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Antithrombotic Agents for the Prevention of Stroke and Systemic Embolism in Patients With Atrial Fibrillation

Supporting Informed Decisions

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Note regarding to changes to the report following stakeholder feedback:

Several modifications were made to the text and data tables of this report following the receipt of feedback in reponse to a draft of this report. These modifications were minor changes and did not alter the results of the analyses or the conclusions of the report. The most notable change to the report is the addition of Appendix 21, which provides the results of an analysis in which two excluded trials, AVERROES and ACTIVE A, were included in a sensitivity analysis. The results of this sensitivity analysis concur with the conclusions based on the primary analysis; therefore, there were no changes made to the conclusions of the report based on this sensitivity analysis.

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ABBREVIATIONS

ACCP	American College of Chest Physicians
AF	atrial fibrillation
ARD	absolute risk difference
ASA	acetylsalicylic acid
CCS	Canadian Cardiovascular Society
CDEC	Canadian Drug Expert Committee
CDR	Common Drug Review
$CHADS_2$	congestive heart failure, hypertension, age > 75, diabetes mellitus, and secondary prevention (prior stroke or transient ischemic attack)
CrI	credible interval
CI	confidence interval
DIC	deviance information criterion
ECH	extracranial hemorrhage
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GI	gastrointestinal
ICER	incremental cost-effectiveness ratio
ICH	intracranial hemorrhage
INR	international normalized ratio
ISTH	International Society on Thrombosis and Haemostasis
MI	myocardial infarction
MTC	mixed treatment comparison
NMA	network meta-analysis
NOAC	new oral anticoagulant
NSAID	non-steroidal anti-inflammatory drug
OHTAC	Ontario Health Technology Advisory Committee
OR	odds ratio
PE	pulmonary embolism
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life years
RCT	randomized controlled trial
SE	systemic embolism
SSE	stroke or systemic embolism
TIA	transient ischemic attack
TTR	time in therapeutic range
VKA	vitamin K antagonist
λ	willingness-to-pay threshold

EXECUTIVE SUMMARY

Context and Policy Issues

Atrial fibrillation (AF) is a common cardiac arrhythmia associated with increased morbidity and mortality.[1,2] Patients with AF are at increased risk of systemic embolism (SE) and stroke, which can cause death, disability, and impaired quality of life.[1] Antithrombotic therapies, such as oral anticoagulant and antiplatelet drugs, can reduce the risk for stroke and systemic thromboembolism and are recommended for most AF patients with risk factors for stroke.[3-7] Antithrombotic therapies are also associated with a risk of bleeding, and their efficacy for stroke prevention should always be balanced against a patient's risk of hemorrhage.[3-7]

Existing guidelines[3-5] recommend antithrombotic therapy based on risk of stroke,[3-5] and most patients with non-valvular AF benefit from some form of antithrombotic therapy with an anticoagulant or antiplatelet drug. However, each oral antithrombotic drug used for stroke prevention in AF has advantages and disadvantages. There are decades of experience with the use of the vitamin K antagonist (VKA) warfarin, as well as compelling evidence of efficacy with regard to stroke prevention.[7-9] However, individualized dose adjustments and laboratory monitoring are required,[10-12] and warfarin remains the most common cause of drug-related emergency hospitalization in the elderly.[13] Because there is less clinical experience with the new oral anticoagulant (NOAC) drugs apixaban, dabigatran, and rivaroxaban outside of randomized controlled trials, it is not yet clear whether the NOACs show increased real-world benefits compared with warfarin. Although less effective at stroke prevention than anticoagulant therapy in most risk categories,[14] antiplatelet agents may still be the best choice for selected patients.[3-5,7,15]

Following individual recommendations for dabigatran and rivaroxaban in AF made by the Common Drug Review (CDR),[16,17] the Canadian Agency for Drugs and Technologies in Health (CADTH) previously reviewed the clinical effectiveness and cost-effectiveness of the NOACs compared with warfarin for CDEC to develop recommendations for policy-makers regarding the NOACs and warfarin.[18] At that time, apixaban was not approved for use in Canada, and was therefore not included in the CDEC recommendation; in addition, antiplatelet drugs were not included. The current review was undertaken to extend the previous review to allow CDEC to develop recommendations that include all the NOACs, as well as the antiplatelet drugs acetylsalicylic acid (ASA) and clopidogrel.

Objectives

1. To conduct a systematic review and mixed treatment comparison (MTC) of the clinical evidence pertaining to antithrombotic agents for the prevention of morbidity and mortality in patients with non-valvular AF.
2. To assess the impact of age, $CHADS_2$ score, and time spent in the therapeutic range (TTR; relevant to warfarin only) on the clinical safety and efficacy of antithrombotic agents.
3. To conduct a cost-effectiveness analysis of antithrombotic agents based on the results of the systematic review and MTC.

Methods

Active and placebo-controlled randomized controlled trials (RCTs) of antithrombotic agents for the prevention of stroke and other thromboembolic events in patients with AF were identified through electronic databases, grey literature, and stakeholder consultation. Two reviewers independently screened the titles and abstracts, and independently evaluated the full-text publications for final article selection. RCTs were considered for inclusion if they compared at least two of the antithrombotic strategies under review, in patients who were eligible for anticoagulant therapy, and reported outcomes related to patient safety or clinical efficacy, as pre-specified in the review protocol. Pairwise and Bayesian MTC network meta-analyses (NMA) were conducted to pool trial results, when appropriate. The results of the MTC were used to evaluate the cost-effectiveness of each intervention following standard procedures. This report was peer-reviewed by clinical experts.

Summary of Findings

The systematic review included 12 individual RCTs (28 publications)[19-46] in which the efficacy and safety of antithrombotic interventions were evaluated in patients with AF. Interventions included the NOACs apixaban, dabigatran, and rivaroxaban; warfarin; or ASA with or without clopidogrel.

Key Clinical Findings

While there were statistically significant differences between the NOACs and warfarin for some outcomes (details to follow), absolute risk differences (ARD) for the NOACs versus warfarin were small and were generally fewer than 10 events per 1,000 patients treated each year. Absolute risk differences were calculated versus warfarin and not among other treatment interventions.

Anticoagulants demonstrated consistently better outcomes compared with the antiplatelet treatments (see subsequent information).

Estimates of effect derived from the direct pairwise comparisons aligned closely with those obtained from NMA in both direction and magnitude. In no case was there a discrepancy in the statistical significance of the effect sizes between the direct pairwise comparisons and the NMA.

The results from the random-effects model were very similar to those of the fixed-effects model for all outcomes, although the confidence intervals (CIs) for each point estimate were wider for the random-effects model.

Reference Case

Stroke and Systemic Embolism

- Apixaban 5 mg twice daily and dabigatran 150 mg twice daily were associated with statistically significantly lower rates of stroke and systemic embolism (SSE) compared with adjusted-dose warfarin. For apixaban, the odds ratio (OR) was 0.8 (95% CI, 0.7 to 0.95) and the ARD 95% CIs ranged from 1 to 6 fewer events per 1,000 patients treated per year. For dabigatran, the OR was 0.7 (95% CI, 0.5 to 0.8), with a range in ARD of 3 to 9 events per 1,000 patients treated per year.
- Dabigatran 150 mg twice daily was associated with statistically significantly fewer SSEs versus dabigatran 110 mg twice daily (OR = 0.7 [95% CI, 0.6 to 0.9]).
- Low-dose ASA and the combination of clopidogrel plus low-dose ASA were statistically significantly less effective at preventing SSE compared with all anticoagulants (OR = 1.9 [95% CI, 1.3 to 2.8] to 2.9 [95% CI, 2.0 to 4.3]).
- No statistically significant differences in the OR for SSE were detected among each of the remaining interventions, including the comparison between rivaroxaban and warfarin or other NOACs.

Major Bleeding

- Apixaban 5 mg twice daily and dabigatran 110 mg twice daily were associated with statistically significantly lower rates of major bleeding compared with warfarin (OR = 0.7 [95% CI, 0.6 to 0.8] and 0.8 [95% CI, 0.7 to 0.9], respectively). ARDs versus warfarin ranged from 6 to 13 fewer events per 1,000 patients treated per year with apixaban and from 2 to 11 fewer events per 1,000 patients treated per year with dabigatran 110 mg.
- Dabigatran 150 mg twice daily and rivaroxaban 20 mg once daily were associated with statistically significantly higher rates of major bleeding compared with apixaban 5 mg twice daily (OR = 1.3 [95% CI, 1.1 to 1.7] and 1.5 [95% CI, 1.2 to 1.8]) and dabigatran 110 mg twice daily (OR = 1.2 [95% CI, 1.0 to 1.4] and 1.3 [95% CI, 1.04 to 1.6]).
- Clopidogrel plus low-dose ASA was associated with statistically significantly higher rates of major bleeding compared with apixaban (OR = 1.6 [95% CI, 1.2 to 2.2]).
- No statistically significant differences in the OR for major bleeding were detected among each of the remaining interventions, including the comparison between rivaroxaban and warfarin.

All-Cause Mortality

- Apixaban 5 mg twice daily was associated with statistically significantly less all-cause mortality compared with warfarin (OR = 0.9 [95% CI, 0.8 to 0.997], ARD = 0 to 8 fewer events per 1,000 patients treated per year).
- No statistically significant differences in the OR for all-cause mortality were detected among each of the remaining interventions, including the comparisons among NOACs and versus warfarin.

Extracranial Hemorrhage

- Apixaban 5 mg twice daily was associated with a statistically significantly lower rate of extracranial hemorrhage compared with warfarin (OR = 0.8 [95% CI, 0.7 to 0.9], ARD = 2 to 8 fewer events per 1,000 patients treated per year).
- All of the following treatments were associated with statistically significantly higher rates of extracranial hemorrhage compared with apixaban: dabigatran 150 mg twice daily (OR = 1.4 [95% CI, 1.1 to 1.7]), rivaroxaban 20 mg OD (OR = 1.4 [95% CI, 1.1 to 1.8]), and medium-dose ASA (OR = 5.2 [95% CI, 1.2 to 39.8]).

Intracranial Hemorrhage

- All NOACs were associated with statistically significant reductions in intracranial hemorrhage (ICH) compared with warfarin. Absolute risk reductions were similar between these interventions and ranged from 1 to 7 fewer events per 1,000 patients treated per year.
- Dabigatran 110 mg twice daily was associated with a statistically significantly lower rate of ICH compared with rivaroxaban 20 mg OD (OR = 2.1 [95% CI, 1.2 to 3.8]). All other comparisons among NOACs did not reach statistical significance.
- Clopidogrel plus low-dose ASA was associated with a statistically significantly higher rate of ICH compared with the NOACs (OR = 3.0 [95% CI, 1.4 to 7.0] to 6.5 [95% CI, 2.8 to 15.7]).

Myocardial Infarction

- Dabigatran 150 mg twice daily was associated with a statistically significantly higher rate of myocardial infarction (MI) compared with warfarin (OR = 1.4 [95% CI, 1.02 to 2.0], ARD = 0 to 4 more events per 1,000 patients treated per year).
- Dabigatran (110 mg and 150 mg twice daily), medium-dose ASA, and the combination of clopidogrel plus low-dose ASA were both associated with statistically significantly higher rates of MI compared with apixaban 5 mg twice daily (OR = 1.6 [95% CI, 1.02 to 2.4], 1.6 [95% CI, 1.04 to 2.5], 1.8 [95% CI, 1.01 to 3.4] and 1.6 [95% CI, 1.2 to 2.2], respectively).
- Medium-dose ASA was associated with a statistically significantly higher rate of MI compared with rivaroxaban 20 mg OD (OR = 2.0 [95% CI, 1.1 to 3.7]).

Subgroup Analyses

$CHADS_2 < 2$

SSE:

- No statistically significant differences were observed between warfarin and each evaluated NOAC for SSE.
- Dabigatran 150 mg twice daily was associated with a statistically significantly lower rate of SSE versus dabigatran 110 mg twice daily (OR = 0.6 [95% CI, 0.4 to 0.996]).
- Low-dose ASA and the combination of clopidogrel plus low-dose ASA were statistically significantly less effective at preventing SSE compared with the anticoagulants (OR ranging from 2.2 [95% CI, 1.03 to 4.9] to 3.6 [95% CI, 1.6 to 8.3] with low-dose ASA and from 3.2 [95% CI, 1.2 to 9.1] to 5.2 [95% CI, 2.0 to 15.2] with the combination of clopidogrel plus low-dose ASA).

Major Bleeding:

- Apixaban 5 mg twice daily and dabigatran 110 mg twice daily were associated with statistically significantly lower rates of major bleeding compared with warfarin (OR = 0.6 [95% CI, 0.4 to 0.8] and OR = 0.7 [95% CI, 0.5 to 0.9], respectively). ARDs versus warfarin ranged from 6 to 17 fewer events

per 1,000 patients treated per year with apixaban and from 3 to 17 fewer events per 1,000 patients treated per year with dabigatran 110 mg. The combination of clopidogrel plus low-dose ASA was associated with statistically significantly higher rates of major bleeding compared with apixaban 5 mg twice daily and dabigatran (110 mg and 150 mg twice daily) (OR = 2.6 [95% CI, 1.4 to 4.8], 2.3 [95% CI, 1.3 to 4.4] and 2.0 [95% CI, 1.1 to 3.7], respectively).

$CHADS_2 \geq 2$

SSE:

- Dabigatran 150 mg twice daily and apixaban 5 mg twice daily were associated with statistically significantly lower rates of SSE compared with warfarin (OR = 0.7 [95% CI, 0.5 to 0.9] and 0.8 [95% CI 0.6 to 0.95], respectively). ARDs versus warfarin ranged from 3 to 10 fewer events per 1,000 patients treated per year with dabigatran 150 mg and from 1 to 7 fewer events per 1,000 patients treated per year with apixaban.
- Low-dose ASA and the combination of clopidogrel plus low-dose ASA were statistically significantly less effective at preventing SSE compared with the NOACs (OR ranging from 2.4 [95% CI, 1.03 to 6.0] to 3.2 [95% CI, 1.3 to 8.0] with low-dose ASA and from 2.0 [95% CI, 1.4 to 3.0] to 2.7 [95% CI, 1.8 to 4.1] with the combination of clopidogrel plus low-dose ASA).

Major Bleeding:

- Apixaban 5 mg twice daily was associated with a statistically significantly lower rate of major bleeding compared with warfarin (OR = 0.7 [95% CI, 0.6 to 0.9], ARD = 5 to14 fewer events per 1,000 patients per year), as well as compared with dabigatran 150 mg twice daily and rivaroxaban 20 mg once daily (OR = 1.4 [95% CI, 1.1 to 1.7] and 1.3 [95% CI], respectively).

Age and Time in Therapeutic Range

SSE:

- In patients 75 years old or older, dabigatran 150 mg twice daily and apixaban 5 mg twice daily were associated with a statistically significantly lower rate of SSE compared with warfarin, and all anticoagulant drugss were significantly superior to low-dose ASA. In patients younger than 75 years, low-dose ASA and the combination of clopidogrel plus low-dose ASA were statistically significantly less effective at preventing SSE compared with warfarin, and dabigatran 150 mg twice daily was associated with statistically significantly fewer SSE versus warfarin, dabigatran 110 mg twice daily, and rivaroxaban 20 mg once daily.
- In centres with poor INR control (TTR < 66%), dabigatran 150 mg twice daily was associated with a statistically significantly lower rate of SSE compared with warfarin and rivaroxaban 20 mg once daily. In centres with good INR control (TTR ≥ 66%), there were no statistically significant differences among treatments.

Major Bleeding:

- In patients 75 years old or older, apixaban 5 mg twice daily was associated with statistically significantly lower rates of major bleeding compared with the other anticoagulant drugs. In patients younger than 75 years, dabigatran 110 mg and 150 mg and apixaban were associated with statistically significantly lower rates of major bleeding compared with warfarin.
- In centres with poor INR control (TTR < 66%), apixaban 5 mg twice daily and dabigatran 110 mg and 150 mg twice daily were all associated with statistically significantly lower rates of major bleeding compared with warfarin. In centres with good INR control (TTR ≥ 66%), apixaban was associated with statistically significantly lower rates of major bleeding compared with warfarin.
- Apixaban 5 mg twice daily was associated with statistically significantly lower rates of major bleeding compared with dabigatran 150 mg twice daily and rivaroxaban 20 mg once daily irrespective of the degree of INR control.

Stroke and Systemic Embolism versus Major Bleeding

Reference Case

The overall comparative benefit/risk profile based on the results for SSE (benefit) and major bleeds (risk) for the nine interventions suggests that the benefit/risk of the NOACs was positive compared with warfarin (decrease in SSE and/or major bleeding) and largely similar among one another. Even where statistically significant differences existed for the OR for the NOACs versus warfarin, the ARD associated with these differences were small and were generally fewer than 10 events per 1,000 patients treated each year.

Comparison of all anticoagulant treatment (including warfarin) to ASA with or without clopidogrel suggests that antiplatelet drugs have a less favourable benefit/risk profile than the NOACs.

Subgroups

For patients with a $CHADS_2$ score < 2, the overall benefit/risk of the NOACs was positive compared with warfarin and closer to the benefit/risk of warfarin than the ASA treatments; whereas the NOACs (except rivaroxaban, which was not included in this analysis) decrease the risk of SSE and major bleeding, antiplatelet drugs had a less favourable benefit/risk profile.

For patients with a $CHADS_2$ score ≥ 2, the benefit/risk of the NOACs was positive compared with warfarin and very similar to the benefit/risk of warfarin. Low-dose ASA had a less favourable benefit/risk profile than the NOACs; however, the benefit/risk profile for clopidogrel plus low-dose ASA appears to be close to the anticoagulants in this subgroup. The level of confidence in this observation is considerably lower than for the anticoagulant drugs, as the estimated effect sizes for clopidogrel plus low-dose ASA were derived from a single RCT with substantially fewer patients.

Comparison of all overall benefit/risk of the anticoagulant treatments versus the antiplatelet drugs suggests that antiplatelet drugs have a less favourable benefit/risk profile than the NOACs irrespective of stroke risk, age, or the degree of INR control.

Key Economic Findings

For patients with $CHADS_2$ < 2, dabigatran 150 mg twice daily was likely the optimal treatment, with an incremental cost per quality-adjusted life-year (QALY) gained versus warfarin of $20,845.

For patients with $CHADS_2$ ≥ 2, dabigatran 150 mg twice daily and apixaban 5 mg twice daily were the most cost-effective treatments among the NOACs, and the incremental cost per QALY gained for both apixaban and dabigatran 150 mg versus warfarin was $17,795. Apixaban 5 mg twice daily was likely optimal, as it dominated dabigatran 150 mg twice daily in probabilistic analyses, but the difference between these two treatments is marginal.

The antiplatelet treatments were all dominated by one or more of the anticoagulants, irrespective of stroke risk ($CHADS_2$ score), age, or degree of INR control (TTR). Therefore, compared with anticoagulant drugs, antiplatelet therapy was never optimal in any of the subgroups analyzed. However, the paucity of data for patients with a $CHADS_2$ score = 0 suggests that these findings cannot be generalized to patients with a low risk of stroke, and must be limited to patients with a moderate or high risk of stroke ($CHADS_2$ score > 0).

Relative cost-effectiveness was influenced by the following:

- Willingness-to-pay threshold (λ): The probability that dabigatran 150 mg twice daily is the most cost-effective NOAC in $CHADS_2$ < 2 increases as the λ increases. Similarly, the probability that apixaban 5 mg twice daily is optimal in patients with a $CHADS_2$ score ≥ 2 increases as the λ increases.
- Age: Dabigatran 150 mg twice daily was optimal in younger patients (60 or 70 years old), whereas apixaban 5 mg twice daily was optimal in older patients (80 years old). None of the antiplatelet agents was optimal irrespective of age.

- Degree of INR control: In centres with poor INR control (TTR < 66%), dabigatran 150 mg twice daily was optimal, while apixaban 5 mg twice daily was optimal in centres with good INR control (TTR ≥ 66%), although there was little difference in cost-effectiveness for both therapies.

Key Limitations

A major limitation of conclusions made in the current report is heterogeneity among the included trials, both for patient characteristics (e.g., differences in baseline patient characteristics of the included studies that may be important predictors of treatment effects, such as stroke risk, differences in the degree of INR control) and trial methodology (e.g., population sizes, definitions, and reporting of outcomes). We also observed variability in definitions (e.g., bleeding) and methodological rigour; indeed, most trials evaluating ASA with or without clopidogrel or placebo/no treatment were substantially smaller, older, and of lower quality than the NOACs trials. Due to the relatively small number of trials available for each individual therapy in the published literature, the limited ability to adjust for such heterogeneity reduces the degree of certainty associated with the results of our analyses.

Other important limitations are presented here:

- There are no direct comparisons of the NOACs available, and indirect comparisons were used to compare the different treatments. This method has inherent limitations, but in the absence of head-to-head trial data, this is the only alternative at present to compare different antithrombotic therapies.
- Data were not available for all outcomes for all treatments in all subpopulations of interest. In particular, there were very few patients for all interventions at low risk of stroke ($CHADS_2$ score = 0). Therefore, our findings cannot be generalized to patients who have a low risk of stroke.
- Limitations based on the comparison of clinical efficacy and safety necessarily apply to the confidence in the results of pharmacoeconomic analyses.

Conclusions and Implications for Decision- or Policy-Making

The results of the current review revealed that there were statistically significant differences in clinical outcomes in AF patients between the NOACs and warfarin, although it is unclear whether the ARD associated with these differences translate into clinically meaningful benefits in practice. The pharmacoeconomic analyses suggested that NOACs may be cost-effective alternatives to warfarin for preventing SSE in AF patients. More specifically, if it is assumed that the λ is $50,000, then among the NOACs, dabigatran 150 mg twice daily is likely the optimal therapy in patients who have a moderate risk of stroke ($CHADS_2$ = 1), or are relatively young (≤ 70 years old), or who cannot maintain an adequate INR control (TTR < 66%); apixaban 5 mg twice daily would likely be the optimal NOAC therapy in patients who have a high risk of stroke ($CHADS_2$ score ≥ 2) or are relatively old (≥ 80 years old).

The current review extends our previous report by demonstrating that anticoagulant therapy is superior to ASA, both regarding clinical benefit and cost-effectiveness, irrespective of whether ASA is co-administered with clopidogrel. Anticoagulant therapy would appear to be a superior treatment option for preventing SSE in patients with non-valvular AF in patients with a moderate or high risk of stroke ($CHADS_2$ score ≥ 1). The superiority of the anticoagulant drugs versus the antiplatelet drugs was consistent irrespective of age and the degree of INR control (TTR). There was, however, insufficient evidence to compare anticoagulant drugs to antiplatelet drugs in patients with a low risk of stroke ($CHADS_2$ score = 0).

These results must be considered in the light of several limitations that create uncertainty, most notably the reliance on indirect comparison methodology to compare the different treatments.

1 CONTEXT AND POLICY ISSUES

1.1 Atrial Fibrillation

AF is a common cardiac arrhythmia[1,2] characterized by disorganized, rapid, and irregular activity of the atria; i.e., the upper chambers of the heart.[47] AF is recognized as a chronic, progressive disorder associated with increased morbidity and mortality.[7,9,48,49] The Heart and Stroke Foundation estimates that approximately 350,000 Canadians are affected by AF.[50,51] The prevalence of AF increases with age and is more prevalent in patients with structural heart diseases, hypertension, obesity, diabetes, and other chronic conditions.[52,53]

AF usually presents with recurrent episodes that are described as either paroxysmal, persistent, or permanent, but there is no evidence that stroke risk varies according to the type of AF.[48,54-56]

1.2 Stroke Prevention

Failure of the atria to contract leads to a reduction in cardiac output and an increase in atrial pressure. These favour blood stasis and thrombus formation, especially in the left atrial appendage.[9,47,48] In all types of AF, embolization of atrial thrombi poses a significant risk of arterial thromboembolism, transient ischemic attack (TIA) and stroke, which are associated with high recurrence and substantial debilitating impact.[7,9,15,57] Stroke alone costs the Canadian economy $3.6 billion a year in physician services, hospital costs, lost wages, and decreased productivity (2000 statistic).[51] For all these reasons, preventing strokes and other thrombotic events is an important part of AF management.[47] The risk of stroke varies according to patient factors; therefore, selecting an appropriate stroke prevention strategy requires risk assessment, based on the presence of several clinical factors, as well as concomitant cardiovascular disorders.[7]

Although various models have been proposed, major clinical guidelines[3-5] select the widely used $CHADS_2$ score to make recommendations based on the risk of stroke.[15,57] This validated index assigns one point for each of the following individual risk factors:[3,9,57]

- Congestive heart failure
- Hypertension
- Age > 75
- Diabetes mellitus
- Secondary prevention — patients with prior stroke or TIA (2 points).

The $CHADS_2$ scoring system leads to the risk stratification in Table 1:[3,15]

Table 1: Risk Stratification According to the $CHADS_2$ Index[3,15]

$CHADS_2$ Score	Assessment of Stroke Risk	Estimated Stroke Rates (%/year)
$CHADS_2 = 0$	Low risk of stroke	0.5% to < 2%
$CHADS_2 = 1$	Intermediate risk of stroke	2%
$CHADS_2 \geq 2$	High risk of stroke	4% to 18%

1.3 Antithrombotic Therapy

Guidelines from the Canadian Cardiovascular Society (CCS),[3] the American College of Chest Physicians (ACCP),[4] and the European Society of Cardiology (ESC)[5] include two classes of antithrombotic medication for stroke prevention in patients with AF: anticoagulant drugs and antiplatelet agents. Each of these therapeutic options is presented in Table 2.

Table 2: Antithrombotic Drugs Used in AF and Included in the Systematic Review			
Drug Class	**Generic Drug Name**	**Mechanism of Action**	**Dosage and Administration[a]**
Anticoagulant Drugs	Warfarin	VKA	Dose adjusted to a target INR of 2.0 to 3.0
	Acenocoumarol		
	Dabigatran	Direct thrombin inhibitor	150 mg b.i.d.[b]
	Apixaban	Direct factor Xa inhibitor	5 mg b.i.d.
	Rivaroxaban		20 mg q.d.
Antiplatelet Agents	ASA	Platelet aggregation inhibitor	80 mg to 325 mg q.d.
	Clopidogrel		75 mg q.d.

ASA = acetylsalicylic acid; b.i.d. = twice daily; INR = international normalized ratio; q.d. = once daily; VKA = vitamin K antagonist.
[a] All drugs are administered orally.
[b] Dabigatran 110 mg b.i.d. may be considered in elderly patients at risk of bleeding.

Low stroke risk: Guidelines[3-5] recommend that AF patients at lowest risk of stroke ($CHADS_2$ = 0 and no additional risk factors) receive no antithrombotic therapy, as the risks usually outweigh the potential benefits.[3-5] Indeed, antithrombotic therapy is associated with an increased risk of major bleeding that may also lead to serious consequences; therefore, the beneficial effect of therapy on the risk of stroke should always be weighed against a patient's risk of hemorrhage.[3]

However, patients presenting with additional risk factors not considered in the $CHADS_2$ score (i.e., age between 65 and 74 years, female sex, and presence of vascular disease) may benefit from antithrombotic therapy, in which case ASA or anticoagulants are recommended.[3-5]

Table 3 summarizes recommendations from current CCS,[3] ACCP,[4] and ESC[5] guidelines for stroke prevention in AF patients, for each level of stroke risk according to the $CHADS_2$ score.

Table 3: Major Clinical Recommendations for Antithrombotic Management in AF			
Risk of Stroke	**Canadian Guidelines CCS[3]**	**American Guidelines ACCP[4]**	**European Guidelines ESC[5,58]**
Low ($CHADS_2$ = 0)	**Higher risk[a] = OAC** *Dabigatran, rivaroxaban, apixaban recommended over warfarin.[b]* **Lower risk[a] = ASA** **Lowest risk[a] = No therapy**	**No therapy**	**Higher risk[a] = OAC** **Lowest risk[a] = No therapy**
Intermediate ($CHADS_2$ = 1)	**OAC** *Dabigatran, rivaroxaban, apixaban recommended over warfarin.[b]*	**OAC** *Dabigatran recommended over warfarin.[c]*	**OAC** *Dabigatran, rivaroxaban, apixaban recommended over warfarin.*
High ($CHADS_2$ ≥ 2)	**OAC** *Dabigatran, rivaroxaban, apixaban recommended over warfarin.[b]*	**OAC** *Dabigatran recommended over warfarin.[c]*	**OAC** *Dabigatran, rivaroxaban, apixaban recommended over warfarin.*

ACCP = American College of Chest Physicians; ASA = acetylsalicylic acid; CCS = Canadian Cardiovascular Society; ESC = European Society of Cardiology; OAC = oral anticoagulants; VKA = vitamin K antagonist.

[a] Based on the consideration of other risk factors (age 65 to 74 years, female sex, and presence of vascular disease).
[b] Preference for newer agents less clear in patients taking warfarin with stable INR and no bleeding complications.
[c] At the time the American Guidelines were published (2012), only dabigatran received regulatory approval for use in AF[4] and therefore the Guidelines do not make recommendations for apixaban and rivaroxaban.

Intermediate to high stroke risk: Most patients at intermediate to high risk of stroke ($CHADS_2$ = 1 or ≥ 2) should receive anticoagulant therapy.[3-5] Warfarin has been the reference treatment for many years, with compelling evidence of efficacy with regard to stroke prevention.[7,9,15] Individualized dose adjustments and laboratory monitoring are required due to a narrow therapeutic index, various food and drug interactions, and a highly variable dose-response relationship.[10-12] As a result, INR control may not be consistently optimal in routine clinical practice. The Canadian guidelines recommend the use of the NOACs apixaban, dabigatran, and rivaroxaban in intermediate- to high-risk patients.[4] While warfarin prevents the synthesis of functional forms of vitamin K-dependent coagulation factors II, VII, IX, and X, NOACs selectively inhibit the active form of a single factor of the coagulation cascade. Therefore, these agents feature a more predictable response with no INR monitoring required; however, they come at a higher cost per pill (although this does not necessarily preclude them from being cost-effective) and have no known antidote or reversing agents in case of serious bleeding.[15,47] In addition, a significant limitation to the use of NOACs in clinical practice is the presence of severe chronic kidney disease.

Alternative treatment options: Antiplatelet agents demonstrate benefits in stroke prevention, but are considered less effective than anticoagulant therapy for this purpose.[7,15,47] A potentially lower risk of bleeding, however, positions ASA as a reasonable low-cost alternative to anticoagulants in some patients with an intermediate to low risk of stroke.[3-5] The combination of ASA plus clopidogrel is also considered an alternative in the occasional patient who cannot be treated with an anticoagulant, or who presents with particular comorbidities, as long as the risk of bleeding is low.[3-5,7]

1.4 Objectives of the Report

There is limited evidence assessing which antithrombotic agents are optimal in the context of stroke prevention in patients with AF from the perspective of the public payer. Uncertainty remains regarding the relative effectiveness of apixaban, dabigatran, and rivaroxaban, as well as whether these agents show increased clinical benefits compared with warfarin. Alternatively, antiplatelet agents may also be beneficial in carefully selected patients. Such uncertainty from a clinical perspective also leads to uncertainty in the cost-effectiveness of these interventions. In addition, it is unclear whether some treatment options are optimal in different patient populations, such as patients with a low versus high risk of stroke.

Table 4 outlines previous CADTH work in this area. In addition to making recommendations for the individual NOACs dabigatran and rivaroxaban, CADTH reviewed the clinical and cost-effectiveness of the NOACs and warfarin.[47] Based on this review, CDEC recommended that NOACs be considered for the prevention of SSE in patients with non-valvular AF and a $CHADS_2$ score ≥ 2 in whom warfarin is indicated but whom are unable to achieve adequate anticoagulation. CDEC recommended that the selection of a NOAC should be made based on individual clinical factors.[18] However, the previous CADTH review did not include apixaban or antiplatelet agents in the recommendations because the former was not yet approved for use in Canada and the latter were not included in the review. To address these outstanding issues, the aim of this report was to compare the clinical and cost-effectiveness of oral antithrombotic agents, including anticoagulants (warfarin, dabigatran, rivaroxaban, and apixaban) and antiplatelet drugs (ASA and clopidogrel), for the prevention of thromboembolic events in patients with AF who are candidates for anticoagulant therapy.

Table 4: Previous CADTH Recommendations for NOACs in AF[16-18]		
Individual Drug Recommendations		
Drug	**Date**	**Recommendation**
Dabigatran[16]	June, 2011	List for patients with AF who meet one of the following criteria: • Patients in whom warfarin is indicated, but who fail to achieve adequate INR control, *or* • Patients who have a history of serious hypersensitivity reaction to warfarin.
Rivaroxaban[17]	April, 2012	List for patients with non-valvular AF in whom warfarin is indicated and who meet all of the following criteria: • Are unable to achieve adequate anticoagulation with warfarin, and • Have a $CHADS_2$ score of ≥ 2.
Apixaban	March 2013	List for the prevention of SSE in patients with AF who meet all of the following clinical criteria: • Patients with a $CHADS_2$ score ≥ 1, and • Patients who are unable to readily achieve adequate anticoagulation with warfarin.
Therapeutic Review		
Title	**Date**	**Recommendation**
New Oral Anticoagulants for the Prevention of Thromboembolic Events in Patients with AF[18]	June, 2012	***Recommendation 1*:** CDEC recommends that new oral anticoagulant agents should be considered for the prevention of SSE in patients with non-valvular AF in whom warfarin is indicated, and who meet all of the following criteria: • Are unable to achieve adequate anticoagulation with warfarin, and • Have a $CHADS_2$ score ≥ 2.* *Note: Patients with a $CHADS_2$ score of 1 may be considered for treatment with warfarin or an appropriate dose of dabigatran, based on individual clinical factors. ***Recommendation 2*:** CDEC recommends that the selection of a NOAC agent should be made based on individual clinical factors.

AF = atrial fibrillation; CADTH = Canadian Agency for Drugs and Technologies in Health; INR = international normalized ratio; NOAC = new oral anticoagulants; SSE = stroke and systemic embolism; TIA = transient ischemic attack.

2 RESEARCH QUESTIONS

1. How do the clinical safety and efficacy of NOACs (apixaban, dabigatran, and rivaroxaban) compare to warfarin, ASA, clopidogrel, or ASA plus clopidogrel in preventing morbidity and mortality in patients with non-valvular AF? Are there any differences in clinical safety and efficacy depending on the dose of ASA?
2. In patients with non-valvular AF, what is the impact on the clinical safety and efficacy of NOACs on the following: $CHADS_2$ score, time spent in the therapeutic range (TTR; applicable only to warfarin), and age?
3. What is the cost-effectiveness, from a public payer's perspective, of NOACs compared with warfarin, ASA, clopidogrel, or ASA plus clopidogrel in preventing morbidity and mortality in patients with non-valvular AF based on the $CHADS_2$ score, age, and TTR?

3 METHODS

3.1 Systematic Review

3.1.1 Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with In-Process records & daily updates via Ovid; Embase (1974-) via Ovid; Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were dabigatran, apixaban, rivaroxaban, clopidogrel, ASA, warfarin, Acenocoumarol, and AF. Methodological filters were applied to limit retrieval to RCTs and controlled clinical trials. Retrieval was limited to English language articles and studies published after 1988. Conference abstracts were excluded from the search results. The initial search was completed on June 7, 2012. Regular alerts have been established.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters), which includes the websites of regulatory agencies, Canadian and major international health technology assessment agencies, clinical practice guidelines, meta-analyses and systematic reviews, as well as The Cochrane Library (2012, Issue 6) and University of York Centre for Reviews and Dissemination (CRD) databases. Google was used to search for additional web-based materials.

Details of the literature search are presented in Appendix 1.

3.1.2 Selection Criteria and Methods

Trials were included in the systematic review based on the pre-specified selection criteria that were established in the review protocol (Table 5). Active and placebo-controlled RCTs were selected for inclusion if they were published in English, included at least one treatment comparison between two of the antithrombotic strategies under review, reported any of the pre-specified outcomes related to patient safety or clinical efficacy, and involved patients with AF eligible to receive anticoagulant therapy, regardless of the level of stroke risk. Trials that included patients with contraindication to anticoagulant treatment were excluded.

Table 5: Inclusion and Exclusion Criteria for Primary Studies	
Inclusion Criteria	
Clinical Trial Design	Published RCTs
Patient Population	Individuals with non-valvular AF requiring anticoagulation[a] (including all risk levels and regardless of any comorbidities). *Potential subgroups*: $CHADS_2$ score, TTR, age, weight, renal function, history of GI bleed, concurrent use of antiplatelet agents (when on oral anticoagulants) or NSAIDs, prior VKA use, type of AF.
Interventions	*Anticoagulants*: Apixaban, dabigatran, rivaroxaban, and dose-adjusted VKA[b] *Antiplatelet drugs*: ASA[c] and clopidogrel *Placebo*
Outcomes	• All-cause SSE • Major bleeding (ISTH definition) • All-cause mortality • Intracranial bleeding (including intracerebral hemorrhage) • Cardiovascular mortality • Ischemic/uncertain SSE (including MI) • Life-threatening bleeds • Extracranial hemorrhage • Minor bleeds • Pulmonary embolism • TIA • Non-cardiovascular mortality
Exclusion Criteria	
Studies in languages other than English. Non-randomized studies.	

AF = atrial fibrillation; ASA = acetylsalicylic acid; GI = gastrointestinal; ISTH = International Society on Thrombosis and Haemostasis; MI = myocardial infarction; NSAIDs = non-steroidal anti-inflammatory drugs; RCTs = randomized controlled trials; SSE = stroke or systemic embolism: TIA = transient ischemic attack; TTR = time in therapeutic range; VKA = vitamin K antagonist.

[a]The intent was to include trials that enrolled patients who were eligible to receive treatment with an anticoagulant, although the trial designs may have resulted in patients being randomized to other interventions such as antiplatelet agents or placebo. Trials conducted in a population of patients who were ineligible to receive anticoagulant treatment for any reason were excluded.
[b]Warfarin or acenocoumarol. VKA trials were included if the dose was adjusted to a target INR of 2 to 3. [c]Any dose of ASA was considered for inclusion, but ASA dose was stratified in the analysis as low, medium, or high (see Methods section).

Two reviewers independently screened citations and selected trials relevant to the research questions on the use of antithrombotic therapy for stroke prevention in patients with AF. The reviewers screened the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria, ordered the full text of any article that appeared to meet those criteria. In cases of insufficient information, the article was ordered for more information. The two reviewers selected the final articles for inclusion based on an examination of the full-text publications. The independently chosen included and excluded studies were then compared, and disagreements were resolved through discussion until consensus was reached.

The trial selection process is presented in an Appendix flowchart based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Appendix 8).

3.1.3 Data Extraction Strategy and Critical Appraisal of Individual Studies

Three reviewers independently extracted the following data for each included article, using a standardized template:

- Baseline characteristics of trial participants
- Intervention(s) evaluated, including dose, duration, and relevant co-medication
- Efficacy and safety results of the interventions for each of the pre-specified outcomes included in the protocol.

All extracted data was checked for accuracy by three independent reviewers. Any disagreements in the assessment of these data were resolved through discussion until consensus was reached. Quality assessment of RCTs was also performed independently by two reviewers using a standardized table based on major items from the SIGN 50 instrument for internal validity.[59] Further critical appraisal was performed based on clinical input from experts.

3.2 Indirect Comparisons

Pairwise and Bayesian MTC NMA were conducted for the outcomes presented in Table 6. NMA for other outcomes were not conducted because data was either sparsely reported (e.g., pulmonary embolism, life-threatening bleeds, transient ischemic stroke), outcome definitions varied considerably (e.g., minor bleeds), or outcomes were redundant (all-cause stroke/SE versus ischemic stroke/SE).

Table 6: Summary of Outcomes Used in the MTC

All-cause SSE
All-cause mortality
Major bleeding
ICH (including intracranial hemorrhage)
Extracranial bleeding
MI

ICH = intracerebral hemorrhage; MI = myocardial infarction; MTC = mixed treatment comparison.

WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) was used to conduct Bayesian NMA using a binomial likelihood model, which allows for the use of multi-arm trials. Pairwise fixed-effects meta-analyses were conducted for outcomes using the R meta package for the statistical software R (www.r-project.org/). Fixed and random-effects meta-analyses were conducted; the fixed-effects results are reported in the main body of the report, as the pairwise comparisons are largely comprised of single studies. Assessment of model fit for NMA comprised of assessment of deviance information criterion (DIC) and comparison of residual deviance to number of unconstrained data points. Small trials (< 100 patients in each arm) with zero cells in both arms or nodes where there were no events were excluded from evidence networks because they do not contribute information or allow interpretable information. Point estimates and 95% credible intervals (CrI; Bayesian confidence interval) were modelled for ORs using Markov chain Monte Carlo methods. The ARD per 1,000 patients treated each year for each outcome was also calculated using the warfarin arm of the RE-LY trial as the baseline event rate. The RE-LY trial was selected because it was the most recent trial which contained data for both $CHADS_2 < 2$ and $CHADS_2 \geq 2$ and had detailed data available from the FDA Public Summary Report.[60] Vague or flat priors, such as $N(0, 100^2)$, were assigned for basic parameters throughout the NMA. To ensure convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed. Three chains were fit in WinBUGS for each analysis, with ≥ 20,000 iterations, and a burn-in of ≥ 20,000 iterations.

Both network and pairwise meta-analysis require that studies be sufficiently similar in order to pool their results. A wide range of patient and trial characteristics were assessed to investigate the potential implications of heterogeneity across the included RCTs. We identified a number of areas where there was clinical and methodological heterogeneity. The issues identified were similar to what has been reported in

previous systematic reviews of drugs (e.g., differences in TTR, $CHADS_2$ score).[47,61] Heterogeneity was assessed by conducting NMA using the following subgroup data reported in the individual RCTs:

- TTR < 66% or ≥ 66%
- $CHADS_2$ score < 2 or ≥ 2
- Age < 75 or ≥ 75 years.

The methodological limitations with this approach are recognized (e.g., lack of information on similarity of patients across subgroups). Subgroup data was only available for the primary efficacy and safety outcomes in each RCT, namely all-cause stroke/SE and major bleeding; therefore, subgroup analyses were limited to these outcomes. Consequently, the ability to explore the impact of heterogeneity between studies regarding patient population and study design for other outcomes considered in the NMA was limited.

3.2.1 Sensitivity analysis

Due to the exclusion of several large trials (see Appendix 10 for excluded studies) that contained potentially useful information that might have altered the results of the primary analysis, we carried out a sensitivity analysis in which data from two studies of particular interest, namely AVERROES and ACTIVE-A, were included (instead of excluded, as in the primary analysis). We used data for the main efficacy and safety outcomes, specifically SSE and major bleeds. The results of this sensitivity analysis are presented in Appendix 21.

3.3 Pharmacoeconomic Analysis

3.3.1 Type of Economic Evaluation

The primary analysis was in the form of a cost-utility analysis, with treatments compared for incremental cost per QALY gained.[62] This analysis provides estimates of the expected values of costs (C) and QALYs (Q) for each of the treatment alternatives considered. The incremental cost per QALY gained or incremental cost-effectiveness ratio (ICER) is simply the ratio of the difference in costs to the difference in QALYs. For example, the following formula illustrates the calculation of the ICER for dabigatran versus warfarin, two of the interventions under review.

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

3.3.2 Target Population

The target population for the analysis was Canadians with non-valvular AF requiring anticoagulation. We used patient profile data from the RE-LY RCT, because this study reported the most complete data on the risk of events on warfarin by a $CHADS_2$ score.[35] For patients with a $CHADS_2$ score < 2, the average age was 70 years and patients with 13.5% having experienced a previous MI. For patients with a $CHADS_2$ score ≥ 2, the average age was 72 years, with 18.1% having experienced a previous MI and 29.4% having experienced a previous stroke. Transition probabilities were weighted to allow for the increased risk of events given previous event history.

In addition, a more detailed stratification by $CHADS_2$ score (0, 1, ≥ 2 no previous stroke, ≥ 2 previous mild stroke, ≥ 2 previous major stroke) was conducted. Further stratified analysis was conducted for different age subgroups (< 65 = 60, ≥ 65 = 70 and < 75 = 70, ≥ 75 = 80) and based on centre-specific average TTR (< 66%, ≥ 66%).

3.3.3 Treatments

The treatments considered in the pharmacoeconomic (PE) analysis are presented in Table 7. No data were available for high-dose ASA, and this treatment was therefore not included in the analysis. For $CHADS_2$ score < 2, no data were available for rivaroxaban, but data were available for all other treatments (except high-dose ASA). For $CHADS_2$ score ≥ 2, data were available for all treatments except medium-dose ASA (and high-dose ASA).

Table 7: Treatments Considered in the Pharmacoeconomic Analysis

Treatments	Data Available	
	$CHADS_2 < 2$	CHADS ≥ 2
Adjusted-dose warfarin	Yes	Yes
Apixaban 5 mg b.i.d.	Yes	Yes
Dabigatran 110 mg b.i.d.	Yes	Yes
Dabigatran 150 mg b.i.d.	Yes	Yes
Rivaroxaban 20 mg q.d.	No	Yes
Low-dose ASA (≤ 100 mg q.d.)	Yes	Yes
Medium-dose ASA (> 100 mg and ≤ 300 mg q.d.)	Yes	No
High-dose ASA (> 300 mg q.d.)	No	No
Clopidogrel 75 mg q.d. plus low-dose ASA (≤ 100 mg q.d.)	Yes	Yes

ASA = acetylsalicylic acid; b.i.d. = twice daily; q.d. = once daily.

3.3.4 Perspective

The analysis was conducted from a third-party payer perspective, specifically a Canadian ministry of health.

3.3.5 Efficacy, Safety, and Adverse Events

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

- SSE (fatal and non-fatal)
- MI (fatal and non-fatal)
- Major bleeds (fatal and non-fatal)
- ICH (fatal and non-fatal)
- Minor bleeds
- PE (fatal and non-fatal)
- TIA.

The baseline estimates for the annual rates (r_w) of these events in patients taking warfarin were obtained from the RE-LY RCT. 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. Data from RE-LY were used, as it had the most complete data on the risk of events on warfarin by $CHADS_2$ score. A sensitivity analysis for $CHADS_2$ ≥ 2 is included using the ROCKET-AF data.[43] Details regarding transition probability modelling, as well as clinical parameters related to warfarin use, are presented in Appendices 2 and 3, respectively.

Baseline data for warfarin were available by $CHADS_2$ score for the following events: stroke, ICH, major bleed, and non- event related deaths. For other outcomes, analysis had to adopt event rates for the whole RE-LY population. The probabilities of death due to each event were derived from the warfarin data from the RE-LY trial.[35] No differences in event fatality rates between treatments were assumed.

The network meta-analysis provided relative effects of treatment on SSE, MI, ICH, and major bleeds excluding ICH (extracranial hemorrhage [ECH]). Data on the treatment effect on major bleeds and SSE were available by $CHADS_2$ score and therefore analysis was conducted using ORs specific to the $CHADS_2$ score. Data on MI and ICH were available only for the whole RE-LY treatment population, so that all analyses used generic ORs for these events. All other outcomes for the comparators were assumed to be as for warfarin given the lack of available data to be included in the network meta-analysis (although sensitivity analyses were conducted incorporating the relative risks of non-vascular deaths).

3.3.6 Time Horizon

For the base case analysis, a lifetime horizon (maximum of 40 years post-treatment initiation) was adopted. Sensitivity analysis adopted alternative horizons.

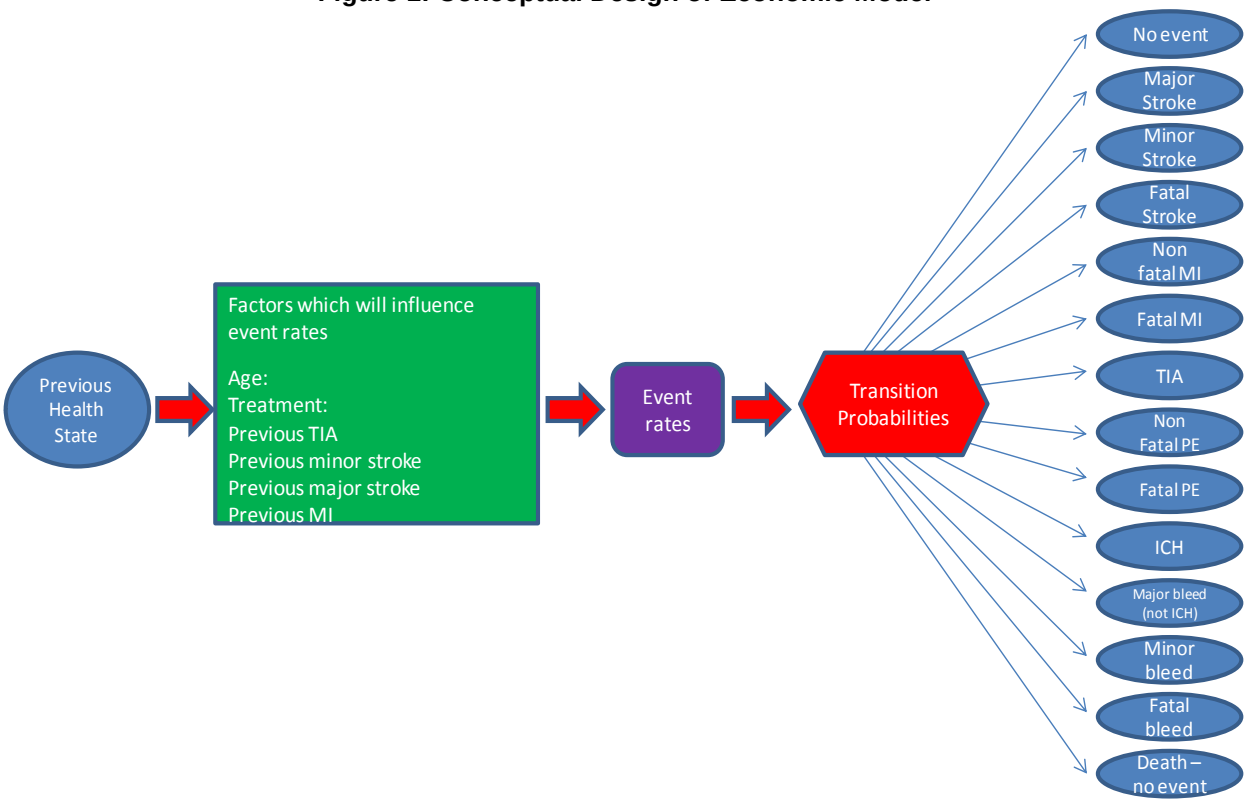
3.3.7 Modelling

The analysis was in the form of a Markov model. The model was a cohort model in that the conceptual framework was to follow a cohort of patients with non-valvular AF receiving pharmacotherapy to prevent stroke.[63] The cohort was followed from initiation of pharmacotherapy to death, while 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 with respect to TIA/SSE (major or minor) and MI. Specific events modelled were TIA, SSE (fatal, major, or minor), bleeding (fatal, ICH, major non-ICH, and minor), MI, PE (fatal or non-fatal), and death without an event. Patients who experienced an SSE, major bleed, or ICH on treatment were assumed to continue with ASA treatment alone.

The conceptual design of the model is detailed in Figure 1. A cycle length of three months was adopted. The relative efficacy of therapies versus warfarin is assumed to continue for the duration of the patient's lifetime while they continue 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 with warfarin. Further details regarding assumptions made for modelling are presented in Appendix 4.

Figure 1: Conceptual Design of Economic Model



ICH = intracranial hemorrhage; MI = myocardial infarction; TIA = transient ischemic attack.

3.3.8 Utility Values

Utility values are required for all health states within the model and are presented in detail in Appendix 5. In the base case, utility values were based on both the patient's previous event history (previous MI or SSE) and whether the patient experienced an event in the current cycle. For patients with no previous event history (i.e., no previous SSE or MI), a utility value of 0.81 was adopted derived from a utility value for AF obtained from a previous study by Sullivan et al.[64]

Utility values for major stroke and minor stroke/SSE were derived from a study by Gage et al.[65] 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 et al.)[66] and are consistent with other values identified in a recent systematic review. Maximum and minimum utility values for both stroke states were obtained from the review by Gage et al. and applied in sensitivity analyses. The utility values for stroke are assumed to apply from the cycle in which the SSE occurred until death.

In the base case, ICH was assumed to have a long-term utility decrement equivalent to minor stroke/SSE, which is within the range of values adopted by previous studies.[67,68] 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.[64] For subsequent months until death a decrement of 0.012 was applied.[69]

Other events were assumed to have a temporary impact on quality of life. Utility estimates were derived from the literature.[64,66,70] Disutilities are presented for impact over a one-month cycle. Thus, for the three-month cycle, the utility weight for a 70-year-old patient with no previous event history experiencing a PE is 0.903 (0.81 to 0.22/3).

Analysis assumed that the utility effects from bleeding were the same regardless of treatment. There are concerns that the consequences of bleeding may be greater with the new oral anticoagulants. However, there is no scientific evidence available demonstrating that the costs and utilities of bleeds vary by treatment. However, sensitivity analysis addressing this by assuming higher consequences for the NOACs and dabigatran in particular is provided.

In a sensitivity analysis, 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[64] — utility values would similarly increase for each year younger than 70.

3.3.9 Costs

Costs for all treatments considered in Canadian dollars for the fiscal year 2011/2012 are detailed in Table 8; other resource costs are presented in Appendix 6. Costs which were obtained for a different base year were inflated using the Bank of Canada Inflation Calculator.[71]

Estimates of drug costs were obtained from the Ontario Drug Benefit Formulary[72] or from the drug manufacturer. Sensitivity analyses were conducted where the drug costs for each drug were reduced by 10% and 20%.

For drug therapy requiring a prescription, 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 Technology 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.[73] 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.[74-78] In sensitivity analyses, the costs of events were increased and decreased by 50%. Long-term care costs associated with MI and stroke/SSE were similarly obtained.[74,77] 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%.

As for utilities, analysis assumed that the costs of bleeding events were the same regardless of treatment. Sensitivity analysis addressing this by assuming higher consequences for the NOACs and dabigatran in particular is provided.

Table 8: Cost Estimates (Per Annum) [a]			
Variable Description	**Base Estimate**	**Probability Distribution**	**Reference**
ASA – low dose	$20.44	Fixed	Manufacturer
ASA – medium dose	$40.88		Manufacturer
Clopidogrel plus ASA	$307.67		Manufacturer/ Ontario MoH (2012)
Warfarin 5 mg daily	$54.61		Ontario MoH (2012)
Dabigatran 110 mg b.i.d.	$1,289.44		Ontario MoH (2012)
Dabigatran 150 mg b.i.d.	$1,289.44		Ontario MoH (2012)
Rivaroxaban 20 mg daily	$1,147.53		Ontario MoH (2012)
Apixaban 5 mg b.i.d.	$1,289.44		Manufacturer
Monitoring INR for warfarin (per annum)	$240.69	Fixed	Medical Advisory Secretariat (2009)[79]

ASA = acetylsalicylic acid; b.i.d. =twice daily; INR = international normalized ratio; M0H = Ministry of Health.
[a] Drug treatment costs include a $7 prescription fee (every three months) and an 8% pharmacist's markup.

Gamma distributions were parameterized by shape and scale, and normal distributions were parameterized by means and standard errors (used when coefficient of variation is minimal).

3.3.10 Sensitivity Analyses

a) 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. Details are provided in Appendix 7.

b) Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis was conducted using a Monte Carlo simulation.[62] For the Monte Carlo 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, while 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 λ for an additional QALY.[62]

3.3.11 Analysis of Variability

In addition to the abovementioned sensitivity analysis, further 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. Where possible, different estimates of the relative treatment effect of the therapies compared with warfarin were included. In addition to further stratification by $CHADS_2$ score, analyses were conducted to stratify patient by age and TTR.

For the refinement of the stratification by $CHADS_2$ score, the network meta-analysis allowed estimation of stratified risk reductions relative to warfarin by $CHADS_2$ score (< 2, ≥ 2) for SSE and major bleeds and these were used for the appropriate populations. For both these outcomes, due to the absence of stratified analysis of the trial results the model did not assume differential efficacy of therapies between

$CHADS_2$ score 0 and 1 and for $CHADS_2$ score with different assumptions relating to the history of SSE. For the analyses by $CHADS_2$ score of 0 and 1, the rate of SSE and bleeding on warfarin is adjusted by the relative rate of events by the score from previous studies.

For stratification by age, the network meta-analysis allowed estimation of stratified risk reductions relative to warfarin by age (< 75 years, ≥ 75 years) for SSE and major bleeds, and these were used for the appropriate populations. To facilitate the required analyses, results were presented for three ages: 60, 70, and 80 years. For other events, the unstratified risk reductions from the network meta-analysis were used. The model incorporates the effect of age on rates of bleeding and SSE on warfarin. Analysis for patients aged less than 75 was restricted to warfarin, dabigatran 150 mg, dabigatran 110 mg, rivaroxaban, and apixaban due to the availability of data. Analysis for patients aged over 75 years also included ASA low-dose.

For stratification by TTR, analysis clinical data relating to centre-specific average TTR, not patient TTR, needed to be used. The network meta-analysis allowed estimation of stratified risk reductions relative to warfarin by centre TTR for SSE 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 SSE, major bleed, ICH, and minor bleeds. For other events, rates for the complete RE-LY trial population were used. Analysis was restricted to warfarin, clopidogrel plus ASA, dabigatran 150 mg, dabigatran 110 mg, rivaroxaban, and apixaban due to the availability of data.

Note that the analyses by age and TTR are for all patients regardless of $CHADS_2$ score due to the absence of data relating to interaction in treatment effect with more than one covariate.

4 RESULTS

4.1 Selection of Primary Studies

The electronic literature search identified 1,580 citations. Upon screening the titles and abstracts, 1,485 citations were excluded. These consisted mainly of reviews, non-relevant study designs or research questions, and studies in which interventions were not of interest. A total of 95 potentially relevant publications were retrieved for full-text review, as well as 5 additional references identified through other sources. Of the 100 potentially relevant reports, 72 articles did not meet the inclusion criteria. Therefore, a total of 28 articles[19-46] reporting results from 12 individual RCTs were included in this review.

To be considered for inclusion, a trial needed to have at least one relevant comparison between two interventions of interest in patients who were eligible for anticoagulant therapy. At least one treatment arm was excluded in 3 of the 12 included trials, as the intervention dosage was not consistent with current recommendations. Placebo-controlled trials were also included, as they provide indirect evidence that can be incorporated in the network meta-analysis.

The trial selection process appears in a PRISMA flowchart (Appendix 8). Included and excluded trials are listed in Appendices 9 and 10, respectively. Note that two studies that were excluded, AVERROES and ACTIVE-A, were included in a sensitivity analysis presented in Appendix 21.

A summary of research available for each treatment strategy included in the MTC is subsequently provided in Table 9. A total of nine treatment strategies were included in the MTC. Information retrieved was not sufficient for the following treatments to be included in the NMA:

- apixaban 2.5 mg twice daily
- high-dose ASA (> 300 mg once daily)
- the combinations of clopidogrel 75 mg once daily with medium-dose ASA (> 100 mg and ≤ 300 mg once daily) and high-dose ASA (> 300 mg once daily).

Table 9: Summary of Interventions Evaluated			
Interventions	**Publications (n)[a]**	**Individual Trials (n)[a]**	**Patients (n)**
Treatment strategies included in the NMA			
Apixaban 5 mg b.i.d.	5	2	9,194
Dabigatran 110 mg b.i.d.	8	1	6,015
Dabigatran 150 mg b.i.d.	9	2	6,242
Rivaroxaban 20 mg q.d.	3	1	7,131
Standard adjusted-dose warfarin	26	10	26,632
ASA ≤ 100 mg q.d. (low dose)	2	2	821
ASA > 100 mg and ≤ 300 mg q.d. (medium dose)	4	3	634
Clopidogrel 75 mg q.d. + low-dose ASA	4	1	3,335
Placebo /No treatment	3	3	972
Treatment strategies *NOT* included in the NMA			
Apixaban 2.5 mg b.i.d.[b]	1	1	74
ASA > 300 mg q.d. (high dose)	0	0	0
Clopidogrel 75 mg q.d. + medium-dose ASA	0	0	0
Clopidogrel 75 mg q.d. + high-dose ASA	0	0	0
Overall[a]	**28**	**12**	**61,050**

ASA = acetylsalicylic acid; b.i.d.= twice daily; n = number of units; NMA = network meta-analysis; q.d. = once daily.

[a] Interventions listed in the table are compared with one another; therefore, the total number of publications and individual trials is not a sum of those for each intervention.

[b] There were no primary efficacy or safety outcome events reported with apixaban 2.5 mg.

4.2 Study and Patient Characteristics

The CADTH systematic review included 12 individual RCTs (reported in 28 publications);[19-46] all evaluated the efficacy and safety of NOACs, warfarin, or ASA with or without clopidogrel in patients with AF. However, no direct treatment comparisons were available to assess the relative efficacy of one new oral anticoagulant drug with another. Details regarding trial characteristics are subsequently presented in Table 10.

Of the 61,050 randomized patients included in this review, 4 large multicentre trials account for 57,284 patients (94%): ARISTOTLE (n = 18,201),[26-29] RE-LY (n = 18,113),[35-42] ROCKET-AF (n = 14,264),[43-45] and ACTIVE-W (n = 6706).[19-22] Trials recruited patients with AF, most of them with at least one risk factor for stroke; however, patients with recent stroke or TIA were usually excluded. Most trials included SSE as a primary efficacy outcome, while bleeding events was a frequent safety outcome. Follow-up ranged between 12 weeks and 3.5 years. All trials published results between 1989 and 2011.

The risk of stroke increases with age and is also substantial in patients with prior stroke or TIA. Higher-risk patients may also present with congestive heart failure, hypertension, and/or diabetes. All these factors are reflected in the $CHADS_2$ score, a commonly used model for risk stratification.[15,57] A mean $CHADS_2$ score was reported in five trials, encompassing the vast majority of patients included in the systematic review: ARISTOTLE (n = 18,201),[26-29] ARISTOTLE-J (n = 222),[30] RE-LY (n = 18,113),[35-42] ROCKET-AF (n = 14,264),[43-45] and ACTIVE-W (n = 6706).[19-22] Reported $CHADS_2$ scores in these trials were consistent with a high-risk population ($CHADS_2 \geq 2$), with patients from ROCKET-AF showing the highest risk for stroke (mean $CHADS_2 = 3.5$) — with 55% of patients with prior stroke or TIA, which is higher than the proportion of these patients included in the other NOAC trials.

Mean age across the included trials ranged from 65 years[33] to 83 years.[46] BAFTA[31] and WASPO[46] both required patients to be ≥ 75 years. Only four other trials reported age categories[26,27,30,34-42] and, in these, the proportions of patients > 75 years ranged from 30%[34] to 40%.[43-45] All trials included patients of both gender and most were relatively balanced. However, the proportions of patients with a prior stroke or TIA varied substantially across the included trials, ranging from 3% in JAST[33] to 55% in ROCKET-AF.[43-45] The same observation can be made regarding the proportions of patients with other concomitant conditions; i.e., congestive heart failure, hypertension, diabetes, and MI. There was also inconsistency in VKA experience among the included populations. VKAs have high inter-individual variability[10-12] and optimal dosing requires time. Therefore, a newly started VKA treatment may very well result in under- or over-anticoagulation, decreasing efficacy or increasing the risk of hemorrhage.

In ARISTOTLE, a dose-modification algorithm was used to reduce the dose of apixaban to 2.5 mg twice daily to minimize the potential for higher exposure in patients who may be at an inherently higher bleeding risk and to maintain a balance between efficacy and safety in such populations. Doses of 2.5 mg twice daily were used in a subset of patients with two or more of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine level ≥ 1.5 mg/dL (133 µmol/L).[26] A reduced dose of apixaban 2.5 mg twice daily was administered to 428 patients in the apixaban group (4.7%).[26] In ROCKET-AF, the dose of rivaroxaban was reduced to 15 mg once daily, but only if creatinine clearance ranged between 30 ml/min and 49 ml/min.[44] As a result, a total of 1,474 patients (20.7%) received a reduced dose of rivaroxaban. By contrast, patients in RE-LY were randomized to two different doses of dabigatran (110 mg and 150 mg), without any dose adjustment and regardless of the patient characteristics.

TTR was reported in all but one trial[24,25] that included a warfarin treatment arm. TTR was ≥ 66% only in BAFTA[31] and WASPO,[46] suggesting moderate to poor INR control in the other trials, with mean TTR ranging from 44%[32] to 64%[19,35]. The rest of the time, the patients may be at risk of bleeding (INR > 3.0) or at risk of thromboembolism (INR< 2.0).

A summary of patient baseline characteristics is subsequently presented in Table 11.

Table 10: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Follow-up**	**Primary Outcome(s)**
ACTIVE-W[19-22] OL RCT, 2006. Multicentre, 32 countries (including Europe / America).	Randomized: n = 6706 Completed: n = 6026 (90%)	AF patients eligible / willing to take anticoagulant therapy, with ≥ 1 pre-specified risk factor for stroke.	**Clopidogrel plus low-dose ASA** (n = 3335) **Warfarin – INR 2.0 to 3.0** (n = 3371)	1.3 years (stopped early)	First occurrence of stroke, non-CNS SE, MI, or vascular death.
AFASAK[23] OL/DB RCT, 1989. Multicentre, Copenhagen.	Randomized: n = 1007 Completed: n = 785 (80%)	AF patients, with no recent anticoagulation or cerebrovascular event, valve replacement or rheumatic heart disease.	**OL Warfarin – INR 2.8 to 4.2** [a] (n = 335) **Low-dose ASA** (n = 336) **PL** (n = 336)	2 years	Thromboembolic complication: stroke, TIA or embolic complication to viscera /extremities.
AFASAK-2[24,25] OL RCT, 1998. Multicentre, Copenhagen.	Randomized: n = 677 Completed: n = 507 (75%)	AF patients ≥ 60 years (unless with CV or pulmonary disease), without recent TIA or risk factors for bleeding.	**Fixed-dose Warfarin** [a] (n = 167) **Fixed-dose Warfarin plus medium-dose ASA** [a] (n = 171) **Medium Dose ASA** (n = 169) **Warfarin – INR 2.0 to 3.0** (n = 170)	3.5 years	Stroke or SE.
ARISTOTLE[26-29] DB RCT, 2011. Multicentre, 39 countries (including Europe / America).	Randomized: n = 18201 Completed: n = 13468 (74%)	AF patients with ≥ 1 risk factor for stroke, without recent stroke or ASA > 165 mg.	**Apixaban 5 mg** b.i.d. (n = 9120; however, 428 of these patients received a reduced dose of 2.5 mg b.i.d.) **Warfarin – INR 2.0 to 3.0** (n = 9081) Concomitant use of **ASA** (≤ 165 mg daily) or **NSAIDs** permitted.	NR	Stroke or SE; Major bleeding.
ARISTOTLE-J[30] OL/DB RCT, 2011. Multicentre, Japan.	Randomized: n = 222 Completed: n = 197 (89%)	AF patients with ≥ 1 risk factor for stroke, without recent TIA or ASA > 100 mg.	**Apixaban 2.5 mg** b.i.d.(n = 74) **Apixaban 5 mg** b.i.d.(n = 74) **OL Warfarin – INR 2.0 to 3.0** (n = 74) Concomitant use of **ASA** (≤ 100 mg daily) permitted.	12 weeks	Composite of major bleeding and CRNM bleeding events.
BAFTA[31] OL RCT, 2007. Multicentre, UK.	Randomized: n = 973 Completed: n = 694 (72%)	AF patients ≥ 75 years, with clinical uncertainty around optimal treatment.	**Low-dose ASA** (n = 485) **Warfarin – INR 2.0 to 3.0** (n = 488)	2.7 years	Disabling stroke, ICH and other clinically significant arterial embolism.
CAFA[32] DB RCT, 1991. Multicentre, Canada.	Randomized: n = 378 Completed: n = 286 (76%)	AF patients without recent stroke, TIA or MI, and who did not require antiplatelet drug therapy.	**Warfarin – INR 2.0 to 3.0** (n = 187) **PL** (n = 191)	1.2 years (stopped early)	Ischemic stroke, SE, ICH or fatal hemorrhage.
JAST[33]	Randomized: n = 871	AF patients without	**Medium-dose ASA** (n = 426)	2.1 years	CV death,

Table 10: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Follow-up**	**Primary Outcome(s)**
OL RCT, 2006. Multicentre, Japan.	Completed: n = 686 (79%)	recent symptomatic thromboembolic disease, ICH or GI bleeding.	**No treatment** (n = 445)	(stopped early)	symptomatic brain infarction, or TIA.
PETRO[34] OL/DB RCT, 2007. Multicentre, 4 countries (Europe and USA).	Randomized: n = 502 Completed: n = 464 (92%)	AF patients with ≥ 1 risk factor for stroke and with coronary artery disease (removed halfway to facilitate recruitment). No recent MI, stroke, TIA or major bleed. Warfarin pre-treatment required for ≥ 8 weeks.	**Dabigatran 50 mg b.i.d. ± Low-dose or High-dose ASA** [a] (n = 105) **Dabigatran 300 mg b.i.d. ± Low-dose or High-dose ASA** [a] (n = 161) **Dabigatran 150 mg b.i.d. ± Low-dose or High-dose ASA** [b] (n = 166) **OL Warfarin – INR 2.0 to 3.0** (n = 70)	12 weeks	Thromboembolic events and bleeding events.
RE-LY[35-42] OL/DB RCT, 2009. Multicentre, 44 countries (including Europe/America).	Randomized: n = 18113 Completed: n = 14580 (80%)	AF patients with ≥ 1 risk factor for stroke, without recent stroke or increased risk of bleeding.	**Dabigatran 110 mg b.i.d.**(n = 6015) **Dabigatran 150 mg b.i.d.**(n = 6076) **OL Warfarin – INR 2.0 to 3.0** (n = 6022) Concomitant use of **ASA** (< 100 mg daily) or other **antiplatelet agents** permitted.	2 years	Stroke or SE and major hemorrhage.
ROCKET-AF[43-45] DB RCT, 2011. Multicentre, 45 countries (including Europe/America).	Randomized: n = 14264 Completed: n = 10957 (77%)	AF patients at moderate to high risk of stroke ($CHADS_2$ score ≥ 2).	**Rivaroxaban 20 mg q.d.** (n = 7131; however, 1,474 of these patients received a reduced dose of 15 mg q.d.) **Warfarin – INR 2.0 to 3.0** (n = 7133) Concomitant use of **ASA** (< 100 mg daily) permitted. Chronic **NSAIDs** not allowed.	1.9 years	Composite of stroke and SE; Composite of major and NMCR bleeding.
WASPO[46] OL RCT, 2007. Multicentre, UK.	Randomized: n = 75 Completed: n = 64 (85%)	Ambulant AF patients > 80 and < 90 years with Folstein score > 25, without previous fall, ICH or GI bleeding. Patients with prior stroke or TIA were excluded.	**Warfarin – INR 2.0 to 3.0** (n = 36) **Medium-dose ASA** (n = 39)	1 year	Combined endpoints: death; stroke, TIA or SE; serious bleeding; withdrawal.

AF = atrial fibrillation; ASA = acetylsalicylic acid; b.i.d. = twice daily CNS = central nervous system; CRNM = clinically relevant non-major bleeding; CV = cardiovascular; DB = double-blind; GI = gastrointestinal; ICH = intracerebral hemorrhage; MI = myocardial infarction; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; OL = open label; PL = placebo; q.d. = once daily; RCT = randomized controlled trial; SE = systemic embolism; TIA = transient ischemic attack; UK = United-Kingdom; VKA = vitamin K antagonist.

[a] No data was extracted from these treatment arms since they did not meet the inclusion criteria specified in the protocol. These trials were nevertheless included in the systematic review because they had at least one relevant comparison between two interventions of interest.

[b] Data was extracted only for dabigatran without ASA (n = 100).

Table 11: Summary of Patient Baseline Characteristics																		
Study	**Baseline Characteristics**															**TTR Throughout Follow-up**		
	Age, Mean ± SD (y)	**Age Category (%)**		**Sex (%)**		**$CHADS_2$, Mean ± SD**	**$CHADS_2$ Category (%)**			**Prior Stroke /TIA (%)**	**DM (%)**	**Heart Failure (%)**	**HBP (%)**	**MI (%)**	**VKA-Naive (%)**	**Mean TTR (%)**	**TTR Category (%)**	
		≤75y	**>75 y**	**M**	**F**		**0**	**1**	**2**								**≤66%**	**>66%**
ACTIVE-W[19-22] n = 6706	70 ± nr	NR	NR	66	34	2 ± 1.1	NR	NR	NR	15	21	30	82	17	23	64	48	52
AFASAK[23] n = 672	75 ± nr	NR	NR	54	46	nr ± nr	NR	NR	NR	6	9	53	32	7	NR	N/A	N/A	N/A
AFASAK-2[24,25] n = 339	73 ± nr	NR	NR	61	39	nr ± nr	NR	NR	NR	8	12	70	45	7	NR	NR	NR	NR
ARISTOTLE[26-29] n = 18201	70 ± nr	69	31	65	35	2.1 ± 1.1	0	34	66	19	25	35	87	14	43	62	NR	NR
ARISTOTLE-J[30] n = 222	70 ± nr	69	31	83	17	1.9 ± nr	1	42	57	28	23	1	83	NR	16	60	NR	NR
BAFTA[31] n = 973	82 ± 4	0	100	55	45	nr ± nr	NR	NR	NR	13	13	20	54	11	NR	67	NR	NR
CAFA[32] n = 378	68 ± nr	NR	NR	75	25	nr ± nr	NR	NR	NR	4	12	22	39	13	NR	44	NR	NR
JAST[33] n = 871	65 ± nr	NR	NR	70	30	nr ± nr	NR	NR	NR	3	14	9	39	NR	92	N/A	N/A	N/A
PETRO[34] n = 236	70 ± nr	70	30	82	18	nr ± nr	NR	NR	NR	18	25	32	71	NR	0	57	NR	NR
RE-LY[35-42] n = 18113	71 ± nr	60	40	64	36	2.1 ± nr	32		68	20	23	32	79	17	50	64	50	50
ROCKET-AF[43-45] n = 14264	73 ± nr	NR	NR	60	40	3.5 ± nr	0	0	100	55	40	62	91	17	38	55	NR	NR
WASPO[46] n = 75	83 ± nr	0	100	47	53	nr ± nr	NR	NR	NR	NR	4	NR	47	NR	NR	69	NR	NR

DM = diabetes mellitus; F = female sex; HBP = high blood pressure; M = male sex; MI = myocardial infarction; N/A = not applicable; NR = not reported; SD = standard deviation; TIA = transient ischemic attack; TTR = time in therapeutic range; VKA = vitamin K antagonist; y = year.
Note: Only data from the included relevant treatment arms have been extracted.

4.3 Critical Appraisal of Included Studies

The studies were individually critically appraised and the details are available in Appendix 11. Overall, there was substantial variation in study quality. However, large multicentre trials such as ARISTOTLE (n = 18,201),[26-29] RE-LY (n = 18,113),[35-42] and ROCKET-AF (n = 14,264),[43-45] which account for the vast majority of patients included in the systematic review, appear to be methodologically rigorous. These trials all compared new anticoagulant agents versus warfarin.

There were various levels of quality concerns with other trials evaluating ASA with or without clopidogrel and placebo/no treatment, especially for ARISTOTLE-J,[30] CAFA,[32] and PETRO.[34] These concerns include open-label designs, differences in baseline characteristics across treatment groups, and discontinuation of up to 29% of randomized patients. Lack of information on allocation concealment for these trials precluded a definite judgment on whether patients and investigators could foresee assignment to the treatment group. In addition, these trials were substantially smaller, older, and overall of lower quality than the anticoagulant trials, therefore affecting our level of confidence in the estimates of effect.

An important aspect of anticoagulant studies that include a VKA group is the quality of INR control, which was adequately reported through TTR. The benefit of warfarin therapy is expected to increase with TTR, which gets higher with improved INR control.[15] However, mean TTR was considered optimal (≥ 66%) only in two trials: BAFTA[31] and WASPO,[46] while it was less but still near the optimal value (between 60% and 66%) in four trials: ACTIVE-W,[19-22] ARISTOTLE,[26-29] ARISTOTLE-J,[30] and RE-LY.[35-42] Mean TTR was sub-optimal (< 60%) in CAFA,[32] PETRO,[34] and ROCKET-AF.[43-45] This suggests moderate to poor INR control, hence favouring the comparator. However, poor INR control could also arguably increase the generalizability of the results, because INR monitoring is often not optimal in clinical practice.[80] AFASAK[23] and JAST[33] did not have a warfarin treatment arm.

Finally, the use of a dose-modification algorithm in ARISTOTLE[26-29] to reduce the dose of apixaban to 2.5 mg twice daily could theoretically have favoured apixaban in an indirect comparison among the NOACs. A lower dose would be expected to minimize the potential for higher exposures in populations that may be at an inherently higher bleeding risk. The fact that fewer than 5% of all patients were treated with the lower dose of apixaban, however, suggests that the potential impact of this potential bias is likely very small.

4.4 Indirect Comparisons

MTCs and pairwise meta-analyses were conducted for each of the six outcomes figuring in Table 12. The number of individual RCTs included in the evidence networks varied from 6 to 10 studies, and these collectively included between 58,457 and 60,592 patients. A summary of data available for the MTC is presented as well in Table 12. Evidence networks for the NMA are presented in Appendix 12. Appendix 13 presents a summary of results from the NMA, with warfarin as a common comparator, while Appendix 14 reports pairwise comparisons among all interventions. Finally, detailed data incorporated into the models are presented in Appendix 15.

Table 12: Summary of Evidence Available for the MTC			
Outcome	**No. of Treatment Strategies**	**No. of Patients**	**No. of RCTs**
All-cause SSE	9	60,424	9
Major Bleeding	9	60,503	10
All-cause mortality	9	60,592	10
ECH	9	60,428	9
ICH	9	59,756	8
MI	8	58,475	6

ECH = extracranial hemorrhage; ICH = intracranial hemorrage; MI = myocardial infarction; MTC = mixed treatment comparison; No. = number; RCT = randomized controlled trial; SSE = stroke or systemic embolism.

All models provided a reasonable fit to the data (Appendix 16) when compared with the unconstrained data points (i.e., values are close to the number of unconstrained data points for all models fitted). In addition, direct estimates of effect sizes aligned closely with the estimated effect sizes derived from the NMA.

The results from the random-effects model were very similar to those of the fixed-effects model for all outcomes (Appendices 16 and 17), with the main difference being the size of the CIs for each point estimate; specifically, the credible intervals were greater for the random-effects model. A detailed comparison of the relative merits of the fixed- versus random-effects model is beyond the scope of this report; results from the fixed-effects model (versus random-effects model) are presented in the main text, for the following reasons:

- The nodes in evidence networks are connected mainly by single studies (Appendix 12).
- Effect estimates derived from the fixed-effects model aligned more closely with direct estimates of effect sizes derived from individual RCTs (Results section).
- The DIC (a measure of model fit that penalizes model complexity) for the fixed-effects model was lower for the fixed-effects model for most of the outcomes considered (Appendix 16).
- The use of non-informative priors had a large impact on credible intervals in the random-effects model.

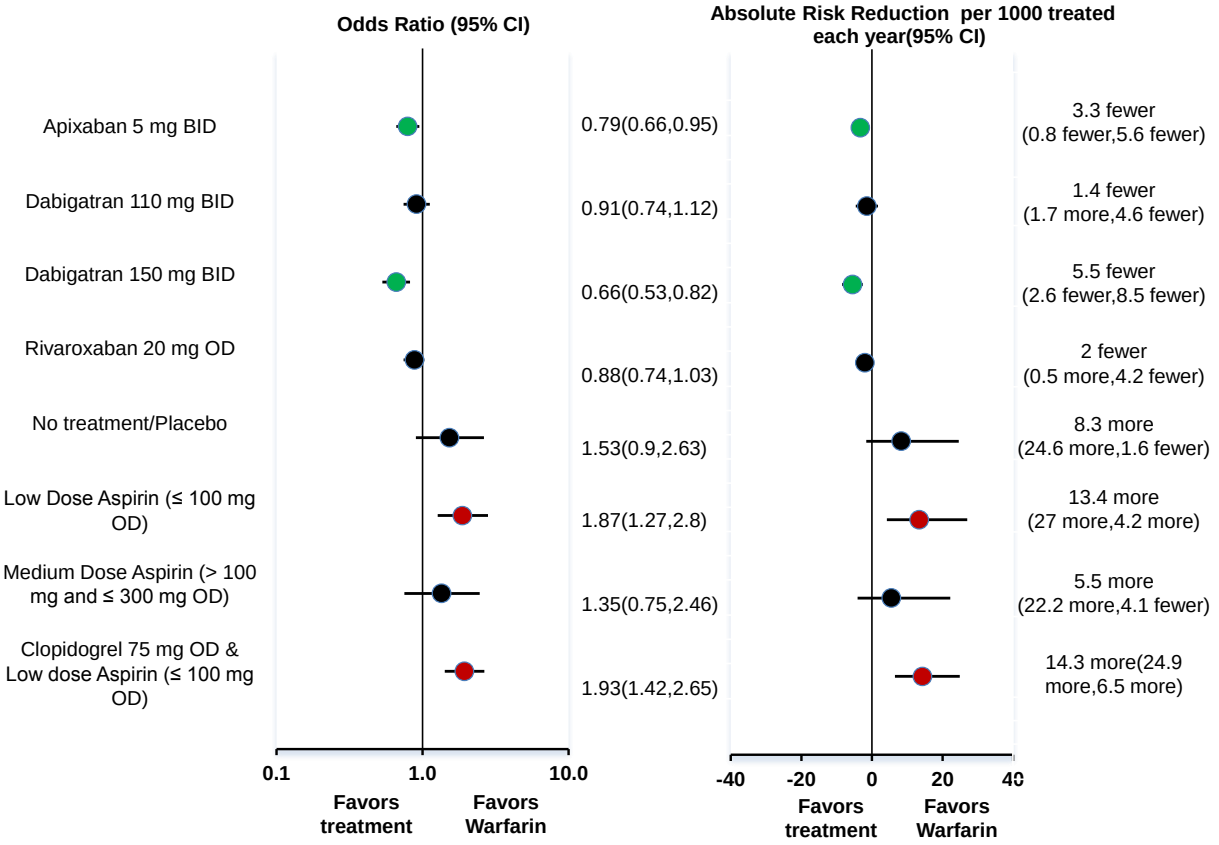
4.4.1 Stroke and Systemic Embolism

There were 9 RCTs (N = 60,424) that reported data for SSE. Results from the NMA are summarized in Figure 2, but are also presented in Appendix 13.

Statistical significance for SSE was reached for apixaban and dabigatran 150 mg compared with adjusted-dose warfarin, based on a lower OR. The use of these two agents led to absolute risk reductions ranging from 1 to 6 fewer events per 1,000 patients treated each year with apixaban and from 3 to 9 fewer events with dabigatran. By contrast, low-dose ASA and the combination of clopidogrel plus low-dose ASA appeared statistically significantly less effective than adjusted-dose warfarin at preventing SSE, with absolute results ranging from 4 to 27 more events per 1,000 patients treated each year. No statistically significant difference was detected between warfarin and each of the following interventions: rivaroxaban, dabigatran 110 mg, medium-dose ASA, and no treatment/placebo.

Among the different treatments, dabigatran 150 mg had the highest probability of having the best outcome on SSE (87.5%) and was ranked highest among the treatment options (Table A13.1 in Appendix 13).

Figure 2: OR and ARD of All-Cause SSE for Antithrombotic Therapies Relative to Adjusted-Dose Warfarin for Patients With AF, Fixed-Effects NMA [a]



AF = atrial fibrillation; ARD = absolute risk difference; BID = twice daily; CI = confidence interval; NMA = network meta-analysis; OD = once daily; SSE = stroke and systemic embolism.

[a] Data points represent the OR ± 95% CI. Green data points indicate statistically lower OR versus warfarin. Red data points indicate statistically higher OR versus warfarin.

Results for pairwise comparisons versus warfarin for SSE are reported in Table A13.1 in Appendix 13. Results for all pairwise contrasts are presented in Table A14.1 in Appendix 14. Estimates of effect relative to warfarin derived from the direct pairwise comparisons aligned closely with those obtained from the NMA in both direction and magnitude — except for low-dose ASA, medium-dose ASA, and no treatment/placebo, for which there was some variation in the OR. However, in no case was there a discrepancy between the direct pairwise comparisons and the NMA in statistical significance of the effect sizes.

As for pairwise comparisons among other treatment options, dabigatran 150 mg was associated with statistically significantly fewer SSE versus dabigatran 110 mg and rivaroxaban. No other differences between the new anticoagulant agents reached statistical significance. The magnitude of the differences among all new anticoagulants was considered relatively small, with OR ranging from 0.83 to 1.33.

There were no statistically significant differences among low-dose ASA, medium-dose ASA, and clopidogrel plus low-dose ASA. However, low-dose ASA and the combination of clopidogrel plus low-dose ASA were statistically significantly less effective at preventing SSE compared with all the anticoagulantdrugs, including adjusted-dose warfarin, dabigatran, apixaban, and rivaroxaban. The effect size for SSE for medium-dose ASA was greater relative to the anticoagulant treatments, but this difference only reached statistical significance versus dabigatran 150 mg.

The point estimates for the Bayesian random-effects NMA were similar to those reported in the fixed-effects NMA, although the credible intervals were wider in the random-effects model (Appendix 17). As a result, some findings that were statistically significant in the fixed-effects model did not retain statistical significance in the random-effects model. This was the case for apixaban and dabigatran 150 mg, as well as low-dose ASA and the combination of clopidogrel plus low-dose ASA, which became non-significant in the random-effects model.

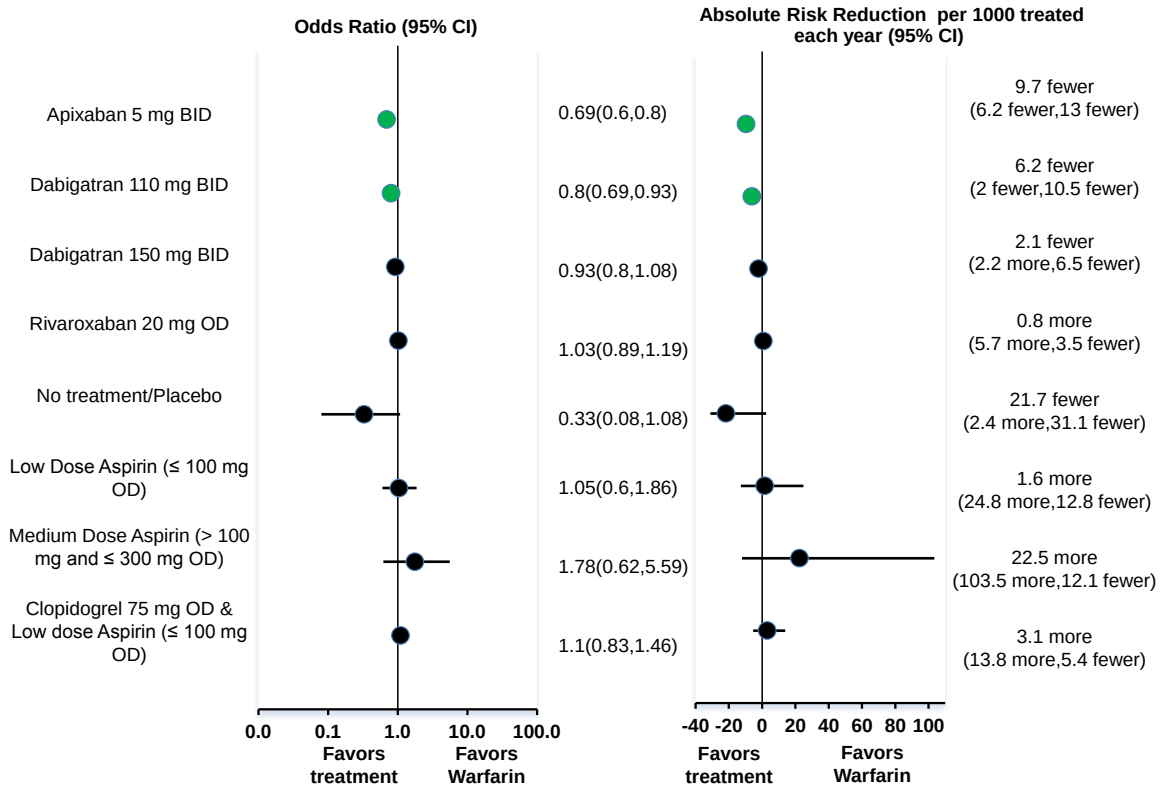
4.4.2 Major Bleeding

Data for major bleeding were available from 10 RCTs (N = 60,503). Results from the NMA are summarized in Figure 3, but are also presented in Appendix 13. Although there were some variations in the definition of major bleeding, most of the trials employed a definition that was consistent with the following: bleeding requiring transfusion of at least two units of red blood cells or the equivalent of whole blood, or associated with a decrease in the hemoglobin level of ≥ 20 g/L, bleeding at a critical site, or fatal bleeding. ICH was typically included in the definition.

Statistical significance for major bleeding was reached for apixaban and dabigatran 110 mg compared with adjusted-dose warfarin, with a lower OR. Absolute risk reductions with these agents ranged from two to 13 fewer events per 1,000 patients treated each year. No statistically significant differences in the OR for major bleeding were detected between warfarin and each of the remaining interventions: rivaroxaban, dabigatran 150 mg, clopidogrel plus low-dose ASA, and all ASA dosages.

No treatment/placebo was associated with the largest positive effects estimate with an OR = 0.33 (22 fewer events per 1,000 patients treated each year), but did not reach statistical significance (95% CrI, 0.08 to 1.08). This intervention had the highest probability of having the best outcome for major bleeding (88.0%) and was ranked highest among all treatments (Table A13.2 in Appendix 13). Among the active treatments, apixaban had the highest probability of having the best outcome for major bleeding (10.1%) and was ranked highest among the active treatments.

Figure 3: Odds Ratio and Absolute Risk Difference of Major Bleeding for Antithrombotic Therapies Relative to Adjusted-Dose Warfarin for Patients With AF, Fixed-Effects NMA



AF = atrial fibrillation; ARD = absolute risk difference; BID = twice daily; CI = confidence interval; NMA = network meta-analysis; OD = once daily.

Results for pairwise comparisons versus warfarin for major bleeding are reported in Table A13.2 in Appendix 13. Results for all pairwise contrasts are presented in Table A14.2 in Appendix 14. Estimates of effects derived from the direct pairwise comparisons aligned closely with those obtained from NMA in both direction and magnitude. In no case was there a discrepancy between the direct pairwise comparisons and the NMA in the statistical significance of the effect sizes.

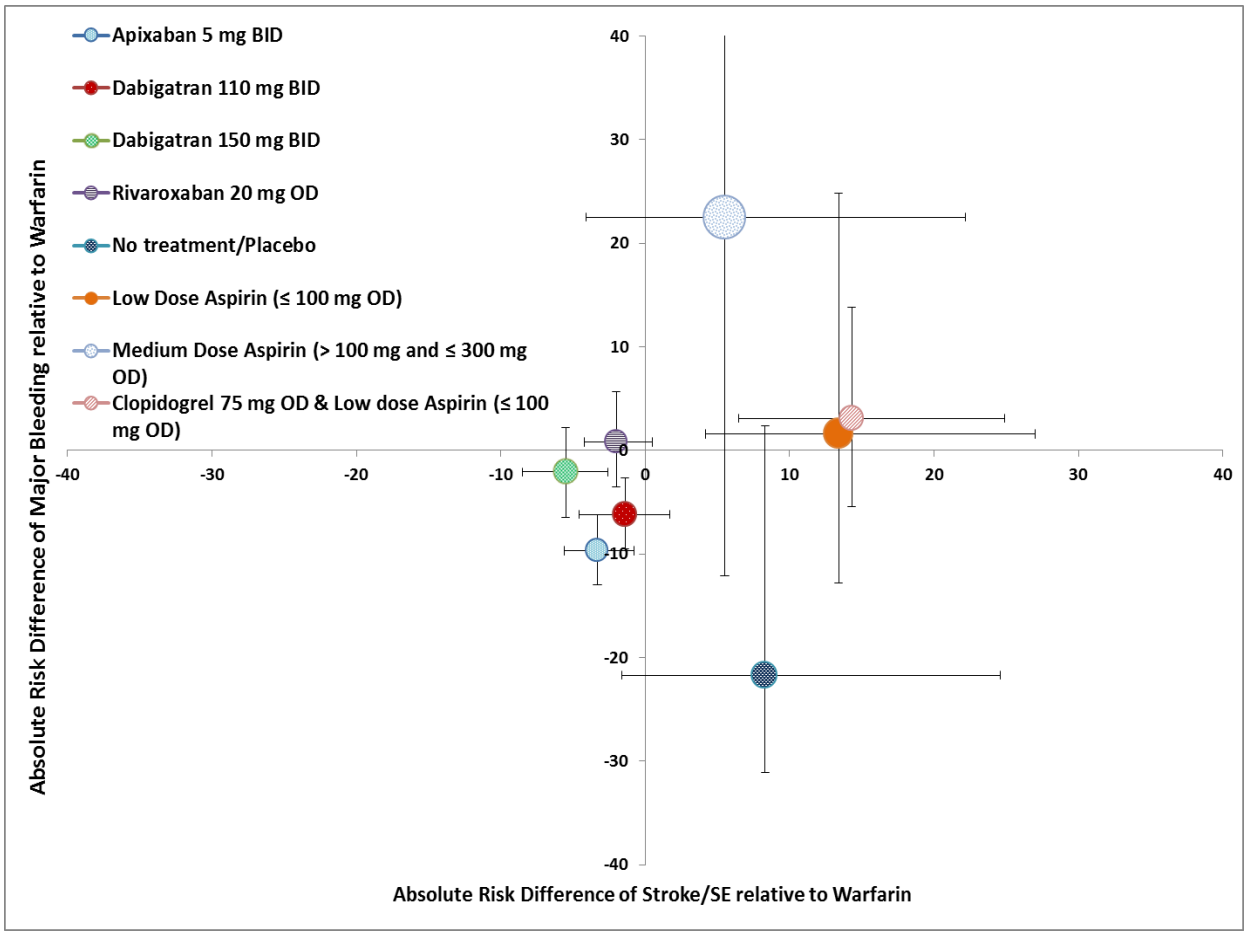
As for pairwise comparisons, apixaban and dabigatran 110 mg were associated with statistically significantly fewer major bleeding events versus dabigatran 150 mg and rivaroxaban. The OR for apixaban was also statistically significantly lower compared with clopidogrel plus low-dose ASA. There were no significant differences associated with the ASA treatments, both for comparisons among themselves and compared with the anticoagulant treatments.

As in the case of SSE, the point estimates for the Bayesian random-effects NMA of the major bleeding data were similar to those reported in the fixed-effects NMA, although the credible intervals were wider in the random-effects model (Appendix 17). As a result, apixaban and dabigatran 110 mg did not retain statistical significance in the random-effects model.

4.4.3 Stroke and Systemic Embolism versus Major Bleeding

Prevention of SSE (i.e., the most important benefit of treatment) must be balanced by the potential for an increased risk of serious bleeding. Plotting the relative effect sizes of the various treatments for these two outcomes, SSE versus major bleeding (which includes ICH) illustrates the overall comparative benefit/risk profile for the nine interventions that we analyzed (Figure 4). Data in Figure 4 were obtained from the results presented in Tables A13.1 and A13.2 (in Appendix 13) for the ARD for SSE and major bleeding versus warfarin, calculated using a fixed-effects NMA. Examination of the data in Figure 4 suggests that the benefit/risk of the NOACs is positive compared with warfarin (decrease in SSE and/or major bleeding) and largely similar among one another. Comparison of all anticoagulant treatment (including warfarin) to ASA with or without clopidogrel indicates that, whereas the NOACs decrease the risk of SSE and major bleeding, ASA clearly has a less favourable benefit/risk profile and fails to minimize the risk of SSE and/or major bleeding.

Figure 4: ARD for SSE versus MB Relative to Warfarin for Nine Different Interventions for the Reference Case [a]



ARD = absolute risk difference; b.i.d. = twice daily; MB = major bleeding; OD = once daily; SE = systemic embolism; SSE = stroke and systemic embolism.
[a]The axes indicate reference treatment (warfarin) where the ARD for SSE and MB is 0.

4.4.4 All-Cause Mortality

Ten RCTs (N = 60,592) reported data for all-cause mortality. Results from the NMA for this outcome are presented in Appendix 13, Table A13.3. Results for all pairwise contrasts are presented in Table A14.3 in Appendix 14.

Only apixaban achieved a statistically significant reduction in all-cause mortality compared with adjusted-dose warfarin in the NMA analysis (OR = 0.89 [0.794 to 0.997]). For this outcome, apixaban led to absolute risk reductions versus warfarin ranging from 0.1 to 8 fewer events per 1,000 patients treated each year. Other antithrombotic therapies did not seem to impact mortality: results from both the NMA and pairwise comparison analyses did not find any statistically significant differences among other treatment options. However, the NMA comparison for warfarin versus dabigatran and rivaroxaban yielded results which, although not statistically significant, were similar in terms of magnitude to those observed for apixaban (Table A13.3 in Appendix 13).

4.4.5 Extracranial Hemorrhage

There were 9 RCTs (N = 60,428) that reported data for extracranial hemorrhage. Results from the NMA are presented in Appendix 13. As was the case for mortality, only apixaban achieved a statistically significant reduction in extracranial hemorrhage compared with adjusted-dose warfarin in the NMA analysis (OR = 0.8 [0.68 to 0.94]), leading to absolute risk reductions versus warfarin ranging from 2 to 8 fewer events per 1,000 patients treated each year. No other treatment options were associated with a statistically significant reduction in extracranial hemorrhage compared with adjusted-dose warfarin.

Results for pairwise comparisons versus warfarin for major bleeding are reported in Table A13.4 in Appendix 13. Results for all pairwise contrasts are presented in Table A14.4 in Appendix 14. Apixaban also resulted in a statistically significant reduction in extracranial hemorrhage compared with dabigatran 150 mg, rivaroxaban, and medium-dose ASA. Medium-dose ASA was also associated with a statistically significant increase in extracranial hemorrhage relative to placebo/no treatment.

4.4.6 Intracranial Hemorrhage

Data for ICH were available from eight RCTs (N = 59,756). Results from the NMA are presented in Appendix 13. All NOACs were associated with statistically significant reductions in ICH compared with adjusted-dose warfarin (OR = 0.42 [0.3 to 0.58] for apixaban, OR = 0.31 [0.19 to 0.47] for dabigatran 110 mg, OR = 0.4 [0.27 to 0.59] for dabigatran 150 mg, and OR = 0.65 [0.46 to 0.92] for rivaroxaban, versus warfarin). Absolute risk reductions were similar between these interventions, ranging from three to seven fewer events per 1,000 patients treated each year. Other antithrombotic therapies did not seem to impact ICH, as there were no other statistically significant differences among treatment options.

Results for pairwise comparisons versus warfarin for ICH are reported in Table A13.5 in Appendix 13. Results for all pairwise contrasts are presented in Table A14.5 in Appendix 14. Dabigatran 110 mg resulted in a statistically significant decrease in ICH compared with rivaroxaban. Clopidogrel plus low-dose ASA was associated with a statistically significant increase in ICH relative to apixaban, dabigatran, rivaroxaban, and no treatment/placebo; however, there is substantial uncertainty surrounding these pairwise comparisons, as expressed by the very large CI.

4.4.7 Myocardial Infarction

A total of six RCTs (N = 58,457) reported data for MI. Results from the NMA are presented in Appendix 13. Dabigatran 150 mg was associated with an increase in MI compared with adjusted-dose warfarin that reached statistical significance (OR = 1.41 [1.02 to 1.96]). ARD versus warfarin ranged from 4 to 0.1 more events per 1,000 patients treated each year. Other antithrombotic therapies did not impact MI, as there were no other statistically significant differences among treatment options.

Results for pairwise comparisons versus warfarin for MI are reported in Table A13.6 in Appendix 13. Results for all pairwise contrasts are presented in Table A14.6 in Appendix 14. Dabigatran (both doses),

medium-dose ASA, and the combination of clopidogrel plus low-dose ASA were associated with a statistically significant increase in MI compared with apixaban. Medium-dose ASA was also associated with a statistically significant increase in MI compared with rivaroxaban.

4.4.8 Subgroup Analyses

a) $CHADS_2$ Score

$CHADS_2 < 2$

We conducted a subgroup analysis where we considered patients who had a lower stroke risk (i.e., $CHADS_2 <2$). Evidence diagrams for the $CHADS_2 < 2$ subgroup analyses are presented in Appendix 12. A breakdown of the proportion of the patients with $CHADS_2 = 0$ and $CHADS_2 = 1$, for which the treatment recommendations[3-5] differ, are provided in Appendix 18. However, there were only very few patients for all interventions with $CHADS_2 = 0$. Therefore, although this subgroup analysis is labelled $CHADS_2 < 2$, almost all included patients had a $CHADS_2 = 1$.

There were limited data for ASA for this subgroups analysis, both for $CHADS_2 < 2$ and for $CHADS_2 \geq 2$. As a result, we were required to use subgroup data that either only partially aligned with the subgroups (i.e., BAFTA had $CHADS_2$ 1-2 versus 0-1) or study-level data from studies consisting of low-risk patients (e.g., CAFA, JAST), although a small proportion of patients (< 25%) had a $CHADS_2 \geq 2$.

Stroke and Systemic Embolism: Table A13.7 in Appendix 13 shows comparisons between warfarin and each NOAC. Whereas dabigatran 150 mg and apixaban were superior to warfarin in the reference case analysis, results differed in the $CHADS_2 < 2$ subgroup. No statistically significant differences were observed between warfarin and each evaluated NOAC for SSE. No data were available for rivaroxaban, so it was not included in the subgroup analysis. SSE results for the ASA treatments in the $CHADS_2 < 2$ analysis matched those of the reference case; specifically, low-dose ASA and the combination of clopidogrel plus low-dose ASA appeared statistically significantly less effective than adjusted-dose warfarin at preventing SSE, this time with an ARD of 12 and 21 more SSE per 1,000 patients treated each year. There was no statistically significant difference between warfarin and medium-dose ASA.

Table A14.7 in Appendix 14 shows all pairwise comparisons. Dabigatran 150 mg was associated with statistically significantly fewer SSE versus dabigatran 110 mg, as in the reference case analysis. However, there were no other statistically significant differences anymore among the NOACs (no data was available for rivaroxaban).

Other results for this subgroup analysis were consistent with those for the overall population. More precisely, there were no statistically significant differences among low-dose ASA, medium-dose ASA, and clopidogrel plus low-dose ASA. However, low-dose ASA and the combination of clopidogrel plus low-dose ASA were statistically significantly less effective at preventing SSE compared with anticoagulant drugs. Results for medium-dose ASA did not reach statistical significance.

Major Bleeding: Table A13.8 in Appendix 13 shows comparisons between warfarin and each NOAC. The results of the analysis for major bleeding in the $CHADS_2 < 2$ subgroup were similar to those of the reference case analysis; statistical significance for major bleeding was reached for apixaban and dabigatran 110 mg compared with adjusted-dose warfarin, while no statistically significant differences in the OR for major bleeding were detected between warfarin and each of the remaining interventions.

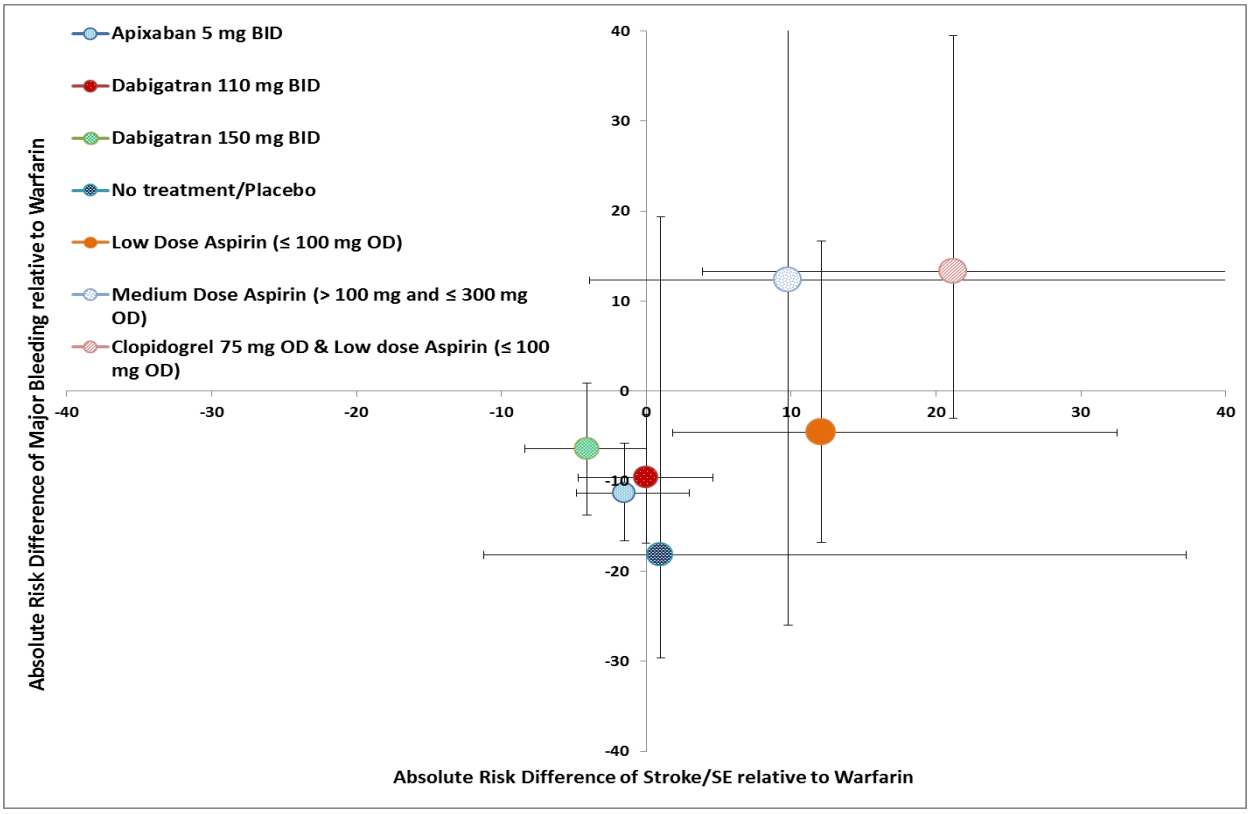
As in the reference case analysis, no treatment/placebo had the highest probability among the different treatments of having the best outcome for major bleeding (67.8%) and was ranked highest (Table A13.8 in Appendix 13). Among the active treatments, apixaban had the highest probability among the different treatments of having the best outcome for major bleeding (16.5%) and was ranked highest.

Table A14.8 in Appendix 14 shows all pairwise comparisons. There were no statistically significant differences among the NOACs for major bleeding (no data was available for rivaroxaban). This is in contrast to the reference case analysis, where apixaban and dabigatran 110 mg were superior to dabigatran 150 mg and rivaroxaban in the overall population. As in the reference case analysis, the OR

for major bleeding was not different among the ASA treatments (low-dose ASA, medium-dose ASA, and clopidogrel plus low-dose ASA), and between ASA monotherapy and anticoagulants; however, the combination of clopidogrel plus low-dose ASA resulted in more major bleeding than apixaban and dabigatran (both doses).

Stroke and Systemic Embolism Versus Major Bleeding: As previously noted for the reference case, plotting the relative effect sizes (regarding ARD versus warfarin) of the various treatments for SSE (benefit) versus major bleeding (risk) illustrates the overall comparative benefit/risk profile for the eight treatments that we analyzed for the CHADS < 2 subgroup (Figure 5). Examination of the data in Figure 5 suggests that the benefit/risk of the NOACs is positive compared with warfarin (decrease in SSE and/or major bleeding) and closer to the benefit/risk of warfarin than the ASA treatments: whereas the NOACs (except rivaroxaban, which was not included in this analysis) decrease the risk of both SSE and major bleeding, ASA has a less favourable benefit/risk profile and fails to reduce the risk of SSE and major bleeding. These results are not dissimilar to the risk/benefit in the reference case (Figure 4).

Figure 5: ARD for SSE versus MB Relative to Warfarin for Eight Different Interventions for $CHADS_2$ Score < 2.[a]



ARD = absolute risk difference; BID = twice daily; MB = major bleeding; OD = once daily; SE = systemic embolism; SSE = stroke and systemic embolism.

[a] The axes indicate reference treatment (warfarin) where the ARD for SSE and MB is 0.

$CHADS_2 \geq 2$

We conducted a subgroup analysis where we considered patients who had a higher stroke risk (i.e., $CHADS_2 \geq 2$). Evidence diagrams for the $CHADS_2 \geq 2$ subgroup analyses are presented in Appendix 12. A breakdown of the proportion of the patients with $CHADS_2 \geq 2$ is provided in Appendix 18. There were limited data for ASA for this subgroups analysis, both for $CHADS_2 < 2$ and for $CHADS_2 \geq 2$. As a result, we were required to use subgroup data that only partially aligned with the subgroups (i.e., BAFTA had $CHADS_2$ 3 to 6 versus 2 to 6).

Stroke and Systemic Embolism: Table A13.7 in Appendix 13 shows comparisons between warfarin and each NOAC. Results for the $CHADS_2 \geq 2$ subgroup were consistent with the reference case analysis: dabigatran 150 mg and apixaban were both statistically significantly superior to warfarin. However, this contrasts with the $CHADS_2 < 2$ subgroup, where no statistically significant differences were observed between warfarin and each evaluated NOAC for SSE. No statistically significant difference was detected between warfarin and each of the following interventions: rivaroxaban, low-dose ASA, and the combination of clopidogrel plus low-dose ASA (medium-dose ASA could not be assessed in the $CHADS_2 \geq 2$ subgroup).

As in the reference case and the $CHADS_2 < 2$ subgroup analyses, dabigatran 150 mg had the highest probability among the different treatments of having the best outcome for SSE (80.9%) and was ranked highest among the treatments.

Table A14.7 in Appendix 14 shows all pairwise comparisons. These results were consistent with the reference case analysis and the $CHADS_2 < 2$ subgroup: superiority of dabigatran 150 mg over dabigatran 110 mg was the only comparison among NOACs reaching statistical significance. Low-dose ASA and the combination of clopidogrel plus low-dose ASA were statistically significantly less effective at preventing SSE compared with anticoagulants. When compared against one another, the combination of clopidogrel plus low-dose ASA led to more SSE events than low-dose ASA alone. No data was available for medium-dose ASA.

Major Bleeding: Table A13.8 in Appendix 13 shows comparisons between warfarin and each NOAC. In the $CHADS_2 \geq 2$ subgroup, only apixaban was statistically significantly superior to warfarin. This contrasts with the reference case and the $CHADS_2 < 2$ subgroup analyses, where dabigatran 110 mg was also superior to warfarin. No statistically significant differences in the OR for major bleeding were detected between warfarin and each of the remaining interventions.

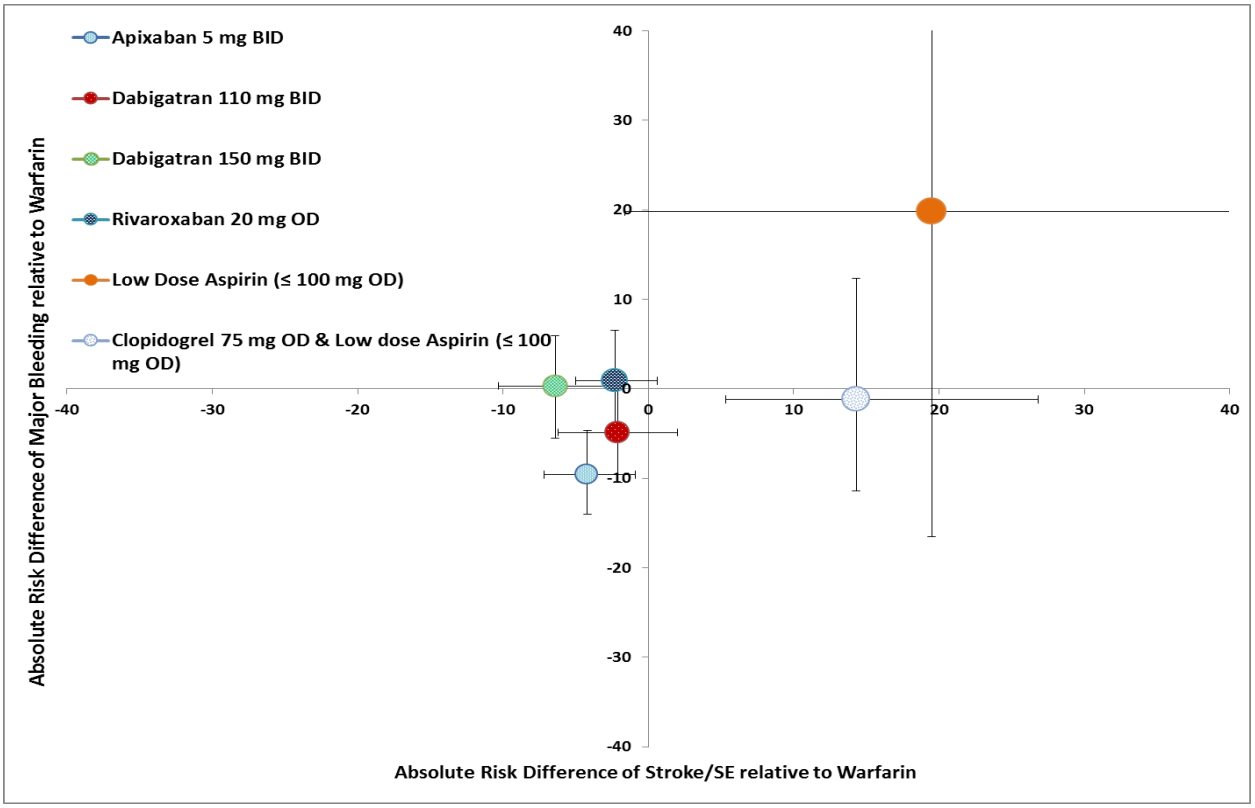
Apixaban had the highest probability among the different treatments of having the best outcome for major bleeds (78.5%) and was ranked highest (Table A13.8 in Appendix 13). Note that no treatment/placebo was not included in this subgroup analysis, but had the highest probability of minimizing major bleeding in the reference case and the $CHADS_2 < 2$ subgroup analyses. However, apixaban was the highest ranked among active treatment options.

Table A14.8 in Appendix 14 shows all pairwise comparisons. In patients with a $CHADS_2 \geq 2$, apixaban was superior to dabigatran 150 mg and rivaroxaban. This contrasts with the absence of any differences among the NOACs in the $CHADS_2 < 2$ subgroup, but is in line with the results of the reference case analysis. There were no statistically significant differences between low-dose ASA and clopidogrel plus low-dose ASA, and between these treatments and the other interventions, as was the case in the reference scenario.

Stroke and Systemic Embolism Versus Major Bleeding: To illustrate the overall comparative benefit/risk profile for the seven treatments that we analyzed for the $CHADS_2 \geq 2$ subgroup, we plotted the relative effect sizes (for ARD versus warfarin) of the various treatments for SSE (benefit) versus major bleeding (risk) in Figure 6. Examination of the data in Figure 6 suggests that the benefit/risk of the NOACs is positive compared with warfarin (decrease in SSE and/or major bleeding) and very similar to the benefit/risk of warfarin. This is consistent with the reference case (Figure 4) and the CHADS < 2 subgroup (Figure 5). As in the reference case and CHADS < 2 subgroup, low-dose ASA has a less favourable benefit/risk profile than the NOACs; however, the benefit/risk profile for clopidogrel plus low-dose ASA

appears to be close to the anticoagulants in this subgroup, which was not the case in the CHADS < 2 subgroup or the reference case. However, the level of confidence in this observation is considerably lower than for the anticoagulant drugs, as the estimated effect sizes for clopidogrel plus low-dose ASA are derived from a single RCT with substantially fewer patients compared with the anticoagulant trials.

Figure 6: ARD for SSE versus MB Relative to Warfarin for Seven Different Interventions for $CHADS_2$ Score ≥ 2[a]



ARD = absolute risk difference; BID = twice daily; MB = major bleeding; OD = once daily; SE = systemic embolism; SSE = stroke and systemic embolism.
[a]The axes indicate reference treatment (warfarin) where the ARD for SSE and MB is 0.

b) Other Subgroups

Age and Time in Therapeutic Range

We also conducted subgroup analyses, where results were stratified by age and TTR. Evidence diagrams for subgroup analyses are presented in Appendix 12. Although fewer data were available for these subgroups compared with the $CHADS_2$ score, analyses could be performed for all anticoagulant drugs (warfarin and the NOACs). Data on antiplatelet agents were scarce; evaluated interventions were limited to low-dose ASA for the age ≥ 75 years subgroup; the combination of clopidogrel and low-dose ASA for the TTR < 66% subgroup; and medium-dose ASA for the TTR ≥ 66% subgroup.

Stroke and Systemic Embolism

Age: Table A13.9 in Appendix 13 shows comparisons between warfarin and each NOAC. The results of the analysis stratified by age for SSE in the ≥ 75 years subgroup were similar to those of the reference case analysis, where dabigatran 150 mg and apixaban were superior to warfarin; however, only dabigatran retained statistical significance in the < 75 years subgroup. SSE results for ASA in the age ≥ 75 years analysis matched those of the reference case; specifically, low-dose ASA was statistically significantly less effective at preventing SSE compared with adjusted-dose warfarin; however, no antiplatelet agents could be included in the evidence network for the age < 75 years subgroup. 4Based on

the increased absolute risk reduction versus warfarin, newer anticoagulants seemed to have a greater benefit for stroke prevention in older patients (≥ 75 years) than in a younger population (< 75 years).

Table A14.9 in Appendix 14 shows all pairwise comparisons. In the < 75 years subgroup, dabigatran 150 mg was associated with statistically significantly fewer SSE versus dabigatran 110 mg, as in the reference case analysis; however, there were no statistically significant differences anymore among the NOACs in the ≥ 75 years subgroup. As in the reference analysis, all anticoagulants were significantly superior to low-dose ASA.

TTR: Table A13.11 in Appendix 13 shows comparisons between warfarin and each NOAC. In the TTR< 66% (poorly controlled) subgroup, only dabigatran 150 mg yielded statistically significant results for stroke prevention over warfarin, as well as over rivaroxaban. Decreases in the number of events observed with apixaban did not reach statistical significance, as it did in the reference case. In the TTR ≥ 66% (adequately controlled) subgroup, no statistically significant improvement was observed across all interventions. Of note, dabigatran 150 mg showed substantially greater benefits when compared with warfarin in patients with a poorly controlled INR compared with adequately controlled patients. Table A14.11 in Appendix 14 shows all pairwise comparisons.

Major Bleeding
Age: Table 13.10 in Appendix 13 shows comparisons between warfarin and each NOAC. As in the reference case analysis, statistical significance for reductions in major bleeding was reached for apixaban and dabigatran 110 mg compared with adjusted-dose warfarin in the < 75 years subgroup. In this younger population, dabigatran 150 mg was also superior to warfarin, which was not the case previously. Table A14.10 shows all pairwise comparisons.There was no difference between warfarin and rivaroxaban; however, rivaroxaban appeared to cause statistically significantly more major bleeding than both doses of dabigatran. In the ≥ 75 years subgroup, apixaban achieved statistical superiority over all other anticoagulant drugs. There was no statistically significant difference between all of the remaining interventions, including between low-dose ASA and anticoagulants.

TTR: Table A13.12 in Appendix 13 shows comparisons between warfarin and each NOAC. While apixaban and both doses of dabigatran led to a statistically significant reduction in major bleeding in the poorly controlled subgroup (TTR < 66%), only apixaban retained statistical significance in the adequately controlled subgroup (TTR ≥ 66%). Notwithstanding statistical significance, all NOACs resulted in substantially greater risk reductions in major bleeding versus warfarin in patients with a poorly controlled INR compared with adequately controlled patients, which was more pronounced than for SSE. Table A14.12 in Appendix 14 shows all pairwise comparisons. As in the reference analysis, apixaban was also superior to dabigatran 150 mg and rivaroxaban in both subgroups.

4.5 Pharmacoeconomic Evaluation

4.5.1 Base Case Analysis

a) $CHADS_2 < 2$

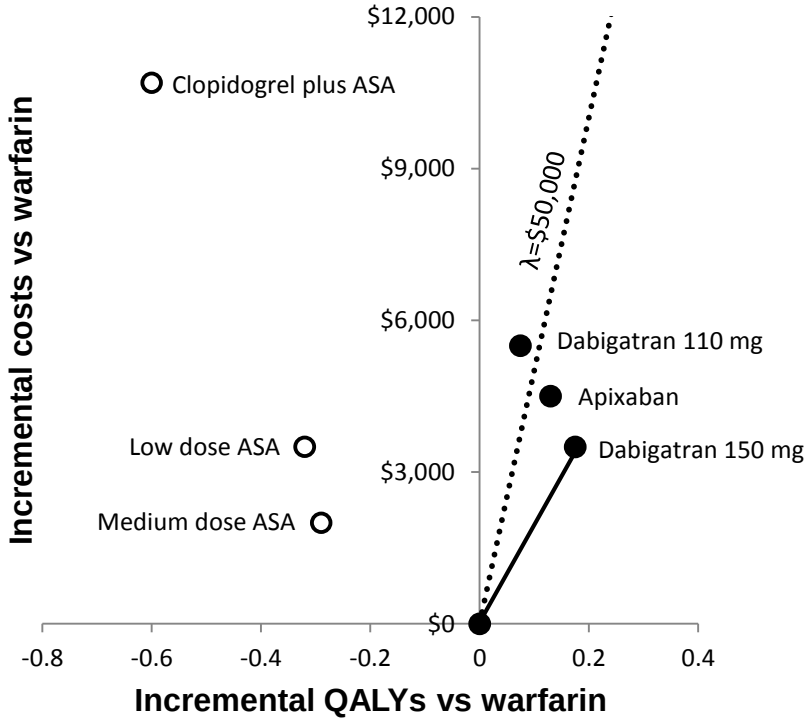
Table 13 and Figure 7 provide the results of the base case analysis for the $CHADS_2$ score < 2. Dabigatran 150 mg was the most effective treatment for QALYs (6.648), followed by apixaban (6.605). ASA medium-dose (6.182), ASA low-dose (6.150), and clopidogrel plus ASA (5.878) all produced less QALYs than the NOACs. No data were available for rivaroxaban in patients with a $CHADS_2$ score < 2; therefore, rivaroxaban was not included in this analysis.

The incremental cost per QALY gained for dabigatran 150 mg versus warfarin was $20,845. As dabigatran 110 mg and apixaban produced fewer QALYs than dabigatran 150 mg but at a greater cost, they were all dominated by dabigatran 150 mg. ASA medium-dose, ASA low-dose, and clopidogrel plus ASA were all dominated by one or more of the NOACs (Table 13).

Table 13: Results of Base Case Deterministic Analysis: $CHADS_2$ Score < 2				
	Cost	QALYs	Incremental Cost per QALY Gained (ICER)	
			vs. warfarin	Sequential ICER
Warfarin	$19,346	6.474		
Dabigatran 150 mg	$22,977	6.648	$20,845	$20,845
Dominated therapies[a]				
Apixaban	$23,874	6.605	$34,572	Dominated[a] by dabigatran 150 mg
Dabigatran 110 mg	$24,796	6.537	$86,831	Dominated by apixaban and dabigatran 150 mg
ASA MD	$21,356	6.182	Dominated	Dominated by warfarin
ASA LD	$23,052	6.150	Dominated	Dominated by warfarin and dabigatran 150 mg
Clopidogrel plus ASA	$30,228	5.878	Dominated	Dominated by all comparators

ASA = acetylsalicylic acid; ICER = incremental cost-effectiveness ratio; LM = low dose; MD = medium-dose; QALY = quality-adjusted life-year; vs. = versus.
[a] Dominated = more costly and fewer QALYs.
A sequential analysis involves the ICER for a less costly comparator compared with the next most costly comparator; excluding all comparators, which are either dominated or subject to extended dominance.

Figure 7: Base Case Results Cost-Effectiveness Plane for $CHADS_2$ < 2



λ = willingness-to-pay threshold; ASA = acetylsalicylic acid; vs. = versus.
Note: open circles indicate treatments that include ASA, and solid circles indicate oral anticoagulant treatments. The solid line is the cost-effectiveness plane versus warfarin as the reference treatment; the broken line represents an ICER versus warfarin of $50,000. Note that all of the ASA treatments are dominated by warfarin, as illustrated by their positions to the upper left of the cost-effectiveness plane. All of the NOACs are both more expensive and more effective than warfarin, as illustrated by their position to the right of the plane.

b) $CHADS_2 \geq 2$

Table 14 and Figure 8 provide the results of the base case analysis for $CHADS_2$ score ≥ 2. Apixaban was the most effective treatment regarding QALYs (5.381), followed by dabigatran 150 mg (5.370). ASA low-dose (4.858) and clopidogrel plus ASA (4.942) all produced less QALYs than the NOACs.

The incremental cost per QALY gained for both apixaban and dabigatran 150 mg versus warfarin was $17,795. The incremental cost per QALY gained for apixaban versus dabigatran 150 mg was $17,799. As dabigatran 110 mg and rivaroxaban produced fewer QALYs than dabigatran 150 mg and apixaban but at a greater cost, both of these treatments were dominated by dabigatran 150 mg and apixaban. As was the case for the $CHADS_2$ <2 subgroup, the ASA treatments were not cost-effective; specifically, ASA low-dose and clopidogrel plus ASA were dominated by all the NOACs.

Table 14: Results of Base Case Deterministic Analysis: $CHADS_2$ Score ≥ 2

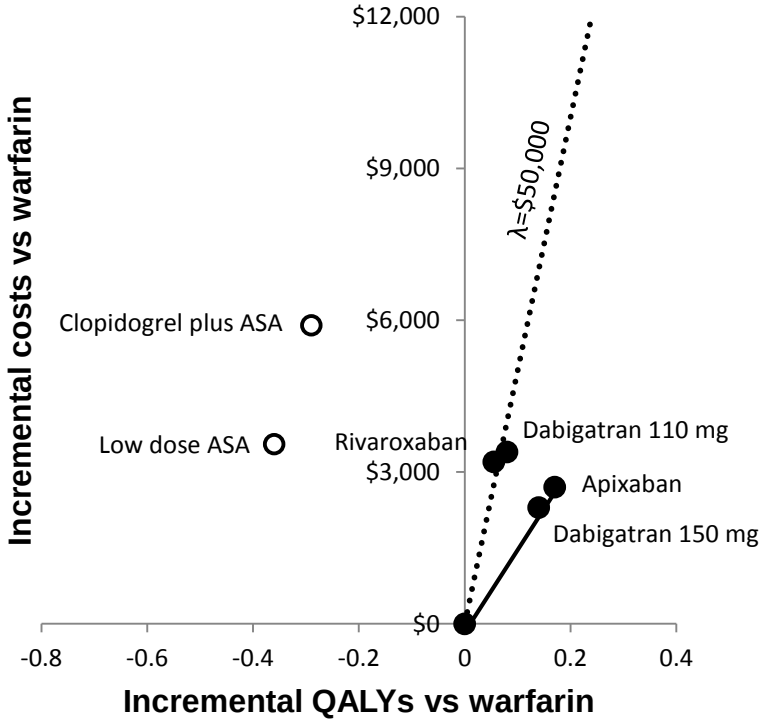
	Cost	QALYs	Incremental Cost per QALY Gained (ICER)	
			vs. warfarin	Sequential ICER
Warfarin	$34,292	5.228		
Dabigatran 150 mg	$36.916	5.370	$17,795	$17,795
Apixaban	$37,123	5.381	$17,795	$17,799
Dominated therapies*				
Rivaroxaban	$37,487	5.287	$52,217	Dominated[a] by dabigatran 150 mg and apixaban
Dabigatran 110 mg	$37,834	5.311	$41,293	Dominated by dabigatran 150 mg and apixaban
Clopidogrel plus ASA	$40,126	4.942	Dominated	Dominated by warfarin, dabigatran 150 mg, apixaban, rivaroxaban, and dabigatran 110 mg
ASA LD	$37,943	4.858	Dominated	Dominated by warfarin, dabigatran 150 mg, apixaban, rivaroxaban, and dabigatran 110 mg

ASA = acetylsalicylic acid; ICER = incremental cost-effectiveness ratio; LD = low-dose; QALY = quality-adjusted life-year; vs. = versus.

[a] Dominated = more costly and fewer QALYs.

A sequential analysis involves the ICER for a less costly comparator compared with the next most costly comparator; excluding all comparators, which are either dominated or subject to extended dominance.

Figure 8: Base Case Results Cost-Effectiveness Plane for $CHADS_2$ ≥2



λ = willingness-to-pay threshold; ASA = acetylsalicylic acid; vs. = versus.
Note: Open circles indicate treatments that include ASA, and solid circles indicate oral anticoagulant treatments. The solid line is the cost-effectiveness plane versus warfarin as the reference treatment; the broken line represents an ICER versus warfarin of $50,000. Note that all of the ASA treatments are dominated by warfarin, as illustrated by their positions to the upper left of the cost-effectiveness plane. All of the NOACs are both more expensive and more effective than warfarin, as illustrated by their position to the right of the plane. This is similar to the data illustrated for the $CHADS_2$ < 2 subgroup in Figure 7.

4.5.2 Sensitivity Analyses

a) Deterministic Sensitivity Analysis

Full details of the results of the univariate sensitivity analyses are presented in Appendices 7 and 19. In addition, parameters for which univariate sensitivity analyses did not substantially alter the results are presented in Appendix 20.

b) $CHADS_2$ < 2

Threshold analysis found that based for λ = $50,000, apixaban would be more cost-effective than dabigatran 150 mg if the price of apixaban was less than $2.12 per day (a 34% reduction). To be cost saving compared with warfarin, dabigatran 150 mg would have to cost $1.91 per day, dabigatran 110 mg would have to cost $1.25, while apixaban would have to cost $1.61 per day. The ASA treatment would not be cost-effective compared with warfarin at any price.

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 $52,953. 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 $371,678.

If the relative effects of treatments on non-vascular deaths were included, apixaban would be optimal if λ was greater than $14,915.

Switching from dabigatran 150 mg to dabigatran 110 mg at age 80 is dominated by remaining on dabigatran 150 mg for lifetime.

c) $CHADS_2$ ≥2

Results were very sensitive to the costs of dabigatran. Threshold analysis found that, based on a λ of $50,000, dabigatran 150 mg would be more cost-effective than apixaban if the price of dabigatran was reduced by 5% (to $3.03 per day). Rivaroxaban would have to be reduced by more than 80% to $0.49 per day to be cost-effective. To be cost saving compared with warfarin, dabigatran 150 mg would have to cost $2.04 per day, dabigatran 110 mg would have to cost $1.47, rivaroxaban would have to cost $1.37 per day, while apixaban would have to cost $2 per day.

Results were sensitive to the time horizon adopted. With a time horizon of two years (the typical duration of the RCTs considered within the MTC), apixaban would only be optimal, if λ was greater than $190,545.

Using event rates from the ROCKET-AF trial had a minor impact, slightly increasing the QALY gains from the new oral anticoagulant drugs leading to lower incremental costs per QALY gained; e.g., $12,544 for dabigatran 150mg and $11,152 for apixaban.

Excluding the effects of treatment on MI decreased the incremental cost per QALY gained for dabigatran 150 mg versus warfarin to $15,563 and increased the ratio for apixaban versus dabigatran 150 mg to $324,407. If the relative effects of treatments on non-vascular deaths were included, rivaroxaban was most effective and would be optimal if λ was greater than $10,259.

Switching from dabigatran 150 mg to dabigatran 110 mg at age 80 is dominated by remaining on dabigatran 150 mg for lifetime.

d) Probabilistic Sensitivity Analysis

$CHADS_2$ < 2

The results of the probabilistic sensitivity analyses for the expected values of costs, effects, and ICERs did not vary significantly from the deterministic base case analysis (Table 15).

Table 15: Results of Probabilistic Analysis: $CHADS_2$ Score < 2

	Cost	QALYs	Incremental Cost per QALY Gained (ICER)	
			vs. warfarin	Sequential ICER
Warfarin	$19,960 ($15,188,$26,265)	6.43 (5.35, 7.4)		
Dabigatran 150 mg	$23,611 ($19,440, $29,218)	6.6 (5.47, 7.62)	$20,862	$20,862
Dominated therapies*				
Apixaban	$24,432 ($20,043, $30,206)	6.56 (5.44, 7.55)	$33,228	Dominated* by dabigatran 150 mg
Dabigatran 110 mg	$25,380 ($20,702, $32,063)	6.49 (5.38, 7.48)	$83,822	Dominated by apixaban and dabigatran 150 mg
ASA LD	$24,532 ($12,043, $44,582)	5.97 (4.52, 7.25)	Dominated	Dominated by warfarin and dabigatran 150 mg
ASA MD	$23,937 ($15,128, $37,631)	6.1 (4.96, 7.14)	Dominated	Dominated by warfarin dabigatran 150 mg, apixaban and ASA LD
Clopidogrel plus ASA	$31,642 ($20,836, $47,206)	5.78 (4.67, 6.82)	Dominated	Dominated by all comparators

ASA = acetylsalicylic acid; ICER = incremental cost-effectiveness ratio; LD = low-dose; MD = medium-dose; QALY = quality-adjusted life-year; vs. = versus.

* Dominated = more costly and fewer QALYs.

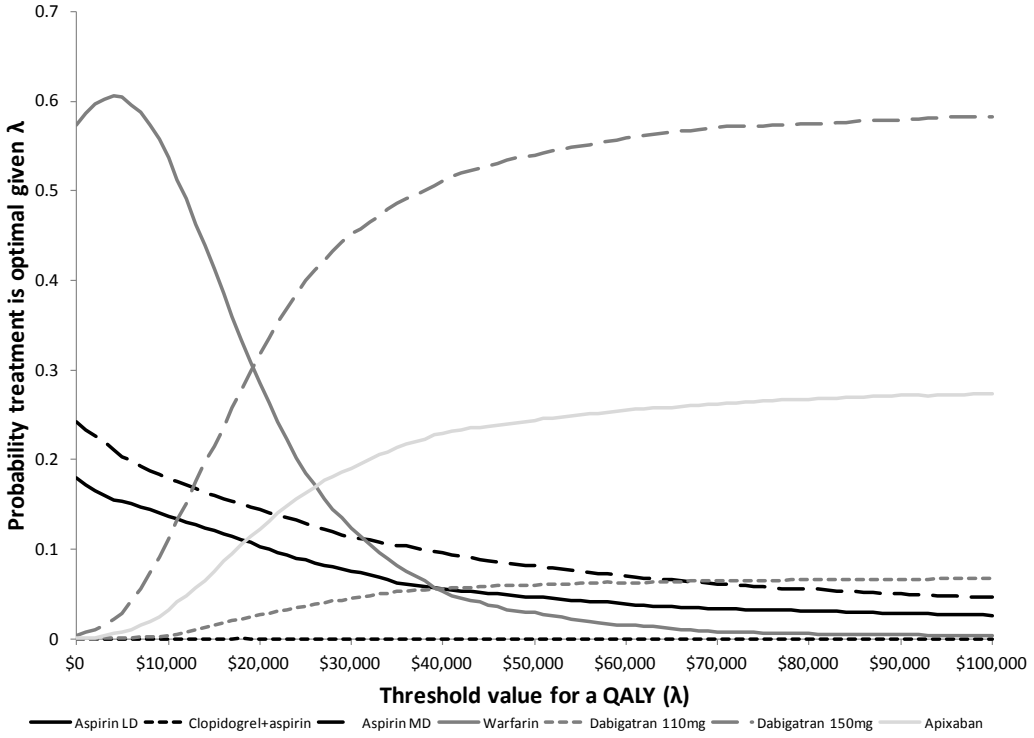
A sequential analysis involves the ICER for a less costly comparator compared with the next most costly comparator; excluding all comparators, which are either dominated or subject to extended dominance.

However, the probabilistic sensitivity analysis demonstrates that there is uncertainty associated with conclusions relating to cost-effectiveness, because no single treatment dominated all other treatments over the whole range of cost-effectiveness thresholds (values of λ); i.e., in no case was a single treatment optimal in all replications.

At a λ of $50,000, dabigatran 150 mg was the optimal treatment in 53.9% of replications, apixaban in 24.3%, ASA medium-dose in 8.1%, dabigatran 110 mg in 6.0%, ASA low-dose in 4.7 %, warfarin in 2.9%, and clopidogrel plus ASA in 0%. Results were similar for all values of λ, from $40,000 to $100,000. If λ = $0 (i.e., costs are the only consideration), warfarin was optimal in 57.4% of replications, ASA medium-dose in 24.3%, ASA low-dose in 17.9%, dabigatran 150 mg in 0.3%, and apixaban in 0.1%.

As shown in Table 15, dabigatran 150 mg is optimal if a decision-maker is willing to pay at least $20,862 per QALY. The uncertainty associated with these results is illustrated by the cost-effectiveness acceptability curves for these two treatments in Figure 9. As illustrated in Figure 9, the probability of warfarin and dabigatran 150 mg being the most cost-effective treatment depends on the willingness-to-pay threshold, such that while warfarin is optimal at lower cost-effectiveness thresholds, dabigatran 150 mg becomes more cost-effective as the willingness-to-pay threshold increases.

Figure 9: Cost-Effectiveness Acceptability Curves for $CHADS_2 < 2$



LD = low dose; MD = medium dose; λ = willingness-to-pay threshold.

$CHADS_2 \geq 2$

The expected values of costs, effects, and ICERs did not vary significantly from the deterministic base case analysis and the probabilistic analysis (Table 16), although dabigatran 150 mg was dominated by apixaban.

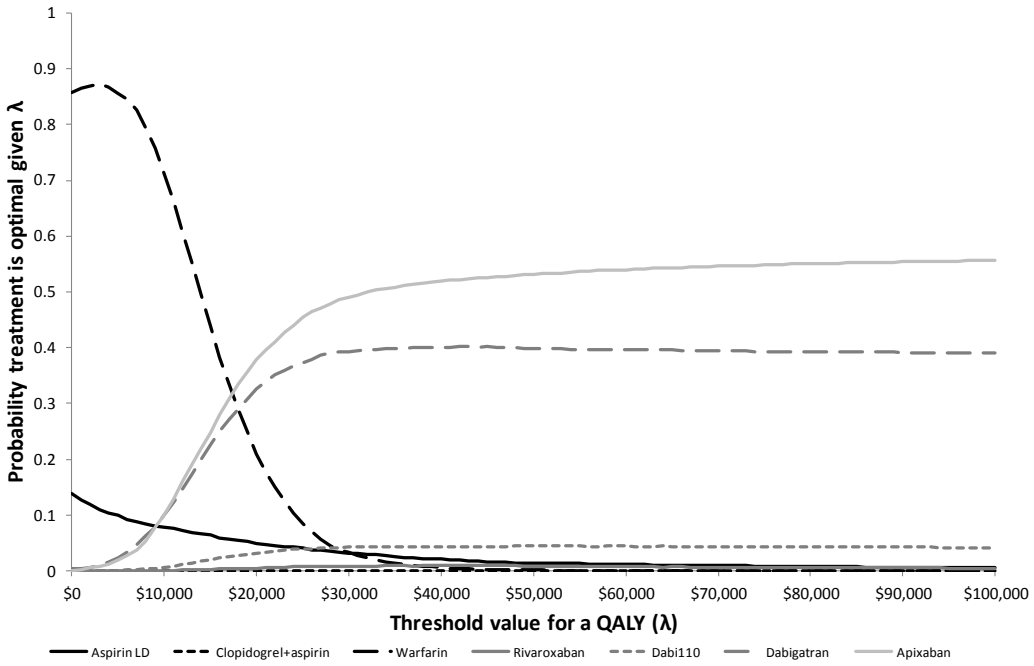
Table 16: Results of Probabilistic Analysis: $CHADS_2$ Score ≥ 2				
	Cost	QALYs	Incremental cost per QALY gained (ICER)	
			vs. warfarin	Sequential ICER
Warfarin	$34,447 ($26,638, $43,846)	5.22 (4.52, 5.83)		
Apixaban	$37,209 ($29,904, $46,034)	5.37 (4.65, 6)	$18,022	$18,022
Dominated therapies*				
Dabigatran 150 mg	$37,064 ($29,751, $45,944)	5.36 (4.64, 5.99)	$18,875	Dominated* by apixaban
Dabigatran 110 mg	$37,934 ($30,614, $46,774)	5.3 (4.58, 5.93)	$42,448	Dominated by apixaban and dabigatran 150 mg
Rivaroxaban	$37,601 ($30,035, $46,820)	5.28 (4.56, 5.9)	$55,197	Dominated by apixaban and dabigatran 150 mg
ASA LD	$38,619 ($26,912, $54,799)	4.8 (3.9, 5.62)	Dominated	Dominated by warfarin, apixaban, dabigatran 150 mg, rivaroxaban and dabigatran 110 mg
Clopidogrel plus ASA	$40,086 ($31,192, $50,927)	4.94 (4.29, 5.5)	Dominated	Dominated by warfarin, apixaban, dabigatran 150 mg, rivaroxaban and dabigatran 110 mg

ASA = acetylsalicylic acid; ICER = incremental cost-effectiveness ratio; LD = low-dose; MD = medium-dose; QALY = quality-adjusted life-year; vs. = versus.
* Dominated = more costly and fewer QALYs.
A sequential analysis involves the ICER for a less costly comparator compared with the next most costly comparator; excluding all comparators, which are either dominated or subject to extended dominance.

The probabilistic sensitivity analysis highlights the uncertainty around conclusions relating to cost-effectiveness that were also observed for the CHADS < 2 analysis. As for the $CHADS_2$ < 2 analysis, for $CHADS_2$ ≥ 2, no single treatment dominated all other treatments over the whole range of cost-effectiveness thresholds (values of λ); i.e., in no case was a single treatment optimal in all replications.

At a λ of $50,000, apixaban was the optimal treatment in 53.2% of replications, dabigatran 150 mg in 39.9%, dabigatran 110 mg in 4.4%, ASA low-dose in 1.5%, warfarin in 1.4%, rivaroxaban in 0.9%, and clopidogrel plus ASA in 0%. Results were similar for all values of λ, from $50,000 to $100,000. If λ = $0 (i.e. costs are the only consideration), warfarin was optimal in 85.7% of replications, ASA low-dose in 13.8%, Dabigatran 150 mg in 0.4%, and apixaban in 0.1%. The cost-effectiveness curves are presented in Figure 10.

Figure 10: Cost-effectiveness acceptability curves for $CHADS_2$ ≥2



LD = low dose; λ = willingness-to-pay threshold.

4.5.3 Analysis of Variability

a) $CHADS_2$ Score

For a $CHADS_2$ score of 0, dabigatran 150 mg would be optimal if λ was greater than $39,730. Apixaban and dabigatran 110 mg were dominated by dabigatran 150 mg. ASA low-dose, ASA medium-dose, and clopidogrel plus ASA were dominated by warfarin.

For a $CHADS_2$ score of 1, dabigatran 150 mg would be optimal if λ was greater than $19,716. Apixaban, dabigatran 110 mg, ASA medium-dose, and ASA low-dose were dominated by dabigatran 150 mg. ASA low-dose, ASA medium-dose, and clopidogrel plus ASA were dominated by warfarin.

For a $CHADS_2$ score ≥ 2 with no previous SSE, apixaban would be optimal if λ was greater than $16,543. Dabigatran 150 mg is subject to extended dominance through warfarin and apixaban. Dabigatran 110 mg, rivaroxaban, ASA low-dose, and clopidogrel plus ASA are all dominated by apixaban.

For a $CHADS_2$ score ≥ 2 with previous minor stroke, dabigatran 150 mg would be optimal if λ was greater than $14,857. Apixaban, dabigatran 110 mg, rivaroxaban, ASA low-dose, and clopidogrel plus ASA are all dominated by dabigatran 150 mg.

For a $CHADS_2$ score ≥ 2 with previous major stroke, apixaban would be optimal if λ was greater than $119,523. Dabigatran 150 mg, rivaroxaban, and dabigatran 110 mg are subject to extended dominance through warfarin and apixaban. ASA low-dose and clopidogrel plus ASA are all dominated by apixaban.

b) Age

For patients aged 60, the incremental cost per QALY gained for dabigatran 150 mg versus warfarin is $19,368. Apixaban, rivaroxaban, and dabigatran 110 mg were dominated by dabigatran 150 mg.

For patients aged 70, the ICERs for all therapies versus warfarin were lower than for patients aged 60, implying that treatment is more cost-effective in older patients. Dabigatran 150 mg would be preferred to

warfarin if λ was greater than $14,752. Apixaban, rivaroxaban, and dabigatran 110 mg were dominated by dabigatran 150 mg.

For patients aged 80, the ICER versus warfarin was lower for rivaroxaban and apixaban but higher for both doses of dabigatran. Apixaban produced most QALYs at an incremental cost per QALY gained of $19,407. Rivaroxaban, dabigatran 150 mg, and dabigatran 110 mg were dominated by apixaban. ASA low-dose was dominated by apixaban, rivaroxaban, dabigatran 150 mg, and warfarin.

c) Time in TherapeuticRrange

In centres with poor INR control (centre-specific TTR < 66%), dabigatran 150 mg was the most effective treatment option, with an incremental cost per QALY gained versus warfarin of $9,993. Clopidogrel plus ASA, rivaroxaban, dabigatran 110 mg, and apixaban were dominated by dabigatran 150 mg. Clopidogrel plus ASA was also dominated by warfarin.

In centres with good INR control (centre-specific TTR > 66%), apixaban was the most effective treatment option, with an incremental cost per QALY gained versus warfarin of $40,023. Rivaroxaban was subject to extended dominance through warfarin and apixaban. Clopidogrel plus ASA, dabigatran 150 mg, and dabigatran 110 mg were dominated by apixaban.

5 DISCUSSION

5.1 Summary of Evidence

In this systematic review, 12 individual RCTs[19-46] were identified that reported the efficacy and safety of antithrombotic interventions to prevent morbidity and mortality in patients with non-valvular AF who were eligible for anticoagulant treatment. Evaluated interventions included anticoagulants (warfarin, apixaban, dabigatran, and rivaroxaban) and antiplatelet drugs (ASA with or without clopidogrel). Data available for six outcomes were analyzed, mainly relating to stroke, arterial embolism, or bleeding. Whenever possible, MTC meta-analyses were conducted to facilitate a unified approach to comparing across interventions that incorporated both direct and indirect evidence.

5.2 Interpretation of the Results

5.2.1 Comparisons Among Anticoagulant Therapies

For any antithrombotic therapy, prevention of SSE comes at the cost of a potential increase in the risk of bleeding. Therefore, the benefits of preventing SSE must necessarily be balanced by assessing the corresponding risk of the increased risk of serious bleeding. In the present review, this balance is reflected in the outcomes of SSE and major bleeding, and the NMA that we employed facilitates an indirect comparison of the various anticoagulant therapies to assess the relative benefit and risk of the various treatments in an unstratified population (reference case).

Regarding efficacy, apixaban and dabigatran 150 mg were associated with statistically significantly reduced rates of SSE versus warfarin, equivalent to an absolute risk reduction of between 1 and 9 fewer events per 1,000 patients treated each year. Dabigatran 150 mg was ranked highest among the treatment options for SSE prevention. On the other hand, our analyses indicated that apixaban and dabigatran 110 mg were associated with significantly fewer major bleeds versus warfarin, equivalent to absolute risk reductions of 2 to 13 fewer events per 1,000 patients treated each year. Apixaban was ranked best among the active treatments with respect to major bleeding. Overall, the NOACs appeared to compare favourably with warfarin (i.e., NOACs are associated with lower rates of SSE and/or major bleeding), but the different NOACs are not readily distinguishable among one another.

Despite the statistical significance of differences achieved among some of the treatments, the fact that the absolute effect size associated with these differences was generally fewer than 10 events per 1,000

patients treated each year indicates that the clinical meaningfulness of differences among the anticoagulants is unclear. While the clinical significance of small ARD values is difficult to assess, the relative importance of small ARDs might be greater for outcomes that have large impacts on health status and/or high associated costs. In that regard, the calculation of cost-effectiveness for an ICER would take into account the impact of even small differences in ARD. It is noteworthy that apixaban was the only NOAC associated both with a reduction in the rate of SSE, as well as major bleeding, compared with warfarin. This appears to be somewhat counterintuitive, as there is a positive correlation between the degree of anticoagulation and the risk of serious bleeding; that is, antithrombotic agents that are more efficacious in preventing thromboembolism are generally associated with higher rates of bleeding, rather than lower rates of bleeding. This is readily exemplified by dabigatran in AF patients: the 150 mg dose is associated with lower rates of SSE but higher rates of bleeding compared with the lower dose of 110 mg.

There are no definitive explanations at this point to account for the apparently superior reduction in SSE coupled with fewer major bleeds for apixaban. However, some differences in the design of the NOAC trials may have favoured apixaban and might, in part, explain its apparently better performance compared with the other treatments. A substantial difference between ARISTOTLE and the other NOAC trials was the use of a dose-modification algorithm to reduce the dose of apixaban to 2.5 mg twice daily in patients with a high risk of bleeding. In contrast, as aforementioned, the RE-LY trial evaluated two different doses of dabigatran using two separate treatment arms, regardless of patient characteristics. This may have led to sub- or supra-therapeutic doses of dabigatran, hence affecting the overall net benefit results in favour of apixaban.

The absence of any substantial and consistent differentiation among the NOACs and warfarin illustrated by the relative benefit/risk profile of these agents based on SSE and major bleeding is further supported by the results for other outcomes; specifically mortality, extracranial hemorrhage, and ICH. As was the case for SSE and major bleeding, there were consistent statistically significant differences among some of the NOACs for some of the aforementioned outcomes, yet the overall magnitude of these differences were relatively small and translated to absolute effect size that were generally fewer than 10 events per 1,000 patients treated each year. For instance, although only apixaban achieved a statistically significant reduction in all-cause mortality compared with adjusted-dose warfarin in the NMA analysis, the comparison for warfarin versus dabigatran and rivaroxaban yielded results which, although not statistically significant, were similar in terms of magnitude to those observed for apixaban. This suggests that the anticoagulants as a class have similar effects on all-cause mortality. A similar conclusion applies to extracranial hemorrhage. While all NOACs were associated with statistically significant reductions in ICH compared with adjusted-dose warfarin, the absolute risk reductions versus warfarin were similar among the individual NOACs and were relatively modest (between 1 and 7 fewer events per 1,000 patients per year).

For MI, dabigatran was the only NOAC that had a significantly greater rate of MI compared with warfarin, and among the NOACs, apixaban was associated with a statistically significantly lower rate of MI compared with dabigatran (both doses).

The aforementioned findings are very similar to those reported in a previous review of anticoagulants in AF patients[47], which is attributable to the fact that despite the expanded scope of the current review, the major sources of data for warfarin and the NOACs are the same trials that were included in the previous review. Moreover, our findings regarding the anticoagulant drugs are similar to those reported by others.[61,81-96] Interestingly, all of the NOAC trials were designed as non-inferiority trials versus warfarin, which implies that demonstrating superiority over warfarin was not the primary intent of these RCTs.

Clinical experience with NOACs is relatively limited at present, given that the first approval (for dabigatran) was granted as recently as 2010. Serious adverse events have been associated with these agents in clinical trials, including death from MI or bleeding. Several ongoing post-marketing surveillance studies have attempted to obtain data to objectively assess the risk of the new agents, but the most recent report from the FDA on dabigatran has not revealed any difference in real-world risks of SAEs versus the statistics available from the RCT data.[97] Indeed, the usefulness of this uncontrolled safety data is not always clear, even to the FDA; the simple comparison between the NOACs and warfarin with

respect to the numbers of post-marketing reports of bleeding is misleading, because bleeding events associated with warfarin (a well-recognized consequence of warfarin use) are likely underreported compared with events occurring with the more recently available NOACs.[97]

In addition, the lack of reversal agent for the NOACs in cases of serious bleeding is a safety concern. A recent report by CADTH[98] revealed that there is no evidence available to evaluate anticoagulation levels in patients taking dabigatran, rivaroxaban, or apixaban; no antidote available for dabigatran, rivaroxaban, or apixaban; limited information related to reversal strategies for the NOACs; and general uncertainty as to whether any of the available reversal strategies would be effective in clinical practice for managing NOAC-treated patients experiencing bleeding. However, the concern related to the reversal of anticoagulation, particularly for severe bleeding events, is not limited to the NOACs. At present, in the event of bleeding in patients taking warfarin, available reversal agents for anticoagulant activity include vitamin K, prothrombin complex concentrate, and fresh frozen plasma.[99-101]

It is important to emphasize that our findings are based both on an indirect comparison of therapies via an NMA, as well as direct comparisons of treatments available from within individual RCTs. While there are limitations to using indirect comparisons to compare different treatments (most notably heterogeneity among patient populations; see subsequent details), it is noteworthy that the results of the direct and indirect comparisons are congruent (for interventions for which data were available for direct comparison). Furthermore, there is no readily available alternative to the use of indirect comparisons to compare the antithrombotic therapies. While comparisons should ideally be direct and be based on head-to-head studies, such data is unavailable at present and unlikely to be available in the near future, for several reasons. First, trials that examine SSE and include mortality as an end point require large populations for adequate statistical power and a follow-up of several years. While manufacturers of the respective NOACs have conducted at least one such large phase 3 trial, additional trials that include other NOACs among the comparators would require a considerable investment of time and money. Second, head-to-head trials require that the included comparators be approved for use within the regions in which the studies are conducted. This is not generally practicable when the timing of regulatory approval of new therapeutic agents varies both within and among different jurisdictions. Third, to include all available comparators in a head-to-head trial would require multiple treatment arms, which would in turn require a correspondingly large population and involve more complex study design and statistical considerations. Therefore, considering the aforementioned issues with direct comparisons, it is reasonable to perform indirect comparisons among the NOACs despite the known limitations of indirect comparisons; this is exemplified by the recent publication of numerous indirect comparisons of the NOACs among themselves and to other therapies such as warfarin. [61,81-96] In clinical practice, other factors that have not been explicitly considered in our analyses will likely be key determinants of which therapy is most appropriate in individual patients (e.g., the lack of available reversal agents for the NOACs).

While heterogeneity among different RCTs, particularly regarding the patient populations, is an acknowledged (but unavoidable) limitation of our review, we attempted to mitigate the effects of heterogeneity by performing subgroup analyses where data were sufficient, to reduce differences in the most relevant patient characteristics. Other sources of heterogeneity include differences in methodology. However, this limitation affects primarily the comparison of the NOACs versus antiplatelet agents, rather than the comparisons among the anticoagulants, for the following reasons. All the NOAC trials were large, methodologically rigorous multicentre studies that employed very similar definitions of major outcomes such as SSE and bleeding, while trials of antiplatelet agents included substantially fewer patients, were of lower quality, and exhibited more variability in the definition and reporting of outcomes.

While the use of indirect comparison of antithrombotic agents is justified in the absence of sufficient data for direct comparisons among the different agents, it should be emphasized that there are inherent limitations to this methodology[102] that mean there is necessarily a high degree of uncertainty associated with the results of our analyses. This uncertainty is exacerbated by the fact that only one study was available for each NOAC, but is counterbalanced by the large size of these studies (which included at least 14,000 patients each) and the methodological rigour of the trials. Nevertheless, the fact that single point estimates of effects are based on single studies raises the possibility that these effect sizes could vary due simply to chance, and it is must be considered possible that the point estimates could differ if

additional studies are carried out. This supports a conservative interpretation of any apparently statistically significant differences among treatment, particularly where these differences reflect relatively small differences in ORs; this applies to the comparisons of the NOACs among themselves and to warfarin, but less so to the comparisons between the anticoagulant and antiplatelet drugs, where the differences in effects were larger. Furthermore, the apparently significant differences in ORs among the anticoagulants translate into relatively modest differences in absolute risk, which were generally within a single order of magnitude. The clinical significance of such differences in absolute effect sizes is not clear. Indeed, several authors that have compared the NOACs among themselves or to warfarin have also concluded that the confidence in the superiority of one anticoagulant over another in clinical practice is limited by uncertainty related to the use of indirect comparisons and the absence of profound differences among anticoagulant agents.[61,84,86-88,90,91]

a) Subgroup analyses

While the results of the reference case are informative, the absence of any substantial differentiation among the anticoagulants reflect the clinical reality that treatment with antithrombotic therapy must be tailored to individual patients according to their individual history and risk profile, among other factors. Moreover, the guidance provided by CADTH to Canadian public payers and health care practitioners regarding the NOACs is structured such that stroke risk ($CHADS_2$ score), age, and TTR are important factors in assessing different NOACs. Therefore, we analyzed the relative clinical efficacy and harms of warfarin, the NOACs, and antiplatelet drugs based on subgroups stratified according to $CHADS_2$ score, age, and TTR, as well as the corresponding cost-effectiveness of the NOACs. Results from subgroup analyses are hypothesis-generating; further research is needed to characterize the potential benefits and risks of each agent in various patient populations. However, in the absence of other evidence, the results of subgroup analyses are used to draw conclusions that bring additional value to the analysis. In this context, it is especially important to consider the uncertainty surrounding the findings.

While data were not available for all treatment for all outcomes, there were sufficient data to perform indirect comparisons for the aforementioned subgroups for the SSE and major bleeds, which consequently allows an assessment of the relative risk and benefit of the various treatments.

Stroke risk ($CHADS_2$ score)

For patients who had a low or moderate risk of stroke (i.e., $CHADS_2 < 2$), there were no statistically significant differences between dabigatran and apixaban versus warfarin. (Rivaroxaban was not included in this analysis because no data were available for rivaroxaban for this subgroup.) Comparisons among the NOACs revealed that dabigatran 150 mg was associated with statistically significantly fewer SSEs than dabigatran 110 mg, but there were no other significant differences. There was significantly less major bleeding associated with apixaban and dabigatran 110 mg compared with warfarin, but there were no statistically significant differences among the NOACs for major bleeding (no data available for rivaroxaban). This is in contrast to the reference case analysis, where apixaban and dabigatran 110 mg were superior to dabigatran 150 mg and rivaroxaban in the overall population.

Taking the results for SSE and major bleeding into account, it would appear that, as in the reference case, in patients with a low or moderate risk of stroke the benefit/risk of the NOACs is positive compared with warfarin, more so in terms of reduced bleeding than enhanced prevention of SSE, but largely similar among the NOACs. A notable exception is rivaroxaban, for which no data were available in this population.

A major limitation associated with this analysis is the fact that there were very limited data available for patients with a $CHADS_2$ score of 0. Therefore, the aforementioned conclusion regarding the relative efficacy of warfarin, dabigatran, and apixaban should be limited to patients with a moderate risk of stroke ($CHADS_2$ score = 1), and cannot be applied to low-risk patients ($CHADS_2$ score = 0). Indeed, although the subgroup was labeled $CHADS_2$ score < 2, almost all included patients had a $CHADS_2$ score = 1. Considering this nuance in the included population, the superiority of anticoagulants over antiplatelet agents in overall benefit/risk that we demonstrated in our review is consistent with the recommendations in major AF treatment guidelines,[3-5] that suggest that most patients at intermediate or high risk of stroke ($CHADS_2 = 1$ and $CHADS_2 \geq 2$) should receive anticoagulant therapy.

For patients who had a high stroke risk (i.e., $CHADS_2 \geq 2$), dabigatran 150 mg and apixaban were both statistically significantly superior to warfarin in preventing SSE, but there was no significant difference between warfarin and rivaroxaban. Among the NOACs, dabigatran 150 mg was significantly superior to dabigatran 110 mg in preventing SSE. By contrast, only apixaban was statistically significantly superior to warfarin in preventing major bleeds, and apixaban was also superior to both dabigatran 150 mg and rivaroxaban.

As is the case in the moderate risk patients, the benefit/risk of the NOACs is positive compared with warfarin. This is consistent with the reference case and the $CHADS_2 < 2$ subgroup. Apixaban would appear to have a slightly more positive benefit/risk profile than the other NOACs, but this is largely based on a reduction in major bleeding, with inherent limitations as described above, and equates to a relatively small absolute difference of approximately 5 to 11 fewer events per 1,000 patients per year.

Age

The results of the analysis stratified by age for SSE in the ≥ 75 years subgroup were similar to those of the reference case analysis, where dabigatran 150 mg and apixaban were superior to warfarin; however, only dabigatran retained statistical significance in the < 75 years subgroup (Table A13.9 in Appendix 13). There was no statistically significant difference between warfarin and rivaroxaban. Based on the increased absolute risk reduction versus warfarin, newer anticoagulants seemed to have a greater benefit on stroke prevention in older patients (≥ 75 years) than in a younger population (< 75 years). Specifically, dabigatran 150 mg was associated with statistically significantly fewer SSEs versus dabigatran 110 mg, as in the reference case analysis; however, there were no statistically significant differences among the NOACs in the ≥ 75 years subgroup. The relevance of this finding is undermined by the fact that dabigatran 150 mg should not be administered to patients older than 80 years, and some guidelines even recommend against the use of this dose of dabigatran in patients older than 75 years. Renal function should also be considered with the use of this agent, particularly given the relatively higher importance of the renal metabolism for dabigatran versus the other NOACs.

As in the reference case analysis, statistical significance for reductions in major bleeding was reached for apixaban and dabigatran 110 mg compared with adjusted-dose warfarin in the age < 75 years subgroup (Table A13.10 in Appendix 13). In this younger population, dabigatran 150 mg was also superior to warfarin. There was no difference between warfarin and rivaroxaban; however, rivaroxaban appeared to cause statistically significantly more major bleeding than both doses of dabigatran. In the age ≥ 75 years subgroup, apixaban achieved statistical superiority over all other anticoagulants.

Time in Therapeutic Range

In the TTR < 66% (poorly controlled) subgroup, only dabigatran 150 mg yielded statistically significant results for stroke prevention over warfarin, as well as over rivaroxaban. Decreases in the number of events observed with apixaban did not reach statistical significance, as it did in the reference case. In the TTR ≥ 66% (adequately controlled) subgroup, no statistically significant difference was observed across all interventions. Of note, dabigatran 150 mg showed substantially greater benefits when compared with warfarin in patients with a poorly controlled INR compared with adequately controlled patients.

While apixaban and both doses of dabigatran led to a statistically significant reduction in major bleeding in the poorly controlled subgroup (TTR < 66%), only apixaban retained statistical significance in the adequately controlled subgroup (TTR ≥ 66%). Notwithstanding statistical significance, all NOACs resulted in substantially greater risk reductions in major bleeding versus warfarin in patients with a poorly controlled INR compared with adequately controlled patients, which was more pronounced than for SSE. As in the reference analysis, apixaban was also superior to dabigatran 150 mg and rivaroxaban in both subgroups.

These results suggest that the relative efficacy of NOACs versus warfarin is enhanced in patients who have poor INR control, although this is controversial and depends on the statistical analysis used. While poor INR control therefore might be a theoretical bias in favour of the NOACs, this is counterbalanced by the fact that INR control is generally superior within RCTs compared with real clinical practice, although INR control in Canada is generally higher than in many other regions.[80]

Finally, in addition to INR control, age, and stroke risk, other factors should be taken into account when determining which treatment might be optimal in individual patients, particularly in patient populations under-represented in the included studies, such as the elderly, those with severe renal failure, and those with multiple comorbidities. There were insufficient data available to include such subgroups in our analyses in this review.

Pharmacoeconomic considerations

The pharmacoeconomic analyses were structured to determine the relative cost-effectiveness of the various antithrombotic treatments, with a focus on those stratification factors that are most important to Canadian public payers, namely stroke risk ($CHADS_2$ score), age, and TTR. Not only are these the factors that have been used as criteria to guide the reimbursement of the NOACs in Canada (as well as in other countries), but these factors also feature prominently in clinical guidelines such as those published by the CCS. The pharmacoeconomic analyses demonstrated that, for patients with a $CHADS_2$ score < 2, dabigatran 150 mg was the most cost-effective treatment among the NOACs, with an incremental cost per QALY gained versus warfarin of $20,845. Moreover, dabigatran 150 mg dominated both dabigatran 110 mg and apixaban, while rivaroxaban was not included for comparison due to the absence of data for this subgroup. For apixaban to be more cost-effective than dabigatran 150 mg (assuming λ = $50,000), it would need cost less than $2.12 per day (a 34% reduction in price). For patients with a $CHADS_2$ score ≥ 2, dabigatran 150 mg and apixaban were the most cost-effective treatment among the NOACs, and the incremental cost per QALY gained for both apixaban and dabigatran 150 mg versus warfarin was $17,795. Apixaban is likely optimal, as it dominated dabigatran 150 mg in probabilistic analyses, but the difference between these two treatments is marginal: dabigatran 150 mg is likely more cost-effective than apixaban if the price of dabigatran was reduced by just 5%. In addition, although for different patient populations, dabigatran 150 mg or apixaban would appear to be the preferred treatment option from a cost-effectiveness standpoint, there was sufficient uncertainty over the results to make a definitive statement concerning which of these two treatments should be preferred. Finally, the sensitivity of results to the costs and consequences from bleeding episodes on NOACs highlights the need for further research in this area.

Which of the anticoagulants is optimal depends on several factors. First, the probability of dabigatran 150 mg being the most cost-effective NOAC for $CHADS_2 < 2$ and apixaban being most cost-effective for $CHADS_2 \geq 2$ NOAC increases as the λ increases. If cost were not a consideration, dabigatran 150 mg is likely optimal in lower-risk patients, while apixaban is likely optimal in higher-risk patients. By contrast, if cost is the only consideration or if the λ is relatively low, warfarin is optimal irrespective of stroke risk.

Second, age is important: dabigatran 150 mg was the optimal NOAC therapy in younger patients (60 or 70 years old), whereas apixaban was optimal in older patients (80 years old). Note that, despite the availability of sufficient data to include rivaroxaban in the analysis based on age, this treatment would likely never be optimal irrespective of age, based on current prices.

Finally, optimal NOAC therapy depended on the degree of INR control, as reflected by TTR: specifically, in centres with poor INR control (TTR < 66%), dabigatran 150 mg was the most cost-effective NOAC, while apixaban was optimal in centres with good INR control (TTR > 66%).

It is important to note that 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 NOACs will be cost-effective in the long term.

5.2.2 Anticoagulant versus antiplatelet drugs

For SSE, there were no statistically significant differences among low-dose ASA, medium-dose ASA, and clopidogrel plus low-dose ASA. However, low-dose ASA and the combination of clopidogrel plus low-dose ASA were statistically significantly less effective at preventing SSE compared with all anticoagulants, including adjusted-dose warfarin, dabigatran, apixaban, and rivaroxaban. For major bleeding, the OR for apixaban was statistically significantly lower compared with clopidogrel plus low-dose ASA, but there were no significant differences associated with the different antiplatelet treatments, both for comparisons among themselves and compared with the anticoagulant treatments.

Comparison of all anticoagulant treatment (including warfarin) to ASA with or without clopidogrel indicates that the antiplatelet drugs therapies have a less favourable benefit/risk profile than the NOACs; specifically, antiplatelet drugs appear to fail to prevent SSE as effectively as the NOACs while at the same time failing to be associated with a lower risk of bleeding or in fact increasing the risk of bleeding.

Because there was no clear differentiation between low-dose ASA and low-dose ASA in combination with clopidogrel, there would not appear to be any benefit to the addition of clopidogrel to ASA in preventing SSE. Indeed, the indirect comparison revealed that low-dose ASA with or without clopidogrel was statistically significantly less effective at preventing SSE compared with all anticoagulants. However, this conclusion is associated with a high degree of uncertainty, and should not be interpreted as contrary to established clinical practice guidelines that recommend the addition of clopidogrel to ASA in appropriate patients. Indeed, the results of ACTIVE A,[103] an RCT comparing low-dose ASA alone and in combination with clopidogrel in 7,554 patients unsuitable for VKA therapy, differ from our indirect comparison in that the addition of clopidogrel to ASA in this trial was associated with a reduction in the risk of stroke, as well as an increase in the risk of major bleeding.[103] ACTIVE A was excluded from our NMA because patients could not receive anticoagulantion with a VKA, which was a reason for exclusion based on our review protocol. However, inclusion of ACTIVE A in a sensitivity analysis did not result in a significant change in the results of our analysis, either for the clinical data (see Appendix 21) or for the pharmacoeconomic results (not shown). Therefore, it is likely prudent to conclude that there is not any substantial evidence to support the use of ASA with or without clopidogrel in patients with AF, especially in those patients who are eligible for anticoagulation with an antithrombotic agent.

There were no significant differences associated with the ASA treatments, both for comparisons among themselves and compared with the anticoagulant treatments. Therefore, we failed to detect a dose-dependent effect of ASA on either efficacy (preventing SSE) or harm (bleeding). However, this result is highly uncertain, and is likely a reflection of a paucity of data, rather than reflecting a real absence of a dose effect; indeed, it is reasonable to assume that higher doses of ASA are associated with an increased risk of bleeding.

Regarding the other outcomes that were examined, there were no statistically significant differences for anticoagulant drugs compared with the antiplatelet drugs for all-cause mortality. This result is somewhat at odds with the clear differentiation between anticoagulant drugs and antiplatelet agents observed when examining the benefit/risk profile generated using SSE and major bleeding, but likely reflects the high degree of uncertainty associated with mortality as an outcome, due to the relatively small populations in the trials that included antiplatelet drugs. This is exemplified by the very large CI associated with the antiplatelet drugs point estimates. Indirect comparison revealed that there were significantly fewer ICH for the NOACs versus clopidogrel plus low-dose ASA, apixaban statistically significantly reduced ECH compared with medium-dose ASA, and apixaban was associated with a statistically significantly lower rate of MI compared with low-dose ASA and the combination of clopidogrel plus low-dose ASA. As in the case of mortality, there is substantial uncertainty associated with these results.

a) Subgroups

Results from subgroup analyses are hypothesis-generating; further research is needed to characterize the potential benefits and risks of each agent in various patient populations. However, in the absence of other evidence, the results of subgroup analyses are used to draw conclusions that bring additional value

to the analysis. In this context, it is especially important to consider the uncertainty surrounding the findings.

The overall risk/benefit profile for the antiplatelet therapies compared with the anticoagulants for patients with a low or moderate risk of stroke for the subgroup based on stoke risk was similar to that of the reference case; specifically, antiplatelet drugs appear to have a less favourable benefit/risk profile largely due to failing to reduce the risk of SSE while being associated with a similar or increased risk of major bleeding.

For SSE in the $CHADS_2 < 2$ subgroup, there were no statistically significant differences among low-dose ASA, medium-dose ASA, and clopidogrel plus low-dose ASA. However, low-dose ASA and the combination of clopidogrel plus low-dose ASA were statistically significantly less effective at preventing SSE compared with warfarin, apixaban, and dabigatran. The OR for major bleeding was not different among the antiplatelet treatments and between ASA monotherapy and the anticoagulants; however, the combination of clopidogrel plus low-dose ASA resulted in more major bleeding than warfarin, apixaban, and dabigatran.

In patients with a high risk of stroke, comparisons between the antiplatelet drugs and the anticoagulants drugs were very similar to the reference case and the CHADS < 2 subgroup. One inconsistency is the observation that the benefit/risk profile for clopidogrel plus low-dose ASA appears to be similar to that of the anticoagulants, which was not the case in the $CHADS_2 < 2$ subgroup or the reference case. However, the level of confidence in this observation is considerably lower than for the anticoagulant drugs, as the estimated effect sizes for clopidogrel plus low-dose ASA are derived from a single RCT with substantially fewer patients compared with the anticoagulant trials.

The aforementioned results suggest that the relatively less favourable benefit/risk profile of the antiplatelet treatments is consistent irrespective of the risk of stroke.

For age and TTR, data on antiplatelet agents were scarce; evaluated interventions were limited to low-dose ASA for the age ≥ 75 years subgroup, the combination of clopidogrel and low-dose ASA for the TTR < 66% subgroup, and medium-dose ASA for the TTR ≥ 66% subgroup.

Nevertheless, where data were available, the results generally confirmed the superiority of the anticoagulant therapies over the antiplatelet drugs in terms of the overall risk/benefit profile, based largely on differential SSE prevention rather than distinctive bleeding risks. For instance, in patients 75 years old or older, low-dose ASA was statistically significantly less effective at preventing SSE than all anticoagulant therapies, while there were no such differences for major bleeding. In centres with poor INR control (TTR < 66%), low-dose ASA plus clopidogrel were also statistically significantly less effective at preventing SSE compared with apixaban and dabigatran 150 mg, while major bleeding was significantly different in this subgroup only between low-dose ASA plus clopidogrel. In centres with good INR control (TTR ≥ 66%), medium-dose ASA was statistically significantly less effective at preventing SSE and major bleeds compared with all the anticoagulant drugs, except for major bleeds for dabigatran 150 mg.

In the pharmacoeconomic analyses, the antiplatelet treatments were all dominated by one or more of the anticoagulant drugs in both the $CHADS_2 < 2$ and ≥ 2 subgroups. This suggests that the anticoagulant drugs are more cost-effective treatments for preventing SSE in patients with non-valvular AF irrespective of stroke risk. The fact that the anticoagulant drugs dominated the antiplatelet therapies in patients with a low or moderate risk of stroke ($CHADS_2$ score <2) supports the guidance of the CCS that anticoagulant drugs be used in preference to ASA in patients with a $CHADS_2$ score < 2, but extends this guidance beyond considerations of clinical data and preference/convenience to include a cost component. More specifically, our results demonstrate that the extremely low cost of ASA compared with the NOACs (and warfarin) does not counterbalance the lack of efficacy and increased risk of harms sufficiently to make antiplatelet therapy a cost-effective alternative to the anticoagulants. It is important to note that this conclusion can be applied with reasonable confidence only to patients with a $CHADS_2$ score of 1, and cannot be applied to patients with a $CHADS_2$ score of 0, because there were almost no data available to us for patients with a $CHADS_2$ score = 0. Therefore, while we stratified according to stoke risk based on a

$CHADS_2$ score ≥ 2 versus < 2, the absence of data for patients with a $CHADS_2$ score = 0 means that our analysis and conclusions are effectively based on a stratification of stroke risk based on a $CHADS_2$ score ≥ 2 versus 1. In addition to stroke risk, the pharmacoeconomic analysis revealed that antiplatelet therapy would appear to not be an optimal therapy for preventing SSEs irrespective of age, the degree of INR control, or the λ . Regarding age, the pharmacoeconomic analyses demonstrated that NOAC therapy was more cost-effective in younger patients, whereas none of the antiplatelet therapies was optimal irrespective of age.

Collectively, these results suggest that antiplatelet drugs should therefore only be considered in patients with at least a moderate risk of stroke who are not suitable for anticoagulant therapy. However, whether antiplatelet therapy is in fact a suitable alternative for patients who are not eligible for treatment with an anticoagulant is a matter of debate and is beyond the scope of this review. It should be noted that because the inclusion criteria for our systematic review required patients to be eligible for anticoagulant therapy, including treatment with a VKA, we were able to include only a small number of trials that studied antiplatelet drugs, most of which included relatively small numbers of patients. This resulted in the exclusion of two large trials, namely AVERROES and ACTIVE A, which contained potentially useful information. The results of our sensitivity analysis (see Appendix 21) in which data from these two trials were included (instead of excluded, as in the primary analysis) suggested that the inclusion of these trials would have resulted in a decrease in the uncertainty related to the conclusions regarding the comparison of antithrombotic to antiplatelet drugs; but it would otherwise not have substantially altered the conclusions of our report.

5.3 Strengths and Limitations of the Systematic Review

5.3.1 Strengths

This systematic review was conducted according to a protocol specified in advance, using standard approaches for identification of evidence, data extraction, quality assessment and analysis. Unlike previous systematic reviews of stroke prevention agents in AF, this review was not limited to anticoagulant drugs, but included the antiplatelet drugs ASA and clopidogrel. By conducting an MTC meta-analysis, both the direct and indirect evidence is presented for comparison; indeed, the results of the indirect comparison were consistent with those of the pairwise comparisons, which supports the robustness of the MTC meta-analysis. Sensitivity analyses were reported to explore heterogeneity; the consistency of these results with the reference case analysis demonstrates the robustness of the findings. A comprehensive economic evaluation was conducted using available cost data and the results of the NMA.

5.3.2 Key Limitations

In addition to the aforementioned strengths, a number of limitations related to the network meta-analysis warrant discussion.

- Variability in the baseline patient characteristics of the included studies that may be important predictors of treatment effects:

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 the baseline patient characteristics of the included studies that may be important predictors of treatment effects. For example, ROCKET-AF[43] included higher-risk patients with a minimum $CHADS_2$ score of 2, whereas CAFA[32] and JAST[33] recruited mostly low-risk patients with lower $CHADS_2$ scores. To address this heterogeneity, we performed subgroup analyses and stratified results across studies by $CHADS_2$, age, and TTR. We opted to perform subgroup analyses as opposed to meta-regression analyses based on the research questions and objectives stated in the project protocol.

Subgroup analyses were able to address some of the limitations noted above; however, the issues with heterogeneity were only partially resolved:

- We have no way of assessing the similarity of patient populations in the subgroups we have considered as the original randomization is broken when the original study arms are divided post hoc. Consequently, while 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.
- Results from subgroup analyses are hypothesis-generating; further research is needed to characterize the potential benefits and risks of each agent in various patient populations. However, in the absence of other evidence, the results of subgroup analyses are used to draw conclusions that bring additional value to the analysis. In this context, it is especially important to consider the uncertainty surrounding the findings.
- We did not have data to conduct multi-way subgroup analyses (e.g., $CHADS_2 \geq 2$ + age≥ 75 + TTR ≥ 66%).

5.3.3 Other Limitations

a) Reference case analysis performed using a fixed-effects model:
While our analysis considered both fixed and random-effects models, the results from the random-effects model had wide credible intervals due to the vague or non-informative prior distributions exerting a large degree of influence on results. Therefore, we reported the results from the fixed-effects model in the main text. We felt that this was appropriate as the nodes in evidence networks are connected largely by single studies. Effect estimates derived from the fixed-effecst model aligned more closely with the direct estimates and the DIC (a measure of model fit that penalizes model complexity). Reporting results from the fixed-effects model in the main text likely biases results in favour of the NOACs, as treatments that achieved statistically significant results in the primary RCTs retained statistically significant findings when using the fixed-effects model, but not always when using the random-effects model. Nevertheless, the results from the random-effects model have been reported, as well. Sensitivity analyses considering more informative priors for the standard deviation (results not shown) in the random-effects model were also conducted. Findings from the random-effects model using more informative priors varied, placing results somewhere between those of the fixed-effects model and the random-effects model, depending on which prior was chosen.

b) Analysis populations:
Whenever possible, data was gathered for the ITT populations. However, some trials did not report data consistently. For example, PETRO only reported data for the per-protocol population, while ROCKET-AF presented data for both the ITT and per-protocol populations.

c) Asymmetry of information:
There is also potential asymmetry of information that may introduce bias. Both dabigatran and rivaroxaban have been reviewed by the FDA for AF and detailed Public Summary Documents were available[60] in addition to the RE-LY[35] and ROCKET-AF[43] publications. FDA Public Summary Documents were not identified for other treatments included in NMA. As a result, we were able scrutinize the data for dabigatran and rivaroxaban more at this time than the data for some of the other treatments included in the networks. If data emerges suggesting that the benefits of these treatments are less favourable (or there is evidence of harm), then the network meta-analysis and cost-effectiveness will have to be revisited.

d) Use of the RE-LY trial to calculate absolute risk reduction:
The absolute risk reduction from NMA was calculated using the event rate in the warfarin arm of the RE-LY study.[35] The RE-LY trial[35] was selected because it was the most recent trial which contained data for both $CHADS_2 < 2$ and $CHADS_2 \geq 2$ and had detailed data made publicly available following the FDA review of dabigatran.[60] Use of a different study (e.g., ARISTOTLE)[26] for baseline event rate data is unlikely to change the results substantially given that the event rates in warfarin arms were similar across studies.

e) Network meta-analysis could not be conducted on some of the secondary outcomes:
The current analysis only reports results from NMA for six outcomes: all-cause stroke or SE, major bleeding, all-cause mortality, ICH (including intracerebral hemorrhage), extracranial bleeding, and MI. Network meta-analysis for other outcomes were not conducted because data was either sparsely reported (e.g., PE, life-threatening bleeds, transient ischemic stroke), outcome definitions varied considerably (e.g., minor bleeds), or outcomes were redundant (all-cause stroke or SE versus ischemic stroke or SE). Further, there was limited subgroup data reported for some outcomes considered in NMA.

f) Limited data on ASA in the $CHADS_2 < 2$ population:
Given that one of the main research objectives was to compare ASA with NOACs in this population, we were required to perform subgroup analyses with data that did not consist solely of patients with $CHADS_2 < 2$. We used subgroup data that either only partially aligned with the subgroups (i.e., BAFTA[31] had $CHADS_2$ 1-2 versus 0-1) or used study-level data from RCTs consisting of low-risk patients (e.g., CAFA,[32] JAST[33]), where a small proportion of patients had $CHADS_2 \geq 2$ (< 25%). This may bias results slightly against ASA, as patients included in the $CHADS_2 < 2$ subgroup in the ASA trials may have had a higher baseline risk.

The lack of raw data from the clinical trials meant that it was not possible to conduct stratified analysis within $CHADS_2$ score (e.g., analysis for a patient with $CHADS_2$ score < 2 with poor INR control). To facilitate such analyses would require network meta-regression analyses of patient-level data.

g) Methodological heterogeneity between NOACs trials and antiplatelet trials:
In addition, critical appraisal reveals that most trials evaluating ASA with or without clopidogrel or placebo/no treatment were substantially smaller, older, and of lower quality than the NOAC trials. This affects our level of confidence, especially in the results of the MTC pairwise comparisons for these interventions, which is considerably lower than for the anticoagulants. For example, the fact that warfarin achieved a non-significant reduction in SSE versus placebo/no treatment in the pairwise comparison should not be interpreted clinically as an absence of difference between the two interventions; indeed, statistical significance was likely not reached due to uncertainty and limitations from the primary trials included in the systematic review, as illustrated by the relatively large CI.

6 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

The results of the current review revealed that there were statistically significant differences in clinical outcomes in AF patients between the NOACs and warfarin, although it is unclear whether the ARD associated with these differences translate into clinically meaningful benefits in practice. In addition, NOACs may be cost-effective alternatives to warfarin for preventing SSE in AF patients. More specifically, if it is assumed that the λ is $50,000, then among the NOACs, dabigatran 150 mg twice daily is likely the optimal therapy in patients who have a moderate risk of stroke ($CHADS_2 = 1$), or are relatively young (≤ 70 years old), or who cannot maintain an adequate INR control (TTR < 66%); apixaban 5 mg twice daily would likely be the optimal NOAC therapy in patients who have a high risk of stroke ($CHADS_2$ score ≥ 2), or are relatively old (≥ 80 years old).

The current review extends our previous report by demonstrating that anticoagulant therapy is superior to ASA, both in terms of clinical benefit and cost-effectiveness, irrespective of whether ASA is co-administered with clopidogrel. Anticoagulant therapy would appear to be a superior treatment option for preventing SSE in patients with non-valvular AF in patients with a moderate or high risk of stroke ($CHADS_2$ score ≥ 1). The superiority of the anticoagulant drugs versus the antiplatelet drugs was consistent irrespective of age and the degree of INR control (TTR). There was, however, insufficient evidence to compare anticoagulant drugss to antiplatelet drugs in patients with a low risk of stroke ($CHADS_2$ score = 0).

These results must be considered in the light of several limitations that create uncertainty, most notably the reliance on indirect comparison methodology to compare the different treatments.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials <May 2012> Ovid Embase 1974 to June 6, 2012 Ovid MEDLINE 1946 to June 7, 2012 Ovid MEDLINE Daily Ovid MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 7, 2012
Alerts:	Monthly search updates began June 11, 2012 and ran until project completion
Study Types:	Randomized Controlled Trials
Limits:	Publication years 1988-present Humans Conference abstracts omitted

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
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.nm.	Name of substance word
.ot	Original title
.pt	Publication type
.rn	CAS registry number
use cctr	Select results from Cochrane database of Clinical Trials
use oemezd	Select results from Embase database
use pmez	Select results from Medline database

Clinical Multi-database Strategy	
Line #	**Search Strategy**
1	(211914-51-1 or 211915-06-9).rn,nm. or (dabigatran* or Pradaxa or Pradax or Prazaxa or Praxada or bibr 1048 or bibr1048 or bibr953 or bibr 953 or rendix).ti,ot,ab,sh,rn,hw,nm.
2	(BMS 562247 or BMS562247 or apixaban* or Eliquis or Eliques).ti,ot,ab,sh,rn,hw,nm. or 503612-47-3.rn,nm.
3	(rivaroxaban* or Xarelto or BAY 59-7939 or BAY59-7939 or BAY597939 or BAY 597939).ti,ot,ab,sh,rn,hw,nm. or 366789-02-8.rn,nm.
4	(90055-48-4 or 113665-84-2).rn,nm. or (clopidogrel* or clopilet or grepid or iscover or plavix or zopya or zylagren or zyllt or duocover or duoplavin).ti,ot,ab,sh,rn,hw,nm.
5	Aspirin/ or 50-78-2.rn,nm. or (acetylsalicylic acid* or aspirin* or acenterine or acesal or acetan or acetard or aceticil or aceticyl or acetilum or acetonyl or acetilum or acetonyl or acetophen or acetosal or acetosalicylic acid or acetosalin or acetosalum or acetyl salicylate or acetyl salicylic acid or acetylin or acetylo or acetylon or acetylosalicylic acid or acetylsal or acetysal or acetylsalicyclic acid or acetylsalicyl or acetylsalicylate or acetylsalycic acid or acetylsalycylic acid or oracidulatum or actorin or Acylpyrin or acylpyrine or acytosal or adiro or alabunkun or alasil or albyl-e or alka seltzer or alkaspirin or Aloxiprimum or anacin or anasprin or anopyrin or ansin or anthrom or aptor or arthralgyl or asaflow or ascription or orasaphen or asapor or asatard or asawin or aspec or aspent or aspergum or aspex or aspilets or aspirem or aspirgran or aspirina or aspirine or aspirinine or aspirisucre or aspisol or aspo cid or aspro or asrina or asrivo or asta or asteric or astrix or bebesan or biprin or bokey or boxazin or breoprin or bufferin or cafenol or caprin or caspirin or catalgine or catalgix or cemerit or cemirit or claradin or claragine or Colfarit or comoprin or contrheuma or daga or darosal or Dispril or dispirin or dolean or dusil or Easprin or ecasil or Ecotrin or egalgic or emocin or empirin or encaprin or encine em or Endosprin or entaprin or entercin or enteroprin or enterosarine or enterospirine or entrophen or eskotrin or euthermine or extren or genasprin or globentyl or godamed or gotosan or helicon or idotyl or infatabs a or istopirin or istopyrine or ivepirine or juvepirine or keypo or kilios or kinderaspirin or Magnecyl or measurin or mejoral or melabon or Micristin or micropyrin or mikristin or miniasal or mycrisitin or naspro or novasen or nu seal or nu seals or ortho acetoxybenzoate or ortho acetoxybenzoic acid or ortho acetyloxybenzoate or ortho acetyloxybenzoic acid or ostoprin or pancemol or paracin or paynocil or pengo or plewin or Polopirin or polopiryna or premaspin or primaspan or proprin or pyronoval or reumyl or rhodine or rhonal or ronal or salacetin or salisalido or sargepirine or soldral or solpyron or Solprin or solucetyl or solupsa or Solupsan or spren or super tru or tapal or temagin or tevapirin or th 2152 or thrombo-aspilets or treupahlin or treuphalin or tromalyt or tromcor or turiital or verin or vitalink or xaxa or Zorprin).ti,ot,ab,sh,rn,hw,nm.
6	Warfarin/ or 81-81-2.rn,nm. or (adoisine or aldocumar or athrombin* or befarin or brumolin or carfin or circuvit or compound 42 or coumadan or coumadin or coumadine or coumafen or coumafene or coumefene or coumaphene or coumarins or dagonal or farin or jantoven or kumatox or maforan or marevan or orfarin or panwarfarin or panwarfin or prothromadin or simarc 2 or sofarin or tedicumar or tintorane or waran or warfant or warfar or warfarin or warfarine or warfil or warfilone or warnerin).ti,ot,ab,sh,rn,hw,nm.
7	Acenocoumarol/ or 152-72-7.rn,nm. or (acenocoumarol* or nicoumalone or acenocoumarin or acenocoumarine or acenocoumarole or acenocoumarolum or acenocumarol or acenocumarolo or acenocumerol or acenkumarin or acitrom or ascumar or neo sintrom or neosintrom or neositron or nicoumalone or nicumalon or nitrovarfarian or nitrowarfarin or sincoumar or sincumar or sinkumar or sinthrom or sinthrome or sintrom or sintroma or sintron or syncoumar or syncumar or synthrom or syntrom or syntroma or sintron or syncoumar or syncumar or syntrom or trombostop or zotil or sinthrome or synthrom or syncoumar or syncumar or sinkumar or sintrom or minisintrom or trombostop or zotil).ti,ot,ab,sh,rn,hw,nm.
8	or/1-7
9	Atrial fibrillation/
10	((atrial or atrium or auricular or heart) adj1 fibrillation*).ti,ab.
11	(a-fib or afib).ti,ab.
12	9 or 10 or 11
13	8 and 12
14	13 use pmez
15	13 use cctr
16	14 or 15
17	*dabigatran/ or (dabigatran* or Pradaxa or Pradax or Prazaxa or praxada or bibr 1048 or bibr1048 or

Clinical Multi-database Strategy	
Line #	**Search Strategy**
	bibr953 or bibr 953 or rendix).ti,ab.
18	*apixaban/ or (BMS 562247 or BMS562247 or apixaban* or Eliquis or Eliques).ti,ab.
19	*rivaroxaban/ or (rivaroxaban* or Xarelto or BAY 59-7939 or BAY59-7939 or BAY597939 or BAY 597939).ti,ab.
20	*clopidogrel/ or *acetylsalicylic acid plus clopidogrel/ or (clopidogrel* or clopilet or grepid or iscover or plavix or zopya or zylagren or zyllt or duocover or duoplavin).ti,ab.
21	*warfarin/ or (adoisine or aldocumar or athrombin* or befarin or brumolin or carfin or circuvit or compound 42 or coumadan or coumadin or coumadine or coumafen or coumafene or coumefene or coumaphene or coumarins or dagonal or farin or jantoven or kumatox or maforan or marevan or orfarin or panwarfarin or panwarfin or prothromadin or simarc 2 or sofarin or tedicumar or tintorane or waran or warfant or warfar or warfarin* or warfarine or warfil or warfilone or warnerin).ti,ab.
22	*acetylsalicylic acid/ or (acetylsalicylic acid* or aspirin* or acenterine or acesal or acetan or acetard or aceticil or aceticyl or acetilum or acetonyl or acetilum or acetonyl or acetophen or acetosal or acetosalicylic acid or acetosalin or acetosalum or acetyl salicylate or acetyl salicylic acid or acetylin or acetylo or acetylon or acetylosalicylic acid or acetylsal or acetysal or acetylsalicyclic acid or acetylsalicyl or acetylsalicylate or acetylsalycic acid or acetylsalycylic acid or oracidulatum or actorin or Acylpyrin or acylpyrine or acytosal or adiro or alabunkun or alasil or albyl-e or alka seltzer or alkaspirin or Aloxiprimum or anasprin or anopyrin or ansin or anthrom or aptor or arthralgyl or asaflow or orasaphen or asapor or asatard or asawin or aspec or aspent or aspergum or aspex or aspilets or aspirem or aspirgran or aspirina or aspirine or aspirinine or aspirisucre or aspisol or aspo cid or aspro or asrina or asrivo or asta or asteric or astrix or bebesan or biprin or bokey or boxazin or breoprin or bufferin or cafenol or caprin or caspirin or catalgine or catalgix or cemerit or cemirit or claradin or claragine or Colfarit or comoprin or contrheuma or daga or darosal or Dispril or dispirin or dolean or dusil or Easprin or ecasil or Ecotrin or egalgic or emocin or empirin or encaprin or encine em or Endosprin or entaprin or entercin or enteroprin or enterosarine or enterospirine or entrophen or eskotrin or euthermine or extren or genasprin or globentyl or godamed or gotosan or helicon or idotyl or infatabs a or istopirin or istopyrine or ivepirine or juvepirine or keypo or kilios or kinderaspirin or Magnecyl or measurin or mejoral or melabon or Micristin or micropyrin or mikristin or miniasal or mycrisitin or naspro or novasen or nu seal or nu seals or ortho acetoxybenzoate or ortho acetoxybenzoic acid or ortho acetyloxybenzoate or ortho acetyloxybenzoic acid or ostoprin or pancemol or paracin or paynocil or pengo or plewin or Polopirin or polopiryna or premaspin or primaspan or proprin or pyronoval or reumyl or rhodine or rhonal or ronal or salacetin or salisalido or sargepirine or soldral or solpyron or Solprin or solucetyl or solupsa or Solupsan or spren or super tru or tapal or temagin or tevapirin or th 2152 or thrombo-aspilets or treupahlin or treuphalin or tromalyt or tromcor or turiital or verin or vitalink or xaxa or Zorprin).ti,ab.
23	*Acenocoumarol/ or (acenocoumarol* or nicoumalone or acenocoumarin or acenocoumarine or acenocoumarole or acenocoumarolum or acenocumarol or acenocumarolo or acenocumerol or acenkumarin or acitrom or ascumar or neo sintrom or neosintrom or neositron or nicoumalone or nicumalon or nitrovarfarian or nitrowarfarin or sincoumar or sincumar or sinkumar or sinthrom or sinthrome or sintrom or sintroma or sintron or syncoumar or syncumar or synthrom or syntrom or syntroma or sintron or syncoumar or syncumar or syntrom or trombostop or zotil or sinthrome or synthrom or syncoumar or syncumar or sinkumar or sintrom or minisintrom or trombostop or zotil).ti,ab.
24	or/17-23
25	Heart atrium fibrillation/
26	((atrial or atrium or auricular or heart) adj1 fibrillation*).ti,ab.
27	(a-fib or afib).ti,ab.
28	25 or 26 or 27
29	24 and 28
30	29 use oemezd
31	30 not conference abstract.pt.
32	16 or 31
33	32
34	limit 33 to english language [Limit not valid in CCTR; records were retained]
35	(Randomized Controlled Trial or Controlled Clinical Trial).pt.

Clinical Multi-database Strategy	
Line #	**Search Strategy**
36	Randomized Controlled Trial/
37	Randomized Controlled Trials as Topic/
38	"Randomized Controlled Trial (topic)"/
39	Controlled Clinical Trial/
40	Controlled Clinical Trials as Topic/
41	"Controlled Clinical Trial (topic)"/
42	Randomization/
43	Random Allocation/
44	Double-Blind Method/
45	Double Blind Procedure/
46	Double-Blind Studies/
47	Single-Blind Method/
48	Single Blind Procedure/
49	Single-Blind Studies/
50	Placebos/
51	Placebo/
52	Control Groups/
53	Control Group/
54	(random* or sham or placebo*).ti,ab,hw.
55	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
56	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
57	(control* adj3 (study or studies or trial*)).ti,ab.
58	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
59	allocated.ti,ab,hw.
60	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
61	or/35-60
62	34 and 61
63	limit 62 to yr = "1988 -Current"
64	remove duplicates from 63

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	**June 12, 2012 – July 8, 2012**
Keywords:	dabigatran, Pradax, Pradaxa, apixaban, Eliquis, rivaroxaban, Xarelto, clopidogrel, Plavix, acetylsalicylic acid, Aspirin, warfarin, Coumadin, acenocoumarol, Sintrom, Sinthrome Atrial fibrillation
Limits:	Publication years 1988-present, English

Relevant items from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/resources/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economic
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

APPENDIX 2: MODELLING OF TRANSITION PROBABILITIES

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 an event 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 treatment comparators other than warfarin was derived by using the odds ratio 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)

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

APPENDIX 3: CLINICAL PARAMETERS RELATED TO WARFARIN USE

Table A3.1: Clinical Parameters Relating to Warfarin Use

Parameters	Base Estimate	Probability Distribution*	Reference
Annual rates of events with Warfarin:			
SSE			
$CHADS_2$ <2	0.011	Beta (40, 3667)	FDA (2010)[104], Oldgren (2011)[39]
$CHADS_2$ ≥2	0.020	Beta (162, 7928)	
TIA	0.008	Beta (99, 11695)	
ICH			
$CHADS_2$ <2	0.005	Beta (20, 3687)	FDA (2010)[104]
$CHADS_2$ ≥2	0.009	Beta (70, 8020)	FDA (2010)[104], Oldgren (2011)[39]
Major bleeds			
$CHADS_2$ <2	0.028	Beta (105, 3602)	
$CHADS_2$ ≥2	0.039	Beta (316, 7774)	FDA (2010)[104], Oldgren (2011)[39]
Minor bleeds	0.164	Beta (1931, 9863)	
MI	0.006	Beta (66, 11728)	
PE	0.001	Beta (12, 11782)	FDA (2010)[104]
Non-vascular death			FDA (2010)[104]
$CHADS_2$ <2	0.033	Beta (90, 3617)	FDA (2010)[104]
$CHADS_2$ ≥2	0.037	Beta (301,7789)	FDA (2010)[104], Oldgren (2011)[39]
Event related probabilities			
Percentage of first SSE which are fatal	0.237	Beta (44, 142)	FDA (2010)[104]
Percentage of non-fatal first SSE which are major	0.333	Beta (39, 78)	FDA (2010)[104]
Increased risk of subsequent SSE being fatal	1.570	Lognormal (0.45, 0.13)	Carter (2007)[105]
Probability major bleed or ICH is fatal	0.084	Beta (40, 436)	FDA (2010)[104]
Probability MI is fatal	0.121	Beta (8, 58)	FDA (2010)[104]
Probability PE is fatal	0.333	Beta (4, 8)	FDA (2010)[104]
Event rate adjustments			
Increase in SSE for each 10 year age increment	1.50	Lognormal (0.40, 0.07)	Stroke Risk in Atrial Fibrillation Working Group (2007)[63]
Increase in SSE given previous SSE/TIA	2.20	Lognormal (0.79, 0.54)	Lip (2010)[106]
Increase in MI given previous MI	2.04	Lognormal (0.71, 0.28)	Cupples (1993)[107]
Increase in bleeding given age over 65	2.66	Lognormal (0.98, 0.35)	Pisters (2010)[108]
Increase in death given previous SSE	2.30	Lognormal (0.83, 0.07)	Dennis (1993)[109]
Increase in death given AF	1.20	Lognormal (0.18, 0.08)	Wyse (2001)[110]

MI = myocardial infarction; ICH = intracranial hemorrhage, PE = pulmonary embolism, TIA = transient ischemic attack, SSE = stroke or systemic embolism.
*Beta distributions parameterized by alpha and beta, lognormal distributions parameterized by log means and log standard errors.

APPENDIX 4: ASSUMPTIONS USED IN THE ECONOMIC MODEL

The patient population in the warfarin arm of RE-LY trial is representative of the Canadian atrial fibrillation population.
Patients who have a SSE, ICH or major bleeding while on clopidogrel plus ASA, warfarin, rivaroxaban, dabigatran or apixaban will continue on treatment with ASA 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 although their previous history may affect the likelihood of such an event.
A patient can experience only one event within a cycle.
The probability of a patient having a SSE will be greater given a previous SSE or TIA.
The probability of a patient having a MI will be greater given a previous MI.
The probability of SSE 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 SSE, ICH or MI is temporary.
The cost of events other than SSE, ICH or MI occurs only within the cycle when they occur.
There are long term costs associated with an MI, ICH and SSE which continue until death.
The relative efficacy of treatments is assumed to be maintained while 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.

ASA = acetylsalicylic acid; ICH = intracranial hemorrhage; MI = myocardial infarction; SSE = stroke and systemic embolism; TIA = transient ischemic attack.

APPENDIX 5: UTILITY VALUES FOR ALL HEALTH STATES WITHIN THE ECONOMIC MODEL

Variable Description	Base Estimate	Probability Distribution	Reference
Long term utilities			
Atrial fibrillation	0.810	Beta (33.82, 7.93)	Sullivan (2006)[64]
Previous major stroke	0.333	N/A	
Rankin score 3-4	0.390	Beta (69.74, 109.08)	Gage (1996)[65]
Rankin score 5	0.110	Beta (18.93, 153.16)	Gage (1996)[65]
Probability major stroke is 5	0.205	Beta (8, 39)	FDA (2010)[104]
Previous minor stroke/SSE			
Previous ICH	0.75	Beta (86.69, 28.90)	Gage (1996)[65]
Previous MI (decrement)	0.75	Beta (86.69, 28.90)	Gage (1996)[65]
	0.012	Normal (0.012, 0.0002)	Sullivan (2005)[69]
Decrements associated with events *			
MI	0.125	Normal (–0.125, 0.009)	Sullivan (2006)[64]
Major bleeds	0.092	Normal (–0.092, 0.010)	Freeman (2011)[66]
Minor bleeds	0.013	Normal (–0.013, 0.001)	Freeman (2011)[66]
PE	0.022	Normal (–0.022, 0.003)	Gould (1999)[70]
TIA	0.103	Normal (–0.103, 0.008)	Sullivan (2006)[64]

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

APPENDIX 6: RESOURCE COST ESTIMATES

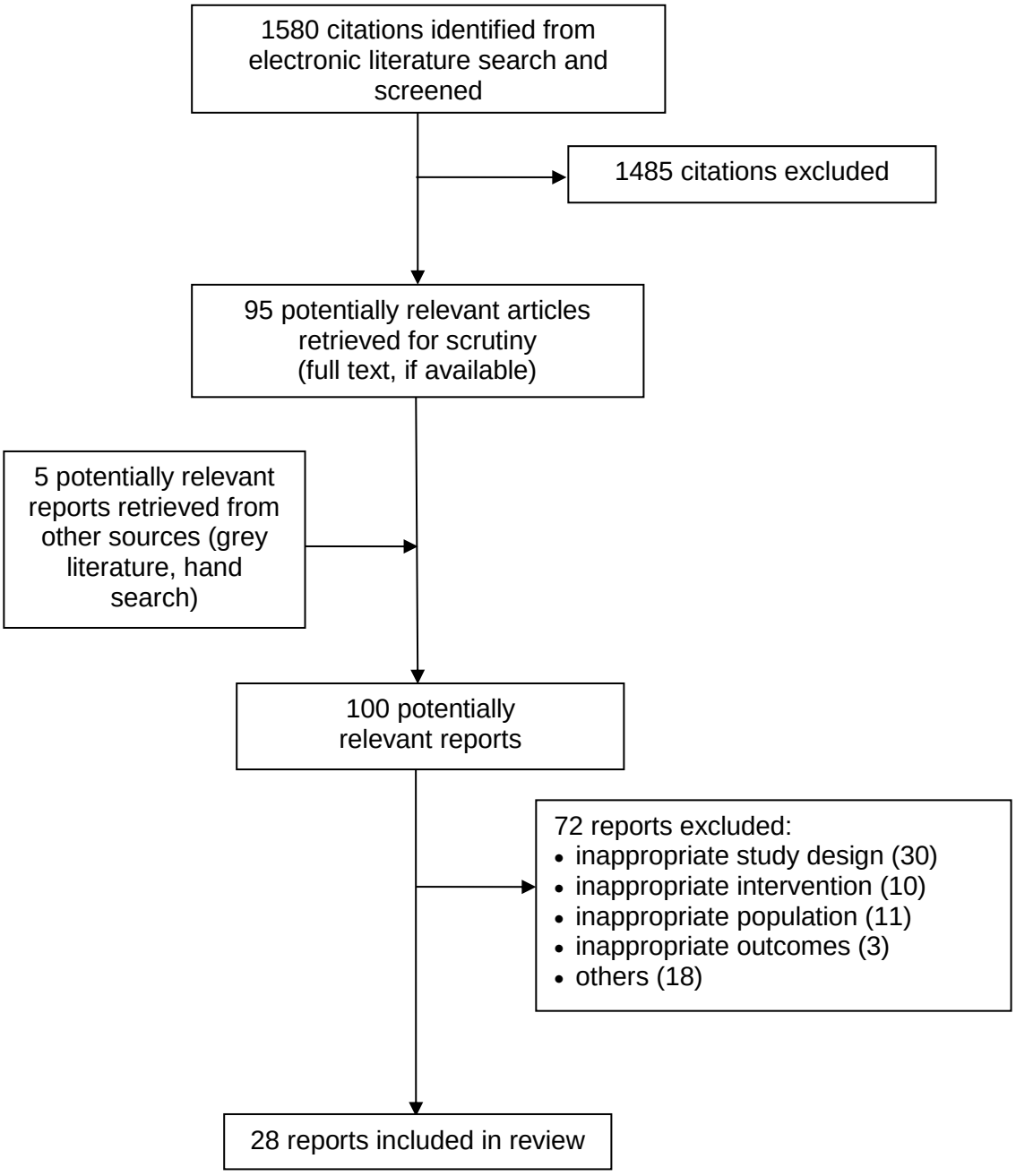
Variable Description	Base Estimate	Probability Distribution	Reference
Events			
Fatal stroke	$16,800	Gamma (16.0, 1050.0)	Sorensen (2011)[74]
Minor stroke/SSE	$16,800	Gamma (16.0, 1050.0)	Sorensen (2011)[74]
Major stroke	$56,864	Gamma (16.0, 3554.0)	Sorensen (2011)[74]
TIA	$4,296	Gamma (16.0, 268.5)	Goeree (2005)[76]
ICH	$16,559	Gamma (16.0, 1035.0)	Sorensen (2011)[74]
Major bleed	$4,392	Gamma (16.0, 274.5)	Sorensen (2011)[74]
Minor bleed	$104	Gamma (6.4, 16.3)	Regier (2006)[78]
Fatal MI	$7,351	Gamma (16.0, 459.5)	Sorensen (2011)[74]
Non-fatal MI	$11,380	Normal (11380.0, 167.0)	Goeree (2009)[77]
PE	$7,442	Normal (7442.0, 7682.1)	OCCI (2012)[75]
Long term costs (per annum)			
MI	$3,272	Gamma (190.6, 17.2)	Sorensen (2011)[74]
Major stroke	$19,069	Gamma (16.0, 1191.8)	Sorensen (2011)[74]
Minor stroke	$7,896	Gamma (16.0, 493.5)	Goeree (2009)[77]
ICH	$7,896	Gamma (16.0, 493.5)	Goeree (2009)[77]

EC = enteric coated, MI = myocardial infarction, ICH = intracranial hemorrhage, PE = pulmonary embolism, TIA = transient ischemic attack.
^ Includes a $7 prescription fee (every three months) and an 8% pharmacist's mark up.
* Personal communication.
Gamma distributions parameterized by shape and scale, normal distributions parameterized by means and standard errors (used when coefficient of variation is minimal).

APPENDIX 7: UNIVARIATE SENSITIVITY ANALYSES

Table A7.1. Summary of univariate sensitivity analyses.	
Parameter	Analysis
Drug costs of rivaroxaban	Reduce by 10% and 20%
Drug costs of dabigatran	
Drug costs of apixaban	
Threshold analysis	Determine the cost at which therapies would be cost-effective
Annual cost of INR monitoring with warfarin	Assume equal to $0
Annual cost of INR monitoring with warfarin	Assume equal to $542.48
Event costs	Increase and decrease by 50%
Long term care costs	Increase and decrease by 50%
Time horizon	Use 20, 10, and 2 years
Discount rate	Apply a rate of 0, 3, and 10%
Maximum utility value for stroke	Major = 0.52, minor = 0.8
Minimum utility value for stroke	Major = 0.22, minor = 0.55
Utility values	Include an age decrement
Utility decrements from events	Increase by 100%
Effect of treatments on non-vascular deaths	Include
Effect of treatments on MI	Exclude
MI	Assume patients had a previous MI
Utility decrements from and costs of minor and major bleeds for the new anticoagulants	Assuming double and quadruple utility decrements
utility decrements from and costs of minor and major bleeds for dabigatran	Assuming double and quadruple utility decrements
disutility and costs of ICH	Assume equivalent to major stroke
Assume patients would continue on low-dose ASA after an event.	Assuming patients remain on therapy for lifetime
Assume that patients would transition from dabigatran 150 mg to dabigatran 110 mg	Transition at age 80

APPENDIX 8: SELECTION OF INCLUDED STUDIES



APPENDIX 9: INCLUDED STUDY LIST

1. Study ACTIVE-W

ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, et al. Clopidogrel plus ASA versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006 Jun 10;367(9526):1903-12.

Related references:

Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation [Internet]. 2008 Nov 11 [cited 2012 Jun 18];118(20):2029-37. Available from: http://circ.ahajournals.org/content/118/20/2029.full.pdf+html

Healey JS, Hart, RG, Pogue J, Pfeffer MA, Hohnloser SH, De Caterina R, et al. Risks and benefits of oral anticoagulation compared with clopidogrel plus ASA in patients with atrial fibrillation according to stroke risk: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE-W). Stroke. 2008 May;39(5):1482-6.

Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, et al. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. J Am Coll Cardiol. 2007 Nov 27;50(22):2156-61.

2. Study AFASAK

Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and ASA for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet. 1989 Jan 28;1(8631):175-9.

3. Study AFASAK 2

Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, et al. Fixed minidose warfarin and ASA alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, ASA, and Anticoagulation Study. Arch Intern Med. 1998 Jul 27;158(14):1513-21.

Related reference:

Gullov AL, Koefoed BG, Petersen P. Bleeding during warfarin and ASA therapy in patients with atrial fibrillation: the AFASAK 2 study. Atrial Fibrillation ASA and Anticoagulation. Arch Intern Med. 1999 Jun 28;159(12):1322-8.

4. Study ARISTOTLE

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med [Internet]. 2011 Sep 15;365(11):981-92. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1107039

Related references:

Easton JD, Lopes RD, Bahit MC, Wojdyla DM, Granger CB, Wallentin L, et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. The Lancet Neurology. 2012;11(6):503-11.

Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J. 2012 Aug 29.

Lopes RD, Al-Khatib SM, Wallertin L, Ansell J, Bahit JC, De Caterina F, et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. Lancet. 2012 Oct 2.

5. Study ARISTOTLE-J

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APPENDIX 10: EXCLUDED STUDY LIST

Inappropriate Study Design

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Inappropriate Population

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APPENDIX 11: CRITICAL APPRAISAL OF INCLUDED STUDIES

Table A11.1: Assessment of Individual Study Quality

Study	Interventions	Randomization	Allocation concealment	Double-blinding	Baseline characteristics similarity	Outcome measures	WDs	ITT analysis	Funding
ACTIVE-W,[19-22] **2006** (n = 6706)	**Clopidogrel+Low-dose ASA** **Adjusted-Dose Warfarin**	Adequate	Adequate	No	Yes	Adequate	10%	Yes	Manufacturer
AFASAK,[23] **1989** (n = 672)	**Low-dose ASA** **Placebo / No Treatment**	Adequate	Adequate	Yes	Yes	Adequate	14%	Yes	Mixed Funding
AFASAK-2,[24,25] **1998** (n = 339)	**Medium-Dose ASA** **Adjusted-Dose Warfarin**	Adequate	Adequate	No	Yes	Adequate	NR	Yes	Mixed Funding
ARISTOTLE,[26-29] **2011** (n = 18201)	**Apixaban 5 mg b.i.d.** **Adjusted-Dose Warfarin**	Adequate	Adequate	Yes	Yes	Adequate	26%	Yes	Manufacturer
ARISTOTLE-J,[30] **2011** (n = 222)	**Apixaban 2.5 mg b.i.d.** **Apixaban 5 mg b.i.d.** **Adjusted-Dose Warfarin**	Adequate	Insufficient reporting	No	No	Adequate	11%	Yes	Manufacturer
BAFTA,[31] **2007** (n = 973)	**Low-dose ASA** **Adjusted-Dose Warfarin**	Adequate	Adequate	No	Yes	Adequate	29%	Yes	Independent
CAFA,[32] **1991** (n = 378)	**Adjusted-Dose Warfarin** **Placebo / No Treatment**	Adequate	Insufficient reporting	Yes	No	Adequate	24%	Yes	NR
JAST[33] **2006** (n = 871)	**Medium-dose ASA** **Placebo / No Treatment**	Adequate	Adequate	No	Yes	Adequate	21%	Yes	Independent
PETRO[34] **2007** (n = 236)	**Dabigatran 150 mg b.i.d.± Low-dose or High-dose ASA** **Adjusted-Dose Warfarin**	Adequate	Insufficient reporting	No	No	Adequate	6%	No	Manufacturer
RE-LY[35-42] **2009** (n = 18113)	**Dabigatran 110 mgb.i.d.**	Adequate	Adequate	No	Yes	Adequate	20%	Yes	Manufacturer

Table A11.1: Assessment of Individual Study Quality									
Study	**Interventions**	**Randomization**	**Allocation concealment**	**Double-blinding**	**Baseline characteristics similarity**	**Outcome measures**	**WDs**	**ITT analysis**	**Funding**
	Dabigatran 150 mg b.i.d. Adjusted-Dose Warfarin								
ROCKET-AF[43-45] **2011** (n = 14264)	**Rivaroxaban 20 mg q.d. Adjusted-Dose Warfarin**	Adequate	Adequate	Yes	Yes	Adequate	23%	Yes	Manufacturer
WASPO[46] **2007** (n = 75)	**Adjusted-Dose Warfarin Medium-dose ASA**	Adequate	Adequate	No	No	Adequate	15%	Yes	Independent

b.i.d. = twice daily; ITT = intention to treat; **NR** = not reported; q.d. = once daily; WDs = withdrawals.

Trials with excluded treatment arms. In such cases, critical appraisal was performed considering only the included treatment groups.
Based on the SIGN50 instrument for internal validity.

APPENDIX 12: EVIDENCE NETWORKS

The size of nodes in each evidence network is proportional to the sample size for each node. The width of connections between nodes is proportional to the number of studies connecting the nodes.

Figure A12.1: Evidence Network for All-cause Stroke or Systemic Embolism

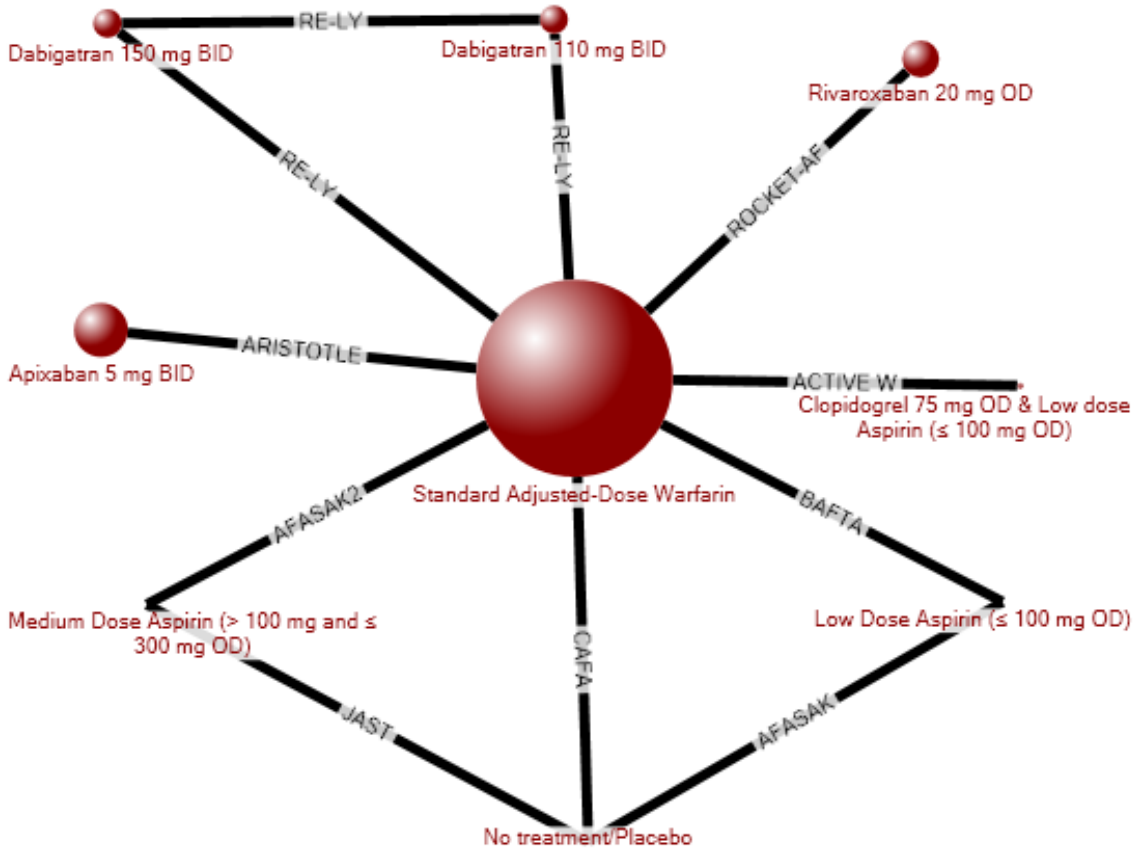


Figure A12.2: Evidence Network for Major Bleeding

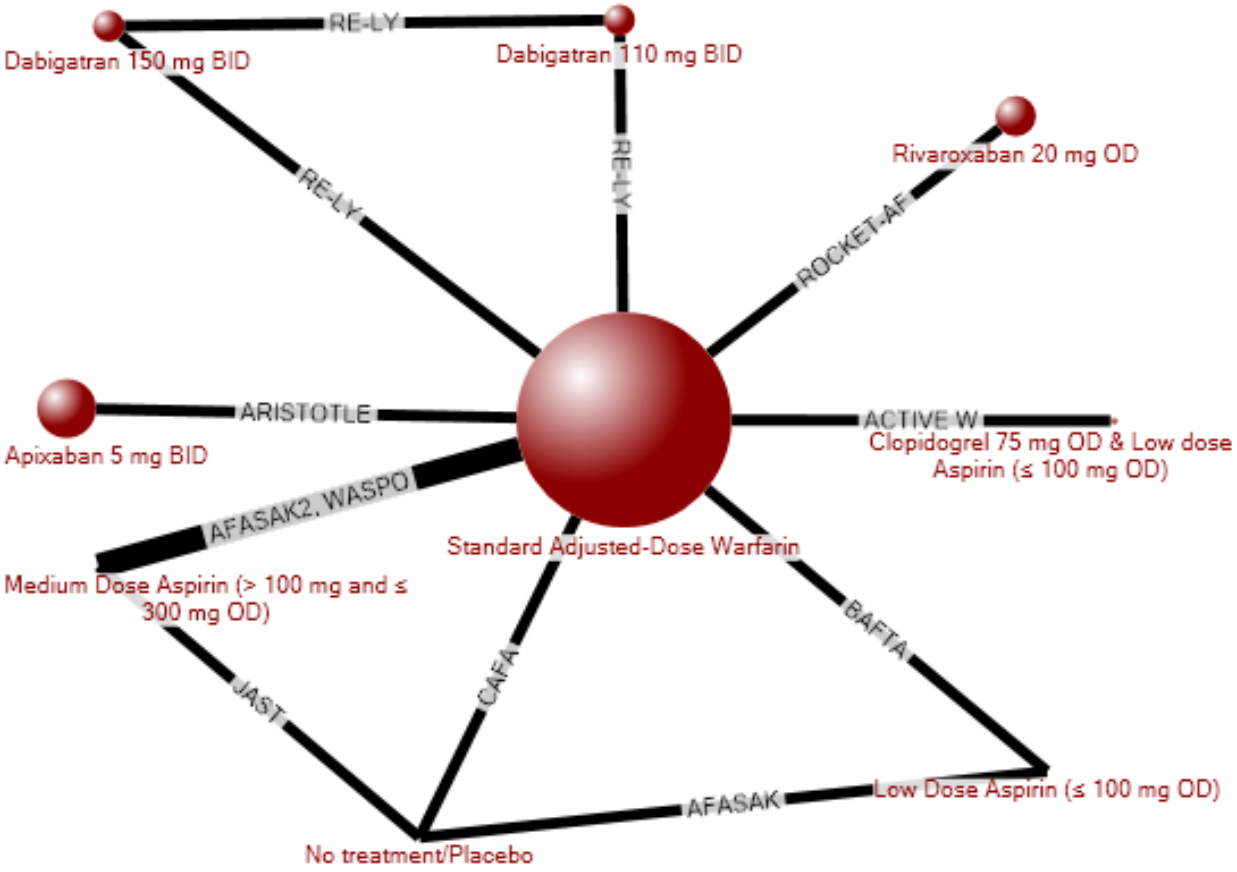


Figure A12.3: Evidence Network for All-cause Mortality

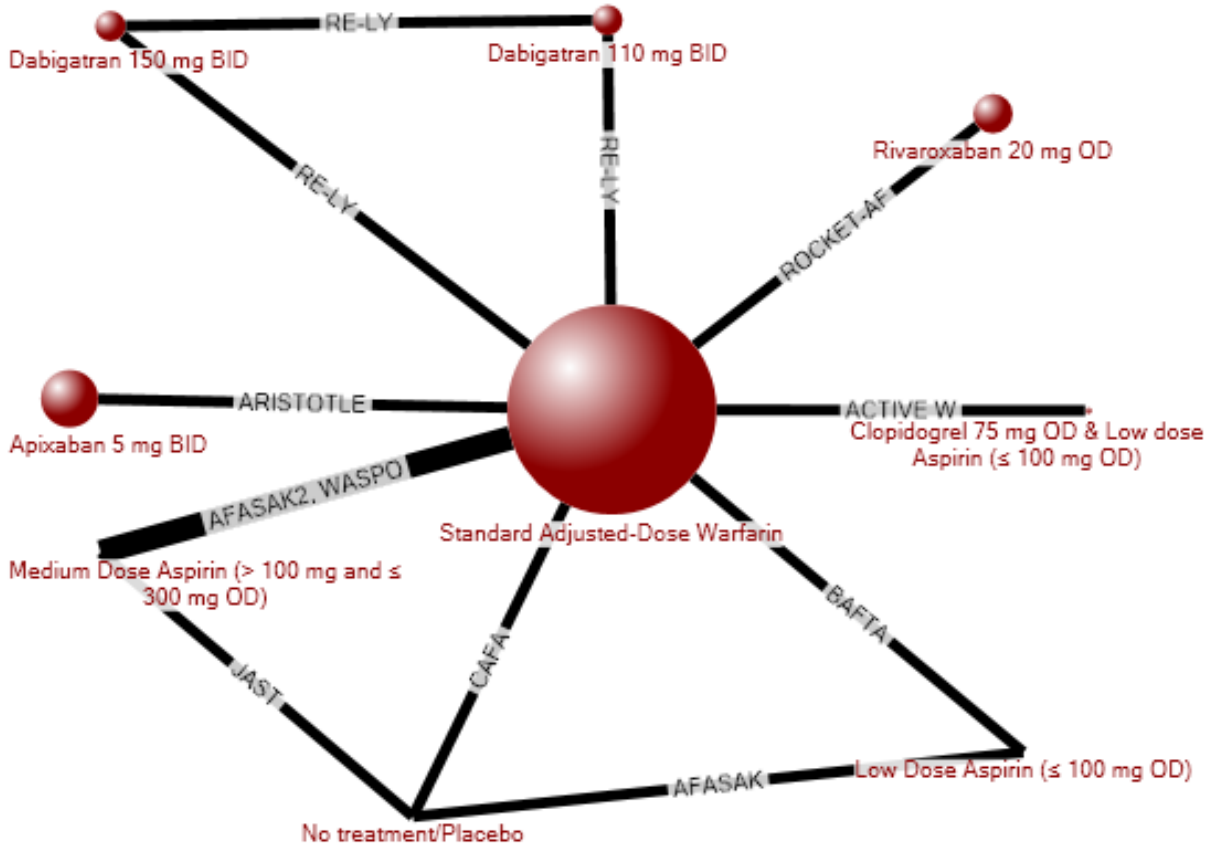


Figure A12.4: Evidence Network for Extracranial Hemorrhage (ECH)

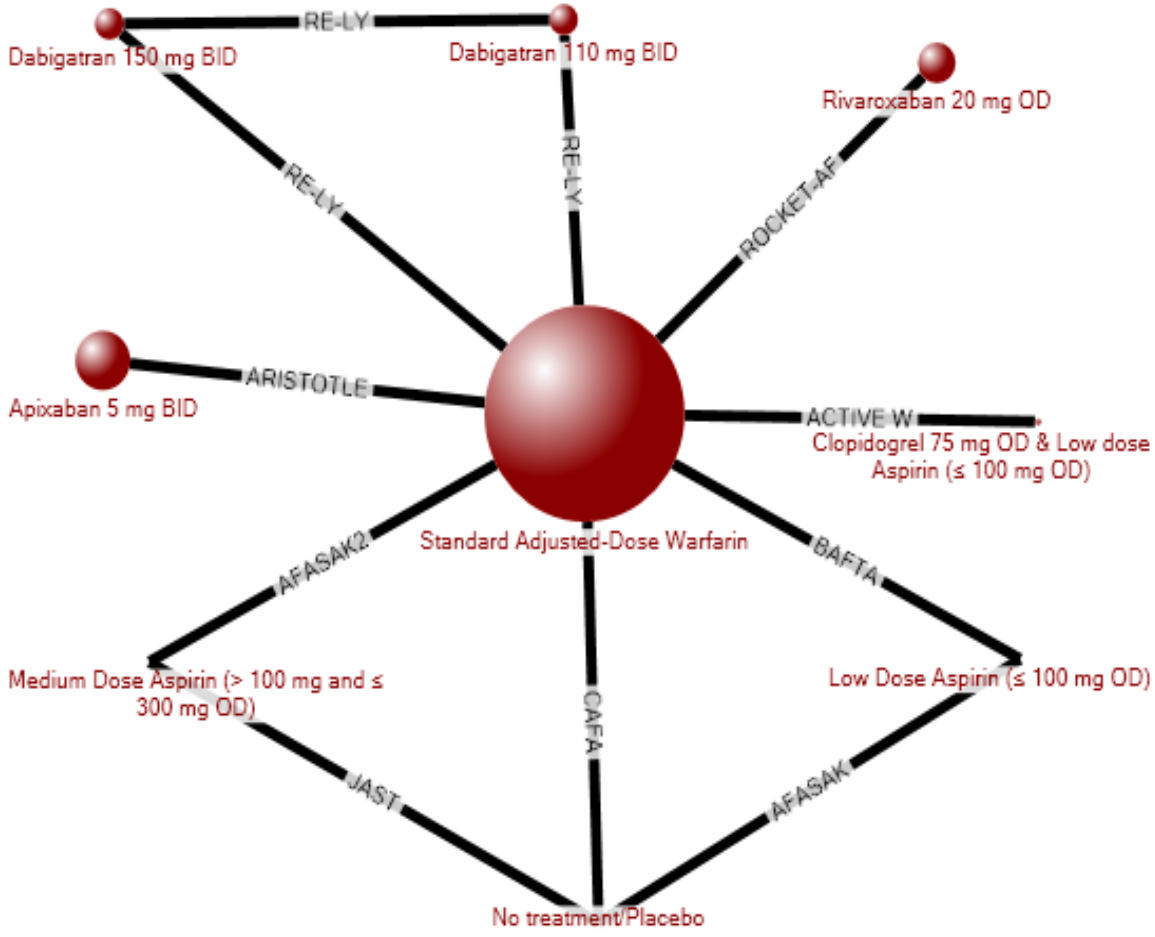


Figure A12.5: Evidence Network for Intracranial Hemorrhage (ICH)

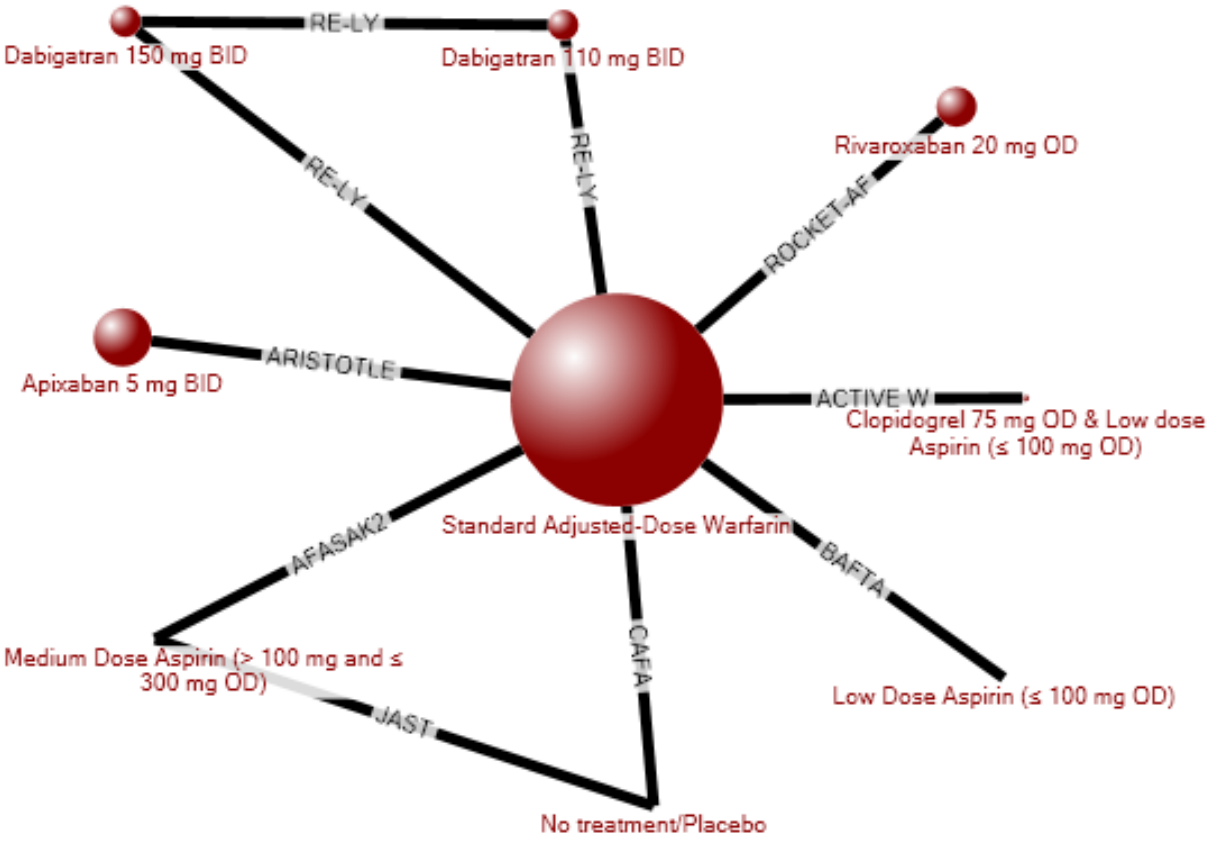


Figure A12.6: Evidence Network for Myocardial infarction (MI)

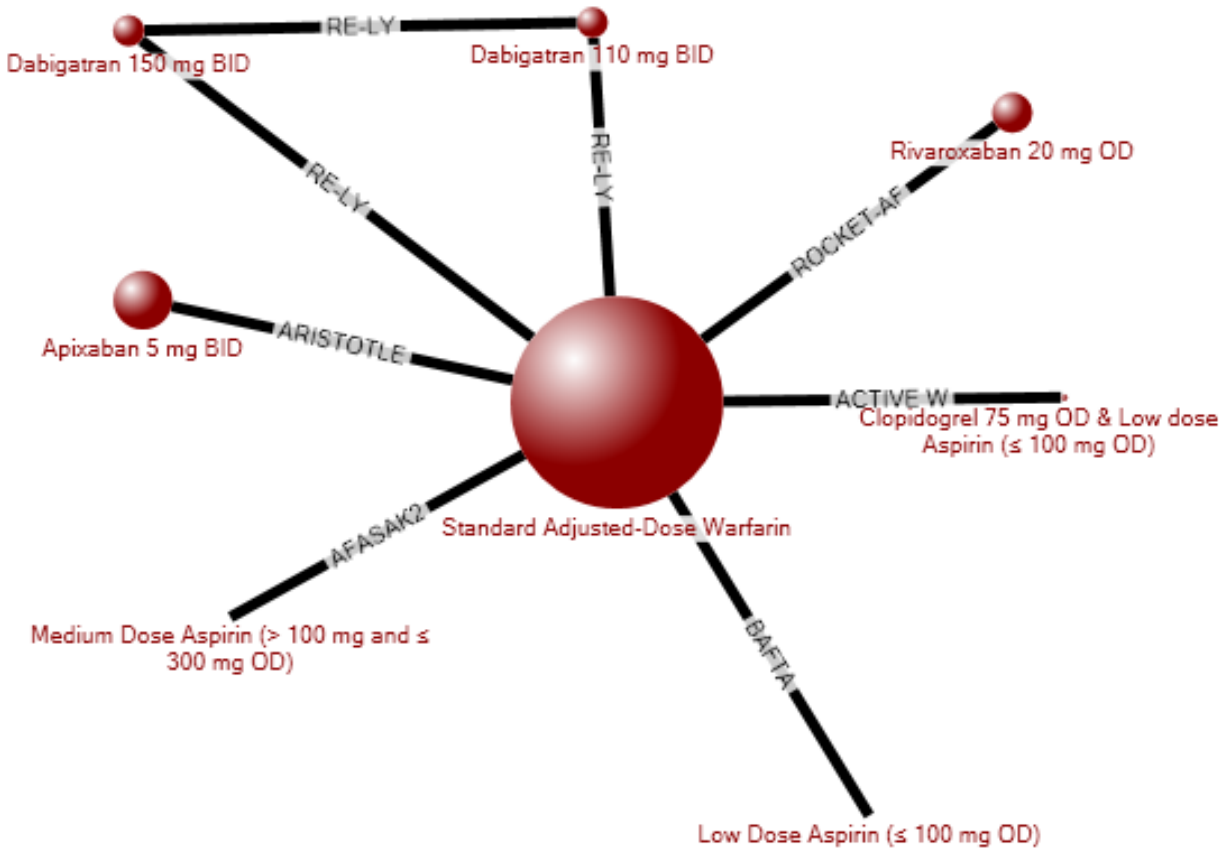
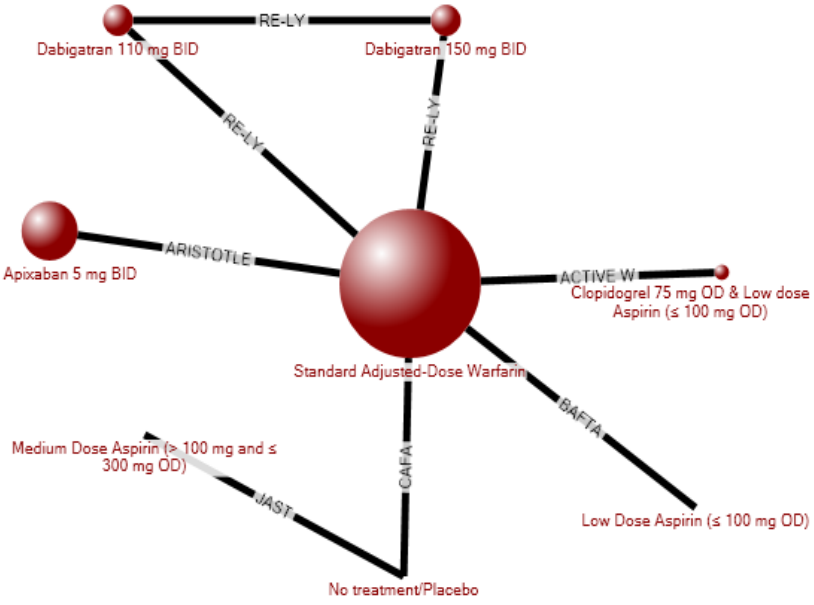


Figure A12.7: Evidence Networks for NMA for Stroke or Systemic Embolism and Major Bleeding, Subgroup analysis by $CHADS_2$

A. $CHADS_2$ <2



B. $CHADS_2$ ≥2

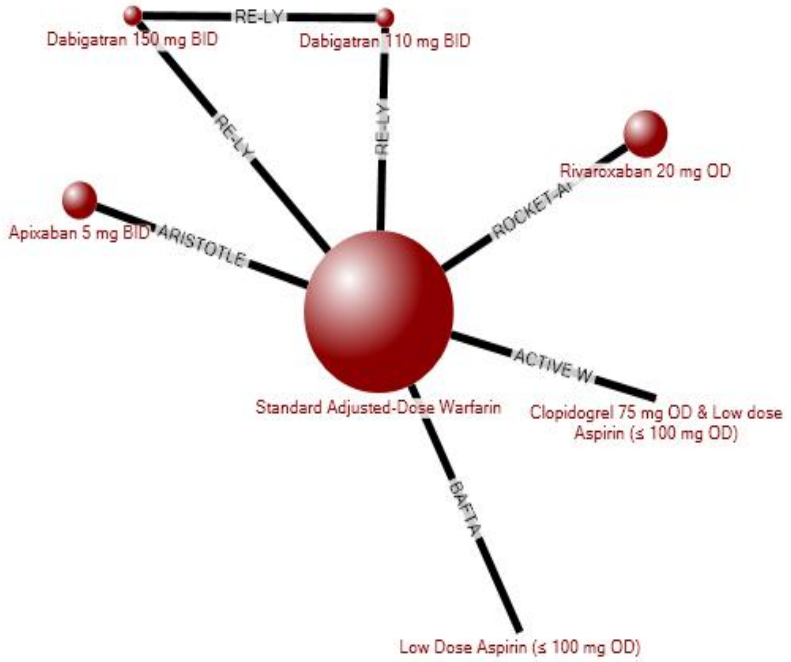
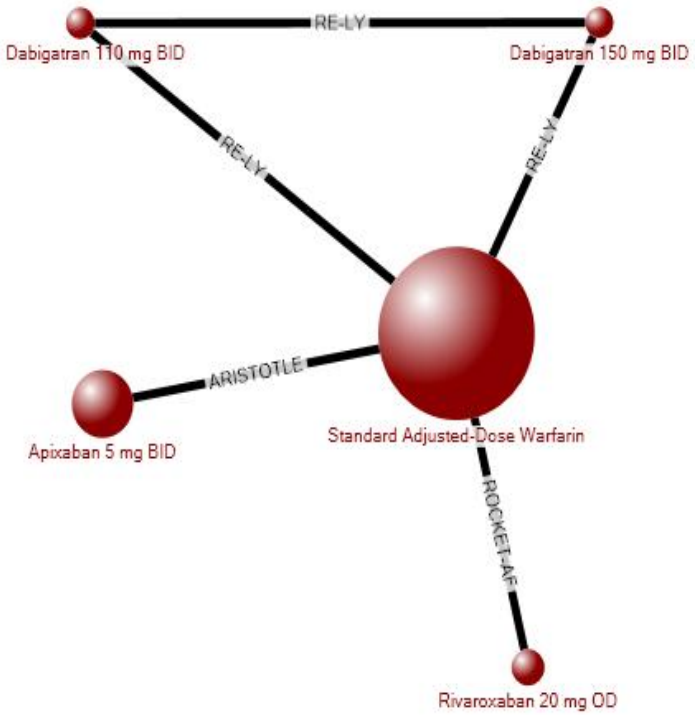


Figure A12.8: Evidence Networks for NMA for Stroke or Systemic Embolism and Major Bleeding, Subgroup analysis by Age

A. Age < 75 years



B. Age ≥ 75 years

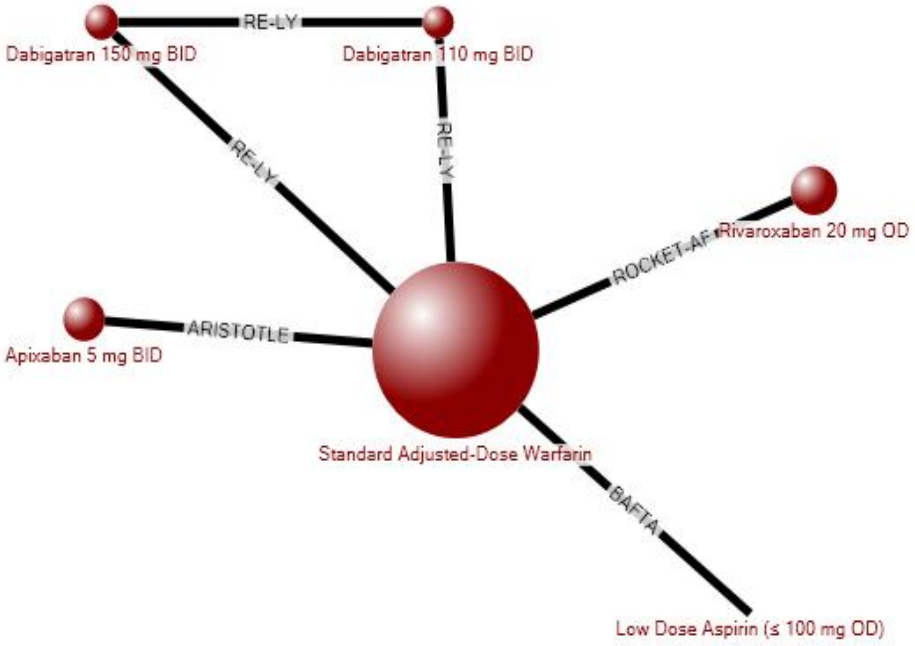
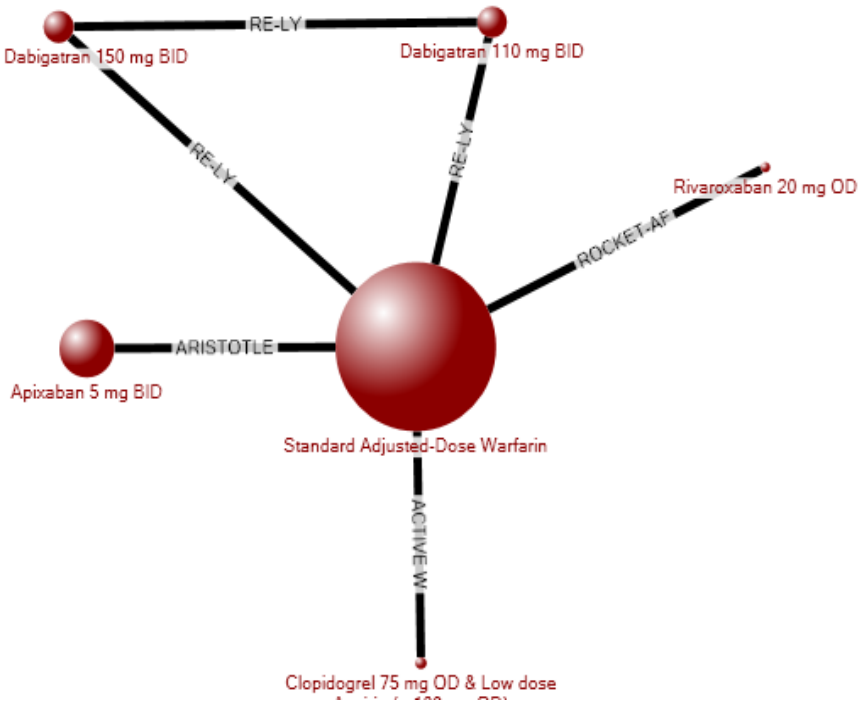
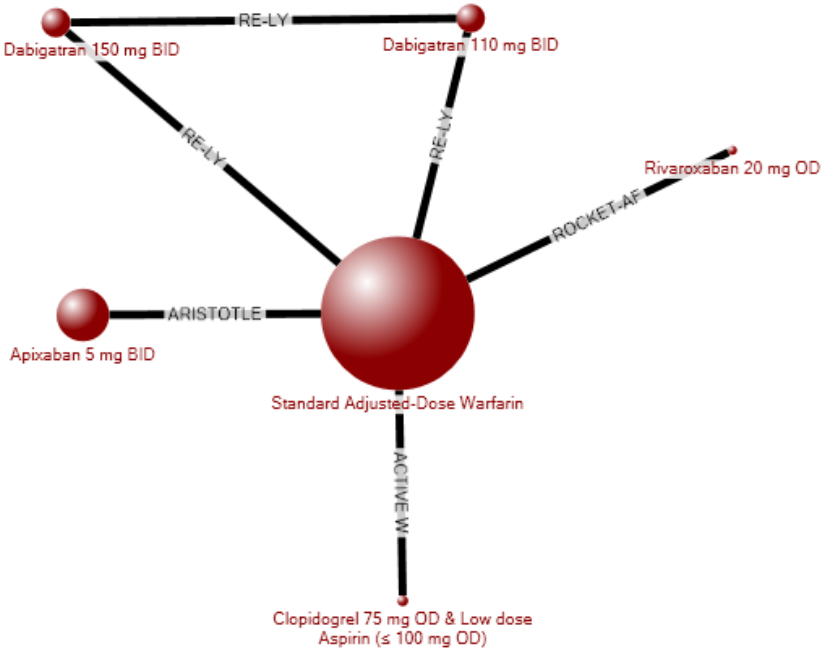


Figure A12.9: Evidence Networks for NMA for Stroke or Systemic Embolism and Major Bleeding, Subgroup analysis by TTR

A. TTR < 66%



B. TTR ≥ 66%



APPENDIX 13: SUMMARY OF RESULTS FOR PAIRWISE META-ANALYSIS AND NETWORK META-ANALYSIS

Table A13.1: Summary of Results from NMA for All-cause SSE, Randomized Population

Treatment	Pairwise Meta-Analysis, OR (95% CI) versus Warfarin	NMA, Odds Ratio (95% CrI) versus Warfarin	NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus Warfarin	Probability Best (%) for Outcome	Rank for Outcome
Adjusted dose Warfarin	NA	NA	NA	0.00%	5.00
Apixaban 5 mg b.i.d.	0.79(0.66,0.94)	0.79(0.66,0.95)	3.3 fewer(0.8 fewer,5.6 fewer)	9.90%	2.30
Dabigatran 110 mg b.i.d.	0.91(0.75,1.11)	0.91(0.74,1.12)	1.4 fewer(1.7 more,4.6 fewer)	0.13%	3.80
Dabigatran 150 mg b.i.d.	0.66(0.53,0.82)	0.66(0.53,0.82)	5.5 fewer(2.6 fewer,8.5 fewer)	87.50%	1.10
Rivaroxaban 20 mg q.d.	0.88(0.74,1.05)	0.88(0.74,1.03)	2 fewer(0.5 more,4.2 fewer)	1.22%	3.30
No treatment/Placebo	1.84(0.66,5.1)	1.53(0.9,2.63)	8.3 more(24.6 more,1.6 fewer)	0.12%	7.00
Low-dose ASA ASA (≤ 100 mg q.d.)	2.03(1.32,3.12)	1.87(1.27,2.8)	13.4 more(27 more,4.2 more)	0.00%	8.10
MDASA (> 100 mg and ≤ 300 mg q.d.)	0.83(0.35,1.97)	1.35(0.75,2.46)	5.5 more(22.2 more,4.1 fewer)	1.14%	6.20
Clopidogrel 75 mg q.d. & Low-dose ASA (≤ 100 mg OD)	1.93(1.41,2.64)	1.93(1.42,2.65)	14.3 more(24.9 more,6.5 more)	0.00%	8.20

b.i.d. = twice daily; CI = confidence interval; CrI = credible interval; OR = odds ratio; q.d. = once daily; SSE = stroke or systemic embolism.

Table A13.2: Summary of results from NMA for Major Bleeding, Randomized Population					
Treatment	**Pairwise Meta-Analysis, OR (95% CI) versus Warfarin**	**NMA, Odds Ratio (95% CrI) versus Warfarin**	**NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus Warfarin**	**Probability Best (%) for Outcome**	**Rank for Outcome**
Adjusted dose Warfarin	NA	NA	NA	0.00%	6.00
Apixaban 5 mg b.i.d.	0.69(0.6,0.79)	0.69(0.6,0.8)	9.7 fewer(6.2 fewer,13 fewer)	10.13%	2.10
Dabigatran 110 mg b.i.d.	0.8(0.68,0.94)	0.8(0.69,0.93)	6.2 fewer(2 fewer,10.5 fewer)	0.84%	3.20
Dabigatran 150 mg b.i.d.	0.93(0.81,1.07)	0.93(0.8,1.08)	2.1 fewer(2.2 more,6.5 fewer)	0.01%	4.90
Rivaroxaban 20 mg q.d.	1.03(0.9,1.18)	1.03(0.89,1.19)	0.8 more(5.7 more,3.5 fewer)	0.00%	6.40
No treatment/Placebo	0.39(0.08,2.02)	0.33(0.08,1.08)	21.7 fewer(2.4 more,31.1 fewer)	87.97%	1.40
low-dose ASA ASA (≤ 100 mg q.d.)	1.01(0.57,1.78)	1.05(0.6,1.86)	1.6 more(24.8 more,12.8 fewer)	0.96%	6.10
MDASA (> 100 mg and ≤ 300 mg q.d.)	1.89(0.59,6.03)	1.78(0.62,5.59)	22.5 more(103.5 more,12.1 fewer)	0.09%	8.10
Clopidogrel 75 mg q.d. & Low dose ASA (≤ 100 mg q.d.)	1.1(0.82,1.48)	1.1(0.83,1.46)	3.1 more(13.8 more,5.4 fewer)	0.02%	7.00

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

Table A13.3: Summary of results from NMA for All-cause Mortality, Randomized Population					
Treatment	**Pairwise Meta-Analysis, OR (95% CI) versus Warfarin**	**NMA, Odds Ratio (95% CrI) versus Warfarin**	**NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus Warfarin**	**Probability Best (%) for Outcome**	**Rank for Outcome**
Adjusted dose Warfarin	NA	NA	NA	0.00%	6.90
Apixaban 5 mg b.i.d.	0.89(0.794,0.997)	0.89(0.794,0.997)	4.1 fewer(0.1 fewer,7.9 fewer)	12.79%	3.60
Dabigatran 110 mg b.i.d.	0.91(0.79,1.04)	0.91(0.8,1.04)	3.3 fewer(1.4 more,8.2 fewer)	6.30%	4.20
Dabigatran 150 mg b.i.d.	0.88(0.77,1.01)	0.88(0.77,1.01)	4.4 fewer(0.3 more,9.2 fewer)	14.72%	3.40
Rivaroxaban 20 mg q.d.	0.92(0.82,1.03)	0.92(0.82,1.03)	3 fewer(1.2 more,6.8 fewer)	5.29%	4.50
No treatment/Placebo	0.77(0.29,2.01)	0.93(0.54,1.59)	2.6 fewer(20.8 more,17.9 fewer)	25.08%	4.90
low-dose ASA ASA (≤ 100 mg q.d.)	1.02(0.76,1.37)	0.99(0.74,1.32)	0.5 fewer(11.6 more,10 fewer)	6.67%	5.90
MDASA (> 100 mg and ≤ 300 mg q.d.)	0.88(0.43,1.78)	0.95(0.52,1.72)	2 fewer(24.9 more,18.8 fewer)	26.15%	5.10

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

Table A13.4: Summary of results from NMA for ECH, Randomized Population					
Treatment	**Pairwise Meta-Analysis, OR (95% CI) versus Warfarin**	**NMA, Odds Ratio (95% CrI) versus Warfarin**	**NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus Warfarin**	**Probability Best (%) for Outcome**	**Rank for Outcome**
Adjusted dose Warfarin	NA	NA	NA	0.00%	4.80
Apixaban 5 mg b.i.d.	0.8(0.68,0.94)	0.8(0.68,0.94)	5 fewer(1.5 fewer,8.2 fewer)	8.92%	2.20
Dabigatran 110 mg b.i.d.	0.95(0.81,1.11)	0.95(0.8,1.12)	1.3 fewer(2.7 more,5.3 fewer)	0.54%	3.90
Dabigatran 150 mg b.i.d.	1.08(0.92,1.26)	1.08(0.92,1.27)	2 more(6 more,2 fewer)	0.00%	6.20
Rivaroxaban 20 mg q.d.	1.13(0.97,1.32)	1.13(0.97,1.33)	3.3 more(8.1 more,0.8 fewer)	0.00%	6.80
No treatment/Placebo	0.48(0.09,2.64)	0.3(0.04,1.43)	18.1 fewer(10.3 more,26.1 fewer)	87.54%	1.50
Low-dose ASA ASA (≤ 100 mg q.d.)	1.12(0.59,2.14)	1.18(0.62,2.28)	4.5 more(29.4 more,9.6 fewer)	1.35%	6.20
Medium-dose ASA (> 100 mg and ≤ 300 mg q.d.)	2.04(0.37,11.23)	4.13(0.92,31.66)	64.4 more(258.2 more,1.9 fewer)	0.28%	8.70
Clopidogrel 75 mg q.d. & low-dose ASA (≤ 100 mg q.d.)	0.99(0.72,1.35)	0.99(0.72,1.35)	0.4 fewer(8.4 more,7.1 fewer)	1.36%	4.70

ASA = acetylsalicylic acid; b.i.d.= twice daily; CI = confidence interval; CrI = credible interval; ECH = extracranial hemorrhage; NMA = network meta-analysis; OR = odds ratio; q.d. = once daily.

Table A13.5: Summary of results from NMA for Intracranial Hemorrhage (ICH), Randomized Population					
Treatment	**Pairwise Meta-Analysis, OR (95% CI) versus Warfarin**	**NMA, Odds Ratio (95% CrI) versus Warfarin**	**NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus Warfarin**	**Probability Best (%) for Outcome**	**Rank for Outcome**
Adjusted dose Warfarin	NA	NA	NA	0.00%	7.50
Apixaban 5 mg b.i.d.	0.42(0.3,0.59)	0.42(0.3,0.58)	4.1 fewer(2.8 fewer,5.5 fewer)	1.90%	4.00
Dabigatran 110 mg b.i.d.	0.31(0.2,0.48)	0.31(0.19,0.47)	5 fewer(3.3 fewer,6.8 fewer)	18.42%	2.60
Dabigatran 150 mg b.i.d.	0.41(0.28,0.61)	0.4(0.27,0.59)	4.3 fewer(2.5 fewer,6.1 fewer)	2.27%	3.90
Rivaroxaban 20 mg q.d.	0.65(0.47,0.91)	0.65(0.46,0.92)	2.5 fewer(0.6 fewer,4.1 fewer)	0.01%	6.00
No treatment/Placebo	0.49(0.02,14.84)	0.11(0,1.65)	6.2 fewer(4.5 more,8.3 fewer)	68.27%	2.00
Low-dose ASA ASA (≤ 100 mg q.d.)	0.75(0.26,2.16)	0.75(0.24,2.18)	1.8 fewer(8.3 more,5.6 fewer)	1.68%	6.20
Medium-dose ASA (> 100 mg and ≤ 300 mg q.d.)	0.5(0.04,5.57)	0.31(0.01,3.12)	4.9 fewer(14.6 more,7.9 fewer)	7.46%	4.00
Clopidogrel 75 mg q.d. & Low dose ASA (≤ 100 mg q.d.)	1.94(0.94,4.01)	1.96(0.95,4.25)	6.7 more(22.1 more,0.3 fewer)	0.00%	8.80

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

Table A13.6: Summary of results from NMA for MI, Randomized Population					
Treatment	**Pairwise Meta-Analysis, OR (95% CI) versus Warfarin**	**NMA, Odds Ratio (95% CrI) versus Warfarin**	**NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus Warfarin**	**Probability Best (%) for Outcome**	**Rank for Outcome**
Adjusted dose Warfarin	NA	NA	NA	0.20%	3.80
Apixaban 5 mg b.i.d.	0.88(0.66,1.18)	0.88(0.66,1.17)	0.6 fewer(0.9 more,1.8 fewer)	15.00%	2.70
Dabigatran 110 mg b.i.d.	1.37(0.98,1.91)	1.37(0.99,1.91)	1.9 more(3.9 more,0 more)	0.05%	6.10
Dabigatran 150 mg b.i.d.	1.41(1.01,1.97)	1.41(1.02,1.96)	2.1 more(4.1 more,0.1 more)	0.03%	6.30
Rivaroxaban 20 mg q.d.	0.8(0.62,1.03)	0.8(0.61,1.04)	1 fewer(0.2 more,2.1 fewer)	33.20%	2.10
Low-dose ASA ASA (≤ 100 mg q.d.)	1.01(0.49,2.09)	1.01(0.48,2.11)	0 more(5.7 more,2.8 fewer)	33.56%	4.10
Medium-dose ASA (> 100 mg and ≤ 300 mg q.d.)	1.01(0.25,4.14)	1(0.22,4.53)	0 more(17.5 more,4.2 fewer)	0.26%	6.80
Clopidogrel 75 mg q.d. & Low dose ASA (≤ 100 mg q.d.)	1.59(0.94,2.7)	1.6(0.95,2.74)	3 more(9 more,0.3 fewer)	0.00%	0.00

b.i.d.= twice daily; CI = confidence interval; CrI = credible interval; MI = myocardial infarction; OR = odds ratio; q.d. = once daily.

Table A13.7: Summary of Results From NMA for SSE, Subgroup Analysis by $CHADS_2$ Score					
Treatment	**Pairwise Meta-Analysis, OR (95% CI) versus Warfarin**	**NMA, Odds Ratio (95% CrI) versus Warfarin**	**NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus Warfarin**	**Probability Best (%) for Outcome**	**Rank for Outcome**
$CHADS_2 < 2$					
Standard Adjusted-Dose Warfarin	NA	NA	NA	0.45%	3.49
Apixaban 5 mg b.i.d.	0.86 (0.57,1.3)	0.86 (0.57,1.28)	1.5 fewer (3 more,4.8 fewer)	13.89%	2.55
Dabigatran 110 mg b.i.d.	1(0.65,1.54)	1(0.64,1.55)	0 more (4.6 more,4.7 fewer)	1.45%	3.46
Dabigatran 150 mg b.i.d.	0.61(0.40,0.93)	0.61(0.37,1)	4.1 fewer (0 more,8.4 fewer)	80.93%	1.26
No treatment/Placebo	1.84 (0.66,5.1)	1.88 (0.69,5.74)	8.9 more (45.2 more,3.3 fewer)	1.15%	5.72
Low-dose ASA (≤ 100 mg q.d.)[a]	2.17(1.16,4.06)	2.2 (1.18,4.25)	12.1 more (32.5 more,1.8 more)	0.02%	6.38
Medium-dose ASA (> 100 mg and ≤ 300 mg q.d.)[b]	NA	1.97(0.63,6.73)	9.8 more (53.1 more,3.9 fewer)	2.11%	5.89
Clopidogrel 75 mg q.d. & Low-dose ASA (≤ 100 mg q.d.)[c]	3.07(1.3,7.27)	3.16 (1.39,8.22)	21.2 more (65 more,3.9 more)	0.02%	7.24
$CHADS_2 \geq 2$					
Standard Adjusted-Dose Warfarin	NA	NA	NA	0.00%	4.81
Apixaban 5 mg b.i.d.	0.78 (0.64,0.95)	0.78 (0.63,0.95)	4.2 fewer (0.9 fewer,7.2 fewer)	16.56%	2.22
Dabigatran 110 mg b.i.d.	0.89 (0.7,1.13)	0.89 (0.71,1.12)	2.1 fewer (2 more,6.2 fewer)	0.64%	3.53
Dabigatran 150 mg b.i.d.	0.67(0.52,0.86)	0.66 (0.52,0.85)	6.4 fewer (2.5 fewer,10.3 fewer)	80.92%	1.22
Rivaroxaban 20 mg OD	0.88(0.74,1.05)	0.88(0.74,1.04)	2.3 fewer(0.6 more,5 fewer)	1.50%	3.32
low-dose ASA ASA (≤ 100 mg q.d.) [a]	2.06 (0.89,4.79)	2.1(0.91,5.15)	19.5 more (64.8 more,1.6 fewer)	0.39%	6.53
Clopidogrel 75 mg q.d. & Low dose ASA (≤ 100 mg q.d.) [c]	1.79 (1.28,2.5)	1.15 (0.84,1.57)	2.2 more (6.7 more,2.9 fewer)	0.00%	6.37

b.i.d. = twice daily; CI = confidence interval; CrI = credible interval; OR = odds ratio; q.d. = once daily; SSE = stroke or systemic embolism.
[a]Derived from BAFTA study where $CHADS_2$ subgroup data stratified by $CHADS_2$ 1 to 2 (versus 0 to 1) and $CHADS_2$ 3 to 6 (vs. 2 to 6).
[b]Based on study-level results from CAFA and JAST studies. Although these studies consisted primarily of low-risk populations, some patients may have $CHADS_2$ scores greater than 2.
[c] Estimated from subgroup study by Healey et al. 2008.

Table A13.8: Summary of Results From NMA for Major Bleeding, Subgroup Analysis by $CHADS_2$ Score					
Treatment	**Pairwise Meta-Analysis, OR (95% CI) versus Warfarin**	**NMA, Odds Ratio (95% CrI) versus Warfarin**	**NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus Warfarin**	**Probability Best (%) for Outcome**	**Rank for Outcome**
$CHADS_2 < 2$					
Standard Adjusted-Dose Warfarin	NA	NA	NA	0.00%	6.00
Apixaban 5 mg b.i.d.	0.59 (0.44,0.79)	0.59 (0.44,0.78)	11.3 fewer (5.8 fewer,16.6 fewer)	16.52%	2.58
Dabigatran 110 mg b.i.d.	0.65 (0.48,0.89)	0.65 (0.47,0.89)	9.6 fewer (2.6 fewer,16.9 fewer)	7.38%	3.13
Dabigatran 150 mg b.i.d.	0.77 (0.57,1.03)	0.77 (0.57,1.04)	6.4 fewer (0.9 more,13.8 fewer)	0.85%	4.33
No treatment/Placebo	0.39 (0.08,2.02)	0.35 (0.04,1.75)	18.2 fewer (19.4 more,29.6 fewer)	67.77%	2.03
Low-dose ASA (≤ 100 mg q.d.)	0.83 (0.42,1.65)	0.83 (0.42,1.64)	4.6 fewer (16.7 more,16.8 fewer)	5.09%	4.68
Medium-dose ASA (> 100 mg and ≤ 300 mg q.d.)	NA	1.48 (0.11,19.07)	12.3 more (216.8 more,26 fewer)	2.39%	5.96
Clopidogrel 75 mg q.d. & Low dose ASA (≤ 100 mg q.d.)	1.51(0.89,2.56)	1.51 (0.89,2.61)	13.3 more (39.5 more,3 fewer)	0.01%	7.29
$CHADS_2 \geq 2$					
Standard Adjusted-Dose Warfarin	NA	NA	NA	0.00%	4.55
Apixaban 5 mg b.i.d.	0.73 (0.61,0.87)	0.73 (0.62,0.87)	9.6 fewer (4.7 fewer,14 fewer)	78.45%	1.25
Dabigatran 110 mg b.i.d.	0.86 (0.72,1.03)	0.86 (0.73,1.02)	4.9 fewer (0.6 more,10.5 fewer)	7.45%	2.45
Dabigatran 150 mg b.i.d.	1.01 (0.86,1.18)	1.01 (0.86,1.19)	0.3 more (5.9 more,5.5 fewer)	0.06%	4.73
Rivaroxaban 20 mg q.d.	1.03 (0.9,1.18)	1.03 (0.89,1.19)	0.9 more (6.5 more,4 fewer)	0.04%	4.98
low-dose ASA ASA (≤ 100 mg q.d.)	1.57 (0.54,4.52)	1.6 (0.55,5.02)	19.8 more (102.7 more,16.5 fewer)	7.45%	6.00
Clopidogrel 75 mg q.d. & Low-dose ASA (≤ 100 mg q.d.)	0.97(0.7,1.35)	0.97(0.69,1.36)	1.2 fewer (12.3 more,11.4 fewer)	6.55%	4.04

b.i.d. = twice daily; CI = confidence interval; CrI = credible interval; OR = odds ratio; q.d. = once daily; SSE = stroke or systemic embolism.

[a] Derived from BAFTA study where $CHADS_2$ subgroup data stratified by $CHADS_2$ 1 to 2 (vs. 0 to 1) and $CHADS_2$ 3 to 6 (vs. 2 to 6).

[b] Based on study-level results from CAFA and JAST studies. Although these studies consisted primarily of low-risk populations, some patients may have $CHADS_2$ scores greater than 2.

† Estimated from subgroup study by Healey et al 2008

b.i.d. = twice daily; CI = confidence interval; CrI = credible interval; OD = once daily; OR = odds ratio

Table A13.9: Summary of results from NMA for Stroke or Systemic Embolism, Subgroup analysis by Age					
Treatment	**Pairwise Meta-Analysis, OR (95% CI) versus Warfarin**	**NMA, Odds Ratio (95% CrI) versus Warfarin**	**NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus Warfarin**	**Probability Best (%) for Outcome**	**Rank for Outcome**
Age < 75 years					
Adjusted dose Warfarin	NA	NA	NA	0.00%	4.29
Apixaban 5 mg b.i.d.	0.85(0.67,1.08)	0.85(0.67,1.07)	2.1 fewer(1 more,4.7 fewer)	6.84%	2.58
Dabigatran 110 mg b.i.d.	0.93(0.71,1.22)	0.93(0.7,1.23)	1 fewer(2.8 more,4.7 fewer)	0.60%	3.45
Dabigatran 150 mg b.i.d.	0.64(0.47,0.88)	0.63(0.46,0.87)	5 fewer(1.6 fewer,8.6 fewer)	91.20%	1.11
Rivaroxaban 20 mg OD	0.95(0.75,1.2)	0.95(0.75,1.2)	0.7 fewer(2.7 more,3.5 fewer)	1.36%	3.58
Age ≥ 75 years					
Adjusted dose Warfarin	NA	NA	NA	0.00%	4.75
Apixaban 5 mg b.i.d.	0.71(0.53,0.95)	0.71(0.53,0.95)	5.8 fewer(0.9 fewer,10.1 fewer)	33.43%	2.05
Dabigatran 110 mg b.i.d.	0.88(0.66,1.18)	0.88(0.66,1.18)	2.3 fewer(3.1 more,7.9 fewer)	1.27%	3.7
Dabigatran 150 mg b.i.d.	0.66(0.48,0.9)	0.66(0.48,0.9)	6.9 fewer(1.8 fewer,12.1 fewer)	57.74%	1.58
Rivaroxaban 20 mg OD	0.8(0.63,1.01)	0.8(0.63,1.02)	3.9 fewer(0.5 more,7.7 fewer)	7.55%	2.93
Low-dose ASA ASA (< 100 mg)	2.03(1.32,3.12)	2.04(1.32,3.19)	19.6 more(40 more,6.3 more)	0.00%	6

b.i.d. = twice daily; CI = confidence interval; CrI = credible interval; OD = once daily; OR = odds ratio

Table A13.10: Summary of results from NMA for Major Bleeding, Subgroup analysis by Age					
Treatment	**Pairwise Meta-Analysis, OR (95% CI) versus Warfarin**	**NMA, Odds Ratio (95% CrI) versus Warfarin**	**NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus Warfarin**	**Probability Best (%) for Outcome**	**Rank for Outcome**
Age < 75 years					
Adjusted dose Warfarin	NA	NA	NA	0.00%	4.77
Apixaban 5 mg b.i.d.	0.73(0.6,0.89)	0.73(0.6,0.89)	7.7 fewer(3.1 fewer,11.9 fewer)	10.87%	2.55
Dabigatran 110 mg b.i.d.	0.62(0.5,0.77)	0.61(0.49,0.77)	11.1 fewer(6.1 fewer,16.2 fewer)	76.49%	1.28
Dabigatran 150 mg b.i.d.	0.7(0.56,0.87)	0.7(0.56,0.86)	8.7 fewer(3.6 fewer,13.9 fewer)	12.55%	2.25
Rivaroxaban 20 mg OD	0.93(0.76,1.13)	0.93(0.76,1.13)	2 fewer(3.7 more,6.9 fewer)	0.10%	4.15
Age ≥ 75 years					
Adjusted dose Warfarin	NA	NA	NA	0.00%	3.04
Apixaban 5 mg b.i.d.	0.65(0.52,0.81)	0.65(0.52,0.81)	14.1 fewer(7.7 fewer,20 fewer)	92.00%	1.08
Dabigatran 110 mg b.i.d.	1.02(0.84,1.24)	1.02(0.84,1.25)	0.9 more(8.8 more,7.1 fewer)	0.08%	3.39
Dabigatran 150 mg b.i.d.	1.19(0.98,1.45)	1.19(0.98,1.45)	7.3 more(15.4 more,0.7 fewer)	0.00%	5.22
Rivaroxaban 20 mg OD	1.15(0.93,1.43)	1.15(0.93,1.41)	5.5 more(15.3 more,2.7 fewer)	0.01%	4.73
Low-dose ASA ASA (< 100 mg)	1.01(0.57,1.78)	1.01(0.57,1.79)	0.3 more(28.6 more,17.7 fewer)	7.90%	3.55

b.i.d. = twice daily; CI = confidence interval; CrI = credible interval; NMA = network meta-analysis; OD = once daily; OR = odds ratio

Table A13.11: Summary of results from NMA for SSE, Subgroup analysis by TTR					
Treatment	**Pairwise Meta-Analysis, OR (95% CI) versus Warfarin**	**NMA, Odds Ratio (95% CrI) versus Warfarin**	**NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus Warfarin**	**Probability Best (%) for Outcome**	**Rank for Outcome**
TTR < 66%					
Standard Adjusted-Dose Warfarin	NA	NA	NA	0.00%	4.73
Apixaban 5 mg b.i.d.*	0.79(0.62,1)	0.79(0.62,1.01)	3.9 fewer(0.1 more,7.3 fewer)	2.48%	2.66
Dabigatran 110 mg b.i.d.	0.91(0.69,1.2)	0.91(0.69,1.19)	1.6 fewer(3.1 more,6.4 fewer)	0.03%	3.79
Dabigatran 150 mg b.i.d.	0.54(0.39,0.74)	0.54(0.39,0.73)	8.7 fewer(4.4 fewer,13.1 fewer)	96.28%	1.04
Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	1.52(0.95,2.43)	1.52(0.96,2.45)	9.3 more(25.4 more,0.7 fewer)	0.00%	5.92
Rivaroxaban 20 mg OD	0.81(0.65,1)	0.81(0.65,1.01)	3.4 fewer(0.2 more,6.7 fewer)	1.21%	2.85
TTR ≥ 66%					
Standard Adjusted-Dose Warfarin	NA	NA	NA	0.02%	4.52
Apixaban 5 mg b.i.d.	0.79(0.59,1.06)	0.79(0.59,1.05)	2.8 fewer(0.7 more,5.9 fewer)	23.53%	2.43
Dabigatran 110 mg b.i.d.	0.9(0.66,1.23)	0.9(0.66,1.24)	1.3 fewer(2.8 more,5.5 fewer)	5.08%	3.54
Dabigatran 150 mg b.i.d.	0.81(0.59,1.11)	0.81(0.58,1.11)	2.7 fewer(1.3 more,6.7 fewer)	20.97%	2.53
Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	2.38(1.58,3.59)	2.4(1.59,3.71)	18.2 more(34.8 more,7.7 more)	0.00%	6.00
Rivaroxaban 20 mg OD	0.73(0.47,1.12)	0.72(0.47,1.1)	3.8 fewer(1.4 more,7.7 fewer)	50.39%	1.98

b.i.d. = twice daily; CI = confidence interval; CrI = credible interval; OD = once daily; OR = odds ratio; SSE = stroke or systemic embolism; TTR = time in therapeutic range.

Table A13.12: Summary of results from NMA for Major Bleeding, Subgroup analysis by TTR					
Treatment	**Pairwise Meta-Analysis, OR (95% CI) versus Warfarin**	**NMA, Odds Ratio (95% CrI) versus Warfarin**	**NMA, Absolute Risk Difference per 1,000 treated (95% CrI) versus Warfarin**	**Probability Best (%) for Outcome**	**Rank for Outcome**
TTR < 66%					
Standard Adjusted-Dose Warfarin	NA	NA	NA	0.00%	5.78
Apixaban 5 mg b.i.d.	0.57(0.46,0.71)	0.57(0.45,0.71)	15.5 fewer(10.2 fewer,20.6 fewer)	70.28%	1.34
Dabigatran 110 mg b.i.d.	0.74(0.61,0.9)	0.74(0.61,0.91)	9 fewer(2.7 fewer,15.3 fewer)	1.82%	3.13
Dabigatran 150 mg b.i.d.	0.76(0.62,0.92)	0.76(0.62,0.94)	8.3 fewer(2 fewer,14.6 fewer)	1.03%	3.39
Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	0.66(0.43,1.02)	0.66(0.42,1.02)	12.1 fewer(0.7 more,21.4 fewer)	26.87%	2.42
Rivaroxaban 20 mg OD	0.92(0.77,1.1)	0.92(0.77,1.1)	2.7 fewer(3.3 more,8.1 fewer)	0.01%	4.95
TTR ≥ 66%					
Standard Adjusted-Dose Warfarin	NA	NA	NA	0.13%	3.01
Apixaban 5 mg b.i.d.	0.81(0.67,0.99)	0.81(0.67,0.98)	5.8 fewer(0.5 fewer,10.5 fewer)	65.19%	1.37
Dabigatran 110 mg b.i.d.	0.86(0.69,1.07)	0.86(0.69,1.06)	4.3 fewer(1.8 more,10.4 fewer)	34.58%	1.75
Dabigatran 150 mg b.i.d.	1.15(0.95,1.4)	1.15(0.94,1.4)	4.5 more(10.8 more,1.9 fewer)	0.02%	4.18
Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	1.65(1.11,2.44)	1.66(1.12,2.47)	18.9 more(40.1 more,3.7 more)	0.02%	5.78
Rivaroxaban 20 mg OD	1.3(1.01,1.68)	1.3(1.01,1.69)	8.9 more(20 more,0.2 more)	0.05%	4.90

b.i.d. = twice daily; CI = confidence interval; CrI = credible interval; OD = once daily; OR = odds ratio; TTR = time in therapeutic range.

APPENDIX 14: PAIRWISE COMPARISONS FROM NETWORK META-ANALYSIS

Table A14.1: NMA results for All-cause Stroke or Systemic Embolism

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	Rivaroxaban 20 mg q.d.	No Treatment/ Placebo	LDASA	MDASA
Apixaban 5 mg b.i.d.	**0.79(0.66,0.95)**							
Dabigatran 110 mg b.i.d.	0.91(0.74,1.12)	1.15(0.88,1.52)						
Dabigatran 150 mg b.i.d.	**0.66(0.53,0.82)**	0.83(0.62,1.11)	**0.72(0.58,0.9)**					
Rivaroxaban 20 mg q.d.	0.88(0.74,1.03)	1.11(0.86,1.42)	0.96(0.74,1.25)	**1.33(1.01,1.76)**				
No treatment/Placebo	1.53(0.9,2.63)	**1.94(1.1,3.43)**	1.68(0.95,3)	**2.33(1.3,4.18)**	**1.75(1,3.08)**			
LDASA	**1.87(1.27,2.8)**	**2.37(1.54,3.68)**	**2.05(1.32,3.23)**	**2.84(1.82,4.5)**	**2.14(1.4,3.31)**	1.22(0.72,2.08)		
MDASA	1.35(0.75,2.46)	1.71(0.92,3.19)	1.48(0.79,2.8)	**2.05(1.09,3.9)**	1.55(0.83,2.87)	0.88(0.55,1.41)	0.72(0.39,1.35)	
Clopidogrel 75 mg q.d. & LDASA	**1.93(1.42,2.65)**	**2.44(1.71,3.51)**	**2.12(1.46,3.08)**	**2.93(2.01,4.31)**	**2.21(1.55,3.15)**	1.26(0.68,2.34)	1.03(0.62,1.7)	1.43(0.73,2.79)

b.i.d. = twice daily; LDASA = low-dose acetylsalicylic acid; MDASA = moderate-dose acetylcalicylic acid; NMA = network meta-analysis.

Table A14.2: NMA results for Major Bleeding

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	Rivaroxaban 20 mg OD	No treatment/Placebo	LDASA	MDASA
Apixaban 5 mg b.i.d.	**0.69(0.6,0.8)**							
Dabigatran 110 mg b.i.d.	**0.8(0.69,0.93)**	1.15(0.94,1.43)						
Dabigatran 150 mg b.i.d.	0.93(0.8,1.08)	**1.34(1.09,1.65)**	**1.16(1,1.36)**					
Rivaroxaban 20 mg OD	1.03(0.89,1.19)	**1.48(1.2,1.82)**	**1.28(1.04,1.58)**	1.1(0.9,1.35)				
No treatment/Placebo	0.33(0.08,1.08)	0.48(0.12,1.57)	0.41(0.1,1.36)	0.35(0.09,1.16)	0.32(0.08,1.06)			
LDASA	1.05(0.6,1.86)	1.52(0.85,2.73)	1.31(0.74,2.37)	1.13(0.63,2.04)	1.03(0.57,1.84)	3.19(0.89,13.74)		
MDASA	1.78(0.62,5.59)	2.57(0.88,8.16)	2.23(0.77,7.06)	1.91(0.66,6.06)	1.73(0.6,5.5)	**5.41(1.6,23.81)**	1.69(0.52,5.94)	
Clopidogrel 75 mg OD & LDASA	1.1(0.83,1.46)	**1.59(1.15,2.19)**	1.38(0.997,1.9)	1.18(0.86,1.63)	1.07(0.78,1.48)	3.33(0.99,13.6)	1.05(0.55,1.97)	0.62(0.19,1.84)

Table A14.3: NMA results for All-cause Mortality

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	Rivaroxaban 20 mg OD	No treatment/Placebo	LDASA	MDASA
Apixaban 5 mg b.i.d.	**0.89(0.794,0.997)**							
Dabigatran 110 mg b.i.d.	0.91(0.8,1.04)	1.02(0.86,1.22)						
Dabigatran 150 mg b.i.d.	0.88(0.77,1.01)	0.99(0.83,1.18)	0.97(0.85,1.11)					
Rivaroxaban 20 mg OD	0.92(0.82,1.03)	1.03(0.88,1.22)	1.01(0.85,1.21)	1.04(0.87,1.24)				
No treatment/Placebo	0.93(0.54,1.59)	1.05(0.6,1.81)	1.02(0.59,1.78)	1.05(0.61,1.83)	1.01(0.58,1.75)			
LDASA	0.99(0.74,1.32)	1.11(0.81,1.52)	1.08(0.79,1.5)	1.12(0.81,1.54)	1.07(0.78,1.47)	1.06(0.62,1.82)		
MDASA	0.95(0.52,1.72)	1.07(0.58,1.96)	1.04(0.56,1.91)	1.07(0.58,1.97)	1.03(0.56,1.88)	1.02(0.53,1.96)	0.96(0.51,1.82)	
Clopidogrel 75 mg OD & LDASA	1.02(0.81,1.28)	1.14(0.89,1.47)	1.12(0.86,1.45)	1.15(0.89,1.5)	1.11(0.86,1.42)	1.09(0.61,1.96)	1.03(0.71,1.49)	1.08(0.57,2.04)

Table A14.4: NMA results for Extracranial Hemorrhage (ECH)

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	Rivaroxaban 20 mg OD	No treatment/Placebo	LDASA	MDASA
Apixaban 5 mg b.i.d.	**0.8(0.68,0.94)**							
Dabigatran 110 mg b.i.d.	0.95(0.8,1.12)	1.19(0.94,1.49)						
Dabigatran 150 mg b.i.d.	1.08(0.92,1.27)	**1.35(1.08,1.7)**	1.14(0.97,1.34)					
Rivaroxaban 20 mg OD	1.13(0.97,1.33)	**1.42(1.13,1.78)**	1.2(0.95,1.5)	1.05(0.84,1.31)				
No treatment/Placebo	0.3(0.04,1.43)	0.37(0.05,1.8)	0.32(0.04,1.52)	0.28(0.04,1.32)	0.26(0.03,1.27)			
LDASA	1.18(0.62,2.28)	1.48(0.76,2.91)	1.25(0.64,2.46)	1.1(0.56,2.16)	1.04(0.54,2.05)	3.98(0.78,32.42)		
MDASA	4.13(0.92,31.66)	**5.17(1.15,39.75)**	4.36(0.97,33.69)	3.82(0.85,29.45)	3.64(0.81,28.08)	**14.62(1.56,239)**	3.5(0.68,29.72)	
Clopidogrel 75 mg OD & LDASA	0.99(0.72,1.35)	1.23(0.87,1.76)	1.04(0.73,1.48)	0.91(0.64,1.29)	0.87(0.61,1.23)	3.3(0.67,26.23)	0.83(0.4,1.7)	0.24(0.03,1.1)

Table A14.5: NMA results for Intracranial Hemorrhage (ICH)

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	Rivaroxaban 20 mg OD	No treatment/Placebo	LDASA	MDASA
Apixaban 5 mg b.i.d.	**0.42(0.3,0.58)**							
Dabigatran 110 mg b.i.d.	**0.31(0.19,0.47)**	0.73(0.42,1.24)						
Dabigatran 150 mg b.i.d.	**0.4(0.27,0.59)**	0.96(0.58,1.6)	1.33(0.81,2.21)					
Rivaroxaban 20 mg OD	**0.65(0.46,0.92)**	1.56(0.97,2.51)	**2.14(1.24,3.76)**	1.61(0.96,2.72)				
No treatment/Placebo	0.11(0,1.65)	0.26(0.01,3.98)	0.36(0.01,5.58)	0.27(0.01,4.19)	0.17(0,2.58)			
LDASA	0.75(0.24,2.18)	1.78(0.55,5.5)	2.45(0.73,7.82)	1.85(0.56,5.77)	1.14(0.35,3.53)	6.83(0.36,330.1)		
MDASA	0.31(0.01,3.12)	0.73(0.02,7.64)	1.01(0.03,10.71)	0.76(0.02,8.02)	0.47(0.02,4.95)	2.62(0.5,21.73)	0.41(0.01,5.45)	
Clopidogrel 75 mg OD & LDASA	1.96(0.95,4.25)	**4.7(2.12,10.8)**	**6.47(2.79,15.67)**	**4.86(2.14,11.56**)	**3.01(1.36,7)**	**18.09(1.09,808.2)**	2.65(0.72,10.41)	6.48(0.56,207.7)

Table A14.6: NMA results for Myocardial infarction (MI)

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	Rivaroxaban 20 mg OD	No treatment/Placebo	LDASA	MDASA
Apixaban 5 mg b.i.d.	0.88(0.66,1.17)							
Dabigatran 110 mg b.i.d.	1.37(0.99,1.91)	**1.57(1.02,2.43)**						
Dabigatran 150 mg b.i.d.	**1.41(1.02,1.96)**	**1.61(1.04,2.49)**	1.03(0.76,1.39)					
Rivaroxaban 20 mg OD	0.8(0.61,1.04)	0.91(0.62,1.35)	0.58(0.38,0.88)	0.57(0.37,0.86)				
No treatment/Placebo	1.01(0.48,2.11)	1.15(0.52,2.53)	0.73(0.33,1.64)	0.72(0.32,1.6)	1.26(0.57,2.75)			
LDASA	1(0.22,4.53)	1.14(0.25,5.3)	0.73(0.16,3.39)	0.71(0.15,3.32)	1.25(0.27,5.78)	1(0.19,5.3)		
MDASA	1.6(0.95,2.74)	**1.82(1.01,3.36)**	1.17(0.63,2.19)	1.14(0.61,2.13)	**2(1.11,3.65)**	1.59(0.65,3.98)	1.59(0.32,7.97)	
Clopidogrel 75 mg OD & LDASA	1.1(0.83,1.46)	**1.59(1.15,2.19)**	1.38(0.997,1.9)	1.18(0.86,1.63)	1.07(0.78,1.48)	3.33(0.99,13.6)	1.05(0.55,1.97)	0.62(0.19,1.84)

Table A14.7: NMA results for Stroke or Systemic Embolism stratified by $CHADS_2$ score

$CHADS_2$< 2

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	No treatment/Placebo	LDASA	MDASA
Apixaban 5 mg b.i.d.	0.86(0.57,1.28)						
Dabigatran 110 mg b.i.d.	1(0.64,1.55)	1.17(0.64,2.13)					
Dabigatran 150 mg b.i.d.	0.61(0.37,1)	0.71(0.37,1.36)	**0.61(0.37,0.996)**				
No treatment/Placebo	1.88(0.69,5.74)	2.21(0.74,7.29)	1.89(0.62,6.26)	**3.11(1.01,10.5)**			
LDASA	**2.2(1.18,4.25)**	**2.57(1.22,5.6)**	**2.21(1.03,4.87)**	**3.62(1.62,8.29)**	1.17(0.33,3.91)		
MDASA	1.97(0.63,6.73)	2.31(0.69,8.45)	1.98(0.59,7.3)	3.25(0.94,12.12)	1.05(0.62,1.77)	0.9(0.24,3.53)	
Clopidogrel 75 mg OD & LDASA	**3.16(1.39,8.22)**	**3.71(1.48,10.4)**	**3.18(1.24,9.05)**	**5.22(1.98,15.2)**	1.69(0.42,6.77)	1.44(0.5,4.47)	1.61(0.36,7.07)

$CHADS_2$≥ 2

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	Rivaroxaban 20 mg OD	LDASA
Apixaban 5 mg b.i.d.	**0.78(0.63,0.95)**					
Dabigatran 110 mg b.i.d.	0.89(0.71,1.12)	1.15(0.84,1.57)				
Dabigatran 150 mg b.i.d.	**0.66(0.52,0.85)**	0.86(0.62,1.18)	**0.75(0.58,0.96)**			
Rivaroxaban 20 mg OD	0.88(0.74,1.04)	1.13(0.87,1.47)	0.98(0.74,1.31)	1.32(0.98,1.78)		
Low-dose ASA	2.1(0.91,5.15)	**2.71(1.15,6.8)**	**2.37(1,5.95)**	**3.17(1.33,7.99)**	**2.4(1.03,5.98)**	
Clopidogrel 75 mg OD & Low-dose ASA	**1.8(1.29,2.52)**	**2.32(1.57,3.44)**	**2.02(1.35,3.04)**	**2.7(1.79,4.12)**	**2.05(1.42,3)**	0.85(0.33,2.09)

Table A14.8: NMA results for Major Bleeding stratified by $CHADS_2$ score

$CHADS_2 < 2$

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	No treatment/Placebo	LDASA	MDASA
Apixaban 5 mg b.i.d.	**0.59(0.44,0.78)**						
Dabigatran 110 mg b.i.d.	**0.65(0.47,0.89)**	1.1(0.72,1.7)					
Dabigatran 150 mg b.i.d.	0.77(0.57,1.04)	1.3(0.86,1.98)	1.18(0.85,1.64)				
No treatment/Placebo	0.35(0.04,1.75)	0.59(0.07,3.05)	0.53(0.07,2.8)	0.45(0.06,2.37)			
Low-dose ASA	0.83(0.42,1.64)	1.41(0.67,2.97)	1.28(0.6,2.71)	1.08(0.51,2.28)	2.41(0.41,21.31)		
Medium-dose ASA	1.48(0.11,19.07)	2.5(0.19,32.92)	2.27(0.17,29.98)	1.92(0.15,25.39)	4.22(0.94,32.19)	1.78(0.13,25.24)	
Clopidogrel 75 mg OD & Low-dose ASA	1.51(0.89,2.61)	**2.57(1.4,4.77)**	**2.33(1.25,4.36)**	**1.97(1.07,3.68)**	4.39(0.79,37.14)	1.83(0.77,4.38)	1.03(0.08,14.05)

$CHADS_2 \geq 2$

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	No treatment/Placebo	LDASA
Apixaban 5 mg b.i.d.	**0.73(0.62,0.87)**					
Dabigatran 110 mg b.i.d.	0.86(0.73,1.02)	1.18(0.93,1.49)				
Dabigatran 150 mg b.i.d.	1.01(0.86,1.19)	**1.38(1.09,1.74)**	1.17(0.99,1.39)			
Rivaroxaban 20 mg OD	1.03(0.89,1.19)	**1.4(1.12,1.75)**	1.19(0.96,1.49)	1.02(0.82,1.27)		
Low-dose ASA	1.6(0.55,5.02)	2.19(0.74,6.9)	1.86(0.63,5.9)	1.59(0.54,5.01)	1.56(0.53,4.93)	
Clopidogrel 75 mg OD & Low-dose ASA	0.97(0.69,1.36)	1.32(0.9,1.93)	1.12(0.77,1.64)	0.96(0.66,1.4)	0.94(0.65,1.37)	0.6(0.18,1.84)

Table A14.9: NMA results for Stroke or Systemic Embolism stratified by Age

Age< 75 years

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.
Apixaban 5 mg b.i.d.	0.85(0.67,1.07)			
Dabigatran 110 mg b.i.d.	0.93(0.7,1.23)	1.1(0.76,1.59)		
Dabigatran 150 mg b.i.d.	**0.63(0.46,0.87)**	0.75(0.5,1.11)	**0.68(0.49,0.94)**	
Rivaroxaban 20 mg OD	0.95(0.75,1.2)	1.12(0.8,1.56)	1.02(0.71,1.47)	**1.5(1.01,2.21)**

Age≥ 75 years

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	Rivaroxaban 20 mg OD
Apixaban 5 mg b.i.d.	**0.71(0.53,0.95)**				
Dabigatran 110 mg b.i.d.	0.88(0.66,1.18)	1.24(0.82,1.89)			
Dabigatran 150 mg b.i.d.	**0.66(0.48,0.9)**	0.93(0.6,1.43)	0.75(0.54,1.03)		
Rivaroxaban 20 mg OD	0.8(0.63,1.02)	1.13(0.78,1.66)	0.91(0.62,1.34)	1.22(0.82,1.81)	
Low-dose ASA ASA (< 100 mg)	**2.04(1.32,3.19)**	**2.88(1.71,4.91)**	**2.31(1.37,3.94)**	**3.1(1.81,5.34)**	**2.54(1.55,4.22)**

Table A14.10: NMA results for Major Bleeding stratified by Age

Age< 75 years

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	Rivaroxaban 20 mg OD
Apixaban 5 mg b.i.d.	**0.73(0.6,0.89)**				
Dabigatran 110 mg b.i.d.	**0.61(0.49,0.77)**	0.84(0.63,1.13)			
Dabigatran 150 mg b.i.d.	**0.7(0.56,0.86)**	0.95(0.71,1.28)	1.13(0.89,1.43)		
Rivaroxaban 20 mg OD	0.93(0.76,1.13)	1.27(0.96,1.68)	**1.51(1.12,2.04)**	**1.33(1,1.79)**	

Age≥ 75 years

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	Rivaroxaban 20 mg OD
Apixaban 5 mg b.i.d.	**0.65(0.52,0.81)**				
Dabigatran 110 mg b.i.d.	1.02(0.84,1.25)	**1.57(1.17,2.12)**			
Dabigatran 150 mg b.i.d.	1.19(0.98,1.45)	**1.83(1.37,2.45)**	1.17(0.96,1.42)		
Rivaroxaban 20 mg OD	1.15(0.93,1.41)	**1.76(1.31,2.38)**	1.12(0.84,1.5)	0.96(0.72,1.28)	
Low-dose ASA ASA (< 100 mg)	1.01(0.57,1.79)	1.55(0.84,2.86)	0.99(0.54,1.81)	0.85(0.46,1.55)	0.88(0.48,1.63)

Table A14.11: NMA results for Stroke or Systemic Embolism stratified by TTR

TTR<66%

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)
Apixaban 5 mg b.i.d.	0.79(0.62,1.01)				
Dabigatran 110 mg b.i.d.	0.91(0.69,1.19)	1.15(0.8,1.65)			
Dabigatran 150 mg b.i.d.	**0.54(0.39,0.73)**	0.68(0.46,1.01)	**0.59(0.43,0.81)**		
Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	1.52(0.96,2.45)	**1.92(1.14,3.29)**	1.67(0.98,2.89)	**2.83(1.62,5)**	
Rivaroxaban 20 mg OD	0.81(0.65,1.01)	1.03(0.74,1.42)	0.89(0.63,1.27)	**1.51(1.04,2.21)**	0.53(0.32,0.89)

TTR≥ 66%

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	MDASA (> 100 mg and ≤ 300 mg OD)
Apixaban 5 mg b.i.d.	0.79(0.59,1.05)				
Dabigatran 110 mg b.i.d.	0.9(0.66,1.24)	1.14(0.75,1.74)			
Dabigatran 150 mg b.i.d.	0.81(0.58,1.11)	1.02(0.66,1.56)	0.89(0.64,1.24)		
Medium-dose ASA (> 100 mg and ≤ 300 mg OD)	***2.4(1.59,3.71)***	***3.03(1.83,5.09)***	***2.66(1.58,4.54)***	***2.98(1.76,5.11)***	
Rivaroxaban 20 mg OD	0.72(0.47,1.1)	0.91(0.55,1.52)	0.8(0.47,1.35)	0.9(0.52,1.53)	0.3(0.16,0.55)

Table A14.12: NMA results for Major Bleeding stratified by TTR

TTR<66%

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)
Apixaban 5 mg b.i.d.	**0.57(0.45,0.71)**				
Dabigatran 110 mg b.i.d.	**0.74(0.61,0.91)**	1.32(0.97,1.79)			
Dabigatran 150 mg b.i.d.	**0.76(0.62,0.94)**	**1.35(1,1.83)**	1.03(0.83,1.28)		
Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	0.66(0.42,1.02)	1.17(0.71,1.91)	0.88(0.54,1.44)	0.86(0.53,1.4)	
Rivaroxaban 20 mg OD	0.92(0.77,1.1)	**1.63(1.23,2.17)**	1.24(0.94,1.63)	1.21(0.92,1.58)	1.4(0.87,2.26)

TTR≥ 66%

	Standard Adjusted-Dose Warfarin	Apixaban 5 mg b.i.d.	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	MDASA (> 100 mg and ≤ 300 mg OD)
Apixaban 5 mg b.i.d.	**0.81(0.67,0.98)**				
Dabigatran 110 mg b.i.d.	0.86(0.69,1.06)	1.06(0.8,1.41)			
Dabigatran 150 mg b.i.d.	1.15(0.94,1.4)	**1.42(1.08,1.87)**	***1.34(1.09,1.65)***		
Medium-dose ASA (> 100 mg and ≤ 300 mg OD)	**1.66(1.12,2.47)**	**2.04(1.33,3.18)**	**1.93(1.24,3.03)**	1.44(0.93,2.25)	
Rivaroxaban 20 mg OD	**1.3(1.01,1.69)**	**1.61(1.16,2.22)**	**1.52(1.09,2.12)**	1.13(0.82,1.57)	0.78(0.49,1.26)

APPENDIX 15: DETAILED DATA

Table A15.1: Data used in NMA for All-cause Stroke or Systemic Embolism										
Study	Publication Year	Treatment 1	Treatment 2	Treatment 3	Treatment 1		Treatment 2		Treatment 3	
					n	N	n	N	n	N
ACTIVE W	2006	Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	118	3335	63	3371	NA	NA
AFASAK	1989	low-dose ASA ASA (≤ 100 mg OD)	No treatment/Placebo	NA	18	336	18	336	NA	NA
AFASAK2	1998	MDASA (> 100 mg and ≤ 300 mg OD)	Standard Adjusted-Dose Warfarin	NA	10	169	12	170	NA	NA
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	212	9120	265	9081	NA	NA
BAFTA	2007	low-dose ASA ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	64	485	34	488	NA	NA
CAFA	1991	No treatment/Placebo	Standard Adjusted-Dose Warfarin	NA	11	191	6	187	NA	NA
JAST	2006	MDASA (> 100 mg and ≤ 300 mg OD)	No treatment/Placebo	NA	31	426	31	445	NA	NA
RE-LY	2009	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	199	6022	182	6015	134	6076
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	269	7081	306	7090	NA	NA

b.i.d. = twice daily; CI = confidence interval; mg = milligram; n = number of patients in each arm with events; N = total number of patients in each arm; NA = not applicable

Table A15.2: Data used in NMA for Major Bleeding										
Study	**Publication Year**	**Treatment 1**	**Treatment 2**	**Treatment 3**	**Treatment 1**		**Treatment 2**		**Treatment 3**	
					n	**N**	**n**	**N**	**n**	**N**
ACTIVE W	2006	Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	101	3335	93	3371	NA	NA
AFASAK	1989	low-dose ASA ASA (≤ 100 mg OD)	No treatment/Placebo	NA	2	336	0	336	NA	NA
AFASAK2	1998	MDASA (> 100 mg and ≤ 300 mg OD)	Standard Adjusted-Dose Warfarin	NA	5	169	4	170	NA	NA
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	327	9088	462	9052	NA	NA
BAFTA	2007	low-dose ASA ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	25	485	25	488	NA	NA
CAFA	1991	No treatment/Placebo	Standard Adjusted-Dose Warfarin	NA	2	191	5	187	NA	NA
JAST	2006	MDASA (> 100 mg and ≤ 300 mg OD)	No treatment/Placebo	NA	7	426	2	445	NA	NA
RE-LY	2009	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	397	6022	322	6015	375	6076
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	395	7111	386	7125	NA	NA
WASPO	2007	MDASA (> 100 mg and ≤ 300 mg OD)	Standard Adjusted-Dose Warfarin	WASPO	3	39	0	36	NA	NA

b.i.d. = twice daily; CI = confidence interval; mg = milligram; n = number of patients in each arm with events; N = total number of patients in each arm; NA = not applicable

Table A15.3: Data used in NMA for All-cause Mortality										
Study	Publication Year	Treatment 1	Treatment 2	Treatment 3	Treatment 1		Treatment 2		Treatment 3	
					n	N	n	N	n	N
ACTIVE W	2006	Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	159	3335	158	3371	NA	NA
AFASAK	1989	low-dose ASA ASA (≤ 100 mg OD)	No treatment/Placebo	NA	15	336	17	336	NA	NA
AFASAK2	1998	Medium-dose ASA (> 100 mg and ≤ 300 mg OD)	Standard Adjusted-Dose Warfarin	NA	14	169	17	170	NA	NA
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	603	9120	669	9081	NA	NA
BAFTA	2007	Low-dose ASA ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	108	485	107	488	NA	NA
CAFA	1991	No treatment/Placebo	Standard Adjusted-Dose Warfarin	NA	8	191	10	187	NA	NA
JAST	2006	Medium-dose ASA (> 100 mg and ≤ 300 mg OD)	No treatment/Placebo	NA	10	426	9	445	NA	NA
RE-LY	2009	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	487	6022	446	6015	438	6076
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	582	7131	632	7133	NA	NA
WASPO	2007	Medium-dose ASA (> 100 mg and ≤ 300 mg OD)	Standard Adjusted-Dose Warfarin	NA	2	39	1	36	NA	NA

b.i.d. = twice daily; CI = confidence interval; mg = milligram; n = number of patients in each arm with events; N = total number of patients in each arm; NA = not applicable

Table A15.4: Data used in NMA for Extracranial Hemorrhage (ECH)										
Study	**Publication Year**	**Treatment 1**	**Treatment 2**	**Treatment 3**	**Treatment 1**		**Treatment 2**		**Treatment 3**	
					n	**N**	**n**	**N**	**n**	**N**
ACTIVE W	2006	Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	80	3335	82	3371	NA	NA
AFASAK	1989	Low-dose ASA ASA (≤ 100 mg OD)	No treatment/Placebo	NA	2	336	0	336	NA	NA
AFASAK2	1998	Medium-dose ASA (> 100 mg and ≤ 300 mg OD)	Standard Adjusted-Dose Warfarin	NA	4	169	2	170	NA	NA
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	275	9088	340	9052	NA	NA
BAFTA	2007	Low-dose ASA ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	20	485	18	488	NA	NA
CAFA	1991	No treatment/Placebo	Standard Adjusted-Dose Warfarin	NA	2	191	4	187	NA	NA
JAST	2006	Medium-dose ASA (> 100 mg and ≤ 300 mg OD)	No treatment/Placebo	NA	3	426	0	445	NA	NA
RE-LY	2009	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	315	6022	299	6015	342	6076
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	340	7111	302	7125	NA	NA

b.i.d. = twice daily; CI = confidence interval; mg = milligram; n = number of patients in each arm with events; N = total number of patients in each arm; NA = not applicable

Table A15.5: Data used in NMA for Intracranial Hemorrhage (ICH)										
Study	**Publication Year**	**Treatment 1**	**Treatment 2**	**Treatment 3**	**Treatment 1**		**Treatment 2**		**Treatment 3**	
					n	**N**	**n**	**N**	**n**	**N**
ACTIVE W	2006	Clopidogrel 75 mg OD & Low-dose Aspirin (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	21	3335	11	3371	NA	NA
AFASAK2	1999	Medium-dose Aspirin (> 100 mg and ≤ 300 mg OD)	Standard Adjusted-Dose Warfarin	NA	1	169	2	170	NA	NA
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	52	9088	122	9052	NA	NA
BAFTA	2007	Low-dose ASA Aspirin (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	6	485	8	488	NA	NA
CAFA	1991	No treatment/Placebo	Standard Adjusted-Dose Warfarin	NA	0	191	1	187	NA	NA
JAST	2006	Medium-dose Aspirin (> 100 mg and ≤ 300 mg OD)	No treatment/Placebo	NA	4	426	2	445	NA	NA
RE-LY	2009	Standard Adjusted-dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	87	6022	27	6015	36	6076
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	55	7111	84	7125	NA	NA

b.i.d. = twice daily; CI = confidence interval; mg = milligram; n = number of patients in each arm with events; N = total number of patients in each arm; NA = not applicable

Table A15.6: Data used in NMA for Myocardial infarction (MI)										
Study	**Publication Year**	**Treatment 1**	**Treatment 2**	**Treatment 3**	**Treatment 1**		**Treatment 2**		**Treatment 3**	
					n	**N**	**n**	**N**	**n**	**N**
ACTIVE W	2006	Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	36	3335	23	3371	NA	NA
AFASAK2	1998	Medium-dose ASA (> 100 mg and ≤ 300 mg OD)	Standard Adjusted-Dose Warfarin	NA	4	169	4	170	NA	NA
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	90	9120	102	9081	NA	NA
BAFTA	2007	low-dose ASA ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	15	485	15	488	NA	NA
RE-LY	2009	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	63	6022	86	6015	89	6076
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	101	7061	126	7082	NA	NA

b.i.d. = twice daily; CI = confidence interval; mg = milligram; n = number of patients in each arm with events; N = total number of patients in each arm; NA = not applicable

Table A15.7: Data used in NMA for All-cause Stroke or Systemic Embolism stratified by $CHADS_2$										
Study	**Publication Year**	**Treatment 1**	**Treatment 2**	**Treatment 3**	**Treatment 1**		**Treatment 2**		**Treatment 3**	
					n	**N**	**n**	**N**	**n**	**N**
$CHADS_2$ < 2										
ACTIVE W†	2008	Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	21	1300	7	1314	NA	NA
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	44	3100	51	3083	NA	NA
CAFA**	1991	No treatment/Placebo	Standard Adjusted-Dose Warfarin	NA	11	191	6	187	NA	NA
JAST**	2006	Medium-dose ASA (> 100 mg and ≤ 300 mg OD)	No treatment/Placebo	NA	31	426	31	445	NA	NA
BAFTA*	2007	Low-dose ASA ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	31	349	15	349	NA	NA
RE-LY	2011	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	40	1859	42	1958	26	1958
$CHADS_2$ ≥ 2										
ACTIVE W†	2011	Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	97	2035	56	2057	NA	NA
ARISTOTLE	1991	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	168	6020	214	5998	NA	NA
BAFTA*	2006	Low-dose ASA ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	17	136	9	139	NA	NA
RE-LY	2011	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	162	4163	141	4056	108	4118
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	269	7081	306	7090	NA	NA

* Derived from BAFTA study where $CHADS_2$ subgroup data stratified by $CHADS_2$ 1 to 2 (vs. 0 to 1) and $CHADS_2$ 3 to 6 (vs. 2 to 6)
** Based on study-level results from CAFA and JAST studies
† Estimated from subgroup study by Healey et al 2008

b.i.d. = twice daily; CI = confidence interval; mg = milligram; n = number of patients in each arm with events; N = total number of patients in each arm; NA = not applicable

Table A15.8: Data used in NMA for Major Bleeding stratified by $CHADS_2$										
Study	**Publication Year**	**Treatment 1**	**Treatment 2**	**Treatment 3**	**Treatment 1**		**Treatment 2**		**Treatment 3**	
					n	**N**	**n**	**N**	**n**	**N**
$CHADS_2$ < 2										
ACTIVE W†	2006	Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	34	1300	23	1314	NA	NA
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	76	3100	126	3083	NA	NA
CAFA**	1991	No treatment/Placebo	Standard Adjusted-Dose Warfarin	NA	2	191	5	187	NA	NA
JAST**	2006	Medium-dose ASA (> 100 mg and ≤ 300 mg OD)	No treatment/Placebo	NA	7	426	2	445	NA	NA
BAFTA*	2007	Low-dose ASA ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	16	349	19	349	NA	NA
RE-LY	2011	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	98	1707	69	1809	81	1815
$CHADS_2$ ≥ 2										
ACTIVE W†	2006	Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	67	2035	70	2057	NA	NA
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	251	6020	336	5998	NA	NA
BAFTA*	2007	Low-dose ASA ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	9	136	6	139	NA	NA
RE-LY	2011	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	NA	316	4160	268	4054	315	4115
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	Dabigatran 150 mg b.i.d.	395	7111	386	7125	NA	NA

* Derived from BAFTA study where $CHADS_2$ subgroup data stratified by $CHADS_2$ 1 to 2 (vs. 0 to 1) and $CHADS_2$ 3 to 6 (vs. 2 to 6)
** Based on study-level results from CAFA and JAST studies
† Estimated from subgroup study by Healey et al 2008

b.i.d. = twice daily; CI = confidence interval; mg = milligram; n = number of patients in each arm with events; N = total number of patients in each arm; NA = not applicable

Table A15.9: Data used in NMA for All-cause Stroke or Systemic Embolism stratified by Age										
Study	**Publication Year**	**Treatment 1**	**Treatment 2**	**Treatment 3**	**Treatment 1**		**Treatment 2**		**Treatment 3**	
					n	**N**	**n**	**N**	**n**	**N**
Age< 75 years										
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	133	6270	156	6253	NA	NA
RE-LY	2011	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	101	3599	96	3666	65	3610
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	144	3999	152	4008	NA	NA
Age ≥ 75 years										
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	79	2850	109	2828	NA	NA
RE-LY	2011	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	101	2423	87	2349	69	2466
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	125	3082	154	3082	NA	NA
BAFTA	2007	Low-dose ASA ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	64	485	34	488	NA	NA

b.i.d. = twice daily; CI = confidence interval; mg = milligram; n = number of patients in each arm with events; N = total number of patients in each arm; NA = not applicable

Table A15.10: Data used in NMA for Major Bleeding stratified by Age										
Study	**Publication Year**	**Treatment 1**	**Treatment 2**	**Treatment 3**	**Treatment 1**		**Treatment 2**		**Treatment 3**	
					n	**N**	**n**	**N**	**n**	**N**
Age < 75 years										
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	176	6238	238	6224	NA	NA
RE-LY	2011	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	215	3599	138	3666	153	3610
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	192	3988	207	4005	NA	NA
Age ≥ 75 years										
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	151	2850	224	2828	NA	NA
RE-LY	2011	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	206	2423	204	2349	246	2466
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	203	3073	179	3077	NA	NA
BAFTA	2007	Low-dose ASA ASA (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	25	485	25	488	NA	NA

b.i.d. = twice daily; CI = confidence interval; mg = milligram; n = number of patients in each arm with events; N = total number of patients in each arm; NA = not applicable

Table A15.11: Data used in NMA for All-cause Stroke or Systemic Embolism stratified by TTR										
Study	**Publication Year**	**Treatment 1**	**Treatment 2**	**Treatment 3**	**Treatment 1**		**Treatment 2**		**Treatment 3**	
					n	**N**	**n**	**N**	**n**	**N**
TTR < 66%										
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	124	4517	156	4530	NA	NA
ACTIVE W	2008	Clopidogrel 75 mg OD & Low dose Aspirin (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	45	1598	30	1600	NA	NA
RE-LY	2010	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	116	3018	106	3021	64	3035
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	152	5215	187	5254	NA	NA
TTR ≥ 66%										
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	87	4522	109	4517	NA	NA
ACTIVE W	2008	Clopidogrel 75 mg OD & Low dose Aspirin (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	73	1737	32	1771	NA	NA
RE-LY	2010	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	85	2996	76	2956	69	2998
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	37	1676	55	1826	NA	NA

b.i.d. = twice daily; CI = confidence interval; mg = milligram; n = number of patients in each arm with events; N = total number of patients in each arm; NA = not applicable

Table A15.12: Data used in NMA for Major Bleeding stratified by TTR										
Study	**Publication Year**	**Treatment 1**	**Treatment 2**	**Treatment 3**	**Treatment 1**		**Treatment 2**		**Treatment 3**	
					n	**N**	**n**	**N**	**n**	**N**
TTR < 66%										
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	125	4517	217	4530	NA	NA
ACTIVE W	2008	Clopidogrel 75 mg OD & Low dose Aspirin (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	34	1598	51	1600	NA	NA
RE-LY	2010	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	225	3018	171	3021	176	3035
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	249	5252	271	5284	NA	NA
TTR ≥ 66%										
ARISTOTLE	2011	Apixaban 5 mg b.i.d.	Standard Adjusted-Dose Warfarin	NA	201	4522	245	4517	NA	NA
ACTIVE W	2008	Clopidogrel 75 mg OD & Low dose Aspirin (≤ 100 mg OD)	Standard Adjusted-Dose Warfarin	NA	67	1737	42	1771	NA	NA
RE-LY	2010	Standard Adjusted-Dose Warfarin	Dabigatran 110 mg b.i.d.	Dabigatran 150 mg b.i.d.	194	2996	166	2956	221	2998
ROCKET-AF	2011	Rivaroxaban 20 mg OD	Standard Adjusted-Dose Warfarin	NA	135	1689	115	1839	NA	NA

b.i.d. = twice daily; CI = confidence interval; mg = milligram; n = number of patients in each arm with events; N = total number of patients in each arm; NA = not applicable

APPENDIX 16: COMPARISON OF MODEL FIT STATISTICS: FIXED-EFFECTS VS RANDOM-EFFECTS MODELS

Outcome	Fixed-effects Model	Random-effects Model
All-cause Stroke or Systemic Embolism*	DIC = 146.15 Deviance vs. unconstrained data points: 19.28 vs 19	DIC = 147.07 Deviance vs. unconstrained data points: 18.83 vs 19
Major Bleeding†	DIC = 141.66 Deviance vs. unconstrained data points: 22.15 vs. 22	DIC = 142.14 Deviance vs. unconstrained data points: 21.59 vs.22
All-cause Mortality	DIC = 158.64 Deviance vs. unconstrained data points: 19.13 vs. 21	DIC = 160.40 Deviance vs. unconstrained data points: 19.72 vs. 21
Extracranial hemorrhage‡	DIC = 129.13 Deviance vs. unconstrained data points: 20.34 vs. 19	DIC = 128.88 Deviance vs. unconstrained data points: 19.81 vs. 19
Intracranial hemorrhage	DIC = 102.90 Deviance vs. unconstrained data points: 16.11 vs. 17	DIC = 103.15 Deviance vs. unconstrained data points: 16.21 vs. 17
Myocardial Infarction	DIC = 96.40 Deviance vs. unconstrained data points: 13.11 vs. 13	DIC = 96.45 Deviance vs. unconstrained data points: 13.13 vs. 13

* Small differences in fit between fixed and random-effects model driven by deviance in warfarin arm of AFASAK study.
† Small differences in fit between fixed and random-effects model driven by deviance in both arms of WASPO study.
‡ Small differences in fit between fixed and random-effects model driven by deviance in both arms of JAST study.
DIC = Deviance information criterion (a measure of model fit that penalizes model complexity). The lower the number the better the fit.

APPENDIX 17: RESULTS FROM RANDOM-EFFECTS NMA MODEL

Table A17.1: Summary of Results from Random-Effects NMA Versus Adjusted-Dose Warfarin — OR (95% CI) for Each Outcome						
	Stroke/SE	**Major Bleeding**	**All-cause Mortality**	**Intracranial Bleeding**	**Extracranial Bleeding**	**Myocardial Infarction**
Apixaban 5 mg b.i.d.	0.79(0.14,4.35)	0.7(0.07,7.16)	0.89(0.23,3.46)	0.42(0.04,4.59)	0.8(0.06,10.34)	0.88(0.07,10.96)
Dabigatran 110 mg b.i.d.	0.91(0.16,4.99)	0.8(0.07,8.15)	0.91(0.23,3.6)	0.31(0.03,3.42)	0.95(0.07,12.11)	1.37(0.11,17.19)
Dabigatran 150 mg b.i.d.	0.66(0.12,3.68)	0.93(0.09,9.54)	0.88(0.23,3.51)	0.41(0.03,4.5)	1.08(0.08,13.78)	1.4(0.11,17.4)
Rivaroxaban 20 mg OD	0.88(0.15,4.98)	1.03(0.1,10.81)	0.92(0.23,3.63)	0.66(0.06,6.98)	1.14(0.09,14.59)	0.8(0.06,9.8)
No treatment/Placebo	1.52(0.41,5.71)	0.31(0.04,2.24)	0.91(0.31,2.62)	0.08(0,2.62)	0.24(0.01,2.9)	
Low-dose ASA ASA (≤ 100 mg OD)	1.82(0.43,7.36)	1.28(0.23,18.21)	0.95(0.3,2.78)	0.74(0.05,9.04)	1.48(0.19,24.22)	1(0.08,13.27)
MDASA (> 100 mg and ≤ 300 mg OD)	1.25(0.27,5.07)	2.1(0.39,17.52)	0.97(0.36,3.1)	0.26(0,4.97)	5.51(0.56,113)	1.01(0.06,17.52)
Clopidogrel 75 mg OD & Low dose ASA (≤ 100 mg OD)	1.93(0.34,10.98)	1.1(0.11,11.51)	1.02(0.26,4.12)	1.95(0.16,18.24)	0.98(0.07,12.61)	1.59(0.12,20.37)

APPENDIX 18: SUMMARY OF $CHADS_2$ SCORES IN INCLUDED TRIALS

Study	Treatments	Subgroup $CHADS_2$ <2		Subgroup $CHADS_2$ ≥2	Source
		$CHADS_2$ = 0	$CHADS_2$ = 1		
ACTIVE-W	**Clopidogrel+Low-dose ASA** **Adjusted-dose warfarin**	3%	36%	61%	ACTIVE-W publication(s)[19-22]
AFASAK	**Low-dose ASA** **Placebo/No Treatment**	15%	39%	46%	$CHADS_2$ score distribution estimate calculated using patient characteristics from the trial[23] (see Table 11, online calculator in press)
AFASAK-2	**Medium Dose ASA** **Adjusted-dose warfarin**	9%	34%	57%	$CHADS_2$ score distribution estimate calculated using patient characteristics from the trial[24,25] (see Table 11, online calculator in press)
ARISTOTLE	**Apixaban 5 mg b.i.d.** **Adjusted-dose warfarin**	0%	34%	66%	ARISTOTLE publication(s)[26-28]
ARISTOTLE-J	**Apixaban 2.5 mg b.i.d.** **Apixaban 5 mg b.i.d.** **Adjusted-dose warfarin**	1%	42%	57%	ARISTOTLE-J publication(s)[30]
BAFTA	**Low-dose ASA** **Adjusted-dose warfarin**	0%	29%	71%	$CHADS_2$ score distribution estimate calculated using patient characteristics from the trial[31] (see Table 11, online calculator in press). No $CHADS_2$ = 0 because all patients aged ≥75 years.
CAFA	**Adjusted-dose warfarin** **Placebo / No Treatment**	36%	41%	23%	$CHADS_2$ score distribution estimate calculated using patient characteristics from the trial[32] (see Table 11, online calculator in press).
JAST	**Medium-dose ASA** **Placebo / No Treatment**	40%	42%	18%	$CHADS_2$ score distribution estimate calculated using patient characteristics from the trial[33] (see Table 11, online calculator in press).
PETRO	**Dabigatran 150 mg b.i.d. ±** **Low-dose or high-dose ASA** **Adjusted-dose warfarin**	9%	32%	61%	$CHADS_2$ score distribution estimate calculated using patient characteristics from the trial[34] (see Table 11, online calculator in press).
RE-LY	**Dabigatran 110 mg b.i.d.** **Dabigatran 150 mg b.i.d.** **Adjusted-dose warfarin**	3%	29%	68%	RE-LY FDA Public Summary Document[60]
ROCKET-AF	**Rivaroxaban 20 mg OD** **Adjusted-dose warfarin**	0%	0%	100%	ROCKET-AF publication(s)[43-45]

Study	Treatments	Subgroup $CHADS_2$ <2		Subgroup $CHADS_2$ ≥2	Source
		$CHADS_2$ = 0	$CHADS_2$ = 1		
WASPO	**Adjusted-dose warfarin** **Medium-dose ASA**	0%	NA	NA	Insufficient reporting in WASPO publication(s)[46] to allow estimate of breakdown by $CHADS_2$ score. No $CHADS_2$ = 0 (all patients ≥ 80 years). ≥ 50% of patients with $CHADS_2$ ≥2 due to hypertension.

APPENDIX 19: RESULTS OF UNIVARIATE SENSITIVITY ANALYSES

Scenario	$CHADS_2$ <2	$CHADS_2$ ≥2
Base case^	If λ< $20,845, warfarin is optimal If λ> $20,845, dabigatran 150 mg is optimal	If λ< $17,795, warfarin is optimal If λ> $17,795 but < $17,799, dabigatran 150 mg is optimal. If λ> $17,799, apixaban is optimal
Drug costs of rivaroxaban reduced by 10%	N/A	If λ< $17,795, warfarin is optimal If λ> $17,795 but < $17,799, dabigatran 150 mg is optimal. If λ> $17,799, apixaban is optimal
Drug costs of rivaroxaban reduced by 20%	N/A	If λ< $17,795, warfarin is optimal If λ> $17,795 but < $17,799, dabigatran 150 mg is optimal. If λ> $17,799, apixaban is optimal
Drug costs of dabigatran reduced by 10%	If λ< $15,551, warfarin is optimal If λ> $15,551, dabigatran 150 mg is optimal	If λ< $12,876, warfarin is optimal If λ> $12,876 but < $77,820, dabigatran 150 mg is optimal. If λ> $77,820, apixaban is optimal
Drug costs of dabigatran reduced by 20%	If λ< $10,276, warfarin is optimal If λ> $10,276, dabigatran 150 mg is optimal	If λ< $7,957, warfarin is optimal If λ> $7,597 but < $137,840, dabigatran 150 mg is optimal. If λ> $137,840, apixaban is optimal
Drug costs of apixaban reduced by 10%	If λ< $20,845, warfarin is optimal If λ> $20,845, dabigatran 150 mg is optimal	If λ< $13,067, warfarin is optimal If λ> $13,067, apixaban is optimal
Drug costs of apixaban reduced by 20%	If λ< $20,649, warfarin is optimal If λ> $20,649 but < $21,439, apixaban is optimal If λ> $21,439, dabigatran 150 mg is optimal	If λ< $8,339, warfarin is optimal If λ> $8,339, apixaban is optimal
Annual cost of INR monitoring with warfarin = $0	If λ< $29,937, warfarin is optimal If λ> $29,937, dabigatran 150 mg is optimal	If λ< $25,998, warfarin is optimal If λ> $25,998, apixaban is optimal
Annual cost of INR monitoring with warfarin = $542.48	If λ< $9,445, warfarin is optimal If λ> $9,445, dabigatran 150 mg is optimal	If λ< $6,673, warfarin is optimal If λ> $6,673 but < $17,799, dabigatran 150 mg is optimal. If λ> $17,799, apixaban is optimal
Increase event costs by 50%	If λ< $15,640, warfarin is optimal If λ> $15,640, dabigatran 150 mg is optimal	If λ< $10,984, warfarin is optimal If λ> $10,984 but < $11,538, dabigatran 150 mg is optimal. If λ> $11,538, apixaban is optimal
Decrease event costs by 50%	If λ< $26,051, warfarin is optimal If λ> $26,051, dabigatran 150 mg is optimal	If λ< $24,564, warfarin is optimal If λ> $24,564, apixaban is optimal
Increase long term care costs by 50%	If λ< $18,218, warfarin is optimal If λ> $18,218, dabigatran 150 mg is optimal	If λ< $13,819, warfarin is optimal If λ> $13,819 but < $20,886, dabigatran 150 mg is optimal. If λ> $20,886, apixaban is optimal
Decrease long term care costs by 50%	If λ< $28,650, warfarin is optimal If λ> $28,650, dabigatran 150 mg is optimal	If λ< $21,235, warfarin is optimal If λ> $21,235, apixaban is optimal
Time horizon of 20 years	If λ< $25,668, warfarin is optimal If λ> $25,668, dabigatran 150 mg is optimal	If λ< $18,348, warfarin is optimal If λ> $18,348 but < $19,525, dabigatran 150 mg is optimal. If λ> $19,525, apixaban is optimal
Time horizon of 10 years	If λ< $52,953, warfarin is optimal If λ> $52,953, dabigatran 150 mg is optimal	If λ< $30,166, warfarin is optimal If λ> $30,166 but < $44,032, dabigatran 150 mg is optimal. If λ> $44,032, apixaban is optimal

Scenario	$CHADS_2$ <2	$CHADS_2$ ≥2
Time horizon of 2 years	If λ< $371,678, warfarin is optimal If λ> $371,678, dabigatran 150 mg is optimal	If λ< $190,545, warfarin is optimal If λ> $190,545, apixaban is optimal
Discount rate = 0%	If λ< $15,625, warfarin is optimal If λ> $15,625, dabigatran 150 mg is optimal	If λ< $12,576, warfarin is optimal If λ> $12,576 but < $12,908, dabigatran 150 mg is optimal. If λ> $12,908, apixaban is optimal
Discount rate = 3%	If λ< $20,076, warfarin is optimal If λ> $20,076, dabigatran 150 mg is optimal	If λ< $15,602, warfarin is optimal If λ> $15,602 but < $15,777, dabigatran 150 mg is optimal. If λ> $15,777, apixaban is optimal
Discount rate = 10%	If λ< $33,045, warfarin is optimal If λ> $33,045, dabigatran 150 mg is optimal	If λ< $23,723, warfarin is optimal If λ> $23,723, apixaban is optimal
Maximum utility value for stroke from literature Major = 0.52, minor = 0.8	If λ< $23,586, warfarin is optimal If λ> $23,586, dabigatran 150 mg is optimal	If λ< $19,535, warfarin is optimal If λ> $19,535, apixaban is optimal
Minimum utility value for stroke from literature Major = 0.22, minor = 0.55	If λ< $16,722, warfarin is optimal If λ> $16,722, dabigatran 150 mg is optimal	If λ< $15,634, warfarin is optimal If λ> $15,634 but < $20,378, dabigatran 150 mg is optimal. If λ> $20,378, apixaban is optimal
Include age decrement to utility values	If λ< $20,930, warfarin is optimal If λ> $20,930, dabigatran 150 mg is optimal	If λ< $17,852, warfarin is optimal If λ> $17,852 but < $17,919, dabigatran 150 mg is optimal. If λ> $17,919, apixaban is optimal
Increase utility decrements from events by 100%	If λ< $22,478, warfarin is optimal If λ> $22,478, dabigatran 150 mg is optimal	If λ< $17,746, warfarin is optimal If λ> $17,746, apixaban is optimal
Include effect of treatments on non-vascular deaths	If λ< $14,915, warfarin is optimal If λ> $14,915, apixaban is optimal	If λ< $10,259, warfarin is optimal If λ> $10,259, rivaroxaban is optimal
Not including effect on MI	If λ< $27,782, warfarin is optimal If λ> $27,782, dabigatran 150 mg is optimal	If λ< $15,563, warfarin is optimal If λ> $15,563 but < $324,407, dabigatran 150 mg is optimal. If λ> $324.407, apixaban is optimal
Patients with previous MI	If λ< $23,648, warfarin is optimal If λ> $23,648, dabigatran 150 mg is optimal	If λ< $20,112, warfarin is optimal If λ> $20.112 but < $24,345, dabigatran 150 mg is optimal. If λ> $24,345, apixaban is optimal
Analysis based on warfarin event rates from ROCKET-AF	N/A	If λ< $11,152 warfarin is optimal If λ> $11,152 apixaban is optimal
Costs and utilities associated with an ICH are equivalent to a major stroke	If λ< $20,845, warfarin is optimal If λ> $20,845, dabigatran 150 mg is optimal	If λ< $2,544, warfarin is optimal If λ> $2,544 but < $19,619, dabigatran 150 mg is optimal. If λ> $19,619, apixaban is optimal
Double utility decrements from and costs of minor and major bleeds for all newer anticoagulants	If λ< $25,989, warfarin is optimal If λ> $25,989, dabigatran 150 mg is optimal	If λ< $23,604, warfarin is optimal If λ> $23,604, apixaban is optimal
Double utility decrements from and costs of minor and major bleeds for dabigatran	If λ< $25,989, warfarin is optimal If λ> $25,989, dabigatran 150 mg is optimal	If λ< $17,795, warfarin is optimal If λ> $17,795, apixaban is optimal
Quadruple utility decrements from and costs of minor and major bleeds for all newer anticoagulants	If λ< $36,933, warfarin is optimal If λ> $36,933, dabigatran 150 mg is optimal	If λ< $35,743, warfarin is optimal If λ> $35,743, apixaban is optimal

Scenario	$CHADS_2$ <2	$CHADS_2$ ≥2
Quadruple utility decrements from and costs of minor and major bleeds for dabigatran	If λ< $34,474, warfarin is optimal If λ> $34,474 but < $46,648, apixaban is optimal If λ> $46,648, dabigatran 150 mg is optimal	If λ< $17,795, warfarin is optimal If λ> $17,795, apixaban is optimal

λ = maximum willingness to pay for a QALY; MI = myocardial infarction.
Base patient characteristic, lifetime time horizon, cycle length = 3 months, discount rate = 5%

APPENDIX 20: UNIVARIATE SENSITIVITY ANALYSES: PARAMETERS THAT DID NOT SUBSTANTIALLY ALTER THE RESULTS

For all analyses, λ was assumed to be $50,000.

$CHADS_2$ <2

- Drug costs of rivaroxaban, apixaban and dabigatran
- Costs of events and of long term care
- Discount rate = 0%, 3% and 10%
- Costs of INR monitoring for warfarin
- Changing the utility value of SSE
- Assume no age decrement to utility values
- Increase utility decrements from events by 100%
- Exclusion of effects of treatment on MI
- Assume patients had a previous MI
- Increased consequences of bleeding for the new anticoagulants
- Increased consequences of bleeding for dabigatran
- Assume utility decrement and costs for ICH are equivalent to major stroke

$CHADS_2$ ≥2

- Drug costs of rivaroxaban and apixaban
- Costs of events and of long term care
- Time horizon of 20 and 10 years
- Discount rate = 0%, 3% and 10%
- Costs of INR monitoring for warfarin
- Changing the utility value of SSE
- Assuming the utility for ICH is equivalent to major stroke
- Assume no age decrement to utility values
- Increase utility decrements from events by 100%
- Assume patients had a previous MI
- Increased consequences of bleeding for the new anticoagulants
- Increased consequences of bleeding for dabigatran
- Assume utility decrement and costs for ICH are equivalent to major stroke

APPENDIX 21: SENSITIVITY ANALYSES: INCLUSION OF AVERROES AND ACTIVE-A

A. Stroke or SE

Figure A21.1: Evidence Networks for Stroke or SE NMA including AVEROES and ACTIVE A studies

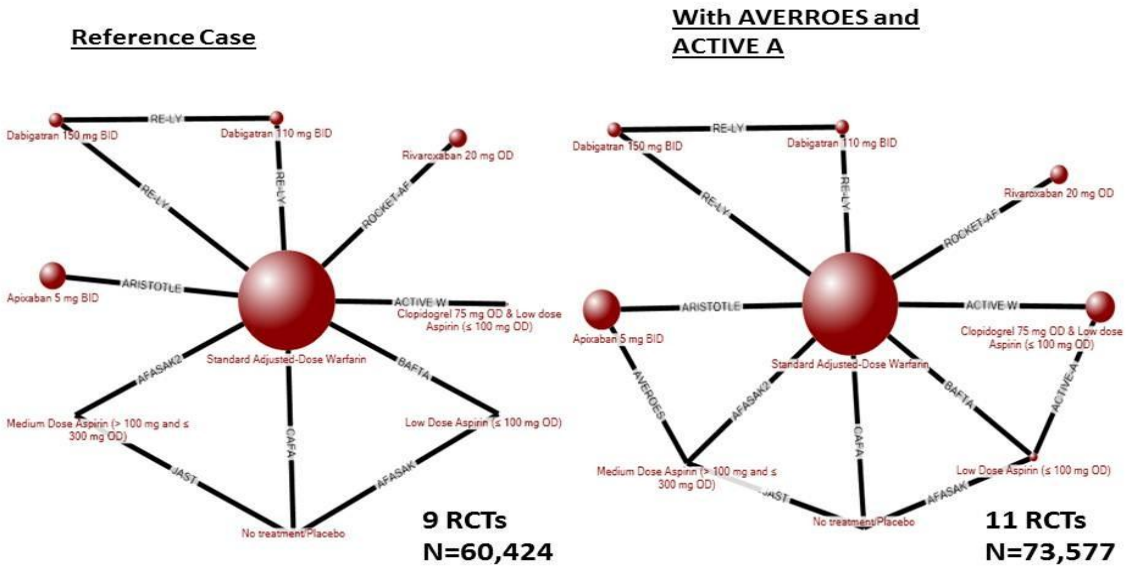
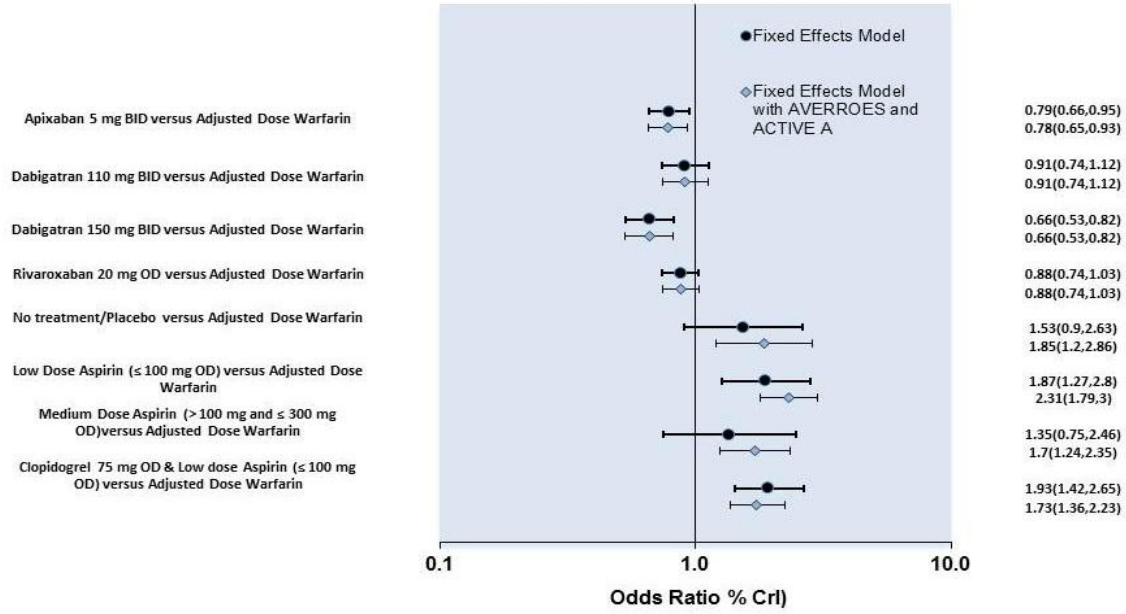


Figure A21.2: Forest Plot for Stroke or SE NMA including AVEROES and ACTIVE A studies



B. Major Bleeding

Figure A21.3: Evidence Networks for Major Bleeding NMA including AVEROES and ACTIVE A studies

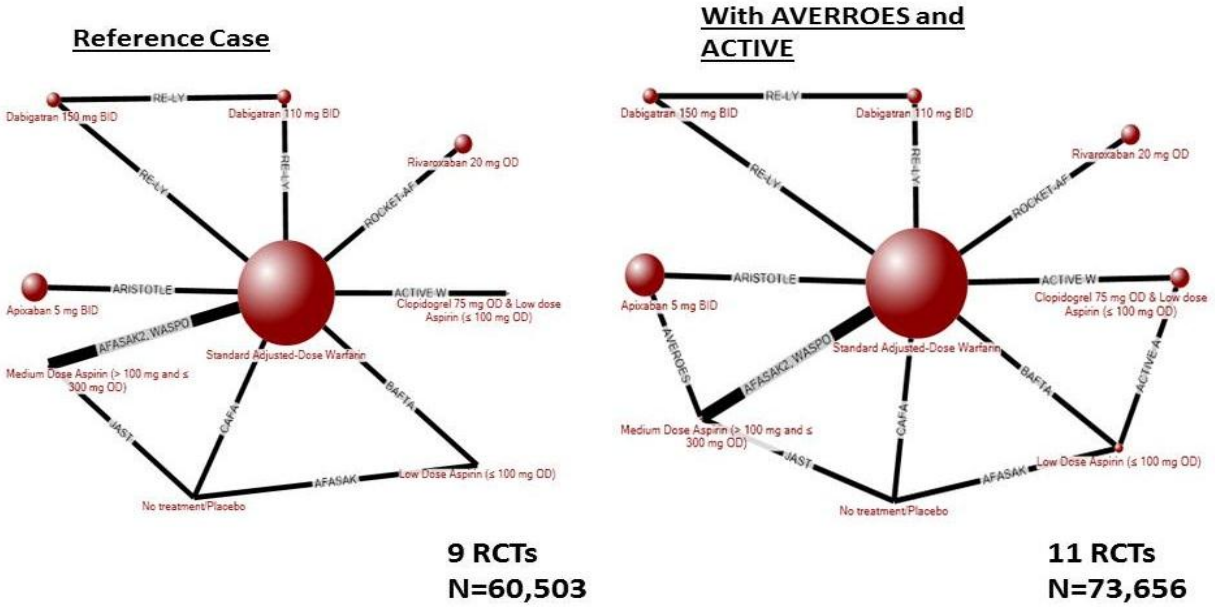


Figure A21.4: Forest Plot for Major Bleeding NMA including AVEROES and ACTIVE A studies