2 Methods

4.2.1 Type of economic evaluation

The primary analysis was in the form of a cost utility analysis, with treatments compared in terms of the incremental cost per QALY gained.[86] This analysis provides estimates of the expected values of costs (C) and QALYs (Q) for each of the five treatment alternatives considered. The incremental cost per QALY gained (ICER) is simply the ratio of the difference in costs to the difference in QALYs.

$$ICER_{dabigatran\ v.warfarin} = \frac{C_{Dabigatran} - C_{Warfarin}}{Q_{Dabigatran} - Q_{Warfarin}}$$

4.2.2 Target population

The target population for the analysis was Canadians with non-valvular atrial fibrillation requiring anticoagulation. For the base case analysis, a typical patient profile from the RE-LY RCT was adopted: an average age of 72 years with no previous stroke or MI.[9] Sensitivity analysis was conducted for assessing the cost-effectiveness of oral anticoagulants for patients with previous MI, previous minor stroke, and previous major stroke. Transition probabilities were weighted to allow for the increased risk of events given the previous event history.

In addition, a stratified analysis was conducted whereby cost-effectiveness was assessed for different age subgroups and by $CHADS_2$ score (< 2, 2, > 2). For this analysis, alternate estimates of treatment effectiveness based on subgroup analysis within the network meta-analysis when available were utilized. A further analysis assessed the difference in cost-effectiveness based on centre-specific average time in therapeutic range.

4.2.3 Treatments

Treatments compared were warfarin, dabigatran 150 mg twice daily and 110 mg twice daily, rivaroxaban, and apixaban. A sensitivity analysis was conducted to examine the impact of switching patients from the dabigatran 150 mg twice daily dose to the 110 mg twice daily dose from age 80 onwards. This was not incorporated within the base case, as age specific data for efficacy and safety of the newer anticoagulants was limited to only two end points; therefore, the results of this analysis should be viewed with caution.

4.2.4 Perspective

Analysis adopts a third-party payer perspective relating to a provincial Ministry of Health.

4.2.5 Efficacy, safety, and adverse events

The analysis incorporated the following outcomes associated with the management of individuals with non-valvular atrial fibrillation requiring anticoagulation:

- Stroke (fatal and non-fatal)
- Myocardial infarction (fatal and non-fatal)
- Major bleeds (fatal and non-fatal)
- Intracranial hemorrhage (ICH) (fatal and non-fatal)
- Minor bleeds
- Pulmonary embolism (fatal and non-fatal)
- Transient ischemic attack (TIA)

The baseline estimates for the annual rates (r_w) of these events on warfarin were obtained from the

RE-LY RCT. Event rates were similar to both the ROCKET-AF and ARISTOTLE trials. However, further sensitivity analyses were conducted to explore the sensitivity of results to using other trial event rates based on ROCKET-AF and ARISTOTLE trials for warfarin. For incorporation into the economic model, transition probabilities between states must be estimated allowing for the duration of cycle length.

The transition probability for warfarin (tp_w) relating to these events for the cycle length (t) within the model was therefore estimated using standard methodology:

$$tp_w = 1 - e^{r_w t}$$

The estimate for the transition probability for each event for dabigatran, apixaban and rivaroxaban was derived by using the OR for each treatment obtained from the network meta-analysis. The methodology was as follows.

1. Derive the probability of an event on warfarin for the average duration (d) within the RE-LY RCT

   $$p_w = 1 - e^{r_w d}$$

2. Derive the probability of an event on the new anticoagulant (e.g. p_{dab}) using the OR from the network meta-analysis for the average duration (d)

   $$p_{dab} = \frac{OR\left(\frac{p_w}{1 - p_w}\right)}{1 + OR\left(\frac{p_w}{1 - p_w}\right)}$$

3. Derive the annual event rate for the new anticoagulant (r_{dab}) from the probability for the average duration

   $$r_{dab} = \frac{-ln(1 - p_{dab})}{d}$$

4. Derive the transition probability of an event on the new anticoagulant (e.g. tp_{dab}) from the annual event rate for the cycle length (t)

   $$tp_{dab} = 1 - e^{r_{dab} t}$$

The following is a list of event rates which were assumed to vary by anticoagulation treatment (based on the results of the network meta-analysis). All other parameters for the newer anticoagulants were assumed to be as for warfarin given the lack of available data to be included in the network meta-analysis.

- Stroke
- Myocardial infarction
- Major bleeds
- ICH.

Sensitivity analyses were conducted incorporating the relative risks of minor bleeds and non-vascular deaths. These values were sourced from the original RCT, as there were inadequate data to allow for inclusion within the network meta-analysis.

The effect of treatment on GI bleeds has been incorporated within the model states relating to bleeds. The nature of the data reported within the clinical trials did not allow incorporation of GI bleeds as a separate state.

The probabilities of death due to each event were derived from the warfarin data from the RE-LY trial.[9] No differences in event fatality rates between treatments were assumed.

The clinical parameters related to warfarin and aspirin use are provided in Table 28.

Table 28: Clinical Parameters Relating to Warfarin and Aspirin Use			
Parameters	**Base Estimate**	**Probability Distribution***	**Reference**
Annual rates of events with Warfarin			
Stroke	0.016	Beta (186, 11608)	FDA (2010)[79]
TIA	0.008	Beta (99, 11695)	FDA (2010)[79]
ICH	0.008	Beta (90, 11704)	FDA (2010)[79]
Major bleeds	0.033	Beta (386, 11408)	FDA (2010)[79]
Minor bleeds	0.164	Beta (1931, 9863)	Connolly et al. (2009)[9]
MI	0.006	Beta (66, 11728)	FDA (2010)[79]
PE	0.001	Beta (12, 11782)	FDA (2010)[79]
Non-vascular death	0.033	Beta (391, 11403)	FDA (2010)[79]
Event related probabilities			
Percentage of first strokes which are fatal	0.237	Beta (44, 142)	FDA (2010)[79]
Percentage of non-fatal first strokes which are major	0.333	Beta (39, 78)	FDA (2010)[79]
Increased risk of subsequent strokes being fatal	1.570	Lognormal (0.45, 0.13)	Carter et al. (2007)[87]
Probability major bleed or ICH is fatal	0.084	Beta (40, 436)	
Probability MI is fatal	0.121	Beta (8, 58)	FDA (2010)[79]
Probability PE is fatal	0.333	Beta (4, 8)	FDA (2010)[79]
			FDA (2010)[79]
Event rate adjustments			
Increase in stroke for each 10-year age increment	1.50	Lognormal (0.40, 0.07)	Stroke Risk in Atrial Fibrillation Working Group (2007)[35]
Increase in stroke given previous stroke/TIA	2.20	Lognormal (0.79, 0.54)	
Increase in MI given previous MI	2.04	Lognormal (0.71, 0.28)	Lip et al. (2010)[88]
Increase in bleeding given age over 65	2.66	Lognormal (0.98, 0.35)	Cupples et al. (1993)[89]
Increase in death given previous stroke	2.30	Lognormal (0.83, 0.07)	Pisters et al. (2010)[90]
Increase in death given AF	1.20	Lognormal (0.18, 0.08)	Dennis et al. (1993)[91]
			Wyse et al. (2001)[92]
Relative risks for aspirin versus warfarin			
Stroke	1.62	Lognormal (0.48, 0.25)	Sorensen et al. (2009)[54]
MI	1.42	Lognormal (0.35, 0.27)	
ICH	0.51	Lognormal (-0.67, 0.59)	Sorensen et al. (2009)[54]
Minor bleed	0.63	Lognormal (-0.46, 0.34)	Sorensen et al. (2009)[54]
Major bleed	1.14	Lognormal (0.13, 0.45)	Sorensen et al. (2009)[54]
TIA	1.56	Lognormal (0.44, 0.30)	Sorensen et al. (2009)[54]

ICH = intracerebral hemorrhage; PE = pulmonary embolism; MI = myocardial infarction; TIA = transient ischemic attack.

*Beta distributions parameterized by alpha and beta, lognormal distributions parameterized by log means and log standard errors.

4.2.6 Time Horizon

For the base-case analysis, a lifetime horizon (maximum of 40 years post-treatment initiation) was adopted. Sensitivity analysis adopted alternative horizons of 20 years, 10 years, and 2 years (average duration of major clinical trials).

4.2.7 Modelling

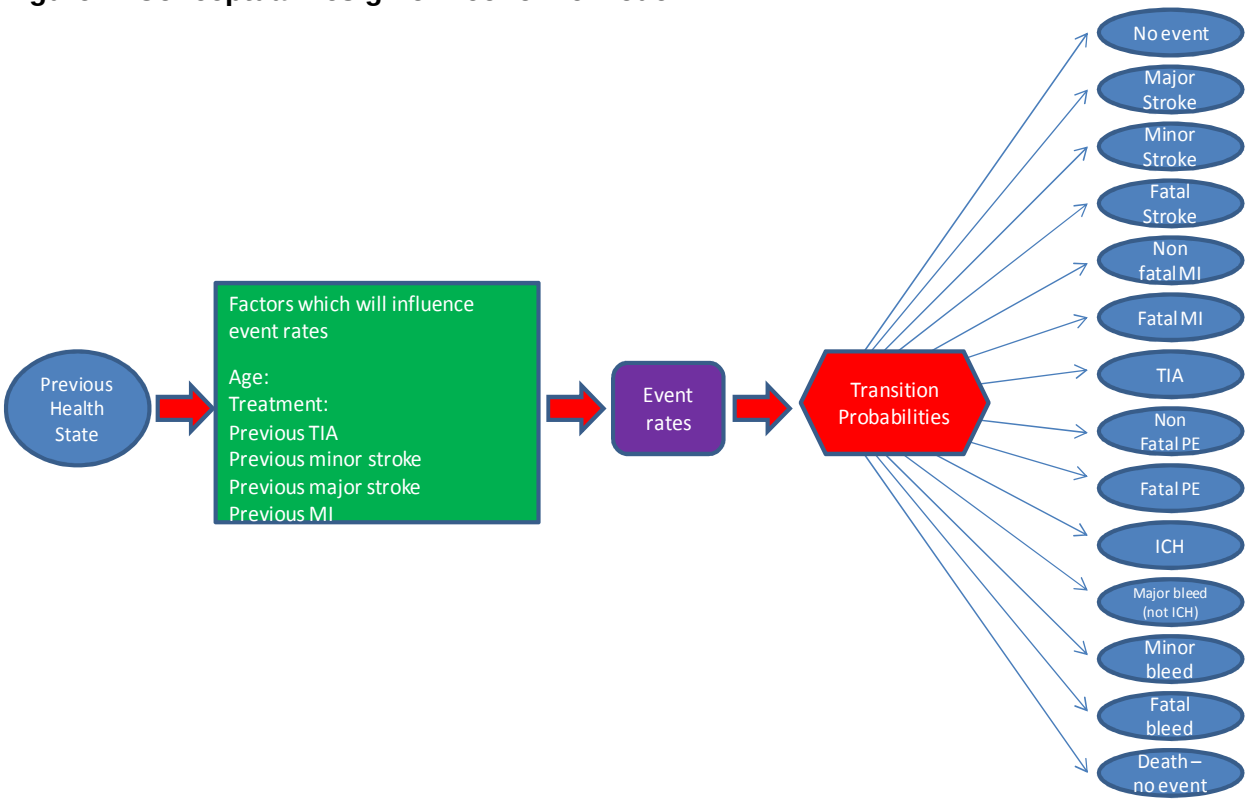
The analysis was in the form of a Markov model. The model was a cohort model in that the conceptual framework for the stroke prevention in atrial fibrillation economic model was to follow a cohort of patients with non-valvular atrial fibrillation receiving pharmacotherapy to prevent stroke.[35] The cohort was followed from initiation of pharmacotherapy to death, whilst simulating the incidence of death-related events associated with the patient population.

Within the model, at any one time a proportion of the cohort can be in one of many health states which relate to the potential events common in this patient group, the treatment currently being received, and previous history regarding TIA/stroke (major or minor) and MI. Specific events modelled were TIA, stroke (fatal, major, or minor), bleeding (fatal, ICH, major non-ICH, and minor), MI, PE (fatal or non-fatal), and death without an event. The probability that such events occur are influenced by a number of factors including treatment and patient characteristics. Patients who experience a stroke, major bleed, or ICH on treatment were assumed to continue with aspirin treatment alone; although a sensitivity analysis was conducted which assumed patients would remain on therapy.

The model assumes no difference in the outcomes of events by treatment. Sensitivity analysis assumed increased costs and disutilities, with bleeding on newer anticoagulants compared to warfarin.

The conceptual design of the model is detailed in Figure 7*.* For the base-case analysis, a cycle length of three months was adopted. The model is fully automated, allowing cycle lengths from between 1 and 12 months. Sensitivity analysis adopted alternative cycle lengths of one month, six months, and one year. The relative efficacy of the newer anticoagulants versus warfarin is assumed to continue for the duration of the patient's lifetime whilst they continue on therapy. This is tested within further analysis. A list of assumptions within the model is found in Table 29.

Figure 7: Conceptual Design of Economic Model



ICH = intracerebral hemorrhage; PE = pulmonary embolism; MI = myocardial infarction; TIA = transient ischemic attack.

Table 29 Assumptions within the Economic Model

Assumption
The patient population in the warfarin arm of the RE-LY trial is representative of the Canadian atrial fibrillation population.
Patients who have a stroke, ICH, or major bleeding whilst on warfarin, rivaroxaban, dabigatran, or apixaban will continue on treatment with aspirin alone.
Patients who have other events (including minor bleeds) continue on their current treatment.
A patient can experience any event within a cycle regardless of their previous history.
A patient can experience only one event within a cycle.
The probability of a patient having a stroke will be greater given a previous stroke or TIA.
The probability of a patient having an MI will be greater given a previous MI.
The probability of stroke will increase with age.
The probability of all-cause mortality will increase with previous stroke.
The probability of bleeding will increase with age.
The disutility from events other than stroke, ICH, or MI is temporary.
The cost of events other than stroke, ICH, or MI occurs only within the cycle when they occur.
There are long-term costs associated with an MI, ICH, and stroke, which continue until death.
The relative efficacy of treatments is assumed to be maintained whilst patients are on treatment.
The long-term costs and utility for patients with a previous ICH are equivalent to outcomes for a minor stroke.
The costs and disutilities associated with bleeds are the same for all treatments.

4.2.8 Utility values

Utility values are required for all health states within the model (Table 30).

Table 30: Utility Values

Variable Description	Base Estimate	Probability Distribution*	Reference
Long-term utilities:			
Atrial fibrillation	0.810	Beta (33.82, 7.93)	Sullivan (2006)[93]
Previous major stroke	0.333	N/A	
Rankin score 3 to 4	0.390	Beta (69.74, 109.08)	Gage (1996)[94]
Rankin score 5	0.110	Beta (18.93, 153.16)	Gage (1996)[94]
Probability major stroke is 5	0.205	Beta (8, 39)	FDA (2010)[79]
Previous minor stroke	0.75	Beta (86.69, 28.90)	Gage (1996)[94]
Previous ICH	0.75	Beta (86.69, 28.90)	Gage (1996)[94]
Previous MI (decrement)	0.012	Normal (0.012, 0.0002)	Sullivan (2005)[95]
Decrement per year over 70 years	0.00029	Normal (0.00029,0.00002)	Sullivan (2006)[93]
Decrements associated with events:†			
MI	0.125	Normal (-0.125, 0.009)	Sullivan (2006)[93]
Major bleeds	0.092	Normal (-0.092, 0.010)	Freeman (2011)[57]
Minor bleeds	0.013	Normal (-0.013, 0.001)	Freeman (2011)[57]
PE	0.022	Normal (-0.022, 0.003)	Gould (1999)[96]
TIA	0.103	Normal (-0.103, 0.008)	Sullivan (2006)[93]

MI = myocardial infarction; ICH = intracerebral hemorrhage; PE = pulmonary embolism; TIA = transient ischemic attack.
* Beta distributions parameterized by alpha and beta, normal distributions parameterized by means and standard errors.
†Derived from; utility decrements calibrated to apply for one month.

In the base case, utility values were based on both the patient's previous event history (previous MI or stroke) and whether the patient experienced an event in the current cycle. For patients with no previous event history (i.e., no previous stroke or MI), a utility value of 0.81 was adopted derived from a utility value for atrial fibrillation obtained from a previous study by Sullivan et al.[93]

Utility values for major and minor stroke were derived from a study by Gage et al.[94] The values for minor (0.75) and major (0.33) stroke obtained from this study have been adopted in a number of previous studies (e.g., Freeman and Turakhia)[57] and are consistent with other values identified in a recent systematic review. Maximum and minimum utility values for both stroke states were obtained from this review and applied in sensitivity analyses. The utility values for stroke are assumed to apply from the cycle in which the stroke occurred until death.

In the base case, ICH was assumed to have a long-term utility decrement equivalent to minor stroke, which is within the range of values adopted by previous studies (references 48 and 50). This assumption was tested within sensitivity analyses by equating the utility decrement and long-term cost of ICH to that of major stroke. The utility values for ICH are assumed to apply from the cycle in which the ICH occurred until death.

Utility values for MI relate to the disutility at the time of the event and the utility decrement subsequent to the event. For the first month in which patients experience an MI, a utility decrement of 0.1247 was applied.[93] For subsequent months until death, a decrement of 0.012 was applied.[95]

Other events were assumed to have a temporary impact on quality of life. Utility estimates were derived from the literature.[57,93,96] Utility values were presented as for a one-month cycle and were varied in sensitivity analysis. Thus, when alternate cycle lengths were adopted, the decrement was only applied to a fraction of the cycle length. For example, the utility decrement for a non-fatal pulmonary embolism is 0.022. If the cycle length is one month, the utility weight for a 70-year-old patient with no previous event history experiencing a pulmonary embolism is 0.788 (0.81 – 0.22). If the cycle length is six months, the utility value for a 70-year-old patient with no previous event history experiencing a PE is 0.806 (0.81 *5/6 + [0.81 – 0.22] *1/6). That is, the weight for one month is 0.788 (0.81 – 0.22, the utility weight for atrial fibrillation minus the utility decrement for PE) and the utility weight for the other five months is 0.81,the utility weight for atrial fibrillation.

In addition, regarding the effect of current and previous events, utility values were assumed to decline with age. For each year older than 70, the utility value was assumed to be reduced by 0.00029[93],utility values would similarly increase for each year younger than 70.

Analysis assumed no difference in utility values for treatment. Sensitivity analysis assumed reduced utility for warfarin and other anticoagulants as per previous studies.[57]

4.2.9 Costs

Costs in 2011 Canadian dollars for all resources are detailed in Table 31. Costs which were obtained for a different base year were inflated using the Bank of Canada Inflation Calculator.[97]

Estimates of drug costs were obtained from the Ontario Drug Benefit Formulary[98] or from the drug manufacturer (Bayer Inc. Canada). No drug costs were available for apixaban at the time of the analysis. We, therefore, assumed that apixaban had the same daily drug costs as dabigatran. Sensitivity analyses were conducted where the drug costs for each drug were reduced by 10% and 20%.

For each drug therapy, annual drug treatment costs include a $7 prescription fee (every three months) and an 8% pharmacist's markup. For warfarin, an additional cost of INR monitoring was added. This was obtained from a recent Ontario Health Technolog Advisory Committee (OHTAC) report and varied in sensitivity analysis. Within the sensitivity analysis, a minimum value of $0 for INR monitoring and a maximum value of $542.48 were considered. The maximum value is based upon a recent study published by Schulman et al.[99] This study reported a mean three-month cost of $198.75 for warfarin management within community-based clinics. However, included within this cost are all consultations related to anticoagulant therapy and the cost of warfarin. As patients on other anticoagulants also incur costs for follow-up physician visits, both the cost of a physician visit every three months and the cost of the medication were removed from this calculation.

Event costs were obtained from the most recently available Canadian sources.[54,100-103] In sensitivity analyses, the costs of events were increased and decreased by 50%. Long-term care costs associated with MI and stroke were similarly obtained.[54,102] Long-term care costs for ICH were assumed to be similar to costs for a minor stroke. In sensitivity analysis, these were also increased and decreased by 50%.

Table 31: Cost Estimates

Variable Description	Base Estimate	Probability Distribution	Reference
Treatment (per annum) *			
Warfarin 5 mg daily	$54.61	Fixed	Ontario MoH (2011)[98]
Aspirin EC 325 mg daily	$39.04	Fixed	Ontario MoH (2011)[98]
Dabigatran 150 mg b.i.d.	$1,289.44	Fixed	Sorensen et al. (2011)[54]
Rivaroxaban 20 mg daily	$1,147.53	Fixed	
Apixaban 5 mg b.i.d.	$1,289.44	Fixed	Bayer Canada Inc.†

			Author assumption
Monitoring (per annum) INR for warfarin	$240.69	Fixed	Medical Advisory Secretariat (2009)[104]
Events Fatal stroke Minor stroke Major stroke TIA ICH Major bleed Minor bleed Fatal MI Non-fatal MI PE	 $16,800 $16,800 $56,864 $4,296 $16,559 $4,392 $104 $7,351 $11,380 $7,442	 Gamma ‡(16.0, 1050.0) Gamma (16.0, 1050.0) Gamma (16.0, 3554.0) Gamma (16.0, 268.5) Gamma (16.0, 1035.0) Gamma (16.0, 274.5) Gamma (6.4, 16.3) Gamma (16.0, 459.5) Normal (11380.0, 167.0) Normal (7442.0, 7682.1)	 Sorensen et al. (2011)[54] Sorensen et al. (2011)[54] Sorensen et al. (2011)[54] Goeree et al. (2005)[101] Sorensen et al. (2011)[54] Regier et al. (2006)[103] Sorensen et al. (2011)[54] Goeree et al. (2009)[102] OCCI (2011)[100]
Long-term costs (per annum) MI Major stroke Minor stroke ICH	 $3,272 $19,069 $7,896 $7,896	 Gamma (190.6, 17.2) Gamma (16.0, 1191.8) Gamma (16.0, 493.5) Gamma (16.0, 493.5)	 Sorensen et al. (2011)[54] Sorensen et al. (2011)[54] Goeree et al. (2009)[102] Goeree et al. (2009)[102]

EC = enteric coated; ICH = intracerebral hemorrhage; MI = myocardial infarction; MoH = Ministry of Health and Long-Term Care; OCCI = Ontario Case Costing Initiative; PE = pulmonary embolism; TIA = transient ischemic attack.
* Includes a $7 prescription fee (every three months) and an 8% pharmacist's markup.
† Kory McDonald Ibarra, Director, Federal Government and External Affairs, Ottawa, Bayer, Inc.: personal communication, 2012 Feb.
‡Gamma distributions parameterized by shape and scale, normal distributions parameterized by means and standard errors (used when coefficient of variation is minimal).

4.2.10 Sensitivity Analysis

i) Deterministic Sensitivity Analysis

A wide range of univariate sensitivity analyses were conducted to test the effect of changes in underlying parameter values and assumptions within the models. The analyses conducted were:

- Drug costs of rivaroxaban reduced by 10% and 20%
- Drug costs of dabigatran reduced by 10% and 20%
- Drug costs of apixaban reduced by 10% and 20%
- Threshold analysis to determine the cost at which rivaroxaban and apixaban would be cost-effective
- Annual cost of INR monitoring with warfarin = $0
- Annual cost of INR monitoring with warfarin = $542.48
- Increase and decrease event costs by 50%
- Increase and decrease long-term care costs by 50%
- Time horizon of 20 years, 10 years, and 2 years
- Discount rate = 0%, 3% and 10%
- Cycle length = one month, six months, and 12 months

- Incorporate a half-cycle correction
- Maximum utility value for stroke from literature: major = 0.52, minor =0.8
- Minimum utility value for stroke from literature: major = 0.22, minor =0.55
- Assume no age decrement to utility values
- Increase utility decrements from events by 100%
- Weight utilities by utility values on treatment: aspirin = 0.998, warfarin = 0.987, other anticoagulants = 0.994
- Include effect of treatments on minor bleeds
- Include effect of treatments on non-vascular deaths
- Exclude effect of treatments on MI
- Assume patients had a previous minor stroke and a previous major stroke
    - For both these analyses, due to the absence of stratified analysis of the trial results, the model did not assume differential efficacy of the newer anticoagulants based on their history of stroke.
- Assume patients had a previous MI
- Assuming double and quadruple utility decrements from minor and major bleeds and double and quadruple costs of minor and major bleeds for the new anticoagulants
- Assume disutility and costs of ICH are equivalent to major stroke
- Assume double the fatality rate of major bleeds and ICH
- Assuming patients remain on therapy for lifetime for the new anticoagulants
- Assuming base-case event rates for warfarin from ROCKET-AF and ARISTOTLE clinical trials
- Incorporate treatment discontinuations not related to events
- Assume that patients would transition from dabigatran 150 mg to dabigatran 110 mg at age 80.

ii) Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis was conducted using a Monte Carlo simulation.[86] For the simulation, probability distributions related to natural history parameters, relative risks and ORs, costs and utilities were incorporated into the analysis.

The analysis adopted standard methods for defining uncertainty around parameters. Transition probabilities were characterized by beta distributions and relative risks and ORs were characterized by log-normal distributions. Utility values for long-term states were characterized by beta distributions whilst utility decrements were characterized by normal distributions. Costs were characterized by Gamma distributions, except where the coefficient of variation was low (< 5%) where a normal distribution was used. Drug costs were assumed fixed. Probability distributions were parameterized using empiric data. For event costs where no measures of dispersion were available, a coefficient of variation of 25% was assumed.

Estimates of incremental costs and QALYs were obtained by re-running the model employing values from the related probability distributions. In this study, 5,000 replications were conducted; i.e., a set of 5,000 outcome estimates was obtained. Cost-effectiveness acceptability curves were derived, which present the probability that each treatment is optimal given different values of willingness to pay for an additional QALY.[86]

4.2.11 Analysis of Variability

In addition to the aforementioned sensitivity analysis, stratified analyses were conducted to assess the sensitivity of the results to changes in the underlying patient population. Stratified analyses incorporated, where possible, different warfarin-related event rates based on the patient profile and available data. In addition, where possible, different estimates of the relative treatment effect of the newer oral

anticoagulants compared with warfarin were included. Analyses were conducted to stratify patients by three criteria: $CHADS_2$ score, age, and TTR.

Analyses were conducted to assess the cost-effectiveness of oral anticoagulants in patients with a $CHADS_2$ score of < 2, 2, and > 2. For patients >2, this was further stratified by those with no previous stroke, previous minor stroke, and previous major stroke. The network meta-analysis allowed estimation of stratified risk reductions relative to warfarin by $CHADS_2$ score (< 2, ≥ 2) for stroke and major bleeds and these were used for the appropriate populations. For other events, the unstratified risk reductions from the network meta-analysis were used. Warfarin event rates were available specific to $CHADS_2$ for stroke, major bleed, ICH, and non-vascular deaths. For other events, rates for the complete RE-LY trial population were used. For rivaroxaban, there were no available data for the risk reduction for stroke with $CHADS_2$ score < 2.

Analysis was conducted to assess the cost-effectiveness of oral anticoagulants in patients aged 60, 70, and 80. The network meta-analysis allowed estimation of stratified risk reductions relative to warfarin by age (< 75, ≥ 75) for stroke and major bleeds and these were used for the appropriate populations. For other events, the unstratified risk reductions from the network meta-analysis were used. Parameters affected by age are: rates of bleeding and stroke on warfarin, and underlying utility values for all health states.

Analysis was conducted to assess the cost-effectiveness of oral anticoagulants in patients according to TTR. Analysis was based on clinical data relating to centre-specific average TTR, not patient TTR. Thus, results can, at best, be seen as a proxy for the cost-effectiveness of newer treatments when compared to warfarin by TTR. To allow comparison between the new anticoagulants, stratified analysis is restricted to comparing an average TTR of < 66% to ≥ 66%. The network meta-analysis allowed estimation of stratified risk reductions relative to warfarin by centre TTR for stroke and major bleeds. For other events, the unstratified risk reductions from the network meta-analysis were used. Warfarin event rates were available specific to TTR for stroke, major bleed, ICH, and minor bleeds. For other events, rates for the complete RE-LY trial population were used. As the distribution of patients in the various trials across TTR differs, the results for each new anticoagulant will not be the same for different categories of TTR.

4.2.12 Analysis of the effect of changes in the duration of treatment effect

Analysis was conducted to assess the cost-effectiveness of oral anticoagulants in patients when varying the duration of time for which it was assumed that the relative benefits of the newer anticoagulants compared to warfarin would be maintained. In the base-case analysis, treatment effect is assumed to be maintained for a lifetime. For this analysis, the duration was varied between two years (the typical duration of the clinical trials in this disease area) and lifetime.

4.2.13 Base-Case Analysis

Table 32 and Figure 8 provide the results of the base-case analysis.

Treatment with dabigatran 110 mg ($22,837) is the most costly treatment alternative, followed by rivaroxaban ($22,016), apixaban ($21,966), dabigatran 150 mg ($21,420), and warfarin ($18,620). For dabigatran 150 mg, treatment costs were the greatest component of costs (Table 33). For all other treatments, stroke-related costs were the greatest cost component.

Dabigatran 150 mg was the most effective treatment regarding QALYs and life-years (6.639 and 8.211), followed by apixaban (6.617, 8.195). Dabigatran 110 mg and rivaroxaban also produce more QALYs and life-years than warfarin but fewer than dabigatran 150 mg and apixaban.

The incremental cost per QALY gained for dabigatran 150 mg versus warfarin was $17,525. As dabigatran 110 mg, apixaban, and rivaroxaban produced fewer QALYs than dabigatran and at a greater cost, they were all dominated by dabigatran 150 mg.

The incremental cost per life-year gained for dabigatran 150 mg versus warfarin was $9,068. Dabigatran 110 mg, apixaban, and rivaroxaban were all dominated by dabigatran 150 mg.

Table 32: Results of Base-Case Deterministic Analysis

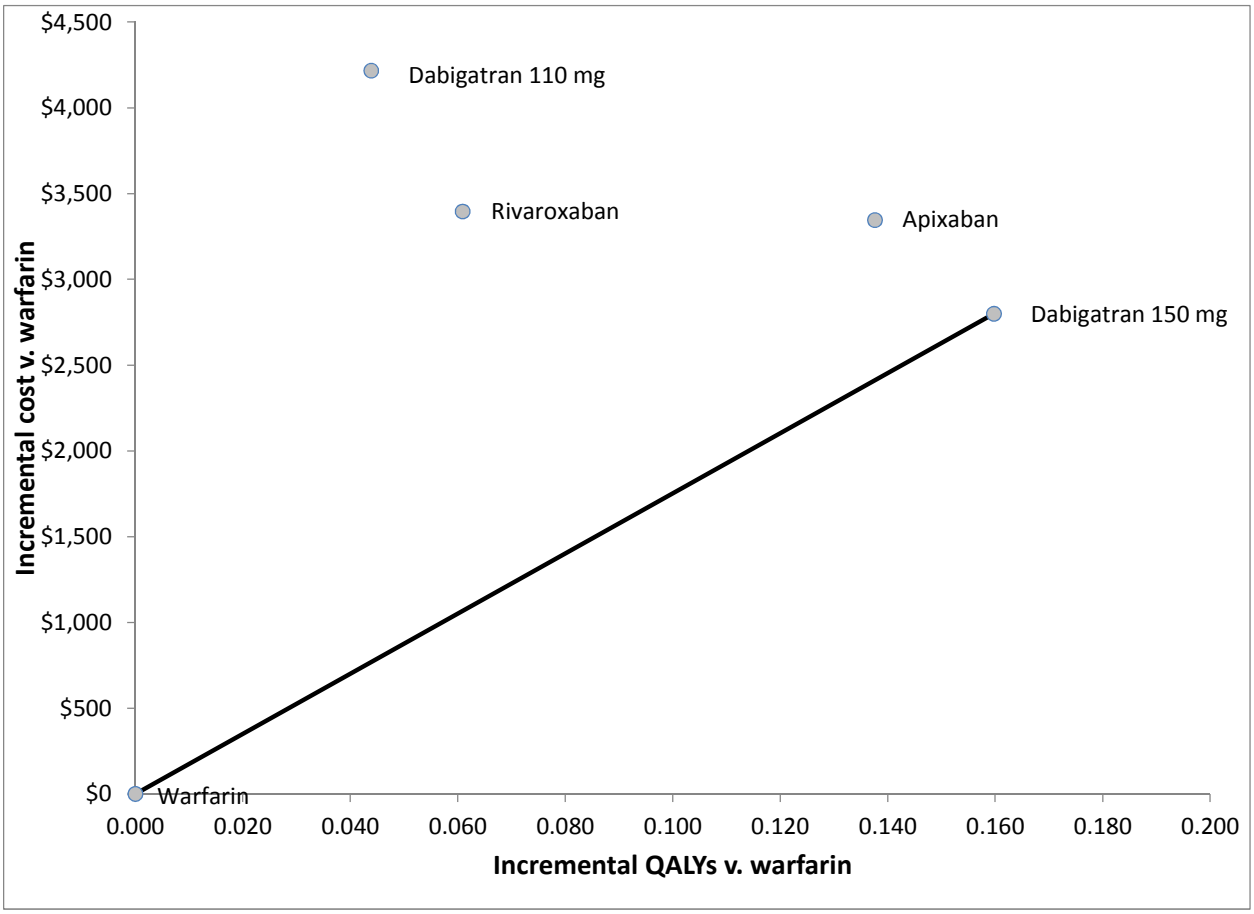
	Cost	QALYs	Life-Years	Incremental Cost Per QALY Gained (ICER)	
				vs. Warfarin	Sequential ICER
Warfarin	$18,620	6.480	7.903		
Dabigatran 150 mg	$21,420	6.639	8.211	$17,525	$17,525
Dominated therapies*					
Apixaban	$21,966	6.617	8.195	$24,312	Dominated by dabigatran 150 mg
Rivaroxaban	$22,016	6.541	8.050	$55,757	Dominated by dabigatran 150 mg and apixaban
Dabigatran 110 mg	$22,837	6.524	8.131	$96,026	Dominated by dabigatran 150 mg, apixaban, and rivaroxaban

ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life-years; vs. = versus.
*Dominated = more costly and fewer QALYs,
Extended dominance = the combination of two other alternatives dominates the treatment

Table 33: Breakdown of Costs by Components

	Warfarin	Dabigatran 110 mg	Dabigatran 150 mg	Rivaroxaban	Apixaban
Drug treatment and monitoring costs	$1,945	$8,416	$8,783	$7,395	$8,899
Stroke-related costs	$10,815	$10,211	$8,164	$9,743	$9,081
Bleeding-related costs	$4,381	$2,475	$2,733	$3,545	$2,608
Other costs	$1,480	$1,734	$1,740	$1,332	$1,377
Total	$18,620	$22,837	$21,420	$22,016	$21,966

Figure 8: Base-Case Results on the Cost-Effectiveness Plane



QALYs = quality-adjusted life-years; v. = versus.

4.3 Results: Sensitivity Analysis

4.3.1 Deterministic sensitivity analysis

Table 34 provides the results of the detailed univariate sensitivity analysis.

Results are insensitive (i.e., the interpretation is unlikely to change) to changes in:

- Drug costs of rivaroxaban and dabigatran
- Costs of events and of long-term care
- Time horizon of 20 and 10 years
- Discount rate = 0%, 3%, and 10%
- Cycle length = one month, six months, and 12 months
- Costs of INR monitoring for warfarin
- Incorporate a half-cycle correction
- Changing the utility value of stroke
- Assume no age decrement to utility values

- Increase utility decrements from events by 100%
- Weight utilities by utility values on treatment
- Include effect of treatments on minor bleeds
- Exclusion of effects of treatment on MI
- Assume patients had a previous minor stroke
- Assume patients had a previous MI
- Increased consequences of bleeding for the new anticoagulants
- Assume utility decrement and costs for ICH are equivalent to major stroke.

Results were sensitive to the drug costs of apixaban. With a 10% reduction in the price of apixaban, apixaban was extendedly dominated by dabigatran 150 mg and warfarin; however, if the cost of apixaban was reduced by 20% to $2.56 per tablet, apixaban would be cost-effective assuming a maximum willingness to pay for a QALY (λ) of at least $11,742 and less than $53,488.

Results were very sensitive to the time horizon adopted. With a time horizon of ten years, dabigatran 150 mg would be optimal if λ was greater than $42,912. With a time horizon of two years (the typical duration of the RCTs considered within the MTC), dabigatran 150 mg would be optimal, but only if λ was greater than $335,542.

If the relative effects of treatments on non-vascular deaths were included, rivaroxaban would be optimal if λ was greater than $8,278.

If extreme assumptions relating to the consequences of bleeding with the NOACs were made, the results would change. Assuming a doubling of the costs, utility and mortality rates associated with major and minor bleeds leads to dabigatran being cost-effective only if λ was greater than $52,456. A more extreme assumption of the effects being four times the baseline estimates leads to all NOACs being dominated by warfarin.

If treatment discontinuations not related to vascular events were included in the analysis, dabigatran 150 mg would be cost-effective if λ was between $19,780 and $38,056. For values of λ greater than $38,056, apixaban would be optimal.

In the analysis where patients would be switched from dabigatran 150 mg to dabigatran 110 mg at age 80, dabigatran 150 mg would be cost-effective if λ was between $23,605 and $71,250. For values of λ greater than $71,250, apixaban would be optimal.

If patients had a previous major stroke, the incremental cost per QALY for all treatments relative to warfarin increased. Dabigatran would be optimal if λ was greater than $133,199.

Threshold analysis found that, based on a λ of $50,000, apixaban would be more cost-effective than dabigatran 150 mg if the price of apixaban was less than $2.58 per tablet. Based on the same threshold, rivaroxaban would need to be equal to or less than 63 cents per tablet to be more cost-effective than dabigatran 150 mg.

Table 34: Results of Deterministic Sensitivity Analysis	
Scenario	**Result**
Base case*	For λ < $17,525, warfarin is optimal. For λ > $17,525, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Drug costs of rivaroxaban reduced by 10%	For λ < $17,525, warfarin is optimal. For λ > $17,525, dabigatran 150 mg is optimal. Apixaban is dominated by dabigatran 150 mg. Rivaroxaban is extendedly dominated by dabigatran 150 mg and warfarin, and by apixaban and warfarin. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Drug costs of rivaroxaban reduced by 20%	For λ < $17,525, warfarin is optimal. For λ>$17,525, dabigatran 150 mg is optimal. Apixaban is dominated by dabigatran 150 mg. Rivaroxaban is extendedly dominated by dabigatran 150 mg and warfarin, and by apixaban and warfarin. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Drug costs of dabigatran reduced by 10%	For λ < $12,185, warfarin is optimal. For λ > $12,185, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Drug costs of dabigatran reduced by 20%	For λ < $6,844, warfarin is optimal. For λ > $6,844, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg and extendedly dominated by apixaban and warfarin, and rivaroxaban and warfarin.
Drug costs of apixaban reduced by 10%	For λ < $17,525, warfarin is optimal. For λ > $17,525, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is extendedly dominated by dabigatran 150 mg and warfarin. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.

Table 34: Results of Deterministic Sensitivity Analysis	
Scenario	**Result**
Drug costs of apixaban reduced by 20%	For λ < $11,742, warfarin is optimal. For λ > $11,742, but λ < $53,488 apixaban is optimal. For λ > $53,488, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Threshold analysis for cost of rivaroxaban and apixaban	For apixaban to be more cost-effective than dabigatran 150 mg, the price of apixaban would need to be equal to or less than $2.58 per tablet. For rivaroxaban to be more cost-effective than dabigatran 150 mg, the price of rivaroxaban would need to be equal to or less than 63 cents per tablet.
Annual cost of INR monitoring with warfarin = $0	For λ < $27,076, warfarin is optimal. For λ > $27,076, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Annual cost of INR monitoring with warfarin = $542.48	For λ < $5,550, warfarin is optimal. For λ > $5,550 dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Increase event costs by 50%	For λ < $11,029, warfarin is optimal. For λ > $11,029, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Decrease event costs by 50%	For λ < $23,372, warfarin is optimal. For λ > $23,372, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg, and extendedly dominated by warfarin and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Increase long-term care costs by 50%	For λ < $10,409, warfarin is optimal. For λ > $10,409, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.

Table 34: Results of Deterministic Sensitivity Analysis	
Scenario	**Result**
Decrease long-term care costs by 50%	For λ < $24,641, warfarin is optimal. For λ > $24,641, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg, and extendedly dominated by warfarin and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Time horizon of 20 years	For λ < $19,233, warfarin is optimal. For λ > $19,233, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Time horizon of 10 years	For λ < $42,912, warfarin is optimal. For λ > $42,912, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg, and extendedly dominated by warfarin and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Time horizon of 2 years	For λ < $335,542, warfarin is optimal. For λ > $335,542, dabigatran 150 mg is optimal. Rivaroxaban is extendedly dominated by warfarin and dabigatran 150 mg, and by warfarin and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Discount rate = 0%	For λ < $10,502, warfarin is optimal. For λ > $10,502, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Discount rate = 3%	For λ < $14,489, warfarin is optimal. For λ > $14,489, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Discount rate = 10%	For λ < $26,280, warfarin is optimal. For λ > $26,280, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg, and extendedly dominated by warfarin and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.

Table 34: Results of Deterministic Sensitivity Analysis	
Scenario	**Result**
Cycle length = 1 month	For λ < $17,867, warfarin is optimal. For λ > $17,867, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Cycle length = 6 months	For λ < $16,962, warfarin is optimal. For λ > $16,962, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Cycle length = 12 months	For λ < $15,877, warfarin is optimal. For λ > $15,877, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Incorporate a half cycle correction	For λ < $17,356, warfarin is optimal. For λ > $17,356, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Maximum utility value for stroke from literature: major = 0.52 minor =0.8	For λ < $20,368, warfarin is optimal. For λ > $20,368, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Minimum utility value for stroke from literature: major = 0.22 minor =0.55	For λ < $13,273, warfarin is optimal. For λ > $13,273, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Assume no age decrement to utility values	For λ < $17,457, warfarin is optimal. For λ > $17,457, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.

Table 34: Results of Deterministic Sensitivity Analysis	
Scenario	**Result**
Increase utility decrements from events by 100%	For λ < $17,533, warfarin is optimal. For λ > $17,533, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Weight utilities by utility values on treatment: aspirin=0.998 warfarin=0.987 other anticoagulants=0.994	For λ < $14,437, warfarin is optimal. For λ > $14,437, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Include effect of treatments on minor bleeds	For λ < $17,449, warfarin is optimal. For λ > $17,449, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Include effect of treatments on non-vascular deaths	For λ < $8,278, warfarin is optimal. For λ > $8,278, rivaroxaban is optimal. Dabigatran 150 mg is extendedly dominated by apixaban and warfarin, and rivaroxaban and warfarin. Dabigatran 110 mg is dominated by apixaban and dabigatran 150 mg warfarin and extendedly dominated by rivaroxaban and warfarin. Apixaban is extendedly dominated by rivaroxaban and warfarin.
Not including effect on MI	For λ < $15,378, warfarin is optimal. For λ > $15,378, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is extendedly dominated by dabigatran 150 mg and warfarin. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Patients with previous minor stroke	For λ < $14,163, warfarin is optimal. For λ > $14,163, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg, and extendedly dominated by warfarin and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.

Table 34: Results of Deterministic Sensitivity Analysis	
Scenario	**Result**
Patients with previous major stroke	For λ < $133,199, warfarin is optimal. For λ > $133,199, dabigatran 150 mg is optimal. Rivaroxaban is extendedly dominated by apixaban and warfarin, and by dabigatran 150 mg and warfarin. Apixaban is extendedly dominated by dabigatran 150 mg and warfarin. Dabigatran 110 mg is dominated by rivaroxaban, and extendedly dominated by both warfarin and apixaban and warfarin and dabigatran 150 mg.
Patients with previous MI	For λ < $20,464, warfarin is optimal. For λ > $20,464, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg, and extendedly dominated by apixaban and warfarin. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Costs and utilities associated with an ICH are equivalent to a major stroke	For λ < $358, warfarin is optimal. For λ > $358. dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg, dabigatran 110 mg, and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg and apixaban.
Double utility decrements from minor and major bleeds, and double costs of minor and major bleeds for all NOACs	For λ < $24,472, warfarin is optimal. For λ > $24,472, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Double utility decrements, costs, and mortality rates associated with minor and major bleeds for all NOACs	For λ < $52,466, warfarin is optimal. For λ > $52,466, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Quadruple utility decrements from minor and major bleeds, and quadruple costs for minor and major bleeds for all NOACs	For λ < $39,100, warfarin is optimal. For λ > $39,100, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Quadruple utility decrements, costs, and mortality rates associated with minor and major bleeds for all NOACs	All treatments dominated by warfarin.

Table 34: Results of Deterministic Sensitivity Analysis	
Scenario	**Result**
Patients remain on therapy for their lifetime (i.e., no switching therapy after an event)	For λ < $19,434, warfarin is optimal. For λ > $19,434, dabigatran is optimal. Rivaroxaban is dominated by dabigatran, and extendedly dominated by apixaban and warfarin. Apixaban is dominated by dabigatran.
Deriving base rates for events for warfarin from ROCKET-AF clinical trial (Patel, 2011[13])	For λ < $22,951, warfarin is optimal. For λ > $22,951, dabigatran 150 mg is optimal. Rivaroxaban is extendedly dominated by dabigatran 150 mg and warfarin, and by apixaban and warfarin. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Deriving base rates for events for warfarin from ARISTOTLE clinical trial (Granger, 2011[11])	For λ < $22,194, warfarin is optimal. For λ > $22,194, dabigatran 150 mg is optimal. Rivaroxaban is dominated by dabigatran 150 mg and warfarin, and extendedly dominated by apixaban and warfarin. Apixaban is dominated by dabigatran 150 mg. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.
Reduction in dose of dabigatran from 150 mg b.i.d. to 110 mg b.i.d. at age 80 and incorporation of age-specific estimates	For λ < $23,605, warfarin is optimal. For λ > $23,605, but λ < $71,250 dabigatran is optimal. For λ > $71,250, apixaban is optimal. Rivaroxaban is dominated by dabigatran and apixaban.
Incorporation of treatment discontinuation rates	For λ < $19,780, warfarin is optimal. For λ > $19,780, but λ < $38,056 dabigatran 150 mg is optimal. For λ > $38,056, apixaban is optimal. Rivaroxaban is dominated by dabigatran 150 mg and apixaban. Dabigatran 110 mg is dominated by dabigatran 150 mg, rivaroxaban, and apixaban.

b.i.d. = twice daily; ICH = intracerebral hemorrhage; QALY = quality-adjusted life-year; λ = maximum willingness to pay for a QALY; NOAC = new oral anticoagulant.
* 72-year-old patient with no previous stroke, lifetime time horizon; cycle length = 3 months, discount rate =5%.

4.3.2 Probabilistic sensitivity analysis

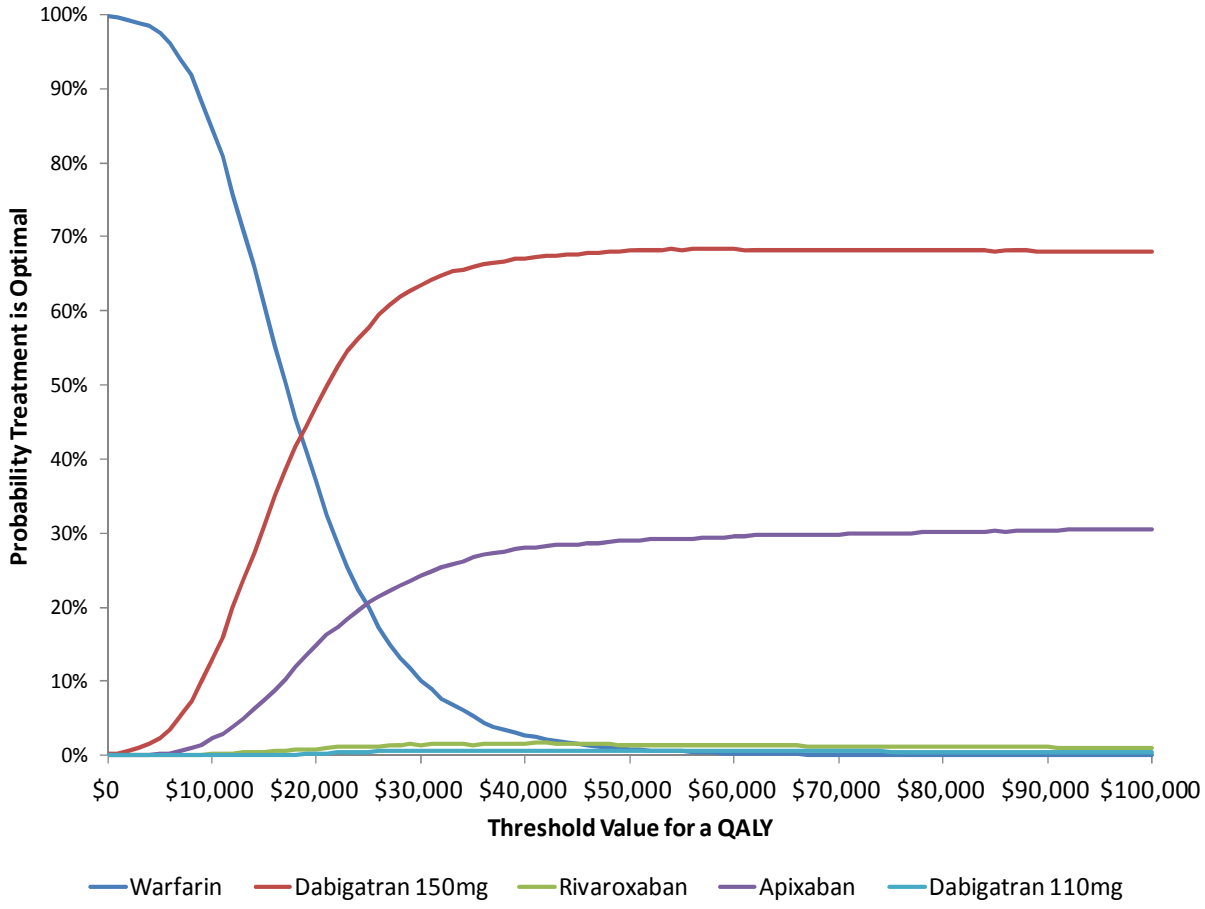
The expected values of costs, effects, and incremental cost-effectiveness ratios did not vary significantly from the deterministic base-case analysis and the probabilistic analysis (Table 35). Dabigatran 150 mg and apixaban were associated with statistically significantly greater costs and greater QALY. However, the 95% credible intervals for QALY gained versus warfarin for rivaroxaban and dabigatran 110 mg crossed zero.

Table 35: Results of Probabilistic Analysis						
	Cost	**QALYs**	**Incremental Cost vs. Warfarin**	**Incremental QALYs vs. Warfarin**	**Incremental Cost Per QALY Gained (ICER)**	
					vs. Warfarin	**Sequential ICER**
Warfarin	$18,618 (14,446 to 23,767)	6,479 (5.482 to 7.309)				
Dabigatran 150 mg	$21,505 (18,269 to 25,675)	6.635 (5.581 to 7.502)	$3,485 (2,085 to 4766)	0.156 (0.069 to 0.252)	$18,479	$18,479
Dominated Therapies*						
Apixaban	$22,023 (18,556 to 26,360)	6.614 (5.569 to 7.477)	$3,405 (1,798 to 4,766)	0.136 (0.060 to 0.222)	$25,123	Dominated by dabigatran 150 mg
Rivaroxaban	$22,103 (18,223 to 26,942)	6.536 (5.581 to 7.502)	$3,485 (2,085 to 4,766)	0.0.057 (–0.009- to 0.133)	$60.817	Dominated by dabigatran 150 mg and apixaban
Dabigatran 110 mg	$22,904 (19,127 to 27,742)	6.520 (5.507 to 7.384)	$4,286 (2,673 to 5,737)	0.042 (–0.035- 0.127)	$102,912	Dominated by dabigatran 150 mg, rivaroxaban, and apixaban

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.
Figures in parenthesis are 95% credible intervals
* Dominated = more costly and fewer QALYs, Extended dominance = the combination of two other alternatives dominates the treatment

However, the probabilistic sensitivity analysis highlights the uncertainty around conclusions relating to cost-effectiveness (Figure 9). At an λ of $50,000, dabigatran 150 mg was the optimal treatment in 68.1% of replications, apixaban in 29.0%, rivaroxaban in 1.4%, dabigatran 110 mg in 0.6%, and warfarin in 0.9%. Results were similar for all values of λ, from $40,000 to $100,000.

Figure 9: Cost-Effectiveness Acceptability Curve



QALY = quality-adjusted life-year.

4.4 Analysis of Variability

4.4.1 $CHADS_2$ score

Analysis was very sensitive to patient's baseline $CHADS_2$ score (Table 36).

For a $CHADS_2$ score of less than 2, dabigatran 150 mg would be optimal if λ was greater than $25,569. Apixaban was dominated by dabigatran 150 mg, with greater costs and fewer QALYs. Dabigatran 110 mg was dominated by both apixaban and dabigatran 150 mg. From the results of a probabilistic analysis, at an λ of $50,000, dabigatran 150 mg was the optimal treatment in 60.7% of replications, apixaban in 24.5%, dabigatran 110 mg in 5.3%, and warfarin in 9.6% of replications.

For a $CHADS_2$ score equalling 2, dabigatran 150 mg would be optimal if λ was greater than $28,407 but less than $48,588. Apixaban would be optimal if λ was greater than $48.588. Rivaroxaban was dominated by both apixaban and dabigatran 150 mg. Dabigatran 110 mg was dominated by apixaban, rivaroxaban, and dabigatran 150 mg. From the results of a probabilistic analysis, at an λ of $50,000, apixaban was the optimal treatment in 44.3% of replications, dabigatran 150 mg in 43.0%, rivaroxaban in 5.4%, dabigatran 110 mg in 3.5%, and warfarin in 3.8% of replications.

For a $CHADS_2$ score greater than 2, with no previous stroke, dabigatran 150 mg would be optimal if λ was greater than $9,559 but less than $44,687. Apixaban would be optimal if λ was greater than $44,687. Rivaroxaban was dominated by both apixaban and dabigatran 150 mg. Dabigatran 110 mg was dominated by apixaban, rivaroxaban, and dabigatran 150 mg. From the results of a probabilistic analysis, at an λ of $50,000, apixaban was the optimal treatment in 48.9% of replications, dabigatran 150 mg in 40.6%, rivaroxaban in 4.8%, dabigatran 110 mg in 5.6%, and warfarin in 0.2% of replications.

For a $CHADS_2$ score greater than 2, with a previous minor stroke, dabigatran 150 mg would be optimal if λ was greater than $9,944. Apixaban was dominated by dabigatran 150 mg. Rivaroxaban was dominated by dabigatran 150 mg and apixaban. Dabigatran 110 mg was dominated by apixaban, rivaroxaban, and dabigatran 110 mg. From the results of a probabilistic analysis, at an λ of $50,000, dabigatran 150 mg was the optimal treatment in 56.9% of replications, apixaban in 29.0%, rivaroxaban in 11.1%, dabigatran 110 mg in 3.0%, and warfarin in 0.02% of replications.

For a $CHADS_2$ score greater than 2, with a previous major stroke, dabigatran 150 mg would be optimal if λ was greater than $121,905. Apixaban was dominated by dabigatran 150 mg. Rivaroxaban was subject to extended dominance through warfarin and apixaban, and through warfarin and dabigatran 150 mg. Dabigatran 110 mg was dominated by rivaroxaban, and subject to extended dominance through warfarin and apixaban, and through warfarin and dabigatran 150 mg. From the results of a probabilistic analysis, at an λ of $50,000, dabigatran 150 mg was the optimal treatment in 0.9% of replications, apixaban in 0.5%, rivaroxaban in 0.3%, dabigatran 110 mg in 0%, and warfarin in 98.4% of replications.

4.4.2 Age

Analysis by patient is summarized in Table 37.

For patients aged 60, dabigatran 150 mg would be optimal if λ was greater than $16,898. Apixaban was dominated by dabigatran 150 mg. Rivaroxaban was dominated by dabigatran 150 mg and subject to extended dominance through warfarin and apixaban. Dabigatran 110 mg was dominated by apixaban, rivaroxaban, and dabigatran 150 mg. From the results of a probabilistic analysis, at an λ of $50,000, dabigatran 150 mg was the optimal treatment in 79.4% of replications, apixaban in 10.9%, rivaroxaban in 2.3%, dabigatran 110 mg in 6.4%, and warfarin in 1.0% of replications.

For patients aged 70, dabigatran 150 mg would be optimal if λ was greater than $12,327. Apixaban was dominated by dabigatran 150 mg. Rivaroxaban was dominated by dabigatran 150 mg, and subject to extended dominance through warfarin and apixaban. Dabigatran 110 mg was dominated by apixaban, rivaroxaban, and dabigatran 150 mg. From the results of a probabilistic analysis, at an λ of $50,000, dabigatran 150 mg was the optimal treatment in 81.1% of replications, apixaban in 9.7%, rivaroxaban in 1.4%, dabigatran 110 mg in 7.5%, and warfarin in 0.3% of replications.

For patients aged 80, apixaban would be optimal if λ was greater than $17,439. Dabigatran 150 mg was dominated by apixaban and rivaroxaban. Rivaroxaban was subject to extended dominance through apixaban and warfarin. Dabigatran 110 mg was dominated by dabigatran 150 mg, apixaban, and rivaroxaban. From the results of a probabilistic analysis, at an λ of $50,000, apixaban was the optimal treatment in 60.0% of replications, dabigatran 150 mg in 13.2%, rivaroxaban in 25.2%, dabigatran 110 mg in 1.2%, and warfarin in 0.5% of replications.

4.4.3 Time in therapeutic range

Analysis by time in therapeutic range (TTR) is summarized in Table 38.

In centres where the TTR was less than 66%, dabigatran 150 mg would be optimal if λ was greater than $7,524. Apixaban was dominated by dabigatran 150 mg. Rivaroxaban was dominated by dabigatran 150 mg, and subject to extended dominance through warfarin and apixaban. Dabigatran 110 mg was dominated by dabigatran 150 mg, apixaban, and rivaroxaban. From the results of a probabilistic analysis,

at an λ of $50,000, apixaban was the optimal treatment in 13.6% of replications, dabigatran 150 mg in 85.1%, rivaroxaban in 0.6%, dabigatran 110 mg in 0.7%, and warfarin in 0% of replications.

In centres where the TTR was equal to or greater than 66%, apixaban would be optimal if λ was greater than $35,358. Dabigatran 150 mg and dabigatran 110 mg were dominated by apixaban and rivaroxaban. Rivaroxaban was subject to extended dominance through apixaban and warfarin. From the results of a probabilistic analysis, at an λ of $50,000, apixaban was the optimal treatment in 46.9% of replications, dabigatran 150 mg in 6.7%, rivaroxaban in 20.9%, dabigatran 110 mg in 12.4%, and warfarin in 13.1% of replications.

Table 36: Results of Stratified Analysis by $CHADS_2$ Score

	Cost	QALYs	Incremental Cost Per QALY Gained (ICER)	
			vs. Warfarin	Sequential ICER
$CHADS_2$ SCORE < 2				
Warfarin	$16,046	7.004		
Dabigatran 150 mg	$20,112	7.163	$25,570	$25,570
Dabigatran 110 mg	$21,947	7.050	$129,575	Dominated by dabigatran 150 mg and apixaban
Apixaban	$21,052	7.117	$44,289	Dominated by dabigatran 150 mg
$CHADS_2$ SCORE = 2				
Warfarin	$15,317	6.084		
Dabigatran 150 mg	$18,694	6.202	$28,407 1	$28,407
Apixaban	$18,916	6.207	$29,156	$48,588
Dabigatran 110 mg	$19,589	6.152	$62,432	Dominated by dabigatran 150 mg, rivaroxaban, and apixaban
Rivaroxaban	$18,615	6.154	$46,575	Extendedly dominated by apixaban and warfarin, and dabigatran 150 mg and warfarin
$CHADS_2$ SCORE > 2 (no previous stroke)				
Warfarin	$23,447	6.548		
Dabigatran 150 mg	$25,183	6.730	$9,559	$9,559
Apixaban	$25,587	6.739	$11,225	$44,687
Dabigatran 110 mg	$26,394	6.661	$26,090	Dominated by rivaroxaban, dabigatran 150 mg, and apixaban
Rivaroxaban	25718.53	6.667	$19,035	Dominated by dabigatran 150 mg and apixaban
$CHADS_2$ SCORE > 2 (with previous minor stroke)				
Warfarin	$73,537	4.448		
Dabigatran 150 mg	$75,392	4.635	$9,944	$9,944
Apixaban	$76,171	4.612	$16,108	Dominated by dabigatran 150 mg
Dabigatran 110 mg	$77,195	4.534	$42,592	Dominated by rivaroxaban, dabigatran 150 mg, and apixaban
Rivaroxaban	$75,610	4.569	$17,121	Dominated by dabigatran 150 mg, and extendedly dominated by apixaban and warfarin
$CHADS_2$ SCORE > 2 (with previous major stroke)				
Warfarin	$134,943	2.153		

Table 36: Results of Stratified Analysis by $CHADS_2$ Score				
	Cost	**QALYs**	**Incremental Cost Per QALY Gained (ICER)**	
			vs. Warfarin	**Sequential ICER**
Dabigatran 150 mg	$140,566	2.200	$121,905	$121,905
Apixaban	$140,734	2.199	$126,252	Dominated by dabigatran 150 mg
Dabigatran 110 mg	$140,270	2.177	$222,599	Dominated by rivaroxaban, and dabigatran 150 mg extendedly dominated by apixaban and warfarin
Rivaroxaban	$139,434	2.184	$145,146	Dominated by dabigatran 150 mg, and extendedly dominated by apixaban and warfarin

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.
Note: Dominated = more costly and less QALYs; extended dominance = the combination of two other alternatives dominates the treatment. Risk reductions relative to warfarin are specific to $CHADS_2$ score for stroke, and are for the complete RE-LY trial population for all other events. Warfarin event rates are specific to $CHADS_2$ for stroke, major bleed, ICH, and non-vascular deaths, and for the complete RE-LY trial population for all other events. For rivaroxaban, there were no available data for the risk reduction for stroke with $CHADS_2$ score <2.

Table 37: Results of Stratified Analysis by Age				
	Cost	**QALYs**	**Incremental Cost Per QALY Gained (ICER)**	
			vs. Warfarin	**Sequential ICER**
AGE 60				
Warfarin	$24,668	9.115		
Dabigatran 150 mg	$29,130	9.379	$16,899	$16,899
Apixaban	$30,356	9.284	$33,796	Dominated by dabigatran 150 mg
Dabigatran 110 mg	$31,210	9.254	$47,032	Dominated by rivaroxaban, dabigatran 150 mg, and apixaban
Rivaroxaban	$30,162	9.205	$61,358	Dominated by dabigatran 150 mg, and extendedly dominated by apixaban and warfarin
AGE 70				
Warfarin	$24,668	9.115		
Dabigatran 150 mg	$29,130	9.379	$16,899	$16,899
Apixaban	$30,356	9.284	$33,796	Dominated by dabigatran 150 mg
Dabigatran 110 mg	$31,210	9.254	$47,032	Dominated by rivaroxaban, dabigatran 150 mg, and apixaban.
Rivaroxaban	$30,162	9.205	$61,358	Dominated by dabigatran 150 mg, and extendedly dominated by apixaban and warfarin
AGE 80				
Warfarin	$13,189	4.738		
Apixaban	$15,455	4.868	$17,439	$17,439
Dabigatran 150 mg	$15,650	4.828	$27,486	Dominated by apixaban and rivaroxaban
Dabigatran 110 mg	$16,477	4.783	$73,278	Dominated by rivaroxaban, dabigatran 150 mg, and apixaban
Rivaroxaban	$15,051	4.834	$19,506	Extendedly dominated by apixaban and warfarin

Table 36: Results of Stratified Analysis by $CHADS_2$ Score				
	Cost	**QALYs**	**Incremental Cost Per QALY Gained (ICER)**	
			vs. Warfarin	**Sequential ICER**

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.
Note: Dominated = more costly and less QALYs; extended dominance = the combination of two other alternatives dominates the treatment. Risk reductions relative to warfarin are specific to age (< 75, > 75) for stroke and major bleeds, and are for the complete RE-LY trial population for all other events. Parameters which are affected by age are rates of bleeding and stroke on warfarin, and underlying utility values for all health states.

Table 38: Results of Stratified Analysis by TTR				
	Cost	**QALYs**	**Incremental Cost Per QALY Gained (ICER)**	
			vs. Warfarin	**Sequential ICER**
TTR < 66%				
Warfarin	$17,203	5.811		
Dabigatran 150 mg	$18,852	6.030	$7,525	$7,525
Apixaban	$20,070	5.973	$17,766	Dominated by dabigatran 150 mg
Dabigatran 110 mg	$20,858	5.899	$41,779	Dominated by rivaroxaban, dabigatran 150 mg, and apixaban
Rivaroxaban	$20,041	5.903	$30,898	Dominated by dabigatran 150 mg, and extendedly dominated by apixaban and warfarin
TTR ≥ 66%				
Warfarin	$14,684	6.036		
Apixaban	$18,346	6.140	$35,358	$35,358
Dabigatran 150 mg	$18,746	6.090	$76,015	Dominated by apixaban and rivaroxaban
Dabigatran 110 mg	$18,883	6.099	$66,555	Dominated by rivaroxaban, dabigatran 150 mg, and apixaban
Rivaroxaban	$17,775	6.095	$52,275	Extendedly dominated by apixaban and warfarin

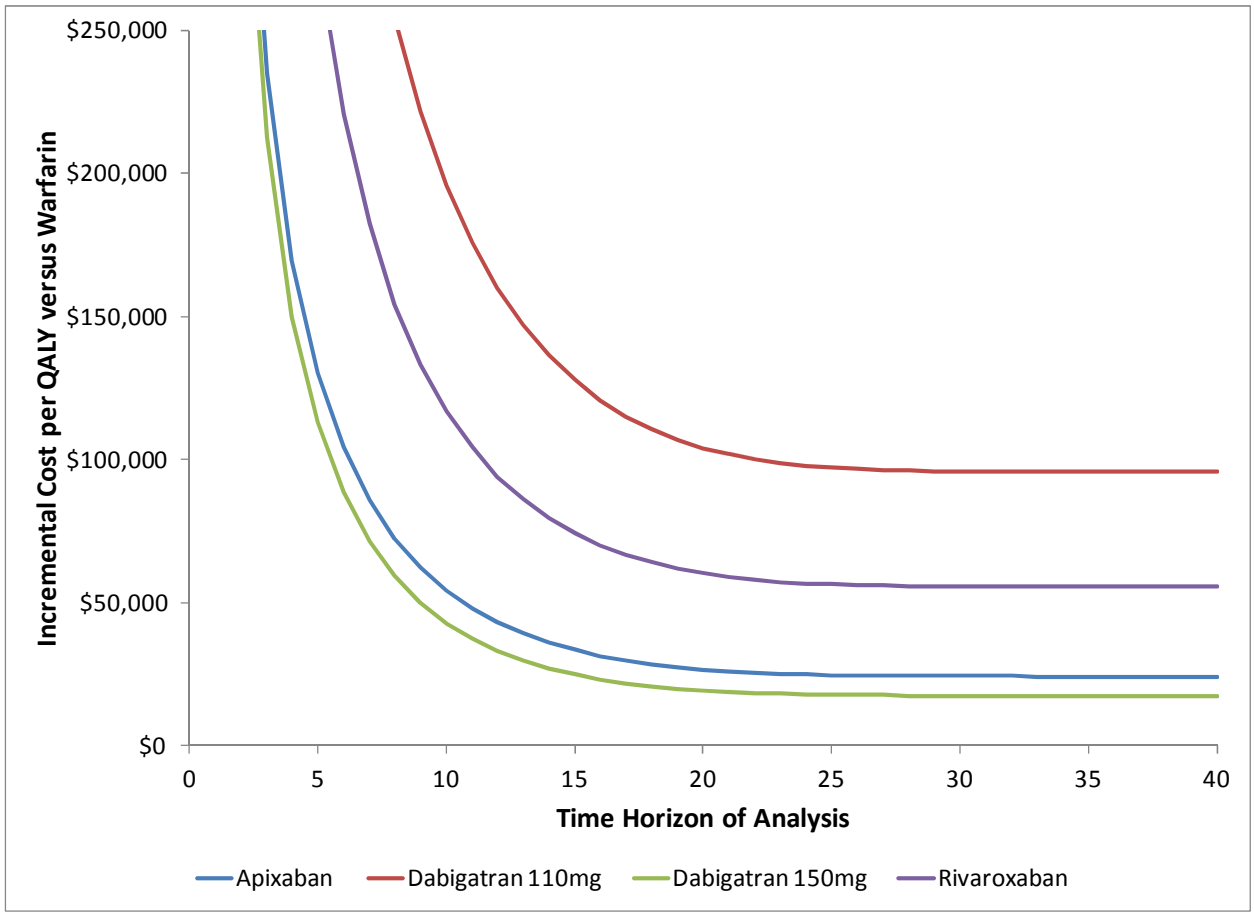
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TTR = time in therapeutic range; vs. = versus.
Note: Dominated = more costly and less QALYs; extended dominance = the combination of two other alternatives dominates the treatment. Risk reductions relative to warfarin are specific to TTR for stroke and major bleeds, and are for the complete RE-LY trial population for all other events. Warfarin event rates are specific to TTR for stroke, major bleed, ICH, and minor bleeds, and for the complete RE-LY trial population for all other events. As the distribution of patients in the various trials across TTR differs, the results for each new anticoagulant will not be the same for different categories of TTR.

4.5 Analysis of the Effect of Changes in the Duration of Treatment Effect

The deterministic sensitivity analysis highlights the sensitivity of the results to the time horizon of the model. This is important given that the typical duration of follow-up in the clinical trials was approximately two years. In this section, further analysis explored the impact of alternate assumptions about the durations of treatment effect beyond the time horizon of the clinical trials.

Figure 10 shows the impact of the time horizon of the economic model on the estimates of the incremental cost per QALY gained. Clearly, shorter time horizons lead to higher ICERs. However, if the concern is the maintenance of treatment effect, simply reducing the time horizon of the model is misleading, because even if treatment effect was not maintained there would be continued accrual of benefit from treatment due to events avoided earlier.

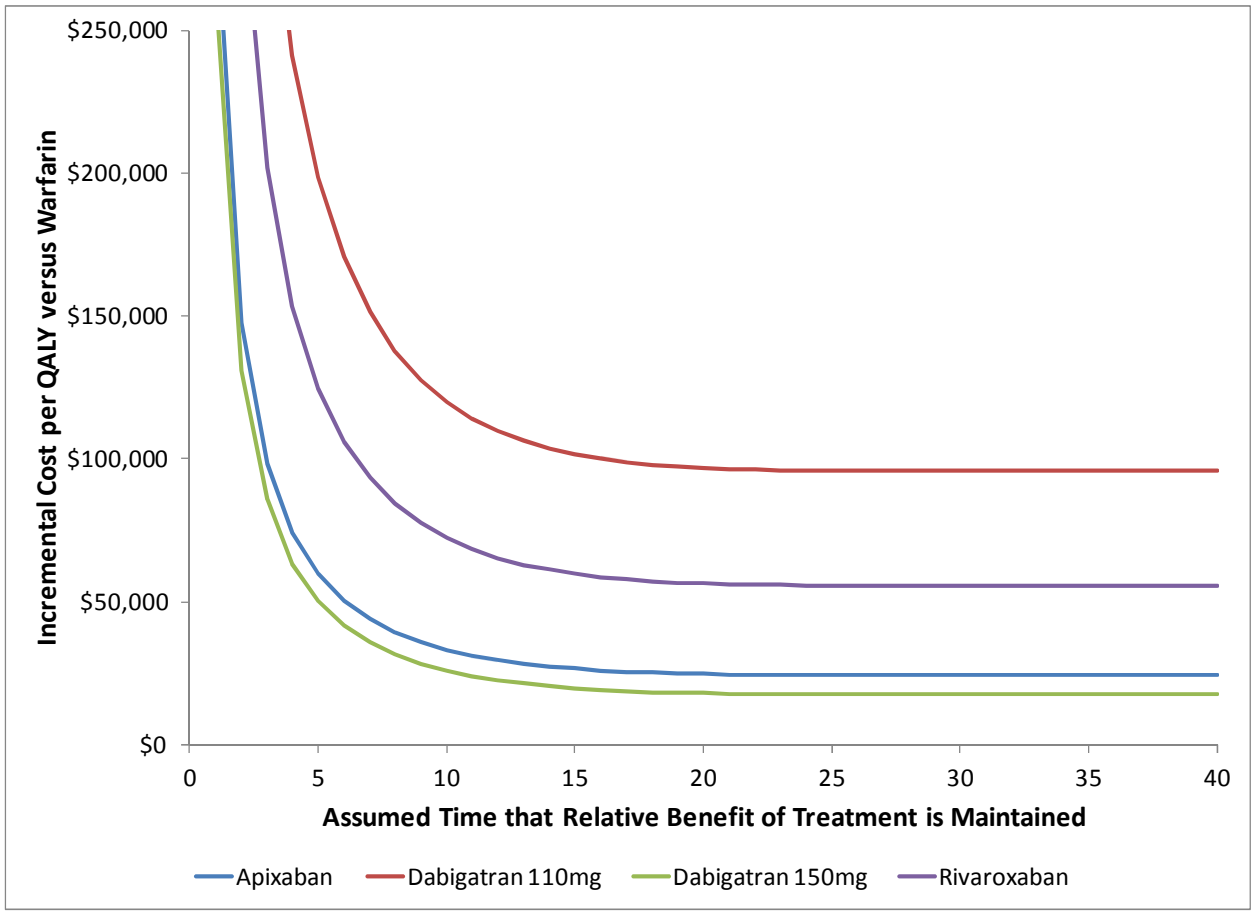
Figure 10: Impact of Time Horizon on Incremental Cost Per QALY Gained Versus Warfarin



QALY = quality-adjusted life-year.

Of more interest is the estimated incremental cost per QALY gained, with a lifetime model horizon based on alternative assumptions regarding the duration of the maintenance of treatment effect. In Figure 11, the analysis is conducted whereby at different points in time the treatment effect of the NOACs relative to warfarin is assumed to end. From the given time point, the new treatments are assumed to have the same efficacy as warfarin. Analysis illustrates that the treatment effect for apixaban and dabigatran must be assumed to last more than five years for continued treatment to be cost-effective assuming that λ equals $50,000.

Figure 11: Duration of Treatment Effect on Incremental Cost Per QALY Gained Versus Warfarin



QALY = quality-adjusted life-year.

5 DISCUSSION

5.1 Summary of Available Evidence

In this systematic review, five unique RCTs evaluating non-inferiority of the three NOACs versus adjusted-dose warfarin were identified. Three large trials were assessed as high quality through critical appraisal (ROCKET-AF, RE-LY, ARISTOTLE), and were included in the network meta-analysis and used to support the economic evaluation. Two RCTs (PETRO, ARISTOTLE-J) were excluded from the analysis because of small sample size and lack of data for the outcomes specified a priori. No non-randomized evidence was located in the published literature.

5.2 Interpretation of Results

5.2.1 Clinical

There are only a few large randomized controlled trials that have assessed the NOACs relative to adjusted-dose warfarin. This, coupled with the clinical and methodological heterogeneity across these studies, make any specific observations and conclusions difficult. It must be noted that ARISTOTLE, RE-LY, and ROCKET-AF were all designed as non-inferiority trials for the primary outcome of all-cause stroke/SE. Takeing the design of the study into consideration, a statistical significance should be noted with the phrase “reduction was non-inferior” and not “significantly reduced” when considering the primary outcome all-cause stroke/SE. However, when results are calculated and interpreted, the interpretation is based on the data reported from the studies and not the specific non-inferior design elements of the studies. With this in mind, the observations that follow are made for the outcomes of all-cause stroke/SE, major bleeding, intracranial bleeding, major GI bleeding, all-cause mortality, and MI.

Dabigatran 150 mg and apixaban significantly reduced all-cause stroke/SE compared with adjusted-dose warfarin. This held true for older patients (age ≥ 75 years); but, for younger patients (i.e., age < 75 years), only dabigatran 150 mg was associated with a significant reduction. Considering patients consistently in therapeutic range (i.e., TTR ≥ 66%), no treatments significantly reduced all-cause stroke/SE relative to adjusted-dose warfarin; whereas, for patients not consistently in range (TTR < 66%), dabigatran 150 mg achieved a significant reduction. For patients with a low risk of stroke ($CHADS_2 < 2$), no treatments achieved a significant reduction relative to adjusted-dose warfarin (note that results for rivaroxaban are not known, as no patients with $CHADS_2 < 2$ were considered); but for high risk patients ($CHADS_2 \geq 2$), all treatments had a significant reduction except for dabigatran 110 mg twice daily and rivaroxaban (the latter when based on an intention-to-treat perspective). Dabigatran 150 mg had the highest probability of being best at reducing all-cause stroke/SE, followed by apixaban and rivaroxaban, respectively, and then dabigatran 110 mg and adjusted-dose warfarin.

Apixaban and dabigatran 110 mg achieved significant reductions in major bleeding relative to adjusted-dose warfarin. For older patients (age ≥ 75 years), only apixaban was associated with a significant reduction; whereas, for younger patients (i.e., age < 75 years), all treatments were associated with a significant reduction relative to adjusted-dose warfarin, with the exception of rivaroxaban. The benefits diminished for age ≥ 75 years compared to age < 75 years, except for apixaban. Considering patients consistently in therapeutic range (i.e., TTR ≥ 66%), only apixaban was associated with a significant reduction in major bleeding; whereas, for patients not consistently in range (TTR < 66%), all treatment except rivaroxaban had a significant reduction relative to adjusted-dose warfarin. For patients with a low risk of stroke ($CHADS_2 < 2$), apixaban and dabigatran 110 mg achieved a statistically significant reduction in major bleeding relative to adjusted-dose warfarin (note that results for rivaroxaban are not known, as no patients with $CHADS_2$ were considered); and for high risk patients ($CHADS_2 \geq 2$), only apixaban was associated with a significant reduction. Apixaban has the highest probability of being best at reducing major bleeding, followed by dabigatran 110 mg and 150 mg, respectively, and then adjusted-dose warfarin and rivaroxaban.

For intracranial bleeding, all treatments were associated with a significant reduction relative to adjusted-dose warfarin. Whereas, for major GI bleeding, no treatments were associated with a significant reduction relative to adjusted-dose warfarin, and dabigatran 150 mg and rivaroxaban were associated with a significant increase.

Apixaban was associated with a significant reduction in all-cause mortality relative to adjusted-dose warfarin.

No treatments were associated with a significant reduction in MI relative to adjusted-dose warfarin, with apixaban associated with the most favourable results.

There are important differences in discontinuation rates among the NOACs that likely reflect tolerability, but the selection of the most tolerable NOAC will likely occur following treatment, not prior to treatment, as tolerability is highly variable and is difficult to predict or assess prior to treatment.

5.2.2 Economic

The base-case analysis concluded that dabigatran 150 mg was likely to be the optimal treatment choice assuming a decision-maker was willing to pay at least $17,525 per QALY. However, the conclusions are uncertain given the results of the probabilistic analysis where the probability that dabigatran was optimal was no higher than 70%. Results were insensitive to many of the parameter assumptions within the model, except for the cost of apixaban. Base analysis incorporated the effect of treatment on MI. The results of the NMA found an odds ratio greater than 1 for dabigatran 110 mg and 150 mg. Sensitivity analysis illustrated the minimal impact this assumption has on the study conclusions.

The cost of apixaban was unknown at the time of the submission of this report. If apixaban costs 20% per day less than dabigatran, analysis would have concluded that apixaban would be optimal assuming a willingness to pay $11,742 per QALY. A price reduction for dabigatran would also increase its probability to be cost-effective. However, a price reduction for rivaroxaban up to 20% did not impact the conclusions of the analysis.

Results are very sensitive to the time horizon of the analysis. With a time horizon of ten years, dabigatran would only be cost-effective if a decision-maker was willing to pay $42,912 per QALY. If analysis was restricted to two years — the typical follow-up period within the major clinical trials — both apixaban and rivaroxaban were dominated, and dabigatran 150 mg would only be cost-effective if a decision-maker was willing to pay over $335,542 per QALY. Thus, the lack of information regarding the long-term harms and benefits of new anticoagulants beyond the clinical trial follow-up period warrants cautious consideration and emphasizes the need for further research.

Rivaroxaban was optimal only when the relative effects of treatment on non-vascular deaths were included. However, what constituted a non-vascular death may have differed across the trials, and the fact that the odd ratios for rivaroxaban for reducing non-vascular death is superior than the odds ratio for reduction in stroke led to the decision to exclude using this effect from the base case.

With respect to the second economic research question, results varied by a centre's average time in therapeutic range. In centres where the TTR was less than 66%, dabigatran would be optimal; but in centres where the TTR was equal orto or greater than 66%, apixaban would be optimal. Analysis compared the NOACs to warfarin use within the clinical trials. Thus, without relevant clinical data, the analysis cannot allow any comparison of the NOACs with optimal use of warfarin.

With respect to the third economic research question, results are very sensitive to patient characteristics. Dabigatran 150 mg is likely to be optimal for patients with a $CHADS_2$ score < 2 and >2 with previous minor stroke. Apixaban is likely to be optimal for a $CHADS_2$ score of 2 and > 2 without previous stroke. Dabigatran 150 mg is optimal for patients aged less than 75, whilst apixaban is optimal for patients aged over 75. None of the NOACs would be cost-effective if patients had a previous major stroke. This is due to the reduced utility value for patients with a previous major stroke (0.33) and the high long-term care costs for these patients. Data did not allow for differential treatment efficacy in this group

Given this, an approach to funding of the NOACs which recognizes that different anticoagulants may be cost-effective for different patient populations may be optimal.

5.3 Knowledge Gaps

No head-to-head studies have been conducted comparing NOACs. As a consequence, there was insufficient evidence to draw definitive conclusions regarding the relative safety and efficacy between the various oral anticoagulants. Rigorously conducted, longer-term studies with larger sample sizes will be required to determine if any of the oral anticoagulants are superior to one another with regards to effectiveness and safety.

Evidence for apixaban has not been reviewed by the FDA (and not approved by Health Canada at the time of this therapeutic review). As a result, detailed data from the FDA Clinical Summary Report was not available for apixaban; only one published subgroup analyses was available.

There was also limited comparative data or subgroups are not consistently defined across the trials for: weight, impaired renal function, prior history of GI bleed, concurrent use of NSAIDs. In addition, detailed subgroup analysis data was only available for two major end points: stroke/SE and major bleeding. Studies in subpopulations, considering a variety of end points, are especially pertinent given the large budget impact of these NOACs. Patient-level network meta-analyses could be helpful to compare risk-benefit profiles of NOACs and warfarin across subpopulations.

5.4 Strengths and Limitations

This is the first systematic review to simultaneously assess the relative safety and cost-effectiveness of warfarin, dabigatran, apixaban, and rivaroxaban in patients with atrial fibrillation. The review was conducted according to Cochrane Collaboration guidelines using standardized, reproducible methods for the identification of evidence, data abstraction, quality assessment, and analysis. Both direct and indirect evidence was synthesized using standard evidence synthesis methodologies, and considering both a Bayesian and frequentist approach to the models. A comprehensive economic evaluation was conducted using available cost data and the results of the network meta-analyses. Other strengths of this analysis were its comprehensiveness regarding the oral anticoagulants considered, the number of outcomes assessed, and the similarity of trials included in analysis regarding year of publication.

Despite the aforementioned strengths, a number of limitations related to the available evidence warrant discussion. Network meta-analysis involves pooling of trials. To avoid the introduction of bias, it is imperative that clinical and methodological variation across studies is minimized. If variability does exist, the assessment of its effects on network meta-analysis results is required. We observed variability in study and subject characteristics that may be important predictors of treatment effects. In particular, ROCKET-AF included higher-risk patients, with a $CHADS_2$ score of at least 2. This limits the comparability of treatment effects to lower-risk patients and to results from RE-LY and ARISTOTLE, which included more patients at low risk. Patients enrolled in ROCKET-AF were also older in age and had more congestive heart failure, more diabetes mellitus, more hypertension, and more prior stroke or transient ischemic attack. ROCKET-AF also reported results using the per-protocol population for many outcomes, whereas RE-LY and ARISTOTLE used ITT.

While some may argue against conducting a network meta-analysis in light of the aforementioned clinical and methodological heterogeneity, the reality is that decisions in the clinical setting and at the policy level have to be made despite these issues. In the absence of a formal indirect comparison or network meta-analysis, health professionals and decisions-makers may make informal comparisons between oral anticoagulants without understanding or acknowledgment of clinical and methodological variation across studies. That being said, a formal network meta-analysis where clinical and methodological variation across studies was well-described, and where formal adjustments were made attempting to resolve some of the heterogeneity across studies, was justified. To address clinical and methodological heterogeneity, we reported results for ROCKET-AF for both intentions to treat, when available. However, this information was not consistently reported in ROCKET-AF. We also performed subgroup analyses where we stratified results across studies by $CHADS_2$, age, and centre TTR. While these subgroup analyses address some

of the limitations, issues regerading heterogeneity are only partly resolved. We do not have information regarding the similarity of patient populations for individual subgroups considered, as randomization is broken. Consequently, whereas some subpopulations (e.g., $CHADS_2 \geq 2$) may be more similar across studies in subgroup analyses relative to reference case analyses, heterogeneity may still remain. Furthermore, we did not have data to conduct multiway subgroup analyses (e.g., $CHADS_2 \geq 2$ and age ≥ 75 and cTTR ≥ 65.5%). In light of the data, therefore, it is difficult to ascertain subpopulations where warfarin use may be appreciably more or less effective, although data from individual one-way subgroup analyses allude to a less favourable risk-benefit profile for newer anticoagulants in patients who are older and well-controlled on warfarin. Given the budget impact of NOACs, patient-level network meta-regression analyses are desperately needed to compare the risk-benefit profiles of NOACs and dose-adjusted warfarin across subpopulations.

While ROCKET-AF and ARISTOTLE were designed as double-blind trials, treatment was not blinded in RE-LY, except for the dose of dabigatran, which might be a potential source of bias such as performance bias (i.e., systematic differences between groups in the care provided or exposure to factors other than the interventions of interest). However, we were unable to adjust for differences in blinding due to the small number of studies identified. Consequently, it is unclear what impact lack of blinding in RE-LY may have on effect estimates, although the effect may not be substantive given the nature of the end points considered in RE-LY (e.g., stroke/SE, major bleeding).

The small number of trials limited our ability to adjust for heterogeneity using other techniques such as meta-regression or sensitivity analysis (i.e., removing results from individual studies). While it was possible to expand the evidence network to include data for other treatments such as aspirin, or aspirin plus clopidogrel, and ultimately facilitate the use of more sophisticated methods to address heterogeneity, this was beyond the scope of this review. It is, however, noteworthy that expanding the evidence network to include additional information (and potentially attempt to address heterogeneity) would involve the potential introduction of heterogeneity — studies comparing aspirin with warfarin are older and may have involved different patients and treatment patterns than those enrolled in newer studies of anticoagulants.

There is a potential asymmetry of information that may introduce bias. Both RE-LY and ROCKET-AF have been reviewed by the FDA, while apixaban is currently under review. Further, several subgroup publications were available for RE-LY and ROCKET-AF, but only one publication and a conference abstract were available for ARISTOTLE. Therefore, data for dabigatran and rivaroxaban may have been more heavily scrutinized than apixaban, potentially biasing results in favour of apixaban. If data emerges over the course of FDA or Health Canada reviews suggesting that the benefits of apixaban are less favourable, then the network meta-analysis and cost-effectiveness will have to be revisited.

While our analysis considered both fixed and random effects models, again the small number of trials limited the analyses. The applicability of random effects models was compromised because vague or non-informative prior distributions exerted a large degree of influence on any inference. While we could have considered the use of more informative priors, this was beyond the purview of this review. Similarly, the random effects interaction term trial-by-treatment had to be excluded from the GLMM model because of the small number of trials. Without including random effects terms, the full variability in the data cannot be included with the results appearing more precise. Due to these limitations, the fixed effects model was associated with a better fit based on the assessment of the deviance information criterion and comparison of residual deviance to the number of unconstrained data points. However, results from the fixed effects model, particularly those for reference case analyses, do not account for heterogeneity across studies and should be interpreted in light of this issue. As a result, results from fixed effects network meta-analysis and those for study-level results are very similar — a finding attributable to the few studies included in the evidence network and lack of a “meta-analysis” for individual pairwise comparisons within the evidence network (i.e., only one study for each pairwise contrast).

The absolute risk reduction was calculated by multiplying the relative risk (and corresponding 95% confidence interval) by the point estimate of the event rate in the warfarin arm. This approach does not take into account the uncertainty around the event rate. Future studies could characterize uncertainty to a

greater degree using a probability distribution of the event rate. Nevertheless, such an approach would likely not produce substantially different results given the large sample sizes in the studies and subgroups.

Not all outcomes of interest were reported, in particular for various predefined subgroups. In particular, life-threatening bleeding and the composite ischemic/uncertain stroke or SE were often not reported in studies, and CV-mortality was reported within vascular mortality. All-cause mortality, intracranial bleeding, MI, and major GI bleeding were not reported by subgroups of interest re TTR, age, and $CHADS_2$ score. Therefore, the complete risk-benefit profile of newer drugs versus warfarin for subpopulations is not known. Given the budget impact of newer anticoagulants, patient-level network meta-analyses are needed to compare the risk-benefit profiles of NOACs and warfarin across subpopulations.

As all major studies were performed as multinational or multicentre trials, generalizability to the Canadian health care system may be limited. Treatment of comorbidities and management of patients who are candidates for warfarin may differ between various countries. Further, TTR of warfarin treatment showed substantial differences between the trials, and was also affected by geography. In RE-LY and ARISTOTLE, INR control rates were substantially better than in ROCKET-AF. Skillful warfarin use as a predictor of treatment success might play a role in transferring trial results to the Canadian setting. In ROCKET-AF, the non-inferiority of rivaroxaban was achieved for the primary outcome stroke and SE in the intention to treat (ITT) population, mostly due to a rather high number of events in the transition phase after stopping the study drug. Thus, the magnitude of treatment effect was smaller in the ITT population. The implication of this observation for drug use in clinical routine is unclear but does indicate differences in methodology between the trials.

While outcome definitions for efficacy end points are similar throughout the included trials, definitions of bleeding events differed substantially, in particular for minor (RE-LY) or non-major clinically-relevant bleeding (ROCKET-AF and ARISTOTLE). Thus, these bleeding rates were markedly higher in RE-LY and ROCKET-AF compared to ARISTOTLE, limiting the comparability of results in network meta-analysis.

Variability in patient risk and VKA experience at baseline, notably in ROCKET-AF, could impact the trial mean TTR, as could the variations in study population assessment (ITT versus as-treated per protocol). Patients who are older or have higher rates of comorbidities could have reduced access to TTR testing. Cross-trial assessment of TTR variations is made difficult by study design, as an open-label design could allow clinicians to make adjustments in warfarin arms more frequently.

The inclusion and exclusion criteria identifying the patients' eligibility for the studies on which the adverse events data are based may be different than the patients seen in clinical practice, leading to altered asdverse events profiles.

The limited follow-up from the clinical trials and the sensitivity of results to the duration of treatment effect leads to uncertainty regarding whether the new anticoagulants will be cost-effective in the long term. Aspirin was not included in the economic evaluation and would have been a relevant comparator for the analysis of patients with a $CHADS_2$ score of 0 or 1.

6 CONCLUSIONS

The results of this report highlight the paucity of clinical evidence available to definitively compare the efficacy and safety of the NOACs as thromboprophylaxis in AF patients. There were three large, well-designed, and properly conducted studies available for analysis, each comparing NOACs and warfarin. However, there was heterogeneity across the three RCTs and, with only three studies handling this, heterogeneity was limited. This should be borne in mind when interpreting the results.

Compared with adjusted-dose warfarin, dabigatran 150 mg and apixaban produced statistically significant reductions in stroke/SE, whereas rivaroxaban and dabigatran 110 mg did not. Apixaban and dabigatran 110 mg were associated with significantly less major bleeding versus adjusted-dose warfarin, whereas there was no association with major bleeding with dabigatran 150 mg and rivaroxaban. All treatments were associated with a significant reduction in intracranial bleeding relative to adjusted-dose warfarin, whereas no treatments were associated with a significant reduction in MI relative to adjusted-dose warfarin. No treatments were associated with a significant reduction in GI bleeding relative to adjusted-dose warfarin, but dabigatran 150 mg and rivaroxaban were associated with a significant increase. Apixaban was associated with a significant reduction in all-cause mortality relative to adjusted-dose warfarin. Even though some differences were statistically significant between treatments for some outcomes, the absolute differences for the NOACs versus warfarin where statistical significance was achieved ranged from two to a maximum of eight fewer events per 1,000 patients.

The results of the subgroup analyses were further limited by a paucity of data, but suggested that there may be subpopulations for which use of NOACs may be more or less beneficial. In patients where warfarin treatment is well-controlled (TTR ≥ 66%), the use of NOACs may be less favourable — the absolute risk increase of a major bleed exceeded the absolute risk reduction of stroke/SE. In elderly patients (≥ 75 years old), the NOACs may be more favourable for preventing thromboembolic events than warfarin, but are associated with a greater risk of major bleeding. Indeed, for dabigatran 150 mg and rivaroxaban, the absolute risk of major bleeding exceeded or approached the absolute risk of stroke/SE, respectively, in this population. For low to moderate risk patients ($CHADS_2 < 2$), the NOACs were less favourable than warfarin for preventing stroke/SE, but were preferable to warfarin in reducing the absolute risk of major bleeding.

In addition to the limitations imposed by the clinical data, the results of the analysis of cost-effectiveness of the NOACs and warfarin were limited by the uncertainty regarding the pricing of the NOACs. Analysis of the base case suggested that either dabigatran 150 mg or apixaban would be the most cost-effective treatment option. Analysis of subpopulations suggested that dabigatran 150 mg was the most cost-effective treatment option in younger patients (< 80 years old), and in centres where the TTR is < 66%, whereas apixaban was the most cost-effective treatment option in older patients (80 years old) and in centres where the TTR was ≥ 66%. None of NOACs were likely to be considered cost-effective for patients with a previous major stroke. However, the results of the cost-effectiveness analysis were highly sensitive to the patient population under consideration, reinforcing the need for tailoring the treatment of individual patients according to individual characteristics that affect treatment outcomes, including the degree of control of warfarin therapy (TTR), age, risk of stroke, and history of thromboembolic events.

In conclusion, the limited number of RCTs available for analysis and heterogeneity in several important features of these RCTs means that there is uncertainty regarding the comparative clinical or cost-effectiveness of the NOACs and warfarin. To fully elucidate the comparative effectiveness of these agents and facilitate the identification of subpopulations within which the NOACs might be more beneficial than warfarin, rigorously conducted comparative RCTs or network meta-regression analyses of patient-level data are required.

7 APPENDICES

7.1 Glossary

Bayesian analysis: A statistical analysis conducted according to Bayesian principles. It involves incorporation of existing information regarding the likelihood of an event (i.e., “priors”) to estimate the likelihood based on additional information (i.e., “posteriors”).

Closed network: A type of network in which all elements are connected to one another.

Confidence interval: The interval in which a population parameter lies, based on a random sample of the population. The most commonly reported confidence interval is the 95% confidence interval.

Credible interval: In Bayesian statistics, an interval in which the actual value of a parameter of interest lies with a defined probability.

Deviance Information Criterion (DIC): A measure of model comparison and accuracy. Smaller DIC values indicate a better-fitting model, with a difference greater than two indicating a much better-fitting model.

Effectiveness: The extent to which an intervention, procedure, regimen, or service produces the intended outcomes when deployed under routine (“real world”) circumstances.

Fixed effects meta-analysis: Methods of fixed effects meta-analysis are based on the mathematical assumption that a single common (or “fixed”) effect underlies every study in the meta-analysis. In other words, if we were doing a meta-analysis of odds ratios, we would assume that every study is estimating the same odds ratios. Under this assumption, if every study were infinitely large, every study would yield an identical result. This is the same as assuming there is no (statistical) heterogeneity among the studies.

Heterogeneity: Variation in treatment effects between RCTs within a pairwise contrast. Heterogeneity is likely to occur if trials have been undertaken on different patient groups, and/or different settings and/or methodological differences in the design and conduct of the trials.

Meta-analysis: Statistical synthesis of the results of individual studies that examine the same question to produce a single estimate of effect.

Mixed-treatment comparison (MTC) meta-analysis: A Bayesian approach that combines direct and indirect evidence in a single analysis, thus enabling simultaneous comparison of multiple treatment interventions.

Non-informative or vague prior distributions: A distribution that will not influence the posterior distribution.

Posterior distribution: A distribution that embodies both the prior distribution and the observed data information.

Prior distribution: A distribution that expresses information available to the researcher before any “data” are involved in the statistical analysis.

Random effects meta-analysis: A random effects analysis makes the assumption that individual studies are estimating different treatment effects. In order to make some sense of the different effects they assume, they have a distribution with some central value and some degree of variability.

Randomized controlled trial (RCT): A prospective experimental study designed to test the efficacy of an intervention in which patients are randomly allocated to either a treatment group or the control group.

Standard deviation: A measure of the variability or spread of the data.

Systematic review: A summary of the medical literature that uses explicit methods to identify, select, appraise, and analyze studies relevant to a particular clinical question.

Transient ischemic attack (TIA): Episodes of stroke symptoms that last only briefly.

7.2 Study Protocol Summary

METHODS

a. Reviewer Information

Both the Therapeutic Review of Clinical Trials and Review in Brief will be prepared by the DSEN Collaborative for Network Meta-Analysis in consultation with two external clinical experts specializing in cardiology.

b. Development of Research Questions

The research questions were developed jointly by jurisdictions, expert committee members, clinical experts, and clinical reviewers in consultation with pharmacoeconomic reviewers.

c. Literature Search Methods

The literature search will be performed by an information specialist. The following bibliographic databases will be searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, DARE (Database of Abstracts of Reviews of Effects) for November 2011 and the Cochrane Central Register of Systematic Reviews, Controlled Trials and Economic Evaluations. Methodological filters will be applied to limit retrieval to RCTs and NRSs. The search will be restricted to clinical articles published from 1980 to December 2, 2011. Where possible, retrieval will be limited to the human population. Grey literature (literature that is not commercially published) searched to December 8, 2011 were identified by searching the websites of health technology assessment and related agencies, guideline producers, and professional associations that maintain safety information on pharmaceutical products.

d. Study Selection

Each review author will independently select studies for inclusion in the review according to the predetermined selection criteria. Review authors will independently make the final selection of studies to be included in the review, and differences will be resolved through discussion. A list of included and excluded studies will be listed in the report.

RCTs and NRSs will be selected for inclusion if they were published in English, assessed the desired intervention and comparators, reported relevant outcomes, and involved patients with non-valvular atrial fibrillation.

e. Quality Assessment

Quality assessment of RCTs will be conducted independently by two reviewers, with a third reviewer used to resolve disputes. Assessment of study quality for RCTs will be performed using the SIGN 50 instrument for RCTs for interval validity and the Cochrane Collaboration's Tool for Assessing Risk of Bias. In addition, for NRS, the SIGN 50 instrument for cohort studies and an adaptation of the Cochrane Collaboration's Tool for Assessing Risk of Bias will be applied.

f. Data Analysis

Two levels of analyses will be conducted. First, a meta-analysis will be conducted (RevMan 5.0 software from the Cochrane Collaboration will be used) and heterogeneity will be assessed leading to a fixed or random effects model or no analysis being considered. For each outcome, the weighted odds ratio and corresponding 95% confidence interval will be calculated for the overall treatment effect. At the next level, network meta-analyses (NMAs) will be conducted. Two approaches will be considered: the Bayesian

mixed-treatment comparison model and the frequentist general linear mixed model. Following careful assessment of heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols, NMAs will be conducted for the pre-specified outcomes. The effect estimate chosen (e.g., odds ratio, relative risk, or hazard ratio for stroke) will depend on the outcome of interest and the availability of data. For reference case NMAs, comparators considered will be dabigatran, rivaroxaban, apixaban, adjusted-dose warfarin, fixed low-dose warfarin, and fixed low-dose warfarin plus aspirin; however, some comparators (e.g., dabigatran) may be stratified by dose.

For Bayesian NMA, both fixed and random-effects models will be conducted; model selection will be based on the DIC and residual deviance. R (R Foundation for Statistical Computing, Vienna, Austria) and WinBUGS (MRC Biostatistics Unit, Cambridge, UK) will be used for Bayesian network meta-analyses according to the routine which accommodates evidence structures (which may consist of multi-arm trials as developed at the Universities of Bristol and Leicester (www.bris.ac.uk/cobm/research/mpes/). Adjusted-dose warfarin therapy will be the reference group for all Bayesian NMAs. Posterior densities for unknown parameters will be estimated using MCMC methods. Basic parameters will be assigned non-informative or vague prior distributions; more informative priors may be considered after evaluation of the information base and clinical expert advice. Point estimates and 95% credible intervals will be used to summarize findings. The probability of a comparator being optimal will be estimated for each outcome based on the proportion of MCMC simulations in which its relative measure of effect was best. The mean rank for each comparator will also be calculated. Consistency between direct and indirect evidence will be formally assessed using back-calculation and node-splitting techniques.[67] Graphical methods and numerical summaries will be developed for presenting results from network meta-analysis.[71] Model diagnostics will also include trace plots and the Brooks-Gelman-Rubin statistic[72] to assess and ensure model convergence. Two chains will be fit in WinBUGS for each analysis, each usually employing ≥ 20,000 iterations, with a burn-in of ≥ 20,000 iterations. Whether novel agent effects are present will be examined and their magnitude of effect estimated.[70,71]

For frequentist NMA, a GLMM will be used. According to the outcome of interest, the GLMM model that follows the different distribution will be conducted (e.g., if the outcome follows a binomial distribution, then a mixed log-binomial model will be employed, with the log link function to generate the relative risk or with the logit link function to generate the odds ratio estimates). Adjusted-dose warfarin therapy will be the reference group for all NMAs. For reference case NMAs, comparators considered will be dabigatran, rivaroxaban, apixaban, adjusted-dose warfarin, fixed low-dose warfarin, and fixed low-dose warfarin plus aspirin; however, some comparators (e.g., dabigatran) may be stratified by dose. The random effect GLIMMIX model will be conducted. Two random effects can be considered in the model. The random effects trial accounts for the response variables of patients within a given trial being correlated. The random effects trial-by-treatment accounts for the correlation of responses between any two patients from the same treatment arm within a given study. The GLIMMIX procedure in SAS/STAT (SAS Institute Inc., Cary, North Carolina, USA) will be used for GLMM NMAs. Point estimates and 95% confidence intervals will be used to summarize findings. The rank for each comparator being the best treatment will also be calculated. Consistency between direct and indirect evidence will be formally assessed using back-calculation.[67] Graphical methods and numerical summaries will be developed for presenting results from network meta-analysis.[70,71] Model diagnostics will be evaluated using the diagnostic plots (e.g., residual plots) to assess and ensure model convergence.

For both the Bayesian and frequentist approach, and provided sufficient data are available to inform the evidence network, we will conduct meta-regression and/or subgroups analyses to adjust for $CHADS_2$ score, TTR, age, year of study, length of follow-up, gender, and history of a stroke to test the robustness of reference case analyses. In other sensitivity analyses, we will remove studies from the network that are of poor methodological quality.

Subgroups of interest include: time spent within the therapeutic range (TTR), $CHADS_2$ (or CHA_2DS_2-VASc) score, age (stratified as < 65 years, 65 years to 74 years, and ≥ 75 years), weight, impaired renal function (including mild, moderate, and severe), prior history of GI bleed, concurrent use of antiplatelet agents, concurrent use of NSAIDs.

If relevant heterogeneity is present, sensitivity analysis will be conducted based on aspects of the PICO statement and study methodology. Reporting bias will be assessed by constructing funnel plots for each outcome.

g. Writing of the Review Report

The review report will be written by the DSEN Collaborative for Network Meta-Analysis, with input from two clinical experts. A detailed internal review of the review report will be undertaken. Comments will be received from peer and external reviewers.

PROTOCOL FOR PRIMARY RESEARCH QUESTIONS

a. Clinical Systematic Review

Objective(s)

The objective of this review is to assess the comparative efficacy and safety of new oral anticoagulant drugs in patients with non-valvular atrial fibrillation who require anticoagulation therapy

Selection Criteria

A study was included if it met all of the inclusion criteria and none of the exclusion criteria summarized in Table 39.

Table 39: Inclusion and Exclusion Criteria for Primary Studies

Inclusion Criteria	
Population	Individuals with non-valvular atrial fibrillation requiring anticoagulation
Intervention	dabigatran, rivaroxaban, apixaban
Comparators	Warfarin (or other coumadin derivatives)
Outcomes	• All-cause stroke or SE • Major bleeding (ISTH definition) • All-cause mortality • Intracranial bleeding (including ICH) • Cardiovascular mortality • Ischemic/uncertain stroke or SE • Life-threatening bleeds • Stroke • ICH • Extracranial hemorrhage (ECH) • Minor bleeds • Myocardial infarction (MI) • Pulmonary embolism (PE) • Transient ischemic attacks (TIAs) • Non-cardiovascular mortality.
Study Types	Randomized controlled trials (head-to-head parallel, crossover) or non-randomized studies (with control group)
Exclusion Criteria	
	• Studies in languages other than English • Placebo-controlled RCTs • Non-randomized studies without control group

ICH = intracerebral hemorrhage; ISTH = International Society on Thrombosis and Haemostasis; RCTs = randomized controlled trials; SE = systemic embolism.

7.3 Literature Search Strategy

OVERVIEW	
Interface:	OVID
Databases:	• Medline (In-Process & Other Non-indexed Citations and OVID Medline (1948 to Dec 2, 2011); • Embase Classic and Embase (1947 to Dec 02, 2011) • Wiley Cochrane Database for Systematic Reviews • DARE (Database of Reviews of Effectiveness)
Date of Search:	December 2, 2011
Study Types:	Randomized controlled trials, non-randomized studies
Limits:	• English language

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
fs	Floating subheading
exp	Explode a subject heading
$	Truncation symbol, or wildcard: retrieves plural or variations of a word
*	Indicates that the marked subject heading is a primary topic
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication Type
.rn	CAS registry number

MEDLINE Search Strategy

1. (review or review, tutorial or review, academic).pt.
2. (medline or medlars or embase or pubmed or cochrane).tw,sh.
3. (scisearch or psychinfo or psycinfo).tw,sh.
4. (psychlit or psyclit).tw,sh.
5. cinahl.tw,sh.
6. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
7. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
8. (pooling or pooled or mantel haenszel).tw,sh.
9. (peto or dersimonian or der simonian or fixed effect).tw,sh.
10. (retraction of publication or retracted publication).pt.
11. or/2-10
12. 1 and 11
13. meta-analysis.pt.
14. meta-analysis.sh.
15. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
16. (systematic adj5 review$).tw,sh.
17. (systematic adj5 overview$).tw,sh.
18. (quantitativ$ adj5 review$).tw,sh.
19. (quantitativ$ adj5 overview$).tw,sh.
20. (quantitativ$ adj5 synthesis$).tw,sh.
21. (methodologic$ adj5 review$).tw,sh.
22. (methodologic$ adj5 overview$).tw,sh.
23. (intergrative research review$ or research integration).tw.
24. or/13-23

25. 12 or 24
26. "randomized controlled trial".pt.
27. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
28. (retraction of publication or retracted publication).pt.
29. or/26-28
30. (animals not humans).sh.
31. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
32. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.
33. 29 not (30 or 31 or 32)
34. ((oral or direct) adj3 thrombin inhibitor$).ti,ab.
35. ((factor$ or antifactor$) adj3 (Xa inhibitor$ or drug$)).ti,ab.
36. (edoxaban or lixiana).ti,ab.
37. DU176b.mp.
38. 36 or 37
39. (apixaban or eliquis).ti,ab.
40. BMS-562247-01.mp.
41. (dabigatran or pradaxa or pradax or prazaxa).ti,ab.
42. EC3-4-21-5.mp.
43. (rivaroxaban or xarelto).ti,ab.
44. BAY59-7939.mp.
45. or/34-44
46. 45 and 25
47. 45 and 33
48. exp cohort studies/
49. cohort$.tw.
50. controlled clinical trial.pt.
51. epidemiologic methods/
52. limit 51 to yr=1966-1989
53. exp case-control studies/
54. (case$ and control$).tw.
55. or/48-50,52-54
56. 45 and 55
57. (ae or si or to or co).fs.
58. (safe or safety).ti,ab.
59. side effect$.ti,ab.
60. ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
61. exp product surveillance, postmarketing/
62. exp adverse drug reaction reporting systems/
63. exp clinical trials, phase iv/
64. exp poisoning/
65. exp substance-related disorders/
66. exp drug toxicity/
67. exp abnormalities, drug induced/
68. exp drug monitoring/
69. exp drug hypersensitivity/
70. (toxicity or complication$ or noxious or tolerability).ti,ab.
71. exp Postoperative Complications/
72. exp Intraoperative Complications/
73. or/57-72
74. or/36-44
75. (73 and 74) not (56 or 46 or 47)

Embase Search Strategy
1. exp review/ 2. (literature adj3 review$).ti,ab. 3. exp meta analysis/ 4. exp "Systematic Review"/ 5. or/1-4 6. (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab. 7. RETRACTED ARTICLE/ 8. 6 or 7 9. 5 and 8 10. (systematic$ adj2 (review$ or overview)).ti,ab. 11. (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanaly$).ti,ab. 12. 9 or 10 or 11 13. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. 14. RETRACTED ARTICLE/ 15. or/13-14 16. (animal$ not human$).sh,hw. 17. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/ 18. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/ 19. 15 not (16 or 17 or 18) 20. exp heart atrium fibrillation/ 21. ((atrial or atrium or auricular) adj3 (fibrillat$ or flutter$)).ti,ab. 22. 20 or 21 23. exp dabigatran etexilate/ or exp dabigatran/ 24. (dabigatran or pradaxa or pradax or prazaxa).ti,ab. 25. exp rivaroxaban/ 26. (rivaroxaban or xarelto).ti,ab. 27. BAY59-7939.mp. 28. exp edoxaban/ 29. (edoxaban or lixiana).mp. 30. DU176b.mp. 31. exp apixaban/ 32. (apixaban or eliquis).mp. 33. BMS-562247-01.mp. 34. ((factor adj3 Xa) or (Xa adj3 inhibitor$) or (FXa adj3 inhibitor$)).mp. 35. exp thrombin inhibitor/ 36. or/23-35 37. 36 and 12 38. 36 and 19 39. exp cohort analysis/ 40. exp longitudinal study/ 41. exp prospective study/ 42. exp follow up/ 43. cohort$.tw. 44. or/39-43 45. 36 and 44 46. 45 not (37 or 38) 47. (ae or si or to or co).fs.

48. (safe or safety).ti,ab.
49. side effect$.ti,ab.
50. ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
51. exp adverse drug reaction/
52. exp drug toxicity/
53. exp intoxication/
54. exp drug safety/
55. exp drug monitoring/
56. exp drug hypersensitivity/
57. exp postmarketing surveillance/
58. exp drug surveillance program/
59. exp phase iv clinical trial/
60. (toxicity or complication$ or noxious or tolerability).ti,ab.
61. exp postoperative complication/
62. exp Peroperative Complication/
63. or/47-62
64. 36 and 63
65. 64 not (37 or 38 or 45)
66. 65 and 22
67. 46 and 22
68. or/23-33
69. 63 and 68
70. 69 not (37 or 38 or 45)

Wiley Cochrane Database of Systematic Reviews, Controlled Trials and Economic Analyses, DARE and Grey Literature

Broad search terms such as atrial fibrillation, anticoagulants, and the drug names dabigatran, rivaroxaban, edoxaban, and apixaban were used.

7.4 Data Extraction Template

Reviewer:

Date:

Source

Study ID (last name of first author, year of primary ref):

REF ID:

Full citation:

Companion study REF ID and citation(s):

Article Screening Confirmation:

Inclusion Criteria (check applicable item)

Population: Individuals with chronic non-valvular atrial fibrillation

Intervention: Dabigatran:
Rivaroxaban:
Apixaban:
Edoxaban: Not applicable for the purposes of this review
Comparator: Coumadin derivate:
Outcomes:
All-cause stroke or systemic embolism:
All-cause stroke:
Systemic embolism:
Ischemic stroke:
Uncertain stroke:
Ischemic or uncertain strokes:
Fatal stroke:
Disabling stroke:
Fatal or disabling stroke:
All-cause mortality:
CV mortality:
Major bleeding:
Minor bleeding:
Major or minor bleeding:
GI Bleeding:
Intracranial bleeding (ICH):
Hemorragic stroke:
Extracranial bleeding:
Life threatening bleeding:
Myocardial Infarction:
Pulmonary Embolism/Deep Vein Thrombosis:
Transient Ischemic Attack:
Study drug discontinuation rate: extracted but not a primary outcome of interest
Time in therapeutic range: extracted but not a primary outcome of interest

Methods:	
Study design (e.g. RCT, non-randomized):	
Total study duration (e.g. enrollment)	
Sequence generation, allocation sequence concealment, blinding, other concerns about bias	See risk of bias assessment

Participants:		
Total number		
Setting (e.g. number of sites)		
Countries/Regions		
	Intervention	**Comparator**
No. of patients		
Age, median (IQR)/ mean±SD		
Age group, %		
<65 years		
65 to <75 years		
≥ 75 years		
Male Sex, %		

Type of atrial fibrillation , %		
Persistent		
Paroxysmal		
Permanent		
$CHADS_2$ score, mean±SD		
$CHADS_2$ score, %		
0		
1		
2		
3		
4		
5		
6		
$CHADS_2VASC$ score, mean±SD		
$CHADS_2VASC$ score, %		
0-1		
2-3		
4-5		
6-7		
8-9		
Medical History, %		
Prior stroke/TIA		
Heart failure		
Prior MI		
Diabetes mellitus		
Hypertension		
History of GI bleeds		
Creatinine clearance (ml/min), median (IQR)/ mean±SD		
Renal function, %		
Normal		
Mildly impaired		
Moderately impaired		
Severely impaired		
Prior/Baseline Medication, %		
Aspirin		
Low dose aspirin (≤100 mg/d)		
High dose aspirin (>100 mg/d)		
Thienopyridine (e.g. clopidogrel)		
Long-term VKA therapy		
NSAID		

*** Significant differences between the study groups.**

Interventions:	Intervention	Comparator
Specific intervention		
Dosing		
Intervention details		
Time points collected		
Duration of follow-up		

Lost to FU		
Time in Therapeutic range in the vitamin K antagonist group		

Outcome Definitions:	Definition Provided:
Efficacy end points	
1°. Stroke or systemic embolism	
2°. Stroke	
2°. Ischemic Stroke	
2°. Disabling Stroke	
2°. Hemorrhagic Stroke	
2°. Systemic embolism	
Other (e.g.) death, myocardial infarction, pulmonary embolism, deep venous thrombosis, TIA, hospitalization	
Key safety end points	
Major bleeding	
Minor bleeding	
Major or minor bleeding	
Intracranial bleeding (ICH)	
Life threatening bleeding	
Extracranial bleeding	
GI bleeding	
Study drug discontinuation	
Time in therapeutic range:	
Outcome adjudication	
Statistical Analysis	
Primary analysis	
Intention to treat	
Subsequent analysis	

Study Results:	Intervention	Comparator
All results are given for primary analysis population as reported! EXTRA analysis population are given below		
ANALYSIS POPULATION:		
EFFICACY OUTCOMES		
Stroke or systemic embolism		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
All-cause stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Systemic embolism		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Ischemic/unspecified stroke		
Sample size for this outcome		

Summary data (n, %)		
Effect estimate, p-value		
Ischemic stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Unspecified stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Fatal or disabling stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Disabling stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Fatal stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
All-cause mortality		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
CV mortality		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Myocardial infarction		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Pulmonary embolism/ Deep venous thrombosis		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Transient ischemic attack		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
SAFETY END POINTS		
Major bleeding	Classified according to (e.g. ISTH criteria):	
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Major or minor bleeding		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		

Life-threatening bleeding		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Intracranial bleeding (ICH)		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Hemorrhagic stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Extracranial bleeding		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
GI bleeding		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Minor bleeding		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Study-drug discontinuation		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		

Results	**Intervention**	**Comparator**
Results for ADDITONAL analysis populations provided		
ANALYSIS POPULATION:		
EFFICACY OUTCOMES		
Stroke or systemic embolism		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
All-cause stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Systemic embolism		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Ischemic/unspecified stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Ischemic stroke		
Sample size for this outcome		

Summary data (n, %)		
Effect estimate, p-value		
Unspecified stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Disabling stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Fatal stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
All-cause mortality		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
CV mortality		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Myocardial infarction		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Pulmonary embolism/ Deep venous thrombosis		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Transient ischemic attack		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
SAFETY END POINTS		
Major bleeding	Classified according to (e.g. ISTH criteria):	
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Major or minor bleeding		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Life-threatening bleeding		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Intracranial bleeding (ICH)		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		

Hemorrhagic stroke		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Extracranial bleeding		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
GI bleeding		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Minor bleeding		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		
Study-drug discontinuation		
Sample size for this outcome		
Summary data (n, %)		
Effect estimate, p-value		

Subgroups of Interest

Results for		**Intervention**	**Comparator**	
SUBGROUP: AGE				
Stroke or systemic embolism				
Category	Total n	n/N	n/N	**P-value for interaction**
<65 years				
65 to <75y				
≥ 75 years				
Major bleeding				
Category	Total n	n/N	n/N	**P-value for interaction**
<65 years				
65 to <75y				
≥ 75 years				
Outcome (add available outcome):				
Category	Total n	n/N	n/N	**P-value for interaction**
<65 years				
65 to <75y				
≥ 75 years				

Results for		Intervention	Comparator	
SUBGROUP: Gender				
Stroke or systemic embolism				
Category	Total n	n/N	n/N	**P-value for interaction**
Female				
Male				
Major bleeding				
Category	Total n	n/N	n/N	**P-value for interaction**
Female				
Male				
Outcome (add available outcome):				
Category	Total n	n/N	n/N	**P-value for interaction**
Female				
Male				

Results for		Intervention	Comparator	
SUBGROUP: Renal impairment				
Stroke or systemic embolism				
Category	Total n	n/N	n/N	**P-value for interaction**
Severe or moderate				
Mild				
None				
Major bleeding				
Category	Total n	n/N	n/N	**P-value for interaction**
Severe or moderate				
Mild				
None				
Outcome (add available outcome):				
Category	Total n	n/N	n/N	**P-value for interaction**
Severe or moderate				
Mild				
None				

Results for		Intervention	Comparator	
SUBGROUP: $CHADS_2$ Score				
Stroke or systemic embolism				
Category	Total n	n/N	n/N	**P-value for**

				interaction
0-1				
2				
3				
4				
5				
6				
Major bleeding				
Category	Total n	n/N	n/N	**P-value for interaction**
0-1				
2				
3				
4				
5				
6				
Outcome (add available outcome):				
Category	Total n	n/N	n/N	**P-value for interaction**
0-1				
2				
3				
4				
5				
6				

Results for	**Intervention**		**Comparator**	
SUBGROUP: $CHADS_2$ –VASC Score				
Stroke or systemic embolism				
Category	Total n	n/N	n/N	**P-value for interaction**
0-1				
2-3				
4-5				
6-7				
8-9				
Major bleeding				
Category	Total n	n/N	n/N	**P-value for interaction**
0-1				
2-3				
4-5				
6-7				

8-9				
Outcome (add available outcome):				
Category	Total n	n/N	n/N	**P-value for interaction**
0-1				
2-3				
4-5				
6-7				
8-9				

Results for		**Intervention**	**Comparator**	
SUBGROUP: Prior use of Vitamin K antagonist				
Stroke or systemic embolism				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				
Major bleeding				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				
Outcome (add available outcome):				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				

Results for		**Intervention**	**Comparator**	
SUBGROUP: Prior/Baseline use of Aspirin				
Stroke or systemic embolism				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				
Major bleeding				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				
Outcome (add available outcome):				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				

Results for		Intervention	Comparator	
SUBGROUP: History of stroke/TIA				
Stroke or systemic embolism				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				
Major bleeding				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				
Outcome (add available outcome):				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				

Results for		Intervention	Comparator	
SUBGROUP: History of GI bleeding				
Stroke or systemic embolism				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				
Major bleeding				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				
Outcome (add available outcome):				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				

Results for		Intervention	Comparator	
SUBGROUP: Concurrent use of antiplatelets				
Stroke or systemic embolism				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				
Major bleeding				

Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				
Outcome (add available outcome):				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				

Results for		**Intervention**	**Comparator**	
SUBGROUP: Concurrent use of NSAID				
Stroke or systemic embolism				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				
Major bleeding				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				
Outcome (add available outcome):				
Category	Total n	n/N	n/N	**P-value for interaction**
YES				
NO				

Results for		**Intervention**	**Comparator**	
SUBGROUP: Time in Therapeutic range				
Stroke or systemic embolism				
Category	Total n	n/N	n/N	**P-value for interaction**
<Median/mean TTR				
≥Median/mean TTR				
Major bleeding				
Category	Total n	n/N	n/N	**P-value for interaction**
<Median/mean TTR				
≥Median/mean TTR				
Outcome (add available outcome):				
Category	Total n	n/N	n/N	**P-value for interaction**

<Median/mean TTR				
≥Median/mean TTR				

Results for		**Intervention**		**Comparator**		
SUBGROUP: Time in Therapeutic Range x Age						
Stroke or systemic embolism						
Category	Total n	n/N	n/N	n/N	n/N	**P-value for interaction**
		Age<75y	**Age≥75y**	**Age<75y**	**Age≥75y**	
<Median/mean TTR						
≥Median/mean TTR						
Major bleeding						
Category	Total n	n/N	n/N	n/N	n/N	**P-value for interaction**
		Age<75y	**Age≥75y**	**Age<75y**	**Age≥75y**	
<Median/mean TTR						
≥Median/mean TTR						
Outcome (add available outcome):						
Category	Total n	n/N	n/N	n/N	n/N	**P-value for interaction**
		Age<75y	**Age≥75y**	**Age<75y**	**Age≥75y**	
<Median/mean TTR						
≥Median/mean TTR						

Miscellaneous:	
Funding source	
Coordination	
Key conclusion of the study authors	
Miscellaneous comments of the study authors	
Miscellaneous comments of the review authors	

7.5 SIGN50 Quality Assessment Instrument for RCT

S I G N	**Methodology Checklist 2: Controlled Trials**
Study identification (*Include author, title, year of publication, journal title, pages*)	
Guideline topic:	Key Question No:

Before completing this checklist, consider:

1. Is the paper a **randomized controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Checklist completed by:

SECTION 1: INTERNAL VALIDITY

	In a well conducted RCT study…	**In this study this criterion is:**	
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.2	The assignment of subjects to treatment groups is randomised	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	An adequate concealment method is used	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	The treatment and control groups are similar at the start of the trial	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	The only difference between groups is the treatment under investigation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? Code ++, +, or –		
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?		

2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question.	

The following section is provided for non-SIGN users of this checklist and is being developed to conform to the standards set by the Guidelines International Network Evidence Tables Working Group.

Members of SIGN guideline groups do not need to complete this section.

SECTION 3: DESCRIPTION OF THE STUDY		
3.1	*Do we know who the study was funded by?*	□ Academic Institution □ Healthcare Industry □ Government □ NGO □ Public funds □ Other
3.2	*How many centres are patients recruited from?*	
3.3	*From which countries are patients selected? (Select all those involved. Note additional countries after "Other")*	□ Scotland □ UK □ USA □ Canada □ Australia □ New Zealand □ France □ Germany □ Italy □ Netherlands □ Scandinavia □ Spain □ Other:
3.4	*What is the social setting (ie type of environment in which they live) of patients in the study?*	□ Urban □ Rural □ Mixed
3.5	*What criteria are used to decide who should be INCLUDED in the study?*	
3.6	*What criteria are used to decide who should be EXCLUDED from the study?*	
3.7	*What intervention or risk factor is investigated in the study? (Include dosage where appropriate)*	
3.8	*What comparisons are made in the study (ie what alternative treatments are used to compare the intervention with). Include dosage where appropriate.*	
3.9	*What methods were used to randomize patients, blind patients or investigators, and to conceal the randomization process from investigators?*	

3.10	*How long did the active phase of the study last?*			
3.11	*How long were patients followed-up for, during and after the study?*			
3.12	*List the key characteristics of the patient population. Note if there are any significant differences between different arms of the trial.*			
3.13	*Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page.*			
	Arm 1: **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 2:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 3:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 4:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**
3.14	*Record the basic data for each IMPORTANT outcome in the study. If there are more than four, not data for additional outcomes at the bottom of the page.*			
	Outcome 1: **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 2:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 3:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 4:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**
3.15	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *(Much of this is likely to be contributed by GDG members).*			

7.5.1 SIGN-50 Assessment for Included RCTs (n=5)

SIGN	Methodology Checklist 2: Controlled Trials

Study identification (*Include author, title, year of publication, journal title, pages*)

ROCKET-AF: Manesh R. Patel, Kenneth W. Mahaffey, Jyotsna Garg, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

N Engl J Med 2011;365:883-91

Guideline topic:	Key Question No:

Before completing this checklist, consider:

3. Is the paper a **randomized controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
4. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Checklist completed by: DSEN

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study…		**In this study this criterion is:**	
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.2	The assignment of subjects to treatment groups is randomised	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

1.3	An adequate concealment method is used	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	The treatment and control groups are similar at the start of the trial	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	The only difference between groups is the treatment under investigation (previous MI)	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	24.0 % (1709/7131) and 22.4% (1598/7133) of patients in rivaroxaban and warfarin group dropped out before the study was completed, respectively.	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? Code ++, +, or –	++	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical	Yes	

	power of the study, are you certain that the overall effect is due to the study intervention?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.	

The following section is provided for non-SIGN users of this checklist and is being developed to conform to the standards set by the Guidelines International Network Evidence Tables Working Group.

Members of SIGN guideline groups do not need to complete this section.

SECTION 3: DESCRIPTION OF THE STUDY		
3.1	*Do we know who the study was funded by?*	□ Academic Institution ■ Healthcare Industry □ Government □ NGO □ Public funds □ Other
3.2	*How many centres are patients recruited from?*	
	From which countries are patients selected? (Select all those involved. Note additional countries after "Other")	□ Scotland □ UK □ USA □ Canada □ Australia □ New Zealand □ France □ Germany □ Italy □ Netherlands □ Scandinavia □ Spain □ Other:
3.4	*What is the social setting (ie type of environment in which they live) of patients in the study?*	□ Urban □ Rural □ Mixed
3.5	*What criteria are used to decide who should be INCLUDED in the study?*	
3.6	*What criteria are used to decide who should be EXCLUDED from the study?*	
3.7	*What intervention or risk factor is investigated in the study? (Include dosage where appropriate)*	
3.8	*What comparisons are made in the study (ie what alternative treatments are used to compare the intervention with). Include dosage where appropriate.*	

3.9	*What methods were used to randomize patients, blind patients or investigators, and to conceal the randomization process from investigators?*			
3.10	*How long did the active phase of the study last?*			
3.11	*How long were patients followed-up for, during and after the study?*			
3.12	*List the key characteristics of the patient population. Note if there are any significant differences between different arms of the trial.*			
3.13	*Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page.*			
	Arm 1: **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 2:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 3:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 4:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**
3.14	*Record the basic data for each IMPORTANT outcome in the study. If there are more than four, not data for additional outcomes at the bottom of the page.*			
	Outcome 1: **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 2:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 3:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 4:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**
3.15	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *(Much of this is likely to be contributed by GDG members).*			

SIGN	Methodology Checklist 2: Controlled Trials

Study identification (*Include author, title, year of publication, journal title, pages*)

PETRO: Michael D. Ezekowitz, Paul A. Reilly, Gerhard Nehmiz, et al. Dabigatran With or Without Concomitant Aspirin Compared With Warfarin Alone in Patients With Nonvalvular Atrial Fibrillation (PETRO Study). Am J Cardiol 2007;100:1419 –1426

Guideline topic:	Key Question No:

Before completing this checklist, consider:

1. Is the paper a **randomized controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Checklist completed by: DSEN

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study…		**In this study this criterion is:**	
1.1	The study addresses an appropriate and clearly focused question.	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable
1.2	The assignment of subjects to treatment groups is randomised	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable
1.3	An adequate concealment method is used	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable

1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	The treatment and control groups are similar at the start of the trial	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	The only difference between groups is the treatment under investigation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	8.3% (36/432) and 2.9% (2/70) of patients in dabigatran and warfarin group dropped out before the study was completed.	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? Code ++, +, or –	++	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Yes	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes	

2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. Major bleeding events were limited to patients treated with dabigatran 300 mg plus aspirin and thromboembolic episodes were limited to the 50-mg dabigatran groups. In this multi-dose study, only those doses approved or sought at regulatory boards in North America and Europe was included, i.e. dabigatran 150 and 110 mg twice daily.

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Members of SIGN guideline groups do not need to complete this section.

SECTION 3: DESCRIPTION OF THE STUDY		
3.1	*Do we know who the study was funded by?*	□ Academic Institution ■ Healthcare Industry □ Government □ NGO □ Public funds □ Other
3.2	*How many centres are patients recruited from?*	
3.3	*From which countries are patients selected? (Select all those involved. Note additional countries after "Other")*	□ Scotland □ UK □ USA □ Canada □ Australia □ New Zealand □ France □ Germany □ Italy □ Netherlands □ Scandinavia □ Spain □ Other:
3.4	*What is the social setting (ie type of environment in which they live) of patients in the study?*	□ Urban □ Rural □ Mixed
3.5	*What criteria are used to decide who should be INCLUDED in the study?*	
3.6	*What criteria are used to decide who should be EXCLUDED from the study?*	
3.7	*What intervention or risk factor is investigated in the study? (Include dosage where appropriate)*	
3.8	*What comparisons are made in the study (ie what alternative treatments are used to compare the intervention with). Include dosage where appropriate.*	
3.9	*What methods were used to randomize patients, blind patients or investigators, and to conceal the randomization process from investigators?*	

3.10	*How long did the active phase of the study last?*			
3.11	*How long were patients followed-up for, during and after the study?*			
3.12	*List the key characteristics of the patient population. Note if there are any significant differences between different arms of the trial.*			
3.13	*Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page.*			
	Arm 1: **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 2:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 3:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 4:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**
3.14	*Record the basic data for each IMPORTANT outcome in the study. If there are more than four, not data for additional outcomes at the bottom of the page.*			
	Outcome 1: **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 2:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 3:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 4:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**
3.15	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *(Much of this is likely to be contributed by GDG members).*			

Study identification (*Include author, title, year of publication, journal title, pages*) ARISTOTLE: Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981-92.	
Guideline topic:	Key Question No:

Before completing this checklist, consider:

1. Is the paper a **randomized controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Checklist completed by: DSEN

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study…		**In this study this criterion is:**	
1.1	The study addresses an appropriate and clearly focused question.	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable
1.2	The assignment of subjects to treatment groups is randomised	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable
1.3	An adequate concealment method is used	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable
1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable

1.5	The treatment and control groups are similar at the start of the trial	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	The only difference between groups is the treatment under investigation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	25.3% and 27.5% of patients in apixaban and warfarin group dropped out before the study was completed, respectively.	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? Code ++, +, or –	++	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Yes	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes	
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. Apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.		

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Members of SIGN guideline groups do not need to complete this section.

SECTION 3: DESCRIPTION OF THE STUDY		
3.1	*Do we know who the study was funded by?*	□ Academic Institution ■ Healthcare Industry □ Government □ NGO □ Public funds □ Other
3.2	*How many centres are patients recruited from?*	
3.3	*From which countries are patients selected? (Select all those involved. Note additional countries after "Other")*	□ Scotland □ UK □ USA □ Canada □ Australia □ New Zealand □ France □ Germany □ Italy □ Netherlands □ Scandinavia □ Spain □ Other:
3.4	*What is the social setting (ie type of environment in which they live) of patients in the study?*	□ Urban □ Rural □ Mixed
3.5	*What criteria are used to decide who should be INCLUDED in the study?*	
3.6	*What criteria are used to decide who should be EXCLUDED from the study?*	
3.7	*What intervention or risk factor is investigated in the study? (Include dosage where appropriate)*	
3.8	*What comparisons are made in the study (ie what alternative treatments are used to compare the intervention with). Include dosage where appropriate.*	
3.9	*What methods were used to randomize patients, blind patients or investigators, and to conceal the randomization process from investigators?*	
3.10	*How long did the active phase of the study last?*	
3.11	*How long were patients followed-up for, during and after the study?*	
3.12	*List the key characteristics of the patient population.*	

	Note if there are any significant differences between different arms of the trial.			
3.13	*Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page.*			
	Arm 1: **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 2:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 3:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 4:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**
3.14	*Record the basic data for each IMPORTANT outcome in the study. If there are more than four, not data for additional outcomes at the bottom of the page.*			
	Outcome 1: **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 2:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 3:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 4:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**
3.15	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *(Much of this is likely to be contributed by GDG members).*			

S I G N	Methodology Checklist 2: Controlled Trials
Study identification (*Include author, title, year of publication, journal title, pages*) ARISTOTLE-J: Satoshi Ogawa, Yukito Shinohara, Kazuhiro Kanmuri. Safety and Efficacy of the Oral Direct Factor Xa Inhibitor Apixaban in Japanese Patients With Non-Valvular Atrial Fibrillation – The ARISTOTLE-J Study. Circ J 2011; 75: 1852 – 1859	
Guideline topic:	Key Question No:

Before completing this checklist, consider:

1. Is the paper a **randomized controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Checklist completed by: DSEN

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study…		**In this study this criterion is:**	
1.1	The study addresses an appropriate and clearly focused question.	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable
1.2	The assignment of subjects to treatment groups is randomised	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable
1.3	An adequate concealment method is used	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable
1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable
1.5	The treatment and control groups are similar at the start of the trial	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable

1.6	The only difference between groups is the treatment under investigation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	9%, 7% and 12% of the patients in apixaban-2.5, apixaban-5 and warfarin group dropped out before the study was completed, respectively.	
1.9	*All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)*	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? Code ++, +, or –	+	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Yes	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes	
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question.		

The following section is provided for non-SIGN users of this checklist and is being developed to conform to the standards set by the Guidelines International Network Evidence Tables Working Group.

Members of SIGN guideline groups do not need to complete this section.

SECTION 3: DESCRIPTION OF THE STUDY		
3.1	*Do we know who the study was funded by?*	□ Academic Institution ■ Healthcare Industry □ Government □ NGO □ Public funds □ Other
3.2	*How many centres are patients recruited from?*	
3.3	*From which countries are patients selected? (Select all those involved. Note additional countries after "Other")*	□ Scotland □ UK □ USA □ Canada □ Australia □ New Zealand □ France □ Germany □ Italy □ Netherlands □ Scandinavia □ Spain □ Other:
3.4	*What is the social setting (ie type of environment in which they live) of patients in the study?*	□ Urban □ Rural □ Mixed
3.5	*What criteria are used to decide who should be INCLUDED in the study?*	
3.6	*What criteria are used to decide who should be EXCLUDED from the study?*	
3.7	*What intervention or risk factor is investigated in the study? (Include dosage where appropriate)*	
3.8	*What comparisons are made in the study (ie what alternative treatments are used to compare the intervention with). Include dosage where appropriate.*	
3.9	*What methods were used to randomize patients, blind patients or investigators, and to conceal the randomization process from investigators?*	
3.10	*How long did the active phase of the study last?*	
3.11	*How long were patients followed-up for, during and after the study?*	
3.12	*List the key characteristics of the patient population. Note if there are any significant differences between different arms of the trial.*	

3.13	*Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page.*			
	Arm 1: **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 2:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 3:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 4:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**
3.14	*Record the basic data for each IMPORTANT outcome in the study. If there are more than four, not data for additional outcomes at the bottom of the page.*			
	Outcome 1: **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 2:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 3:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 4:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**
3.15	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *(Much of this is likely to be contributed by GDG members).*			

SIGN	Methodology Checklist 2: Controlled Trials

Study identification (*Include author, title, year of publication, journal title, pages*)

RE-LY: Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51.

Guideline topic:	Key Question No:

Before completing this checklist, consider:

1. Is the paper a **randomized controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Checklist completed by: DSEN

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study…		**In this study this criterion is:**	
1.1	The study addresses an appropriate and clearly focused question.	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable
1.2	The assignment of subjects to treatment groups is randomised	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable
1.3	An adequate concealment method is used	Well covered	Not addressed
		Adequately addressed	Not reported
		Poorly addressed	Not applicable

1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	The treatment and control groups are similar at the start of the trial	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	The only difference between groups is the treatment under investigation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	The rates of discontinuation for dabigatran-110 mg, dabigatran-150 mg, and warfarin were 14.5%, 15.5%, and 10.2% at year 1, and 20.7%, 21.2%, and 16.6% at years 2, respectively.	
1.9	*All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)*	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? Code ++, +, or –	+	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Yes	

2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. In atrial fibrillation, dabigatran given at dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.	

The following section is provided for non-SIGN users of this checklist and is being developed to conform to the standards set by the Guidelines International Network Evidence Tables Working Group.

Members of SIGN guideline groups do not need to complete this section.

SECTION 3: DESCRIPTION OF THE STUDY		
3.1	*Do we know who the study was funded by?*	□ Academic Institution ■ Healthcare Industry □ Government □ NGO □ Public funds □ Other
3.2	*How many centres are patients recruited from?*	
3.3	*From which countries are patients selected? (Select all those involved. Note additional countries after "Other")*	□ Scotland □ UK □ USA □ Canada □ Australia □ New Zealand □ France □ Germany □ Italy □ Netherlands □ Scandinavia □ Spain □ Other:
3.4	*What is the social setting (ie type of environment in which they live) of patients in the study?*	□ Urban □ Rural □ Mixed
3.5	*What criteria are used to decide who should be INCLUDED in the study?*	
3.6	*What criteria are used to decide who should be EXCLUDED from the study?*	
3.7	*What intervention or risk factor is investigated in the study? (Include dosage where appropriate)*	
3.8	*What comparisons are made in the study (ie what alternative treatments are used to compare the intervention with). Include dosage where appropriate.*	
3.9	*What methods were used to randomize patients, blind patients or investigators, and to conceal the*	

	randomization process from investigators?			
3.10	*How long did the active phase of the study last?*			
3.11	*How long were patients followed-up for, during and after the study?*			
3.12	*List the key characteristics of the patient population. Note if there are any significant differences between different arms of the trial.*			
3.13	*Record the basic data for each arm of the study. If there are more than four arms, note data for subsequent arms at the bottom of the page.*			
	Arm 1: **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 2:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 3:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**	**Arm 4:** **Treatment:** **Sample size:** **No. analysed** **With outcome:** **Without outcome:** **Primary outcome?**
3.14	*Record the basic data for each IMPORTANT outcome in the study. If there are more than four, not data for additional outcomes at the bottom of the page.*			
	Outcome 1: **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 2:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 3:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**	**Outcome 4:** **Value:** **Measure:** **P value** **Upper CI** **Lower CI** **Primary outcome?**
3.15	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *(Much of this is likely to be contributed by GDG members).*			

7.6 Risk of Bias Assessment Tool

Table 40: ROB Assessment Tool		
Item	**Reviewer Assessment**	**Description**
Adequate sequence generation?		
Allocation concealment?		
Blinding of objective outcomes assessment?		
Blinding of subjective outcomes assessment?		
Incomplete outcomes data addressed? Efficacy outcomes		
Incomplete outcomes data addressed? Safety outcomes		
Free of selective reporting?		
Free of other bias?		

7.6.1 Risk of Bias Assessment for Included Studies (n=5)

RE-LY: Connolly 2009[9]		
Item	**Reviewer Assessment**	**Description**
Adequate sequence generation?	Unclear	"…were randomly assigned to receive…" Method for sequence generation not provided.
Allocation concealment?	Unclear	Method for allocation concealment not provided.
Blinding of objectives outcomes assessment?	Low	"Dabigatran was administered in a blinded fashion …Warfarin was administered in an unblinded fashion…" "Each primary and secondary outcome event was adjudicated by two independent investigators who were unaware of the treatment assignments. All transient ischemic attacks were reviewed to ensure that strokes had not been missed. To detect possible unreported events, symptom questionnaires were regularly administered to patients, and adverse event and hospitalization reports were scrutinized for unreported primary or secondary outcomes." A blinding approach was not provided, and blinding for the warfarin group was infeasible, judged a low risk of bias given that the objective outcomes should be based on participants' signs and symptoms, radiographic and/or laboratory evidence, and objective criteria, which were unlikely to be influenced by incomplete or ineffective blinding.
Blinding of subjective outcomes assessment?	High	"Dabigatran was administered, in a blinded fashion.…Warfarin was administered, in an unblinded fashion…" "To detect possible unreported events, symptom questionnaires were regularly administered to patients…" A blinding approach was not provided, and blinding for the warfarin group was infeasible, judged a high risk of bias given that the subjective outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions following assignment if the blinding was incomplete or ineffective.
Incomplete outcomes	Unclear	"All analyses were based on the intention-to-treat principle." "Two

data addressed? Efficacy outcomes		protocol changes were made by the operations committee during the enrollment period, without knowledge of emerging treatment effects." "The median duration of the follow-up period was 2.0 years" "The rates of discontinuation for 110 mg of dabigatran, 150 mg of dabigatran, and warfarin were 14.5%, 15.5%, and 10.2%, respectively, at one year, and 20.7%, 21.2%, and 16.6% at two years." All randomized and included participants were included in the analysis. However, they were judged an uncertain risk of bias given that the overall completion rate at two years (the median duration of the follow-up period) was 82% (14,839/18,113), with comparatively more patients in dabigatran groups (19% and 20%) than in the warfarin group (15%) discontinuing the study. As well, the approach to handling missing data was not provided.
Incomplete outcomes data addressed? Safety outcomes	Unclear	"All analyses were based on the intention-to-treat principle." "Two protocol changes were made by the operations committee during the enrollment period, without knowledge of emerging treatment effects." "The median duration of the follow-up period was 2.0 years" "The rates of discontinuation for 110 mg of dabigatran, 150 mg of dabigatran, and warfarin were 14.5%, 15.5%, and 10.2%, respectively, at one year and 20.7%, 21.2%, and 16.6% at two years." However, they were judged an uncertain risk of bias given that the overall completion rate at two years (the median duration of the follow-up period) was 82% (14,839/18,113), with comparatively more patients in dabigatran groups (19% and 20%) than in the warfarin group (15%) discontinuing the study. As well, the approach to handling missing data was not provided.
Free of selective reporting?	Low	Judged a low risk of bias given that outcomes of interest were pre-specified in the protocol (NCT00262600 in ClinicalTrials.gov) and reported in the published paper.
Free of other bias?	High	"Supported by a grant from Boehringer Ingelheim." Three among 21 authors were employed by "Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (P.A.R., J.V., S.W.)." Some authors received grant support and fees by providing consultations and lectures.

PETRO: Ezekowits 2007[10]		
Item	**Reviewer Assessment**	**Description**
Adequate sequence generation?	Unclear	"Randomization was stratified in the ratio 6:9:9:4." Method for sequence generation not provided.
Allocation concealment?	Unclear	Method for allocation concealment not provided.
Blinding of objective outcomes assessment?	Low	"The trial was double-blind with respect to dabigatran dose but open-label for concomitant aspirin treatment, and for randomization between dabigatran and warfarin groups." "Two identical matching capsules containing 50 mg or 150 mg dabigatran or placebo were taken twice daily for 12 weeks."
Blinding of subjective outcomes assessment?	low	"The trial was double-blind with respect to dabigatran dose, but open-label for concomitant aspirin treatment, and for randomization between dabigatran and warfarin groups." "Two identical matching capsules containing 50 mg or 15 mg dabigatran or placebo were taken twice daily for 12 weeks."
Incomplete outcomes data addressed? Efficacy outcomes	Unclear	All randomized participants were included in the analysis, in which 92.4% (464/502) completed the 12-week study, with 91.7% (396/432) in the dabigatran groups and 97.1% (68/70) in the warfarin group. They were judged a low risk of bias given that the completion rates in each group were quite high, and the reported numbers and reasons of discontinuations in each group seemed unlikely to bias the outcome estimate.
Incomplete outcomes data addressed?	Unclear	All randomized participants were included in the analysis, in which 92.4% (464/502) completed the 12-week study, with 91.7% (396/432) in

Safety outcomes		the dabigatran groups and 97.1% (2/70) in the warfarin group. They were judged a low risk of bias given that the completion rates in each group were quite high and the reported numbers and reasons of discontinuations in each group seemed unlikely to bias the outcome estimate.
Free of selective reporting?	Low	They were judged a low risk of bias given that outcomes of interest were pre-specified in the protocol (NCT01227629 in ClinicalTrials.gov) and reported in the published paper.
Free of other bias?	High	"Boehringer Ingelheim Pharmaceuticals, Biberach, Germany, is the sponsor of this study and has provided a research grant." Two among ten authors were employed by "Departments of Medical Data Services and Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharmaceuticals, Biberach, Germany."

ARISTOTLE: Granger 2011[11]		
Item	**Reviewer Assessment**	**Description**
Adequate sequence generation?	Unclear	"… we randomly assigned patients to treatment with apixaban or dose-adjusted warfarin." Method for sequence generation not provided.
Allocation concealment?	Unclear	Method for allocation concealment not provided.
Blinding of objectives outcomes assessment?	Low	"…a double-blind, double-dummy design…" "To maintain blinding, study medications are packaged using a double-dummy design. The two sets of tablets each subject receives are distinguishable by colour and size, but active apixaban tablets match placebo apixaban tablets and active warfarin tablets match placebo warfarin tablets to ensure blinding of the patient and investigator. After randomization, patients receive either apixaban and warfarin placebo or apixaban placebo and warfarin." "Subjects, investigators, members of the steering and adjudication committees, and the sponsor's staff conducting the study do not have access to individual subject treatment assignments."
Blinding of subjective outcomes assessment?	Low	"…a double-blind, double-dummy design…" "To maintain blinding, study medications are packaged using a double-dummy design. The two sets of tablets each subject receives are distinguishable by colour and size, but active apixaban tablets match placebo apixaban tablets and active warfarin tablets match placebo warfarin tablets to ensure blinding of the patient and investigator. After randomization, patients receive either apixaban and warfarin placebo or apixaban placebo and warfarin." "Subjects, investigators, members of the steering and adjudication committees, and the sponsor's staff conducting the study do not have access to individual subject treatment assignments."
Incomplete outcomes data addressed? Efficacy outcomes	High	"The primary and secondary efficacy analyses included all patients who underwent randomization (intention-to-treat population) and included all events from the time of randomization until the cut-off date for efficacy outcomes (predefined as January 30, 2011)." "Fewer patients in the apixaban group than in the warfarin group discontinued a study drug before the end of the study: 25.3% of the patients in the apixaban group, with 3.6% of the discontinuations due to death, versus 27.5% of patients in the warfarin group, with 3.8% due to death (P = 0.001)." All randomized participants were included in the efficacy analysis, judged a high risk of bias given that the overall completion rate was less than 80%, and the approach to handling missing data was not provided.
Incomplete outcomes data addressed? Safety outcomes	High	"The analyses of bleeding events included all patients who received at least one dose of a study drug and included all events from the time the first dose of a study drug was received until two days after the last dose was received."

		"Fewer patients in the apixaban group than in the warfarin group discontinued a study drug before the end of the study: 25.3% of the patients in the apixaban group, with 3.6% of the discontinuations due to death, versus 27.5% of patients in the warfarin group, with 3.8% due to death (P = 0.001)." 99.7% (18,140/18,201) of the randomized participants were included in the bleeding analysis (primary safety outcome) and other safety outcome analysis, with 32 in the apixaban group and 29 in the warfarin group not taking the medication; they were judged a high risk of bias given that the overall completion rate was less than 80%, and the approach to handling missing data was not provided.
Free of selective reporting?	Low	They were judged a low risk of bias given that outcomes of interest were pre-specified in the protocol (NCT00412984 in ClinicalTrials.gov) and reported in the published paper.
Free of other bias?	High	"Supported by Bristol-Myers Squibb and Pfizer." Three among 32 authors were employed by "Bristol-Myers Squibb, Princeton, New Jersey (M.H., M.G., P.M.)". Most of the authors claimed relationship with pharmaceutical companies in the form of receiving grants and providing education and consultancy.

ARISTOTLE-J: Ogawa 2011[12]		
Item	**Reviewer Assessment**	**Description**
Adequate sequence generation?	Unclear	"…patients were randomized in a 1:1:1 fashion to receive…" Method for sequence generation not provided.
Allocation concealment?	Unclear	Method for allocation concealment not provided.
Blinding of objective outcomes assessment?	Low	"…two double-blinded doses of apixaban with open-label warfarin…" Blinding approach not provided; judged a low risk of bias given that the objective outcomes were based on radiographic and laboratory evidences (central laboratories) and objective criteria, which were unlikely to be influenced by ineffective or incomplete blinding.
Blinding of subjective outcomes assessment?	High	"…two double-blinded doses of apixaban with open-label warfarin…" Blinding approach not provided; judged an uncertain risk of bias given that the subjective or minor outcomes might probably be influenced by the participants' or assessors' knowledge of the allocated interventions following assignment if the blinding was ineffective or incomplete.
Incomplete outcomes data addressed? Efficacy outcomes	Low	"Efficacy determinations were based on the intent-to-treat population, which included all randomized patients….Analyses of efficacy end points were based on the "intended treatment period," defined as starting on the day of randomization and ending either two days after the last dose of study drug or at the week 12 visit, whichever came last." "In our smaller and shorter duration phase II study, we observed no imbalance in discontinuations and no MI [myocardial infarction]." All randomized participants were included in the analysis, including four not taking medications and two being treated in error (n = 222). 91%, 93%, and 88% of the patients in the apixaban-2.5, apixaban-5, and warfarin groups completed the 12-week study, respectively. They were judged a low risk of bias given that the completion rates in each group were quite high, and the reported numbers and reasons of discontinuations in each group seemed unlikely to bias the outcome estimate.
Incomplete outcome data addressed? Safety outcomes	Low	"The safety population comprised all randomized patients who received at least one dose of the study drug. All randomized participants were included in the analysis, except for four not taking medications (n = 218). 91%, 93%, and 88%, of the patients in the apixaban-2.5, apixaban-5, and warfarin groups completed the 12-week study, respectively. They were judged a low risk of bias given that the completion rates in each group were quite high, and the reported numbers and reasons of discontinuations in each

		group seemed unlikely to bias the outcome sestimate.
Free of selective reporting?	Low	Judged a low risk of bias given that outcomes of interest were pre-specified in the protocol (NCT00787150 in ClinicalTrials.gov) and reported in the published paper.
Free of other bias?	High	"This study was funded by Pfizer Inc. and Bristol-Myers Squibb." One of three authors was employed by "Cardiovascular and Metabolism Therapeutics, Pfizer Japan Inc., Tokyo (K.K.), Japan." The other two authors also related to the funders by providing consultancy.

ROCKET-AF: Patel 2011[13]		
Item	**Reviewer Assessment**	**Description**
Adequate sequence generation?	Low	"Randomization was performed with the use of a central 24-hour, computerized, automated voice-response system."
Allocation concealment?	Uncertain	Method for allocation concealment not provided.
Blinding of objective outcomes assessment?	Low	"Patients in each group also received a placebo tablet in order to maintain blinding." "…sham values (for patients in the rivaroxaban group receiving placebo warfarin) during the course of the trial."
Blinding of subjective outcomes assessment?	Low	"Patients in each group also received a placebo tablet in order to maintain blinding." "…sham values (for patients in the rivaroxaban group receiving placebo warfarin) during the course of the trial."
Incomplete outcomes data addressed? Efficacy outcomes	High	"The primary analysis was pre-specified to be performed in the per-protocol population, which included all patients who received at least one dose of a study drug, did not have a major protocol violation, and were followed for events while receiving a study drug or within two days after discontinuation….If non-inferiority was achieved in the primary analysis, a closed testing procedure was to be conducted for superiority in the safety population during treatment, which included patients who received at least one dose of a study drug and were followed for events, regardless of adherence to the protocol, while they were receiving the assigned study drug or within two days after discontinuation…. Testing for non-inferiority and superiority was also performed in the intention-to-treat population, which included all patients who underwent randomization and were followed for events during treatment or after premature discontinuation." 97.6%, 99.0%, and 99.3% of randomized populations in the rivaroxaban group and 98.2%, 99.3%, and 99.4% of those in the warfarin group were included in the analysis of per-protocol, safety on treatment and the intention-to-treat population, respectively. 76.0 % (5,422/7,131) and 77.6% (5,535/7,133) of patients in the rivaroxaban and warfarin groups completed the study, respectively. They were judged a high risk of bias given that the completion rates were less than 80% and the approach to handling missing data was not provided.
Incomplete outcomes data addressed? Safety outcomes	High	"The primary analysis was prespecified to be performed in the per-protocol population, which included all patients who received at least one dose of a study drug, did not have a major protocol violation, and were followed for events while receiving a study drug or within two days after discontinuation….If non-inferiority was achieved in the primary analysis, a closed testing procedure was to be conducted for superiority in the safety population during treatment, which included patients who received at least one dose of a study drug and were followed for events, regardless of adherence to the protocol, while they were receiving the assigned study drug or within two days after discontinuation…. Testing for noninferiority and superiority was also performed in the intention-to-treat population, which included all patients who underwent randomization and were followed for events during treatment or after premature discontinuation." 97.6%, 99.0%, and 99.3% of the randomized population in the rivaroxaban group and 98.2%, 99.3%, and 99.4% of those in the

		warfarin group were included in the analysis of per-protocol, safety on treatment and the intention-to-treat population, respectively. 76.0 % (5,422/7,131) and 77.6% (5,535/7,133) of patients in the rivaroxaban and warfarin groups completed the study, respectively. They were judged a high risk of bias given that the completion rates were less than 80% and the approach to handling missing data was not provided.
Free of selective reporting?	Low	They were judged a low risk of bias given that outcomes of interest were pre-specified in the protocol (NCT00403767 in ClinicalTrials.gov) and reported in the published paper.
Free of other bias?	High	"Supported by Johnson & Johnson Pharmaceutical Research and Development and Bayer HealthCare." Two among 16 authors were employed by "Bayer HealthCare Pharmaceuticals, Montville (J.F.P., S.D.B.)."

7.7 Risk Estimates Reported and Computed

7.7.1 Reported hazard ratios

Table 41: Summary of Individual Study Results — Hazard Ratio (95% CI) for Each Outcome

	Stroke/SE	Major Bleeding	All-cause Mortality	Intracranial Bleeding	Major GI Bleeding	Myocardial Infarction
Apixaban 5 mg b.i.d.	0.79 (0.66 to 0.95)	0.68 (0.61 to 0.75)	0.89 (0.80 to1.00)	0.42 (0.30 to 0.58)	0.89 (0.70 to 1.14)	0.88 (0.66 to 1.17)
Dabigatran 110 mg b.i.d.	0.91 (0.74 to 1.11)	0.80 (0.69 to 0.93)	0.91 (0.80 to 1.03)	0.31 (0.20 to 0.47)	1.10 (0.86 to 1.41)	1.35 (0.98 to 1.87)
Dabigatran 150 mg b.i.d.	0.66 (0.53 to 0.82)	0.93 (0.81 to 1.07)	0.88 (0.77 to 1.00)	0.40 (0.27 to 0.60)	1.50 (1.19 to 1.89)	1.38 (1.00 to 1.91)
Rivaroxaban 20 mg q.d.	0.88 (0.75 to 1.03)	1.03 (0.89 to 1.19)	0.92 (0.82 to 1.04)	0.67 (0.47 to 0.93)	1.60 (1.29 to 1.98)	0.81 (0.63 1.06)*

b.i.d. = twice daily; CI = confidence interval; GI = gastrointestinal; q.d. = once daily; SE = systemic embolism
*Mahaffey 2010[78] (AHA) reports intention-to-treat hazard ratio(HR) in ROCKET AF for MI as 0.91 (0.72-1.16)

7.7.2 Computed relative risks

Table 42: Summary of Individual Study Results — Relative Risks (95% CI) for Each Outcome

	Stroke/SE	Major Bleeding	All-cause Mortality	Intracranial Bleeding	Major GI Bleeding	Myocardial Infarction
Apixaban 5 mg b.i.d.	0.8 (0.67 to 0.96)	0.71 (0.62 to 0.81)	0.9 (0.81 to 1)	0.43 (0.31 to 0.59)	0.88 (0.68 to 1.15)	0.88 (0.67 to 1.17)
Dabigatran 110 mg b.i.d.	0.91 (0.75 to 1.11)	0.82 (0.71 to 0.94)	0.92 (0.82 to 1.04)	0.31 (0.2 to 0.47)	1.08 (0.84 to 1.39)	1.31 (0.98 to 1.77)
Dabigatran 150 mg b.i.d.	0.66 (0.54 to 0.82)	0.94 (0.83 to 1.08)	0.9 (0.79 to 1.01)	0.42 (0.29 to 0.62)	1.44 (1.14 to 1.83)	1.29 (0.96 to 1.73)
Rivaroxaban 20 mg q.d.	0.89 (0.75 to1.04)	1.03 (0.9 to 1.18)	0.93 (0.84 to 1.04)	0.66 (0.47 to 0.93)	1.59 (1.29 to 1.95)	0.81 (0.63 to 1.05)

b.i.d. = twice daily; CI = confidence interval; GI = gastrointestinal; q.d. = once daily; SE = systemic embolism

7.8 Included and Excluded Studies

7.8.1 List of included studies (n = 15)

Table 43: Included Studies

Unique RCT	Companion or Subgroup Studies	Updated or Readjudicated data	Other
PETRO Ezekowitz et al., 2007[10]			
RE-LY Connolly et al.al., 2009[9]	Eikelbloom et al, 2011[75] Oldgren et al., 2011[81] Ezekowitz et al., 2010[76] Wallentin et al., 2010[82] Connolly 2010[74]	Supplemental. appendix available online with main RCT publication at NEJM[†]	FDA Report, 2010[79]
ARISTOTLE Granger et al., 2011[11]	Wallentin, 2011 (PPT)[83]		
ARISTOTLE-J Ogawa et al., 2011[12]			
ROCKET-AF Patel et al., 2011[13]	Fox et al., 2011[77] Mahaffey and Fox, 2010 (PPT)[78]	Supplemental appendix available online with main RCT publication at *NEJM**	FDA Report, 2011[80]

FDA = Food and Drug Administration; *NEJM* = *New England Journal of Medicine*; RCT = randomized controlled trial.
*Not included in reference count for PRISMA

7.8.2 List of excluded studies (n=51)

Table 44: Excluded Studies

Author, Year	Full Citation
Review or commentary (n = 5)	
Augoustides et al., 2011	Augoustides JG. Advances in anticoagulation: focus on dabigatran, an oral direct thrombin inhibitor. *J Cardiothorac Vasc Anesth*. 2011;25(6):1208-12.
Camm, 2009	Camm AJ. The RE-LY study: Randomized evaluation of long-term anticoagulant therapy: dabigatran vs. warfarin. *Eur Heart J*. 2009;30(21):2554-55.
Battistelli et al., 2009	Battistelli S, Genovese A, Gori T. Heparin-induced thrombocytopenia in surgical patients. *Am J Surg*. 2010;199(1):43-51.
Aymanns, 2010	Aymanns C, Keller F, Maus S, et al. Review on pharmacokinetics and pharmacodynamics and the aging kidney. *Clin J the Am Soc Nephrol*. 2010;5(2):314-27.

Hankey, 2009	Hankey GJ. At last, a RE-LYable alternative to warfarin for atrial fibrillation. *Int J stroke*. 2009;4(6):454-5.
Population not of interest (n = 5)	
Huang et al., 2011	Huang J, Cao Y, Liao C, et al. Apixaban versus enoxaparin in patients with total knee arthroplasty. A meta-analysis of randomised trials. *Thromb Haemost*. 2011;105(2):245-53.
Barrett et al., 2003	Barrett YC, Wang J, Knabb R, et al. Apixaban decreases coagulation activity in patients with acute deep-vein thrombosis. *Thromb Haemost*. 2003;105(1):181-9.
Bauer et al., 2009 (poster)	Bauer KA, Turpie AGG, Lassen MR, et al. Effects of age, weight, gender and renal function in a pooled analysis of four rivaroxaban studies. Poster presented at: 22nd Congress of the International Society on Thrombosis and Haemostasis; 2009 Jun 11-18; Boston, MA.
Lassen et al., 2008	Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*. 2008;358(26):2776-86.
Berges et al., 2007	Berges A, Laporte S, Epinat M, et al. Anti-factor Xa activity of enoxaparin administered at prophylactic dosage to patients over 75 years old. *Br J Clin Pharmacol*. 2007;64(4):428-38.
Study design not of interest (n = 25)	
Banerjee et al., 2011	Banerjee A, Marin F, Lip GY. A new landscape for stroke prevention in atrial fibrillation: focus on new anticoagulants, antiarrhythmic drugs, and devices. *Stroke*. 2011;42(11);3316-22.
Roskell et al., 2010	Roskell NS, Lip GY, Noack H, et al. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate. *Thromb Haemost*. 2010;104(6):1106-15.
Ezekowitz et al., 2011	Ezekowitz MD, Nagarakanti R. Dabigatran in atrial fibrillation: pharmacology and clinical trials. *J Interv Card Electrophysiology*. 2011;32(3):173-80.
Atay et al., 2011 (poster)	Atay J, Fiumara K, Piazza G, et al. Cost analysis of substituting dabigatran for warfarin in an anticoagulation management service. JACC. 2011;57(14 Suppl):E1188. (Poster presented at: ACC.11 & i2 60th Annual Scientific Session and Expo; 2011 Apr 2-5; New Orleans, LA).
Beyer-Westendorf et al., 2011	Beyer-Westendorf J, Buller H. External and internal validity of open label or double-blind trials in oral anticoagulation: better, worse or just different? *J Thromb Haemost*. 2011;9(11):2153-8.
Camm et al., 2011	Camm AJ, Bounameaux H. Edoxaban: a new oral direct factor Xa inhibitor. Drugs. 2011;71(12):1503-26.
Cooper et al., 2009	Cooper NJ, Sutton AJ, Morris D, et al. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. *Stat Med*. 2009;28(14):1861-81.
Cooper et al., 2011	Cooper PC, Coath FL, Daly M, et al. Assessment of antithrombin deficiency in the real world. *Int J Lab Hematol*. 2011;33(6):659-60.

Deremer et al., 2011	Deremer CE, Gujral JS, Thornton JW, et al. Dabigatran falsely elevates point of care international normalized ratio results. *Am J Med.* 2011;124(9):e5-6.
Ezekowitz et al., 2009	Ezekowitz MD, Connolly S, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J*. 2009;157(5):805-10.
Freeman et al., 2004	Freeman JV, Zhu RP, Owens DK, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med*. 2004;154(1):1-11.
From et al., 2002	From AM, Hoganson DD, Erwin PJ. Does a longer duration of oral factor Xa therapy increase the risk of bleeding or transaminitis? *Thromb Res*. 2002;127(3):2-209.
Gage, 2011	Gage L. Dabigatran in Patients With Nonvalvular Atrial Fibrillation. *J Am Coll Cardiol*. 2011;58(5):551.
Garcia et al., 2010	Garcia D, Libby E, Crowther MA. The NOAC. *Blood.* 2010;115:15-20.
Hankey et al., 2011	Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. *Circ*. 2011;123:1436-50.
Holmes, 2010	Holmes DR. Atrial fibrillation and stroke management: present and future. *Semin Neurol*. 2010;30(5):528-36.
Nutescu, 2009	Nutescu E. A pound of cure: prevention of ischemic stroke in atrial fibrillation. *Pharm Times*. 2009;75(12):110-9.
Patel et al., 2009	Patel M, Becker R, Breithardt G, et al. Rationale and design of the ROCKET-AF study: comparison of rivaroxaban with warfarin for the prevention of stroke and SE in patients with atrial fibrillation. *Eur Heart J*. 2009;30:705. (Presented at: European Society of Cardiology, ESC Congress; 2009 Aug 29 to Sep 2; Barcelona, Spain).
Pengo et al,. 2011	Pengo V, Crippa L, Falanga A, et al. Questions and answers on the use of dabigatran and perpectives on the use of other NOAC in patients with atrial fibrillation; a consensus document of the Italian federation of thrombosis centers (FCSA). *Thromb Haemost*. 2011;106(5):868-76.
Becker et al., 2010	Becker R, Berkowitz SC, Breithardt G, et al. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: rationale and design of the ROCKET-AF study. *Am Heart J*. 2010;159(3):340-7e1.
Shah et al., 2011	Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circ.* 2011;123(22):2562-70.
Siddiqui et al., 2008	Siddiqui FA, Ehrinpreis MN, Janisse J, et al. Demographics of a large cohort of urban chronic hepatitis C patients. *Hepatol Int*. 2008 Sep;2(3):376-81.
Sorensen et al., 2011	Sorensen SV, Kansal AR, Connolly S, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and SE in atrial fibrillation: a Canadian payer perspective. *Thromb Haemost*. 2011;105(5):908-19.
Steffel et al., 2011	Steffel J, Braunwald E. Novel oral anticoagulants: focus on stroke

	prevention and treatment of venous thrombo-embolism. *Eur Heart J*. 2011;32:1968-76.
Wyse, 2007	Wyse DG. Bleeding while starting anticoagulation for thromboembolism prophylaxis in elderly patients with atrial fibrillation: from bad to worse. *Circ.* 2007;115(21):2684-86.
Comparator not of interest (n = 1)	
Connolly et al., 2011	Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-17.
Outcome not of interest (n = 1)	
Braidy et al., 2011	Braidy N, Bui K, Bajorek B. Evaluating the impact of new anticoagulants in the hospital setting. *Pharm Prac*. 2011;9(1):1-10.
Intervention not of interest (n = 1)	
Flaker et al., 2006	Flaker GC, Gruber M, Connolly SJ, et al. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: an exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials. *Am Heart J*. 2006;152(5):967-73.
Subgroup – population or outcome not of interest, no useable data (n = 14)	
Hori et al., 2011	Hori M, Connolly SJ, Ezekowitz MD, et al. Efficacy and safety of dabigatran vs. warfarin in patients with atrial fibrillation — sub-analysis in Japanese population in RE-LY trial. *Circ J*. 2011;75(4):800-5.
Chung et al., 2011	Chung N, Jeon HK, Lien LM, et al. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. *Thromb & Haemost*. 2011;105(3):535-44.
Diener et al., 2010	Diener HC, Connolly SJ, Ezekowitz MD, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol*. 2010;9(12):1157-63.
Panichpisal et al., 2011	Panichpisal K, Szarek M, Sareen A. Dabigatran for stroke prevention in patients with atrial fibrillation and previous stroke or transient ischemic attack: does dose matter? *Future Neurol*. 2011;6(2):155-8.
Nagarakanti et al., 2011	Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: An analysis of patients undergoing cardioversion. *Circ.* 2011;123(2):131-6.
Eikelboom et al., 2010 (conference abstract)	Eikelboom J, Hijazi Z, Oldgren J, et al. D-dimer is prognostic for stroke, major bleeding and death during anticoagulation of atrial fibrillation — a RE-LY substudy; *Circ* 2010; 122 (21 Suppl): A18321. (Abstract presented at: American Heart Association (AHA) Scientific Sessions 2010; 2010 Nov 13-17; Chicago, IL).
Flaker et al., 2011 (poster)	Flaker GC, Reilly P, Yusuf S, et al. Dabigatran etexilate versus warfarin in patients with different types of atrial fibrillation: A RE-LY subgroup analysis. *J Am Coll Cardiol*. 2011; 57(14 Suppl): E62. (Poster presented at: ACC.11 & i2 American College of Cardiology's 60th Annual Scientific Session and Expo; 2011 Apr 2 to 5; New Orleans, LA).

Ferreiral et al., 2011	Ferreiral J, Ezekowitz MD, Connolly SJ, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial. *Circ.* 2011;124(21 Suppl):A10956. (Abstract presented at: American Heart Association (AHA) Scientific Sessions 2011; 2011 Nov 12 to 16; Orlando, FL).
Healey et al., 2010 (poster)	Healey JS, Eikelboom J, Wallentin L, et al. Effect of age and renal function on the risks of stroke and major bleeding with dabigatran compared to warfarin: an analysis from the RE-LY study. *J Am Coll Cardiol*. 2010;55(10A):A4.E37. (Poster presented at: ACC.10 & i2 American College of Cardiology's 59th Annual Scientific Session and Expo; 2010 Mar 14 to 16; Atlanta, GA).
Koti et al., 2010 (poster)	Koti MJ, Parekh A, Connolly SJ, et al. Dabigatran versus warfarin in patients with atrial fibrillation — an analysis of patients undergoing cardioversion. *J Am Coll Cardiol*. 2010;55(10A):A4.E40. (Poster session presented at: ACC.10 & i2 American College of Cardiology's 59th Annual Scientific Session and Expo; 2010 Mar 14 to 16; Atlanta, GA).
Nagarakanti et al., 2008	Nagarakanti R, Ezekowitz MD, Parcham-Azad K, et al. Long-term open label extension of the prevention of embolic and thrombotic events on dabigatran in atrial fibrillation (PETRO- Ex study). *Circ*. 2008;118(18 Suppl):S_922. (Abstract presented at: American Heart Association (AHA) Scientific Sessions 2008; 2008 Nov 8 to 12; New Orleans, LA).
Oldgren et al., 2010 (poster)	Oldgren J, Alings M, Darius H, et al. Dabigatran versus warfarin in atrial fibrillation patients with low, moderate and high CHADS2 score: a RE-LY subgroup analysis. *J Am Coll Cardiol*. 2010;55(10A):A1.E2. (Oral session presented at: ACC.10 & i2 American College of Cardiology's 59th Annual Scientific Session and Expo; 2010 Mar 14 to 16; Atlanta, GA.)
Uchino et al., 2011	Uchino K, Hernandez AV. Dabigatran is associated with higher risk of MI or acute coronary syndromes: a meta-analysis of non-inferiority randomized controlled trials. *Circ*. 2011;124(21 Suppl):A15500. (Abstract presented at: American Heart Association (AHA) Scientific Sessions 2011; 2011 Nov 12-16; Orlando, FL.)

7.9 Patient Inclusion and Exclusion Criteria from Included Studies

Table 45: Patient Inclusion and Exclusion Criteria

Author, Year	Trial name	Inclusion Criteria	Exclusion Criteria
Granger et al., 2011[11]	ARISTOTLE	Eligible patients had atrial fibrillation or flutter at enrollment or two or more episodes of atrial fibrillation or flutter, as documented by electrocardiography, at least two weeks apart in the 12 months before enrollment. In addition, at least one of the following risk factors for stroke was required: an age of at least 75 years; previous stroke, transient ischemic attack, or systemic embolism; symptomatic heart failure within the previous three months or left ventricular ejection fraction of no more than 40%; diabetes mellitus; or hypertension requiring pharmacologic treatment.	Atrial fibrillation due to a reversible cause, moderate or severe mitral stenosis, conditions other than atrial fibrillation that required anticoagulation (e.g., a prosthetic heart valve), stroke within the previous seven days, a need for aspirin at a dose of > 165 mg a day or for both aspirin and clopidogrel, and severe renal insufficiency, serum creatinine level of > 2.5 mg per decilitre (221 µmol per litre or calculated creatinine clearance of < 25 mL per minute).
Patel et al., 2011[13]	ROCKET-AF	• Men or women aged ≥18 years with non-valvular atrial fibrillation • Atrial fibrillation must be documented by electrocardiogram (ECG) evidence (e.g., 12-lead ECG, rhythm strip, Holter, pacemaker interrogation) within 30 days before randomization. In addition, subjects must have medical evidence of atrial fibrillation within one year before and at least one day before the qualifying ECG evidence. This could be obtained from a notation in the subject's record (e.g., medical chart, hospital discharge summary). • Subjects with newly diagnosed atrial fibrillation are eligible, provided that: – there is evidence that the atrial fibrillation is non-valvular – cardioversion is not planned – there is ECG evidence on two occasions, 24 hours apart, demonstrating atrial fibrillation • History of prior ischemic stroke, transient ischemic attack, or non-central nervous system (CNS) systemic embolism believed to be cardioembolic in origin or has two or more of the following risk factors: – heart failure and/or left ventricular ejection fraction ≤ 35% – hypertension (defined as use of antihypertensive medications within six months before the screening visit or persistent systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg) – age ≥ 75 years – diabetes mellitus (defined as a history of type 1 or type 2 diabetes mellitus or use of antidiabetic medications within six months before screening visit) • Female subjects must be postmenopausal (for at least two years),	Potential subjects who meet any of the following criteria will be excluded from participating in the study: *Cardiac-Related Conditions* • Hemodynamically significant mitral valve stenosis • Prosthetic heart valve (annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty are permitted) • Planned cardioversion (electrical or pharmacological) • Transient atrial fibrillation caused by a reversible disorder (e.g., thyrotoxicosis, pulmonary embolism, recent surgery, myocardial infacrtion) • Known presence of atrial myxoma or left ventricular thrombus • Active endocarditis *Hemorrhage Risk-Related Criteria* • Active internal bleeding • History of or condition associated with increased bleeding risk including, but not limited to: – major surgical procedure or trauma within 30 days before the randomization visit – clinically significant gastrointestinal bleeding within six months before the randomization visit – history of intracranial, intraocular, spinal, or atraumatic intra-articular bleeding – chronic hemorrhagic disorder – known intracranial neoplasm, arteriovenous malformation, or aneurysm • Planned invasive procedure with potential for uncontrolled bleeding, including major surgery • Platelet count < 90,000/µL at the screening visit • Sustained uncontrolled hypertension: systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg *Concomitant Conditions and Therapies* • Severe, disabling stroke (modified Rankin score of 4 to 5, inclusive) within three months or any

Table 45: Patient Inclusion and Exclusion Criteria			
Author, Year	**Trial name**	**Inclusion Criteria**	**Exclusion Criteria**
		surgically sterile, abstinent, or, if sexually active, be practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study; and, for those of childbearing potential, have a negative serum β-hCG pregnancy test at screening. • Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. • In order to participate in the optional pharmacogenomic component, subjects must have signed the informed consent for DNA research document indicating willingness to participate in the pharmacogenomics component of the study (where local regulations permit).	stroke within 14 days before the randomization visit • Transient ischemic attack within three days before the randomization visit • Indication for anticoagulant therapy for a condition other than atrial fibrillation (e.g., venous thrombolembolism) • Treatment with: – Aspirin > 100 mg daily – Aspirin in combination with thienopyridines within five days before randomization – Intravenous antiplatelets within five days before randomization – Fibrinolytics within 10 days before randomization [Note: Aspirin ≤100 mg monotherapy is allowed and thienopyridine monotherapy is allowed.] • Anticipated need for chronic treatment with a non-steroidal anti-inflammatory drug • Systemic treatment with a strong inhibitor of cytochrome P450 3A4, such as ketoconazole or protease inhibitors, within four days before randomization, or planned treatment during the time period of the study • Treatment with a strong inducer of cytochrome P450 3A4, such as rifampin/rifampicin, within four days before randomization, or planned treatment during the time period of the study • Anemia (hemoglobin <10 g/dL) at the screening visit • Pregnancy or breast-feeding • Any other contraindication to warfarin • Known HIV infection at time of screening • Calculated CLCR < 30 mL/min at the screening visit • Known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis), or ALT > 3 x the ULN
Connolly et al, 2009[9]	RE-LY	1. Atrial fibrillation documented as follows: a. There is atrial fibrillation documented by electrocardiogram on the day of screening or randomization. b. The patient has had a symptomatic episode of paroxysmal or persistent atrial fibrillation documented by 12-lead electrocardiogram within six months before randomization. c. There is documentation of symptomatic or asymptomatic paroxysmal or persistent atrial fibrillation on two separate occasions, at least one day apart, one of which is within six months before randomization. In this case, atrial fibrillation may be documented by 12-lead electrocardiogram, rhythm strip, pacemaker/ICD electrogram, or Holter electrocardiogram. The duration of atrial fibrillation should be at least 30 seconds. Electrograms (not marker channels or mode switch episodes) from pacemakers and defibrillators can be used to document only one episode of	• History of heart valve disorder (i.e., prosthetic valve or hemodynamically relevant valve disease). • Severe, disabling stroke within the previous six months, or any stroke within the previous 14 days. • Conditions associated with an increased risk of bleeding: a. Major surgery within the previous month. b. Planned surgery or intervention within the next 3 months. c. History of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding. d. Gastrointestinal hemorrhage within the past year. e. Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days. f. Hemorrhagic disorder or bleeding diathesis. g. Need for anticoagulant treatment of disorders other than atrial fibrillation. h. Fibrinolytic agents within 48 hours of study entry. i. Uncontrolled hypertension (systolic blood pressure greater than 180 mmHg and/or diastolic blood pressure greater than 100 mmHg). j. Recent malignancy or radiation therapy (within

Table 45: Patient Inclusion and Exclusion Criteria			
Author, Year	**Trial name**	**Inclusion Criteria**	**Exclusion Criteria**
		paroxysmal or persistent atrial fibrillation. 2. In addition to documented atrial fibrillation, patients must have one of the following: a. History of previous stroke, transient ischemic attack, or systemic embolism b. Ejection fraction less than 40% documented by echocardiogram, radionuclide or contrast angiogram in the last six months c. Symptomatic heart failure, New York Heart Association class 2 or higher in the last 6 months d. Age at least 75 years e. Age at least 65 years and one of the following: i. Diabetes mellitus on treatment ii. Documented coronary artery disease (any of: prior myocardial infarction, positive stress test, positive nuclear perfusion study, prior coronary artery bypass graft surgery or percutaneous coronary intervention, angiogram showing at least 75% stenosis in a major coronary artery) iii. Hypertension requiring medical treatment. 3. Age at least 18 years at study entry. 4. Written, informed, consent.	six months) and not expected to survive three years. • Contraindication to warfarin treatment. • Reversible causes of atrial fibrillation (e.g., cardiac surgery, pulmonary embolism, untreated hyperthyroidism). • Plan to perform a pulmonary vein ablation or surgery for cure of the atrial fibrillation. • Severe renal impairment (estimated creatinine clearance 30 mL/min or less). • Active infective endocarditis. • Active liver disease, including but not limited to: a. Persistent alanine transaminase ALT, aspartate aminotransferase (AST), alkaline phosphatase greater than twice the upper limit of the normal range b. Active hepatitis C (positive HCV RNA) c. Active hepatitis B (HBs antigen +, anti HBc IgM +) d. Active hepatitis A. • Women who are pregnant or of childbearing potential who refuse to use a medically acceptable form of contraception throughout the study. • Anemia (hemoglobin level less than 100 g/L) or thrombocytopenia (platelet count less than 100 × 109/L). • Patients who have developed transaminase elevations upon exposure to ximelagatran • Patients who have received an investigational drug in the past 30 days. • Patients considered unreliable by the investigator, or having a life expectancy less than the expected duration of the trial because of concomitant disease, or having any condition which, in the opinion of the investigator, would not allow safe participation in the study (e.g., drug addiction, alcohol abuse).
Ezekowitz et al, 2007[10]	PETRO	Inclusion criteria were documented atrial fibrillation with coronary artery disease plus one of the following: hypertension requiring medical treatment, diabetes mellitus (type 1 or 2), symptomatic heart failure or left ventricular dysfunction (ejection fraction 40%), previous stroke or transient ischemic attack, or age 75 years. After entry of approximately half of the patients, the requirement for coronary artery disease was removed to facilitate recruitment.	Exclusion criteria were mitral stenosis, prosthetic heart valves, planned cardioversion, recent (≤ 1 month) mtocardial infarction, recent stroke or transient ischemic attack, coronary stent placement within six months, any contraindication to or another indication for anticoagulant therapy, major hemorrhage in the past six months, severe renal impairment (glomerular filtration rate ≤ 30 mL/min), abnormal liver function, risk of pregnancy, investigational drug use within 30 days, or any other condition that would not allow participation in the study.

Table 45: Patient Inclusion and Exclusion Criteria			
Author, Year	**Trial name**	**Inclusion Criteria**	**Exclusion Criteria**
Ogawa et al, 2011[12]	ARISTOTLE-J	Patients aged ≥ 20 years with a history of documented non-valvular atrial fibrillation and at least one additional risk factor for stroke were enrolled. Instances of atrial fibrillation (confirmed by electrocardiogram, Holter recording, or intracardiac electrogram) were required to be at least one minute in duration and to have occurred on two separate occasions, at least two weeks apart, within 12 months prior to enrollment. Study participants had at least one of the following stroke risk factors: age ≥ 75 years, congestive heart failure (left ventricular ejection fraction ≤ 40%), hypertension requiring medication, diabetes mellitus deemed to require treatment based on the physician's discretion, or history of cerebral infarction or transient ischemic attack.	Recent cerebral infarction (including transient ischemic attack); valvular heart disease; sick sinus syndrome or severe conduction disturbance; non-cardiogenic stroke requiring acetylsalicylic acid > 100 mg/day or concomitant acetylsalicylic acid and antiplatelet agents; contraindications for warfarin use (e.g., thrombocytopenic purpura, suspected intracranial bleeding, bleeding tendency due to angiopathy, blood coagulation disorder such as hemophilia, recent major operation, peptic ulcer, or dementia); severe or refractory hypertension; New York Heart Association class IV heart failure; current thrombocytopenia (platelet count < 100 ×109/L or hemoglobin < 10 g/dL); liver function test abnormalities (alanine aminotransferase or aspartate aminotransferase ≥ 2 × upper limit of normal [ULN]) or renal dysfunction (creatinine clearance < 25 mL/min by Cockcroft-Gault calculation); known or suspected hereditary bleeding tendencies; and scheduled electrical, pharmacological, or surgical cardioversion during the treatment period.

7.10 Subgroup Data Reporting

Table 46: Subgroup Data Reporting — Comparison By Trial

		RE-LY		ARISTOTLE		ROCKET-AF		PETRO		ARISTOTLE-J	
Major SubGroup	**Minor Subgroup (if applicable)**	**Outcome**	**Categories**	**Outcomes**	**Categories**	**Outcome**	**Categories**	**Outcome**	**Categories**	**Outcomes**	**Categories**
Weight	**BMI**	A	BMI < 28 BMI ≥ 28	NR	NR	A,B	BMI ≤2 5 BMI 25 ≤ 35 BMI > 35	NR	NR	NR	NR
	Kg	A	< 50 kg 50 to 99 kg > 100 kg	A,C	≤ 60 kg > 60 kg	A	≤ 70 kg 70 ≤ 90 kg > 90kg	NR	NR	NR	NR
Age	**2 Categories Reported**	A,C,D,E,F	< 75 ≥ 75	NR	NR	A	< 75 > 75	NR	NR	K	2.5 mg Apix < 65 ≥ 65 5 mg Apix < 75 ≥ 75 Warfarin < 75 ≥ 75
	3 Categories Reported	C	< 65 65 to 74 ≥ 75	A,C	< 65 65 to < 75 ≥ 75	B	< 65 65 to < 75 ≥ 75	NR	NR	NR	NR
Renal Impairment	**Creatinine Clearance**	A,C*	-Moderate (cClear < 50) -Mild (cClear 50 to 79) -Mild (cClear 80+)	A,C†	-Severe or moderate -Mild -None	A,B*	-Moderate (cClear < 50) -Mild (cClear 50 to 79) -None (cClear 80+)	NR	NR	NR	NR
$CHADS_2$ Score		A,C,D,G,H	0 to 1 2 3 to 6	A,C	1,2, ≥ 3	A,B	No 0 or 1 (excluded) 2,3,4,5,6	NR	NR	NR	NR
$CHADS_2VASC$ Score		A, C	0-2 3 4 5-9	NR	NR	NR	NR	NR	NR	NR	NR
Prior use of VKA‡		A,C, D,H, I	YES NO	A,C	YES NO	A,B	YES NO	NR	NR	NR	NR

Table 46: Subgroup Data Reporting — Comparison By Trial											
		RE-LY		**ARISTOTLE**		**ROCKET-AF**		**PETRO**		**ARISTOTLE-J**	
Major SubGroup	**Minor Subgroup (if applicable)**	**Outcome**	**Categories**	**Outcomes**	**Categories**	**Outcome**	**Categories**	**Outcome**	**Categories**	**Outcomes**	**Categories**
History of GI Bleed		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Concurrent use of NSAID		NR	NR	NR	NR	Excluded	Excluded	NR	NR	NR	NR
Concurrent use of Antiplatelets		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
TTR		A,C,D,G,J,K	< 57.1% 57.1% to 65.5% 65.5% to 72.6% > 72.6%	A,B,C,L	Center TTR < 58% 58.0% to 65.7% 65.7% to 72.2% ≥ 72.2	A,B	Quartile Centre TTR 0 to 50.6% 50.7% to 58.5% 58.6% to 65.7% 65.7% to 100%	NR	NR	NR	NR

Apix = apixaban; BMI = body mass index; GI = gastrointestinal; NR = not reported; NSAID = nonsteroidal antiinflammatory drug; TTR = time in therapeutic range.
* Excluded below 30 ml/min.
† Excluded calculated creatinine clearance of < 25 mL per minute.
‡Definitions may vary across trials.
Outcome Legend:

A	Stroke or systemic embolism
B	Major and non-major clinically relevant bleeding while on treatment
C	Major bleeding
D	Intracranial bleeding
E	Extracranial bleeding
F	GI Bleeding
G	Total mortality
H	cardiovascular mortality
I	Myocardial infarction
J	Major GI Bleeding
K	Total bleeding
L	Hemorrhagic stroke

7.11 Random Effects MTC Network Meta-analysis Results versus adjusted-dose warfarin

Table 47: Summary of Results from Random-Effects MTC Network Meta-Analyses Versus Adjusted-Dose Warfarin

		Stroke/SE	Major Bleeding	All-cause Mortality	Intracranial Bleeding	Major GI Bleeding	Myocardial Infarction
Apixaban 5 mg b.i.d.		0.79 (0.07, 9.74)	0.70 (0.06, 8.79)	0.9 (0.08, 11.07)	0.70 (0.06, 8.79)	0.88 (0.08, 11.05)	0.88 (0.08,10.79)
Dabigatran 110 mg b.i.d.		0.91 (0.08, 11.27)	0.81 (0.07, 10.13)	0.91 (0.08, 11.70)	0.81 (0.07, 10.13)	1.08 (0.09, 13.58)	1.32 (0.11,16.51)
Dabigatran 150 mg b.i.d.		0.65 (0.06, 8.10)	0.94 (0.08, 11.78)	0.89 (0.08, 11.03)	0.94 (0.08, 11.78)	1.46 (0.12, 18.48)	1.29 (0.11,15.97)
Rivaroxaban 20 mg q.d.		0.78 (0.07, 9.64)	1.03 (0.09, 12.97)	0.93 (0.08, 11.44)	1.03 (0.09, 12.97)	1.60 (0.13, 20.23)	0.80 (0.07, 9.91)
Model fit statistics	Residual deviance	6.997	6.999	7.013	6.999	7.014	7.013
	DIC	63.728	68.188	70.528	68.188	61.09	58.84

b.i.d. = twice daily; DIC = deviance information criterion;GI = gastrointestinal; q.d. = once daily; MTC = mixed treatment comparison.

7.12 Specific Outcome Results

7.12.1 All-cause stroke or systemic embolism

7.12.1.1 Individual study results

A summary of study level results are shown in Table 48. Information on follow-up time and control event rate are provided alongside the relative and absolute risk. With the exception of dabigatran 110 mg, all treatments achieved statistically significant reductions in all-cause stroke/SE relative to adjusted-dose warfarin (Table 46). The use of dabigatran 150 mg produced the largest effects, with a reduction in odds of all-cause stroke/SE (OR [95% CI]: 0.65 [0.52 to 0.81]) and a corresponding absolute risk reduction of six fewer events per 1,000 patients treated each year. Relative to adjusted-dose warfarin, the reduction in odds for dabigatran 110 mg, apixaban 5 mg, and rivaroxaban 20 mg ranged from 0.78 to 0.90, with an absolute risk reduction of two to three fewer events per 1,000 patients treated each year.

Table 48: Summary of Study-level Results for All-Cause Stroke/Systemic Embolism Compared with Adjusted-Dose Warfarin

	Mean or Median Follow-Up	Warfarin Event Rate	OR (95% CI)	Absolute Risk Reduction per 1,000 patients Treated Each Year
Apixaban 5 mg b.i.d.	1.8 y	2.9%	0.79 (0.66, 0.95)	3 fewer (1 fewer, 5 fewer)
Dabigatran 110 mg b.i.d.	2 y	3.4%	0.90 (0.74, 1.11)	2 fewer (2 more, 4 fewer)
Dabigatran 150 mg b.i.d.	2 y	3.4%	0.65 (0.52, 0.81)	6 fewer (3 fewer, 8 fewer)
Rivaroxaban 20 mg q.d.	Trt exposure 1.6y; median follow-up,1.9y	3.4%	0.88 (0.74,1.03)	3 fewer (1 more, 6 fewer)

b.i.d. = twice daily; q.d. = once daily; CI = confidence interval; OR = odds ratio; y = years.

7.12.1.2 Network meta-analyses

Both Bayesian and frequentist evidence networks were comprised of three RCTs — ARISTOTLE, RE-LY, ROCKET-AF — representing four treatments, each relative to adjusted-dose warfarin (N = 50,276). The first network meta-analysis was unadjusted, not taking any possible differences in the patient populations across the studies into consideration. A summary of the unadjusted results for the fixed-effects Bayesian MTC are shown in Table 49, along with model fit statistics. With the exception of dabigatran 110 mg and rivaroxaban, all treatments achieved statistically significant reductions in the odds of all-cause stroke/SE relative to adjusted-dose warfarin. The use of dabigatran 150 mg produced the largest effects, with a reduction in odds of stroke/ SE (OR [95% CrI]: 0.65 [0.52 to 0.81]) relative to adjusted-dose warfarin. Data on the probability of an event in the warfarin arm provides a reflection of potential heterogeneity across studies, which are partially adjusted for in Section 8.12.1.3. Complete results from the MTC meta-analysis for all possible comparisons are presented in Table 24. The estimates of effect derived from fixed-effects Bayesian MTC analyses aligned closely with study level results and frequentist network meta-analysis results (see Table 49) in both direction and magnitude. The point estimates for the Bayesian random-effects MTC analysis were similar to those reported in the Bayesian fixed-effects MTC, although the credible intervals were much wider (see Appendix 7.11).

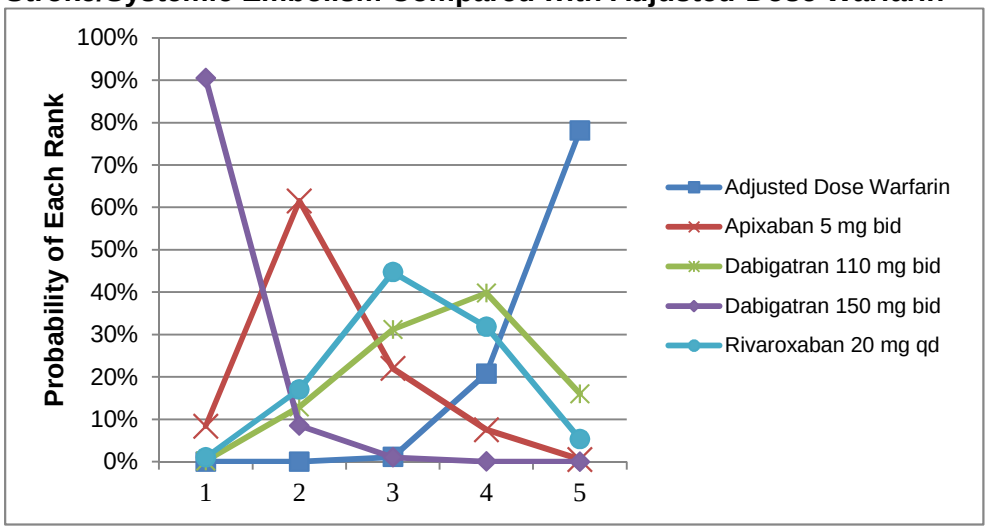
Table 49: Summary of Unadjusted Fixed-Effects Bayesian MTC Results for All-cause Stroke/Systemic Embolism Compared with Adjusted-Dose Warfarin

	Warfarin		NOAC		Warfarin Event rate	Bayesian MTC OR (95% CrI)	Frequentist GLMM OR (95% CI)
	N	N	N	N			
Apixaban 5 mg b.i.d.	265	9081	212	9120	2.9%	0.8(0.66 to 0.95)	0.76 (0.52 to 1.10)
Dabigatran 110 mg b.i.d.	202	6022	183	6015	3.4%	0.91(0.74 to 1.11)	0.93 (0.62 to 1.39)
Dabigatran 150 mg b.i.d.	202	6022	134	6076	3.4%	0.65(0.52 to 0.81)	0.66 (0.42 to 1.04)
Rivaroxaban 20 mg q.d.	306	7090	269	7081	4.3%	0.88(0.74 to 1.04)	0.81 (0.54 to 1.20)*
Model fit statistics for Bayesian MTC	Posterior mean residual deviance (6.99) less than the number of unconstrained data points (7), which is an indication of good model fit						

b.i.d. = twice daily; CI = confidence interval; CrI = credible interval; GLMM = generalized linear mixed model; MTC = mixed treatment cpmparison; OR = odds ratio; q.d. = once daily.
*Safety on treatment population.

Figure 12 shows the distribution of the probabilities, considered from a descriptive statistics perspective, of each treatment being ranked at each of the possible five ranking positions for the unadjusted Bayesian MTC meta-analysis. Dabigatran 150 mg had the highest probability of being best at reducing all-cause stroke/SE; apixaban and rivaroxaban have the highest probability of being second and third best, respectively; whereas dabigatran 110 mg and adjusted-dose warfarin have the highest probability of being fourth and fifth best, respectively.

Figure 12: Rankogram for Unadjusted Fixed-Effects Bayesian MTC Results for All-cause Stroke/Systemic Embolism Compared with Adjusted-Dose Warfarin



b.i.d. = twice daily; MTC = mixed treatment comparison; q.d. = once daily.

7.12.1.3 Sensitivity and sub-group analysis

Time in therapeutic range

A summary of results from a subgroup analysis by TTR are reported in Table 50. Odds ratios are derived from a Bayesian fixed-effects MTC analysis, whereas absolute risk reduction results are based on study-level results. For TTR < 66%, dabigatran 150 mg had a strong trend in reducing the odds of all-cause stroke/SE relative to adjusted-dose warfarin (OR [95% CrI]: 0.54 [0.40 to 0.74]), with an absolute risk reduction of nine fewer events per 1,000 treated each year relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for the other treatments ranged from 0.80 to 0.91 with absolute risk reduction ranging from two to four per 1,000 treated each year. For TTR ≥ 65%, no treatments had a strong trend in reducing the odds of all-cause stroke/SE relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for all treatments ranged from 0.80 to 0.91.

Table 50: Results from Fixed-Effects Bayesian MTC Sub-Group Analysis for All-Cause Stroke/Systemic Embolism Compared with Adjusted-Dose Warfarin by TTR

	Warfarin		NOAC		Warfarin Event Rate	ARR per 1,000 Patients Treated Each Year, Study-Level	Bayesian MTC, Median OR (95% CrI)
	n	N	n	N			
TTR < 66%							
Apixaban 5 mg b.i.d.	156	4,530	124	4,517	3.44%	4 fewer (0 more, 7 fewer)	0.80 (0.63 to 1.01)
Dabigatran 110 mg b.i.d.	116	3,018	106	3,021	3.84%	2 fewer (4 more, 6 fewer)	0.91 (0.70 to 1.20)
Dabigatran 150 mg b.i.d.	116	3,018	64	3035	3.84%	9 fewer (5 fewer,12 fewer)	0.54 (0.40 to 0.74)
Rivaroxaban 20 mg q.d.	187	5,254	152	5,215	3.56%	3 fewer* (0 more, 6 fewer)	0.82 (0.66 to 1.01)
TTR ≥ 66%							

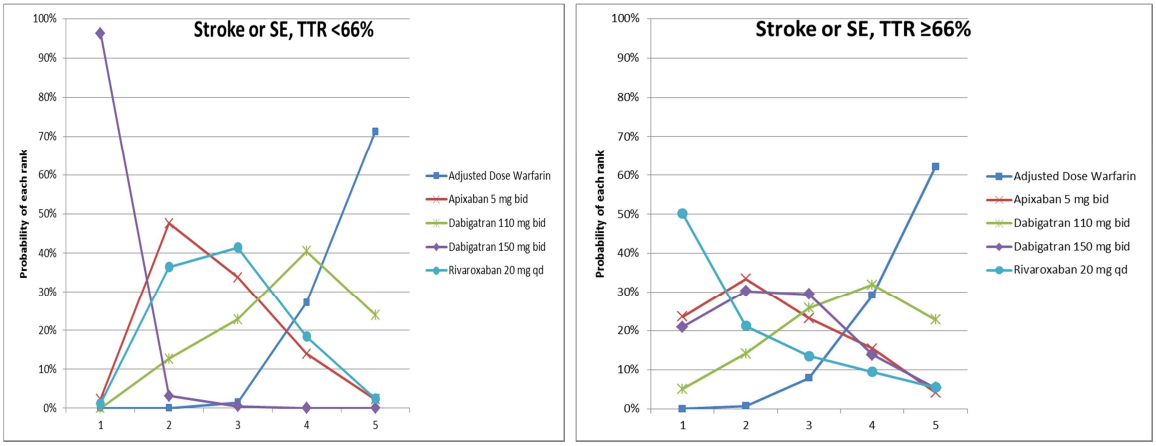
Table 50: Results from Fixed-Effects Bayesian MTC Sub-Group Analysis for All-Cause Stroke/Systemic Embolism Compared with Adjusted-Dose Warfarin by TTR

	Warfarin		NOAC		Warfarin Event Rate	ARR per 1,000 Patients Treated Each Year, Study-Level	Bayesian MTC, Median OR (95% CrI)
	n	N	n	N			
Apixaban 5 mg b.i.d.	109	4,517	87	4,522	2.41%	3 fewer (1 more,5 fewer)	0.80 (0.60 to 1.06)
Dabigatran 110 mg b.i.d.	85	2,996	76	2,956	2.84%	1 fewer (3 more, 5 fewer)	0.91 (0.66 to 1.24)
Dabigatran 150 mg b.i.d.	85	2,996	69	2,998	2.84%	3 fewer (2 more, 6 fewer)	0.81 (0.59 to 1.11)
Rivaroxaban 20 mg q.d.	55	1,826	37	1,676	3.01%	5 fewer* (2 more,10 fewer)	0.73 (0.48 to 1.11)

ARR = absolue risk reduction; b.i.d. = twice daily; CrI = credible interval; MTC = mixed treatment comparison; OR = odds ratio; q.d. = once daily; TTR = time in therapeutic range.
* Safety on treatment population for rivaroxaban sub-groups — ITT data was not available for TTR subgroups

Figure 13 shows the distribution of probabilities, considered from a descriptive statistics perspective, of each treatment being ranked at each of the possible five ranking positions for the Bayesian MTC meta-analysis by TTR subgroup. For TTR< 66%, dabigatran 150 mg has the highest probability of being best at reducing all-cause stroke/SE; apixaban and rivaroxaban have the highest probability of being second and third best, respectively; whereas dabigatran 110 mg and adjusted-dose warfarin have the highest probability of being fourth and fifth best, respectively — the same ordering that was found based on the unadjusted analysis. For TTR ≥ 66%, rivaroxaban has the highest probability of being best; apixaban and dabigatran 150 mg have a similar probability of being second or third best, respectively; whereas dabigatran 110 mg and adjusted-dose warfarin have the highest probability of being fourth and fifth best, respectively (Figure 13).

Figure 13: Rankograms for Fixed-Effects Bayesian MTC for All-Cause Stroke/Systemic Embolism Compared with Adjusted-Dose Warfarin By Time in Therapeutic Range



b.i.d. = twice daily; q.d. = once daily; MTC = mixed treatment comparison; SE = systemic embolism; TTR = time in therapeutic range.

Age

A summary of results from a subgroup analyses by age are reported in Table 51. Odds ratios are derived from Bayesian fixed-effects MTC analyses, whereas absolute risk reductions are based on study-level results. For age < 75 years, dabigatran 150 mg had a strong trend of reducing the odds of all-cause stroke/SE relative to adjusted-dose warfarin (OR [95% CrI]: 0.64 [0.46 to 0.87]), with an absolute risk reduction of 5 fewer per 1,000 treated each year. Relative to adjusted-dose warfarin, the reduction in odds for other treatments ranged from 0.85 to 0.94, with absolute risk reduction ranging from one to five fewer. For age ≥ 75 years, apixaban, dabigatran 150 mg, and rivaroxaban all had strong trends in reducing the odds of all-cause stroke/SE relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for dabigatran 110 mg was 0.89.

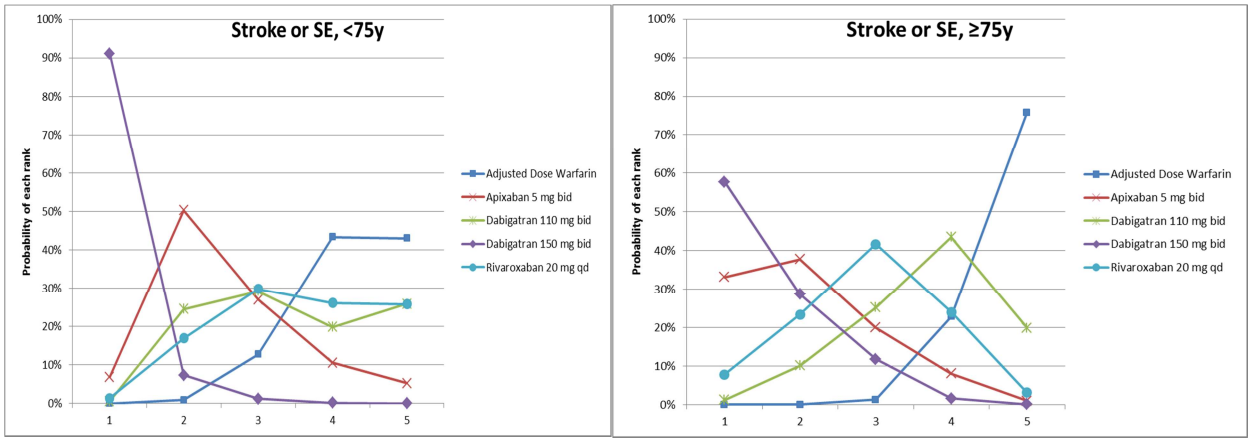
Table 51: Results from Fixed-Effects Bayesian MTC Sub-Group Analysis for All-cause Stroke/Systemic Embolism Compared with Adjusted-Dose Warfarin By Age

	Warfarin		Treatment		Warfarin Event Rate	ARR Per 1,000 Patients Treated Each Year, Study-Level	Bayesian MTC, Median OR (95% CrI)
	n	N	n	N			
Age < 75 y							
Apixaban 5 mg b.i.d.	156	6,253	133	6,270	2.5%	2 fewer (1 more, 4 fewer)	0.85 (0.67 to 1.08)
Dabigatran 110 mg b.i.d.	101	3,599	96	3,666	2.8%	1 fewer (3 more, 4 fewer)	0.94 (0.71 to 1.24)
Dabigatran 150 mg b.i.d.	101	3,599	65	3,610	2.8%	5 fewer (2 fewer, 7 fewer)	0.64 (0.46 to 0.87)
Rivaroxaban 20 mg q.d.	119	4,005	107	3,988	3.0%	1 fewer (5 more, 6 fewer)	0.91 (0.70 to 1.18)
Age ≥ 75 y							
Apixaban 5 mg b.i.d.	109	2,828	79	2,850	3.9%	6 fewer (1 fewer, 10 fewer)	0.72 (0.53 to 0.96)
Dabigatran 110 mg b.i.d.	101	2,423	87	2,349	4.2%	2 fewer (4 more, 7 fewer)	0.89 (0.66 to 1.19)
Dabigatran 150 mg b.i.d.	101	2,423	69	2,466	4.2%	7 fewer (2 fewer, 11 fewer)	0.67 (0.49 to 0.90)
Rivaroxaban 20 mg q.d.	124	3,077	82	3,073	4.0%	6 fewer (1 more, 11 fewer)	0.66 (0.49 to 0.87)

ARR = absolue risk reduction; b.i.d. = twice daily; CrI = credible interval; MTC = mixed treatment comparison; OR = odds ratio; q.d. = once daily; y = years.

Figure 14 shows the distribution of probabilities, considered from a descriptive statistics perspective, of each treatment being ranked at each of the possible five ranking positions for the Bayesian MTC meta-analysis by age sub-groups. For age < 75 years, dabigatran 150 mg has the highest probability of being best at reducing all-cause stroke/SE; apixaban and rivaroxaban have the highest probability of being second and third best, respectively; whereas dabigatran 110 mg and adjusted-dose warfarin have the highest probability of being fourth and fifth best, respectively. For age ≥ 75 years, dabigatran 150 mg and rivaroxaban have a similar probability of being best; apixaban has the highest probability of being third best; whereas dabigatran 110 mg and adjusted-dose warfarin have the highest probability of being fourth and fifth best, respectively (Figure 14).

Figure 14: Rankograms for Fixed-Effects Bayesian MTC for All-Cause Stroke/Systemic Embolism Compared with Adjusted-Dose Warfarin By Age



b.i.d. = twice daily; MTC = mixed treatment comparison; q.d. = once daily; SE = systemic embolism; y = year.

$CHADS_2$ score

A summary of results from a subgroup analysis by $CHADS_2$ score is reported in Table 52. Odds ratios are derived from Bayesian fixed-effects MTC analyses, whereas ARR results are based on study-level results. For $CHADS_2 < 2$, dabigatran 150 was associated with a strong trend to reducing the odds of all-cause stroke/SE relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for apixaban and dabigatran 110 mg was 0.86 and 1.00, respectively. The corresponding ARR were low. For rivaroxaban, results were not available, as no patients with a $CHADS_2 < 2$ were recruited into the study. For $CHADS_2 \geq 2$, apixaban and dabigatran 150 mg were associated with strong trends in reducing the odds of all-cause stroke/SE relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for dabigatran 110 mg and rivaroxaban was 0.89 and 0.88, respectively. The ARR ranged from 2 to 6 for $CHADS_2 \geq 2$.

Table 52: Results from Fixed-Effects Bayesian MTC Sub-Group Analysis for All-Cause Stroke/Systemic Embolism Compared with Adjusted-Dose Warfarin By $CHADS_2$

	Warfarin		Treatment		Warfarin Event Rate	ARR per 1,000 Patients Treated Each Year, Study-Level	Bayesian MTC, Median OR (95% CrI)
	n	N	N	N			
$CHADS_2 < 2$							
Apixaban 5 mg b.id.	51	3,083	44	3,100	1.7%	1 fewer (3 more, 4 fewer)	0.86 (0.57 to 1.29)
Dabigatran 110 mg b.i.d.b.i.d.	40	1,859	42	1,958	2.2%	0 more (6 more, 4 fewer)	1.00 (0.65 to 1.56)
Dabigatran 150 mg b.i.d.	40	1,859	26	1,958	2.2%	4 fewer (0 more, 7 fewer)	0.61 (0.37 to 0.997)
Rivaroxaban 20 mg q.d.	NA	NA	NA	NA	NA		NA
$CHADS_2 \geq 2$							
Apixaban 5 mg b.i.d.	214	5,998	168	6,020	3.6%	4 fewer (1 fewer, 7 fewer)	0.78 (0.64 to 0.96)
Dabigatran 110 mg b.i.d.	162	4,163	141	4,056	3.9%	2 fewer (2 more, 6 fewer)	0.89 (0.71 to 1.12)
Dabigatran 150 mg b.i.d.	162	4,163	108	4,118	3.9%	6 fewer (3 fewer, 9 fewer)	0.67 (0.52 to 0.85)

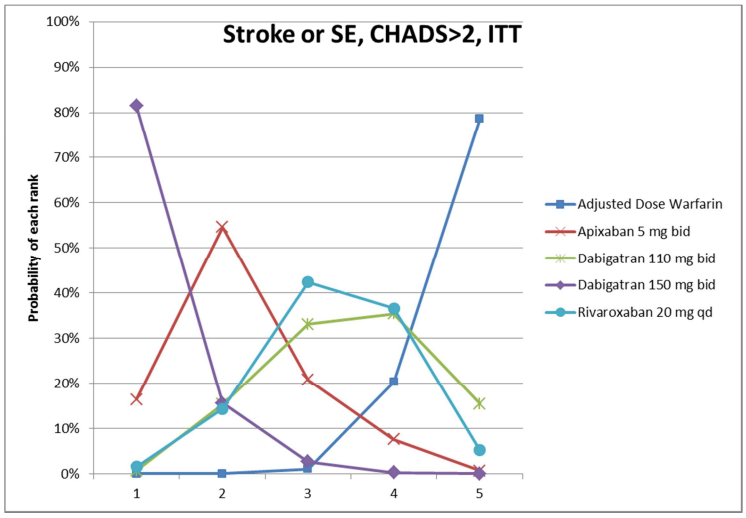
Table 52: Results from Fixed-Effects Bayesian MTC Sub-Group Analysis for All-Cause Stroke/Systemic Embolism Compared with Adjusted-Dose Warfarin By $CHADS_2$

	Warfarin		Treatment		Warfarin Event Rate	ARR per 1,000 Patients Treated Each Year, Study-Level	Bayesian MTC, Median OR (95% CrI)
	n	N	N	N			
Rivaroxaban 20 mg q.d.	306	7,090	269	7,081	4.3%	3 fewer (1 more, 7 fewer)	0.88 (0.75 to 1.04)

ARR = absolue risk reduction; b.i.d. = twice daily; CrI = confidence interval; MTC = mixed treatment comparison; OR = odds ratio; q.d. = once daily; y = years.

Figure 15 shows the distribution of probabilities, considered from a descriptive statistics perspective, of each treatment being ranked at each of the possible five ranking positions based on the Bayesian MTC meta-analysis for the sub-group $CHADS_2 \geq 2$ for the ITT analysis population. For $CHADS_2 \geq 2$ and per ITT population, dabigatran 150 mg has the highest probability of being best at reducing all-cause stroke/SE, apixaban has the highest probability of being second best, rivaroxaban has the highest probability of being third best, whereas dabigatran 110 mg and adjusted-dose warfarin have the highest probability of being fourth and fifth best, respectively (Figure 15).

Figure 15: Rankograms for Fixed-Effects Bayesian MTC for All-Cause Stroke/Systemic Embolism Compared with Adjusted-Dose Warfarin for $CHADS_2 \geq 2$



b.i.d. = twice daily; MTC = mixed treatment comparison; q.d. = once daily; SE = systemic embolism; ITT = intention to treat.

7.12.2 Major Bleeding

7.12.2.1 Individual Study Results

A summary of study level results are shown in Table 53, with information on follow-up time and control event rate provided alongside relative and absolute risks. Apixaban and dabigatran 110 mg achieved statistically significant reductions in major bleed relative to adjusted-dose warfarin (Table 53). The use of apixaban produced the largest effects, with a reduction in odds of major bleed (OR [95% CI]: 0.69 [0.60 to 0.80]) and a corresponding absolue risk reduction of eight fewer events per 100 treated each year.

Table 53: Summary of Study-Level Results for Major Bleeding Compared with Adjusted-Dose Warfarin				
	Mean Or Median Follow-Up	**Warfarin Event Rate**	**OR (95% CI)**	**ARR per 1,000 Patients Treated Each Year, Study-Level**
Apixaban 5 mg b.i.d.	1.8 y	5.1%	0.69 (0.60 to 0.80)	8 fewer (6 fewer to11 fewer)
Dabigatran 110 mg b.i.d.	2 y	7.0%	0.80 (0.69 to 0.93)	7 fewer (2 fewer to 11 fewer)
Dabigatran 150 mg b.i.d.	2 y	7.0%	0.94 (0.81 to 1.08)	2 fewer (3 more to 6 fewer)
Rivaroxaban 20 mg q.d.	Treatment exposure 1.5y; median follow-up,1.9y	5.4%	1.03 (0.89 to 1.19)	1 more (6 more, to 3 fewer)

ARR= absolute risk reduction; CI = confidence interval; OR = odds ratio; y = years.

7.12.2.2 Network meta-analyses

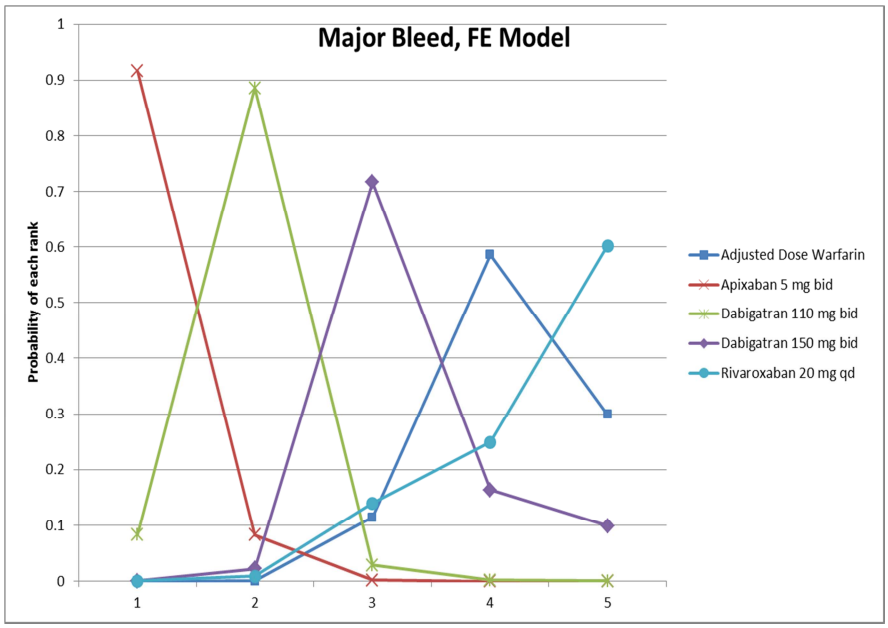
Both Bayesian and frequentist evidence networks were comprised of three RCTs — ARISTOTLE, RE-LY, ROCKET-AF— representing four treatments, each relative to adjusted-dose warfarin (N = 50,276). A summary of unadjusted results for the fixed-effects Bayesian MTC are shown in Table 54, along with model fit statistics. Apixaban and dabigatran 110 mg achieved statistically significant reductions in the odds of major bleed relative to adjusted-dose warfarin. The use of apixaban produced the largest effects, with a reduction in odds of major bleeding (OR [95% CrI]: 0.70 [0.61 to 0.81]) relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for other treatments ranged from 0.81 to 1.03. There were no statistically significant differences between agents, the exception being dabigatran 110 mg versus 150 mg (OR [95% CrI]: 0.81 [0.70 to 0.93]). Data on the probability of an event in the warfarin arm provide a reflection of potential heterogeneity across studies, which are partially adjusted for in Section 8.12.2.3. Complete results from the MTC meta-analysis for all possible comparisons are presented in Table 24. The estimates of effects derived from fixed-effects Bayesian MTC analyses aligned closely with study level results and frequentist network meta-analysis results (see Table 54) in both direction and magnitude. The point estimates for the Bayesian random-effects MTC meta-analysis were similar to those reported in the Bayesian fixed-effects MTC, although the credible intervals were much wider (see Appendix 7.11).

Table 54: Summary of Unadjusted Fixed-Effects Bayesian MTC Results for Major Bleed Compared with Adjusted-Dose Warfarin							
	Warfarin		**NOAC**		**Warfarin Event Rate**	**Bayesian MTC OR (95% CrI)**	**Frequentist GLMM OR (95% CI)**
	N	**N**	**n**	**N**			
Apixaban 5 mg b.i.d.	462	9052	327	9088	5.1%	0.70 (0.61, 0.81)	0.69 (0.50, 0.94)
Dabigatran 110 mg b.i.d.	421	6022	342	6015	7.0%	0.81 (0.70, 0.93)	0.82 (0.59, 1.12)
Dabigatran 150 mg b.i.d.	421	6022	399	6076	7.0%	0.94 (0.82, 1.08)	0.95 (0.70, 1.29)
Rivaroxaban 20 mg q.d.	386	7125	395	7111	5.4%	1.03 (0.89, 1.19)	1.02 (0.75, 1.39)
Model fit statistics for Bayesian MTC	Posterior mean residual deviance (6.99) less than the number of unconstrained data points (7), which is an indication of good model fit						

ARR= absolute risk reduction; CI = confidence interval; CrI = credible interval; GLMM = generalized linear mixed models; MTC = mixed treatment comparison; NOAC = new oral anticoagulant;OR = odds ratio.

Figure 16 shows the distribution of probabilities, considered from a descriptive statistics perspective, of each treatment being ranked at each of the possible five ranking positions for unadjusted Bayesian MTC meta-analyses. Apixaban has the highest probability of being best at reducing all major bleeding. Dabigatran 110 mg and 150 mg have the highest probability of being second and third best, whereas adjusted-dose warfarin and rivaroxaban have the highest probability of being fourth and fifth best, respectively.

Figure 16: Rankogram for Unadjusted Fixed-Effects Bayesian MTC Results for Major Bleeding Compared with Adjusted-Dose Warfarin



b.i.d. = twice daily; FE = fixed effects; MTC = mixed treatment comparison; q.d. = once daily..

7.12.2.3 Sensitivity and sub-group analysis

Time in therapeutic range

A summary of results from a subgroup analyses by TTR are reported in Table 55. Odds ratios were derived from Bayesian fixed-effects MTC meta-analyses, whereas absolute risk reduction results were based on study-level results. For TTR < 66%, apixaban, dabigatran 110 mg, and dabigatran 150 mg were all associated with a strong trend in reducing the odds of major bleeding relative to adjusted-dose warfarin, with absolute risk reduction ranging from 9 to 11 fewer per 1,000 treated each year. Relative to adjusted-dose warfarin, rivaroxaban was associated with a reduction in odds of 0.92, with an absolute risk reduction of two fewer per 1,000 treated each year. For TTR ≥ 66%, apixaban was associated with a strong trend in reducing the odds of major bleeding relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, rivaroxaban had a trend of an increase in the odds of major bleeding (OR [95% CrI]: 1.30 [1.01 to 1.69]), and dabigatran 110 mg and 150 mg had an odds of 0.86 and 1.15, respectively. The absolute risk reduction ranged from six fewer to 11 more per 1,000 treated each year.

Table 55: Results from fixed-effects Bayesian MTC Sub-Group Analysis for Major Bleeding Compared with Adjusted-Dose Warfarin by TTR

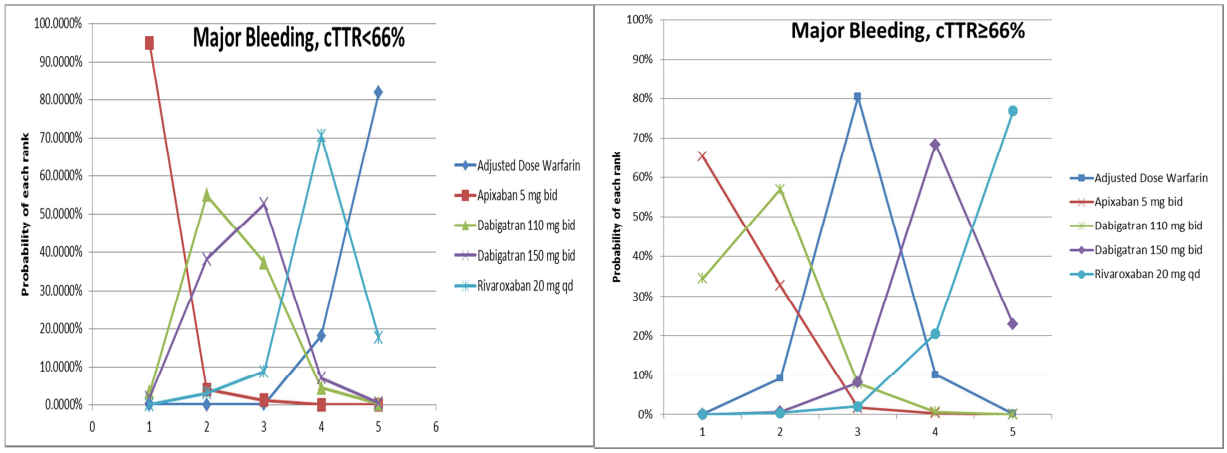
	Warfarin	Treatment	Warfarin	ARR Per 1,000	Bayesian

	N	N	N	N	Event Rate	Patients Treated Each Year, Study-Level	MTC, Median OR (95% CrI)
TTR < 66%							
Apixaban 5 mg b.i.d.	217	4,530	125	4,517	4.8%	11 fewer (8 fewer, 14 fewer)	0.57 (0.46 to 0.71)
Dabigatran 110 mg b.i.d.	225	3,018	171	3,021	7.5%	9 fewer (3 fewer, 14 fewer)	0.75 (0.61 to 0.92)
Dabigatran 150 mg b.i.d.	225	3,018	176	3,035	7.5%	9 fewer (2 fewer, 14 fewer)	0.77 (0.63 to 0.94)
Rivaroxaban 20 mg q.d.	271	5,284	249	5,252	5.1%	2 fewer (3 more, 6 fewer)	0.92 (0.78 to 1.10)
TTR ≥ 66%							
Apixaban 5 mg b.i.d.	245	4,517	201	4,522	5.4%	6 fewer (0 more, 10 fewer)	0.82 (0.67 to 0.99)
Dabigatran 110 mg b.i.d.	194	2996	166	2,956	6.5%	4 fewer (2 more, 10 fewer)	0.86 (0.70 to 1.07)
Dabigatran 150 mg b.i.d.	194	2,996	221	2,998	6.5%	5 more (13 more, 2 fewer)	1.15 (0.95 to 1.41)
Rivaroxaban 20 mg q.d.	115	1,839	135	1,689	6.3%	11 more (25 more, 0 more)	1.30 (1.01 to 1.69)

ARR= absolute risk reduction; CrI = credible interval; MTC = mixed treatment comparison; OR = odds ratio; TTR = time in therapeutic range.

Figure 17 shows the distribution of probabilities, considered from a descriptive statistics perspective, of each treatment being ranked at each of the possible five ranking positions for the TTR sub-groups. For TTR < 66%, apixaban has the highest probability of being best at reducing major bleeding; dabigatran 110 mg and dabigatran 150 mg have the highest probability of being second and third best, respectively; whereas rivaroxaban and adjusted-dose warfarin have the highest probability of being fourth and fifth best, respectively. For TTR ≥ 66%, apixaban has the highest probability of being best at reducing major bleeding; dabigatran 110 mg and adjusted-dose warfarin have the highest probability of being second and third best, respectively; whereas dabigatran 150 mg and rivaroxaban have the highest probability of being fourth and fifth best, respectively (Figure 17).

Figure 17: Rankograms for Fixed-Effects Bayesian MTC for All-Cause Stroke/Systemic Embolism Compared with Adjusted-Dose Warfarin by Time in Therapeutic Range



b.i.d. = twice daily; MTC = mixed treatment comparison; q.d. = once daily; cTTR = centre time in therapeutic range.

Age

A summary of the results from a subgroup analyses by age are reported in Table 56. Odds ratios are derived from Bayesian fixed-effects MTC meta-analyses, whereas absolute risk reduction results are based on study-level results. For age < 75 years, apixaban, dabigatran 110 mg and dabigatran 150 mg all were associated with a strong trend in reducing the odds of major bleeding relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for rivaroxaban was 0.93. The absolute risk reductions ranged between two and eleven fewer per 1,000 treated each year relative to adjusted-dose warfarin. For age ≥ 75 years, apixaban was associated with a strong trend in reducing the odds of major bleeding relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the other treatments were associated with an odds ranging from 1.03 to 1.20. With the exception of apixaban, the benefits diminished for age ≥ 75 years compared to age < 75 years, with absolute risk reduction ranging from 15 fewer to eight more per 1,000 treated each year for age ≥ 75 years.

Table 56: Results from Fixed-Effects Bayesian MTC Sub-Group Analysis for Major Bleeding Compared with Adjusted-Dose Warfarin By Age

	Warfarin		Treatment		Warfarin Event Rate	ARR Per 1,000 Patients Treated Each Year, Study-Level	Bayesian MTC, Median OR (95% CrI)
	N	N	n	N			
Age < 75 y							
Apixaban 5 mg b.i.d.	238	6224	176	6238	3.8%	6 fewer (2 fewer, 8 fewer)	0.73 (0.60, 0.89)
Dabigatran 110 mg b.i.d.	215	3599	138	3666	6.0%	11 fewer (7 fewer, 15 fewer)	0.62 (0.50, 0.77)
Dabigatran 150 mg b.i.d.	215	3599	153	3610	6.0%	9 fewer (4 fewer,13 fewer)	0.70 (0.57, 0.87)
Rivaroxaban 20 mg q.d.	207	4005	192	3988	5.2%	2 fewer (4 more, 8 fewer)	0.93 (0.76, 1.14)
Age ≥75 y							

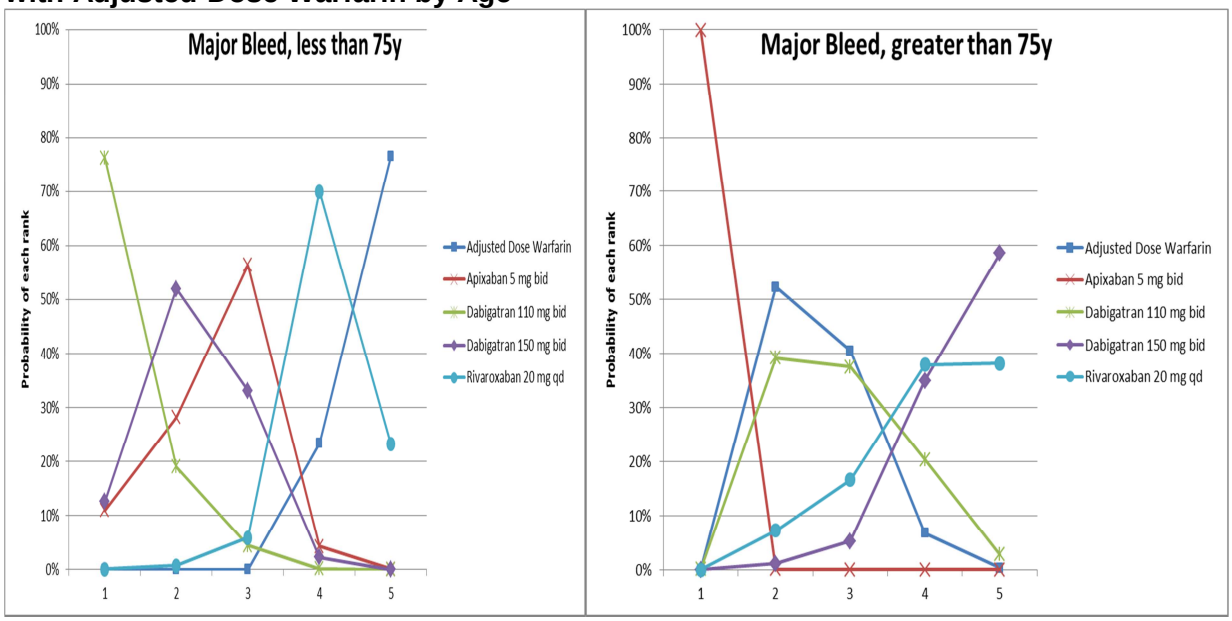
Table 56: Results from Fixed-Effects Bayesian MTC Sub-Group Analysis for Major Bleeding Compared with Adjusted-Dose Warfarin By Age

	Warfarin		Treatment		Warfarin Event Rate	ARR Per 1,000 Patients Treated Each Year, Study-Level	Bayesian MTC, Median OR (95% CrI)
	N	N	n	N			
Apixaban 5 mg b.i.d.	224	2828	151	2850	7.9%	15 fewer (8 fewer, 21 fewer)	0.65 (0.53, 0.81)
Dabigatran 110 mg b.i.d.	206	2423	204	2349	8.5%	1 more (10 more, 7 fewer)	1.03 (0.84, 1.26)
Dabigatran 150 mg b.i.d.	206	2423	246	2466	8.5%	8 more (18 more, 0 more)	1.20 (0.99, 1.45)
Rivaroxaban 20 mg q.d.	179	3077	203	3073	5.8%	5 more (14 more, 2 fewer)	1.15 (0.94, 1.42)

ARR= absolute risk reduction; CrI = credible interval; MTC = mixed treatment comparison; OR = odds ratio; y = years.

Figure 18 shows the distribution of probabilities, considered from a descriptive statistics perspective, of each treatment being ranked at each of the possible five ranking positions for subgroup analyses by age. For age < 75 years, dabigatran 110 mg has the highest probability of being best at reducing major bleeding; dabigatran 150 mg and apixaban have the highest probability of being second and third best, respectively; whereas rivaroxaban and adjusted-dose warfarin have the highest probability of being fourth and fifth best, respectively. For age ≥ 75 years, apixaban has the highest probability of being best at reducing major bleeding, adjusted-dose warfarin has the highest probability of being second best, whereas dabigatran 110 mg, rivaroxaban and dabigatran 150 mg appear to have the highest likelihood of being third, fourth, and fifth best, respectively (Figure 18).

Figure 18: Rankograms for Fixed-Effects Bayesian MTC for Major Bleeding Compared with Adjusted-Dose Warfarin by Age



b.i.d. = twice daily; MTC = mixed treatment comparison; q.d. = once daily;y = years.

$CHADS_2$ Score

A summary of results from subgroup analyses by $CHADS_2$ are reported in Table 57. The ORs are derived from Bayesian fixed-effects MTC meta-analyses, absolute risk reduction results are based on study-level

results. For $CHADS_2 < 2$, apixaban and dabigatran 110 mg had a strong trend in reducing the odds of major bleeding relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for dabigatran 150 mg was 0.77. The absolute risk reduction s ranged from 7 to 10 fewer per 1,000 patients treated each year relative to adjusted-dose warfarin. Results were not available for rivaroxaban, as patients with $CHADS_2 < 2$ were not included in the study. For $CHADS_2 \geq 2$, apixaban was associated with a strong trend in reducing the odds of major bleeding relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for all treatments ranged from 0.74 to 1.03. The absolute risk reduction ranged from eight fewer to one more per 1,000 patients treated each year for $CHADS_2 \geq 2$.

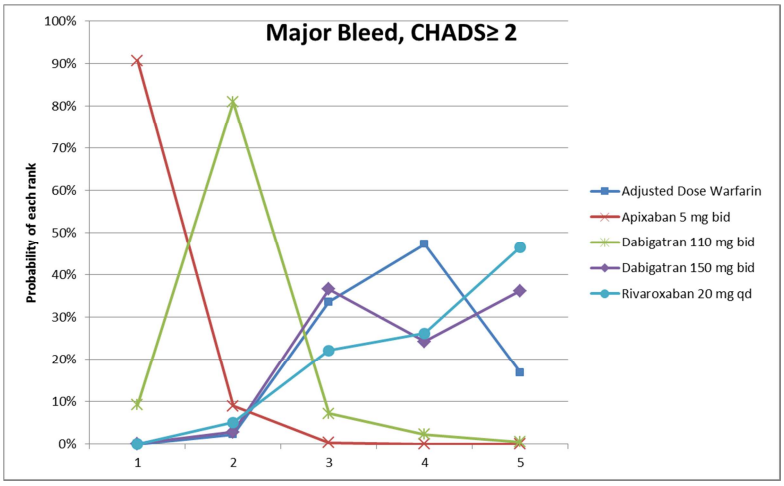
Table 57: Results from Fixed-Effects Bayesian MTC Sub-Group Analysis for Major Bleeding Compared with Adjusted-Dose Warfarin by $CHADS_2$

	Warfarin		Treatment				
	N	N	n	N	Warfarin Event Rate	ARR Per 1,000 Patients Treated Each Year, Study-Level	Bayesian MTC, Median OR (95% CrI)
$CHADS_2 < 2$							
Apixaban 5 mg b.i.d.	126	3,083	76	3,100	4.1%	9 fewer (5 fewer, 13 fewer)	0.59 (0.44 to 0.79)
Dabigatran 110 mg b.i.d.	98	1,707	69	1,809	5.7%	10 fewer (3 fewer, 15 fewer)	0.65 (0.48 to 0.89)
Dabigatran 150 mg b.i.d.	98	1,707	81	1,815	5.7%	7 fewer (1 more, 12 fewer)	0.77 (0.57 to 1.04)
Rivaroxaban 20 mg q.d.	NA	NA	NA	NA	NA	NA	NA
$CHADS_2 \geq 2$							
Apixaban 5 mg b.i.d.	336	5,998	251	6,020	5.6%	8 fewer (4 fewer, 12 fewer)	0.74 (0.62 to 0.87)
Dabigatran 110 mg b.i.d.	316	4,160	268	4,054	7.6%	5 fewer (1 more, 10 fewer)	0.87 (0.73 to 1.02)
Dabigatran 150 mg b.i.d.	316	4,160	315	4,115	7.6%	0 more (7 more, 5 fewer)	1.01 (0.86 to 1.19)
Rivaroxaban 20 mg q.d.	386	7,125	395	7,111	5.4%	1 more (6 more, 3 fewer)	1.03 (0.89 to 1.19)

ARR= absolute risk reduction; CrI = credible interval; MTC = mixed treatment comparison; NA = not applicable; OR = odds ratio.

Figure 19 shows the distribution of probabilities, considered from a descriptive statistics perspective, of each treatment being ranked at each of the possible five ranking positions for $CHADS_2 \geq 2$. Apixaban has the probability of being best at reducing major bleeding; dabigatran 110 mg has the highest probability of being second best; whereas dabigatran 150 mg, adjusted-dose warfarin, and rivaroxaban have the highest probability of being third, fourth, and fifth best, respectively (Figure 19).

Figure 19: Rankograms for Fixed-Effects Bayesian MTC for Major Bleeding Compared with Adjusted-Dose Warfarin for $CHADS_2 \geq 2$



b.i.d. = twice daily; MTC = mixed treatment comparison; q.d. = once daily.

7.12.3 All-cause mortality

7.12.3.1 Individual Study Results

A summary of study level results are shown in Table 58, with information on follow-up time and control event rate provided alongside relative and absolute risks including the number needed to treat. Apixaban approached a statistically significant reduction in all-cause mortality relative to adjusted-dose warfarin (OR [95% CI]: 0.89 [0.79 to 0.998]) with corresponding absolute risk reductions of four fewer deaths per 1,000 treated each year relative to adjusted-dose warfarin. Relative to adjusted-dose warfarin, the reduction in odds for dabigatran 110 mg, apixaban 5 mg, and rivaroxaban 20 mg ranged from 0.88 to 0.92, with absolute risks ranging from three to four fewer.

Table 58: Summary of Study-Level Results for All-Cause Mortality Compared with Adjusted-Dose Warfarin

	Mean Or Median Follow-Up	Warfarin Event Rate	OR (95% CI)	ARR per 1,000 Patients Treated Each Year, Study-Level
Apixaban 5 mg b.i.d.	1.8 y	7.4%	0.89 (0.79 to 0.998)	4 fewer (0 more, 8 fewer)
Dabigatran 110 mg b.i.d.	2 y	8.1%	0.91 (0.8 to 1.04)	3 fewer (2 more, 8 fewer)
Dabigatran 150 mg b.i.d.	2 y	8.1%	0.88 (0.77 to 1.01)	4 fewer (0 more, 9 fewer)
Rivaroxaban 20 mg q.d.	Treatment exposure 1.6 y; median follow-up,1.9 y	9.4%	0.92 (0.82 to 1.04)	4 fewer (2 more, 8 fewer)

ARR= absolute risk reduction; CI = confidence interval; OR = odds ratio; y = years.

7.12.3.2 Network meta-analyses

Both Bayesian and frequentist evidence networks were comprised of three RCTs — ARISTOTLE, RE-LY, ROCKET-AF — representing four treatments, each relative to adjusted-dose warfarin (N = 50,276). A summary of unadjusted results for the fixed-effects Bayesian MTC are shown in Table 59, along with model fit statistics. There were no statistically significant differences between agents and adjusted-dose warfarin; however, apixaban approached statistical significance (OR [95% CrI]: 0.90 [0.80 to 1.00]). Data on probability of an event in the warfarin arm is also provided to reflect potential heterogeneity across studies. The estimates of effects derived from fixed-effects Bayesian MTC analyses aligned closely with study level results and frequentist network meta-analysis results (see Table 59) in both direction and magnitude. The point estimates for the Bayesian random-effects MTC meta-analysis were similar to those reported in the Bayesian fixed-effects MTC, although the credible intervals were much wider (see Appendix 7.11).

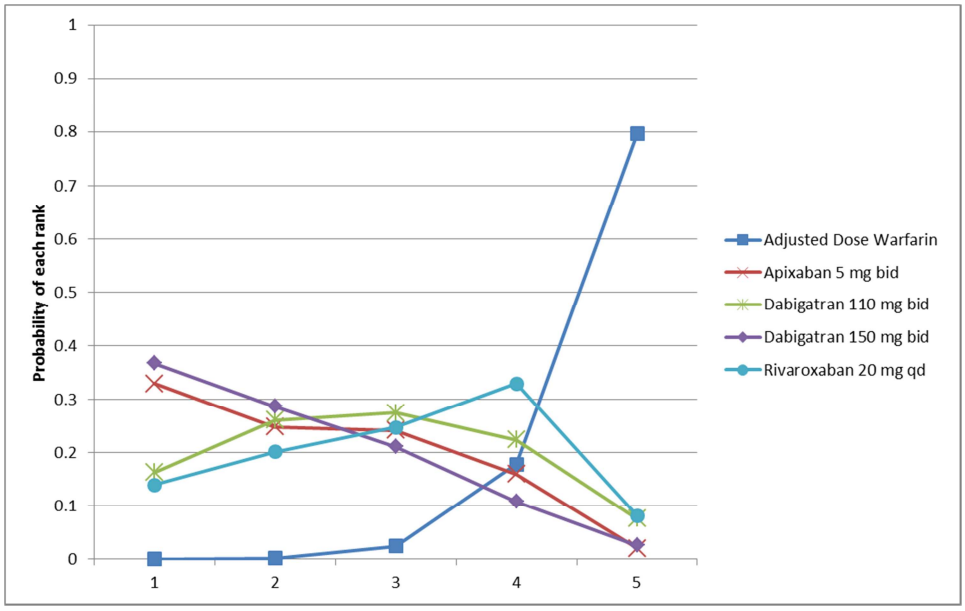
Table 59: Summary of Unadjusted Fixed-Effects Bayesian MTC Results for All-cause Mortality Compared with Adjusted-Dose Warfarin

	Warfarin		NOAC		Warfarin Event Rate	Bayesian MTC OR (95% CrI)	Frequentist GLMM OR (95% CI)
	n	N	N	N			
Apixaban 5 mg b.i.d.	669	9,081	603	9,120	7.4%	0.89 (0.79 to 0.997)	0.89 (0.69 to 1.15)
Dabigatran 110 mg b.i.d.	487	6,022	446	6,015	8.1%	0.91 (0.80 to1.04)	0.91 (0.68 to 1.22)
Dabigatran 150 mg b.i.d.	487	6,022	438	6,076	8.1%	0.88 (0.77 to1.01)	0.89 (0.66 to 1.19)
Rivaroxaban 20 mg q.d.	667	7,082	619	7,061	9.4%	0.92 (0.82 to1.04)	0.82 (0.55 to 1.24)

CrI = credible interval; GLMM = generalized linear mixed models; MTC = mixed treatment comparison; NOAC = new oral anticoagulant; OR = odds ratio.

Figure 20 shows the distribution of probabilities, considered from a descriptive statistics perspective, of each treatment being ranked at each of the possible five ranking positions for unadjusted Bayesian MTC meta-analyses. Dabigatran 150 mg and apixaban had the highest probability of being best and second best at reducing all-cause mortality. Dabigatran 110 mg and rivaroxaban had the highest probability of being third and fourth best, whereas adjusted-dose warfarin had the highest probability of being fifth best.

Figure 20: Rankogram for Unadjusted Fixed-Effects Bayesian MTC Results for All-Cause Mortality



b.i.d. = twice daily; MTC = mixed treatment comparison; q.d. = once daily.

7.12.4 Intracranial bleeding (includes intracerebral hemorrhage)

7.12.4.1 Individual study results

A summary of study level results are shown in Table 60 ,with information on follow-up time and control event rate provided alongside relative and absolute risks including the number needed to treat benefit. All treatments were associated with a statistically significant reduction in intracranial bleeding with ORs ranging from 0.30 to 0.65 and corresponding absolute risk reductions ranging from three to five fewer per 1,000 treated each year.

Table 60: Summary of Study-level Results for Intracranial Bleeding Compared with Adjusted-Dose Warfarin

	Mean Or Median Follow-Up	Warfarin Event Rate	OR (95% CI)	ARR per 1,000 patients Treated Each Year, Study-Level
Apixaban 5 mg b.i.d.	1.8 y	1.3%	0.42 (0.30, 0.58)	4 fewer (3 fewer, 5 fewer)
Dabigatran 110 mg b.i.d.	2 y	1.5%	0.3 (0.19, 0.46)	5 fewer (4 fewer, 6 fewer)
Dabigatran 150 mg b.i.d.	2 y	1.5%	0.41 (0.28, 0.61)	4 fewer (3 fewer, 5 fewer)
Rivaroxaban 20 mg q.d.	treatment exposure 1.6y;	1.2%	0.65 (0.46, 0.92)	3 fewer (1fewer, 4 fewer)

Table 60: Summary of Study-level Results for Intracranial Bleeding Compared with Adjusted-Dose Warfarin				
	Mean Or Median Follow-Up	**Warfarin Event Rate**	**OR (95% CI)**	**ARR per 1,000 patients Treated Each Year, Study-Level**
	median follow-up,1.9 y			

ARR= absolute risk reduction; CI = confidence interval; NOAC = new oral anticoagulant; OR = odds ratio; y = years.

7.12.4.2 Network meta-analyses

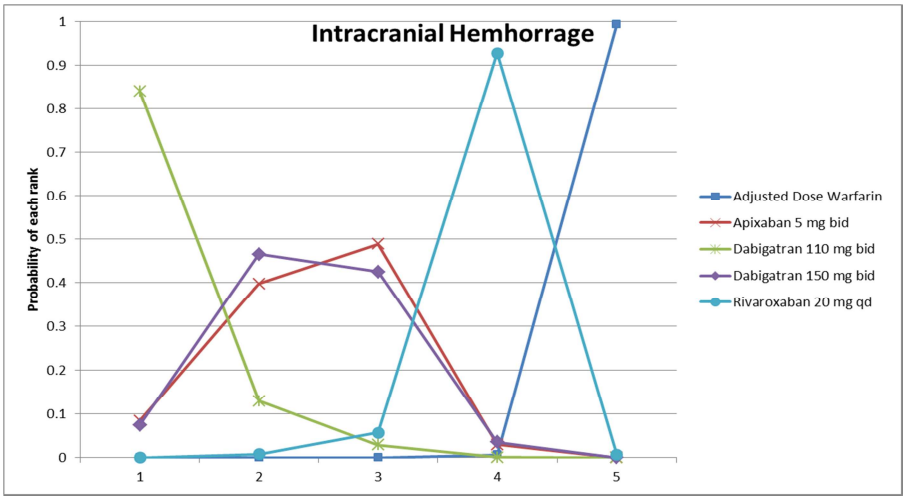
Both Bayesian and frequentist evidence networks were comprised of 3 RCTs — ARISTOTLE, RE-LY, ROCKET-AF — representing four treatments, each relative to adjusted-dose warfarin (N = 50,276). A summary of unadjusted results for the fixed-effects Bayesian MTC are shown in Table 61, along with model fit statistics. All treatments were associated with a statistically significant difference in intracranial bleeding compared with adjusted-dose warfarin, with ORs ranking from 0.30 to 0.66. Data on probability of an event in the warfarin arm is also provided to reflect potential heterogeneity across studies. The estimates of effect derived from fixed-effects Bayesian MTC analyses aligned closely with study level results and frequentist network meta-analysis results (see Table 61) in both direction and magnitude. The point estimates for the Bayesian random-effects MTC meta-analysis were similar to those reported in the Bayesian fixed-effects MTC, although the credible intervals were much wider (see Appendix 7.11).

Table 61: Summary of Unadjusted Fixed-Effects Bayesian MTC Results for Intracranial Bleeding Compared with Adjusted-Dose Warfarin							
	Warfarin		**NOAC**		**Warfarin Event Rate**	**Bayesian MTC OR (95% CrI)**	**Frequentist GLMM OR (95% CI)**
	n	**N**	**N**	**N**			
Apixaban 5 mg b.i.d.	122	9,052	52	9,088	1.3%	0.42 (0.30 to 0.58)	0.43 (0.22 to 0.82)
Dabigatran 110 mg b.i.d.	90	6,022	27	6,015	1.5%	0.30 (0.19 to 0.45)	0.33 (0.14 to 0.79)
Dabigatran 150 mg b.i.d.	90	6,022	38	6,076	1.5%	0.42 (0.28 to 0.60)	0.46 (0.22 to 0.98)
Rivaroxaban 20 mg q.d.	84	7,125	55	7,111	1.2%	0.66 (0.47 to 0.92)	0.59 (0.31 to 1.12)
Model fit statistics for Bayesian MTC	Posterior mean residual deviance (7.00) same as the number of unconstrained data points (7), which is an indication of good model fit						

CrI = credible interval; CI = confidence interval; GLMM = generalized linear mixed models; MTC = mixed treatment comparison; NOAC = new oral anticoagulant; OR = odds ratio.

Figure 21 shows the distribution of probabilities, considered from a descriptive statistics perspective, of each treatment being ranked at each of the possible five ranking positions for unadjusted Bayesian MTC meta-analyses. Dabigatran 110 mg had the highest probability of being associated with reduced intracranial bleeding. Dabigatran 150 mg and apixaban were second and third best, whereas rivaroxaban and adjusted-dose warfarin were fourth and fifth best, respectively.

Figure 21: Rankogram for Unadjusted Fixed-Effects Bayesian MTC Results for Intracranial Bleeding



b.i.d. = twice daily; MTC = mixed treatment comparison; q.d. = once daily.

7.12.5 Myocardial infarction

7.12.5.1 Individual study results

A summary of study level results are shown in Table 62, with information on follow-up time and control event rate provided alongside relative and absolute risks including the number needed to treat to benefit . No treatments were associated with a statistically significant reduction in MI relative to adjusted-dose warfarin. The ORs for other treatments ranged from 0.88 to 1.31, with corresponding absolute risk reductions ranging from one fewer to two more per 1,000 treated per year.

Table 62: Summary of Study-Level Results for Myocardial Infarction Compared with Adjusted-Dose Warfarin

	Mean or Median Follow-Up	Warfarin Event Rate	OR (95% CI)	ARR per 1,000 Patients Treated Each Year, Study-Level
Apixaban 5 mg b.i.d.	1.8 y	1.1%	0.88 (0.66 to 1.17)	1 fewer (1 more, 2 fewer)
Dabigatran 110 mg b.i.d.	2 y	1.2%	1.31 (0.97 to 1.78)	2 more (5 more, 0 more)
Dabigatran 150 mg b.i.d.	2 y	1.2%	1.29 (0.95 to 1.74)	2 more (5 more, 0 more)
Rivaroxaban 20 mg q.d.	Trt exposure 1.5y; median follow-up,1.9y	1.8%	0.80* (0.62 to1.04)	2 fewer (1 more, 4 fewer)

ARR= absolute risk reduction; CI = confidence interval; OR = odds ratio.
*Safety on treatment for rivaroxaban. Mahaffey 2010[78] (AHA) reports ITT HR in ROCKET AF for MI as 0.91 (0.72-1.16)

7.12.5.2 Network meta-analyses

Both Bayesian and frequentist evidence networks were comprised of 3 RCTs — ARISTOTLE, RE-LY, ROCKET-AF — representing four treatments, each relative to adjusted-dose warfarin (N = 50,276). A

summary of unadjusted results for the fixed-effects Bayesian MTC are shown in Table 63, along with model fit statistics. No treatments were associated with a statistically significant reduction in MI relative to adjusted-dose warfarin. The ORs for treatments ranged from 0.80 to 1.32. Data on probability of an event in the warfarin arm is also provided to reflect potential heterogeneity across between studies. The estimates of effects derived from fixed-effects Bayesian MTC analyses aligned closely with study level results and frequentist network meta-analysis results (see Table 63) in both direction and magnitude. The point estimates for the Bayesian random-effects MTC meta-analysis were similar to those reported in the Bayesian fixed-effects MTC, although the credible intervals were much wider (see Appendix 7.11).

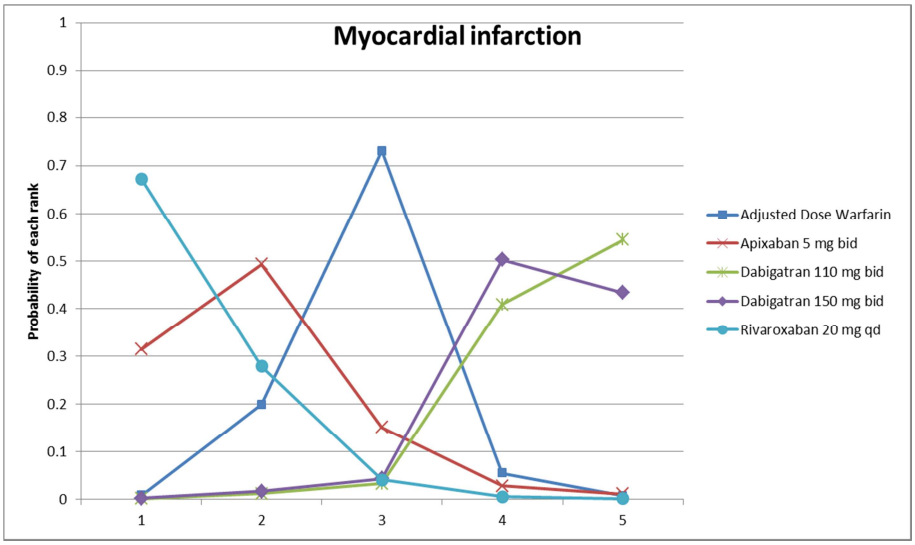
Table 63: Summary of Unadjusted Fixed-Effects Bayesian MTC Results for Myocardial Infarction Compared with Adjusted-Dose Warfarin

	Warfarin		NOAC		Warfarin Event Rate	Bayesian MTC OR (95% CrI)	Frequentist GLMM OR (95% CI)
	n	N	N	N			
Apixaban 5 mg b.i.d.	102	9081	90	9120	1.1%	0.88 (0.66 to 1.17)	0.85 (0.46 to 1.56)
Dabigatran 110 mg b.i.d.	75	6022	98	6015	1.2%	1.32 (0.98 to 1.79)	1.29 (0.68 to 2.43)
Dabigatran 150 mg b.i.d.	75	6022	97	6076	1.2%	1.29 (0.96 to 1.75)	1.26 (0.67 to 2.39)
Rivaroxaban 20 mg q.d.	126	7082	101	7061	1.8%	0.80 (0.62 to 1.05)*	0.83 (0.47 to 1.47)
Model fit statistics for Bayesian MTC	Posterior mean residual deviance (7.00) less than the number of unconstrained data points (7), which is an indication of good model fit						

CI = confidence interval; CrI= credible interval; GLMM = generalized linear mixed models; MTC = mixed treatment comparison; NOAC = new oral anticoagulant; OR = odds ratio.
*Safety on treatment for rivaroxaban. Mahaffey 2010[78] (AHA) reports ITT HR in ROCKET AF for MI as 0.91 (0.72-1.16)

Figure 22 shows the distribution of probabilities, considered from a descriptive statistics perspective, of each treatment being ranked at each of the possible five ranking positions for unadjusted Bayesian MTC meta-analyses. Rivaroxaban and apixaban had the highest probability of being best and second best at reducing MI, adjusted-dose warfarin had the highest probability of being third best, and dabigatran 150 mg and dabigatran 110 mg had the highest probability of being fourth and fifth best, respectively.

Figure 22: Rankogram for Unadjusted Fixed-effects Bayesian MTC Results for Myocardial Infarction*



b.i.d. = twice daily; MTC = mixed treatment comparison; q.d. = once daily.
*Safety on treatment for rivaroxaban. Mahaffey 2010[78] (AHA) reports ITT HR in ROCKET AF for MI as 0.91 (0.72-1.16)

7.12.6 Major gastrointestinal bleeding

7.12.6.1 Individual study results

A summary of study level results are shown in Table 64, with information on follow-up time and control event rate provided alongside relative and absolute risks. No treatments were associated with a statistically significant reduction in major GI bleeding relative to adjusted-dose warfarin. However, dabigatran 150 mg (OR [95% CI]: 1.45 [1.13 to 1.85]) and rivaroxaban (OR [95% CI]: 1.60 [1.29 to 1.98]) were associated with a statistically significant increase in major GI bleeding, with corresponding absolute risk increase of four and eight events per 1,000 treated per year, respectively.

Table 64: Summary of Study-Level Results for Major Gastrointestinal Bleeding Compared with Adjusted-Dose Warfarin

	Mean or Median Follow-Up	Warfarin Event Rate	OR (95% CI)	ARR per 1,000 Patients Treated Each Year, Study-Level
Apixaban 5 mg b.i.d.	1.8 y	1.3%	0.88 (0.67 to 1.14)	1 fewer (1 more, 2 fewer)
Dabigatran 110 mg b.i.d.	2 y	1.9%	1.08 (0.83 to 1.40)	1 more (4 more, 1 fewer)
Dabigatran 150 mg b.i.d.	2 y	1.9%	1.45 (1.13 to 1.85)	4 more (8 more, 1 more)
Rivaroxaban 20 mg q.d.	Treatment exposure 1.6y; median follow-up,1.9y	2.0%	1.60 (1.29 to1.98)	8 more (13 more, 4 more)

ARR= absolute risk reduction; b.i.d. = twice daily; CI = confidence interval; OR = odds ratio; q.d. = once daily; y = years.

7.12.6.2 Network meta-analyses

Both Bayesian and frequentist evidence networks were comprised of three RCTs — ARISTOTLE, RE-LY, ROCKET-AF — representing four treatments, each relative to adjusted-dose warfarin (N = 50,276). A summary of unadjusted results for the fixed-effects Bayesian MTC are shown in Table 65, along with model fit statistics. No treatments were associated with a statistically significant reduction in major GI bleeding relative to adjusted-dose warfarin. However, dabigatran 150 mg (OR [95% CrI]: 0.1.45 [1.14 to 1.86]) and rivaroxaban (OR [95% CrI]: 1.61 [1.30 to 1.99]) were associated with a statistically significant increase in major GI bleeding. Data on probability of an event in the warfarin arm is also provided to reflect potential heterogeneity across studies. The estimates of effect derived from fixed-effects Bayesian MTC analyses aligned closely with study level results and frequentist network meta-analysis results (see Table 65) in both direction and magnitude. The point estimates for the Bayesian random-effects MTC meta-analysis were similar to those reported in the Bayesian fixed-effects MTC, although the credible intervals were much wider (see Appendix 7.11).

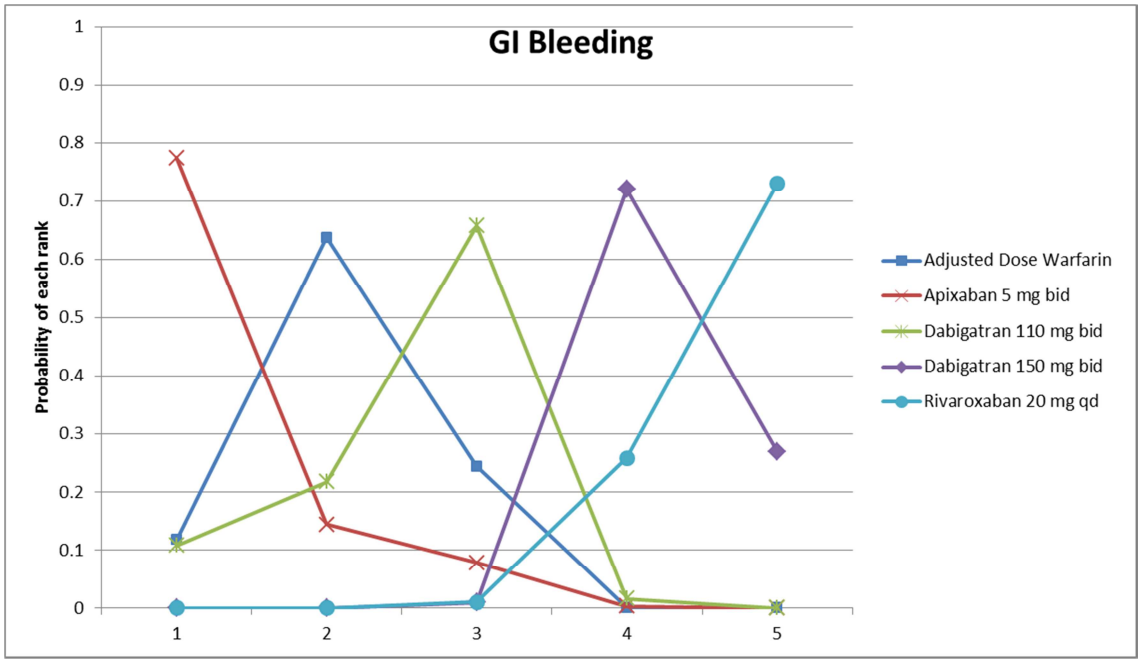
Table 65: Summary of Unadjusted Fixed-Effects Bayesian MTC Results for Major Gastrointestinal Bleeding Compared with Adjusted-Dose Warfarin

	Warfarin		NOAC		Warfarin Event Rate	Bayesian MTC OR (95% CrI)	Frequentist GLMM OR (95% CI)
	n	N	N	N			
Apixaban 5 mg b.i.d.	119	9052	105	9088	1.3%	0.88 (0.68 to 1.15)	0.85 (0.48 to 1.49)
Dabigatran 110 mg b.i.d.	111	5998	119	5983	1.9%	1.08 (0.84 to 1.40)	1.11 (0.65 to 1.88)
Dabigatran 150 mg b.i.d.	111	5998	161	6059	1.9%	1.45 (1.14 to 1.86)	1.52 (0.93 to 2.48)
Rivaroxaban 20 mg q.d.	140	7125	221	7111	2.0%	1.61 (1.30 to 1.99)	1.50 (0.95 to 2.35)
Model fit statistics for Bayesian MTC	Posterior mean residual deviance (6.99) is less than the number of unconstrained data points (7), which is an indication of good model fit						

b.i.d. = twice daily; CI = confidence interval; Crl= credible interval; GLMM = generalized linear mixed models; MTC = mixed treatment comparison; NOAC = new oral anticoagulant; OR = odds ratio; q.d. = once daily.

Figure 23 shows the distribution of probabilities, considered from a descriptive statistics perspective, of each treatment being ranked at each of the possible five ranking positions for unadjusted Bayesian MTC meta-analyses. Apixaban and adjusted-dose warfarin had the highest probability of being best and second best at reducing major GI bleeding. Dabigatran 110 mg and 150 had the highest probability of being third and fourth best, respectively, whereas rivaroxaban had the highest probability of being fifth best.

Figure 23: Rankogram for Unadjusted Fixed-Effects Bayesian MTC Results for Major Gastrointestinal Bleeding



b.i.d. = twice daily; MTC = mixed treatment comparison; q.d. = once daily

7.12.7 Cardiovascular mortality, life-threatening bleeds, ischemic/uncertain stroke, or systemic embolism

There was insufficient information on ischemic/uncertain stroke or SE, life-threatening bleeds, and cardiovascular mortality for network meta-analyses to be conducted. No studies reported information on ischemic/uncertain stroke or systemic embolism. No data was available on life-threatening bleeds in ARISTOTLE and ROCKET-AF. In RE-LY, 1.85% of patients who received warfarin had a life-threatening bleed compared with 1.24% and 1.45% of patients receiving dabigatran 110 mg and 150 mg, respectively. Raw data was not available for cardiovascular mortality from ARISTOTLE. The risk of cardiovascular mortality was lower in patients receiving dabigatran 110 mg (2.43%) and 150 mg (2.28%) in RE-LY, compared with those receiving warfarin (2.69%). In ROCKET-AF, the risk of cardiovascular mortality was lower in patients receiving rivaroxaban (2.41%) compared with those receiving warfarin (2.73%).

7.13 Random-Effects Frequentist GLMM Network Meta-analysis

Table 66: Summary of Results from Random-Effects Frequentist GLMM Network Meta-analysis Versus Adjusted-Dose Warfarin — OR (95% CI) for Each Outcome

	Stroke/SE	Major Bleeding	All-cause Mortality	Intracranial Bleeding	Major GI Bleeding	Myocardial Infarction
Apixaban 5 mg b.i.d.	0.76 (0.52 to 1.10)	0.69 (0.50 to 0.94)	0.89 (0.69 to 1.15)	0.43 (0.22 to 0.82)	0.85 (0.48 to 1.49)	0.85 (0.46 to 1.56)
Dabigatran 110 mg b.i.d.	0.93 (0.62 to 1.39)	0.82 (0.59 to 1.12)	0.91 (0.68 to 1.22)	0.33 (0.14 to 0.79)	1.11 (0.65 to 1.88)	1.29 (0.68 to 2.43)
Dabigatran 150 mg b.i.d.	0.66 (0.42 to 1.04)	0.95 (0.70 to 1.29)	0.89 (0.66 to 1.19)	0.46 (0.22 to 0.98)	1.52 (0.93 to 2.48)	1.26 (0.67 to 2.39)
Rivaroxaban 20 mg q.d.	0.81 (0.54 to 1.20)	1.02 (0.75 to 1.39)	0.82 (0.55 to 1.24)	0.59 (0.31 to 1.12)	1.50 (0.95 to 2.35)	0.83 (0.47 to 1.47)

b.i.d. = twice daily; CI = confidence interval; GI = gastrointestinal; GLMM = generalized linear mixed models; q.d. = once daily.

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