National Institute for Health and Care Excellence

Final

Atrial fibrillation: diagnosis and management

Evidence review G1: Anticoagulant therapy for stroke prevention in people with atrial fibrillation

NICE guideline NG196

Intervention evidence review

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Developed by the National Guideline Centre, Royal College of Physicians

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1.1 Review question: What is the most clinically and cost-effective anticoagulant therapy for stroke prevention in people with atrial fibrillation?

1.2 Introduction

Atrial fibrillation (AF) is associated with a five-fold increase in the risk of thromboembolic events (stroke/systemic embolism). When initiated in individuals at risk of a thromboembolic event, oral anticoagulation with either a vitamin K antagonist (VKA) or non-vitamin K oral anticoagulant (DOAC), is highly effective at preventing an ischaemic stroke in people diagnosed with AF. Warfarin is well established and supported by a robust evidence base spanning decades, however, it's use in the context of stroke prevention in AF is limited by significant inter-individual variability in response, resulting in unpredictable levels of anticoagulation, necessitating frequent monitoring and dose adjustments. In addition, concerns over intracranial haemorrhage, frequent drug-drug and drug-food interactions limit its use in practice. DOACs address some of these limitations, providing more consistent and predictable levels of anticoagulation with fixed daily doses. Whilst DOACs have been extensively investigated against warfarin, there are little data regarding direct comparisons between the different DOACs available. Deciding which oral anticoagulant to initiate for stroke prevention can be challenging. In this chapter, we review the different oral anticoagulant therapies available with a view to determining which is the most clinically and cost-effective agent for stroke prevention in atrial fibrillation.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People aged 18 or over with a diagnosis of NVAF, and identified as needing anticoagulant therapy
Intervention(s)	DOACs; Apixaban 2.5mg daily DOACs; Apixaban 5 mg twice daily DOACs; Dabigatran 110mg twice daily DOACs; Dabigatran 150 mg twice daily DOACs; Rivaroxaban 20mg once daily DOACs; Rivaroxaban 15 mg once daily DOACs; Edoxaban 30mg once daily DOACs; Edoxaban 60 mg once daily Antiplatelets; Aspirin Antiplatelets; Clopidogrel Vitamin K antagonists; Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5) Vitamin K antagonists; Warfarin INR 3-4 placebo No treatment Usual care
Comparison(s)	All interventions compared with each other
Outcomes	Quality of life (Continuous) CRITICAL All stroke or systemic embolism (Dichotomous) CRITICAL All-cause mortality (Dichotomous) CRITICAL

	Myocardial infarction (Dichotomous) CRITICAL Clinically relevant non-major bleeding (CRNMB) (Dichotomous) CRITICAL Minor bleeding (Dichotomous) CRITICAL Major bleeding (Dichotomous) CRITICAL Intracranial bleeding (ICH) (Dichotomous) CRITICAL GI bleeding (Dichotomous) CRITICAL
Study design	RCTs and SRs of RCTs

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[126] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

A search was conducted for randomised trials comparing the effectiveness of anticoagulants as prophylactic treatment for patients at risk of stroke because of non-valvular atrial fibrillation (NVAF). Twenty six studies (28 articles) were included in the review;[1, 8, 12, 13, 29, 30, 33, 37-40, 60, 67, 69, 71, 74, 81, 91, 92, 116, 118, 137, 140, 141, 147, 158, 171, 177] which are summarised in table 2. Evidence from these studies is summarised in the clinical evidence summary below (Table 3 and Table 4).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

In the 26 included randomised trials, several different anticoagulants were compared to warfarin or antiplatelets (see Table 2). In this review Warfarin was given at a variable dose required to attain an INR of 2-3, unless stated otherwise.

- One study evaluated rivaroxaban 15 mg qd versus dabigatran 150 mg bd[92]
- Eight studies evaluated antiplatelets versus warfarin[1, 8, 13, 29, 30, 71, 74, 116, 147]. Of these, most used aspirin but one used a mixture of aspirin and clopidogrel[1]
- Two studies evaluated placebo versus warfarin[12, 40]
- One evaluated apixaban 2.5mg bid versus warfarin[137]
- Two evaluated apixaban 5mg bid versus warfarin[69, 137]
- One evaluated dabigatran 110mg bid versus warfarin[38, 39]
- Two evaluated dabigatran 150mg bid versus warfarin[38, 39, 60]
- Four evaluated rivaroxaban 20mg qd versus warfarin[91, 118, 140, 158]
- 1 evaluated rivaroxaban 15mg qd versus warfarin[81]
- Four evaluated Edoxaban 30mg qd versus warfarin[33, 67, 171, 177]
- Four evaluated edoxaban 60mg qd versus warfarin[33, 67, 171, 177]
- One evaluated placebo versus warfarin (INR 3-4)[141]
- One evaluated antiplatelets versus warfarin (INR 3-4)[141].

It should be noted that in one study comparing Apixaban 5mg bid versus warfarin[57] a small percentage of participants (<5%) were given 2.5mg because they had additional risk factors. Similarly, in one study comparing rivaroxaban 20mg qd versus warfarin[115] 21.1% of participants were given 15mg because of renal impairment. However both studies were respectively categorised as Apixaban 5mg bid and Rivaroxaban 20mg qd because the majority of participants were receiving these doses.

All the studies listed above were in a population of people with NVAF who were eligible for warfarin. However one further study evaluated apixaban 5mg qd versus antiplatelets[37], as the sample in that study were not eligible for warfarin. Nevertheless, the ineligibility for warfarin in these patients was highly specific to Warfarin itself, and the reasons cited for ineligibility did not imply that the population in that study would have responded differently to apixaban 5mg qd compared to a population that were eligible for Warfarin. For example, there were no factors such as renal failure conferring warfarin ineligibility that might also imply a different response to other drugs. The aim of all studies was to assess the relative efficacy of different anticoagulants for people with NVAF.

Four sub-grouping strategies were designed pre-hoc, in the event of significant heterogeneity in any of the fixed event meta-analyses conducted for each comparison (see protocol in Appendix A). These were only used in one meta-analysis that had serious heterogeneity (I^2 >50%), but these strategies failed to resolve heterogeneity.

1.5.2 Network meta-analysis

The committee was given the choice of developing a new NMA from the pairwise data presented in this review, or using an existing NMA, published in 2017. For purposes of discussion the existing NMA will be referred to as Lopez-Lopez[114]. Our review contained seven studies not included by Lopez-Lopez. Two of these were not included by Lopez-Lopez because they were in a paroxysmal AF population, one was not included because the data were viewed as suspect by the Lopez-Lopez team, three were not included because the paper was published after Lopez-Lopez had been published, and one was not included because relevant data in the paper had not been discerned. Six of these studies made little difference to the overall pairwise meta-analysis estimates in our review, largely because they were small studies with consequently low weighting. A further study comparing rivaroxaban and dabigatran was regarded as very low quality and did not have sufficient power to provide certain conclusions. The committee were therefore confident that the lack of these studies in Lopez-Lopez would not change their results significantly, and that confidence in their findings would therefore not be reduced. Furthermore, Lopez-Lopez contained three studies that were not included in our current review because they contravened our protocol – one was written in Chinese, one was unpublished and one evaluated betrixaban. The two former studies left out of our review were regarded as potentially important and might lead to greater confidence in overall findings in Lopez-Lopez than an NMA based on our data. The committee thus agreed that the body of evidence included in Lopez-Lopez was at least as useful as the body of evidence from our review. On the basis of all these facts, the committee agreed that it was highly unlikely that the resources allocated to performing a new NMA based on our own data would be justified by any gains over Lopez-Lopez, and therefore that using Lopez-Lopez might be preferable to carrying out our own NMA.

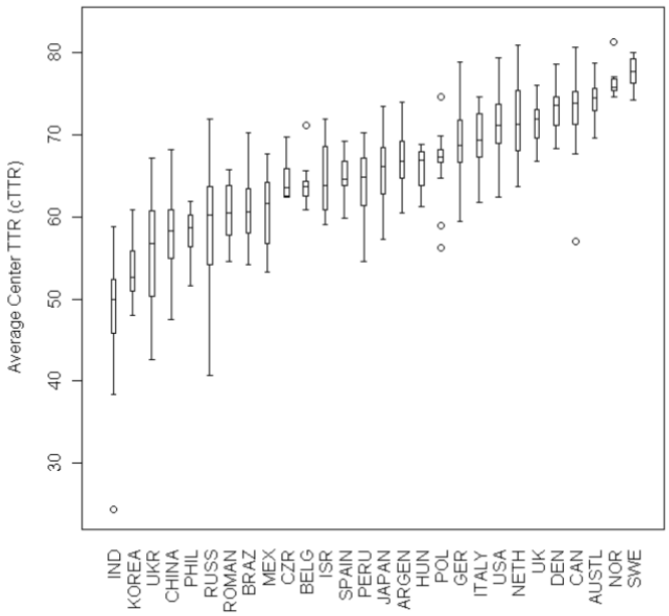
There was some concern that some studies in Lopez Lopez had used INR targets below or above the INR 2-3 range. However the committee discussed how the studies departures from INR2-3 in the relevant trials were relatively unimportant because they came from small trials and, furthermore, did not involve many of the patients in these trials. The committee therefore agreed that it was unlikely that the departures from INR2-3 would have affected results significantly.

There were some reservations about the low time in therapeutic range (TTR) in some of the warfarin arms in Lopez-Lopez, with one trial having a TTR of only 55%, and with several more having <65%. The committee suggested that values <60% would be considered too low to allow a fair comparison between the DOACs and warfarin, as such low TTRs would mean that warfarin was being used ineffectively. The committee suggested that stratified data from the main trials might allow consideration of TTR evidence that was more typical of the TTRs that might be observed in the UK.

The committee therefore discussed the possibility of using trial data stratified by TTR in five studies.[41, 142, 157, 168, 169] Although there was not a clear pattern, the sub-group analyses in these five studies suggested that there might be an association between lower cTTR (cTTR is the mean centre TTR, by which measure stratification was generated) and increased efficacy of DOACS or antiplatelets relative to warfarin in some of the outcomes, as would be expected. The lack of a more definitive and consistent pattern between cTTR and effect size may have resulted from the effects of other covariates (such as age or co-morbidities) that differ between the TTR strata. Because the mean TTR in the overall (non-stratified) trials were lower than TTRs achieved in UK trial centres, the overall results may have demonstrated a greater benefit for DOACs than those which might be observed if UK trial data were used alone. The sub-grouped data from the ARISTOTLE, ROCKET and RE-LY trials suggested that the most relevant quartile for UK patients is the 3rd highest quartile, as this included the mean TTR value for UK centres. Thus at first glance it seemed there may be some justification for using the sub-grouped data from the 3rd quartile rather than the overall trial data, as it would seem to make the data more applicable to the UK.

However, the caveat to the above is that if the typical UK primary care TTR were sufficiently lower than the UK trial-based TTR, to the extent that it was comparable to the overall trial TTRs, then the overall trial TTRs could be regarded as clinically applicable to the UK. Observational studies (which should give a more realistic impression of clinical TTRs) have had variable results, with TTRs as high as 71% (Abohelaika et al. 2014 [Age and Ageing 2014; 43: 708–711]) in GP practice patients in the north of England and as low as 57% in a UK study using the post-trial results of a control group (McCahon et al. 2007 [J Clin pathol 60; 1263-67]). Perhaps more revealingly, Macedo et al. (2015)[Thrombosis Research 136 (2015) 250–260] showed that in a large (N=29,717) observational cohort of UK primary care patients with AF, 43.8% had a TTR of >70 but 30% had a TTR of <55. A mean TTR figure was not provided, but these statistics concurred with the committee's strong opinion, based on their extensive clinical experience, that in UK clinical practice there is a significant proportion of people with very poor INR control. In spite of constituting only a third of people, it could be argued that this is the group that are most important in any consideration of whether to use DOACs or warfarin, because these are the people that will benefit most from DOACs. For groups with higher TTRs it may not matter to quite the same extent if warfarin or DOACs are given. Very importantly, data from Wallentin (2013) [supplemental data, figure 1 – see below] shows that a far smaller proportion of people from the centres in the 3rd quartile of cTTRs would have had TTRs <55. Hence, using the third quartile data only for decision making would lead to a very important group of people in the real world being unrepresented. Use of the overall trial data might therefore avoid this problem.

Supplemental Figure 1
The variability in center based TTR (cTTR) by country with cTTR predicted according to the mixed model with a fixed effect for country and random effect for center (Countries with less than 10 sites were excluded to simplify the plot).



In addition, the committee felt that there were two major problems with using the stratified data in an NMA. The first problem was that similarly stratified data for all the studies in the NMA did not exist. This is certainly true for many of the smaller aspirin versus warfarin trials, where sub-grouped data does not appear to exist. Even for one of the DOACS – edoxaban – there is not a sufficiently good sub-group analysis available. Shimada, 2015 (described in the attachment) compared edoxaban to warfarin in a small Japanese subset that happened to have a similar TTR to UK trial centres but evidence from this is probably inadequate. If stratified and non-stratified data are used together in an NMA, this juxtaposes essentially different populations which may create incoherence in the NMA that could potentially invalidate it. Secondly, and just as importantly, the lack of overlapping outcomes in these sub-analyses would severely curtail the number of outcomes usefully included in the NMA. In fact, only 1 outcome (SSE) is common to all the sub-grouped DOAC analyses. The view of the committee was that this could result in a protocol that was less, rather than more robust and would also be open to stakeholder challenge.

In summary, the committee felt that although the subgroup analyses may indicate a lower efficacy of DOACs with higher TTRs, the committee was very concerned that the use of subgroups to fit with a mean UK TTR would inevitably result in underrepresentation of patients with poor INR control typically seen in UK clinical practice. Hence, the committee view was that use of whole trial data by Lopez & Lopez was appropriate to produce an evidence based guideline relevant to the NHS.

1.5.3 Excluded studies

See the excluded studies list in appendix I.

1.5.4 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Studies (n)	Population characteristics (for further details see evidence tables in Appendix D)	Intervention	Comparator	Recent stroke (<6 months)?	Renal impairment (CrCl < 50)?	Threshold stroke risk score for inclusion (CHADS2 score <2 or ≥2)	TTR ≥65%?
ACTIVE W[1]	1(6706)	Multinational study. ECG evidence of AF, and at least one of: age >=75, on treatment for systemic hypertension, previous stroke, TIA or non-CNS systemic embolus, LVEF <45%, PAD. If aged 55-74 and had no other inclusion criteria they had to have DM requiring drug therapy or previous CAD. Exclusions: Contraindications to clopidogrel or anticoagulants; documented peptic ulcer disease within past 6 months; previous intracerebral haemorrhage; significant thrombocytopenia or mitral stenosis.	Clopidogrel 75mg qd) + Aspirin(75-100mg qd)	VKA INR2-3	UNCLEAR	UNCLEAR	<2	NO (63.8%)
AFASAK2 1998[71]	1(339)	Conducted in Denmark - general practices in Copenhagen and surrounding areas. Aged 18 or older; chronic NVAF; AF needed to be documented twice using ECG with an interval of at least 1 month. Exclusion: patients younger than 60 with lone AF (ie no IHD, hypertension, CHF, hyperthyroidism or COPD); systolic or diastolic bp > 180/100; stroke or TIA in past 6 months; risk factors for bleeding; contraindications for warfarin or aspirin; already on dose adjusted warfarin.	Aspirin 300 mg qd	VKA INR 2-3	NO	UNCLEAR	UNCLEAR	YES (73%)
ARISTOTLE 2011[69]	1(18201)	Multinational study. AF or flutter at enrolment or at least 2 episodes at least 2 weeks apart documented by ECG in prior 12 months; one of the following: age >75, previous stroke/TIA/SEE,	Apixaban 5mg bid [<5%, who had additional risk factors,	VKA INR 2-3	UNCLEAR	No. 83% >50	<2	UNCLEAR

Study	Studies (n)	Population characteristics (for further details see evidence tables in Appendix D)	Intervention	Comparator	Recent stroke (<6 months)?	Renal impairment (CrCl < 50)?	Threshold stroke risk score for inclusion (CHADS2 score <2 or ≥2)	TTR ≥65%?
		symptomatic HF in previous 3 months or LVEF no more than 40, DM, hypertension requiring treatment. Exclusion: AF due to a reversible cause; moderate/severe mitral stenosis; non AF conditions requiring anticoagulation; stroke in previous 7 days; need for daily aspirin at dose of >165mg/day or for both aspirin and clopidogrel; severe renal insufficiency CrCl<25	were given 2.5mg bid]					
ARISTOTLE - J 2011[137]	1(222)	Multiple settings in Japan. Aged >20; history of documented NVAF (AF confirmed by ECG, Holter or intracardiac electrogram, needed to be at least 1 minute in duration on 2 occasions at least 2 weeks apart during the preceding 2 weeks); at least one of the following: age >75, CHF (LVEF <40%), hypertension requiring meds, DM requiring treatment, history of stroke/TIA. Exclusion: Recent stroke/TIA; valvular disease; sick sinus syndrome or severe conduction disturbance; non-cardiogenic stroke requiring ASA>100 mg/day or concomitant ASA and antiplatelet agents; contraindications to warfarin use; severe or refractory hypertension; NYHA class IV; current thrombocytopenia; liver function test abnormalities; renal dysfunction (CrCl < 25); known or suspected hereditary bleeding disorders; scheduled electrical, pharmacological or surgical cardioversion during the treatment period.	Apixaban 2.5mg bid Apixaban 5mg bid	VKA INR 2-3	UNCLEAR	UNCLEAR	<2	UNCLEAR [>60% had INR in target range >60% of the time]
AVERROES 2011[37]	1(5599)	Patients considered unsuitable for VKA treatment because of demonstrated or anticipated concerns about contraindications. 50 years or older; AF documented in 6 months pre-enrolment or by 12 lead ECG on the day of screening; one of the following: prior stroke/TIA, aged 75+, treated	Apixaban 5mg bid	Aspirin approximately 81mg qd	UNCLEAR	UNCLEAR	<2	NA

Study	Studies (n)	Population characteristics (for further details see evidence tables in Appendix D)	Intervention	Comparator	Recent stroke (<6 months)?	Renal impairment (CrCl < 50)?	Threshold stroke risk score for inclusion (CHADS2 score <2 or ≥2)	TTR ≥65%?
		arterial hypertension, DM on treatment, NYHA class II or higher, documented PAD. Exclusion: presence of conditions other than AF for which patient required anticoagulants; valvular disease requiring surgery; serious bleeding event in previous 6 months or high risk of bleeding, current ETOH abuse or psychosocial issues; life expectancy <12 months; severe renal insufficiency CrCl < 25 ml per minute; alanine aminotransferase or aspartate aminotransferase level > 2x ULN; bilirubin > 1.5X ULN; allergy to aspirin.						
BAFTA 2007[116]	1(973)	UK study, conducted at 260 GP practices. Aged 75 or older; AF or flutter on study ECG or in ECG done in past 2 years. Exclusion: rheumatic heart disease; major non-traumatic haemorrhage within previous 5 years; ICH; endoscopically proven peptic ulcer disease in previous year; oesophageal varices; allergic sensitivity to either study drug; terminal illness; surgery in past 3 months; bp > 180/110; primary care physician judges should not be on warfarin	Aspirin 75mg qd	VKA INR 2-3	UNCLEAR	UNCLEAR	<2	YES (67%)
CAFA 1991[40]	1(378)	11 settings in Canada. Chronic AF present >1 month or paroxysmal AF occurring at least 3 times in the previous 3 months (documented at least twice on ECG); age >19 years; absence of mitral valve prosthesis or mechanical aortic valve prosthesis; absence of mitral valve stenosis of echocardiography. Exclusion: medical contraindications to OACs; stroke or TIA within 1 year; requirement for antiplatelet therapy; hyperthyroidism; uncontrolled hypertension; MI in past month	Placebo	VKA INR 2-3	NO	UNCLEAR	UNCLEAR	NO (43.7% of days when in target range)

Study	Studies (n)	Population characteristics (for further details see evidence tables in Appendix D)	Intervention	Comparator	Recent stroke (<6 months)?	Renal impairment (CrCl < 50)?	Threshold stroke risk score for inclusion (CHADS2 score <2 or ≥2)	TTR ≥65%?
CHEN 2012[29]	1(521)	75 institutions in China. Mean age 67. Little information on population.	Aspirin 200mg qd	VKA INR 2-3	NO	UNCLEAR	UNCLEAR	NO. 51.2% in target range of 2.1 to 2.5
CHEN 2013[30]	1(378)	Multicentre study in China. Mean age 72. Little information on population.	Aspirin 150mg qd	VKA INR 2-3	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
CHUNG 2011[33]	1(235)	Conducted in Hong Kong, Singapore, South Korea and Taiwan. Aged 18-80; NVAF confirmed on ECG twice within 6 months before randomisation); CHADS > =1. Exclusion: Previous valve surgery; contraindications to anticoagulants; known bleeding disorders; conditions associated with high risk of bleeding; antiplatelet agents; AF due to reversible causes; ACS or revascularisation procedures; stroke/TIA/major surgery in past 30 days; left ventricular aneurysm or atrial myxoma; impaired hepatic function; serum Cr >1.5 mg/dl; pregnancy or lactating.	Edoxaban 30mg qd Edoxaban 60mg qd	VKA INR 2-3	UNCLEAR	NO. 80% >50	<2	NO. 45%
COPENHAGAN AFASAK STUDY 1989[141]	1(1007)	ECG clinics in Denmark. 18 years or over, with ECG verified AF. Exclusion: Previous anticoagulation therapy for >6 months; CVA in past month; contraindication to warfarin/aspirin; previous AEs of warfarin/aspirin; current Rx with aspirin/warfarin; breast feeding or pregnancy; persistent bp >180/100; psychiatric diseases, including chronic alcoholism, Heart surgery with valve replacement; sinus rhythm, rheumatic heart disease.	Placebo Aspirin	VKA INR 3-4	NO	UNCLEAR	UNCLEAR	NO. In 2.8-4.2 range 42% of time

Study	Studies (n)	Population characteristics (for further details see evidence tables in Appendix D)	Intervention	Comparator	Recent stroke (<6 months)?	Renal impairment (CrCl < 50)?	Threshold stroke risk score for inclusion (CHADS2 score <2 or ≥2)	TTR ≥65%?
ENGAGE AF-TIMI 48 INVESTIGATORS TRIAL 2013[67]	1(21105)	Multinational study. Aged 21 or older; AF diagnosed with ECG within past 12 months; CHADS2 of 2 or more. Exclusion: AF due to a reversible disorder, creatine clearance <30ml/min; high risk of bleeding; use of dual antiplatelet therapy; moderate to severe mitral stenosis; other indications for anticoagulation therapy; acute coronary syndromes; coronary revascularisation; stroke in past month	Edoxaban 30mg qd Edoxaban 60mg qd	VKA INR 2-3	UNCLEAR	NO. 80% with CrCl >50	≥2	YES (68.4%)
J-ROCKET 2012[81]	1(1280)	167 settings in Japan. Japanese patients; aged >20 years; NVAF diagnosed by EMG <30 days prior to randomisation; history of prior stroke/TIA/SEE or had 2 or more of the following: CHF (or LVEF <35%), hypertension, age >75 years, DM. Exclusion: not reported.	Rivaroxaban 15mg qd	VKA INR 2-3	UNCLEAR	NO. 77.8% with CrCl >50	≥2	YES (65%)
Ke, 2019[91]	1(80)	1 setting in China. Aged >=18 yrs; NVAF; LA thrombus confirmed by TEE; oral anticoagulation untreated for at least 1 month Exclusion: Haematological disease; previous 1 year history of GI bleeding/urinary tract bleeding; previous 1 year history of stroke; known malignancy; Crcl <15 mL/min; hepatic disease associated with coagulopathy	Rivaroxaban 20mg qd	VKA INR 2-3	No	UNCLEAR	≥2	UNCLEAR
Kikuchi, 2019[92]	1(193)	1 secondary care setting in Japan; NVAF; CHDSVASC score of 1 or more (2 in women); no contraindications for OACs Exclusion: Stroke or SSE within 6 months; ACS or peripheral artery disease within 6 months before enrolment; HF; severe CRF (CrCl <30ml/min); dual antiplatelet therapy; BW 50kg or less; uncontrolled hypertension; active malignancy;	Dabigatran 150 mg bd	Rivaroxaban 15mg qd	No	UNCLEAR	UNCLEAR	NA

Study	Studies (n)	Population characteristics (for further details see evidence tables in Appendix D)	Intervention	Comparator	Recent stroke (<6 months)?	Renal impairment (CrCl < 50)?	Threshold stroke risk score for inclusion (CHADS2 score <2 or ≥2)	TTR ≥65%?
		surgery within 6 months before enrolment; collagen disease; infectious disease; scheduled for catheter ablation; contraindications to rivaroxaban or dabigatran						
MAO 2014[118]	1(353)	China (possibly a single setting). Patients with AF documented in previous 6 months or by 12 lead ECG on day of screening; at least one of the following: prior stroke/TIA, age >75, hypertension requiring meds, DM requiring treatment, LVEF <35%, documented PAD. Exclusion: AF due to reversible causes; moderate to severe mitral stenosis; conditions other than AF requiring anticoagulation; stroke within previous 7 days; need for aspirin of >165 mg/day or for both aspirin and clopidogrel; severe renal dysfunction (CrCl <30 mL/min); current alcohol or drug abuse or psychological conditions; life expectancy <1 year	Rivaroxaban 20mg qd	VKA INR 2-3	UNCLEAR	UNCLEAR	≥2	UNCLEAR
PATAF[74]	1(272)	Patients aged >60 years with electrocardiographically confirmed chronic atrial fibrillation or intermittent atrial fibrillation (electrocardiography within past two years) were eligible. Exclusion criteria were treatable causes of atrial fibrillation, previous stroke, rheumatic valvular disease, myocardial infarction or cardiovascular surgery in past year, cardiomyopathy (left ventricular ejection fraction <40%), chronic heart failure, cardiac aneurysm, history of systemic embolism, retinal infarction, coumarin use in the past three months, contraindications for aspirin or coumarin (haemoglobin concentration <7.0 mmol/l, ventricular or duodenal ulcer in the past three years, gastrointestinal or urogenital bleeding in the	Aspirin 150mg qd	VKA INR 2-3	NO	UNCLEAR	UNCLEAR	UNCLEAR

Study	Studies (n)	Population characteristics (for further details see evidence tables in Appendix D)	Intervention	Comparator	Recent stroke (<6 months)?	Renal impairment (CrCl < 50)?	Threshold stroke risk score for inclusion (CHADS2 score <2 or ≥2)	TTR ≥65%?
		past year, aspirin intolerance, coagulation disorder, and severe hepatic or renal disease), pacemaker, and a life expectancy less than two years. Exclusion criteria for standard anticoagulation were age >78, retinopathy, ventricular or duodenal ulcer, history of gastrointestinal or genitourinary bleeding, and diastolic blood pressure >105 mmHg or systolic pressure >185mmHg, or both.						
PETRO 2007[60]	1(170)	Conducted in 53 centres in Denmark, Netherlands, Sweden and USA. Documented AF plus at least one of: hypertension requiring meds, DM, symptomatic HF or LV dysfunction (LVEF <40%), previous stroke/TIA, or age >75. Exclusion: mitral stenosis; prosthetic heart valves; planned cardioversion; recent (<1 month) MI; recent stroke/TIA; coronary stent placement within 6 months; contraindications to OACs; major haemorrhage in past 6 months; severe renal impairment (eGFR < 30); abnormal liver function; risk of pregnancy; investigational drug use within 30 days; any other prohibitive medical condition	Dabigatran 150mg bid	VKA INR 2-3	UNCLEAR	UNCLEAR	UNCLEAR	NO (57.2%)
RE-LY 2009[38, 39]	2(18113)	951 clinical centres in 44 countries. AF documented on ECG performed at screening or within 6 months of starting; one of the following: prev stroke or TIA, LVEF <40%, NYHA class II or higher, age of at least 75, age of 65-74 with DM, hypertension or CAD. Exclusion: Heart valve disorders; stroke within 14 days or severe stroke within 6 months before screening; conditions increasing the risk of bleeding; CrCl <30; active liver disease; pregnancy	Dabigatran 110mg bid Dabigatran 150mg bid	VKA INR 2-3	UNCLEAR	UNCLEAR	<2	NO (64%)

Study	Studies (n)	Population characteristics (for further details see evidence tables in Appendix D)	Intervention	Comparator	Recent stroke (<6 months)?	Renal impairment (CrCl < 50)?	Threshold stroke risk score for inclusion (CHADS2 score <2 or ≥2)	TTR ≥65%?
ROCKET 2011[140]	1(14264)	1178 settings in 45 countries. NVAF as shown on ECG; at moderate or high risk for stroke as shown by a history of stroke or TIA or SEE or at least 2 of the following: HF (or LVEF <35%), hypertension, age >75, DM. No exclusion criteria reported	Rivaroxaban 20mg qd [21.1%, who had CrCl <50, were given 15mg qd]	VKA INR 2-3	UNCLEAR	NO. >75% of sample above CrCl of 52	≥2	NO (55%)
SHOSHA 2017[158]	1(60)	Conducted in a single centre in Egypt. aged 18-60; NVAF based on clinical and physical examination and ECG/echocardiography; previous CVA/TIA/SEE confirmed by CT and at least one of: hypertension, HF (LVEF <40%), DM. Exclusion: organic valvular heart disease; hepatic failure; renal failure.	Rivaroxaban 20mg qd	VKA INR 2-3	UNCLEAR	UNCLEAR	<2	NO (assuming a parametric distribution >80% were below mean INR of 1.82)
SPAF[12]	1(421)	15 centres in USA. Adults with ECG evidence of AF in past 12 months; no prosthetic heart valves or echographic evidence of mitral stenosis. Exclusion: Stroke/TIA within past 2 years; transient AF; mitral stenosis; NYHA class IV; MI in past 3 months; CABG in past year; PTCA in previous 3 months, unstable angina pectoris in past year; life expectancy < 2 years; chronic renal failure, Thrombocytopenia; prior arterial embolism requiring warfarin; alcoholism; other indications for warfarin; requirements for NSAIDS	Placebo	VKA INR 2-3	NO	UNCLEAR	UNCLEAR	UNCLEAR
SPAF II[8, 13]	1(1100)	16 clinical centres in USA. AF in previous 12 months, with no prosthetic heart valves, mitral stenosis or requirements for or contraindications to aspirin or warfarin. Exclusion: ischaemic stroke or TIA within past 2 years; <60 years old without overt cardiac disease	Aspirin 325 mg qd	VKA INR 2-3	NO	UNCLEAR	UNCLEAR	YES (75% in those at or under 75 years and 72% in those

Study	Studies (n)	Population characteristics (for further details see evidence tables in Appendix D)	Intervention	Comparator	Recent stroke (<6 months)?	Renal impairment (CrCl < 50)?	Threshold stroke risk score for inclusion (CHADS2 score <2 or ≥2)	TTR ≥65%?
								over 75 years)
WASPO 2007[147]	1(75)	Medical outpatient clinics and ECG clinics in the UK. Aged >80 and <90; permanent AF; ambulant. Exclusion: one or more fall or syncopal episode within the past 12 months; epileptiform seizures; alcoholic liver disease or excess alcohol intake; previous history of thromboembolism; gastrointestinal or genitourinary bleeding in the previous 6 months; previous IC haemorrhage; abnormal resting prothrombin time; Folstein mini mental state examination score <26; previous intolerance/allergy to warfarin or aspirin; already taking warfarin.	Aspirin 300mg qd	VKA INR 2-3	NO	UNCLEAR	UNCLEAR	YES (69.2%)
WEITZ 2010[171]	1(719)	Conducted in multiple countries. 18-85 years; persistent NVAF confirmed by ECG at screening and baseline over an interval of up to 30 days; CHADS2 of at least 2; women 2 years menopausal minimum/ bilateral oophorectomy. Exclusion: mitral valve disease; endocarditis or a mechanical valve; contraindications to OACs; need for ongoing treatment with thienopyridine; AF secondary to reversible disorders; LV aneurysm or atrial myxoma; estimated life expectancy <12 months; planned surgery or intervention within study period; history of Hep B or C or HIV; serum transaminase and/or alkaline phosphatase >1.5 times ULN; CrCl <30; cardiac pacemaker or implantable cardioverter-defibrillator; investigational treatment or device implantation during previous 3 months	Edoxaban 30mg qd Edoxaban 60mg qd	VKA INR 2-3	UNCLEAR	UNCLEAR	≥2	NO (approximately 50%)
YAMASHITA 2012[177]	1(401)	61 centres in Japan. Aged >20 years; NVAF documented by ECG at least twice within 12 months; CHADS2 >1.	Edoxaban 30mg qd	VKA INR 2-3	UNCLEAR	NO. 88-90% with CrCl over 50	<2	YES (73% for people less than

Study	Studies (n)	Population characteristics (for further details see evidence tables in Appendix D)	Intervention	Comparator	Recent stroke (<6 months)?	Renal impairment (CrCl < 50)?	Threshold stroke risk score for inclusion (CHADS2 score <2 or ≥2)	TTR ≥65%?
		Exclusion: history of IC, intraocular, intraspinal, retroperitoneal or atraumatic intra-articular bleeding; GI bleeding within past year; Hb <100g/L or platelets <100,000/microliter at screening; cerebral infarction or TIA in past month; valvular surgery; concurrent treatment with anticoagulants excluding warfarin; comorbid rheumatic valvular disease, infective endocarditis, atrial myxoma or serious heart disease; left ventricular or left atrial thrombus; renal or hepatic dysfunction; bodyweight <40kg; pregnancy of lactating.	Edoxaban 60mg qd					70 and 83% for those ≥70)

See appendix D for full evidence tables.

1.5.5 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Dabigatran 150 mg bd versus Rivaroxaban 15mg qd

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Dabigatran 150mg bd versus Rivaroxaban 15mg qd (95% CI)
Health related quality of life	0(0)		Not estimable		
Stroke and systemic embolism	117 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RD: 0.00 (-0.03 to 0.03)	Moderate	
				0 per 1000	0 more per 1000 (from 30 fewer to 30 more)
All cause mortality	0(0)		Not estimable		
Myocardial infarction	0(0)		Not estimable		
Clinically relevant non major bleeding	0(0)		Not estimable		
Minor bleeding	0(0)		Not estimable		
Major bleeding	117 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 1.48 (0.37 to 5.9)	Moderate	
				55 per 1000	26 more per 1000 (from 35 fewer to 270 more)
Intracranial bleeding	117 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RD: 0.00 (-0.03 to 0.03)	Moderate	
				0 per 1000	0 more per 1000 (from 30 fewer to 30 more)
Gastrointestinal bleeding	0(0)		Not estimable		

[a] Very serious risk of bias due to unclear allocation concealment and very serious attrition
[b] Very serious imprecision because the sample size did not reach the optimum information size
[c] very serious risk of imprecision because the 95% Cis crossed both MIDS

Table 4: Clinical evidence summary: Antiplatelets versus warfarin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Antiplatelets versus warfarin (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	10283 (8) 1 – 4.25 years	VERY LOW[a,d] due to risk of bias, indirectness	RR 1.78 (1.47 to 2.17)	Moderate	
				38 per 1000	30 more per 1000 (from 18 more to 44 more)
All cause mortality	10283 (8) 1- 4.25 years	VERY LOW[a,d] due to risk of bias, indirectness	RR 1.04 (0.91 to 1.19)	Moderate	
				69 per 1000	3 more per 1000 (from 6 fewer to 14 more)
Myocardial infarction	9768 (6) 1.25 – 3.1 years	VERY LOW[a,b,d] due to risk of bias, indirectness, imprecision	RR 1.28 (0.92 to 1.78)	Moderate	
				22 per 1000	6 more per 1000 (from 2 fewer to 17 more)
Clinically relevant non-major bleeding	0 (0)		Not estimable		
Minor bleeding	7938 (5) 1 – 4.25 years	VERY LOW[a,b,c,d] due to risk of bias, indirectness, imprecision and inconsistency	Random effects RR 0.63 (0.36 to 1.1)	Moderate	
				143 per 1000	53 fewer per 1000 (from 92 fewer to 14 more)
major bleeding	10283 (8) 1 – 4.25 years	VERY LOW[a,b,d] due to risk of bias, indirectness imprecision	RR 0.92 (0.74 to 1.13)	Moderate	
				28 per 1000	2 fewer per 1000 (from 7 fewer to 4 more)
Intracranial bleeding	1439 (2) 3.1 – 3.5 years	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.41 (0.16 to 1.04)	Moderate	
				18 per 1000	11 fewer per 1000 (from 15 fewer to 1 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Antiplatelets versus warfarin (95% CI)
GI bleeding	1999 (3) 2 – 4.25 years	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.52 (0.26 to 1.04)	Moderate	
				23 per 1000	11 fewer per 1000 (from 17 fewer to 1 more)

[a] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.

[b] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given.

[c] I2 was >75%. Sub-grouping using the 4 pre-specified strategies was attempted but none resolved heterogeneity, so random effects model was used.

[d] Downgraded for imprecision, resulting from the ACTIVE W trial using a non-warfarin VKA and combining aspirin with clopidogrel.

Table 5: Clinical evidence summary: Placebo versus warfarin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Placebo versus warfarin (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	799 (2) 1.3 – 2 years	VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	RR 1.92 (1.07 to 3.45)	Moderate	
				40 per 1000	37 more per 1000 (from 3 more to 98 more)
All cause mortality	799 (2) 1.3 – 2 years	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.99 (0.5 to 1.94)	Moderate	
				41 per 1000	0 fewer per 1000 (from 20 fewer to 39 more)
Myocardial infarction	421 (1) 1.3 years	VERY LOW[a,b] due to risk of bias, imprecision	RR 1 (0.14 to 7)	Moderate	
				10 per 1000	0 fewer per 1000 (from 9 fewer to 60 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Placebo versus warfarin (95% CI)
Clinically relevant non-major bleeding	0 (0)		Not estimable		
Minor bleeding	378 (1) 2 years	LOW[a,b] due to risk of bias, imprecision	RR 0.59 (0.34 to 1.02)	Moderate	
				160 per 1000	66 fewer per 1000 (from 106 fewer to 3 more)
major bleeding	799 (2) 1.3 – 2 years	VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	RR 0.55 (0.19 to 1.62)	Moderate	
				23 per 1000	10 fewer per 1000 (from 19 fewer to 14 more)
Intracranial bleeding	378 (1) 2 years	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.33 (0.01 to 7.96)	Moderate	
				5 per 1000	3 fewer per 1000 (from 5 fewer to 35 more)
GI bleeding	0 (0)		Not estimable		

[a] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.

[b] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given.

[c] For SSE, the CAFA trial only looked at stroke and not SE, and for major bleeding the SPAF trial used an outcome that was not strictly defined as major bleeding (but was very similar)

Table 6: Clinical evidence summary: Apixaban 2.5mg bid versus warfarin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Apixaban 2.5mg bid versus warfarin (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	146 (1) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.13 (0.02 to 0.97)	Moderate	
				54 per 1000	48 fewer per 1000 (from 53 fewer to 58 more)
All cause mortality	147 (1) 3 months	VERY LOW[a,b] due to risk of bias and imprecision	RD 0.00 (-0.03 to 0.03)	Moderate	0 fewer per 1000 (from 30 fewer to 30 more)
Myocardial infarction	146 (1) 3 months	VERY LOW[a,b] due to risk of bias and imprecision	RD 0.00 (-0.03 to 0.03)	Moderate	0 fewer per 1000 (from 30 fewer to 30 more)
				0 per 1000	
Clinically relevant non-major bleeding	147 (1) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.35 (0.04 to 3.26)	Moderate	
				40 per 1000	26 fewer per 1000 (from 38 fewer to 90 more)
Minor bleeding	147 (1) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.83 (0.35 to 1.99)	Moderate	
				133 per 1000	23 fewer per 1000 (from 86 fewer to 132 more)
major bleeding	147 (1) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0.00 to 7.10)	Moderate	
				13 per 1000	8 fewer per 1000 (from 13 fewer to 96 more)
Intracranial bleeding	0 (0)		Not estimable		
GI bleeding	0 (0)		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Apixaban 2.5mg bid versus warfarin (95% CI)

[a] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.

[b] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious)

Table 7: Clinical evidence summary: Apixaban 5mg bid versus warfarin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Apixaban 5mg bid versus warfarin (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	18347 (2) 3 months – 1.8 years	LOW[a,b] due to risk of bias, imprecision	RR 0.79 (0.66 to 0.94)	Moderate	
				41 per 1000	9 fewer per 1000 (from 2 fewer to 14 fewer)
All cause mortality	18347 (2) 3 months – 1.8 years	VERY LOW[a,b] due to risk of bias, imprecision	RD -0.01 (-0.01 to 0.00)	Moderate	
				73 per 1000	10 fewer per 1000 (from 10 fewer to 0 more)
Myocardial infarction	18347 (2) 3 months – 1.8 years	VERY LOW[a,b] due to risk of bias, imprecision	RD 0.00 (-0.00 to 0.00)	Moderate	
				11 per 1000	0 fewer per 1000 (from 0 fewer to 0 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Apixaban 5mg bid versus warfarin (95% CI)
Clinically relevant non-major bleeding	146 (1) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.35 (0.04 to 3.31)	Moderate	
				40 per 1000	26 fewer per 1000 (from 38 fewer to 92 more)
Minor bleeding	146 (1) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.8 (0.88 to 3.65)	Moderate	
				133 per 1000	106 more per 1000 (from 16 fewer to 352 more)
major bleeding	18286 (2) 3 months – 1.8 years	LOW[a,b] due to risk of bias, imprecision	RR 0.7 (0.61 to 0.81)	Moderate	
				32 per 1000	10 fewer per 1000 (from 6 fewer to 12 fewer)
Intracranial bleeding	18140 (1) 1.8 years	MODERATE[a] due to risk of bias	RR 0.42 (0.31 to 0.59)	Moderate	
				14 per 1000	8 fewer per 1000 (from 6 fewer to 10 fewer)
GI bleeding	18140 (1) 1.8 years	LOW[a,b] due to risk of bias, imprecision	RR 0.88 (0.68 to 1.14)	Moderate	
				13 per 1000	2 fewer per 1000 (from 4 fewer to 2 more)

[a] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.

[b] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious)

Table 8: Clinical evidence summary: Dabigatran 110mg bid versus warfarin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Dabigatran 110mg bid versus warfarin (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	12037 (1) 2 years	LOW[a,b] due to risk of bias, imprecision	RR 0.91 (0.74 to 1.1)	Moderate	
				34 per 1000	3 fewer per 1000 (from 9 fewer to 3 more)
All cause mortality	12037 (1) 2 years	MODERATE[a] due to risk of bias	RR 0.92 (0.81 to 1.04)	Moderate	
				81 per 1000	6 fewer per 1000 (from 15 fewer to 3 more)
Myocardial infarction	12037 (1) 2 years	LOW[a,b] due to risk of bias, imprecision	RR 1.31 (0.97 to 1.76)	Moderate	
				13 per 1000	4 more per 1000 (from 0 fewer to 10 more)
Clinically relevant non-major bleeding	0 (0)		Not estimable		
Minor bleeding	0 (0)		Not estimable		
major bleeding	12037 (1) 2 years	LOW[a,b] due to risk of bias, imprecision	RR 0.81 (0.71 to 0.93)	Moderate	
				70 per 1000	13 fewer per 1000 (from 5 fewer to 20 fewer)
Intracranial bleeding	12037 (1) 2 years	MODERATE, due to risk of bias	RR 0.31 (0.2 to 0.48)	Moderate	
				14 per 1000	10 fewer per 1000 (from 7 fewer to 11 fewer)
GI bleeding	0 (0)		Not estimable		

[a] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.

[b] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given.

Table 9: Clinical evidence summary: Dabigatran 150mg bid versus warfarin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Dabigatran 150mg bid versus warfarin (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	12268 (2) 3 months – 2 years	MODERATE[a] due to risk of bias	RD -0.01 (-0.02 to -0.01)	Moderate	
				33 per 1000	10 fewer per 1000 (from 20 fewer to 10 fewer)
All cause mortality	12098 (1) 2 years	LOW[a,b] due to risk of bias, imprecision	RR 0.89 (0.79 to 1.01)	Moderate	
				81 per 1000	9 fewer per 1000 (from 17 fewer to 1 more)
Myocardial infarction	12098 (1) 2 years	LOW[a,b] due to risk of bias, imprecision	RR 1.28 (0.95 to 1.73)	Moderate	
				13 per 1000	4 more per 1000 (from 1 fewer to 9 more)
Clinically relevant non-major bleeding	170 (1) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.57 (0.5 to 4.91)	Moderate	
				57 per 1000	33 more per 1000 (from 28 fewer to 223 more)
Minor bleeding	0 (0)		Not estimable		
major bleeding	12268 (2) 3 months- 2 years	VERY LOW[a,b] due to risk of bias, imprecision	RD -0.00 (-0.01 to 0.00)	Moderate	
				69 per 1000	10 fewer per 1000 (from 20 fewer to 0 more)
Intracranial bleeding	12098 (1) 2 years	MODERATE[a] due to risk of bias	RR 0.41 (0.28 to 0.6)	Moderate	
				14 per 1000	8 fewer per 1000 (from 6 fewer to 10 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Dabigatran 150mg bid versus warfarin (95% CI)
GI bleeding	0 (0)		Not estimable		

[a] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.

[b] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious)

Table 10: Clinical evidence summary: Rivaroxaban 20mg qd versus warfarin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Rivaroxaban 20mg qd versus warfarin (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	14664 (4) 3 months – 707 days	MODERATE[b] due to imprecision	RD: -0.01 (-0.01 to 0.00)	Moderate	
				43 per 1000	5 fewer per 1000 (from 10 fewer to 0 more)
All cause mortality	14584 (3) 3 months – 707 days	LOW[a,b] due to imprecision	RD -0.01 (-0.02 to 0.00)	Moderate	
				87 per 1000	10 fewer per 1000 (from 20 fewer to 0 more)
Myocardial infarction	14236 (1) 707 days	MODERATE[b] due to imprecision	RR 0.8 (0.62 to 1.04)	Moderate	
				18 per 1000	4 fewer per 1000 (from 7 fewer to 1 more)
Clinically relevant non-major bleeding		HIGH		Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Rivaroxaban 20mg qd versus warfarin (95% CI)
	14296 (2) 3 months – 707 days		RR 1.03 (0.96 to 1.11)	214 per 1000	6 more per 1000 (from 9 fewer to 24 more)
Minor bleeding	0 (0)		Not estimable		
major bleeding	14669 (3) 3 months – 707 days	HIGH	RD: 0.00 (-0.01 to 0.01)	Moderate	
				54 per 1000	2 more per 1000 (from 10 fewer to 10 more)
Intracranial bleeding	14649 (3) 3 months – 707 days	MODERATE[b] due to imprecision	RR 0.63 (0.45 to 0.88)	Moderate	
				17 per 1000	6 fewer per 1000 (from 2 fewer to 9 fewer)
GI bleeding	353 (1) unclear	LOW[a,b] due to risk of bias, imprecision	RR 7.95 (1.01 to 62.94)	Moderate	
				6 per 1000	42 more per 1000 (from 0 more to 372 more)

[a] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.

[b] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious)

Table 11: Clinical evidence summary: Rivaroxaban 15mg qd versus warfarin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Rivaroxaban 15mg qd versus warfarin (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	1274 (1) 900 days	LOW[a,b] due to risk of bias, imprecision	RR 0.5 (0.24 to 1.02)	Moderate	
				35 per 1000	18 fewer per 1000 (from 27 fewer to 1 more)
All cause mortality	1274 (1) 900 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.4 (0.45 to 4.39)	Moderate	
				8 per 1000	3 more per 1000 (from 4 fewer to 27 more)
Myocardial infarction	1274 (1) 900 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 3 (0.31 to 28.76)	Moderate	
				2 per 1000	4 more per 1000 (from 1 fewer to 56 more)
Clinically relevant non-major bleeding	0 (0)		Not estimable		
Minor bleeding	0 (0)		Not estimable		
major bleeding	0 (0)		Not estimable		
Intracranial bleeding	1278 (1) 900 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.5 (0.17 to 1.45)	Moderate	
				16 per 1000	8 fewer per 1000 (from 13 fewer to 7 more)
GI bleeding	1278 (1) 900 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.5 (0.19 to 1.32)	Moderate	
				19 per 1000	9 fewer per 1000 (from 15 fewer to 6 more)

[a] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.

[b] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given.

Table 12: Clinical evidence summary: Edoxaban 30mg qd versus warfarin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Edoxaban 30mg qd versus warfarin (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	14814 (3) 3 months – 2.8 years	VERY LOW[b,c] due to imprecision, inconsistency	RD 0.00 (-0.01 to 0.01)	Moderate	
				46 per 1000	0 more per 1000 (from 10 fewer to 10 more)
All cause mortality	14968 (4) 3 months – 2.8 years	HIGH	RR 0.88 (0.8 to 0.96)	Moderate	
				17 per 1000	2 fewer per 1000 (from 1 fewer to 3 fewer)
Myocardial infarction	14555 (2) 3 months – 2.8 years	MODERATE[b] due to imprecision	RR 1.21 (0.97 to 1.51)	Moderate	
				10 per 1000	2 more per 1000 (from 0 fewer to 5 more)
Clinically relevant non-major bleeding	14653 (3) 3 months – 2.8 years	HIGH	RR 0.7 (0.65 to 0.75)	Moderate	
				40 per 1000	12 fewer per 1000 (from 10 fewer to 14 fewer)
Minor bleeding	14653 (3) 3 months – 2.8 years	LOW[a,b] due to risk of bias, imprecision	RR 0.75 (0.67 to 0.83)	Moderate	
				102 per 1000	25 fewer per 1000 (from 17 fewer to 34 fewer)
major bleeding	14912 (4)	VERY LOW[c] due to risk of bias, inconsistency	RD -0.02 (-0.05 to 0.01)	Moderate	
				71 per 1000	20 fewer per 1000 (from 50 fewer to 10 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Edoxaban 30mg qd versus warfarin (95% CI)
	3 months – 2.8 years				
Intracranial bleeding	14014 (1) 2.8 years	HIGH	RR 0.31 (0.22 to 0.44)	Moderate	
				19 per 1000	13 fewer per 1000 (from 11 fewer to 15 fewer)
GI bleeding	14168 (2) 3 months – 2.8 years	MODERATE[b] due to imprecision	RR 0.68 (0.54 to 0.84)	Moderate	
				20 per 1000	6 fewer per 1000 (from 3 fewer to 9 fewer)

[a] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.

[b] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious)

[c] If I2 was 50-74% then a rating of serious inconsistency was made, and if I2 was 75% or higher a rating of very serious imprecision was made

Table 13: Clinical evidence summary: Edoxaban 60mg qd versus warfarin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Edoxaban 60mg qd versus warfarin (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	14814 (3) 3 months – 2.8 years	LOW[a] due to imprecision	RD -0.01 (-0.01 to 0.00)	Moderate	
				46 per 1000	10 fewer per 1000 (from 10 fewer to 0 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Edoxaban 60mg qd versus warfarin (95% CI)
All cause mortality	14969 (4) 3 months – 2.8 years	HIGH	RR 0.92 (0.84 to 1.01)	Moderate	
				17 per 1000	1 fewer per 1000 (from 3 fewer to 0 more)
Myocardial infarction	14555 (2) 3 months – 2.8 years	MODERATE[a] due to imprecision	RR 0.96 (0.76 to 1.21)	Moderate	
				10 per 1000	0 fewer per 1000 (from 2 fewer to 2 more)
Clinically relevant non-major bleeding	14663 (3) 3 months – 2.8 years	HIGH	RR 0.87 (0.82 to 0.94)	Moderate	
				40 per 1000	5 fewer per 1000 (from 2 fewer to 7 fewer)
Minor bleeding	14663 (3) 3 months – 2.8 years	MODERATE[a] due to imprecision	RR 0.84 (0.76 to 0.93)	Moderate	
				102 per 1000	16 fewer per 1000 (from 7 fewer to 24 fewer)
major bleeding	14918 (4) 3 months – 2.8 years	MODERATE[a] due to imprecision	RR 0.8 (0.71 to 0.9)	Moderate	
				15 per 1000	3 fewer per 1000 (from 2 fewer to 4 fewer)
Intracranial bleeding	14024 (1) 2.8 years	HIGH	RR 0.46 (0.34 to 0.62)	Moderate	
				19 per 1000	10 fewer per 1000 (from 7 fewer to 13 fewer)
GI bleeding	14179 (2) 3 months – 2.8 years	MODERATE[a] due to imprecision	RR 1.21 (1.01 to 1.47)	Moderate	
				20 per 1000	4 more per 1000 (from 0 more to 9 more)

[a] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious)

Table 14: Clinical evidence summary: Apixaban 5mg bid versus antiplatelets

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Apixaban 5mg bid versus antiplatelets (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	5599 (1) 1.1 years	HIGH	RR 0.45 (0.32 to 0.62)	Moderate	
				41 per 1000	23 fewer per 1000 (from 16 fewer to 28 fewer)
All cause mortality	5599 (1) 1.1 years	MODERATE[a] due to imprecision	RR 0.79 (0.62 to 1.01)	Moderate	
				50 per 1000	10 fewer per 1000 (from 19 fewer to 0 more)
Myocardial infarction	5599 (1) 1.1 years	LOW[a] due to imprecision	RR 0.85 (0.5 to 1.47)	Moderate	
				10 per 1000	1 fewer per 1000 (from 5 fewer to 5 more)
Clinically relevant non-major bleeding	5599 (1) 1.1 years	MODERATE[a] due to imprecision	RR 1.14 (0.85 to 1.52)	Moderate	
				30 per 1000	4 more per 1000 (from 4 fewer to 16 more)
Minor bleeding	5599 (1) 1.1 years	MODERATE[a] due to imprecision	RR 1.22 (0.99 to 1.5)	Moderate	
				55 per 1000	12 more per 1000 (from 1 fewer to 27 more)
major bleeding	5599 (1) 1.1 years	LOW[a] due to imprecision	RR 1.12 (0.73 to 1.72)	Moderate	
				14 per 1000	2 more per 1000 (from 4 fewer to 10 more)
Intracranial bleeding	5599 (1) 1.1 years	LOW[a] due to imprecision	RR 0.84 (0.38 to 1.87)	Moderate	
				5 per 1000	1 fewer per 1000 (from 3 fewer to 4 more)
GI bleeding		LOW[a]		Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Apixaban 5mg bid versus antiplatelets (95% CI)
	5599 (1) 1.1 years	due to imprecision	RR 0.85 (0.39 to 1.84)	5 per 1000	1 fewer per 1000 (from 3 fewer to 4 more)

[a] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given.

Table 15: Clinical evidence summary: Placebo versus warfarin INR 3-4

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Placebo versus warfarin INR 3-4 (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	671 (1) 2 years	LOW[a] due to risk of bias	RR 4.19 (1.6 to 10.97)	Moderate	
				15 per 1000	48 more per 1000 (from 9 more to 150 more)
All cause mortality	671 (1) 2 years	VERY LOW[a,c] due to risk of bias, indirectness	RR 4.74 (1.63 to 13.77)	Moderate	
				12 per 1000	45 more per 1000 (from 8 more to 153 more)
Myocardial infarction	0 (0)		Not estimable		
Clinically relevant non-major bleeding	0 (0)		Not estimable		
Minor bleeding	0 (0)		Not estimable		
major bleeding	0 (0)		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Placebo versus warfarin INR 3-4 (95% CI)
Intracranial bleeding	0 (0)		Not estimable		
GI bleeding	671 (1) 2 years	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.13 (0.02 to 0.95)	Moderate	
				12 per 1000	11 fewer per 1000 (from 12 fewer to 13 more)

[a] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.

[b] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given.

[c] Mortality, but not all-cause mortality

Table 16: Clinical evidence summary: Antiplatelets versus warfarin INR 3-4

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Antiplatelets versus warfarin INR 3-4 (95% CI)
Health related quality of life	0 (0)		Not estimable		
All stroke and systemic thromboembolism	671 (1) 2 years	LOW[a] due to risk of bias	RR 3.99 (1.51 to 10.5)	Moderate	
				15 per 1000	45 more per 1000 (from 8 more to 142 more)
All cause mortality	671 (1) 2 years	VERY LOW[a,c] due to risk of bias, indirectness	RR 3.74 (1.25 to 11.15)	Moderate	
				12 per 1000	33 more per 1000 (from 3 more to 122 more)
Myocardial infarction	0 (0)		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Antiplatelets versus warfarin INR 3-4 (95% CI)
Clinically relevant non-major bleeding	0 (0)		Not estimable		
Minor bleeding	0 (0)		Not estimable		
major bleeding	0 (0)		Not estimable		
Intracranial bleeding	0 (0)		Not estimable		
GI bleeding	671 (1) 2 years	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.25 (0.03 to 2.22)	Moderate	
				12 per 1000	9 fewer per 1000 (from 12 fewer to 15 more)

[a] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.

[b] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious)

[c] Mortality, but not all-cause mortality

See appendix F for full GRADE tables.

1.5.6 Network meta-analysis study

Background

The detailed reasons for the post-hoc inclusion of the network meta-analysis (NMA) by Lopez-Lopez, 2017[113, 160] are explained in the 'discussion of evidence' section. In brief, the intention had been to use the pairwise meta-analyses from this review to inform the development of a new NMA, but after committee discussion it was decided to make use of the NMA findings from Lopez-Lopez, 2017[113, 160] on the grounds that our pairwise analyses showed relatively little new data had emerged since the publication of Lopez-Lopez, 2017[113, 160] and that Lopez-Lopez, 2017[113, 160] was a high quality analysis of the important data.

Methodology

The NMA[160] included RCTs evaluating the use of DOACs, VKAs or antiplatelets for the prevention of stroke in people with NVAF.

Inclusion criteria

Randomised controlled trials including people with NVAF, and comparing outcomes between apixaban, betrixaban, edoxaban, rivaroxaban, dabigatran, warfarin with a therapeutic INR range, aspirin and/or clopidogrel were included.

Exclusion criteria

Trials investigating eribaxaban (stage of development unclear), otamixaban (administered parenterally), darexaban (discontinued), LY517717 and letaxaban (no information on any further clinical development), ximelagatran (withdrawn), AZD0837 (discontinued) were excluded. Other exclusions were:

- trials comparing different doses of the same drug,
- trials reporting only follow-up data <3 months,
- studies with patients without thrombogenic characteristics,
- studies with a fixed dose of warfarin, or where warfarin was given with a sub-optimal target INR compared with UK guidelines (<2 or significantly outside the range of INR 2-3)
- trials in people only eligible for parenteral anticoagulation.

This NMA included 23 trials, based on a systematic search of the literature. From an initial search tally of 1852 papers, 201 were inspected as full-text papers, from which 41 articles (23 trials) were included.

The trials included in the NMA[114, 160] are shown in the table below, together with relevant population characteristics and treatment parameters. Four of these - one unpublished paper and 3 published papers[36, 83, 111] - had not been included in our pairwise systematic review because they contravened our protocol. AF-DABIG-VKA-JAPAN was not included in our pairwise analysis because it was unpublished, and Chinese ATAFS[83] was not included because it was not written in English. AF-ASA-VKA-CHINA[111] was not included because it involved INR doses extending below 2.0, although it should be noted that this paper was not included in the main analysis of Lopez-Lopez, 2017[114, 160]. Finally, Explore Xa[36] was not included in our pairwise review because it included Betrixaban. Furthermore, there were 5 studies[12, 30, 40, 118, 158] present in our pairwise analysis that were not present in the existing NMA[114, 160]. SPAF I[12] contained some eligible data but was not detected by Lopez-Lopez[114, 160], Shosha[158] was published after the NMA, Mao[118] was not included because the data were regarded as suspect (information derived from personal communication), and Chen[30] and

CAFA[40] were not included as they only included people with paroxysmal AF (information derived from personal communication). Despite these discrepancies the committee felt that the existing NMA[114, 160] would provide more valid conclusions than an NMA derived from our pairwise comparisons: the additional papers in the existing NMA[114, 160] were regarded as important for decision-making, whilst its missing papers were regarded as less important as they were mostly small studies that would lend little weight to an NMA.

Table 17: Table of included studies

Studies included in Lopez-Lopez[114]	Intervention and comparator(s) [interventions used that were not included in NMA are not included here]	Treatment duration	Country and number randomised	Mean TTR during treatment
ACTIVE W[1]	Clopidogrel 75mg + aspirin 75-100mg) od v VKA INR 2-3	Not reported	Multinationals, 6706	63.8%
AFASAK[141]	Aspirin 75mg od v VKA INR 2-3 v placebo od	24 months	Denmark, 1007	73%
AFASAK II[71]	Aspirin 300mg od v VKA INR 2-3	42 months	Denmark, 677	73%
AF-ASA-VKA-CHINA[111]	Aspirin 100mg od v VKA INR 1.6-2.5	24 months	China, 110	Not reported
AF-DABIG-VKA-JAPAN (unpublished)	Dabigatran 110mg bd v 150mg bd v VKA INR 2-3	3 months	Japan, 174	Not reported
AF-EDOX-VKA-ASIA[33]	Edoxaban 30mg od v 60mg od v VKA INR 2-3	3 months	Multinational, 235	45.1%
AF-EDOX-VKA-JAPAN[177]	Edoxaban 30 mg od v 45 mg od v 60 mg od v VKA INR 2-3 (INR 1.6-2.6 in >70 yrs)	3 months	Japan, 536	83% (≥70 yrs) 73% (<70 yrs)
AF-EDOX-VKA-MULTI[171]	Edoxaban 30mg od v 60mg od v 30mg bd v 60mg bd VKA INR 2-3	3 months	Multinational, 1146	49.7%
AF-VKA-ASA-CHINA[29]	Aspirin 200mg od v VKA INR 2.1-2.5	15 months	China, 690	Not reported
ARISTOTLE[69]	Apixaban 5mg bd (2.5mg bd in small subset) v VKA INR 2-3	21.6 months	Multinational, 18,201	62.2%
ARISTOTLE J[137]	Apixaban 2.5mg bd v 5mg bd v VKA INR 2-3	3 months	Japan, 222	60%
AVERROES[37]	Apixaban 5mg bd (2.5 mg bd in small subset) v aspirin 81-324 mg od	13.1 months	Multinational, 5599	NA

Studies included in Lopez-Lopez[114]	Intervention and comparator(s) [interventions used that were not included in NMA are not included here]	Treatment duration	Country and number randomised	Mean TTR during treatment
BAFTA[116]	Aspirin 75mg od v VKA INR 2-3	32.4 months	UK, 973	67%
Chinese ATAFS[83]	Aspirin 150-160 mg od v VKA INR 2-3 (INR 1.6-2.5 in >75yrs)	Not reported	China, 704	Not reported
ENGAGE AF-TIMI 48[67]	Edoxaban 30mg od v 60 mg od (half dose in subset) v VKA INR 2-3	29.8 months	Multinational, 21,105	64.9%
EXPLORE-Xa[36]	Betrixaban 40mg od v 60mg od v 80mg od v VKA INR 2-3	4.9 months	Multinational, 508	63.4%
J ROCKET[81]	Rivaroxaban 25 mg od (10 mg in subset) v VKA INR 2-3 (INR 1.6 – 2.6 age >70 yrs)	30 months	Japan, 1280	65%
PATAF[74]	Aspirin 150 mg od v VKA INR 2.5-3.5	32.4 months	Netherlands, 729	Not reported
PETRO[60]	Dabigatran 50mg bd v 150 mg bd v 300mg bd v VKA INR 2-3	3 months	Multinational, 502	57.2%
RE-LY[38]	Dabigatran 110mg bd v 150mg bd v VKA INR 2-3	24 months	Multinational, 18,113	64%
ROCKET[140]	Rivaroxaban 20mg (15 mg in subset) v VKA INR 2-3	19.4 months	Multinational, 14,264	55%
SPAF II[13]	Aspirin 325 mg od v VKA INR 2- 2.5	37.2 months	USA, 1100	Not reported
WASPO[147]	Aspirin 300mg od v VKA INR 2-3	12 months	UK, 75	69.2%

Outcomes

NMA outcomes included stroke or systemic embolism, ischaemic stroke, myocardial infarction, all-cause mortality, major bleeding, intracranial bleeding, gastrointestinal bleeding, and clinically relevant bleeding. These were chosen for the NMA because of their clinical importance and the consistency of reporting across studies.

Risk of bias in included studies

Risk of bias for each of the 23 trials was reported for the domains of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcomes, incomplete outcome data and elective reporting using the Cochrane assessment tool. The judgements of bias were broadly similar to those in our pairwise comparisons review, although greater leniency was given where methodology was unclear.

Data synthesis

Network plots of comparisons of direct comparison were generated. Different doses of DOACs were analysed as separate nodes in the NMA. There were two independent nodes for warfarin interventions (INR 2.0-3.0 and INR 3.0-4.0). The former was the reference treatment in the NMA. Within the category of INR 2-3 were included some trials with an INR range of 2.5-3.5 or 2.0-4.5. Two separate nodes for antiplatelets were used (<150 mg once daily and 150 mg or more once daily). Longest available follow up was used.

In the primary network meta-analyses, data were treated as binomial, modelling the number of events out of the total number of participants using a logistic model. Trials with no events in any arm were omitted and where there were events in at least one arm of a trial but no events in one or more other arms, 0.5 events to all cells in the 2×2 table were added. The network meta-analyses used a fixed effect logistic regression approach, implemented in a Bayesian framework using WinBUGS software (version 1.4.3). Inconsistency in the network loops was investigated, where possible, using a Bucher-type approach.

A meta-regression was also carried out, with the pre-specified important characteristics being age, sex, ethnicity or race, body mass index or weight, renal status or creatinine clearance, blood pressure, diabetes mellitus, hypertension, previous thrombotic event, liver disease, chronic heart failure, cancer, pregnancy, intervention dose, mean time in warfarin therapeutic range, CHADS2 score, CHA2DS2-VASc score, HAS-BLED score, history of previous stroke or transient ischaemic attack, previous myocardial infarction, and summary assessment of the risk of bias for each outcome. Meta-regression determined the influence of these potential effect modifiers.

Results

Network plots

Network plots were generated for the 8 main outcomes, as follows (figures reproduced from Lopez-Lopez, 2017)[114].

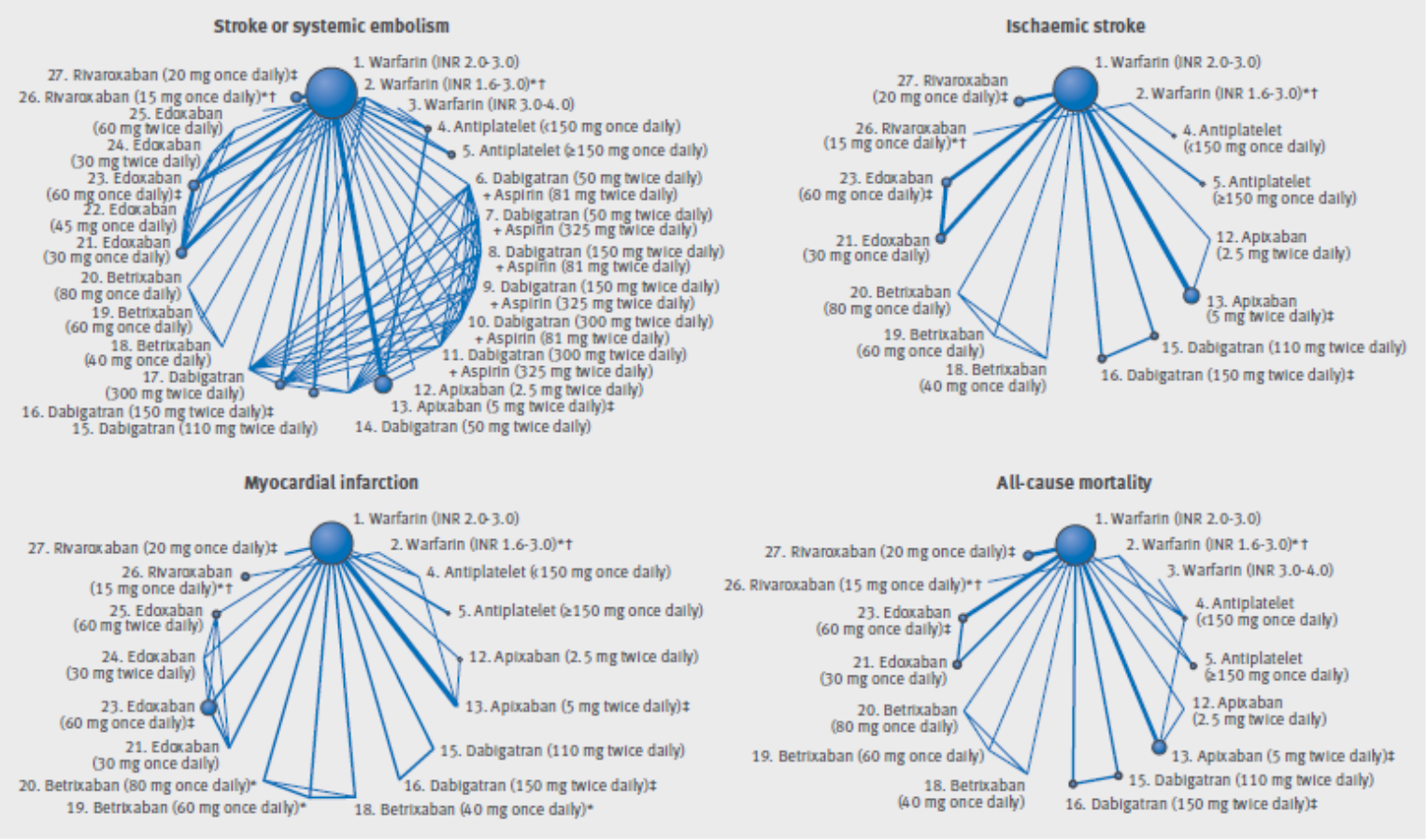


Fig 2 | Network plots of stroke or systemic embolism, ischaemic stroke, myocardial infarction, and all-cause mortality outcomes for review of prevention of stroke in patients with atrial fibrillation. Line thickness is proportional to the number of patients that contributed to the comparison
***Doses of direct acting oral anticoagulants (DOACs) that were excluded from the primary analysis owing to not being considered to be of interest to inform health decisions in the UK (eg, warfarin interventions using subtherapeutic INR ranges), the total number of events was zero so they are uninformative, or they did not connect with the other trials in the network.**
†Excluded doses of DOACs that were included in sensitivity analyses.
‡Recommended doses of DOACs evaluated in a phase III trial; these are interventions of primary interest

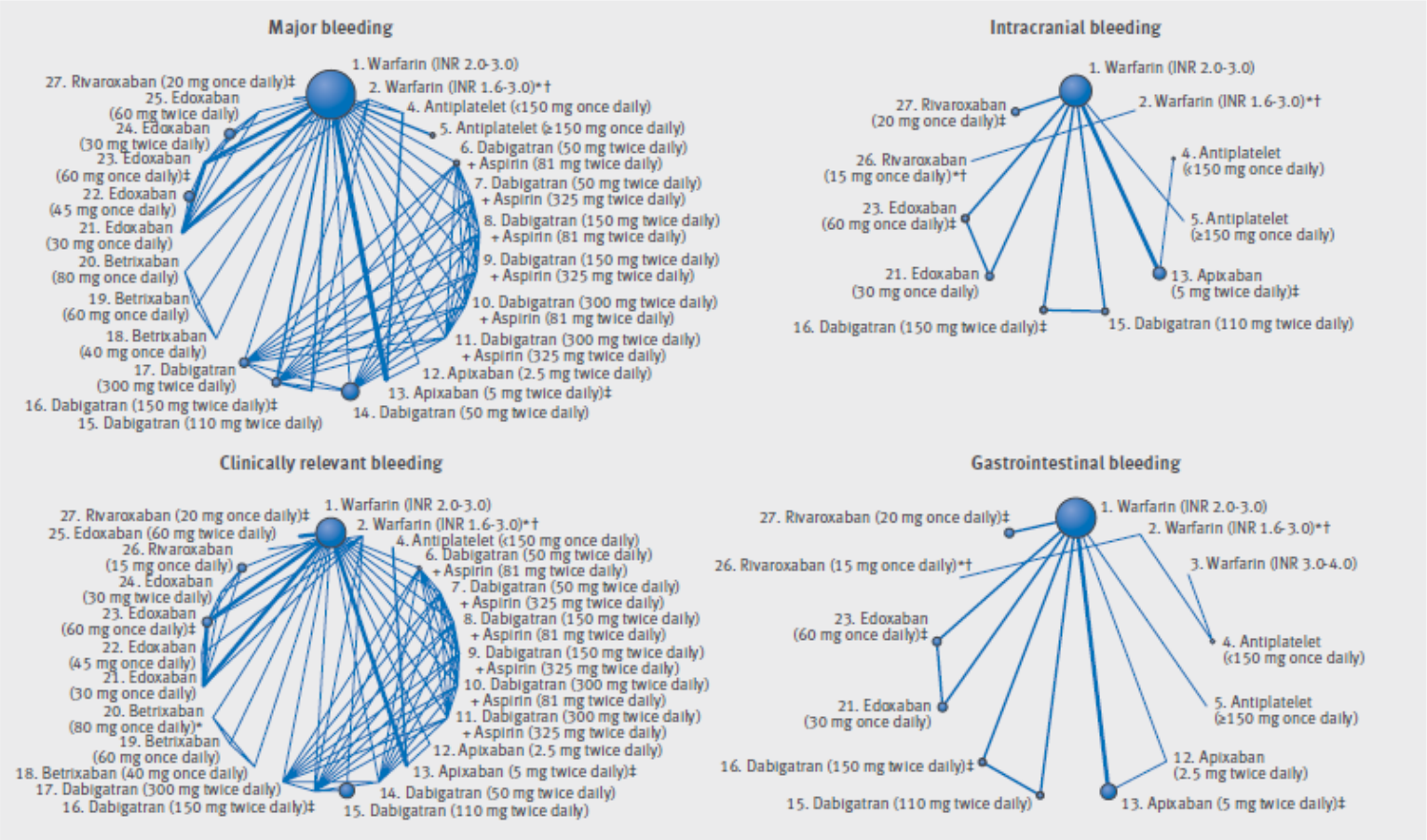


Fig 3 | Network plots of bleeding outcomes for review of prevention of stroke in patients with atrial fibrillation. Line thickness is proportional to the number of patients that contributed to the comparison

***Doses of direct acting oral anticoagulants (DOACs) that were excluded from the primary analysis owing to not being considered to be of interest to inform health decisions in the UK (eg, warfarin interventions using subtherapeutic INR ranges), the total number of events was zero so they are uninformative, or they did not connect with the other trials in the network.**

†Excluded doses of DOACs that were included in sensitivity analyses.

‡Recommended doses of DOACs evaluated in a phase III trial; these are interventions of primary interest

Efficacy and safety results

The following tables show the direct and indirect estimates of effect, and the overall NMA results, for efficacy and safety outcomes. Posterior median ORs and 95% credible intervals from Bayesian fixed-effects analyses are shown in the tables below (CI = credible interval). For the comparisons with warfarin, the lack of indirect evidence to combine with (and thus strengthen) the direct evidence is a result of the lack of closed loops that do not comprise 3 arm trials (loops formed by 3 arm trials cannot be used to create informative indirect evidence because, by definition, they will always produce indirect evidence that is identical to the direct evidence). The lack of closed loops is because the different agents have rarely been compared directly to each other (except in the AVERROES trial). Hence for the between-DOAC comparisons only indirect evidence is available. Imprecisely estimated results (with a ratio between interval limits of >9) are presented separately in Sterne, 2017[160] but for brevity are not presented here.

Table 18: Stroke or SE

Comparison with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	NMA OR (95% CI)
Antiplatelet (<150mg od)	1.99 (1.28 to 3.15)	1.80 (1.22 to 2.65)	1.88 (1.40 to 2.51)
Antiplatelet (>150 mg od)	1.61 (1.25 to 2.07)	-	1.61 (1.25 to 2.07)
Apixaban (5mg bd)	0.79 (0.66 to 0.94)	-	0.79 (0.66 to 0.94)
Dabigatran (110mg bd)	0.90 (0.74 to 1.10)	-	0.90 (0.74 to 1.10)
Dabigatran (150mg bd)	0.65 (0.52 to 0.81)	-	0.65 (0.52 to 0.81)
Edoxaban (30mg od)	1.13 (0.97 to 1.32)	-	1.13 (0.97 to 1.32)
Edoxaban (60 mg od)	0.86 (0.74 to 1.01)	-	0.86 (0.74 to 1.01)
Rivaroxaban (20mg od)	0.88 (0.74 to 1.03)	-	0.88 (0.74 to 1.03)
DOAC comparisons	**Direct evidence OR (95% CI)**	**Indirect evidence OR (95% CI)**	**NMA OR (95% CI)**
Dabigatran (150 mg bd) vs. apixaban (5 mg bd)	-	0.82 (0.62 to 1.08)	0.82 (0.62 to 1.08)
Edoxaban (60 mg od) vs. apixaban (5 mg bd)	-	1.09 (0.87 to 1.39)	1.09 (0.87 to 1.39)
Rivaroxaban (20mg od) vs. apixaban (5 mg bd)	-	1.11 (0.87 to 1.41)	1.11 (0.87 to 1.41)
Edoxaban (60 mg od) vs. dabigatran (150 mg bd)	-	1.33 (1.02 to 1.75)	1.33 (1.02 to 1.75)
Rivaroxaban (20 mg od) vs. dabigatran (150 mg bd)	-	1.35 (1.03 to 1.78)	1.35 (1.03 to 1.78)
Rivaroxaban (20 mg od) vs. edoxaban (60 mg od)	-	1.01 (0.80 to 1.27)	1.01 (0.80 to 1.27)

Table 19: Ischaemic stroke

Comparison with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	NMA OR (95% CI)
Antiplatelet (<150mg od)	-	2.52 (1.62 to 3.99)	2.52 (1.62 to 3.99)
Antiplatelet (>150 mg od)	2.00 (1.51 to 2.67)	-	2.00 (1.51 to 2.67)
Apixaban (5mg bd)	0.92 (0.74 to 1.14)	-	0.92 (0.74 to 1.14)
Dabigatran (110mg bd)	1.14 (0.90 to 1.44)	-	1.14 (0.90 to 1.44)
Dabigatran (150mg bd)	0.76 (0.58 to 0.98)	-	0.76 (0.58 to 0.98)
Edoxaban (30mg od)	1.44 (1.21 to 1.71)	-	1.44 (1.21 to 1.71)
Edoxaban (60 mg od)	1.01 (0.84 to 1.21)	-	1.01 (0.84 to 1.21)
Rivaroxaban (20mg od)	0.93 (0.74 to 1.16)	-	0.93 (0.74 to 1.16)
DOAC comparisons	**Direct evidence OR (95% CI)**	**Indirect evidence OR (95% CI)**	**NMA OR (95% CI)**
Dabigatran (150 mg bd) vs. apixaban (5 mg bd)	-	0.83 (0.59 to 1.16)	0.83 (0.59 to 1.16)
Edoxaban (60 mg od) vs. apixaban (5 mg bd)	-	1.10 (0.83 to 1.46)	1.10 (0.83 to 1.46)
Rivaroxaban (20 mg od) vs. apixaban (5 mg bd)	-	1.01 (0.74 to 1.38)	1.01 (0.74 to 1.38)
Edoxaban (60 mg od) vs. dabigatran (150 mg bd)	-	1.33 (0.97 to 1.83)	1.33 (0.97 to 1.83)
Rivaroxaban (20 mg od) vs. dabigatran (150 mg bd)	-	1.22 (0.87 to 1.73)	1.22 (0.87 to 1.73)
Rivaroxaban (20 mg od) vs. edoxaban (60 mg od)	-	0.92 (0.69 to 1.23)	0.92 (0.69 to 1.23)

Table 20: Myocardial Infarction

Comparison with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	NMA OR (95% CI)
Antiplatelet (<150mg od)	1.00 (0.47 to 2.10)	2.52 (1.62 to 3.99)	1.01 (0.64 to 1.61)
Antiplatelet (>150 mg od)	1.38 (0.94 to 2.03)	-	1.38 (0.94 to 2.03)
Apixaban (5mg bd)	0.87 (0.66 to 1.15)	-	0.87 (0.66 to 1.15)
Dabigatran (110mg bd)	1.32 (0.97 to 1.79)	-	1.32 (0.97 to 1.79)
Dabigatran (150mg bd)	1.29 (0.96 to 1.75)	-	1.29 (0.96 to 1.75)
Edoxaban (30mg od)	1.22 (0.97 to 1.53)	-	1.22 (0.97 to 1.53)
Edoxaban (60 mg od)	0.96 (0.75 to 1.22)	-	0.96 (0.75 to 1.22)
Rivaroxaban (20mg od)	0.80 (0.61 to 1.04)	-	0.80 (0.61 to 1.04)
DOAC comparisons	**Direct evidence OR (95% CI)**	**Indirect evidence OR (95% CI)**	**NMA OR (95% CI)**
Dabigatran (150 mg bd) vs. apixaban (5 mg bd)	-	1.48 (0.98 to 2.22)	1.48 (0.98 to 2.22)
Edoxaban (60 mg od) vs. apixaban (5 mg bd)	-	1.10 (0.76 to 1.58)	1.10 (0.76 to 1.58)
Rivaroxaban (20 mg od) vs. apixaban (5 mg bd)	-	0.92 (0.63 to 1.34)	0.92 (0.63 to 1.34)
Edoxaban (60 mg od) vs. dabigatran (150 mg bd)	-	0.74 (0.50 to 1.09)	0.74 (0.50 to 1.09)
Rivaroxaban (20 mg od) vs. dabigatran (150 mg bd)	-	0.62 (0.41 to 0.93)	0.62 (0.41 to 0.93)
Rivaroxaban (20 mg od) vs. edoxaban (60 mg od)	-	0.84 (0.59 to 1.20)	0.84 (0.59 to 1.20)

Table 21: All cause mortality

Comparison with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	NMA OR (95% CI)
Antiplatelet (<150mg od)	1.02 (0.75 to 1.38)	1.13 (0.87 to 1.47)	1.08 (0.88 to 1.33)
Antiplatelet (>150 mg od)	1.04 (0.87 to 1.25)	-	1.04 (0.87 to 1.25)
Apixaban (5mg bd)	0.88 (0.79 to 0.98)	-	0.88 (0.79 to 0.98)
Dabigatran (110mg bd)	0.91 (0.80 to 1.04)	-	0.91 (0.80 to 1.04)
Dabigatran (150mg bd)	0.88 (0.77 to 1.01)	-	0.88 (0.77 to 1.01)
Edoxaban (30mg od)	0.86 (0.78 to 0.96)	-	0.86 (0.78 to 0.96)
Edoxaban (60 mg od)	0.91 (0.82 to 1.01)	-	0.91 (0.82 to 1.01)
Rivaroxaban (20mg od)	0.83 (0.69 to 1.00)	-	0.83 (0.69 to 1.00)
DOAC comparisons	**Direct evidence OR (95% CI)**	**Indirect evidence OR (95% CI)**	**NMA OR (95% CI)**
Dabigatran (150 mg bd) vs. apixaban (5 mg bd)	-	1.00 (0.84 to 1.19)	1.00 (0.84 to 1.19)
Edoxaban (60 mg od) vs. apixaban (5 mg bd)	-	1.03 (0.89 to 1.20)	1.03 (0.89 to 1.20)
Rivaroxaban (20 mg od) vs. apixaban (5 mg bd)	-	0.94 (0.76 to 1.17)	0.94 (0.76 to 1.17)
Edoxaban (60 mg od) vs. dabigatran (150 mg bd)	-	1.03 (0.87 to 1.22)	1.03 (0.87 to 1.22)
Rivaroxaban (20 mg od) vs. dabigatran (150 mg bd)	-	0.94 (0.74 to 1.18)	0.94 (0.74 to 1.18)
Rivaroxaban (20 mg od) vs. edoxaban (60 mg od)	-	0.91 (0.73 to 1.13)	0.91 (0.73 to 1.13)

Table 22: Major bleeding

Comparison with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	NMA OR (95% CI)
Antiplatelet (<150mg od)	1.00 (0.56 to 1.77)	0.63 (0.40 to 0.98)	0.75 (0.52 to 1.06)
Antiplatelet (>150 mg od)	1.07 (0.82 to 1.42)	-	1.07 (0.82 to 1.42)
Apixaban (5mg bd)	0.71 (0.61 to 0.81)	-	0.71 (0.61 to 0.81)
Dabigatran (110mg bd)	0.80 (0.69 to 0.93)	-	0.80 (0.69 to 0.93)
Dabigatran (150mg bd)	0.94 (0.81 to 1.08)	-	0.94 (0.81 to 1.08)
Edoxaban (30mg od)	0.46 (0.40 to 0.54)	-	0.46 (0.40 to 0.54)
Edoxaban (60 mg od)	0.78 (0.69 to 0.90)	-	0.78 (0.69 to 0.90)
Rivaroxaban (20mg od)	1.03 (0.89 to 1.18)	-	1.03 (0.89 to 1.18)
DOAC comparisons	**Direct evidence OR (95% CI)**	**Indirect evidence OR (95% CI)**	**NMA OR (95% CI)**
Dabigatran (150 mg bd) vs. apixaban (5 mg bd)	-	1.33 (1.09 to 1.62)	1.33 (1.09 to 1.62)
Edoxaban (60 mg od) vs. apixaban (5 mg bd)	-	1.11 (0.92 to 1.35)	1.11 (0.92 to 1.35)
Rivaroxaban (20 mg od) vs. apixaban (5 mg bd)	-	1.45 (1.19 to 1.78)	1.45 (1.19 to 1.78)
Edoxaban (60 mg od) vs. dabigatran (150 mg bd)	-	0.84 (0.69 to 1.02)	0.84 (0.69 to 1.02)
Rivaroxaban (20 mg od) vs. dabigatran (150 mg bd)	-	1.10 (0.90 to 1.34)	1.10 (0.90 to 1.34)
Rivaroxaban (20 mg od) vs. edoxaban (60 mg od)	-	1.31 (1.07 to 1.59)	1.31 (1.07 to 1.59)

Table 23: Clinically relevant bleeding

Comparison with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	NMA OR (95% CI)
Antiplatelet (<150mg od)	-	0.59 (0.45 to 0.77)	0.59 (0.45 to 0.77)
Apixaban (5mg bd)	0.67 (0.60 to 0.75)	-	0.67 (0.60 to 0.75)
Edoxaban (30mg od)	0.59 (0.54 to 0.64)	-	0.59 (0.54 to 0.64)
Edoxaban (45mg od)	1.09 (0.37 to 3.04)	-	1.09 (0.37 to 3.04)
Edoxaban (60mg od)	0.84 (0.77 to 0.90)	-	0.84 (0.77 to 0.90)
Edoxaban (30mg bd)	1.97 (1.04 to 3.67)	-	1.97 (1.04 to 3.67)
Edoxaban (60 mg bd)	2.76 (1.46 to 5.17)	-	2.76 (1.46 to 5.17)
Rivaroxaban (20mg od)	1.03 (0.95 to 1.11)	-	1.03 (0.95 to 1.11)
DOAC comparisons	**Direct evidence OR (95% CI)**	**Indirect evidence OR (95% CI)**	**NMA OR (95% CI)**
Edoxaban (60 mg od) vs. apixaban (5 mg bd)	-	1.24 (1.09 to 1.42)	1.24 (1.09 to 1.42)
Rivaroxaban (20 mg od) vs. apixaban (5 mg bd)	-	1.53 (1.33 to 1.75)	1.53 (1.33 to 1.75)
Rivaroxaban (20 mg od) vs. edoxaban (60 mg od)	-	1.23 (1.10 to 1.37)	1.23 (1.10 to 1.37)

Table 24: Intracranial bleeding

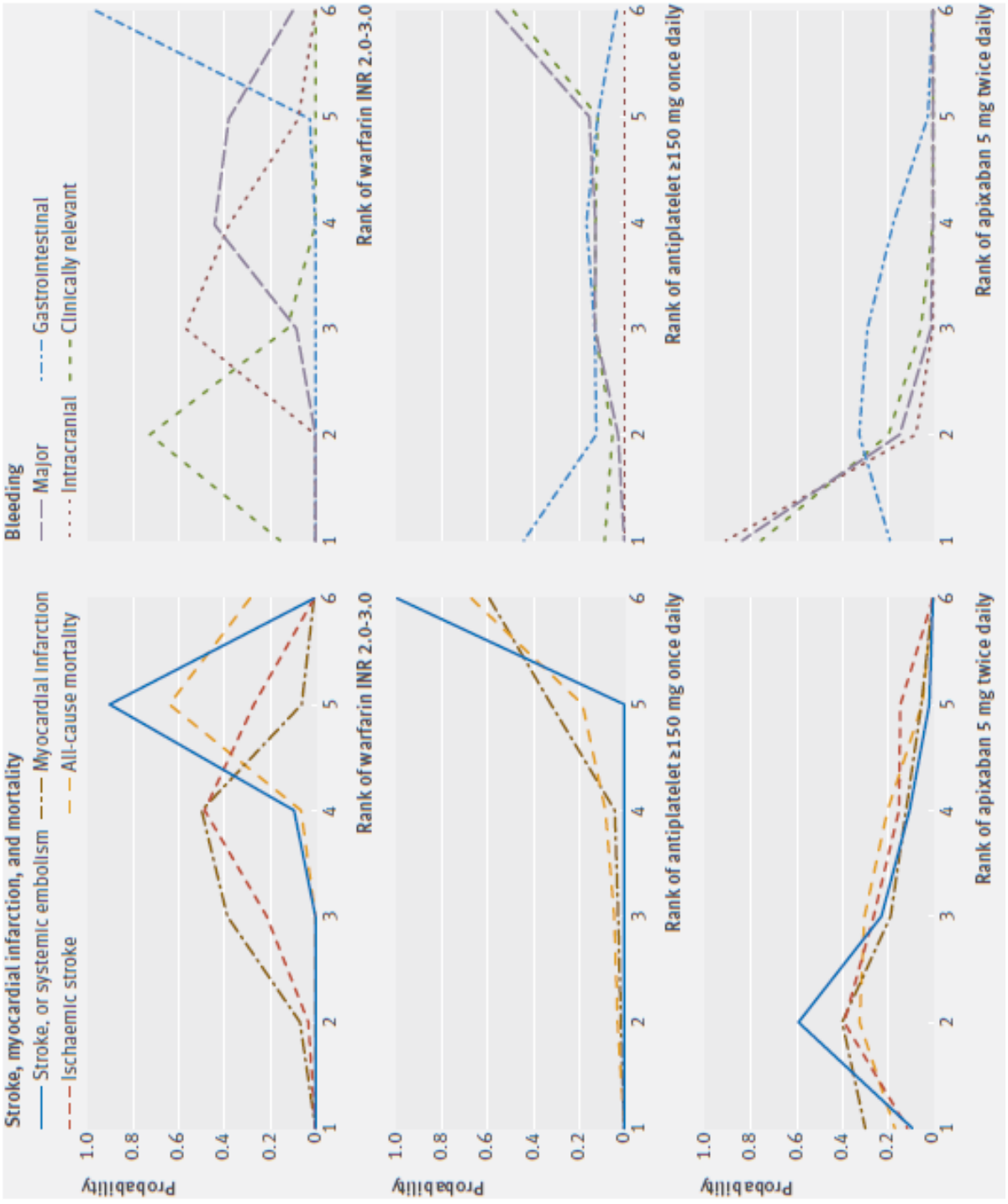
Comparison with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	NMA OR (95% CI)
Antiplatelet (<150mg od)	-	0.50 (0.21 to 1.23)	0.50 (0.21 to 1.23)
Antiplatelet (>150 mg od)	0.39 (0.13 to 0.98)	-	0.39 (0.13 to 0.98)
Apixaban (5mg bd)	0.42 (0.30 to 0.58)	-	0.42 (0.30 to 0.58)
Dabigatran (110mg bd)	0.31 (0.19 to 0.47)	-	0.31 (0.19 to 0.47)
Dabigatran (150mg bd)	0.40 (0.27 to 0.59)	-	0.40 (0.27 to 0.59)
Edoxaban (30mg od)	0.31 (0.21 to 0.43)	-	0.31 (0.21 to 0.43)
Edoxaban (60 mg od)	0.46 (0.33 to 0.62)	-	0.46 (0.33 to 0.62)
Rivaroxaban (20mg od)	0.65 (0.46 to 0.91)	-	0.65 (0.46 to 0.91)
DOAC comparisons	**Direct evidence OR (95% CI)**	**Indirect evidence OR (95% CI)**	**NMA OR (95% CI)**
Dabigatran (150 mg bd) vs. apixaban (5 mg bd)	-	0.96 (0.58 to 1.60)	0.96 (0.58 to 1.60)
Edoxaban (60 mg od) vs. apixaban (5 mg bd)	-	1.09 (0.69 to 1.70)	1.09 (0.69 to 1.70)
Rivaroxaban (20 mg od) vs. apixaban (5 mg bd)	-	1.55 (0.97 to 2.49)	1.55 (0.97 to 2.49)
Edoxaban (60 mg od) vs. dabigatran (150 mg bd)	-	1.13 (0.69 to 1.87)	1.13 (0.69 to 1.87)
Rivaroxaban (20 mg od) vs. dabigatran (150 mg bd)	-	1.61 (0.96 to 2.72)	1.61 (0.96 to 2.72)
Rivaroxaban (20 mg od) vs. edoxaban (60 mg od)	-	1.43 (0.90 to 2.26)	1.43 (0.90 to 2.26)

Table 25: GI bleeding

Comparison with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	NMA OR (95% CI)
Antiplatelet (<150mg od)	-	1.03 (0.46 to 2.35)	1.03 (0.46 to 2.35)
Antiplatelet (>150 mg od)	1.60 (0.70 to 3.85)	-	1.60 (0.70 to 3.85)
Apixaban (5mg bd)	0.89 (0.68 to 1.15)	-	0.89 (0.68 to 1.15)
Dabigatran (110mg bd)	1.11 (0.87 to 1.42)	-	1.11 (0.87 to 1.42)
Dabigatran (150mg bd)	1.52 (1.20 to 1.91)	-	1.52 (1.20 to 1.91)
Edoxaban (30mg od)	0.67 (0.53 to 0.84)	-	0.67 (0.53 to 0.84)
Edoxaban (60 mg od)	1.22 (1.01 to 1.49)	-	1.22 (1.01 to 1.49)
Rivaroxaban (20mg od)	1.47 (1.20 to 1.81)	-	1.47 (1.20 to 1.81)
DOAC comparisons	**Direct evidence OR (95% CI)**	**Indirect evidence OR (95% CI)**	**NMA OR (95% CI)**
Dabigatran (150 mg bd) vs. apixaban (5 mg bd)	-	1.71 (1.21 to 2.43)	1.71 (1.21 to 2.43)
Edoxaban (60 mg od) vs. apixaban (5 mg bd)	-	1.38(1.00 to 1.92)	1.38(1.00 to 1.92)
Rivaroxaban (20 mg od) vs. apixaban (5 mg bd)	-	1.66 (1.19 to 2.33)	1.66 (1.19 to 2.33)
Edoxaban (60 mg od) vs. dabigatran (150 mg bd)	-	0.81 (0.60 to 1.09	0.81 (0.60 to 1.09
Rivaroxaban (20 mg od) vs. dabigatran (150 mg bd)	-	0.97 (0.71 to 1.33)	0.97 (0.71 to 1.33)
Rivaroxaban (20 mg od) vs. edoxaban (60 mg od)	-	1.21 (0.90 to 1.60)	1.21 (0.90 to 1.60)

Rankograms

The figures below, reproduced from Lopez-Lopez, 2017[114], show that rivaroxaban was likely to be the best DOAC for minimising MI and all-cause mortality, at a probability of around 60% for each outcome. In addition, apixaban was likely to be the best DOAC for minimising major bleeding, intracranial bleeding and clinically relevant bleeding, at a probability of around 80% for each. Meanwhile, dabigatran was most likely to be the best DOAC for minimising Stroke or Systemic embolism, and Ischaemic Stroke, again at a probability of about 80% for each. Edoxaban was not ranked as the best treatment for any outcome, but emerged as the second best for reducing major bleeding and intracranial bleeding. The non-DOAC interventions (warfarin dosed to achieve an INR 2.0-3.0 and antiplatelet ≥150 mg once daily) had the lowest rankings for stroke or systemic embolism.


Stroke, myocardial infarction, and mortality
Stroke, or systemic embolism
Myocardial infarction
Ischaemic stroke
All-cause mortality
Bleeding
Major
GastroIntestinal
Intracranial
Clinically relevant
Probability
Rank of warfarin INR 2.0-3.0
Rank of antiplatelet ≥150 mg once daily
Rank of apixaban 5 mg twice daily

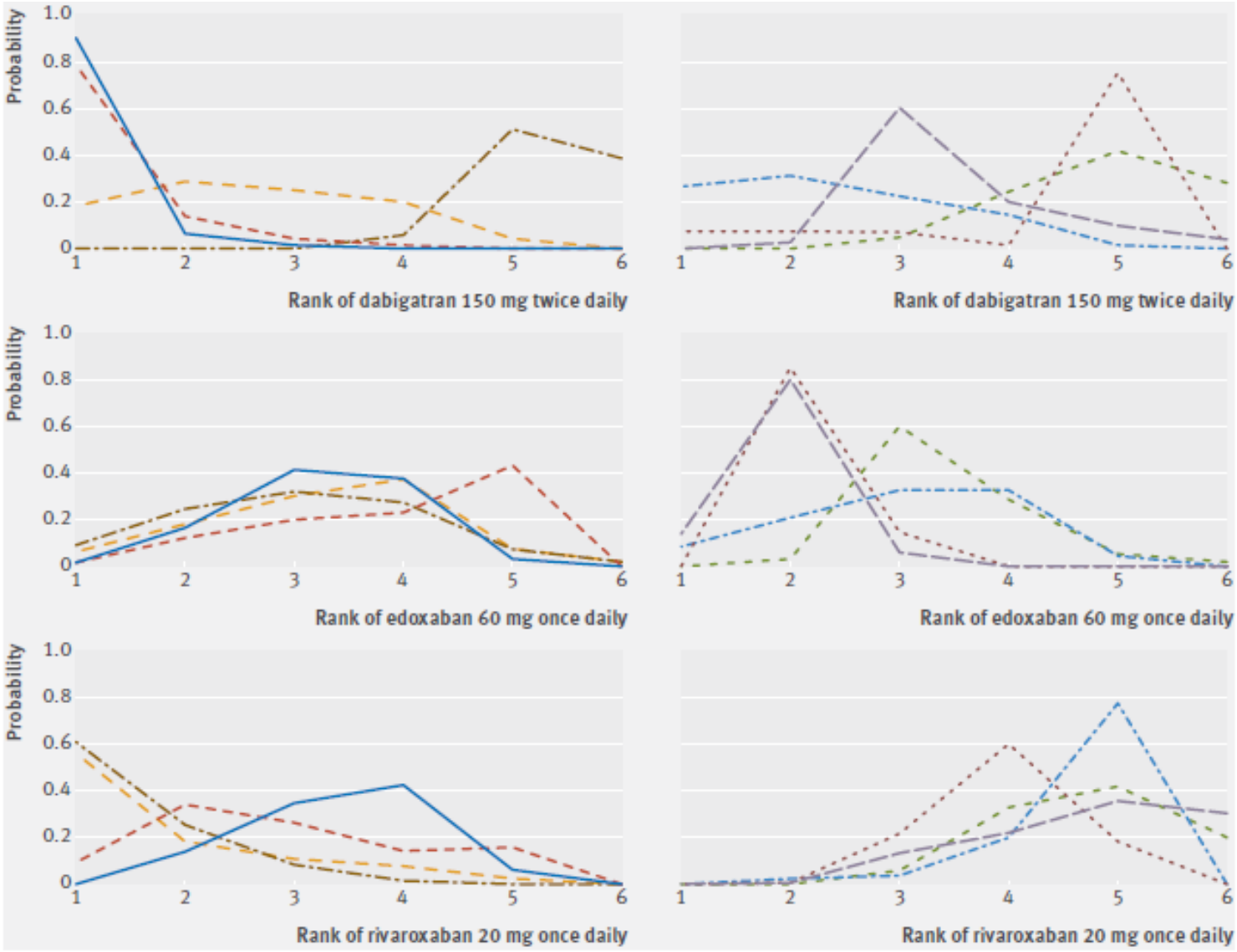


Fig 4 | Rankograms for doses of licensed products examined in prevention of stroke in patients with atrial fibrillation

Inconsistency

There are no direct reports of inconsistency in the network, though this is unsurprising given the few closed loops in the network. The only comparisons in each outcome with both direct and indirect estimates were between aspirin <150mg and Warfarin, and observation of the similarity between these direct and indirect estimates for this comparison suggests adequate consistency for most outcomes, but clear inconsistency for major bleeding and MI.

Meta-regression

For mean TTR, there was no evidence that effect modification had taken place for the outcome of stroke/SE (estimated coefficient 0.0021 with 95% CI −0.07 to 0.08 per 1% increase in mean TTR) or major bleeding (estimated coefficient 0.04 with 95% CI −0.03 to 0.12 per 1% increase). The estimated co-efficients were not reported for the other NMA outcomes but Sterne, 2017[160] stated in their conclusions that there was no evidence of effect modification due to TTR.

Mean age, percentage of male patients, mean CHADS2 score, or follow up time also did not significantly influence the effects for the main outcomes. There were insufficient data to evaluate other potential effect modifiers.

Checklist of quality of the NMA (based on NICE DSU Technical support document 7, January 2012, as recommended in Appendix H of the NICE Manual, 2018)

Based on the NICE DSU Technical support document 7 checklist in Table 26, the NMA[114, 160] evidence was regarded as suitable for clinical decision-making.

Conclusions

The conclusions in Lopez-Lopez were as follows: “apixaban 5 mg twice daily was ranked as being the most effective intervention for several of the outcomes evaluated including stroke or systemic embolism, myocardial infarction, and all-cause mortality. It was also ranked as being the safest with lowest incidence of major and gastrointestinal bleeding. Edoxaban 60 mg once daily was ranked second for major bleeding and all-cause mortality. Except for the outcome of all-cause mortality, rivaroxaban 20 mg once daily was ranked lowest of the DOACs”.

However, these conclusions did not tally with our impressions from the NMA tables and rankograms, which were that rivaroxaban 20mg od was likely to be the best DOAC for minimising MI and all-cause mortality, at a probability of around 60% for each outcome. In addition, apixaban 5mg bd was likely to be the best DOAC for minimising major bleeding, intracranial bleeding and clinically relevant bleeding, at a probability of around 80% for each. Meanwhile, dabigatran 150mg bd was most likely to be the best DOAC for minimising Stroke or Systemic embolism, and Ischaemic Stroke, again at a probability of about 80% for each. Edoxaban 60mg od was not ranked as the best treatment for any outcome, but emerged as the second best for reducing major bleeding and intracranial bleeding.

Committee opinion

Initially the committee were satisfied that the coherence of the model was adequate; that is, there were no differences in populations between direct treatment comparisons that could lead to invalid indirect treatment estimates. However after further discussion, and after listening to the views of stakeholders, it was felt that the coherence of the model could not be

assumed. This was partly because statistical consistency was difficult to evaluate given the lack of evidence loops. However it was also because the clinical heterogeneity between different treatment comparisons was unlikely to have been adequately adjusted by the meta-regression. The committee felt that for those confounders where the meta-regression had made some adjustments, adequate adjustment was unlikely given the small number of studies in the NMA. In addition, several potential effect modifiers could not be adjusted at all because of the lack of adequate data. Therefore, the committee agreed that the validity of the NMA estimates of effect were made uncertain as a result of the difficulties in being able to assume that the NMA model was coherent.

Table 26: NICE DSU Technical support document 7 checklist

A. DEFINITION OF THE DECISION PROBLEM

A1. Target population for decision

A1.1 Has the target patient population for decision been clearly defined? YES.

A2. Comparators

A2.1 Decision Comparator Set: Have all the appropriate treatments in the decision been identified? YES.

A2.2 Synthesis Comparator Set: Are there additional treatments in the Synthesis Comparator Set, which are not in the Decision Comparator Set? YES. If so, is this adequately justified? YES.

A3 Trial inclusion / exclusion

A3.1 Is the search strategy technically adequate and appropriately reported? YES.

A3.2 Have all trials involving at least two of the treatments in the Synthesis Comparator Set been included? YES.

A3.3 Have all trials reporting relevant outcomes been included? YES.

A3.4 Have additional trials been included? YES. If so, is this adequately justified? YES.

A4 Treatment Definition

A4.1 Are all the treatment options restricted to specific doses and co-treatments, or have different doses and co-treatments been "lumped" together? THE FORMER. If the latter, is it adequately justified? NA.

A4.2 Are there any additional modelling assumptions? YES.

A5 Trial outcomes and scale of measurement chosen for the synthesis

A5.1 Where alternative outcomes are available, has the choice of outcome measure used in the synthesis been justified? YES.

A5.2 Have the assumptions behind the choice of scale been justified? NA.

A6 Patient population: trials with patients outside the target population

A6.1 Do some trials include patients outside the target population? NO. If so, is this adequately justified? NA.

A6.2 What assumptions are made about the impact, or lack of impact this may have on the relative treatment effects? NA. Are they adequately justified? NA.

A6.3 Has an adjustment been made to account for these differences? NA. If so, comment on the adequacy of the evidence presented in support of this adjustment, and on the need for a sensitivity analysis.NA

A7 Patient population: heterogeneity within the target population

A7.1 Has there been a review of the literature concerning potential modifiers of treatment effect? YES.

A7.2 Are there apparent or potential differences between trials in their patient populations,

albeit within the target population? YES. If so, has this been adequately taken into account? YES.

A8 Risk of Bias

A8.1 Is there a discussion of the biases to which these trials, or this ensemble of trials, are vulnerable? YES.

A8.2 If a bias risk was identified, was any adjustment made to the analysis and was this adequately justified? NO.

A9. Presentation of the data

A9.1 Is there a clear table or diagram showing which data have been included in the base-case analysis? YES.

A9.2 Is there a clear table or diagram showing which data have been excluded and why? YES.

B. METHODS OF ANALYSIS AND PRESENTATION OF RESULTS

B1 Meta-analytic methods

B1.1 Is the statistical model clearly described? YES.

B1.2 Has the software implementation been documented? YES.

B2. Heterogeneity in the relative treatment effects

B2.1 Have numerical estimates been provided of the degree of heterogeneity in the relative treatment effects? YES.

B2.2 Has a justification been given for choice of random or fixed effect models? YES. Should sensitivity analyses be considered? YES.

B2.3 Has there been adequate response to heterogeneity? YES.

B2.4 Does the extent of unexplained variation in relative treatment effects threaten the robustness of conclusions? NO.

B2.5 Has the statistical heterogeneity between baseline arms been discussed? YES.

B3 Baseline model for trial outcomes

B3.1 Are baseline effects and relative effects estimated in the same model? NO. If so, has this been justified? NA.

B3.2 Has the choice of studies to inform the baseline model been explained? YES.

B4 Presentation of results of analyses of trial data

B4.1 Are the relative treatment effects (relative to a placebo or "standard" comparator) tabulated, alongside measures of between-study heterogeneity if a RE model is used? NA – FE model used

B4.2 Are the absolute effects on each treatment, as they are used in the CEA, reported? YES.

B5 Synthesis in other parts of the natural history model

B5.1 Is the choice of data sources to inform the other parameters in the natural history model adequately described and justified? YES.

B5.2 In the natural history model, can the longer-term differences between treatments be explained by their differences on randomised trial outcomes? YES.

C. ISSUES SPECIFIC TO NETWORK SYNTHESIS

C1 Adequacy of information on model specification and software implementation

C2. Multi-arm trials

C2.1 If there are multi-arm trials, have the correlations between the relative treatment effects been taken into account? Unclear

C3 Connected and disconnected networks

C3.1 Is the network of evidence based on randomised trials connected? YES.

C4 Inconsistency

C4.1 How many inconsistencies could there be in the network? 2 detected (for the comparison between aspirin <150mg v VKA, for the outcomes of major bleeding and MI).

C4.2 Are there any a priori *reasons for concern that inconsistency might exist, due to systematic clinical differences between the patients in trials comparing treatments A and B, and the patients in trials comparing treatments A and C, etc? YES.*

C4.3 Have adequate checks for inconsistency been made? YES.

C4.4 If inconsistency was detected, what adjustments were made to the analysis, and how was this justified? No adjustments have been made to the analysis. However the inconsistencies detected would not significantly affect the estimates for the DOACS.

D EMBEDDING THE SYNTHESIS IN A PROBABILISTIC COST EFFECTIVENESS ANALYSIS

D1. Uncertainty Propagation

D1.1 Has the uncertainty in parameter estimates been propagated through the CEA model? YES.

D2 Correlations

D2.1 Are there correlations between parameters? YES. If so, have the correlations been propagated through the CEA model? YES.

1.6 Economic evidence

1.6.1 Included studies

Two health economic studies were identified with all relevant comparison and have been included in this review.[114, 127, 160, 163] These are summarised in the health economic evidence profile below (Table 27) and the health economic evidence tables in appendix H.

1.6.2 Excluded studies

One health economic study comparing apixaban to warfarin was excluded due to limited applicability.[103] This is listed in appendix I, with reasons for exclusion given.

Fifty-three health economic studies relating to this review question were selectively excluded due to combination of limited applicability and methodological limitations and the availability of more applicable evidence.[2, 3, 7, 15, 16, 19, 25, 31, 42, 43, 45, 44, 51, 62, 68, 72, 82, 86, 87, 88, 89, 90, 94, 96, 97, 98, 99, 100, 101, 103, 102, 108, 109, 110, 121, 122, 139, 131, 129, 130, 135, 143, 144, 145, 149, 150, 159, 161, 164, 175, 176, 180, 170] These are listed in appendix I, with reasons for exclusion given. The primary reasons for their selective exclusion were because they only compared a single DOAC to warfarin and/or were in non-UK settings. These types of studies were deemed less relevant than the more comprehensive UK analyses presented below.

In the previous guideline updated (CG180), four published health economic studies were reported as well as a de novo health economic model. None of these were carried forward to this guideline. Two were excluded at first sift as they were from a US healthcare payer perspective and therefore did not meet our health economic protocol. As a result these are not listed in Appendix I. Jowett 2011 and Kansal 2012 were selectively excluded due to the availability of more applicable evidence and are listed in the excluded studies table in appendix I.[87,90] Of note, the de novo model conducted in CG180 did not meet our protocol as it included classes of anticoagulants rather than individual drugs and therefore was excluded at first sift and so is not presented here.

Of the fifty-three selectively excluded studies, three of these are NICE technology appraisals, TA249, TA256 and TA275, for dabigatran, rivaroxaban and apixaban respectively.[131,130,129] As the latest technology appraisal (TA355[127]) compares all relevant anticoagulants, it was considered more useful for the committee's consideration and therefore is presented instead of TA249, TA256 and TA275.

See also the health economic study selection flow chart in appendix F.

1.6.3 Summary of studies included in the economic evidence review

Table 27: Health economic evidence profile: warfarin versus apixaban versus dabigatran versus edoxaban versus rivaroxaban

<table>
<tr><th>Study</th><th>Applicability</th><th>Limitations</th><th>Other comments</th><th>Incremental cost</th><th>Incremental effects</th><th>Cost effectiveness</th><th>Uncertainty</th></tr>
<tr>
<td>Sterne 2017[160]/Lopez-Lopez 2017[114]/ Thom 2019[163] (UK)</td>
<td>Directly applicable[a]</td>
<td>Minor limitations [b]</td>
<td>
• Probabilistic decision analytic model, incorporating differences in QOL related to clinically relevant (extracranial) bleed, ICH, ischaemic stroke, MI, TIA, SE. Discontinuation/switch and mortality modelled.
• Cost-utility analysis (QALYs)
• Population: Patients with non-valvular atrial fibrillation eligible for anticoagulation
• Five comparators (ongoing treatment):
1. Warfarin, target INR 2-3
2. Apixaban, 5mg bd
3. Dabigatran, 150mg bd
4. Edoxaban, 60mg od
5. Rivaroxaban, 20mg od
Time horizon: lifetime
</td>
<td colspan="4">
Full incremental analysis (pa):[c] [d]
<table>
<tr><th>Int</th><th>Cost (e)</th><th>QALY</th><th>Inc cost</th><th>Inc QALY</th><th>ICER</th><th>% most CE at £20K:</th></tr>
<tr><td>1</td><td>£24,418</td><td>5.166</td><td colspan="3">Dominated by 3</td><td>0%</td></tr>
<tr><td>4</td><td>£23,985</td><td>5.405</td><td colspan="3">Dominated by 3</td><td>5%</td></tr>
<tr><td>3</td><td>£23,064</td><td>5.416</td><td colspan="3">Baseline</td><td>25%</td></tr>
<tr><td>5</td><td>£24,841</td><td>5.451</td><td colspan="3">Dominated by 2</td><td>10%</td></tr>
<tr><td>2</td><td>£23,340</td><td>5.488</td><td>£276</td><td>0.072</td><td>£3,833</td><td>60%</td></tr>
</table>
A number of scenario analyses were undertaken, most did not change conclusions found in the base case (intervention 2 remains most cost effective).
Two scenarios resulted in a change in results:
• All switch after ischaemic stroke, bleed, SE and TIA as well as switch to no treatment after ICH or MI (if on dabigatran): intervention 1 most cost effective
• Different doses for apixaban and dabigatran (2.5mg bd and 110mg bd, respectively): apixaban 2.5mg bd most likely to be cost effective but probability it is most cost effective at £20K is ~50%

Key drivers of results noted by authors:
• Lower rates of MI, ICH and other CRB for apixaban.
• High cost and disutility of ICH has great influence on total costs, total QALYs and net benefits.
</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Applicability</th><th>Limitations</th><th>Other comments</th><th>Incremental cost</th><th>Incremental effects</th><th>Cost effectiveness</th><th>Uncertainty</th></tr>
<tr>
<td>NICE 2015[127] (UK)</td>
<td>Directly applicable[f]</td>
<td>Potentially serious limitations[g]</td>
<td>

Probabilistic decision analytic model, incorporating differences in QOL related to non-ICH major bleeds, clinically relevant non-major bleeds, ICH, ischaemic and haemorrhagic stroke, MI, TIA and SE. Discontinuation/switch and mortality modelled.
Cost-utility analysis (QALYs)
Population: Patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥75years, diabetes mellitus, prior stroke or TIA. CHADS2>2
Six comparators (ongoing treatment):

Warfarin, average daily dose 4.5mg od
Apixaban, 5mg bd
Dabigatran, 110mg bd
Dabigatran, 150mg bd reducing to 110mg bd after 80 years

</td>
<td colspan="4">
Full incremental analysis (pa):[c] [d]
<table>
<tr><th>Int</th><th>Cost [h]</th><th>QALY</th><th>Inc cost</th><th>Inc QALY</th><th>ICER</th><th>% most CE at £20K:</th></tr>
<tr><td>1</td><td>£12,868</td><td>6.56</td><td colspan="3">Baseline</td><td>36.8%</td></tr>
<tr><td>6</td><td>£16,313</td><td>6.65</td><td colspan="3">Dominated by 4</td><td>~1%</td></tr>
<tr><td>3</td><td>£15,732</td><td>6.66</td><td colspan="3">Dominated by 4</td><td>~10%</td></tr>
<tr><td>5</td><td>£15,471</td><td>6.72</td><td colspan="3">Dominated by 4</td><td>2.9%</td></tr>
<tr><td>4</td><td>£15,293</td><td>6.75</td><td>£2,425</td><td>0.185</td><td>Extendedly dominated by 2</td><td>~25%</td></tr>
<tr><td>2</td><td>£15,531</td><td>6.77</td><td>£2,662</td><td>0.204</td><td>£13,036</td><td>~25%</td></tr>
</table>

Deterministic and probabilistic results differ. Base case presented deterministically by manufacturer: all interventions are dominated by intervention 4, ICER of intervention 4 vs. 1 £7,645 per QALY.[i]
Manufacturer conducted number of pairwise sensitivity analyses (5 vs 1 and 5 vs 4) Analyses sensitive to start age, cost of treatment and addition of monitoring cost for those receiving edoxaban.
• Subgroup analyses conducted by manufacturer:
○ Higher risk of stroke (CHADS2≥3): Intervention 2 most cost effective (ICER £3,730 per QALY vs intervention 1).
○ cTTR on warfarin≥60%: Intervention 4 most cost effective (ICER £11,696 vs intervention 1)

The ERG made a number of adjustments to correct for methodological errors and to use alternative data sources. Most resulted in no change in the probabilistic results (intervention 2 remained the most cost effective). Some adjustments resulted in intervention 4 being most cost effective.
</td>
</tr>
</table>

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			5. Edoxaban, 60mg od 6. Rivaroxaban, 20mg od Time horizon: 30 years (remaining lifetime)				

Abbreviations: bd = twice daily; cTTR= centre time in therapeutic range; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ERG= Evidence review group; HS= haemorrhagic stroke; ICER= incremental cost-effectiveness ratio; ICH= intracranial haemorrhage; IS= ischaemic stroke; MI= myocardial infarction; NMA= network meta-analysis; NR= not reported; od = once daily; pa= probabilistic analysis; QALYs= quality-adjusted life years; SE= systemic embolism; TA= technology appraisal; TIA = transient ischaemic attack.

(a) EQ-5D data identified via systematic review of literature, unclear however if all are from UK representative population. No stratification by stroke or bleeding risk.

(b) Seven studies identified in our systematic review of the evidence are not included in the NMA used in this model and so this may not reflect the full body of evidence. The cost of edoxaban is assumed to be the same as dabigatran. Reversal agents for DOACs not included in costs/effects of treating bleeds (not available at time of publication).

(c) Intervention number in order of least to most effective (in terms of QALYs).

(d) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.

(e) Costs incorporated include: drug costs (including monitoring costs for warfarin), acute event costs (ischaemic stroke, ICH, SE (non-fatal), TIA, clinically relevant bleed and MI), chronic care costs (post ischaemic stroke [same assumed for ICH]: weighted average of non-disabling, moderately disabling, totally disabling). Unit cost of edoxaban not available at the time of publication and so assumed to be equal to dabigatran. Cost of reversal agents not explicitly costed (note the reversal agents for DOACs were not available when this model was conducted).

(f) EQ-5D data identified via systematic review of literature; however the source of data used to adjust utilities to reflect a reduction of HRQoL with increasing age are based on data from a US population to which a UK utility weight was applied, the ERG noted UK data would be more appropriate. ERG also identified an error in the application of the utility decrement which led to double counting. An addendum was submitted by the ERG and upon correction of the error and use of UK utility data source no significant change in the results was reported.

(g) The incremental analysis is based upon the company's NMA. Analysis by the ERG has shown that assumptions of proportional hazards required for this analysis do not hold. The results of the incremental analysis are therefore highly uncertain. Subgroup analyses were conducted to stratify by stroke risks, however as there was limited data available to inform these analyses, much of the data on relative effectiveness is the same as that used in the base case analysis. Therefore this assumes no differences in relative treatment effects between subgroups. Twenty studies identified in our systematic review of the evidence are not included in the NMA used in this model and so this may not reflect the full body of evidence. Reversal agents for DOACs not included in costs/effects of treating bleeds (not available at time of publication). Potential financial conflict of interest funded by manufacturers of edoxiban.

(h) Costs incorporated include: Drug costs (including monitoring costs for warfarin), acute event costs (IS and HS by severity, SE, MI, other ICH, TIA, non-ICH major bleed, clinically relevant non-major bleed, and death), and chronic care costs (post IS and HS by severity, SE, MI). Cost of reversal agents not explicitly costed (note the reversal agents for DOACs were not available when this model was conducted).

(i) Deterministic and probabilistic results differ. The ERG considers that this is due to the very small differences in QALYs between dabigatran 150mg and apixaban in all analyses. In addition the results of the probabilistic analysis are not completely stable (repeated runs of the same analyses give slightly different results).

1.6.4 Health economic modelling

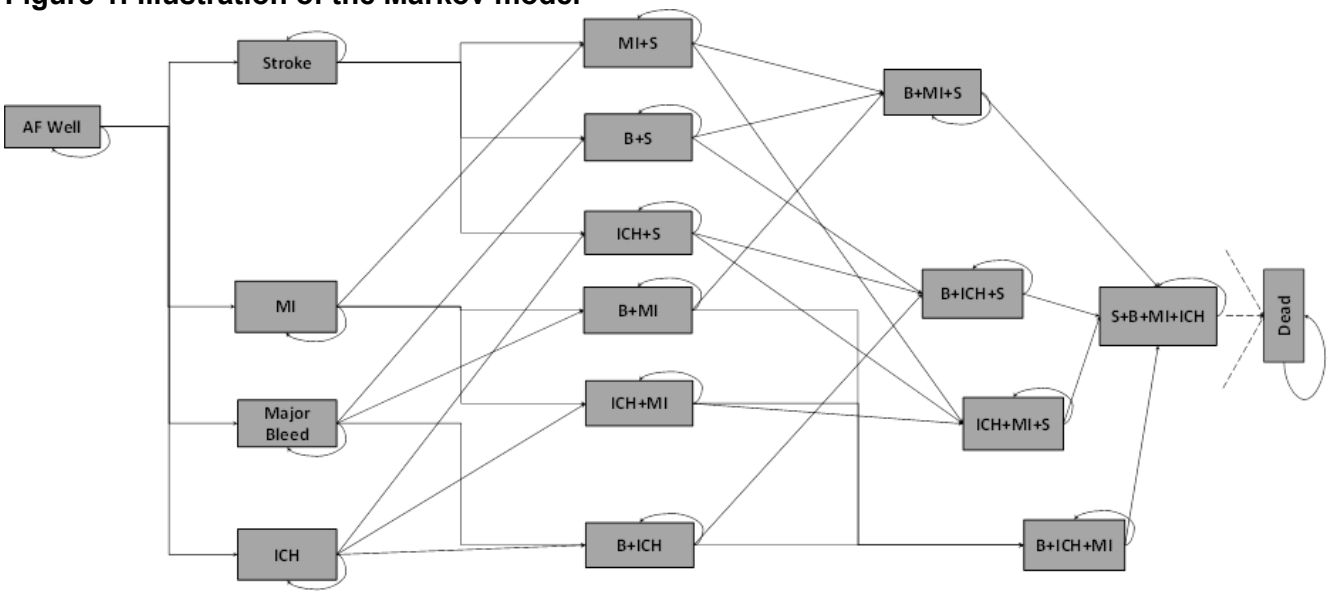
The committee decided that this topic area was the highest priority for economic modelling on the account of the large number of patients affected by potential recommendations and the current variation in uptake of DOACs nationally. An update of the Sterne 2017[160] health economic analysis was agreed which enable the explicit incorporation of reversal agents costs for all anticoagulants and to stratify the population by stroke risk (CHADSVASC). This analysis was conducted by the original authors of the model (Howard Thom and Nicky Welton), with guidance from the technical team and guideline committee.

Model methods

A technical report for this analysis including full details of all methods and model inputs is available in a separate PDF: 'G2. Health Economic Analysis Anticoagulants'.

A cost-utility analysis was undertaken to compare warfarin (target INR 2-3), apixaban (5mg bd), dabigatran (150mg bd), edoxaban (60mg od), rivaroxaban (20mg od) and no treatment in people with non-valvular AF who are eligible for anticoagulation. This analysis was undertaken from a current UK NHS perspective. This model utilised a Markov model structure where from any state, a person can have a clinically relevant (extracranial) bleed, an intracranial haemorrhage (ICH), an ischaemic stroke, a myocardial infarction (MI), a transient ischaemic attack (TIA), a systemic embolism (SE), can discontinue or switch treatment due to these events, or die. The model had 3-month cycle durations and is run over a lifetime. The model structure is illustrated in Figure 1.

Figure 1: Illustration of the Markov model*



** Patients can experience transient events (TIA or SE) but stay in same health state, with possibly changed treatment, thereafter. (S = ischaemic stroke, B = other clinically relevant bleed, ICH = intra-cranial haemorrhage, MI = myocardial infarction)*

Model assumptions of note were:

- No distinction between severity of ischaemic stroke
- Costs and impact on utility of stroke were averaged across different severities
- Non-clinically relevant minor bleed events not included
- SE and TIA assumed to be transient without long-term consequences
- Dose of apixaban and dabigatran do not reduce with age
- No distinction between bleed locations (other than ICH)

- Treatment effects (proportion risk reduction) are the same for all patients

A more comprehensive list of model assumptions is available in 'G2. Health Economic Analysis Anticoagulants'. As this was a model update, the committee were limited in their ability to change these assumptions, however they did deemed these to be reasonable. Model inputs are described in full in the separate technical report. In summary, baseline and relative treatment effects were based on systematic reviews, network meta analyses (NMA) and meta analyses undertaken by or identified by the authors of the original model. UK costs were used. Health-related quality of life weights were based on the published literature.

The main changes to the original Sterne 2017[160] model were: scenario analyses on age, gender and stroke risk (CHADSVASC), the inclusion of no treatment as a comparator (this was important when considering a CHADSVASC=0), updating of all unit costs to 2019 costs and inclusion of the cost for the currently available reversal agents in a sensitivity analysis. This was of particular interest as two DOAC specific reversal agents are licensed for use in the UK: idarucizumab (used for dabigatran) and andexanet alpha (used for apixaban and rivaroxaban) and none of the existing health economic models explicitly included these. Both reversal agents have a high acquisition cost.

To model baseline stroke rates by CHADSVASC score, stroke rates for untreated AF by CHADSVASC score were taken from Aspberg 2016.[14] The health states in the economic model adjust stroke risk through their impact on the CHADSVASC score. Age and gender also impact the score. The starting distribution of CHADSVASC scores were based on a published meta-analysis of screen detected AF with CHADSVASC2 ≥ 2 (Welton 2017)[173].

Anticoagulant unit costs and costs associated with reversal agents are summarized in Table 28 and Table 29, respectively.

Table 28: Drug dose, duration and costs

Intervention	Dose per day (mg)	mg per tablet	Number in pack	Cost per pack	Cost per day	Cost per 3 month cycle AF model
Apixaban	10	5	56	£53.20	£1.90	£173.38
Apixaban	5	2.5	60	£57.00	£1.90	£173.38
Dabigatran	300	150	60	£51.00	£1.70	£155.13
Dabigatran	220	110	60	£51.00	£1.70	£155.13
Rivaroxaban	20	20	100	£180.00	£1.80	£164.25
Edoxaban	60	60	28	£49.00	£1.75	£159.69
Warfarin						£70.66*

** Inflated from a 2014 annual cost of £241.54 to 2019 annual cost of £282.62 using the ONS Consumer Price Inflation index for medical services (DKC3)[136]*
Source: BNF[22] and NICE CG180 costing report[125]

Table 29: Parameters used for costing reversal agent use

	Mean	Source
Bleeding event reversal unit costs		
Vitamin K - Phytomenadione 10mg/1ml solution for injection (£)	0.378	NHS Drug Tariff 2019[132]
Octaplex - 1,000 IU vial (£)	416.5	Octaplex prescribing information[56]
Octaplex - ml per 1,000 IU vial (£)	40	Octaplex prescribing information[56]
Beriplex - 1,000 IU vial (£)	600	Beriplex prescribing information[55]
Idarucizumab (Praxbind) - 2.5 g/50 ml vial (£)	1200	NICE evidence summary[128]

	Mean	Source
Andexanet alfa per dose (£)	11,100	4 x 200mg powder for solution vials = £11,100 using NICE indicative price[124]
Bleeding events resource use		
Percentage reversal agents on warfarin	87.5%	Clinical advice range is 75% to 100% Considered 50% and 10% (with no uncertainty distribution) as sensitivity analyses.
Percentage reversal agents (non-dabigatran DOACs)	3%	Clinical advice range is 1% to 5%
Percentage reversal agents (dabigatran)	3%	Clinical advice range is 1% to 5%
Percentage of PCC usage which is Octaplex	50%	Clinical advice range is 40% to 60%
Percentage of low-dose Octaplex use	50%	Clinical advice range is 40% to 60%
Reversal agent dose		
Vitamin K - ampoules used	1.5	Assumption
Octaplex - INR 2-2.5 - 0.9-1.3 ml/kg body weight	1.1	Octaplex prescribing information[56]
Octaplex - INR 2.5-3 - 1.3-1.6 ml/kg body weight	1.45	Octaplex prescribing information[56]
Beriplex - INR 2.0-3.9 - 25 IU/kg body weight	25	Beriplex prescribing information[55]
PCC - number of doses	1.25	Assumption
Andexanet alpha (200mg vial)	4	Assumption
Idarucizumab – vials used	2	Assumption
Reversal agent dose		
Average weight males (kg)	83.5	Health Survey England 2014 average weight for 65-74 year olds[133]
Average weight females (kg)	72.1	Health Survey England 2014 average weight for 65-74 year olds[133]

Abbreviations:DOACs = directly acting oral anticoagulants; IU=international unit; PCC=prothrombin complex.

The health economic model was validated by the British Medical Journal Group.

Results

The results of the basecase are presented in Table 30. This analysis found that at a threshold of £20,000 per QALY all DOACs have positive incremental net monetary benefit compared to warfarin, suggesting they are cost effective options Apixaban (5mg bd) has the highest expected incremental net benefit (£10,369), followed by dabigatran (150mg bd) (£8,963), edoxaban (60mg od) (£7,000), and rivaroxaban (20mg od) (£6,594). Apixaban (5mg bd) is the only DOAC for which the 95% confidence interval around incremental net benefit is positive, although the lower bound for dabigatran (150mg bd) is only -£90, suggesting that dabigatran and apixaban are cost-effective compared with warfarin. Apixaban (5mg bd) had a probability of being the most cost effective of 47.5% and dabigatran (150mg) had a probability of being most cost effectivwe of 32.3% at £20,000 per QALY . The driver of this result is the lower rates of MI, ICH, and other clinically relevant bleed on apixaban. Dabigatran has a greater reduction in stroke risk than apixaban, and this has a greater impact on expected costs and QALYs as the stroke risk (represented by CHA_2DS_2-VASc) increases; this is confirmed in scenario analyses. The high cost and disutility of ICH has a great influence on total costs, total QALYs, and net benefits. Apixaban also has a low rate of TIA but the uncertainty surrounding the other treatment effects, and the minimal impact of this event means it is not a driving factor in the results. Dabigatran also

has a low rate of ICH but the higher rate of MI offsets this benefit. Dabigatran (150mg bd) or Apixaban (5mg bd) are likely to be the most cost-effective first line therapy for AF, under the assumptions of our model.

Table 30: Base case analysis full incremental analysis

Int	Cost	QALY (a)	Inc Costs	Inc QALY	ICER	INMB at £20,000 per QALY (95%CI) (b)	% most CE at £20K: (c)
No treatment	£20,117	4.637	Dominated by dabigatran			-£22,585 (-£76,970, £22,554)	0.4%
Warfarin (INR 2-3)	£18,910	5.35	Dominated by dabigatran			0 (0,0)	0%
Edoxaban (60mg od)	£18,763	5.692	Dominated by dabigatran			£10,426 (-£1,056, £20,837)	5.9%
Dabigatran (150mg bd)	£17,710	5.738	Baseline			£12,845 (-£96.91, £2,5554)	32.3%
Rivaroxaban (20mg od)	£20,734	5.771	Dominated by apixaban			£10,804 (-£1,907, £23,370)	10.1%
Apixaban (5mg bd)	£18,3221	5.839	£612	0.101	£6,059	£15,259 (£5,411, £26,430)	47.5%

Abbreviations: CE = cost effective; CI = confidence intervals; ICER = incremental cost effectiveness ratio; INMB = incremental net monetary benefit; QALYs= quality adjusted life years
(a) Intervention number in order of least to most effective (in terms of QALYs).
(b) INMB are relative to warfarin (INR 2-3).
(c) Estimated from graph

A number of sensitivity and scenario analyses were conducted exploring structural and parameter assumptions of the model. The scenario analyses stratified people by age, gender and CHADSVASC score and indicated that for all men and for all women apixaban (5mg bd) has highest incremental net benefit at the £20,000-30,000 range of willingness-to-pay thresholds. It was noted however that the probabilities that apixaban was the most cost-effective were around the 50% mark for all ages, genders, and CHADSVASC scores. In the scenarios that modelled higher CHADSVASC scores, dabigatran had a probability of being most cost-effective that was very close to that of apixaban indicating low certainty that one is better than the other. A limitation of this stroke risk stratification was that only the baseline stroke risk is adjusted, it is assumed the relative effect of the anticoagulants in terms of stroke risk reduction remains the same irrespective of baseline stroke risk.

Part of this update of the Sterne 2017 model was to run sensitivity analyses to see the impact of the cost of reversal agents on the model conclusions. The first sensitivity analysis tried to reflect current standard of care reversal agents. It assumed a proportion of bleeds are treated with reversal agents; reversal of warfarin always uses vitamin K and a proportion of bleeds are managed with prothrombin complex concentrate (PCC) with the exception of those who are taking dabigatran where idarucizumab is given instead. Due to uncertainty regarding the proportion of bleeds managed with PCC when taking warfarin, additional sensitivity analyses were conducted varying this 87.5% to 50% and 10%. A further exploratory analysis was conducted where andexanet alpha was used for a proportion of bleeds in those taking rivaroxaban and apixaban. All sensitivity analyses found that apixaban was the most cost effective option, however the certainty around that was below 50%. Thus indicating that the cost of reversal agents do not significantly change the conclusions of the base case analysis. A limitation of these sensitivity analyses is that the relative efficacy of these reversal agents was not included in the model, furthermore some reversal agent use may have already been counted in the NHS reference costs for extracranial bleeds.

Our conclusion that apixaban (5mg bd) and dabigatran (150mg bd) have the highest incremental net benefits at willingness-to-pay thresholds in the range £20,000-30,000 was changed only by the sensitivity using Bakhai 2020[18] for the acute and management stroke costs, in which dabigatran (150mg bd) has highest net benefit.

1.6.5 Health economic evidence statements

- One cost-utility analysis found that in people with non-valvular AF, apixaban (5mg bd) was cost effective compared to dabigatran (150mg bd), warfarin (target INR 2-3), edoxaban (60mg od) and rivaroxaban (20mg od) (ICER: £3,833 per QALY gained compared to dabigatran (150mg bd)). It also found that dabigatran (20mg BD) was dominant (less costly and more effective) compared to warfarin (target INR 2-3) and edoxaban (60mg od). This analysis was assessed as directly applicable with minor limitations.
- One cost-utility analysis found that in people with non-valvular AF, apixaban (5mg bd) was cost effective compared to warfarin (average daily dose 4.5mg od), dabigatran (110mg bd), edoxaban (60mg od) and rivaroxaban (20mg od) (ICER: £13,036 per QALY gained compared to warfarin). It also found that dabigatran (150mg bd reducing to 110mg bd after 80 years) was dominant (less costly and more effective) compared to dabigatran (110mg bd), edoxaban (60mg od) and rivaroxaban (20mg od). Furthermore apixaban (5mg bd) extendedly dominated dabigatran (150mg bd reducing to 110mg bd after 80 years). This analysis was assessed as directly applicable with potential serious limitations.
- One original cost-utility analysis found that in people with non-valvular AF, dabigatran (150mg bd) was cost effective compared to no treatment, warfarin (INR 2-3), edoxaban (60mg od), rivaroxaban (20mg od) and apixaban (5mg bd). Dabigatran (150mg) was dominant (less costly and more effective) compared to no treatment, warfarin (INR 2-3) and edoxaban (60mg od). Apixaban (5mg bd) was dominant (less costly and more effective) compared to rivaroxaban (20mg od). Apixaban (5mg bd) was cost effective compared to dabigatran (150mg bd) (ICER of £6,059 per QALY gained). This analysis was assessed as directly applicable with minor limitations.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

Outcomes were quality of life, stroke/systemic embolism, mortality, MI, major bleeding, clinically relevant non-major bleeding, intra-cranial bleeding, GI bleeding and minor bleeding. All were regarded as critical by the committee, but quality of life, stroke/systemic embolism, mortality, major bleeding and intracranial bleeding were deemed the most relevant for decision-making. Quality of life was prioritised because it encompasses all aspects of a patient's health outcome, and stroke /systemic embolism was deemed a priority because the purpose of treatment was to influence this outcome. Mortality, major bleeding and intracranial bleeding were also prioritised over MI and other bleeding outcomes because of their greater impact. The only outcome not available in the included literature was Health-related quality of life.

1.7.1.2 The quality of the evidence

For the pairwise analyses, the quality of evidence varied. For comparisons utilising the newer larger trials (principally the trials comparing the standard doses of direct oral anticoagulants (DOACs) to warfarin) the risk of bias was absent or serious. Any downgrading for risk of bias was due to a lack of clear reporting about allocation concealment. However for older studies which principally compared warfarin to antiplatelets, the risk of bias was usually serious or

very serious. This was largely because of a failure to clearly report allocation concealment, a tendency to not blind treatments in these studies and potential attrition bias.

Only one outcome demonstrated any heterogeneity and so this did not contribute to overall quality. For some outcomes downgrading for indirectness was made, due to the study outcomes being slightly different to the protocol outcomes. The other contributor to overall grading was imprecision. Overall, the quality of evidence of most outcomes comparing antiplatelets to warfarin were graded 'very low'. The quality of evidence of key outcomes comparing dabigatran and apixaban to warfarin were graded 'low' or 'very low', and the quality of evidence of key outcomes comparing rivaroxaban and edoxaban to warfarin were graded 'medium' or 'high'.

The committee highlighted that the description of the dose for the main apixaban trial (5mg) might be misleading as a small number of participants with additional risk factors were allowed to use 2.5mg. However over 95% used 5mg so it was agreed that it was acceptable to categorise the dose as 5mg. The committee also noted a similar anomaly relating to the dose in the main rivaroxaban trial (20mg), where some people with CrCl <50 ml/min (21%) were assigned to a lower dose. Again it was agreed that it was acceptable to categorise the dose as 20mg.

The committee were made aware of some irregularities in collection of data at some of the clinical centres in the ARISTOTLE trial. This was examined in detail, making reference to a recent report, and the committee agreed that the effect on results was very small, and in fact went against the expected direction of bias, slightly favouring warfarin. The committee decided that the effects were so insignificant that there was no need to exclude the ARISTOTLE trial, and that the results from the trial could be evaluated alongside other evidence.

1.7.1.3 Benefits and harms

The pairwise analyses suggested that warfarin was better than antiplatelets, and that the DOAC drugs were better than warfarin, in terms of the prioritised critical outcomes. Whilst many of these sample differences suggested real population differences (that is, sample differences were unlikely to be explained by sampling error) the magnitude of effects were quite small and were not necessarily clinically important. Nevertheless, the committee concluded that the results indicated superiority of the DOACs over warfarin, and also warfarin over antiplatelets.

Apixaban appeared to have the best overall performance of all the DOACs against the common comparator of warfarin. For example (using warfarin as the common comparator), apixaban had the second lowest odds for stroke/systemic embolism of all the DOACs, was the only DOAC to demonstrate a statistically significant benefit for mortality, had the lowest odds for major bleeding and had the second lowest odds for intracranial bleeding. However this impression was based merely on the point estimates in the pairwise comparisons, and the uncertainties around these point estimates made it difficult to be sure that this reflected a real difference in efficacy. Only one study directly compared DOAC drugs, showing that dabigatran 150mg bd and rivaroxaban 15mg qd had similar effects on stroke and intracranial bleeding. Dabigatran led to more cases of major bleeding than rivaroxaban but there was great uncertainty in this finding. Due to the quality of the study this did not assist decision-making.

The need for a network meta-analysis (NMA) to facilitate interpretation was recognised by the committee. It was accepted that an NMA would allow the use of indirect estimates derived from connected loops of evidence to bolster the direct estimates. In addition, Bayesian methodology would allow Monte Carlo simulations to generate probabilistic rankings of the efficacy of each DOAC.

After discussion of the results of the pairwise analyses the committee decided to also make use of a recent network meta-analysis[113] (for the purposes of discussion the existing NMA will be referred to as Lopez Lopez, Sterne et al. 2017) to assist in decision making (see section 1.5.2 for a discussion of the decision to use a published NMA). See section 1.5.6 for methodology and results. Risk of bias in the Lopez Lopez NMA was evaluated slightly differently to that in the pairwise reviews but in general the committee agreed that the rating of potential bias was very similar, and that this would not affect the interpretation of the evidence.

The technical team therefore presented the findings of the Lopez-Lopez (2017) and Sterne (2017) NMA to the committee. The committee were agreed that the evidence pointed clearly to a superiority of the DOAC drugs over warfarin, both in terms of benefits and harms. The committee therefore unanimously agreed that DOACS should be recommended. Results from the NMA showed that the DOACs performed differently depending on the outcome. The NMA estimated a ranking of the efficacies of treatments per outcome, taking all data and uncertainties into account. These rankings showed that Rivaroxaban was likely to be the best DOAC for minimising MI and all-cause mortality, at a probability of around 60% for each outcome. In addition, Apixaban was likely to be the best DOAC for minimising major bleeding, intracranial bleeding and clinically relevant bleeding, at a probability of around 80% for each. Meanwhile, dabigatran was most likely to be the best DOAC for minimising Stroke or Systemic embolism, and Ischaemic Stroke, again at a probability of about 80% for each. Edoxaban was not ranked as the best treatment for any outcome, but emerged as the second best for reducing major bleeding and intracranial bleeding.

The committee had a number of concenrs regarding the NMA findings. The committee's main concern was that the populations in different direct treatment comparisons were sufficiently different to increase the risk that the indirect estimates of effects between DOACs could be invalid. This is because indirect estimates can only be validly estimated if an assumption of population transitivity is made. The NMA had used a meta-regression approach to try to adjust for any between-comparison population covariates, but the small number of studies made this difficult to achieve, and for many covariates adjustments were not possible. This made it possible that the indirect estimates of effects between DOACs could be both invalid and also overly precise. Altogether, this made the committee more wary of the possibility that the apparent differences observed in clinical effect might not be as clear-cut as they appeared. These NMA findings were incorporated into the economic model, which found that dabigatran and apixaban were the most cost-effective treatments (please see 1.7.2). However, due to the concerns on the validity of NMA estimates, the committee agreed that there was too much uncertainty to recommend specific DOACs and their conclusions about cost-effectiveness were revised.

Although this reasoning led to the committee concluding that the DOACs should be regarded as equivalent in terms of efficacy and cost-effectiveness, this reasoning did not affect the decision to put the DOACs above warfarin. This is because the evidence for DOACs over warfarin was based on direct estimates, which are not dependent on model coherence for their validity. The revised overall conclusion was therefore that although DOACs were more cost-effective than warfarin, there was insufficient certainty in the evidence that any DOAC was more cost-effective than any other.

The committee discussed the patient experience of using DOACs, and described how dabigatran may lead to more upper GI side effects. It was also discussed how dabigatran and apixaban may be associated with less compliance because of the greater number of doses per day, although the lack of published evidence for this was agreed. The NMA and pairwise data did not provide information to substantiate these concerns and so the committee decided that these issues should not influence the recommendation. The committee therefore agreed to recommend that the first line anticoagulants should be any of the following DOACs – apixaban, dabigatran, edoxaban and rivaroxaban - without any differentiation between them. A decision on the best drug to use should be based on shared

decision-making between the clinician and patient, taking into account all risk factors and preferences.

The committee made a relatively tentative recommendation that DOACs be 'considered' for men with CHADSVASC scores of 1 or more, but a relatively stronger recommendation that DOACS be 'offered' to either men and women with CHADSVASC scores of 2 or more. These recommendations were consensus-based and related to the committee's understanding of the CHADSVASC scoring system alongside the risks of stroke at different scores for men and women. Thus the 'consider' recommendation aimed only at men was based on the fact that men with a single risk factor (usually giving a CHADSVASC score of 1) will have a small but appreciable risk of stroke, but that women with a score of 1 will only have this score by virtue of their gender, which is a risk modifier. The stronger 'offer' recommendation aimed at both men and women was based on the fact that men with two risk factors are at a significant risk of stroke, and that women with a single risk factor (other than the risk conferred by being female) are at a higher risk of stroke than men with a single risk factor.

The committee discussed the situation for people already on warfarin. The committee considered these people could reasonably continue on their current regimen until their next routine appointment. The decision to switch should be discussed in the context of shared decision making and time in therapeutic range should be taken into consideration. Finally, the committee agreed that the decision to precribe anticoagulation should also be subject to regular review and reconsideration as appropriate.

1.7.2 Cost effectiveness and resource use

Two published UK cost-utility analyses were identified comparing all the relevant interventions (apixaban, dabigatran, edoxaban, rivaroxaban and warfarin) in people with AF (NICE TA355 and Sterne 2017). In addition, an adaptation of one of these two models (Sterne 2017) was conducted as part of the guideline development process (further details below). Fifty one other health economic analyses were identified but were all selectively excluded because they only compared a single DOAC to warfarin and/or were in non-UK settings. These types of studies were deemed less relevant than the more comprehensive UK analyses identified.

The NICE TA355 was a technology appraisal of edoxaban, this analysis found that apixaban was cost effective compared to warfarin, dabigatran, edoxaban and rivaroxaban for preventing stroke in adults with non-valvular AF (ICERs: £13,036 per QALY gained compared to warfarin). The probability that apixaban was the most cost effective at £20,000 was highly uncertain (circa 25%). The model also found that dabigatran (starting dose 150mg, reduced to 110mg after 80 years old) dominated (less costly and more effective) dabigatran (150mg), rivaroxaban and edoxaban and that apixaban extendedly dominated dabigatran (150mg/110mg dosage). This analysis was assessed as directly applicable with potentially serious limitations. The limitations included concerns from the Technology Appraisal Evidence Review Group regarding the assumption of proportional hazards made for the NMA conducted by the model developers, which are likely to have contributed to the uncertainty seen in the model results. Subgroup analyses were conducted in this analysis to stratify by stroke risks and found that in people with a higher stroke risk (CHADS2≥ 3) apixaban was the most cost effective option. However as there was limited data available to inform this sensitivity analysis, much of the data on relative effectiveness is the same as that used in the base case analysis. Therefore this assumes no differences in relative treatment effects between subgroups. Another limitation of this model is that over 20 studies identified in our systematic review of the evidence are not included in their NMA and so this may not reflect the full body of evidence. A further limitation of the model was that it did not capture the potential costs and effects associated with treating bleeds with reversal agents for DOACs as these were not available at time of the TA publication. Finally there is a potential financial conflict of interest as this analysis is funded by manufacturers of edoxaban.

The second cost-utility analysis was by Sterne 2017/Lopez-Lopez 2017 and was published alongside the Lopez-Lopez 2017 NMA used in this guideline and described in the 'Benefits and Harms' section. This analysis found that apixaban was cost effective compared to warfarin, dabigatran, edoxaban and rivaroxaban for preventing stroke in adults with non-valvular AF (ICERs: £3,833 per QALY gained compared to dabigatran). The probability that apixaban was the most cost effective at a threshold of £20,000 was 60%. It also found that dabigatran dominated (less costly and more effective) warfarin and edoxaban and that apixaban dominated rivaroxaban. This analysis was assessed as directly applicable with minor limitations. This analysis did not stratify people by stroke or bleeding risk. The model used the Lopez Lopez 2017 NMA for the main treatment effects however, as noted in the 'Benefits and Harms' section above, seven studies identified in our clinical review are not included in the NMA. However the committee was confident that the lack of these studies in Lopez-Lopez would not change their results significantly, and that confidence in their findings would therefore not be reduced. Another limitation of the model was that the cost of edoxaban was unavailable at the time of publication and therefore assumed to equal dabigatran. This was not considered to be a significant limitation as the costs of the DOACs are all very similar. Finally, as with the NICE TA355, the model did not include the costs and effects associated with treating bleeds with reversal agents for DOACs.

The need for a new health economic analysis was discussed with the committee and it was agreed that an update of the Sterne health economic analysis would be of value in particular to explicitly incorporate the costs of reversal agents for all anticoagulants and to stratify the population by stroke risk (CHADSVASC). This de novo analysis was conducted by the original authors of the model (Howard Thom and Nicky Welton), with guidance from the technical team and guideline committee. The main changes to the model were: scenario analyses on age, gender and stroke risk (CHADSVASC), the inclusion of no treatment as a comparator (this was important when considering a CHADSVASC=0), updating of all unit costs to 2019 costs and inclusion of the cost of the currently available reversal agents in a sensitivity analysis. This de novo analysis found that at a threshold of £20,000 per QALY all DOACs have positive incremental net monetary benefit compared to warfarin, suggesting they are cost effective options. Apixaban had the highest incremental net monetary benefit and a probability of being the most cost effective of 47.5%. Dabigatran and rivaroxavan were next with probabilities of being most cost effective of 32.3% and 10.1% respectively. Apixaban was the only DOAC for which the 95% confidence interval around incremental net benefit were positive, although the lower bound for dabigatran (150mg bd) was only -£90, suggesting that dabigatran and apixaban are cost-effective compared with warfarin. The driver of this result is the lower rates of MI, intracranial haemorrhage, and other clinically relevant bleed on apixaban. Dabigatran has a greater reduction in stroke risk than apixaban, and this has a greater impact on expected costs and QALYs as the stroke risk (represented by CHA_2DS_2-VASc) increases; this is confirmed in scenario analyses.

A number of sensitivity and scenario analyses were conducted exploring structural and parameter assumptions of the model. The scenario analyses stratified people by age, gender and CHADSVASC score and indicated that for all men and for all women apixaban (5mg bd) has highest incremental net benefit at the £20,000-30,000 range of willingness-to-pay thresholds. It was noted however that the probabilities that apixaban was the most cost-effective was around the 50% mark for all ages, genders, or CHADSVASC scores. In the scenarios that modelled higher CHADSVASC scores, dabigatran had a probability of being most cost-effective that was very close to that of apixaban indicating low certainty that one is better than the other. A limitation of this stroke risk stratification was that only the baseline stroke risk is adjusted, it is assumed the relative effect of the anticoagulants in terms of stroke risk reduction remains the same irrespective of baseline stroke risk.

Part of this update of the Sterne 2017 model was to run sensitivity analyses to see the impact of the cost of reversal agents on the model conclusions. This was of particular interest as two DOAC specific reversal agents are licensed for use in the UK: idarucizumab (used for dabigatran) and andexanet alpha (used for apixaban and rivaroxaban) and none of the

existing health economic models explicitly included these. Both reversal agents have a high acquisition cost. The first sensitivity analysis tried to reflect current standard of care reversal agents. It assumed a proportion of bleeds are treated with reversal agents; reversal of warfarin always uses vitamin K and a proportion of bleeds are managed with prothrombin complex concentrate with the exception of those who are taking dabigatran where idarucizumab is given instead. Due to uncertainty regarding the proportion of bleeds managed with PCC when taking warfarin, additional sensitivity analyses were conducted varying this 87.5% to 50% and 10%. A further exploratory analysis was conducted where andexanet alpha was used for a proportion of bleeds in those taking rivaroxaban and apixaban. All sensitivity analyses found that apixaban was the most cost effective option, however the certainty around that was below 50%. Thus indicating that the cost of reversal agents do not significantly change the conclusions of the base case analysis. A limitation of these sensitivity analyses is that the relative efficacy of these reversal agents was not included in the model, furthermore some reversal agent use may have already been counted in the NHS reference costs for extracranial bleeds. The committee noted that the availability of a specific reversal agent for some of the DOACs was not a deciding factor when considering which anticoagulant to prescribe. In particular it was discussed that reversal agents for DOACs are infrequently used in current practice. This is because DOACs have a much shorter half-life and therefore a reversal agent may not be required if the last dose was >12 hours before the bleed.

Overall this updated analysis of Sterne 2017 indicates that apixaban (5mg bd) and dabigatran (150mg bd) have the highest incremental net benefits at willingness-to-pay thresholds in the range £20,000-30,000, this was changed only by the sensitivity using Bakhai 2020 for the acute and management stroke costs, in which dabigatran (150mg bd) has highest net benefit. . Following stakeholder consultation, the committee reviewed the NMA and health economic model and expressed concerns regarding the validity of the NMA (see 1.7.1.3) and discussed the uncertainty around the health economic model conclusion as the credible intervals between DOACs overlapped and the probability most cost effective for apixaban was below 50% making it challenging to choose between the DOACs with confidence. They were confident however that DOACs were cost effective compared to warfarin as they all had positive incremental net monetary benefit compared to warfarin. As a result the committee decided to recommend all DOACs as first line options. The committee discussed the importance of patient choice when deciding on the best anticoagulant and this was reflected in the wording of the recommendations. Finally the committee agreed that patients, who are already taking warfarin and are stable, the potential risks and benefits of switching to a DOAC should be considered in light of their TTR. t. The committee acknowledged that these recommendations will lead to a reduction of warfarin use. A reduction in warfarin prescribing has been a growing prescribing trend over the last few years. This may lead to a contraction in warfarin clinic services.

1.7.3 Other factors the committee took into account

The committee decided to reword the 2014 recommendation to emphasise that the elements of the CHAD2SVASC2 and ORBIT risk scores that should be considered.

The committee highlighted the importance of explaining to people that the benefits of anticoagulation needed to be balanced against the risk of bleeding. The group agreed that it was important to ensure that information and education was provided to ensure the benefits and harms were fully understood (see the NICE patient experience guideline and the NICE patient decision aid). In particular, knowledge of the risks of bleeding should be used as a stimulus to encourage modification of bleeding risk factors alongside appropriate vigilance, and should only rarely be viewed as a reason to withhold anticoagulation. As a number of factors contributing to bleeding risk are dynamic and also potentially correctable, the committee considered that any decision to withhold anticoagulation should be subject to regular review and reconsideration as appropriate. The committee were also aware of the NICE guideline on multimorbidity (NG56).

The committee noted that what anticoagulant to offer should be made in the context of shared decision making and cross referred to the NICE guideline on medicines adherence, medicines optimization and patient experience of adult services. The risks and benefits of each DOAC should be discussed with the person taking into consideration personal preferences and factors likely to affect adherence such as drug forumation and frequency of dosing. The committee noted that the risks of bleeding on DOACs should also be discussed.

The committee noted that people on warfarin need to seek medical advice in the event of a head injury (see NICE guidance on head injury: Assessment and early management).

The committee highlighted the risks of concomitant use of DOACs with liver enzyme inducing drugs such as anti-epileptic medicines.

The pairwise analyses (see 1.5.5) conducted by our technical team were not deemed by the committee to have any advantage over the NMA findings, as a series of pairwise analyses are unable to consider the full network of comparisons, an essential feature of any analysis aiming to evaluate the best of several treatments. These were therefore not utilised in lieu of the NMA results. It was also agreed that an alternative NMA based on our pairwise results would be unable to overcome the limitations observed in Lopez-Lopez. This was because these limitations were related to the sparsity of the very similar, overlapping, studies and data, and not to limitations of methodology that could be potentially overcome. Furthermore, such a post-hoc decision made after seeing the results would be prone to bias.

The committee were aware that a Danish head to head randomised controlled trial of DOACs is currently recruiting (DANDOAC-AF). This study is not due to complete until September 2021.

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Appendices

Appendix A: Review protocols

Table 31: Review protocol: Efficacy and cost-effectiveness of anticoagulant for people with NVAF

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	Clinical and cost-effectiveness of anticoagulant therapy for stroke prevention in people with atrial fibrillation
2.	Review question	What is the most clinically and cost-effective anticoagulant therapy for stroke prevention in people with atrial fibrillation?
3.	Objective	To identify the most clinically and cost effective pharmacological therapy to reduce the risk of stroke or any thromboembolic event in this population
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Epistemonikos Searches will be restricted by: English language Human studies Letters and comments are excluded. Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Atrial Fibrillation
6.	Population	Inclusion: People aged over 18 with a diagnosis of non-valvular AF and identified as requiring anticoagulant therapy, in any clinical setting Exclusion: People with AF due to severe valvular disease
7.	Intervention/Exposure/Test	Warfarin (INR 2-3; including ranges of 2.5 to 3.5 and 2-4.5) [Reference treatment if NMA done] Warfarin (INR 3-4) Apixaban 2.5 mg twice daily

ID	Field	Content
		Apixaban 5 mg twice daily Dabigatran 110 mg twice daily Dabigatran 150 mg twice daily Rivaroxaban 20mg once daily Rivaroxaban 15mg once daily Edoxaban 30 mg once daily Edoxaban 60 mg once daily Different doses or frequencies of administration of DOACS will be analysed separately (ie Apixaban at 2.5 mg twice daily vs warfarin will be treated as a different comparison to Apixaban at 5 mg twice daily vs warfarin) Exclusions Combination interventions Any parenteral anticoagulation Studies with a fixed dose of warfarin, or where the regimen had a sub-optimal INR target (<2) Betrixaban – used in NMA by Lopez Lopez, but suspended by the Committee for Medicinal Products for Human Use (CHMP) on 22 March 2018. https://www.nice.org.uk/guidance/indevelopment/gid-ta10154 The following DOACS are excluded (following the rationale of Lopez Lopez): Eribaxaban (unclear stage of development) Otamixaban (parenteral) Darexaban (discontinued) LYS17717 (no info on further development) Letaxaban (no info on further development) Ximelagatran (withdrawn) AZD0837 (discontinued) Trials comparing different doses of the same drug Follow up < 3 months
8.	Comparator/Reference standard/Confounding factors	Placebo Aspirin Clopidogrel No treatment Each other [but no comparisons of different doses of the same drug will be undertaken as that is beyond the scope of this question. Although different doses of a drug will be compared separately with other drugs/placebo, this is solely to avoid problems with combining doses in meta-analyses (such as differing effects from different doses cancelling each other out in a combined analysis) and this is not intended to allow indirect comparison of different doses]. Each permutation of intervention and comparator will form a discrete comparison. These comparisons will be evaluated independently first, in terms of the outcomes below. If appropriate these comparisons will then be combined in a network meta-analysis

ID	Field	Content
9.	Types of study to be included	Systematic reviews RCTs (including those with a cross-over design). Non-randomised studies will be excluded.
10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	All stroke or systemic embolism Myocardial Infarction All-cause mortality Clinically relevant non-major bleeding Minor bleeding Major bleeding Intracranial bleeding GI bleeding health-related quality of life Longest follow up point always used
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)

ID	Field	Content	
		Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis/ meta-regression.	
17.	Analysis of sub-groups	Stratification No initial stratification Sub-grouping If serious or very serious heterogeneity (I2>50%) is present within any meta-analysis, sub-grouping will occur according to the following strategies: Threshold stroke risk score for inclusion (CHADS2 <2 versus >2) Recent stroke (post stroke versus not post stroke) Renal impairment (creatinine clearance: <50 ml/min versus >50 ml/min) Time in therapeutic range (< 65% versus >65%)	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic

ID	Field	Content		
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Sharon Swain Mark Perry Nicole Downes Sophia Kemmis Betty Elizabeth Pearton		

ID	Field	Content	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Atrial Fibrillation, anticoagulation, stroke	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 32: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.

Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. For questions being updated from NICE guideline CG180, the search will be run from October 2013, which was the cut-off date for the searches. For questions being updated from the NICE guideline CG36 and for new questions, the search will be run from 2003.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2003 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual.[126] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 (including any such studies included in the previous guideline(s))will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

This literature search strategy was used for the following reviews:

- **What is the most clinically and cost-effective anticoagulant therapy for stroke prevention in people with atrial fibrillation?**

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[126]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 33: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 –10 September 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 10 September 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 9 of 12 CENTRAL to 2020 Issue 9 of 12	None
Epistemonikos (Epistemonikos Foundation)	Inception – 10 September 2020	Systematic review studies

Medline (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.

13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	Anticoagulants/
26.	Anticoagulat*.ti,ab.
27.	Warfarin/
28.	Dabigatran/
29.	Rivaroxaban/
30.	(warfarin or apixaban or dabigatran or rivaroxaban or edoxaban).ti,ab.
31.	Coumarins/
32.	(coumarins or coumadin*).ti,ab.
33.	Antithrombins/ or Factor Xa Inhibitors/
34.	(factor xa adj2 (antagonist* or inhibit*)).ti,ab.
35.	xabans.ti,ab.
36.	(vitamin k adj2 antagonist*).ti,ab.
37.	direct antithrombin*.ti,ab.
38.	direct thrombin* inhibit*.ti,ab.
39.	or/25-38
40.	24 and 39
41.	randomized controlled trial.pt.
42.	controlled clinical trial.pt.
43.	randomi#ed.ab.
44.	placebo.ab.
45.	randomly.ab.
46.	clinical trials as topic.sh.
47.	trial.ti.
48.	or/41-47
49.	Meta-Analysis/
50.	Meta-Analysis as Topic/
51.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
52.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
53.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
54.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
55.	(search* adj4 literature).ab.

56.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
57.	cochrane.jw.
58.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
59.	or/49-58
60.	Epidemiologic studies/
61.	Observational study/
62.	exp Cohort studies/
63.	(cohort adj (study or studies or analys* or data)).ti,ab.
64.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
65.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
66.	Controlled Before-After Studies/
67.	Historically Controlled Study/
68.	Interrupted Time Series Analysis/
69.	(before adj2 after adj2 (study or studies or data)).ti,ab.
70.	exp case control study/
71.	case control*.ti,ab.
72.	Cross-sectional studies/
73.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
74.	or/63-76
75.	40 and (48 or 59 or 74)

Embase (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20

22.	limit 21 to English language
23.	*Anticoagulant agent/
24.	Anticoagulat*.ti,ab.
25.	*Warfarin/
26.	*Apixaban/
27.	*Dabigatran/
28.	*Rivaroxaban/
29.	*Edoxaban/
30.	(warfarin or apixaban or dabigatran or rivaroxaban or edoxaban).ti,ab.
31.	*Coumarin derivative/
32.	(coumarins or coumadin*).ti,ab.
33.	*Antithrombin/ or *Blood clotting factor 10a inhibitor/
34.	(factor xa adj2 (antagonist* or inhibit*)).ti,ab.
35.	xabans.ti,ab.
36.	(vitamin k adj2 antagonist*).ti,ab.
37.	direct antithrombin*.ti,ab.
38.	direct thrombin* inhibit*.ti,ab.
39.	or/23-38
40.	22 and 39
41.	random*.ti,ab.
42.	factorial*.ti,ab.
43.	(crossover* or cross over*).ti,ab.
44.	((doubl* or singl*) adj blind*).ti,ab.
45.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
46.	crossover procedure/
47.	single blind procedure/
48.	randomized controlled trial/
49.	double blind procedure/
50.	or/41-49
51.	systematic review/
52.	Meta-Analysis/
53.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
54.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
55.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
56.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
57.	(search* adj4 literature).ab.
58.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
59.	cochrane.jw.
60.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
61.	or/51-60
62.	Clinical study/
63.	Observational study/
64.	family study/

65.	longitudinal study/
66.	retrospective study/
67.	prospective study/
68.	cohort analysis/
69.	follow-up/
70.	cohort*.ti,ab.
71.	69 and 70
72.	(cohort adj (study or studies or analys* or data)).ti,ab.
73.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
74.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
75.	(before adj2 after adj2 (study or studies or data)).ti,ab.
76.	exp case control study/
77.	case control*.ti,ab.
78.	cross-sectional study/
79.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
80.	or/65-71,74-82
81.	40 and (50 or 61 or 80)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Atrial Fibrillation] explode all trees
#2.	((atrial or atria or atrium or auricular) near/3 fibrillat*):ti,ab
#3.	AF:ti,ab
#4.	#1 or #2 or #3
#5.	MeSH descriptor: [Anticoagulants] this term only
#6.	Anticoagulant*:ti,ab
#7.	MeSH descriptor: [Warfarin] this term only
#8.	MeSH descriptor: [Dabigatran] this term only
#9.	MeSH descriptor: [Rivaroxaban] this term only
#10.	(warfarin or apixaban or dabigatran or rivaroxaban or edoxaban):ti,ab
#11.	MeSH descriptor: [Coumarins] this term only
#12.	(coumarins or coumadin*):ti,ab
#13.	MeSH descriptor: [Antithrombins] this term only
#14.	MeSH descriptor: [Factor Xa Inhibitors] this term only
#15.	(factor xa near/2 (antagonist* or inhibit*)):ti,ab
#16.	xabans:ti,ab
#17.	(vitamin k near/ antagonist*)ti,ab
#18.	direct antithrombin*:ti,ab
#19.	direct thrombin* inhibit*:ti,ab
#20.	(or #5-#19)
#21.	#4 and #20

Epistemonikos search terms

1.	(title:(atrial fibrillation OR "AF") OR abstract:(atrial fibrillation OR "AF")) OR (title:(atria fibrillat* OR atrium fibrillat* OR auricular fibrillat*) OR abstract:(atria fibrillat* OR atrium fibrillat* OR auricular fibrillat*))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the Atrial Fibrillation population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA - this ceased to be updated after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run on Medline and Embase.

Table 34: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2003– 10 September 2020	Exclusions Health economics studies
Embase	2003– 10 September 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	NHSEED - 2003 to March 2015 HTA - 2003 to 31 March 2018	None

Medline (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	economics/
26.	value of life/
27.	exp "costs and cost analysis"/
28.	exp Economics, Hospital/

29.	exp Economics, medical/
30.	Economics, nursing/
31.	economics, pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	24 and 41

Embase (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/

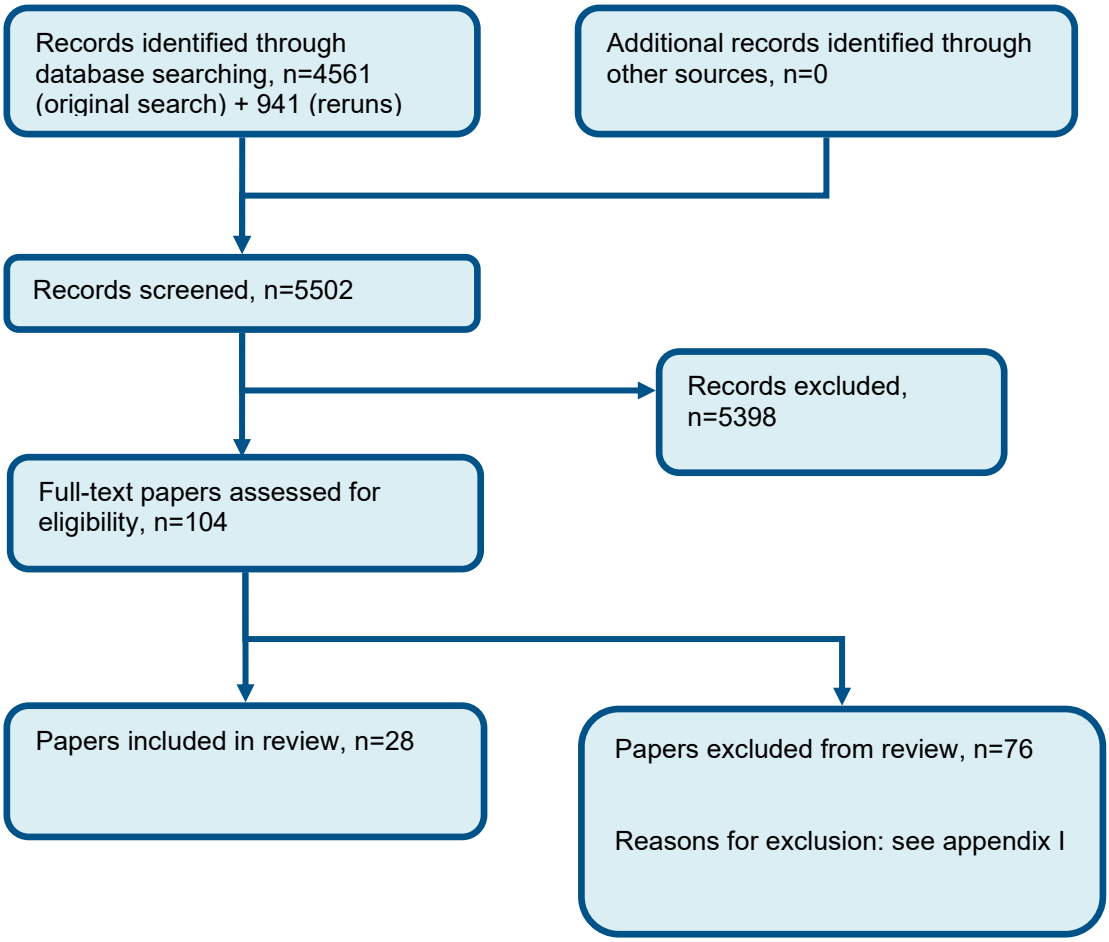
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Atrial Fibrillation EXPLODE ALL TREES
#2.	(((atrial or atria or atrium or auricular) adj3 fibrillat*))
#3.	(AF)
#4.	(#1 or #2 or #3)

Appendix C: Clinical evidence selection

Figure 2: Flow chart of clinical study selection for the review of anticoagulation



Appendix D: Clinical evidence tables

Study	**ACTIVE W trial: Active writing group of the active investigators 2006[1]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=6706)
Countries and setting	Conducted in Multiple countries
Line of therapy	1st line
Duration of study	Follow up (post intervention): 15.4 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ECG evidence of AF, and at least one of: age >=75, on treatment for systemic hypertension, previous stroke, TIA or non-CNS systemic embolus, LVEF <45%, PAD. If aged 55-74 and had no other inclusion criteria they had to have DM requiring drug therapy or previous CAD.
Exclusion criteria	Contraindications to clopidogrel or anticoagulants; documented peptic ulcer disease within past 6 months; previous intracerebral haemorrhage; significant thrombocytopenia or mitral stenosis.
Age, gender and ethnicity	Age - Mean (SD): 70.2. Gender (M:F): 66:44. Ethnicity: Unclear
Further population details	1. Recent stroke: Not stated / Unclear 2. Renal impairment: Not stated / Unclear 3. Threshold stroke risk score: CHADS2 <2 (Mean was 2). 4. Time in therapeutic range: <65% (63.8%).

Extra comments	Clop and aspirin vs VKA. Paroxysmal 18%/18%; history of hypertension 83%/82%; history of stroke or TIA 15%/15%; history of MI 17%/18%; DM 21%/21%; PAD 4%/4%; HF 30%/31%; baseline OACs: 76%/78%; baseline aspirin 30%/26%; baseline clopidogrel 3%/2%
Indirectness of population	No indirectness
Interventions	(n=3371) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). VKA at INR 2-3. The VKA used was the one in use in the respective country; thus not all on warfarin.. Duration Unclear. Concurrent medication/care: NA. Indirectness: Serious indirectness; Indirectness comment: VKA but not Warfarin (n=3335) Intervention 2: Antiplatelets - Clopidogrel. Clopidogrel 75mg once daily PLUS aspirin 75-100mg/day. Duration Unclear. Concurrent medication/care: None. Indirectness: Serious indirectness; Indirectness comment: Combined aspirin and clopidogrel
Funding	Study funded by industry (Sanofi-Aventis and Bristol-Myers-Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus CLOPIDOGREL

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Stroke + non CNS embolus at 15.4 months; Group 1: 63/3371, Group 2: 118/3335
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: Myocardial infarction
- Actual outcome: MI at 15.4 months; Group 1: 23/3371, Group 2: 36/3335
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: All cause mortality
- Actual outcome: total mortality at 15.4 months; Group 1: 158/3371, Group 2: 159/3335
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 4: Minor bleeding - Actual outcome: minor haemorrhage at 15.4 months; Group 1: 481/3371, Group 2: 568/3335 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 5: Major bleeding - Actual outcome: major haemorrhage at 15.4 months; Group 1: 93/3371, Group 2: 101/3335 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; CRNM bleeding ; ICH ; GI bleeding ; Length of stay

Study	AFASAK 2 trial: Gullov 1998[71]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=339)
Countries and setting	Conducted in Denmark; Setting: General practices in Copenhagen and surrounding areas
Line of therapy	1st line
Duration of study	Intervention + follow up: 171 days

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18 or older; chronic NVAF; AF needed to be documented twice using ECG with an interval of at least 1 month
Exclusion criteria	Patients younger than 60 with lone AF (ie no IHD, hypertension, CHF, hyperthyroidism or COPD); systolic or diastolic bp > 180/100; stroke or TIA in past 6 months; risk factors for bleeding; contraindications for warfarin or aspirin; already on dose adjusted warfarin
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Median (range): 74 (50-89). Gender (M:F): 261:78. Ethnicity: Unclear
Further population details	1. Recent stroke: Not immediately post stroke (>6 months) (Stroke/TIA less than 6 months ago exclusion criterion). 2. Renal impairment: Not stated / Unclear 3. Threshold stroke risk score: Not stated / Unclear 4. Time in therapeutic range: >=65% (73%).
Extra comments	Warfarin/aspirin: history of hypertension 47%/43%; previous AMI 8%/7%; heart failure 70%/70%; previous TIA 3%/3%; previous stroke 5%/5%; DM 10%/14%; sbp 147.2/149.2; . Only the groups with Warfarin INR 2-3 and aspirin alone were included in this review. The minidose warfarin and warfarin plus aspirin groups are not included in this extraction.
Indirectness of population	No indirectness
Interventions	(n=170) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration 42 months. Concurrent medication/care: None. Indirectness: No indirectness

	(n=169) Intervention 2: Antiplatelets - Aspirin. 300 mg / day. Duration 42 months. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Study funded by industry (Nycomed DAK A/S, Du Pont Pharma)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus ASPIRIN

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Stroke + other TE at 42 months; Group 1: 12/170, Group 2: 10/169
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: Myocardial infarction
- Actual outcome: AMI at 42 months; Group 1: 4/170, Group 2: 4/169
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: All-cause mortality
- Actual outcome: Death due to vascular, non-vascular and unknown causes at 42 months; Group 1: 17/170, Group 2: 14/169
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 4: Minor bleeding
- Actual outcome: Minor bleeding at 42 months; Group 1: 42/170, Group 2: 26/169
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 5: Major bleeding - Actual outcome: Major bleeding at 42 months; Group 1: 4/170, Group 2: 5/169 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 6: ICH - Actual outcome: Intracerebral bleeding at 42 months; Group 1: 2/170, Group 2: 1/169 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not intracranial bleeding; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; CRNM bleeding ; GI bleeding ; Length of stay

Study	ARISTOTLE trial: Granger 2011[69]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=18201)
Countries and setting	Conducted in Multiple countries; Setting: Multiple sites in multiple countries
Line of therapy	1st line
Duration of study	Intervention + follow up: 1.8 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	AF or flutter at enrollment or at least 2 episodes at least 2 weeks apart documented by ECG in prior 12 months; one of the following: age >75, previous stroke/TIA/SEE, symptomatic HF in previous 3 months or LVEF no more than 40, DM, hypertension requiring treatment.
Exclusion criteria	AF due to a reversible cause; moderate/severe mitral stenosis; non AF conditions requiring anticoagulation; stroke in previous 7 days; need for daily aspirin at dose of >165mg/day or for both aspirin and clopidogrel; severe renal insufficiency CrCl<25;
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Median (IQR): 70 (63-76). Gender (M:F): 11785:6416. Ethnicity: Unclear

Further population details	1. Recent stroke: Not stated / Unclear (exclusion criteria 1 week so possible that people with stroke in past 6 months included but unclear). 2. Renal impairment: 50 ml/min (83% >50). 3. Threshold stroke risk score: CHADS2 <2 (There were patients with CHADS scores of 1). 4. Time in therapeutic range:
Extra comments	Apixaban/warfarin: sbp 130/130; prior MI 14.4%/13.9%; prior CR or spontaneous bleeding 16.7%/16.7%; paroxysmal AF 15.1/15.5; prior use of VKA > 30 consecutive days 57.1%/57.2%; age >75 31.2%/31.1%; prior stroke, TIA or systemic embolism 19.2%/19.7%; HF or reduced LVEF 35.5%/35.4%; DM 25%/24.9%; hypertension requiring treatment 87.3%/87.6%; mean CHADs 2.1; aspirin at randomisation 31.3%/30.5%
Indirectness of population	No indirectness
Interventions	(n=9081) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration 1.8 years. Concurrent medication/care: Double dummy apixaban. Indirectness: No indirectness (n=9120) Intervention 2: DOACs - Apixaban 5 mg twice daily. 5 mg twice daily. Duration 1.8 years. Concurrent medication/care: double dummy for warfarin. Indirectness: No indirectness
Funding	Study funded by industry (Bristol-Myers Squibb and Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus APIXABAN 5 MG TWICE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Stroke or systemic embolism at 1.8 years; Group 1: 265/9081, Group 2: 212/9120
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: Myocardial infarction
- Actual outcome: MI at 1.8 years; Group 1: 102/9081, Group 2: 90/9120
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 3: All-cause mortality - Actual outcome: Death from any cause at 1.8 years; Group 1: 669/9081, Group 2: 603/9120 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 4: Major bleeding - Actual outcome: ISTH major bleeding at 1.8 years; Group 1: 462/9052, Group 2: 327/9088 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 34 ; Group 2 Number missing: 35[reasons for missing: Group 1: loss to follow up; Group 2: loss to follow up] Protocol outcome 5: ICH - Actual outcome: IC bleeding at 1.8 years; Group 1: 122/9052, Group 2: 52/9088 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 34 ; Group 2 Number missing: 35[reasons for missing: Group 1: loss to follow up; Group 2: loss to follow up] Protocol outcome 6: GI bleeding - Actual outcome: GI bleeding at 1.8 years; Group 1: 119/9052, Group 2: 105/9088 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 34 ; Group 2 Number missing: 35[reasons for missing: Group 1: loss to follow up; Group 2: loss to follow up]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; CRNM bleeding ; Minor bleeding ; Length of stay

Study	ARISTOTLE-J trial: Ogawa 2011[137]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=222)
Countries and setting	Conducted in Japan; Setting: Multiple settings in Japan
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >20; history of documented NVAF (AF confirmed by ECG, Holter or intracardiac electrogram, needed to be at least 1 minute in duration on 2 occasions at least 2 weeks apart during the preceding 2 weeks); at least one of the following: age >75, CHF (LVEF <40%), hypertension requiring meds, DM requiring treatment, history of stroke/TIA.
Exclusion criteria	Recent stroke/TIA; valvular disease; sick sinus syndrome or severe conduction disturbance; non-cardiogenic stroke requiring ASA>100 mg/day or concomitant ASA and antiplatelet agents; contraindications to warfarin use; severe or refractory hypertension; NYHA class IV; current thrombocytopenia; liver function test abnormalities; renal dysfunction (CrCl < 25); known or suspected hereditary bleeding disorders; scheduled electrical, pharmacological or surgical cardioversion during the treatment period.
Recruitment/selection of patients	Consecutive

Age, gender and ethnicity	Age - Range of means: apix 2.5/apix 5/warfarin: 69.3/70/71.7. Gender (M:F): 124:98. Ethnicity: Unclear
Further population details	1. Recent stroke: Not stated / Unclear (exclusion was 'recent stroke or TIA' but timing unclear). 2. Renal impairment: Not stated / Unclear (exclusion was CrCl <25, but unclear if any patients at 26-49.). 3. Threshold stroke risk score: CHADS2 <2 (Some patients with score of 0 present). 4. Time in therapeutic range: <65% (>60% had INR in target range >60% of the time).
Extra comments	apix 2.5/apix 5/warfarin: bp 131/77 / 125/74 / 126/75; prior warfarin 84.7%/87.3%/84%; Concomitant ASA use 20.8%/28.2%/25.3%; CHADS2 0-1 43.3%/36.5%/50%; CHF 0%/1.4%/2.7%; hypertension 82.4%/82.4%/85.1%; age >75 29.7%/31.1%/31.1%; DM 28.4%/21.6%/20.3%; history of stroke/TIA 21.6%/35.1%/20%
Indirectness of population	No indirectness
Interventions	(n=74) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3 (INR 2-2.6 for people aged >70). Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness (n=74) Intervention 2: DOACs - Apixaban 2.5mg daily. 2.5g b.i.d. Duration 3 months. Concurrent medication/care: apixaban dose blinded (not to warfarin). Indirectness: No indirectness (n=74) Intervention 3: DOACs - Apixaban 5 mg twice daily. 5 mg b.i.d. Duration 3 months. Concurrent medication/care: apixaban dose blinded (not to warfarin). Indirectness: No indirectness
Funding	Study funded by industry (PFizer Inc and Bristol Myers-Squib)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus APIXABAN 2.5MG DAILY

Protocol outcome 1: All stroke or systemic embolism

- Actual outcome: Stroke or systemic embolism at 3 months; Group 1: 4/75, Group 2: 0/72
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in levels of DM (higher for apixaban 2.5), concomitant ASA use (highest for apixaban 5) and history of stroke/TIA (highest for apixaban 5); Group 1 Number missing: 0 ; Group 2 Number missing: 2[reasons for missing: Group 1: NA; Group 2: unclear]

Protocol outcome 2: Myocardial infarction
- Actual outcome: MI at 3 months; Group 1: 0/75, Group 2: 0/72
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in levels of DM (higher for apixaban 2.5), concomitant ASA use (highest for apixaban 5) and history of stroke/TIA (highest for apixaban 5); Group 1 Number missing: 0 ; Group 2 Number missing: 2[reasons for missing: Group 1: NA; Group 2: unclear]

Protocol outcome 3: All-cause mortality
- Actual outcome: Death at 3 months; Group 1: 0/75, Group 2: 0/72
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in levels of DM (higher for apixaban 2.5), concomitant ASA use (highest for apixaban 5) and history of stroke/TIA (highest for apixaban 5); Group 1 Number missing: 0 ; Group 2 Number missing: 2[reasons for missing: Group 1: NA; Group 2: unclear]

Protocol outcome 4: CRNM bleeding
- Actual outcome: CRNMB at 3 months; Group 1: 3/75, Group 2: 1/72
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in levels of DM (higher for apixaban 2.5), concomitant ASA use (highest for apixaban 5) and history of stroke/TIA (highest for apixaban 5); Group 1 Number missing: 0 ; Group 2 Number missing: 2[reasons for missing: Group 1: NA; Group 2: unclear]

Protocol outcome 5: Minor bleeding
- Actual outcome: Minor bleeding at 3 months; Group 1: 10/75, Group 2: 8/72
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in levels of DM (higher for apixaban 2.5), concomitant ASA use (highest for apixaban 5) and history of stroke/TIA (highest for apixaban 5); Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for

missing: Group 1: NA; Group 2: NA]

Protocol outcome 6: Major bleeding
- Actual outcome: Major bleeding at 3 months; Group 1: 1/75, Group 2: 0/72
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in levels of DM (higher for apixaban 2.5), concomitant ASA use (highest for apixaban 5) and history of stroke/TIA (highest for apixaban 5); Group 1 Number missing: 0 ; Group 2 Number missing: 2[reasons for missing: Group 1: NA; Group 2: unclear]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus APIXABAN 5 MG TWICE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Stroke or systemic embolism at 3 months; Group 1: 4/75, Group 2: 0/71
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in levels of DM (higher for apixaban 2.5), concomitant ASA use (highest for apixaban 5) and history of stroke/TIA (highest for apixaban 5); Group 1 Number missing: 0 ; Group 2 Number missing: 3[reasons for missing: Group 1: NA; Group 2: unclear]

Protocol outcome 2: Myocardial infarction
- Actual outcome: MI at 3 months; Group 1: 0/75, Group 2: 0/71
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in levels of DM (higher for apixaban 2.5), concomitant ASA use (highest for apixaban 5) and history of stroke/TIA (highest for apixaban 5); Group 1 Number missing: 0 ; Group 2 Number missing: 3[reasons for missing: Group 1: NA; Group 2: unclear]

Protocol outcome 3: All-cause mortality
- Actual outcome: Death at 3 months; Group 1: 0/75, Group 2: 0/71
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in levels of DM (higher for apixaban 2.5), concomitant ASA use (highest for apixaban 5) and history of stroke/TIA (highest for apixaban 5); Group 1 Number missing: 0 ; Group 2 Number missing: 3[reasons for missing: Group 1: NA; Group 2: unclear]

Protocol outcome 4: CRNM bleeding - Actual outcome: CRNMB at 3 months; Group 1: 3/75, Group 2: 1/71 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in levels of DM (higher for apixaban 2.5), concomitant ASA use (highest for apixaban 5) and history of stroke/TIA (highest for apixaban 5); Group 1 Number missing: 0 ; Group 2 Number missing: 3[reasons for missing: Group 1: NA; Group 2: unclear] Protocol outcome 5: Minor bleeding - Actual outcome: Minor bleeding at 3 months; Group 1: 10/75, Group 2: 17/71 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in levels of DM (higher for apixaban 2.5), concomitant ASA use (highest for apixaban 5) and history of stroke/TIA (highest for apixaban 5); Group 1 Number missing: 0 ; Group 2 Number missing: 3[reasons for missing: Group 1: NA; Group 2: unclear] Protocol outcome 6: Major bleeding - Actual outcome: Major bleeding at 3 months; Group 1: 1/75, Group 2: 0/71 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in levels of DM (higher for apixaban 2.5), concomitant ASA use (highest for apixaban 5) and history of stroke/TIA (highest for apixaban 5); Group 1 Number missing: 0 ; Group 2 Number missing: 3[reasons for missing: Group 1: NA; Group 2: unclear]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; ICH ; GI bleeding ; Length of stay

Study	AVERROES trial: Connolly 2011[37]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=5599)
Countries and setting	Conducted in Multiple countries; Setting: Multicentre in multiple countries
Line of therapy	1st line
Duration of study	Intervention + follow up: 1.1 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	50 years or older; AF documented in 6 months pre-enrollment or by 12 lead ECG on the day of screening; one of the following: prior stroke/TIA, aged 75+, treated arterial hypertension, DM on treatment, NYHA class II or higher, documented PAD; PATIENTS CONSIDERED UNSUITABLE FOR VKA TREATMENT BECAUSE OF DEMONSTRATED OR ANTICIPATED CONCERNS ABOUT CONTRAINDICATIONS.
Exclusion criteria	presence of conditions other than AF for which patient required anticoagulants; valvular disease requiring surgery; serious bleeding event in previous 6 months or high risk of bleeding, current ETOH abuse or psychosocial issues; life expectancy <12 months; severe renal insufficiency CrCl < 25 ml per minute; alanine aminotransferase or aspartate aminotransferase level > 2x ULN; bilirubin > 1.5X ULN; allergy to aspirin
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 70(10). Gender (M:F): 3277:2322. Ethnicity: Unclear

Further population details	1. Recent stroke: Not stated / Unclear 2. Renal impairment: Not stated / Unclear (<25 excluded but possible that 25-49 could be present). 3. Threshold stroke risk score: CHADS2 <2 (People with CHADS2 of 0 included). 4. Time in therapeutic range: Not applicable
Extra comments	Apixaban/aspirin: systolic bp 132/132; prior stroke/TIUA 14%/13%; hypertension 86%/87%; NYHA class I or II 33%/31%; NYHA class III or IV 7%/6%; LVEF <35% 5%/5%; PAD 2%/3%; treated DM 19%/20%; mitral stenosis 2%/2%; paroxysmal AF 27%/27%; CHADS 0 or 1: 26%/37%; use of VKA in 30 days pre-screening 14%/15%; use of aspirin 30 days pre-screening 76%/75%. Special population - people for who VKAs are unsuitable. This probably means that this study cannot be put in the NMA, as it will be clinically heterogeneous.
Indirectness of population	No indirectness
Interventions	(n=2808) Intervention 1: DOACs - Apixaban 5 mg twice daily. 5 mg twice daily. Duration 1.1 years. Concurrent medication/care: with dummy placebo for aspirin. Indirectness: No indirectness (n=2791) Intervention 2: Antiplatelets - Aspirin. 81mg but dose varied. Duration 1.1 years. Concurrent medication/care: With double dummy apixaban. Indirectness: No indirectness
Funding	Study funded by industry (Bristol-Myers Squibb and Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: APIXABAN 5 MG TWICE DAILY versus ASPIRIN

Protocol outcome 1: Hospitalisation
- Actual outcome: hospitalisation for cardiovascular cause at 1.1 years; Group 1: 367/2808, Group 2: 455/2791
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: hospitalisation for cardiovascular cause, not any cause; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: All stroke or systemic embolism
- Actual outcome: Stroke or systemic embolism at 1.1 years; Group 1: 51/2808, Group 2: 113/2791

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: Myocardial infarction
- Actual outcome: MI at 1.1 years; Group 1: 24/2808, Group 2: 28/2791
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 4: All-cause mortality
- Actual outcome: Death from any cause at 1.1 years; Group 1: 111/2808, Group 2: 140/2791
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 5: CRNM bleeding
- Actual outcome: CRNM bleeding at 1.1 years; Group 1: 96/2808, Group 2: 84/2791
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 6: Minor bleeding
- Actual outcome: minor bleeding at 1.1 years; Group 1: 188/2808, Group 2: 153/2791
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 7: Major bleeding
- Actual outcome: Major bleeding at 1.1 years; Group 1: 44/2808, Group 2: 39/2791
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 8: ICH
- Actual outcome: IC bleeding at 1.1 years; Group 1: 11/2808, Group 2: 13/2791
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 9: GI bleeding - Actual outcome: GI bleeding at 1.1 years; Group 1: 12/2808, Group 2: 14/2791 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Length of stay

Study	BAFTA trial: Mant 2007[116]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=973)
Countries and setting	Conducted in United Kingdom; Setting: 260 General Practices in England and Wales
Line of therapy	1st line
Duration of study	Follow up (post intervention): 2.7 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 75 or older; AF or flutter on study ECG or in ECG done in past 2 years
Exclusion criteria	rheumatic heart disease; major non-traumatic haemorrhage within previous 5 years; ICH; endoscopically proven peptic ulcer disease in previous year; oesophageal varices; allergic sensitivity to either study drug; terminal illness; surgery in past 3 months; bp > 180/110; primary care physician judges should not be on warfarin
Recruitment/selection of patients	Patients identified through computer searches of primary care records for diagnoses of atrial fibrillation and opportunistic pulse measurements
Age, gender and ethnicity	Age - Mean (SD): 81.5 (4.3). Gender (M:F): 531:442. Ethnicity: Unclear

Further population details	1. Recent stroke: Not stated / Unclear 2. Renal impairment: Not stated / Unclear 3. Threshold stroke risk score: CHADS2 <2 (Patients with score of 1 in cohort). 4. Time in therapeutic range: >=65% (67%).
Extra comments	Warfarin/aspirin: CHADS >=3 28%/28%; previously on warfarin 40%/39%; previously on aspirin 42%/42%; history of stroke or TIA 13%/12%; history of hypertension 53%/55%; systolic bp 139.9/141.3; DM 14%/13%; HF 20%/19%; MI 10%/12%; Angina 16%/15%
Indirectness of population	No indirectness
Interventions	(n=488) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration Up to 5 years (mean 2.7 years). Concurrent medication/care: None (n=485) Intervention 2: Antiplatelets - Aspirin. 75mg daily. Duration Up to 5 years (Mean 2.7 years). Concurrent medication/care: None. Indirectness: No indirectness
Funding	Principal author funded by industry (Astra Zeneca, Sanofi-Aventis, Bayer, Astellas, Daiichi-Sankyo)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus ASPIRIN

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: First occurrence of fatal or non-fatal disabling stroke, other intracranial hemorrhage, or clinically significant arterial embolism at 2.7 years; Group 1: 24/488, Group 2: 48/485
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: This outcome is more severe than the protocol outcome, requiring disabling and clinically significant events; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: Myocardial infarction
- Actual outcome: MI at 2.7 years; Group 1: 15/488, Group 2: 15/485
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA;

Group 2: NA] Protocol outcome 3: All-cause mortality - Actual outcome: All-cause death at 2.7 years; Group 1: 107/488, Group 2: 108/485 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 4: Major bleeding - Actual outcome: Major bleeding at 2.7 years; Group 1: 25/488, Group 2: 25/485 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; CRNM bleeding ; Minor bleeding ; ICH ; GI bleeding ; Length of stay

Study	CAFA trial: Connolly 1991[40]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=378)
Countries and setting	Conducted in Canada; Setting: 11 Canadian centres
Line of therapy	1st line
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Chronic AF present >1 month or paroxysmal AF occurring at least 3 times in the previous 3 months (documented at least twice on ECG); age >19 years; absence of mitral valve prosthesis or mechanical aortic valve prosthesis; absence of mitral valve stenosis of echocardiography
Exclusion criteria	medical contraindications to OACs; stroke or TIA within 1 year; requirement for antiplatelet therapy; hyperthyroidism; uncontrolled hypertension; MI in past month
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Other: warfarin 68, placebo 67.4. Gender (M:F): 282:96. Ethnicity: Unclear

Further population details	1. Recent stroke: Not immediately post stroke (>6 months) (No strokes within one year). 2. Renal impairment: Not stated / Unclear 3. Threshold stroke risk score: Not stated / Unclear 4. Time in therapeutic range: <65% (43.7% of days when INR2-3).
Extra comments	Warfarin/placebo: angina 21.9%/19.9%; prior MI 15%/12%; HF 23.5%/20.4%; stroke or TIA 3.2%/4.2%; Intermittent claudication 10.2%/4.7%; DM 13.9%/10%; cardiomyopathy 6.4%/5.8%; history of hypertension 43.3%/34%; paroxysmal AF 6.4%/7.3%
Indirectness of population	No indirectness
Interventions	(n=187) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration up to 2 years. Concurrent medication/care: None. Indirectness: No indirectness (n=191) Intervention 2: placebo. Sham dose based on sham INR measurements. Duration up to 2 years. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Academic or government funding (MRC of Canada)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus PLACEBO

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: lacunar or non-lacunar stroke at up to 2 years; Group 1: 6/187, Group 2: 9/191
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: No composite Stroke/TIA/SEE outcome. There was a composite outcome but included fatal hemorrhage. ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: All-cause mortality
- Actual outcome: All death at up to 2 years; Group 1: 10/187, Group 2: 8/191
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: Minor bleeding - Actual outcome: minor bleeding at up to 2 years; Group 1: 30/187, Group 2: 18/191 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 4: Major bleeding - Actual outcome: Life threatening or major bleeding at up to 2 years; Group 1: 5/187, Group 2: 1/191 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 5: ICH - Actual outcome: IC bleeding at up to 2 years; Group 1: 1/187, Group 2: 0/191 Risk of bias: All domain - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Myocardial infarction ; CRNM bleeding ; GI bleeding ; Length of stay

Study	CHEN, 2012 trial: Chen 2012[29]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=521)
Countries and setting	Conducted in China; Setting: 75 institutions in China
Line of therapy	1st line
Duration of study	Follow up (post intervention): 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG and/or Holter
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 67. Gender (M:F): Define. Ethnicity: Unclear
Further population details	1. Recent stroke: Not immediately post stroke (>6 months) (<6 months exclusion criterion). 2. Renal impairment: Not stated / Unclear 3. Threshold stroke risk score: Not stated / Unclear 4. Time in therapeutic range: <65% (51.2% in target range of 2.1 to 2.5 (but probably would have been >65% in 2-3 range)).

Extra comments	Note that this study had 3 groups, including a low dose warfarin group. This low dose is not included in this review. Data are given for standard intensity warfarin (INR 2.1 to 2.5)/aspirin group only: AF > 1 year 71.7%/72.2%; Ischaemic stroke 14.2%/10.4%; TIA 6.7%/5%; Peripheral artery embolism 1.7%/0%; hypertension 59%/66.2%; DM 12.1%/14.9%; MI 5.4%/3%; NYHA III 21.3%/26.4%
Indirectness of population	No indirectness
Interventions	(n=261) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2.1 to 2.5. Duration 2 years. Concurrent medication/care: Initial dose of 1-3 mg/d of warfarin prescribed after baseline INR values were measured. Then INR measured every 1-2 days to titrate dose. Indirectness: No indirectness (n=260) Intervention 2: Antiplatelets - Aspirin. 200mg/d. Duration 2 years. Concurrent medication/care: None. No dummy INR titration undertaken (performance bias?). Indirectness: No indirectness
Funding	Academic or government funding (10th National Five-year Project of China)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus ASPIRIN

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Thrombolic event including ischaemic stroke, TIA or systemic embolism at 2 years; Group 1: 7/239, Group 2: 16/201
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in rates of stroke (14%/10%).; Group 1 Number missing: 22 ; Group 2 Number missing: 59[reasons for missing: Group 1: did not want to do follow up; Group 2: Did not want to do follow up; unlikely to cause attrition bias as probably not related to outcome]

Protocol outcome 2: All-cause mortality
- Actual outcome: All-cause mortality at 2 years; Group 1: 5/239, Group 2: 6/201
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in rates of stroke (14%/10%).; Group 1 Number missing: 22 ;

Group 2 Number missing: 59[reasons for missing: Group 1: did not want to do follow up; Group 2: Did not want to do follow up; unlikely to cause attrition bias as probably not related to outcome]

Protocol outcome 3: Minor bleeding
- Actual outcome: minor bleeding at 2 years; Group 1: 21/239, Group 2: 4/201
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in rates of stroke (14%/10%).; Group 1 Number missing: 22 ; Group 2 Number missing: 59[reasons for missing: Group 1: did not want to do follow up; Group 2: Did not want to do follow up; unlikely to cause attrition bias as probably not related to outcome]

Protocol outcome 4: Major bleeding
- Actual outcome: major bleeding at 2 years; Group 1: 7/239, Group 2: 1/201
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in rates of stroke (14%/10%).; Group 1 Number missing: 22 ; Group 2 Number missing: 59[reasons for missing: Group 1: did not want to do follow up; Group 2: Did not want to do follow up; unlikely to cause attrition bias as probably not related to outcome]

Protocol outcome 5: ICH
- Actual outcome: Intracerebral bleeding at 2 years; Group 1: 1/261, Group 2: 0/260
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: HEM STROKE NOT IC BLEEDING!; Baseline details: Differences in rates of stroke (14%/10%).; Group 1 Number missing: 22 ; Group 2 Number missing: 59[reasons for missing: Group 1: did not want to do follow up; Group 2: Did not want to do follow up; unlikely to cause attrition bias as probably not related to outcome]

Protocol outcome 6: GI bleeding
- Actual outcome: GI bleeding at 2 years; Group 1: 6/261, Group 2: 1/260
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in rates of stroke (14%/10%).; Group 1 Number missing: 22 ; Group 2 Number missing: 59[reasons for missing: Group 1: did not want to do follow up; Group 2: Did not want to do follow up; unlikely to cause attrition bias as probably not related to outcome]

Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Myocardial infarction ; CRNM bleeding ; Length of stay

Study	CHEN, 2013 trial: Chen 2013[30]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=378 (from total cohort of 1162))
Countries and setting	Conducted in China; Setting: Multicentre study in China
Line of therapy	1st line
Duration of study	Not clear: Minimum 6 months treatment duration. Mean FU 51 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Range: 72.2/72.4. Gender (M:F): Define. Ethnicity: Unclear
Further population details	1. Recent stroke: Not stated / Unclear (Only 21% with prior stroke so % with recent stroke likely to be low). 2. Renal impairment: Not stated / Unclear 3. Threshold stroke risk score: Not stated / Unclear 4. Time in therapeutic range: Not stated / Unclear

Extra comments	Data are given for warfarin/aspirin: hypertension 40%/41.6%; DM 36.6%/37.6%; prior stroke 21.5%/21.9%; prior TIA 14.1%/14.5%; LVEF <35% 9.8%/10.4; follow up period 50.7m/51.3m.
Indirectness of population	No indirectness
Interventions	(n=205) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2.6 - 3.0. Duration 51 months. Concurrent medication/care: Initially administered 2.5mg/day of aspirin which was then adjusted to target INR. Indirectness: No indirectness (n=173) Intervention 2: Antiplatelets - Aspirin. 150 mg/day. Duration 51 months. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus ASPIRIN

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Ischaemic stroke at 50 months; Group 1: 2/205, Group 2: 10/173
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: Myocardial infarction
- Actual outcome: Acute MI at 50 months; Group 1: 4/205, Group 2: 3/173
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: All-cause mortality
- Actual outcome: Death at 50 months; Group 1: 4/205, Group 2: 6/173
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 4: Minor bleeding - Actual outcome: Minor bleeding at 50 months; Group 1: 24/205, Group 2: 11/173 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 5: Major bleeding - Actual outcome: Major bleeding at 50 months; Group 1: 13/205, Group 2: 5/173 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 6: ICH - Actual outcome: Cerebral hemorrhage at 50 months; Group 1: 9/205, Group 2: 2/173 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: CEREBRAL HEM NOT IC BLEEDING!; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 7: GI bleeding - Actual outcome: GI bleeding at 50 months; Group 1: 4/205, Group 2: 3/173 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; CRNM bleeding ; Length of stay

Study	CHUNG, 2011 trial: Chung 2011[33]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=235)
Countries and setting	Conducted in Hong Kong (China), Singapore, South Korea, Taiwan; Setting: Four Asian countries
Line of therapy	1st line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-80; NVAF confirmed on ECG twice within 6 months before randomisation); CHADS > =1
Exclusion criteria	Previous valve surgery; contraindications to anticoagulants; known bleeding disorders; conditions associated with high risk of bleeding; antiplatelet agents; AF due to reversible causes; ACS or evascularisation procedures; stroke/TIA/major surgery in past 30 days; left ventricular aneurysm or atrial myxoma; impaired hepatic function; serum Cr >1.5 mg/dl; pregnancy or lactating.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Range of means: Warf/Edox 30/Edox 60: 64.5/64.9/65.9. Gender (M:F): 153:82. Ethnicity: Unclear

Further population details	1. Recent stroke: Not stated / Unclear (Exclusion for <1 month but unclear if any between 1-6 months). 2. Renal impairment: >50 ml/min (About 80% >50). 3. Threshold stroke risk score: CHADS2 <2 (CHADS of >=1 was threshold). 4. Time in therapeutic range: <65% (45%).
Extra comments	Warf/Edox 30/Edox 60: hypertension 69.3%/70.9%/73.8%; DM 22.7%/38%/27.5%; CHF: 32%/22.8%/31.3%; History TIA/stroke 22.7/26.6/23.8; CHADS 1.8/2.0/1.9; previous warfarin treatment 54.7%/50.6%/50%; CrCl<50 ml/min 21.3%/15.2%/17.5%; concomitant aspirin 34.7%/43%/41.3%
Indirectness of population	No indirectness
Interventions	(n=76) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness (n=79) Intervention 2: DOACs - Edoxaban 30mg once daily. 30mg twice daily. Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness (n=80) Intervention 3: DOACs - Edoxaban 60 mg once daily. 60mg twice daily. Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Study funded by industry (Funded by Daiichi Sankyo)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus EDOXABAN 30MG ONCE DAILY

Protocol outcome 1: All-cause mortality
- Actual outcome: Death at 3 months; Group 1: 2/75, Group 2: 0/79
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and then excluded by researchers; Group 2: NA]

Protocol outcome 2: CRNM bleeding
- Actual outcome: CRNM bleeding at 3 months; Group 1: 3/75, Group 2: 0/79
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and then excluded by researchers; Group 2: NA]

Protocol outcome 3: Minor bleeding
- Actual outcome: Minor bleeding at 3 months; Group 1: 17/75, Group 2: 16/79
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and then excluded by researchers; Group 2: NA]

Protocol outcome 4: Major bleeding
- Actual outcome: Major bleeding at 3 months; Group 1: 2/75, Group 2: 0/79
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and then excluded by researchers; Group 2: NA]

Protocol outcome 5: GI bleeding
- Actual outcome: GI bleeding at 3 months; Group 1: 1/75, Group 2: 0/79
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and then excluded by researchers; Group 2: NA]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus EDOXABAN 60 MG ONCE DAILY

Protocol outcome 1: All-cause mortality
- Actual outcome: Death at 3 months; Group 1: 2/75, Group 2: 0/80
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and then excluded by researchers; Group 2: NA]

Protocol outcome 2: CRNM bleeding
- Actual outcome: CRNM bleeding at 3 months; Group 1: 3/75, Group 2: 6/80
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and then excluded by researchers; Group 2: NA]

Protocol outcome 3: Minor bleeding
- Actual outcome: Minor bleeding at 3 months; Group 1: 17/75, Group 2: 15/80
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and then excluded by researchers; Group 2: NA]

Protocol outcome 4: Major bleeding
- Actual outcome: Major bleeding at 3 months; Group 1: 2/75, Group 2: 0/80
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and then excluded by researchers; Group 2: NA]

Protocol outcome 5: GI bleeding
- Actual outcome: GI bleeding at 3 months; Group 1: 1/75, Group 2: 0/80
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and then excluded by researchers; Group 2: NA]

Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; All stroke or systemic embolism ; Myocardial infarction ; ICH ; Length of stay

Study	COPENHAGEN AFASAK STUDY trial: Petersen 1989[141]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1007)
Countries and setting	Conducted in Denmark; Setting: Copenhagen - recruited from ECG clinics, to which they had been referred by primary care.
Line of therapy	1st line
Duration of study	Follow up (post intervention): 2 years or until termination of the trial
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Outpatient ECG laboratories (12 lead ECG)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years or over; ECG verified AF
Exclusion criteria	Previous anticoagulation therapy for >6 months; CVA in past month; contraindication to warfarin/aspirin; previous AEs of warfarin/aspirin; current Rx with aspirin/warfarin; breast feeding or pregnancy; persistent bp >180/100; psychiatric diseases, including chronic alcoholism, Heart surgery with valve replacement; sinus rhythm, rheumatic heart disease.
Recruitment/selection of patients	Consecutive recruitment from2 ECG laboratories
Age, gender and ethnicity	Age - Range of means: 72.8 (warfarin), 75.1 (aspirin) and 74.6 (placebo). Gender (M:F): 53:47. Ethnicity: Unclear

Further population details	1. Recent stroke: Not immediately post stroke (>6 months) (Only 5% had ever had a stroke, so definitely not a recent stroke study; however actual times from strokes unknown, apart from >1 month before.). 2. Renal impairment: Not stated / Unclear 3. Threshold stroke risk score: Not stated / Unclear 4. Time in therapeutic range: <65% (In 2.8 to 4.2 INR range for 42% of the time).
Extra comments	Data given for warfarin/placebo: previous TIA: 1%/2%; previous stroke 5%/4%; previous AMI 8%/8%; Angina 19%/16%; DM 7%/10%; hypertension 32%/31%; smoking 40%/35%; HF 50%/51%; thyrotoxicosis 5%/4%
Indirectness of population	No indirectness
Interventions	(n=335) Intervention 1: Vitamin K antagonists - Warfarin INR 3-4. INR 4.2 to 2.8. Duration 2 years. Concurrent medication/care: Use of the Normotest to evaluate INR. Initially blood samples taken every day for 5 days then every 4 weeks. During each year of treatment a period of 4 weeks was allowed without warfarin treatment. Indirectness: No indirectness (n=336) Intervention 2: placebo. identical to the aspirin drugs (not included in this extraction) but different looking to warfarin tablets.. Duration 2 years. Concurrent medication/care: INR testing done to preserve blinding. Indirectness: No indirectness (n=336) Intervention 3: Antiplatelets - Aspirin. As placebo. Duration 2 years. Concurrent medication/care: INR testing to preserve blinding. Indirectness: No indirectness
Funding	Other (NycoMed AS, Oslo. Also non-industry research funding.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 3-4 versus PLACEBO

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Total embolic complications at 2 years; Group 1: 5/335, Group 2: 21/336
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA;

Group 2: NA]

Protocol outcome 2: All-cause mortality
- Actual outcome: Fatal strokes and vascular deaths at 2 years; Group 1: 4/335, Group 2: 19/336
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not All-cause mortality - data on other causes not complete.; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: GI bleeding
- Actual outcome: GI bleeding at 2 years; Group 1: 4/335, Group 2: 0/336
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 3-4 versus ASPIRIN

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Total embolic complications at 2 years; Group 1: 5/335, Group 2: 20/336
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: All-cause mortality
- Actual outcome: Fatal strokes and vascular deaths at 2 years; Group 1: 4/335, Group 2: 15/336
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not All-cause mortality - data on other causes not complete.; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: GI bleeding
- Actual outcome: GI bleeding at 2 years; Group 1: 4/335, Group 2: 1/336
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Myocardial infarction ; CRNM bleeding ; Minor bleeding ; Major bleeding ; ICH ; Length of stay

Study	ENGAGE AF-TIMI 48 Investigators trial: Giugliano 2013[67]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=21105)
Countries and setting	Conducted in Multiple countries; Setting: Unclear
Line of therapy	1st line
Duration of study	Follow up (post intervention): 2.8 years median
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG diagnosed ASF
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 21 or older; AF diagnosed with ECG within past 12 months; CHADS2 of 2 or more
Exclusion criteria	AF due to a reversible disorder, creatine clearance <30ml/min; high risk of bleeding; use of dual antiplatelet therapy; moderate to severe mitral stenosis; other indications for anticoagulation therapy; acute coronary syndromes; coronary revascularisation; stroke in past month
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Median (IQR): 72 (64-78). Gender (M:F): 62:38. Ethnicity: Unclear
Further population details	1. Recent stroke: Not stated / Unclear (28% with prior stroke; none in past 30 days but unclear how many in past 6 months). 2. Renal impairment: > = 50 ml/min (80% with creatine clearance above 50 ml/min). 3.

	Threshold stroke risk score: CHADS2 >=2 (<2 exclusion criterion). 4. Time in therapeutic range: >=65% (mean TTR 68.4%).
Extra comments	Data given for warfarin/high dose edoxaban/low-dose edoxaban: paroxysmal AF 25.3%/24.9%/26.1%; age >75 40.1%/40.5%/39.9%; previous stroke or TIA 28.3%/28.1%/28.5%; CHF 57.5%/58.2%/56.6%; DM 35.8%/36.4%/36.2%; hypertension requiring treatment 93.6%/93.7%/93.5%; CHADS2 2-3 77.4%/77.1%/77.8%; Cr Cl <50 19.3%/19.6%/19%; previous sue of VKA for >60 days 58.8%/58.8%/59.2%; meds at time of randomisation - aspirin 29.7%/29.4%/28.7%
Indirectness of population	No indirectness
Interventions	(n=7036) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration median 2.8 years. Concurrent medication/care: INR measured at least monthly with encrypted point of care device (sham values for Edoxaban patients to preserve blinding). Double dummy - so patients had warfarin and dummy edoxaban (n=7034) Intervention 2: DOACs - Edoxaban 30mg once daily. Dose halved if any of the following seen at any point: Cr Cl 30-50; BW 60kg or less; concomitant use of verapamil, dronedarone or quinidine. Duration Median 2.8 years. Concurrent medication/care: Double dummy - so each patient had DOAC and dummy warfarin. Indirectness: No indirectness (n=7034) Intervention 3: DOACs - Edoxaban 60 mg once daily. Dose halved as for 30mg. Duration median 2.8 years. Concurrent medication/care: As for 30mg. Indirectness: No indirectness
Funding	Study funded by industry (Daiichi Sankyo Pharma Development NCT00781391)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus EDOXABAN 30MG ONCE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Stroke or systemic embolic events at 2.8 years; Group 1: 337/7036, Group 2: 383/7034

Risk of bias: All domain - --, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: Myocardial infarction
- Actual outcome: Myocardial infarction at 2.8 years; Group 1: 141/7036, Group 2: 169/7034
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: All-cause mortality
- Actual outcome: All-cause mortality at 2.8 years; Group 1: 839/7036, Group 2: 737/7034
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 4: CRNM bleeding
- Actual outcome: CRNMB at 2.8 years; Group 1: 1396/7012, Group 2: 969/7002
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24 ; Group 2 Number missing: 32[reasons for missing: Group 1: unclear; Group 2: unclear]

Protocol outcome 5: Minor bleeding
- Actual outcome: minor bleeding at 2.8 years; Group 1: 714/7012, Group 2: 533/7002
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24 ; Group 2 Number missing: 32[reasons for missing: Group 1: unclear; Group 2: unclear]

Protocol outcome 6: Major bleeding
- Actual outcome: Major bleeding at 2.8 years; Group 1: 524/7012, Group 2: 254/7002
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24 ; Group 2 Number missing: 32[reasons for missing: Group 1: unclear; Group 2: unclear]

Protocol outcome 7: ICH
- Actual outcome: IC bleeding at 2.8 years; Group 1: 132/7012, Group 2: 41/7002
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 24 ; Group 2 Number missing: 32[reasons for missing: Group 1: unclear; Group 2: unclear]

Protocol outcome 8: GI bleeding
- Actual outcome: GI bleeding at 2.8 years; Group 1: 190/7012, Group 2: 129/7002
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 32 ; Group 2 Number missing: 23[reasons for missing: Group 1: unclear; Group 2: unclear]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus EDOXABAN 60 MG ONCE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Stroke or systemic embolic event at 2.8 years; Group 1: 337/7036, Group 2: 296/7035
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: Myocardial infarction
- Actual outcome: Myocardial infarction at 2.8 years; Group 1: 141/7036, Group 2: 133/7035
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: All-cause mortality
- Actual outcome: All-cause mortality at 2.8 years; Group 1: 839/7036, Group 2: 773/7035
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 4: CRNM bleeding
- Actual outcome: CRNMB at 2.8 years; Group 1: 1396/7012, Group 2: 1214/7012
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24 ; Group 2 Number missing: 23[reasons for missing: Group 1: unclear; Group 2: unclear]

Protocol outcome 5: Minor bleeding
- Actual outcome: minor bleeding at 2.8 years; Group 1: 714/7012, Group 2: 604/7012
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of

outcome: No indirectness ; Group 1 Number missing: 24 ; Group 2 Number missing: 23[reasons for missing: Group 1: unclear; Group 2: unclear] Protocol outcome 6: Major bleeding - Actual outcome: Major bleeding at 2.8 years; Group 1: 524/7012, Group 2: 418/7012 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 24 ; Group 2 Number missing: 23[reasons for missing: Group 1: unclear; Group 2: unclear] Protocol outcome 7: ICH - Actual outcome: IC bleeding at 2.8 years; Group 1: 132/7012, Group 2: 61/7012 Risk of bias: All domain - --, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24 ; Group 2 Number missing: 23[reasons for missing: Group 1: unclear; Group 2: unclear] Protocol outcome 8: GI bleeding - Actual outcome: GI bleeding at 2.8 years; Group 1: 190/7012, Group 2: 232/7012 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24 ; Group 2 Number missing: 23[reasons for missing: Group 1: unclear; Group 2: unclear]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Length of stay

Study	J-ROCKET trial: Hori 2012[81]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1280)
Countries and setting	Conducted in Japan; Setting: 167 settings in Japan
Line of therapy	1st line
Duration of study	Intervention + follow up: 900 days+
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Japanese patients; aged >20 years; NVAF diagnosed by EMG <30 days prior to randomisation; history of prior stroke/TIA/SEE or had 2 or more of the following: CHF (or LVEF <35%), hypertension, age >75 years, DM.
Exclusion criteria	Not reported
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (range): 71.1(34-90). Gender (M:F): 1030:248. Ethnicity: Unclear
Further population details	1. Recent stroke: Not stated / Unclear 2. Renal impairment: > = 50 ml/min (77.8% has CrCl > 50). 3. Threshold stroke risk score: CHADS2 >=2 (Nobody with score 0 or 1). 4. Time in therapeutic range: >=65% (65% TTR).

Extra comments	Rivarixaban/Warfarin: baseline Cr Cl <50 22.1%/22.4%; previous warfarin 90.3%/89.7%; prior aspirin 38%/34.7%; mean CHADS2 3.27/3.22; CHF 41.3/40.2; >75 years 39.4%/38.5%; DM 39%/37.1%; stroke/TIA 63.8%/63.4%; prior MI 7%/8.3%
Indirectness of population	No indirectness
Interventions	(n=639) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3 if aged <70; however if aged >70 then INR was 1.6-2.6. Duration 900 days+. Concurrent medication/care: NA. Indirectness: Serious indirectness; Indirectness comment: Patients over 70 received INR of 1.6-2.6 (n=639) Intervention 2: DOACs - Rivaroxaban 15 mg once daily. 15 mg once daily; but 10mg if CrCl <50. Duration 900 days+. Concurrent medication/care: NA. Indirectness: Serious indirectness; Indirectness comment: 10mg given to those with renal dysfunction - non review-protocol dose
Funding	Study funded by industry (Janssen Pharmaceuticals Bayer HealthCare)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus RIVAROXABAN 15 MG ONCE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: stroke plus non CNS systemic embolism at 900 days; Group 1: 22/637, Group 2: 11/637
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2 ; Group 2 Number missing: 2[reasons for missing: Group 1: unclear; Group 2: unclear]

Protocol outcome 2: Myocardial infarction
- Actual outcome: MI at 900 days; Group 1: 1/637, Group 2: 3/637
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2 ; Group 2 Number missing: 2[reasons for missing: Group 1: unclear; Group 2:

unclear] Protocol outcome 3: All-cause mortality - Actual outcome: All-cause mortality at 900 days; Group 1: 5/637, Group 2: 7/637 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2 ; Group 2 Number missing: 2[reasons for missing: Group 1: unclear; Group 2: unclear] Protocol outcome 4: ICH - Actual outcome: Intracranial bleeding at 900 days; Group 1: 10/639, Group 2: 5/639 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 5: GI bleeding - Actual outcome: Major bleeding from upper GI tract at 900 days; Group 1: 12/639, Group 2: 6/639 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; CRNM bleeding ; Minor bleeding ; Major bleeding ; Length of stay

Study	**Ke, 2019[91]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in China; Setting: Unclear but may be a single hospital in China

Line of therapy	1st line
Duration of study	3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >=18 yrs; NVAF; LA thrombus confirmed by TEE; oral anticoagulation untreated for at least 1 month
Exclusion criteria	Haematological disease; previous 1 year history of GI bleeding/urinary tract bleeding; previous 1 year history of stroke; known malignancy; Crcl <15 mL/min; hepatic disease associated with coagulopathy
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age – 64.2/63.7. Gender (M:F): 66:14. Ethnicity: Unclear
Further population details	1. Recent stroke: No. 2. Renal impairment: Not stated / Unclear (exclusion of <15 but may have been some patients between 15 and 49). 3. Threshold stroke risk score: CHADS2 >=2. 4. Time in therapeutic range: Not stated / Unclear (Not reported).
Extra comments	warfarin/rivaroxaban: sbp 130.7/128.3; CHADS2 of ≥2: 57.5%/65%; previous stroke/TIA/SEE 0/2.5%; hypertension 25%/20%; DM 5%/10%;
Indirectness of population	No indirectness
Interventions	(n=176) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration 12 weeks. Concurrent medication/care: None. Indirectness: No indirectness

	(n=177) Intervention 2: DOACs - Rivaroxaban 20mg qd. 20 mg daily. Duration 12 weeks. Concurrent medication/care: Sham INR values taken to maintain treatment blinding. Indirectness: No indirectness
Funding	Non commercial funding (General Program of Natural Science Foundation of Guangxi Province of China, and Key Project of Scientific Research and Technology Development of Qingxiu District of Nanning, Guangxi government.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus RIVAROXABAN 20MG ONCE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Stroke and system embolism at unclear; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: Major bleeding
- Actual outcome: major bleeding at unclear; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Myocardial infarction ; CRNM bleeding ; Minor bleeding ; Length of stay

Study	Kikuchi, 2019[92]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=193)
Countries and setting	Conducted in Japan; Setting: Unclear but may be a single hospital in Japan
Line of therapy	1st line
Duration of study	12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	NVAF; CHDSVASC score of 1 or more (2 in women); no contraindications for OACs
Exclusion criteria	Stroke or SSE within 6 months; ACS or peripheral artery disease within 6 months before enrolment; HF; severe CRF (CrCl <30ml/min); dual antiplatelet therapy; BW 50kg or less; uncontrolled hypertension; active malignancy; surgery within 6 months before enrolment; collagen disease; infectious disease; scheduled for catheter ablation; contraindications to rivaroxaban or dabigatran
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age –. Gender (M:F):. Ethnicity: Unclear
Further population details	1. Recent stroke: No. 2. Renal impairment: Not stated / Unclear (exclusion of <30 but may have been some patients between 30 and 49). 3. Threshold stroke risk score: Unclear. 4. Time in therapeutic range: NA.

Extra comments	Rivaroxaban/dabigatran: CHF 24%/24%; hypertension 84%/92%; DM 22%/34%; hyperlipidaemia 64%/76%; CKD 40%/47%; prior stroke 11%/11%; prior MI 4%/7%; PAD 2%/3%
Indirectness of population	No indirectness
Interventions	(n=176) Intervention 1: DOACs – Dabigatran 150mg twice daily. Duration 12 months. Concurrent medication/care: None. Indirectness: No indirectness (n=177) Intervention 2: DOACs - Rivaroxaban 15mg once daily. Duration 12 months. Concurrent medication/care: Sham INR values taken to maintain treatment blinding. Indirectness: No indirectness
Funding	Bayer Takuhin (commercial)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DABIGATRAN 150 mg twice daily versus RIVAROXABAN 20MG ONCE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Stroke and system embolism at 12 months; Group 1: 0/62, Group 2: 0/55
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 37 ; Group 2 Number missing: 39[reasons for missing: Group 1: 3 discontinued study before baseline, 14 had adverse event, 2 withdrew consent and 18 were lost to follow up; Group 2: 3 discontinued study before baseline, 10 had adverse event, 2 withdrew consent 22 were lost to follow up, 2 other reasons]

Protocol outcome 2: Major bleeding
- Actual outcome: major bleeding at 12 months; Group 1: 5/62, Group 2: 3/55
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 37 ; Group 2 Number missing: 39[reasons for missing: Group 1: 3 discontinued study before baseline, 14 had adverse event, 2 withdrew consent and 18 were lost to follow up; Group 2: 3 discontinued study before baseline, 10 had adverse event, 2 withdrew consent 22 were lost to follow up, 2 other reasons]

Protocol outcome 3: Intracranial bleeding - Actual outcome: intracranial bleeding at 12 months; Group 1: 0/62, Group 2: 0/55 Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 37 ; Group 2 Number missing: 39[reasons for missing: Group 1: 3 discontinued study before baseline, 14 had adverse event, 2 withdrew consent and 18 were lost to follow up; Group 2: 3 discontinued study before baseline, 10 had adverse event, 2 withdrew consent 22 were lost to follow up, 2 other reasons]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Myocardial infarction ; CRNM bleeding ; Minor bleeding ; Length of stay

Study	MAO, 2014 trial: Mao 2014[118]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=353)
Countries and setting	Conducted in China; Setting: Unclear but may be a single hospital in China
Line of therapy	1st line
Duration of study	Not clear: But likely to be >3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with AF documented in previous 6 months or by 12 lead ECG on day of screening; at least one of the following: prior stroke/TIA, age >75, hypertension requiring meds, DM requiring treatment, LVEF <35%, documented PAD
Exclusion criteria	AF due to reversible causes; moderate to severe mitral stenosis; conditions other than AF requiring anticoagulation; stroke within previous 7 days; need for aspirin of >165 mg/day or for both aspirin and clopidogrel; severe renal dysfunction (CrCl <30 mL/min); current alcohol or drug abuse or psychological conditions; life expectancy <1 year
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Median (IQR): 75(68-79). Gender (M:F): 218:135. Ethnicity: Unclear

Further population details	1. Recent stroke: Not stated / Unclear (exclusion criteria <7 days but may be some between 7 days and 6 months). 2. Renal impairment: Not stated / Unclear (exclusion of <30 but may have been some patients between 30 and 49). 3. Threshold stroke risk score: CHADS2 >=2 (No patients with score <2). 4. Time in therapeutic range: Not stated / Unclear (Not reported).
Extra comments	warfarin/rivaroxaban: sbp 131/131; paroxysmal AF 15.9%/17.5%; previous aspirin 34.7%/35.6%; prev VKA 63.6%/62.7%; CHADS2 of >2: 85.2%/84.2%; previous stroke/TIA/SEE 61.4%/60.5%; hypertension 91.5%/90.4%; DM 39.8%/41.8%; prior MI 17.6%/16.9%; CrCl median 66/66
Indirectness of population	No indirectness
Interventions	(n=176) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration Unclear. Concurrent medication/care: None. Indirectness: No indirectness (n=177) Intervention 2: DOACs - Rivaroxaban 20mg once daily. 20 mg daily, or 15mg if CrCl of 30-49. Duration Unclear. Concurrent medication/care: Sham INR values taken to maintain treatment blinding. Indirectness: No indirectness
Funding	No funding (No funding stated and no conflicts of interest stated as well)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus RIVAROXABAN 20MG ONCE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Stroke and system embolism at unclear; Group 1: 7/176, Group 2: 5/177
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: All-cause mortality
- Actual outcome: fatal bleeding at unclear; Group 1: 1/176, Group 2: 2/177

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not All-cause mortality; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 3: Major bleeding - Actual outcome: major bleeding at unclear; Group 1: 10/176, Group 2: 12/177 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 4: ICH - Actual outcome: IC bleeding at unclear; Group 1: 3/176, Group 2: 1/177 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 5: GI bleeding - Actual outcome: GI bleeding at unclear; Group 1: 1/176, Group 2: 8/177 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Myocardial infarction ; CRNM bleeding ; Minor bleeding ; Length of stay

Study	PATAF trial: Hellemons 1999[74]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=272 (729 in total but included patients in non-relevant arms and strata))
Countries and setting	Conducted in Netherlands
Line of therapy	1st line
Duration of study	Follow up (post intervention): 2.7 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged >60 years with electrocardiographically confirmed chronic atrial fibrillation or intermittent atrial fibrillation (electrocardiography within past two years) were eligible.
Exclusion criteria	Exclusion criteria were treatable causes of atrial fibrillation, previous stroke, rheumatic valvular disease, myocardial infarction or cardiovascular surgery in past year, cardiomyopathy (left ventricular ejection fraction <40%), chronic heart failure, cardiac aneurysm, history of systemic embolism, retinal infarction, coumarin use in the past three months, contraindications for aspirin or coumarin (haemoglobin concentration <7.0 mmol/l, ventricular or duodenal ulcer in the past three years, gastrointestinal or urogenital bleeding in the past year, aspirin intolerance, coagulation disorder, and severe hepatic or renal disease), pacemaker, and a life expectancy less than two years. Exclusion criteria for standard anticoagulation were age >78, retinopathy, ventricular or duodenal ulcer, history of gastrointestinal or genitourinary bleeding, and diastolic blood pressure >105 mmHg or systolic pressure >185mmHg, or both.
Age, gender and ethnicity	Age - Mean (SD): 75. Gender (M:F): 125:147. Ethnicity: Unclear

Further population details	1. Recent stroke: Not immediately post stroke (>6 months) (None with previous stroke). 2. Renal impairment: Not stated / Unclear 3. Threshold stroke risk score: Not stated / Unclear 4. Time in therapeutic range: Not stated / Unclear (Not reported).
Extra comments	DM 16%; angina pectoris 11%; MI 9%; hypertension 40%
Indirectness of population	No indirectness
Interventions	(n=131) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). Used Coumarins, which is only a precursor to warfarin. Used phenprocoumon and acenocoumarol that are both VKAs. However our protocol states Warfarin. INR 2.5-3.5. Duration 32.4 months. Concurrent medication/care: NA. Indirectness: Serious indirectness; Indirectness comment: Not warfarin (n=141) Intervention 2: Antiplatelets - Aspirin. 150mg/day. Duration 32.4 months. Concurrent medication/care: NA. Indirectness: Serious indirectness
Funding	Funding not stated (None reported)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus ASPIRIN

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: All stroke and SE at 32.4 months; Group 1: 6/131, Group 2: 9/141
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Myocardial infarction
- Actual outcome: MI at 32.4 months; Group 1: 1/131, Group 2: 1/141
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: All cause mortality
- Actual outcome: All death at 32.4 months; Group 1: 12/131, Group 2: 17/141

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 4: Major bleeding - Actual outcome: Major bleeding at 32.4 months; Group 1: 2/131, Group 2: 4/141; Comments: 6 major bleeds in stratum 1 (23-17). We know there were 2 major bleeding in standard OAC so must be 4 in stratum 1 aspirin Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; CRNM bleeding ; Minor bleeding ; ICH ; GI bleeding ; Length of stay

Study	PETRO trial: Ezekowitz 2007[60]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=170)
Countries and setting	Conducted in Denmark, Netherlands, Sweden, USA; Setting: 53 centres in Denmark, Netherlands, Sweden and USA.
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: The patients included in the review are only a subset of those in the study as other subgroups are non-protocol doses or with concomitant aspirin.
Subgroup analysis within study	Not applicable
Inclusion criteria	Documented AF plus at least one of: hypertension requiring meds, DM, symptomatic HF or LV dysfunction (LVEF <40%), previous stroke/TIA, or age >75
Exclusion criteria	Mitral stenosis; prosthetic heart valves; planned vcardioversion; recent (<1 month) MI; recent stroke/TIA; coronary stent placement within 6 months; contraindications to OACs; major hemorrhage in past 6 months; severe renal impairment (eGFR < 30); abnormal liver function; risk of pregnancy; investigational drug use within 30 days; any other prohibitive medical condition
Recruitment/selection of patients	Consecutive

Age, gender and ethnicity	Age - Other: Approximately 70. Gender (M:F): Unclear as demographic data provided are not applicable to the two groups applicable to this review, But likely to be around 80:20. Ethnicity: Unclear
Further population details	1. Recent stroke: Not stated / Unclear 2. Renal impairment: Not stated / Unclear (Threshold <30 so may have been some people between 30 and 49 but unclear). 3. Threshold stroke risk score: Not stated / Unclear 4. Time in therapeutic range: <65% (57.2%).
Extra comments	Not reported for the subset of patients in this extraction.
Indirectness of population	No indirectness
Interventions	(n=70) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration 3 months . Concurrent medication/care: NA (n=100) Intervention 2: DOACs - Dabigatran 150 mg twice daily. 150 mg twice daily. Duration 3 months. Concurrent medication/care: NO concomitant aspirin, as opposed to other groups (not included in this extraction). Indirectness: No indirectness
Funding	Study funded by industry (Boehringer Ingelheim)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus DABIGATRAN 150 MG TWICE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Thromboembolic events at 3 months; Group 1: 0/70, Group 2: 0/100
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: CRNM bleeding

- Actual outcome: CRNM bleeding at 3 months; Group 1: 4/70, Group 2: 9/100 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 3: Major bleeding - Actual outcome: major bleeding at 3 months; Group 1: 0/70, Group 2: 0/100 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Myocardial infarction ; All-cause mortality ; Minor bleeding ; ICH ; GI bleeding ; Length of stay

Study (subsidiary papers)	Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial: Connolly 2009[38] (Connolly 2010[39])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=18113)
Countries and setting	Conducted in Multiple countries; Setting: 951 clinical centres in 44 countries
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	AF documented on ECG performed at screening or within 6 months of starting; one of the following: prev stroke or TIA, LVEF <40%, NYHA class II or higher, age of at least 75, age of 65-74 with DM, hypertension or CAD
Exclusion criteria	Heart valve disorders; stroke within 14 days or severe stroke within 6 months before screening; conditions increasing the risk of bleeding; CrCl <30; active liver disease; pregnancy
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 71.5(8.7). Gender (M:F): 11514:6599. Ethnicity: Unknown

Further population details	1. Recent stroke: Not stated / Unclear 2. Renal impairment: Not stated / Unclear (Threshold for inclusion was >30 so may be some between 30-49 but not stated). 3. Threshold stroke risk score: CHADS2 <2 (CHADS2 = 0 included). 4. Time in therapeutic range: <65% (64%).
Extra comments	Warfarin/Dab 150/Dab 110: syst bp 131.2/131.0/130.8; paroxysmal AF 33.8%/32.6%/32.1%; CHADS2 0 or 1 30.9%/32.2%/32.4%; previous stroke or TIA 19.8%/20.3%/19.9%; prior MI 16.1%/16.9%/16.8%; HF 31.9%/31.8%/32.2%; DM 23.4%/23.1%/23.4%; hypertension 78.9%/78.9%/78.8%; Aspirin at baseline 40.6%/38.7%/40%
Indirectness of population	No indirectness
Interventions	(n=6022) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration 2 years. Concurrent medication/care: INR testing monthly. Indirectness: No indirectness (n=6015) Intervention 2: DOACs - Dabigatran 110mg twice daily. 110mg twice daily. Duration 2 years. Concurrent medication/care: dose of dab blinded but no blinding with warfarin. Indirectness: No indirectness (n=6076) Intervention 3: DOACs - Dabigatran 150 mg twice daily. 150mg twice daily. Duration 2 years. Concurrent medication/care: See 100mg. Indirectness: No indirectness
Funding	Study funded by industry (Boehringer Ingelheim)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus DABIGATRAN 110MG TWICE DAILY

Protocol outcome 1: Hospitalisation
- Actual outcome: Hospitalisation at 2 years; Group 1: 2458/6022, Group 2: 2311/6015
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: All stroke or systemic embolism
- Actual outcome: Stroke or systemic embolism at 2 years; Group 1: 202/6022, Group 2: 183/6015
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: Myocardial infarction
- Actual outcome: MI at 2 years; Group 1: 75/6022, Group 2: 98/6015
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 4: All-cause mortality
- Actual outcome: Death from any cause at 2 years; Group 1: 487/6022, Group 2: 446/6015
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 5: Major bleeding
- Actual outcome: major bleeding at 2 years; Group 1: 421/6022, Group 2: 342/6015
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 6: ICH
- Actual outcome: IC bleeding at 2 years; Group 1: 87/6022, Group 2: 27/6015
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus DABIGATRAN 150 MG TWICE DAILY

Protocol outcome 1: Hospitalisation
- Actual outcome: Hospitalisation at 2 years; Group 1: 2458/6022, Group 2: 2430/6076
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 2: All stroke or systemic embolism - Actual outcome: Stroke or systemic embolism at 2 years; Group 1: 202/6022, Group 2: 134/6076 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 3: Myocardial infarction - Actual outcome: MI at 2 years; Group 1: 75/6022, Group 2: 97/6076 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 4: All-cause mortality - Actual outcome: Death from any cause at 2 years; Group 1: 487/6022, Group 2: 438/6076 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 5: Major bleeding - Actual outcome: major bleeding at 2 years; Group 1: 421/6022, Group 2: 399/6076 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 6: ICH - Actual outcome: IC bleeding at 2 years; Group 1: 87/6022, Group 2: 36/6076 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; CRNM bleeding ; Minor bleeding ; GI bleeding ; Length of stay

Study	ROCKET trial: Patel 2011[140]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=14264)
Countries and setting	Conducted in Multiple countries; Setting: 1178 settings in 45 countries
Line of therapy	1st line
Duration of study	Intervention + follow up: 707 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	NVAF as shown on ECG; at moderate or high risk for stroke as shown by a history of stroke or TIA or SEE or at least 2 of the following: HF (or LVEF <35%), hypertension, age >75, DM.
Exclusion criteria	None reported in paper
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Median (IQR): 73(65-78). Gender (M:F): 8601:5663. Ethnicity: Unclear
Further population details	1. Recent stroke: Not stated / Unclear 2. Renal impairment: > = 50 ml/min (>75% of sample above 52). 3. Threshold stroke risk score: CHADS2 >=2 (Nobody with score <2). 4. Time in therapeutic range: <65% (mean of 55% of the time).

Extra comments	Rivaroxaban/warfarin: sbp 130/130; paroxysmal AF 17.5%/17.8%; previous VKA 62.3%/62.5%; CHADS2 mean score 3.48/3.46; prev stroke/TIA 54.9%/54.6%; hypertension 90.3%/90.8%; DM 40.4%/39.5%; previous MI 16.6%/18%; PVD 5.6%/6.1%; COPD 10.6%/10.4%; CrCl: median 67 (IQR 52-88)
Indirectness of population	No indirectness
Interventions	(n=7133) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration 707 days. Concurrent medication/care: None. Indirectness: No indirectness (n=7131) Intervention 2: DOACs - Rivaroxaban 20mg once daily. 20 mg daily (or 15 mg daily if CrCl of 30-49). Duration 707 days. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Study funded by industry (Johnson and Johnson and Bayer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus RIVAROXABAN 20MG ONCE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: stroke or systemic embolism at 707 days; Group 1: 306/7090, Group 2: 269/7081
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 43 ; Group 2 Number missing: 50[reasons for missing: Group 1: violation of good practice guidelines at one site; Group 2: violation of good practice guidelines at one site]

Protocol outcome 2: Myocardial infarction
- Actual outcome: MI at 707 days; Group 1: 126/7125, Group 2: 101/7111
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8 ; Group 2 Number missing: 20[reasons for missing: Group 1: unclear; Group 2: unclear]

Protocol outcome 3: All-cause mortality
- Actual outcome: death at 707 days; Group 1: 632/7090, Group 2: 582/7081

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 43 ; Group 2 Number missing: 50[reasons for missing: Group 1: violation of good practice guidelines at one site; Group 2: violation of good practice guidelines at one site] Protocol outcome 4: CRNM bleeding - Actual outcome: CRNMB at 707 days; Group 1: 1151/7125, Group 2: 1185/7111 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8 ; Group 2 Number missing: 20 [reasons for missing: Group 1: unclear; Group 2: unclear] Protocol outcome 5: Major bleeding - Actual outcome: major bleeding at 707 days; Group 1: 386/7125, Group 2: 395/7111 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8 ; Group 2 Number missing: 20 [reasons for missing: Group 1: unclear; Group 2: unclear] Protocol outcome 6: ICH - Actual outcome: ICH at 707 days; Group 1: 84/7125, Group 2: 55/7111 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8 ; Group 2 Number missing: 20 [reasons for missing: Group 1: unclear; Group 2: unclear]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Minor bleeding ; GI bleeding ; Length of stay

Study	SHOSHA 2017 trial: Shosha 2017[158]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Egypt; Setting: A single cardiac department in Egypt.
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	aged 18-60; NVAF based on clinical and physical examination and ECG/echocardiography; previous CVA/TIA/SEE confirmed by CT and at least one of: hypertension, HF (LVEF <40%), DM.
Exclusion criteria	organic valvular heart disease; hepatic failure; renal failure.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Range of means: Warfarin/rivaroxaban: 55/54. Gender (M:F): 27:33. Ethnicity: Unclear
Further population details	1. Recent stroke: Not stated / Unclear 2. Renal impairment: Not stated / Unclear (mean over 50 in each group but unclear how many below threshold of 50). 3. Threshold stroke risk score: CHADS2 <2 (patients with CHADS2 of 0 and 1). 4. Time in therapeutic range: <65% (mean INR was 1.35

	with sd of 0.47. This means that >80% were below INR 0f 1.82. Thus probably a fairly small number with INR over 2).
Extra comments	Warfarin/rivaroxaban: CHADS2 >1: 33.33%/40%; CHF or LVEF <40% 30%/36.6%; hypertension 40%/53.3%; age >75 0%/0%; DM 26.6%/13.3%; previous stroke, TIA or SEE 10%/26.6%; CrCl 57.43/74.54
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness (n=30) Intervention 2: DOACs - Rivaroxaban 20mg once daily. 20 mg once daily. Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus RIVAROXABAN 20MG ONCE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Stroke at 3 months; Group 1: 4/30, Group 2: 2/30
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not on Stroke/TIA/SEE. Data on these separately but because we don't know if any patient had >1 of these we cannot extrapolate a combined data point; Baseline details: Large difference in CrCl, with much better value for those in Rivaroxaban group; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: Myocardial infarction
- Actual outcome: MI at 3 months; Group 1: 1/30, Group 2: 1/30
Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality - Actual outcome: death due to bleeding at 3 months; Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not All-cause bleeding; Baseline details: Large difference in CrCl, with much better value for those in Rivaroxaban group; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 4: CRNM bleeding - Actual outcome: Non-major clinically relevant bleeding at 3 months; Group 1: 8/30, Group 2: 5/30 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Large difference in CrCl, with much better value for those in Rivaroxaban group; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 5: ICH - Actual outcome: intracranial hemorrhage at 3 months; Group 1: 2/30, Group 2: 0/30 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Large difference in CrCl, with much better value for those in Rivaroxaban group; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Minor bleeding ; Major bleeding ; GI bleeding ; Length of stay

Study (subsidiary papers)	SPAF II trial: Anonymous 1994[13] (Anonymous 1996[8])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1100)
Countries and setting	Conducted in USA; Setting: 16 clinical centres in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: 3.1 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	AF in previous 12 months, with no prosthetic heart valves, mitral stenosis or requirements for or contraindications to aspirin or warfarin
Exclusion criteria	Ischaemic stroke or TIA within past 2 years; <60 years old without overt cardiac disease
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 69.6. Gender (M:F): 656:444. Ethnicity: Unclear
Further population details	1. Recent stroke: Not immediately post stroke (>6 months) (Stroke/TIA in previous 24 months an exclusion criterion). 2. Renal impairment: Not stated / Unclear 3. Threshold stroke risk score: Not stated / Unclear 4. Time in therapeutic range: >=65% (TTR was 75% in those aged <=75 and 72% in those aged >75).

Extra comments	Age: 69.6; hypertension 52.6%; DM 15.6%; MI 10%; HF 20.2%
Indirectness of population	No indirectness
Interventions	(n=555) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-4.5. Duration 3.1 years. Concurrent medication/care: None. Indirectness: No indirectness (n=545) Intervention 2: Antiplatelets - Aspirin. 325mg once daily. Duration 3.1 years. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Academic or government funding (Division of stroke and Trauma, National Institute of Neurological Disorders and Stroke)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus ASPIRIN

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Ischaemic stroke and Systemic Emboli plus TIA at 3.1 years; Group 1: 38/555, Group 2: 54/545
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: Myocardial infarction
- Actual outcome: MI at 3.1 years; Group 1: 15/555, Group 2: 19/545
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: All-cause mortality
- Actual outcome: Total mortality at 3.1 years; Group 1: 62/555, Group 2: 65/545
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing:

0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 4: Major bleeding - Actual outcome: Major hemorrhage at 3.1 years; Group 1: 34/555, Group 2: 16/545 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 5: ICH - Actual outcome: IC hemorrhage at 3.1 years; Group 1: 13/555, Group 2: 5/545 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 6: GI bleeding - Actual outcome: GI bleeding at 3.1 years; Group 1: 14/555, Group 2: 8/545 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; CRNM bleeding ; Minor bleeding ; Length of stay

Study	SPAF trial: Anonymous 1991[12]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=421)
Countries and setting	Conducted in USA; Setting: 15 centres
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1.3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with ECG evidence of AF in past 12 months; no prosthetic heart valves or echographic evidence of mitral stenosis
Exclusion criteria	Stroke/TIA within past 2 years; transient AF; mitral stenosis; NYHA class IV; MI in past 3 months; CABG in past year; PTCA in previous 3 months, unstable angina pectoris in past year; life expectancy < 2 years; chronic renal failure, Thrombocytopenia; prior arterial embolism requiring warfarin; alcoholism; other indications for warfarin; requirements for NSAIDS
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Range of means: Warfarin 65, Placebo 66. Gender (M:F): 303:118. Ethnicity: Unclear

Further population details	1. Recent stroke: Not immediately post stroke (>6 months) (stroke/TIA within 2 years was exclusion criterion). 2. Renal impairment: Not stated / Unclear (No Cr Cl or eGFR data). 3. Threshold stroke risk score: Not stated / Unclear 4. Time in therapeutic range: Not stated / Unclear (TTR not reported).
Extra comments	Warfarin/placebo: sbp 136/135; constant AF 62%/66%; history of hypertension 49%/55%; DM 12%/19%; prior stroke/TIA 8%/8%; definite CHF 14%/19%; definite angina 9%/10%; definite MI 10%/6%
Indirectness of population	No indirectness
Interventions	(n=210) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-4.5. Duration 1.3 years. Concurrent medication/care: None. Indirectness: No indirectness (n=211) Intervention 2: placebo. blinded dose. Duration 1.3 years. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Academic or government funding (Division of Stroke and Trauma, National Institute of Neurological Disorders and Stroke)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus PLACEBO

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Ischaemic stroke or systemic embolism or TIA or intracerebral hemorrhage at 1.3 years; Group 1: 10/210, Group 2: 22/211 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: Myocardial infarction
- Actual outcome: MI at 1.3 years; Group 1: 2/210, Group 2: 2/211

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 3: All-cause mortality - Actual outcome: Total mortality at 1.3 years; Group 1: 6/210, Group 2: 8/211 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 4: Major bleeding - Actual outcome: all relevant bleeding - as sole contributor to 'major complications' at 1.3 years; Group 1: 4/210, Group 2: 4/211 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not strictly 'major bleeding'; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; CRNM bleeding ; Minor bleeding ; ICH ; GI bleeding ; Length of stay

Study	WASPO trial: Rash 2007[147]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in United Kingdom; Setting: medical outpatient clinics and ECG clinics in the UK
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >80 and <90; permanent AF; ambulant
Exclusion criteria	one or more fall or syncopal episode within the past 12 months; epileptiform seizures; alcoholic liver disease or excess alcohol intake; previous history of thromboembolism; gastrointestinal or genitourinary bleeding in the previous 6 months; previous IC hemorrhage; abnormal resting prothrombin time; Folsetein mini mental state examination score <26; previous intolerance/allergy to warfarin or aspirin; already taking warfarin.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Other: Warfarin 83.5, Aspirin 82.6. Gender (M:F): 35:40. Ethnicity: Unknown

Further population details	1. Recent stroke: Not immediately post stroke (>6 months) (No stroke history in any participant). 2. Renal impairment: Not stated / Unclear (No report of renal impairment). 3. Threshold stroke risk score: Not stated / Unclear (Not stated). 4. Time in therapeutic range: >=65% (69.2%).
Extra comments	Warfarin/aspirin: hypertension 49%/46%; DM 3%/5%; IHD 11%/28%; Normal LV function on echocardiogram 76%/71%; cardiomegaly on CXR 69%/49%
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration 1 year. Concurrent medication/care: None. Indirectness: No indirectness (n=39) Intervention 2: Antiplatelets - Aspirin. 300mg per day. Duration 1 year. Concurrent medication/care: None. Indirectness: No indirectness
Funding	No funding (No funding or conflicts of interest)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus ASPIRIN

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Stroke/TIA/SEE at 1 year; Group 1: 0/36, Group 2: 1/39
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 2: All-cause mortality
- Actual outcome: Death at 1 year; Group 1: 1/36, Group 2: 2/39
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]

Protocol outcome 3: Minor bleeding - Actual outcome: Minor bleeding at 1 year; Group 1: 6/36, Group 2: 4/39 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA] Protocol outcome 4: Major bleeding - Actual outcome: Serious bleeding (ICH, fall in HB by >2 g/dl, need for blood transfusion) at 1 year; Group 1: 0/36, Group 2: 3/39 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0[reasons for missing: Group 1: NA; Group 2: NA]	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Myocardial infarction ; CRNM bleeding ; ICH ; GI bleeding ; Length of stay

Study	WEITZ, 2010 trial: Weitz 2010[171]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=719 (1146 in study but we have excluded the 427 patients on 30 and 60 mg edoxaban TWICE daily)
Countries and setting	Conducted in Multiple countries; Setting: Multicentre, multinational study
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18-85 years; persistent NVAF confirmed by ECG at screening and baseline over an interval of up to 30 days; CHADS2 of at least 2; women 2 years menopausal minimum/ bilateral oophorectomy
Exclusion criteria	mitral valve disease; endocarditis or a mechanical valve; contraindications to OACs; need for ongoing treatment with thienopyridine; AF secondary to reversible disorders; LV aneurysm or atrial myxoma; estimated life expectancy <12 months; planned surgery or intervention within study period; history of Hep B or C or HIV; serum transaminase and/or alkaline phosphatase >1.5 times ULN; CrCl <30; cardiac pacemaker or implantable cardioverter-defibrillator; investigational treatment or device implantation during previous 3 months
Recruitment/selection of patients	Consecutive

Age, gender and ethnicity	Age - Range of means: warfarin/Edox 30/Edox 60: 66.0/65.2/64.9. Gender (M:F): 446:273. Ethnicity: Unclear
Further population details	1. Recent stroke: Not stated / Unclear 2. Renal impairment: Not stated / Unclear (mean is way above 50 (around 85-88)). 3. Threshold stroke risk score: CHADS2 >=2 (CHADS2 <2 is an exclusion). 4. Time in therapeutic range: <65% (approximately 50%).
Extra comments	Warfarin/edox 30/edox 60: warfarin naive 64.8%/67.7%/66.2%; aspirin on admission 52.8%/52.3%/52.1%; SBP <160 86%/86.4%/89.7%; CrCl 85.32/88.38/86.28; CHADS2 3 or more 36%/37.1%/37.2%
Indirectness of population	No indirectness
Interventions	(n=250) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR 2-3. Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness (n=235) Intervention 2: DOACs - Edoxaban 30mg once daily. 30mg once daily. Duration 3 months. Concurrent medication/care: NOne. Indirectness: No indirectness (n=234) Intervention 3: DOACs - Edoxaban 60 mg once daily. 60mg once daily. Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Study funded by industry (Daiichi Sankyo)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus EDOXABAN 30MG ONCE DAILY

Protocol outcome 1: Hospitalisation
- Actual outcome: Hospitalisation for any cardiac condition at 3 months; Group 1: 1/250, Group 2: 2/235
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for

missing: Group 1: not treated and excluded by researchers; Group 2: NA]

Protocol outcome 2: All stroke or systemic embolism
- Actual outcome: Any stroke, TIA and/or SEE at 3 months; Group 1: 4/250, Group 2: 1/235
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and excluded by researchers; Group 2: NA]

Protocol outcome 3: Myocardial infarction
- Actual outcome: MI at 3 months; Group 1: 0/250, Group 2: 2/235
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and excluded by researchers; Group 2: NA]

Protocol outcome 4: All-cause mortality
- Actual outcome: Cardiovascular death at 3 months; Group 1: 2/250, Group 2: 2/235
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: cardiovascular death, not All-cause death; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and excluded by researchers; Group 2: NA]

Protocol outcome 5: CRNM bleeding
- Actual outcome: CRNM bleeding at 3 months; Group 1: 7/250, Group 2: 7/235
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and excluded by researchers; Group 2: NA]

Protocol outcome 6: Minor bleeding
- Actual outcome: Minor bleeding at 3 months; Group 1: 12/250, Group 2: 6/235
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and excluded by researchers; Group 2: NA]

Protocol outcome 7: Major bleeding
- Actual outcome: Major bleeding at 3 months; Group 1: 1/250, Group 2: 0/235
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement -

Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and excluded by researchers; Group 2: NA]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus EDOXABAN 60 MG ONCE DAILY

Protocol outcome 1: Hospitalisation
- Actual outcome: Hospitalisation for any cardiac condition at 3 months; Group 1: 1/250, Group 2: 7/234
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and excluded by researchers; Group 2: not treated and excluded by researchers]

Protocol outcome 2: All stroke or systemic embolism
- Actual outcome: Any stroke, TIA and/or SEE at 3 months; Group 1: 4/250, Group 2: 1/234
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and excluded by researchers; Group 2: not treated and excluded by researchers]

Protocol outcome 3: Myocardial infarction
- Actual outcome: MI at 3 months; Group 1: 0/250, Group 2: 2/234
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and excluded by researchers; Group 2: not treated and excluded by researchers]

Protocol outcome 4: All-cause mortality
- Actual outcome: Cardiovascular death at 3 months; Group 1: 2/250, Group 2: 0/234
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: cardiovascular death, not All-cause death; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and excluded by researchers; Group 2: not treated and excluded by researchers]

Protocol outcome 5: CRNM bleeding
- Actual outcome: CRNM bleeding at 3 months; Group 1: 7/250, Group 2: 8/234
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for

missing: Group 1: not treated and excluded by researchers; Group 2: not treated and excluded by researchers] Protocol outcome 6: Minor bleeding - Actual outcome: Minor bleeding at 3 months; Group 1: 12/250, Group 2: 8/234 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and excluded by researchers; Group 2: not treated and excluded by researchers] Protocol outcome 7: Major bleeding - Actual outcome: Major bleeding at 3 months; Group 1: 1/250, Group 2: 1/234 Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 ; Group 2 Number missing: 0[reasons for missing: Group 1: not treated and excluded by researchers; Group 2: not treated and excluded by researchers]	
Protocol outcomes not reported by the study	Quality of life ; ICH ; GI bleeding ; Length of stay

Study	YAMASHITA, 2012 trial: Yamashita 2012[177]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=401)
Countries and setting	Conducted in Japan; Setting: 61 study sites in Japan
Line of therapy	1st line
Duration of study	Follow up (post intervention): 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >20 years; NVAF documented by ECG at least twice within 12 months; CHADS2 >1
Exclusion criteria	History of IC, intraocular, intraspinal, retroperitoneal or atraumatic intra-articular bleeding; GI bleeding within past year; Hb <100g/L or platelets <100,000 /microlitre at screening; cerebral infarction or TIA in past month; valvular surgery; concurrent treatment with anticoagulants excluding warfarin; comorbid rheumatic valvular disease, infective endocarditis, atrial myxoma or serious heart disease; left ventricular or left atrial thrombus; renal or hepatic dysfunction; bodyweight <40kg; pregnancy of lactating.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Range of means: warfarin 68.8, Edox 30 69.4, Edox 60 68.4. Gender (M:F): 323:67. Ethnicity: unclear

Further population details	1. Recent stroke: Not stated / Unclear (<1 month exclusion criterion but unclear if anyone there with stroke between 1 and 6 months previously.). 2. Renal impairment: > = 50 ml/min (88-90% over 50 ml/min). 3. Threshold stroke risk score: CHADS2 <2 (Threshold was 1). 4. Time in therapeutic range: >=65% (73% for people aged <70 years and 83% for those aged >70 years).
Extra comments	Data given for warfarin/edox 30/edox 60: hypertension 71%/75%/74%; diabetes 31%/21%/21%; CHF 33%/24%/24%; History stroke or TIA30%/28%/30%; CHADS2 2.2/1.9/2.1; history of warfarin 86%/85%/85%; CrCl <0.835 ml/s: 12%/10%/16%; concomitant aspirin use: 23%/25%/29%
Indirectness of population	No indirectness
Interventions	(n=134) Intervention 1: Vitamin K antagonists - Warfarin INR 2-3 (including 2.5 to 3.5 and 2 to 4.5). INR was 2-3 for those aged <70 but 1.6 to 2.6 for those aged >70 (nearly half of the sample). Duration 3 months. Concurrent medication/care: None. Indirectness: Serious indirectness; Indirectness comment: Over 70s with INR outside inclusion range. (n=135) Intervention 2: DOACs - Edoxaban 30mg once daily. None. Duration 3 months. Concurrent medication/care: None. Indirectness: Serious indirectness (n=132) Intervention 3: DOACs - Edoxaban 60 mg once daily. None. Duration 3 months. Concurrent medication/care: None. Indirectness: Serious indirectness
Funding	Study funded by industry (Daiichi Sankyo)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus EDOXABAN 30MG ONCE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Thromboembolic events at 3 months; Group 1: 0/129, Group 2: 0/130
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5 ; Group 2 Number missing: 5[reasons for missing: Group 1: not

treated and excluded; Group 2: not treated and excluded]

Protocol outcome 2: All-cause mortality
- Actual outcome: Death at 3 months; Group 1: 1/129, Group 2: 0/130
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5 ; Group 2 Number missing: 5[reasons for missing: Group 1: not treated and excluded; Group 2: not treated and excluded]

Protocol outcome 3: Major bleeding
- Actual outcome: Major bleeding at 3 months; Group 1: 0/125, Group 2: 0/130
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9 ; Group 2 Number missing: 5[reasons for missing: Group 1: 5 not treated and excluded and 4 discontinued during run-in period; Group 2: 4 not treated and excluded and 1 discontinued in run-in period]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN INR 2-3 (INCLUDING 2.5 TO 3.5 AND 2 TO 4.5) versus EDOXABAN 60 MG ONCE DAILY

Protocol outcome 1: All stroke or systemic embolism
- Actual outcome: Thromboembolic events at 3 months; Group 1: 0/129, Group 2: 0/130
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5 ; Group 2 Number missing: 2[reasons for missing: Group 1: not treated and excluded; Group 2: not treated and excluded]

Protocol outcome 2: All-cause mortality
- Actual outcome: Death at 3 months; Group 1: 1/129, Group 2: 1/130
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5 ; Group 2 Number missing: 2[reasons for missing: Group 1: not treated and excluded; Group 2: not treated and excluded]

Protocol outcome 3: Major bleeding
- Actual outcome: Major bleeding at 3 months; Group 1: 0/125, Group 2: 2/130
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness Group 1 Number missing: 9 ; Group 2 Number missing: 2[reasons for missing: Group 1: 1 not treated and excluded and 1 discontinued during run-in period; Group 2: 4 not treated and excluded and 1 discontinued in run-in period]

Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Myocardial infarction ; CRNM bleeding ; Minor bleeding ; ICH ; GI bleeding ; Length of stay

Appendix E: Forest plots

Dabigatran 150mg bd versus Rivaroxaban 15mg qd

Figure 3: Health related quality of life

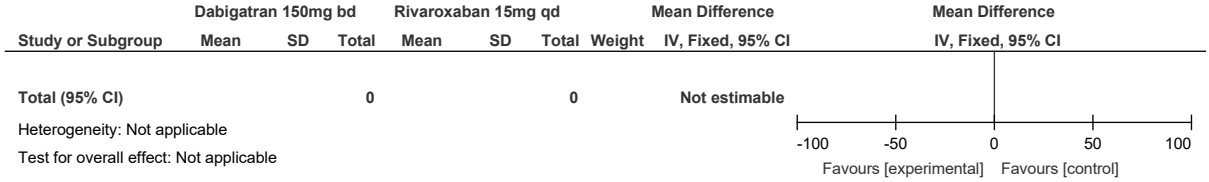


Figure 4: All stroke and systemic embolism

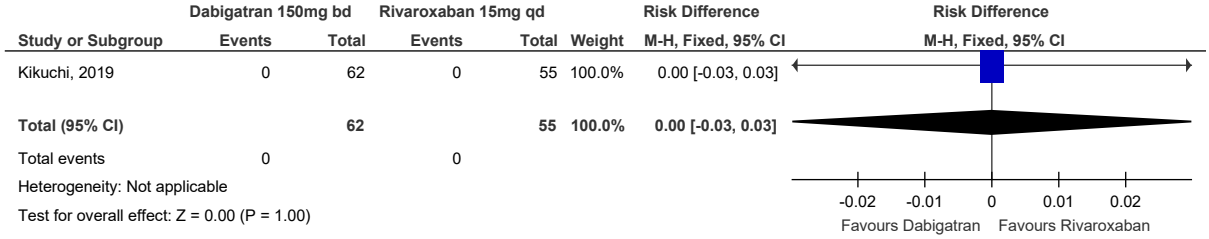


Figure 5: All cause mortality

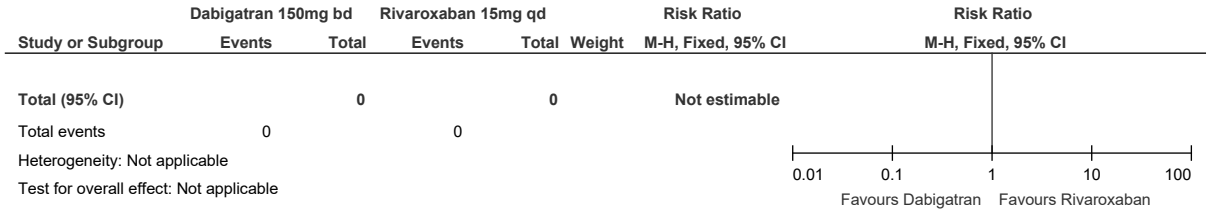


Figure 6: Myocardial infarction

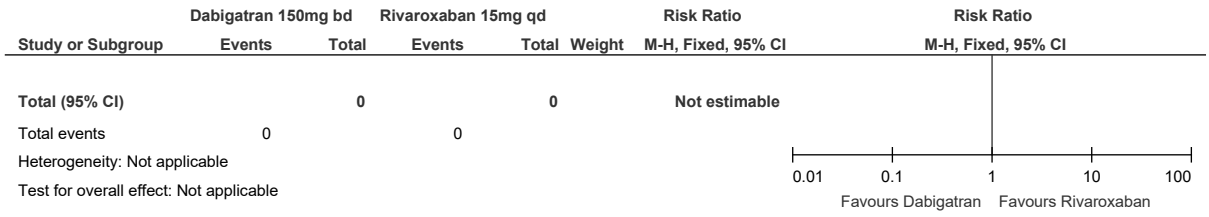


Figure 7: Clinically relevant non major bleeding

Study or Subgroup	Dabigatran 150mg bd Events	Total	Rivaroxaban 15mg qd Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

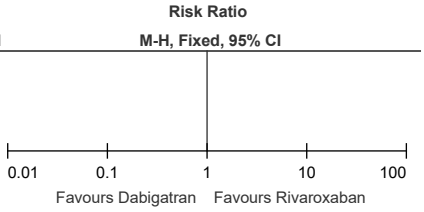


Figure 8: minor bleeding

Study or Subgroup	Dabigatran 150mg bd Events	Total	Rivaroxaban 15mg qd Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

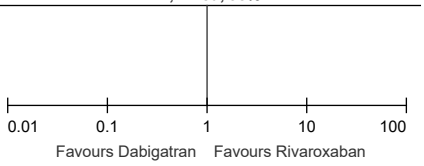


Figure 9: Major bleeding

Study or Subgroup	Dabigatran 150mg bd Events	Total	Rivaroxaban 15mg qd Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kikuchi, 2019	5	62	3	55	100.0%	1.48 [0.37, 5.90]
Total (95% CI)		**62**		**55**	**100.0%**	**1.48 [0.37, 5.90]**
Total events	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						

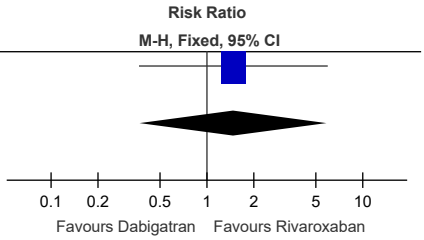


Figure 10: Intracranial bleeding

Study or Subgroup	Dabigatran 150mg bd Events	Total	Rivaroxaban 15mg qd Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Kikuchi, 2019	0	62	0	55	100.0%	0.00 [-0.03, 0.03]
Total (95% CI)		**62**		**55**	**100.0%**	**0.00 [-0.03, 0.03]**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						

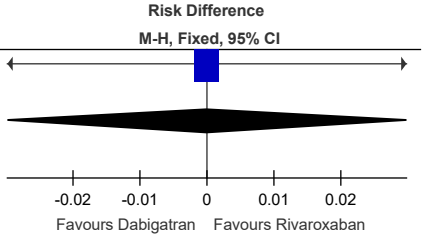
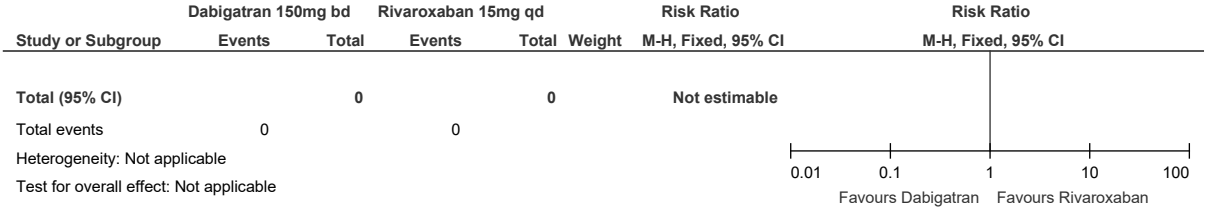


Figure 11: GI bleeding



Antiplatelets versus Warfarin

Figure 12: Health related quality of life

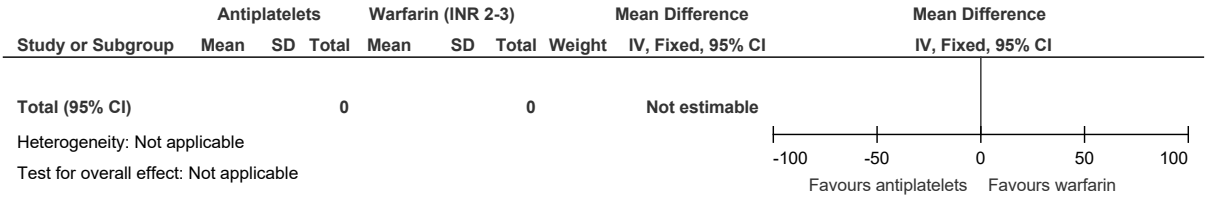


Figure 13: All stroke and systemic embolism

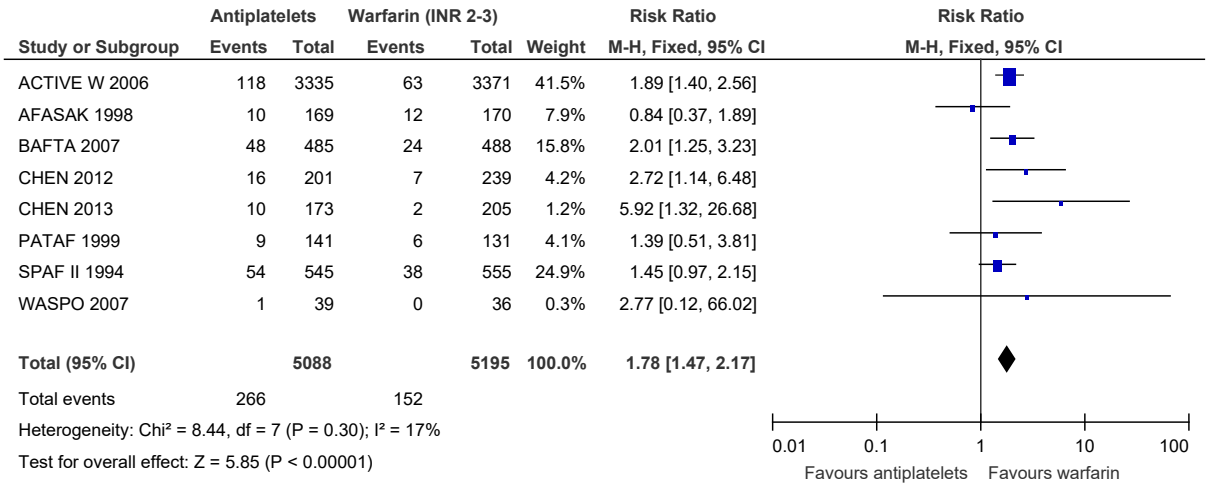


Figure 14: All cause mortality

Study or Subgroup	Antiplatelets Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE W 2006	159	3335	158	3371	43.2%	1.02 [0.82, 1.26]
AFASAK 1998	14	169	17	170	4.7%	0.83 [0.42, 1.63]
BAFTA 2007	108	485	107	488	29.3%	1.02 [0.80, 1.29]
CHEN 2012	6	201	5	239	1.3%	1.43 [0.44, 4.61]
CHEN 2013	6	173	4	205	1.0%	1.78 [0.51, 6.20]
PATAF 1999	17	141	12	131	3.4%	1.32 [0.65, 2.65]
SPAF II 1994	65	545	62	555	16.9%	1.07 [0.77, 1.48]
WASPO 2007	2	39	1	36	0.3%	1.85 [0.17, 19.50]
Total (95% CI)		**5088**		**5195**	**100.0%**	**1.04 [0.91, 1.19]**
Total events	377		366			

Heterogeneity: Chi² = 2.19, df = 7 (P = 0.95); I² = 0%

Test for overall effect: Z = 0.59 (P = 0.55)

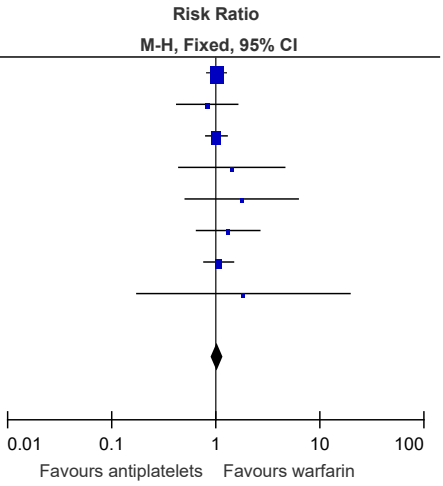


Figure 15: Myocardial infarction

Study or Subgroup	Antiplatelets Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE W 2006	36	3335	23	3371	37.3%	1.58 [0.94, 2.66]
AFASAK 1998	4	169	4	170	6.5%	1.01 [0.26, 3.96]
BAFTA 2007	15	485	15	488	24.4%	1.01 [0.50, 2.04]
CHEN 2013	3	173	4	205	6.0%	0.89 [0.20, 3.92]
PATAF 1999	1	141	1	131	1.7%	0.93 [0.06, 14.70]
SPAF II 1994	19	545	15	555	24.2%	1.29 [0.66, 2.51]
Total (95% CI)		**4848**		**4920**	**100.0%**	**1.28 [0.92, 1.78]**
Total events	78		62			

Heterogeneity: Chi² = 1.49, df = 5 (P = 0.91); I² = 0%

Test for overall effect: Z = 1.47 (P = 0.14)

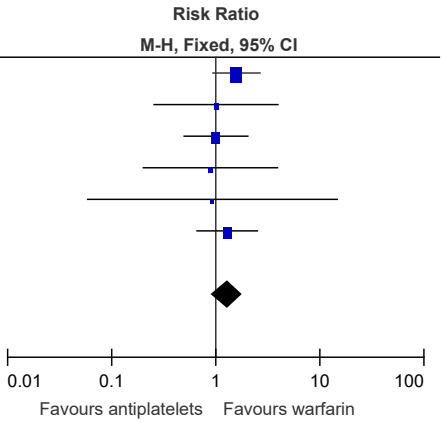


Figure 16: Clinically relevant non major bleeding

Study or Subgroup	Antiplatelets Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable

Test for overall effect: Not applicable

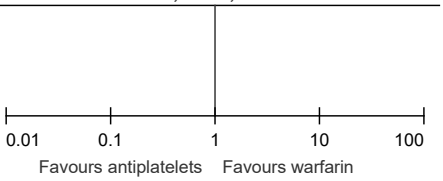


Figure 17: Minor bleeding

Study or Subgroup	Antiplatelets Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ACTIVE W 2006	568	3335	481	3371	28.4%	1.19 [1.07, 1.33]
AFASAK 1998	26	169	42	170	24.4%	0.62 [0.40, 0.97]
CHEN 2012	4	201	21	239	14.3%	0.23 [0.08, 0.65]
CHEN 2013	11	173	24	205	20.2%	0.54 [0.27, 1.08]
WASPO 2007	4	39	6	36	12.7%	0.62 [0.19, 2.01]
Total (95% CI)		**3917**		**4021**	**100.0%**	**0.63 [0.36, 1.10]**
Total events	613		574			

Heterogeneity: Tau² = 0.29; Chi² = 22.21, df = 4 (P = 0.0002); I² = 82%

Test for overall effect: Z = 1.61 (P = 0.11)

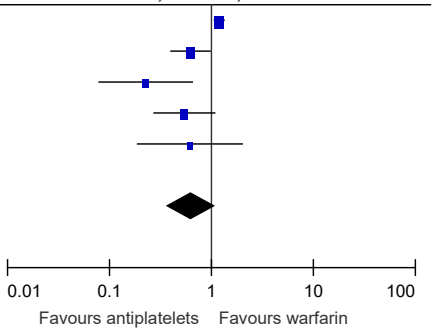


Figure 18: Major bleeding

Study or Subgroup	Antiplatelets Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE W 2006	101	3335	93	3371	52.6%	1.10 [0.83, 1.45]
AFASAK 1998	5	169	4	170	2.3%	1.26 [0.34, 4.60]
BAFTA 2007	25	485	25	488	14.2%	1.01 [0.59, 1.73]
CHEN 2012	1	201	7	239	3.6%	0.17 [0.02, 1.37]
CHEN 2013	5	173	13	205	6.8%	0.46 [0.17, 1.25]
PATAF 1999	4	141	2	131	1.2%	1.86 [0.35, 9.98]
SPAF II 1994	16	545	34	555	19.1%	0.48 [0.27, 0.86]
WASPO 2007	3	39	0	36	0.3%	6.47 [0.35, 121.17]
Total (95% CI)		**5088**		**5195**	**100.0%**	**0.92 [0.74, 1.13]**
Total events	160		178			

Heterogeneity: Chi² = 13.46, df = 7 (P = 0.06); I² = 48%

Test for overall effect: Z = 0.80 (P = 0.42)

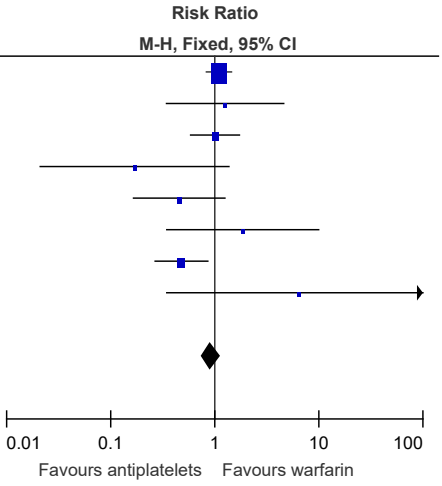


Figure 19: Intracranial bleeding

Study or Subgroup	Antiplatelets Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFASAK 1998	1	169	2	170	13.4%	0.50 [0.05, 5.49]
SPAF II 1994	5	545	13	555	86.6%	0.39 [0.14, 1.09]
Total (95% CI)		**714**		**725**	**100.0%**	**0.41 [0.16, 1.04]**
Total events	6		15			

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%

Test for overall effect: Z = 1.87 (P = 0.06)

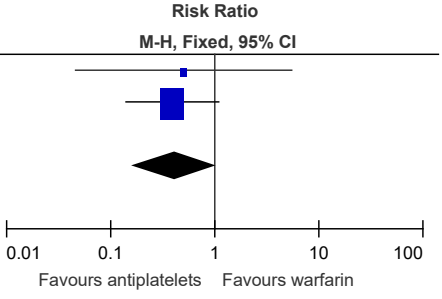
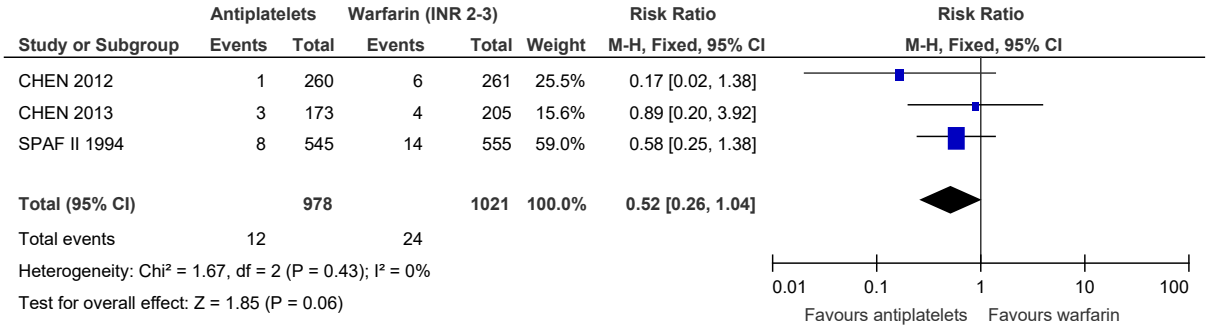


Figure 20: Gastrointestinal bleeding



Placebo versus Warfarin

Figure 21: Health related quality of life

Study or Subgroup	Placebo Mean	SD	Total	Warfarin (INR 2-3) Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

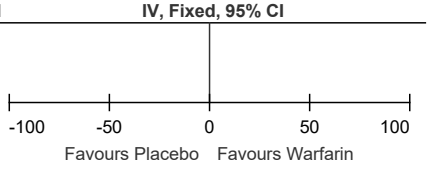


Figure 22: All stroke and systemic embolism

Study or Subgroup	Placebo Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CAFA 1991	9	191	6	187	37.7%	1.47 [0.53, 4.04]
SPAF 1991	22	211	10	210	62.3%	2.19 [1.06, 4.51]
Total (95% CI)		**402**		**397**	**100.0%**	**1.92 [1.07, 3.45]**
Total events	31		16			
Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 2.18 (P = 0.03)						

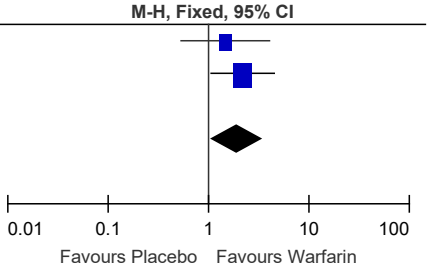


Figure 23: All cause mortality

Study or Subgroup	Placebo Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CAFA 1991	8	191	10	187	62.7%	0.78 [0.32, 1.94]
SPAF 1991	8	211	6	210	37.3%	1.33 [0.47, 3.76]
Total (95% CI)		**402**		**397**	**100.0%**	**0.99 [0.50, 1.94]**
Total events	16		16			
Heterogeneity: Chi² = 0.56, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.04 (P = 0.97)						

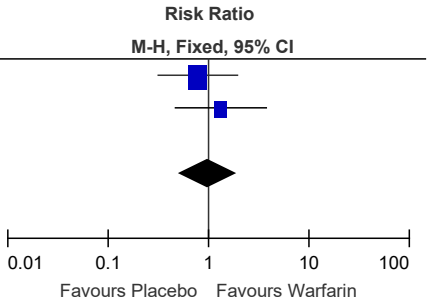


Figure 24: Myocardial infarction

Study or Subgroup	Placebo Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SPAF 1991	2	211	2	210	100.0%	1.00 [0.14, 7.00]
Total (95% CI)		**211**		**210**	**100.0%**	**1.00 [0.14, 7.00]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						

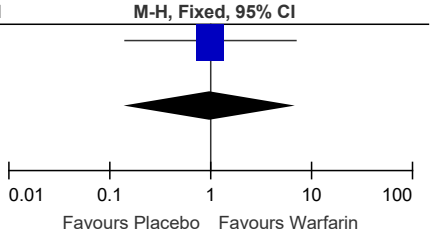


Figure 25: Clinically relevant non major bleeding

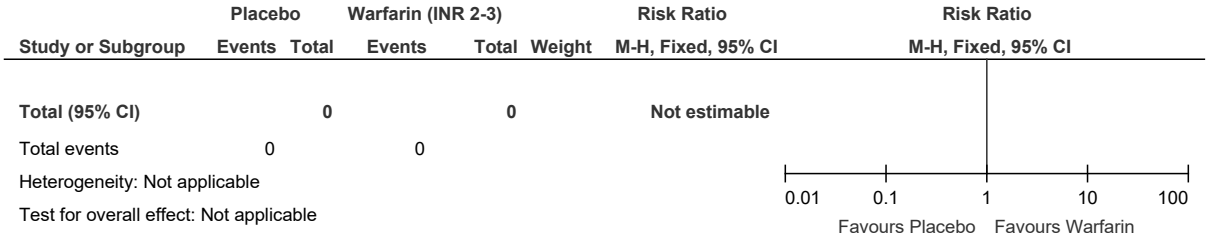


Figure 26: Minor bleeding

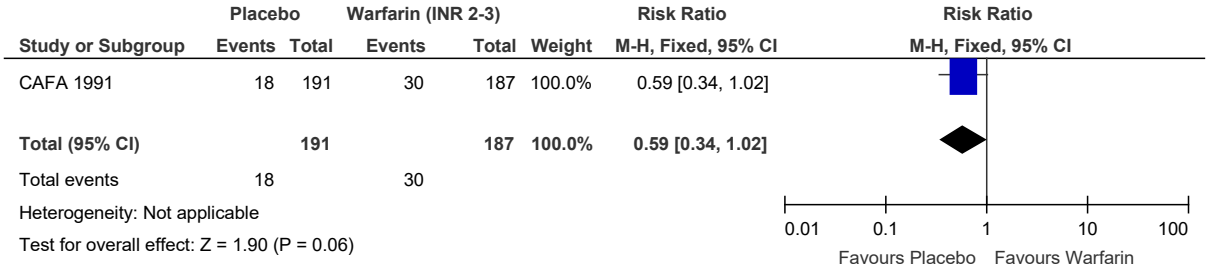


Figure 27: Major bleeding

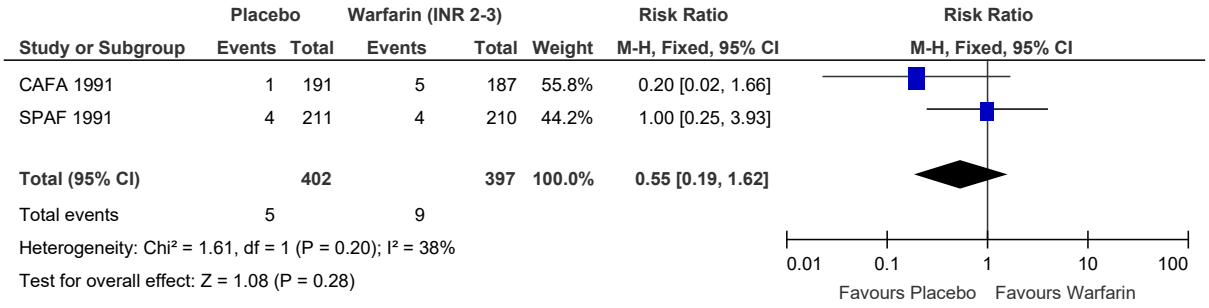


Figure 28: Intracranial bleeding

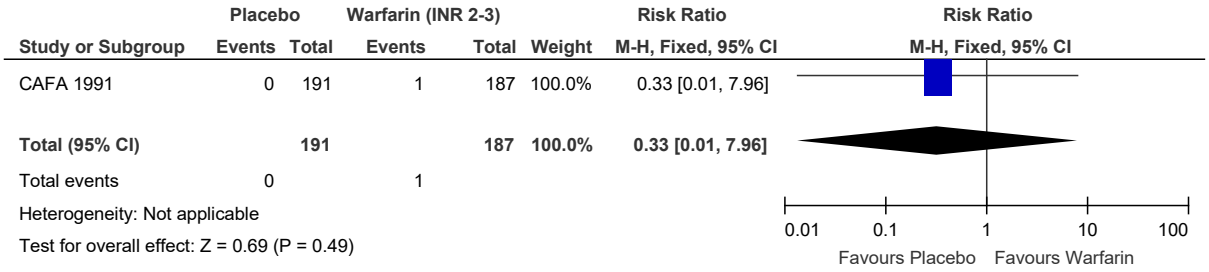
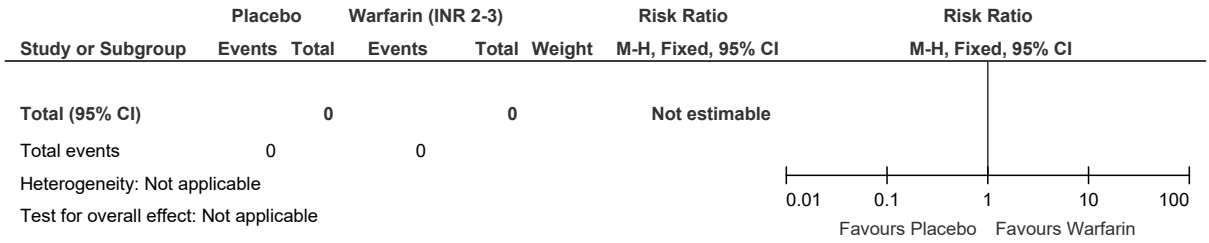


Figure 29: Gastrointestinal bleeding



Apixaban 2.5mg bid versus Warfarin

Figure 30: Health related quality of life

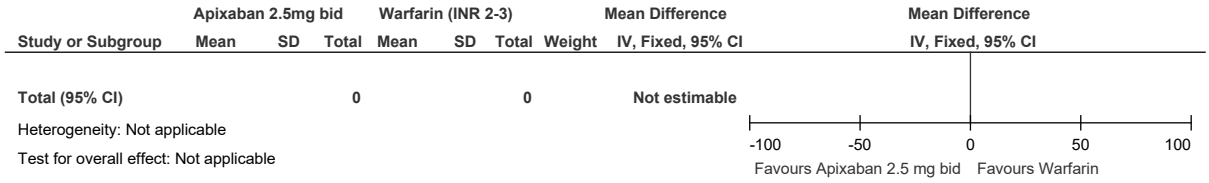


Figure 31: All stroke and systemic embolism

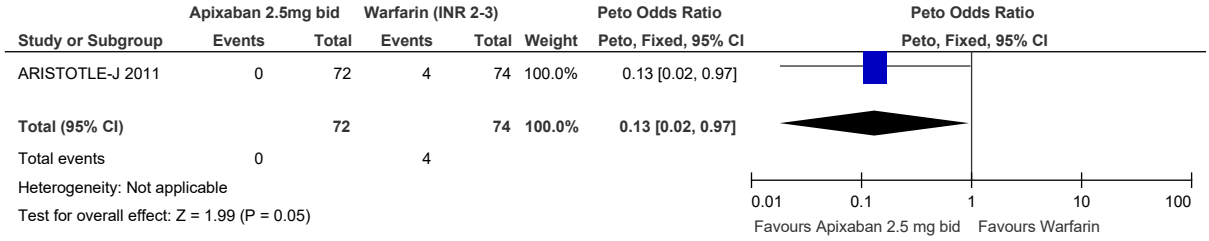


Figure 32: All cause mortality

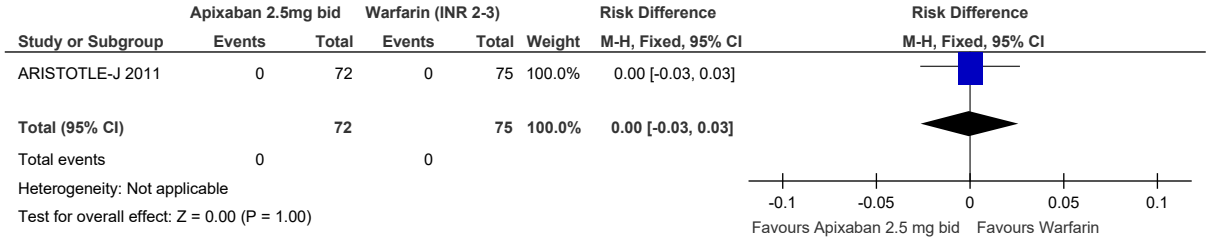


Figure 33: Myocardial infarction

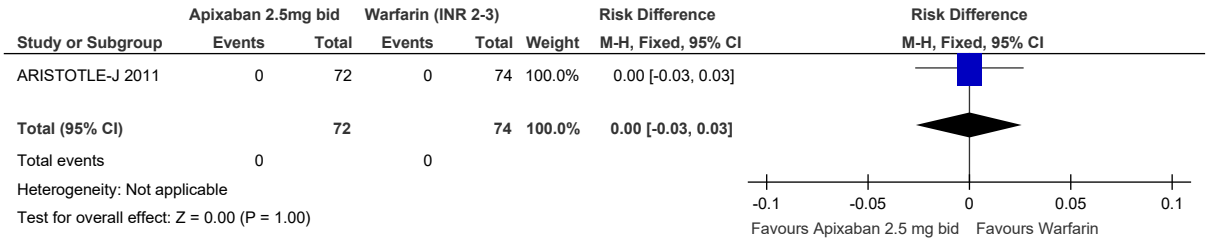


Figure 34: Clinically relevant non major bleeding

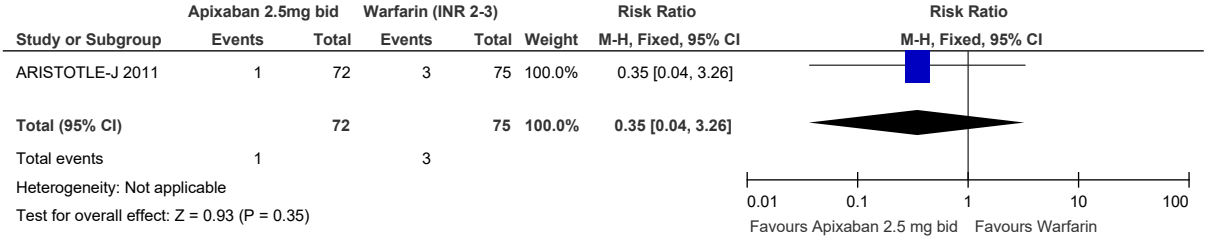


Figure 35: Minor bleeding

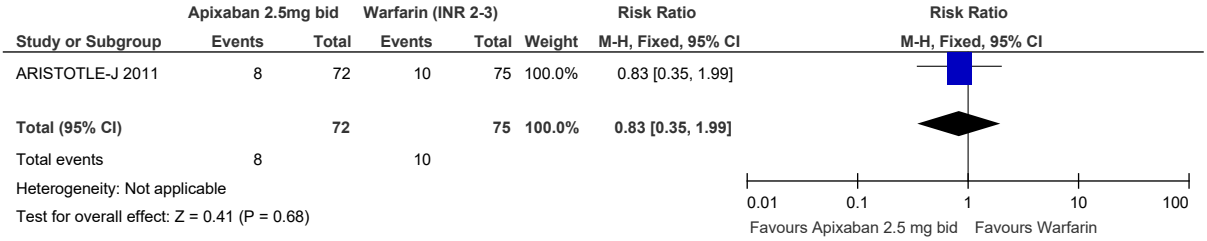


Figure 36: Major bleeding

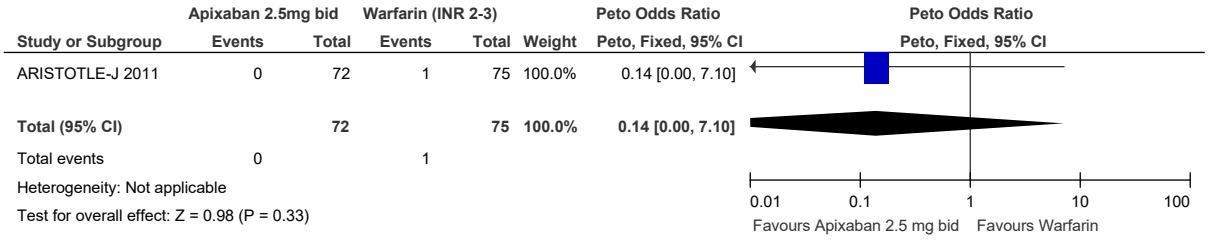


Figure 37: Intracranial bleeding

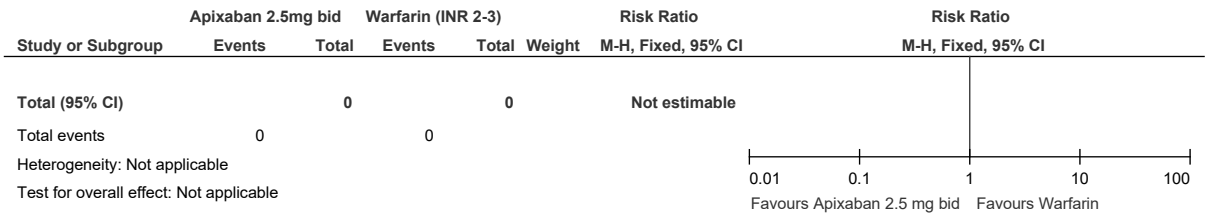
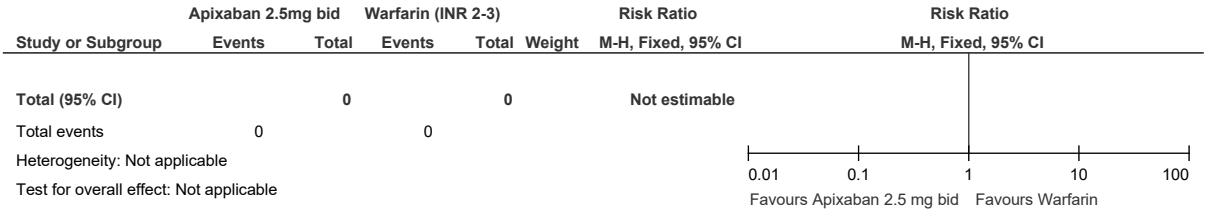


Figure 38: Gastrointestinal bleeding



Apixaban 5mg bid versus Warfarin

Figure 39: Health related quality of life

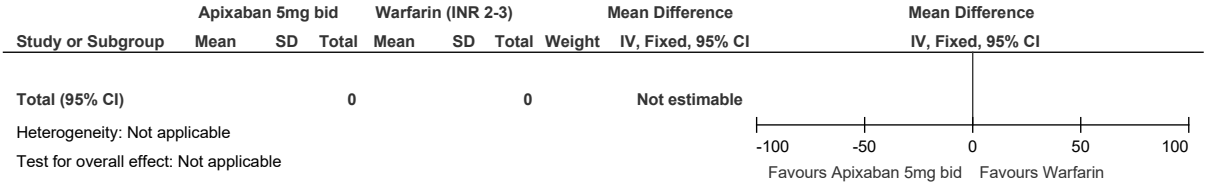


Figure 40: All stroke and systemic embolism

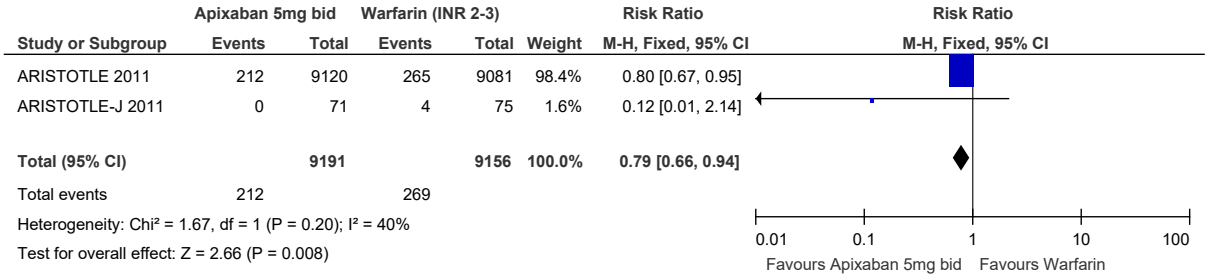


Figure 41: All cause mortality

Study or Subgroup	Apixaban 5mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
ARISTOTLE 2011	603	9120	669	9081	99.2%	-0.01 [-0.01, -0.00]
ARISTOTLE-J 2011	0	71	0	75	0.8%	0.00 [-0.03, 0.03]
Total (95% CI)		**9191**		**9156**	**100.0%**	**-0.01 [-0.01, -0.00]**
Total events	603		669			

Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%

Test for overall effect: Z = 2.00 (P = 0.05)

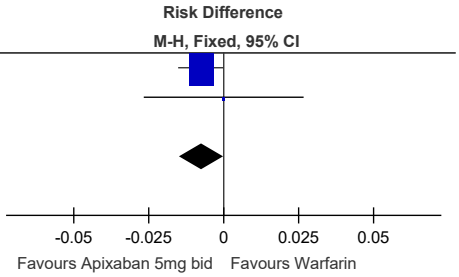


Figure 42: Myocardial infarction

Study or Subgroup	Apixaban 5mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
ARISTOTLE 2011	90	9120	102	9081	99.2%	-0.00 [-0.00, 0.00]
ARISTOTLE-J 2011	0	71	0	75	0.8%	0.00 [-0.03, 0.03]
Total (95% CI)		**9191**		**9156**	**100.0%**	**-0.00 [-0.00, 0.00]**
Total events	90		102			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%

Test for overall effect: Z = 0.90 (P = 0.37)

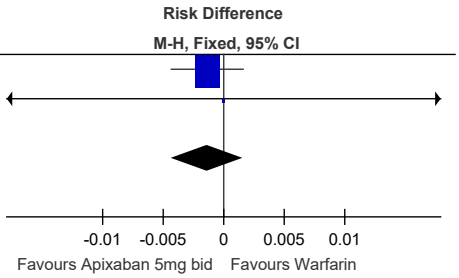


Figure 43: Clinically relevant non major bleeding

Study or Subgroup	Apixaban 5mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARISTOTLE-J 2011	1	71	3	75	100.0%	0.35 [0.04, 3.31]
Total (95% CI)		**71**		**75**	**100.0%**	**0.35 [0.04, 3.31]**
Total events	1		3			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.91 (P = 0.36)

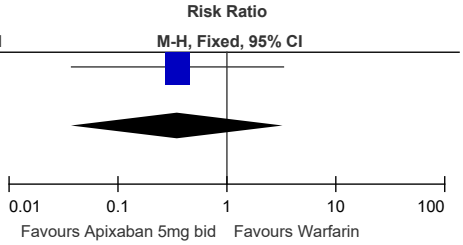


Figure 44: Minor bleeding

Study or Subgroup	Apixaban 5mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARISTOTLE-J 2011	17	71	10	75	100.0%	1.80 [0.88, 3.65]
Total (95% CI)		**71**		**75**	**100.0%**	**1.80 [0.88, 3.65]**
Total events	17		10			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.62 (P = 0.11)

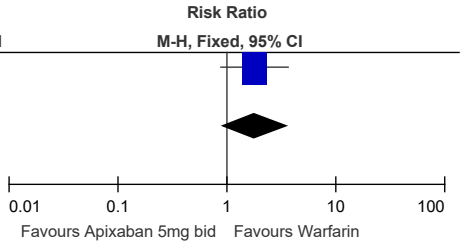


Figure 45: Major bleeding

Study or Subgroup	Apixaban 5mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARISTOTLE 2011	327	9088	462	9052	99.7%	0.70 [0.61, 0.81]
ARISTOTLE-J 2011	0	71	1	75	0.3%	0.35 [0.01, 8.50]
Total (95% CI)		**9159**		**9127**	**100.0%**	**0.70 [0.61, 0.81]**
Total events	327		463			

Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%

Test for overall effect: Z = 4.97 (P < 0.00001)

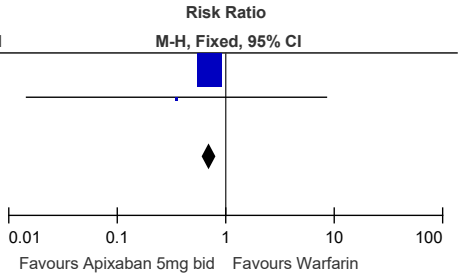


Figure 46: Intracranial bleeding

Study or Subgroup	Apixaban 5mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARISTOTLE 2011	52	9088	122	9052	100.0%	0.42 [0.31, 0.59]
Total (95% CI)		**9088**		**9052**	**100.0%**	**0.42 [0.31, 0.59]**
Total events	52		122			

Heterogeneity: Not applicable

Test for overall effect: Z = 5.19 (P < 0.00001)

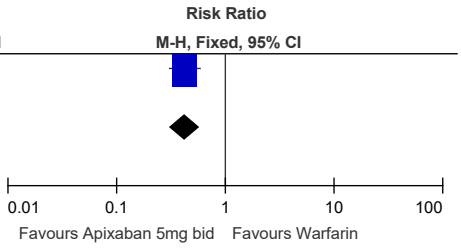
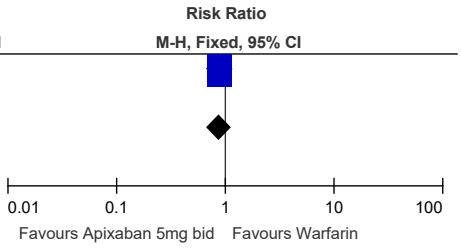


Figure 47: Gastrointestinal bleeding

Study or Subgroup	Apixaban 5mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARISTOTLE 2011	105	9088	119	9052	100.0%	0.88 [0.68, 1.14]
Total (95% CI)		**9088**		**9052**	**100.0%**	**0.88 [0.68, 1.14]**
Total events	105		119			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.97 (P = 0.33)



Dabigatran 110mg bid versus Warfarin

Figure 48: Health related quality of life

Study or Subgroup	Dabigatran 110mg bid Mean	SD	Total	Warfarin (INR 2-3) Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**

Heterogeneity: Not applicable

Test for overall effect: Not applicable

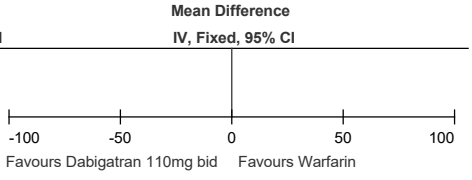


Figure 49: All stroke and systemic embolism

Study or Subgroup	Dabigatran 110mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RE-LY 2009	183	6015	202	6022	100.0%	0.91 [0.74, 1.10]
Total (95% CI)		**6015**		**6022**	**100.0%**	**0.91 [0.74, 1.10]**
Total events	183		202			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)

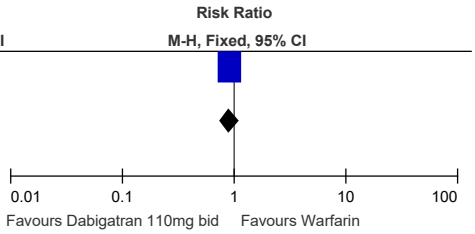


Figure 50: All cause mortality

Study or Subgroup	Dabigatran 110mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RE-LY 2009	446	6015	487	6022	100.0%	0.92 [0.81, 1.04]
Total (95% CI)		**6015**		**6022**	**100.0%**	**0.92 [0.81, 1.04]**
Total events	446		487			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)

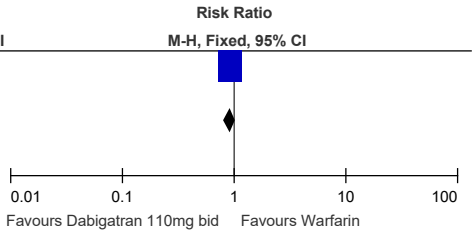


Figure 51: Myocardial infarction

Study or Subgroup	Dabigatran 110mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RE-LY 2009	98	6015	75	6022	100.0%	1.31 [0.97, 1.76]
Total (95% CI)		**6015**		**6022**	**100.0%**	**1.31 [0.97, 1.76]**
Total events	98		75			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.76 (P = 0.08)

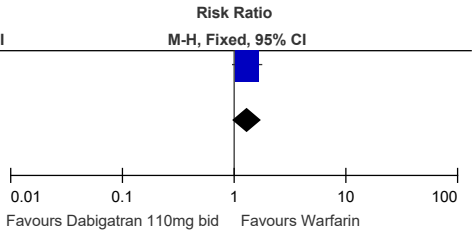


Figure 52: Clinically relevant non major bleeding

Study or Subgroup	Dabigatran 110mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

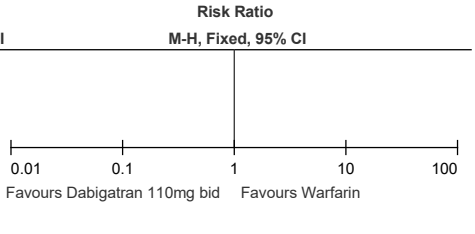


Figure 53: Minor bleeding

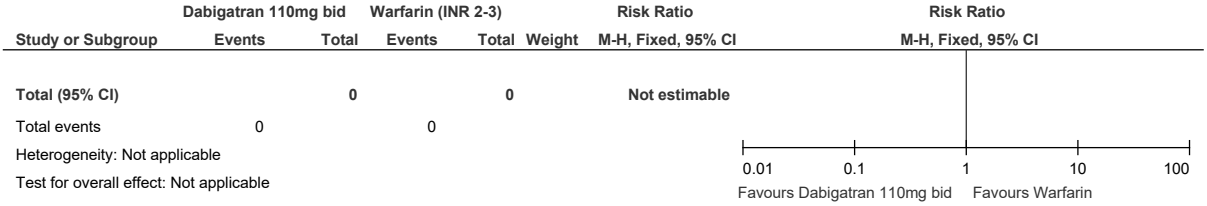


Figure 54: Major bleeding

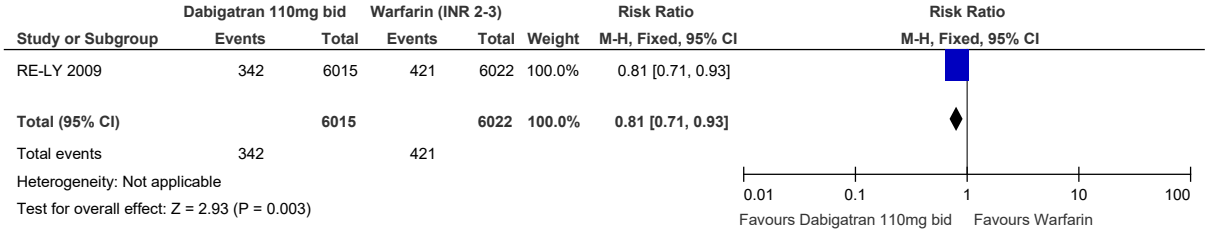


Figure 55: Intracranial bleeding

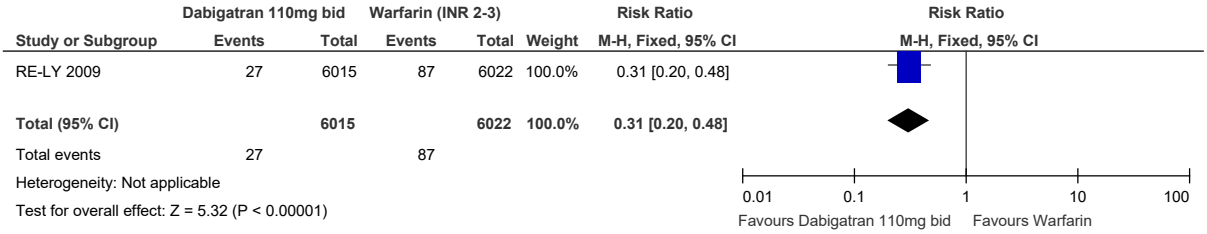
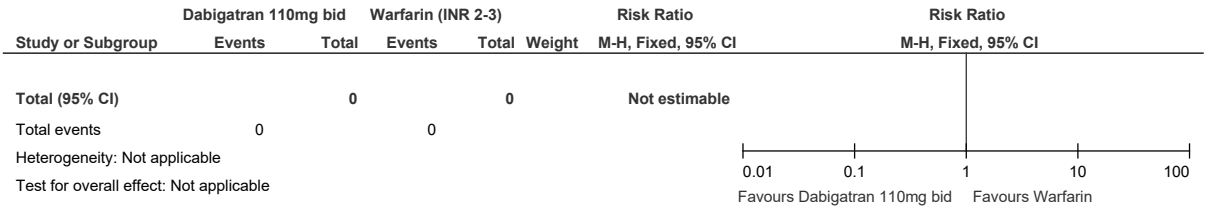


Figure 56: Gastrointestinal bleeding



Dabigatran 150mg bid versus Warfarin

Figure 57: Health related quality of life

Study or Subgroup	Dabigatran 150mg bid Mean	SD	Total	Warfarin (INR 2-3) Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

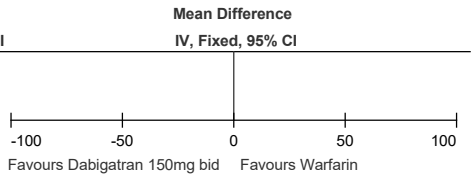


Figure 58: All stroke and systemic embolism

Study or Subgroup	Dabigatran 150mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
PETRO 2007	0	100	0	70	1.3%	0.00 [-0.02, 0.02]
RE-LY 2009	134	6076	202	6022	98.7%	-0.01 [-0.02, -0.01]
Total (95% CI)		**6176**		**6092**	**100.0%**	**-0.01 [-0.02, -0.01]**
Total events	134		202			
Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 3.84 (P = 0.0001)						

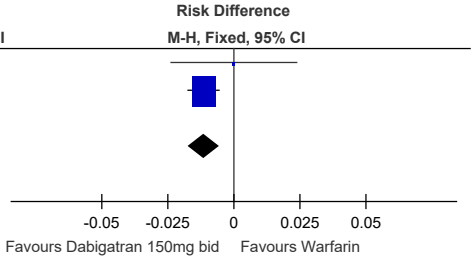


Figure 59: All cause mortality

Study or Subgroup	Dabigatran 150mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RE-LY 2009	438	6076	487	6022	100.0%	0.89 [0.79, 1.01]
Total (95% CI)		**6076**		**6022**	**100.0%**	**0.89 [0.79, 1.01]**
Total events	438		487			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						

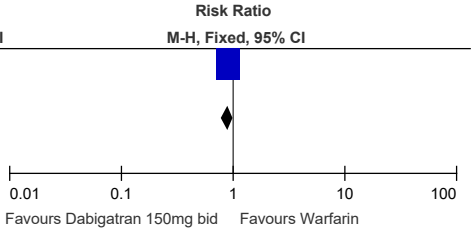


Figure 60: Myocardial infarction

Study or Subgroup	Dabigatran 150mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RE-LY 2009	97	6076	75	6022	100.0%	1.28 [0.95, 1.73]
Total (95% CI)		**6076**		**6022**	**100.0%**	**1.28 [0.95, 1.73]**
Total events	97		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						

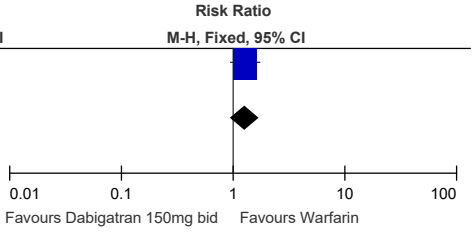


Figure 61: Clinically relevant non major bleeding

Study or Subgroup	Dabigatran 150mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PETRO 2007	9	100	4	70	100.0%	1.57 [0.50, 4.91]
Total (95% CI)		**100**		**70**	**100.0%**	**1.57 [0.50, 4.91]**
Total events	9		4			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.78 (P = 0.43)

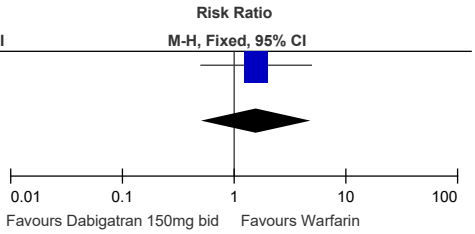


Figure 62: Minor bleeding

Study or Subgroup	Dabigatran 150mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable

Test for overall effect: Not applicable

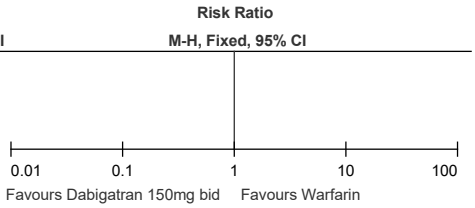


Figure 63: Major bleeding

Study or Subgroup	Dabigatran 150mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
PETRO 2007	0	100	0	70	1.3%	0.00 [-0.02, 0.02]
RE-LY 2009	399	6076	421	6022	98.7%	-0.00 [-0.01, 0.00]
Total (95% CI)		**6176**		**6092**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	399		421			

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%

Test for overall effect: Z = 0.93 (P = 0.35)

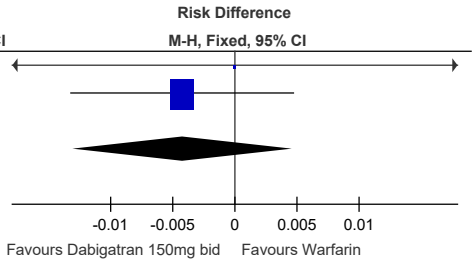


Figure 64: Intracranial bleeding

Study or Subgroup	Dabigatran 150mg bid Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RE-LY 2009	36	6076	87	6022	100.0%	0.41 [0.28, 0.60]
Total (95% CI)		**6076**		**6022**	**100.0%**	**0.41 [0.28, 0.60]**
Total events	36		87			

Heterogeneity: Not applicable

Test for overall effect: Z = 4.52 (P < 0.00001)

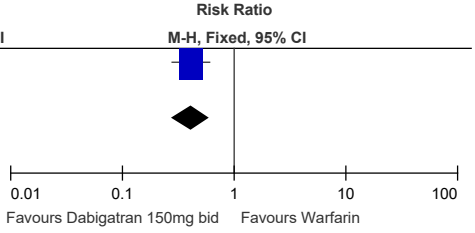
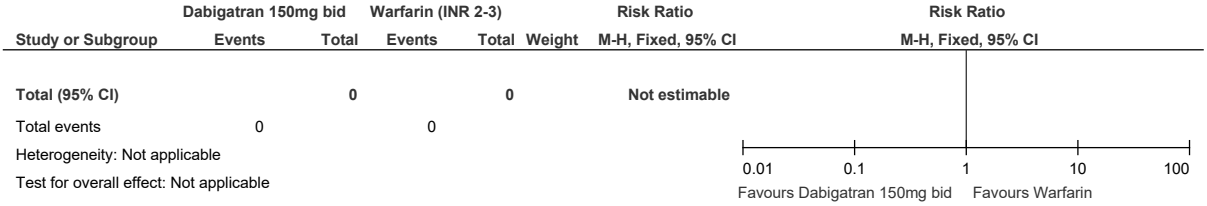


Figure 65: Gastrointestinal bleeding



Rivaroxaban 20mg qd versus Warfarin

Figure 66: Health related quality of life

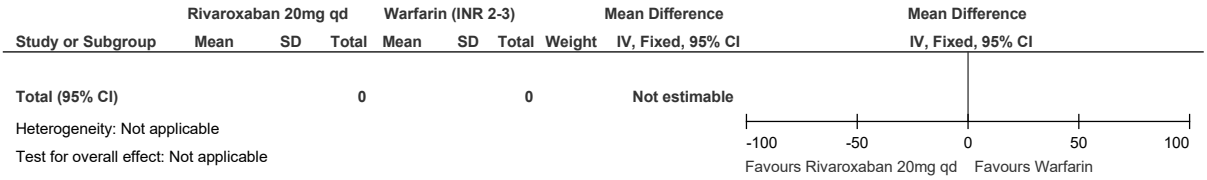


Figure 67: All stroke and systemic embolism

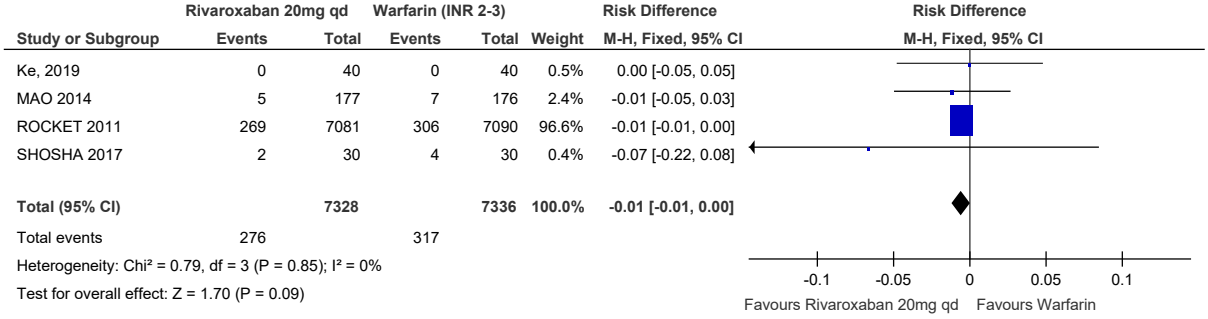


Figure 68: All cause mortality

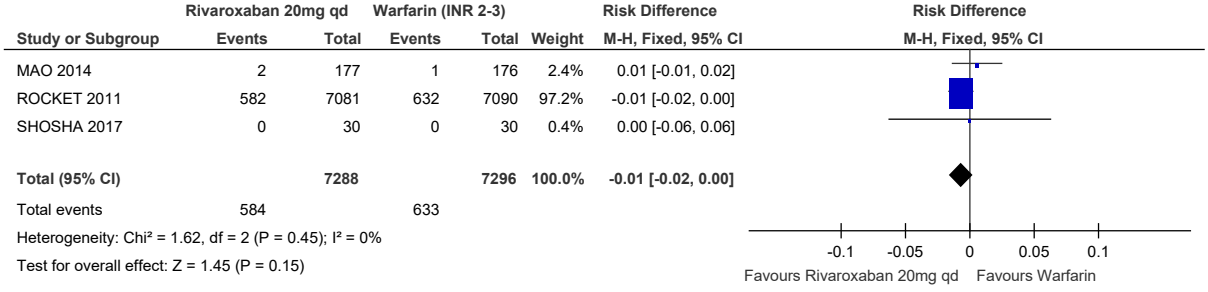


Figure 69: Myocardial infarction

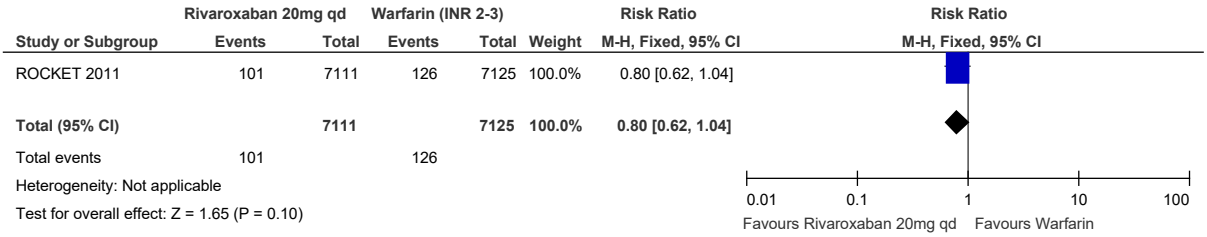


Figure 70: Clinically relevant non major bleeding

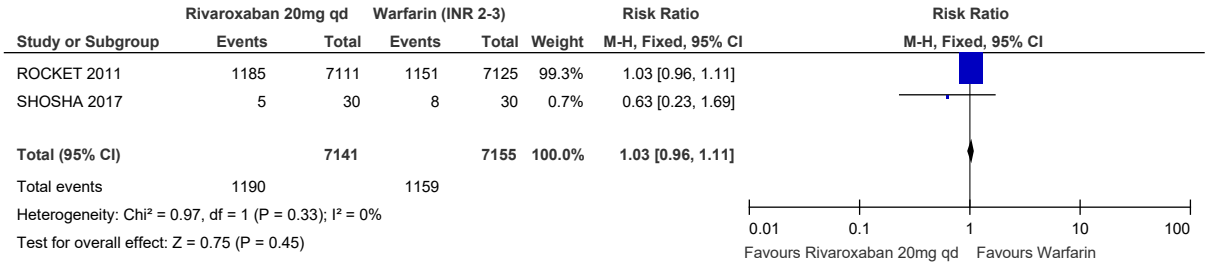


Figure 71: Minor bleeding

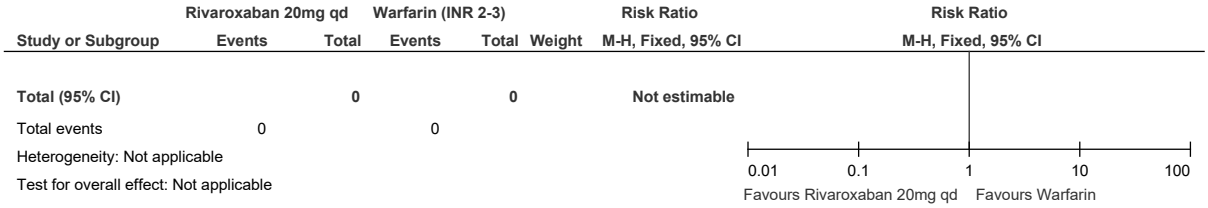


Figure 72: Major bleeding

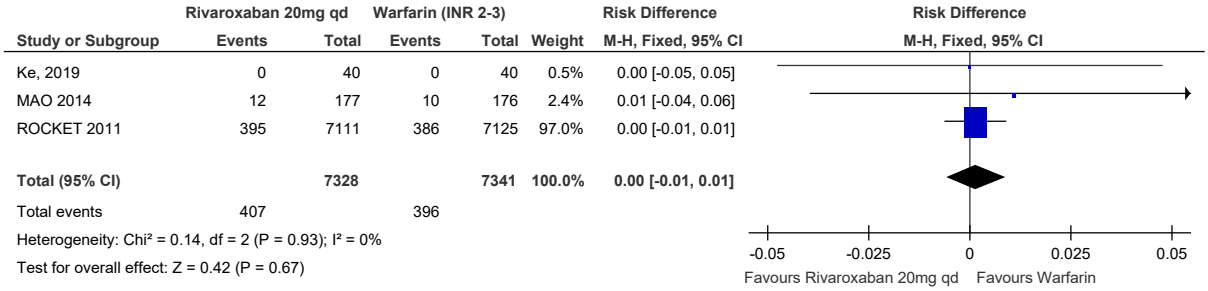


Figure 73: Intracranial bleeding

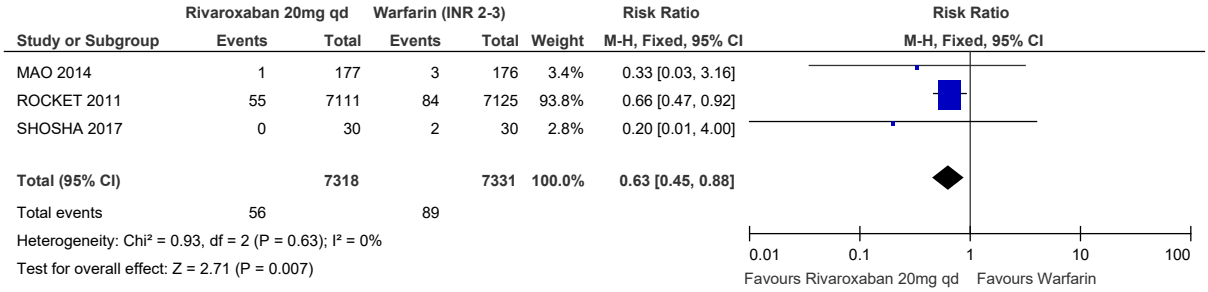
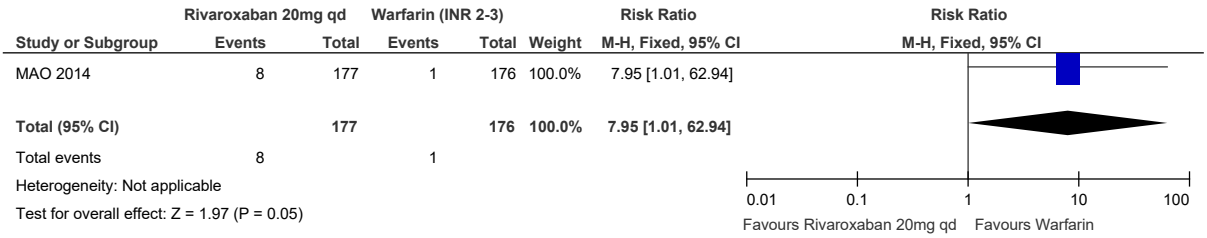


Figure 74: Gastrointestinal bleeding



Rivaroxaban 15mg qd versus Warfarin

Figure 75: Health related quality of life

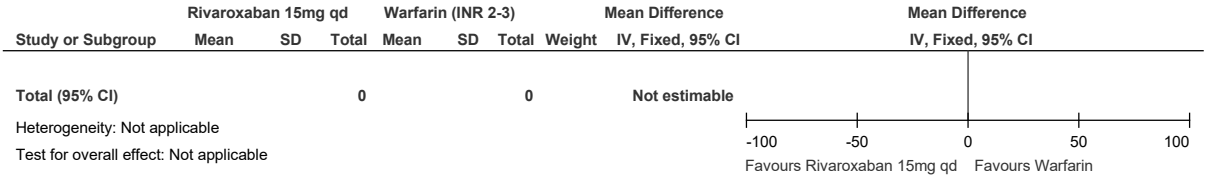


Figure 76: All stroke and systemic embolism

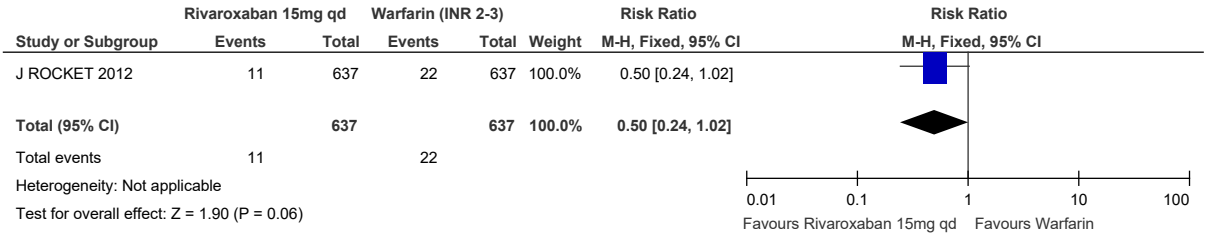


Figure 77: All cause mortality

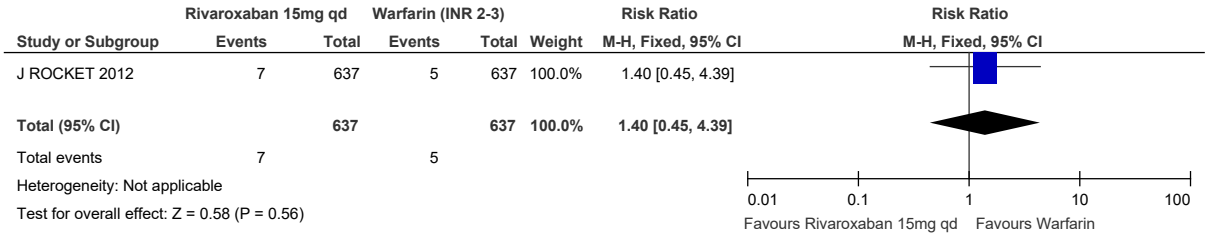


Figure 78: Myocardial infarction

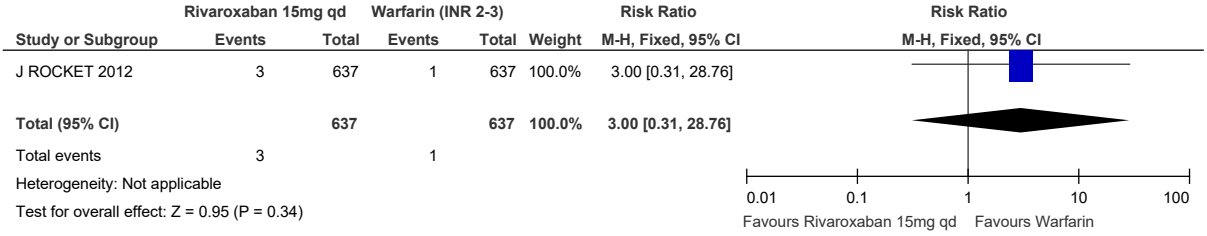


Figure 79: Clinically relevant non major bleeding

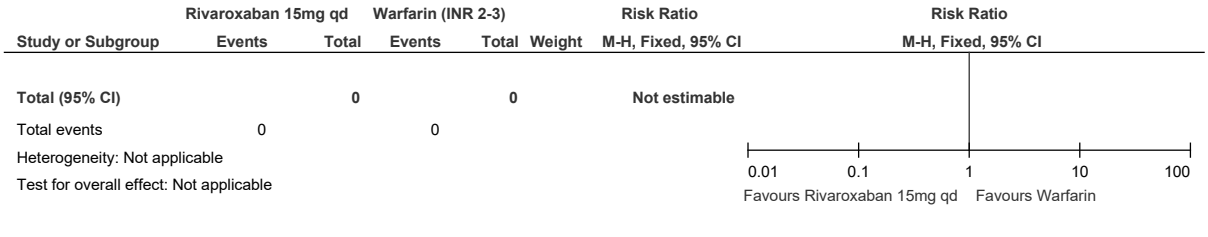


Figure 80: Minor bleeding

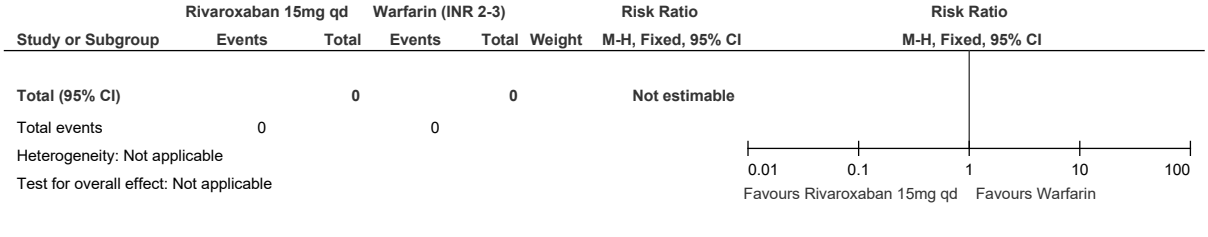


Figure 81: Major bleeding

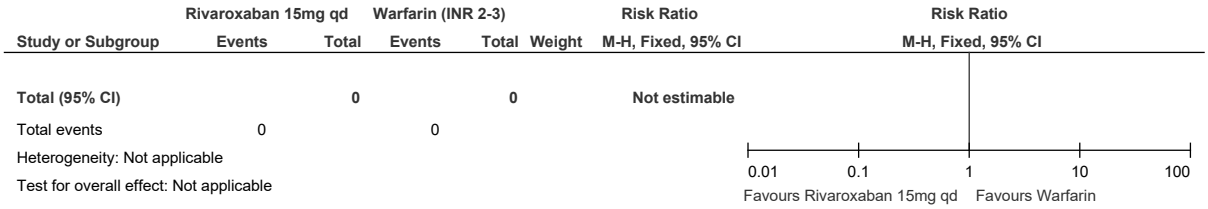


Figure 82: Intracranial bleeding

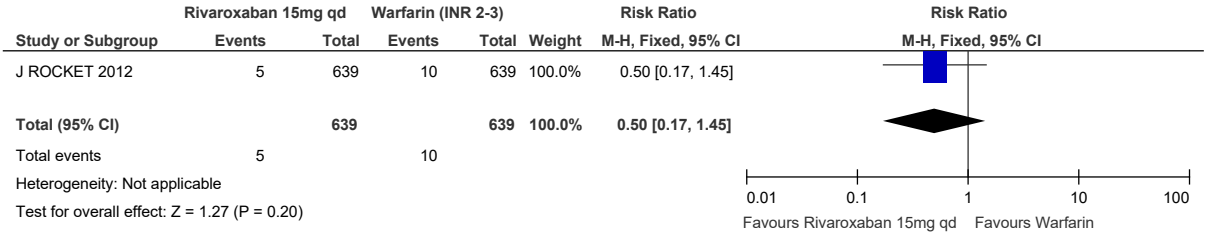
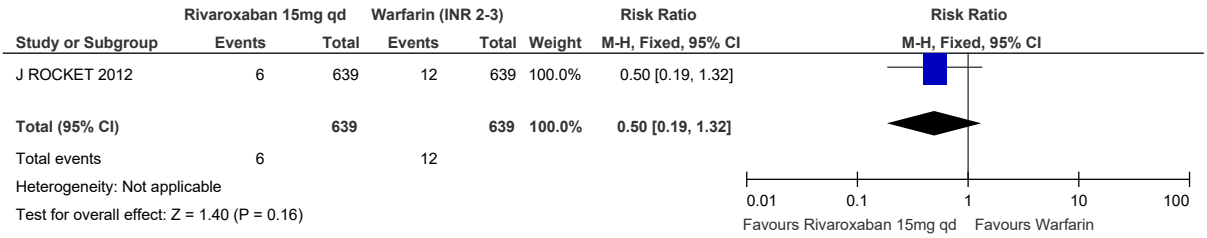


Figure 83: Gastrointestinal bleeding



Edoxaban 30mg qd versus Warfarin

Figure 84: Health related quality of life

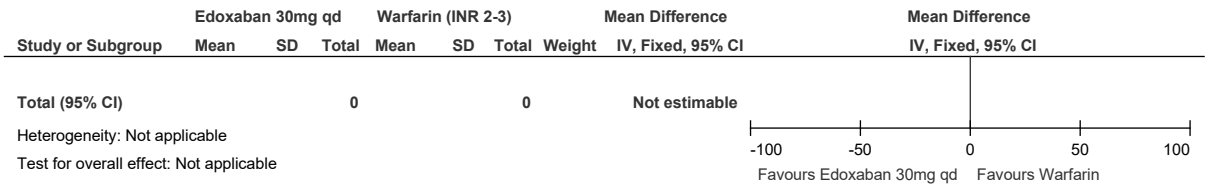


Figure 85: All stroke and systemic embolism

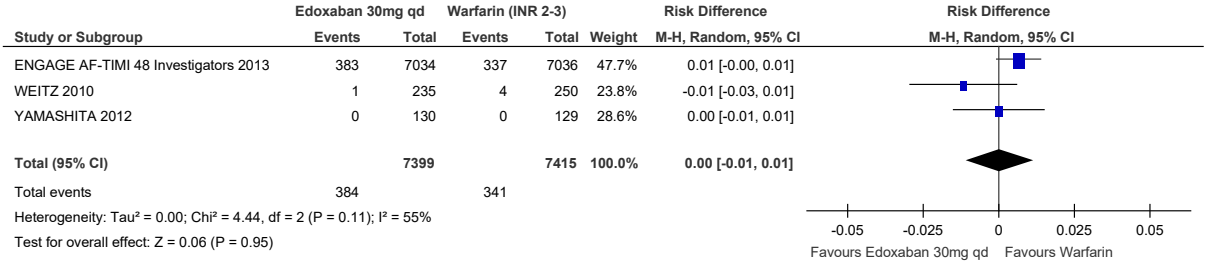


Figure 86: All cause mortality

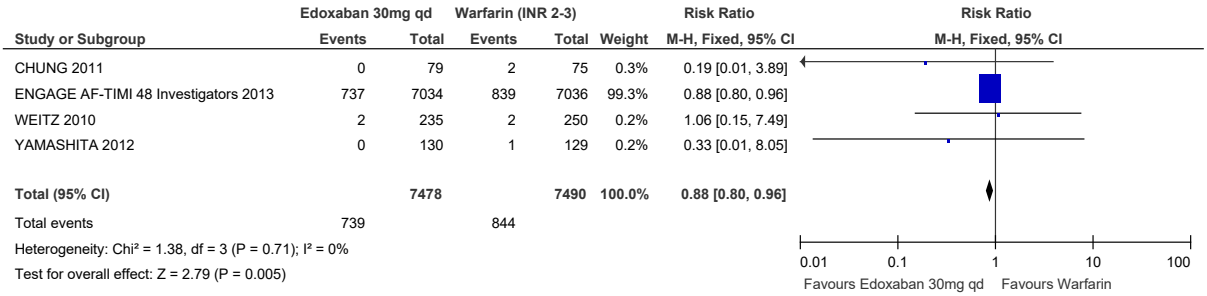


Figure 87: Myocardial infarction

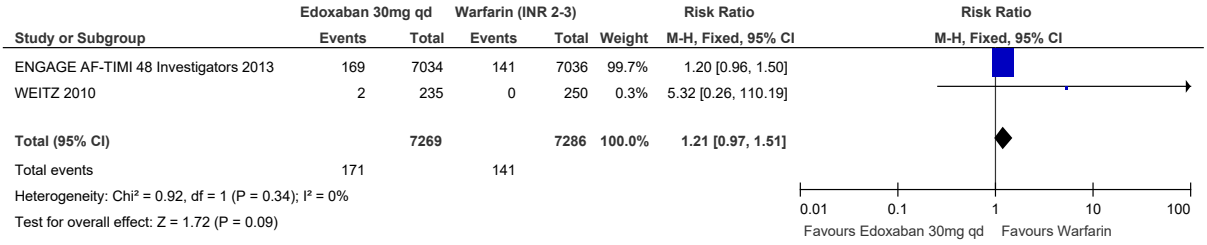


Figure 88: Clinically relevant non major bleeding

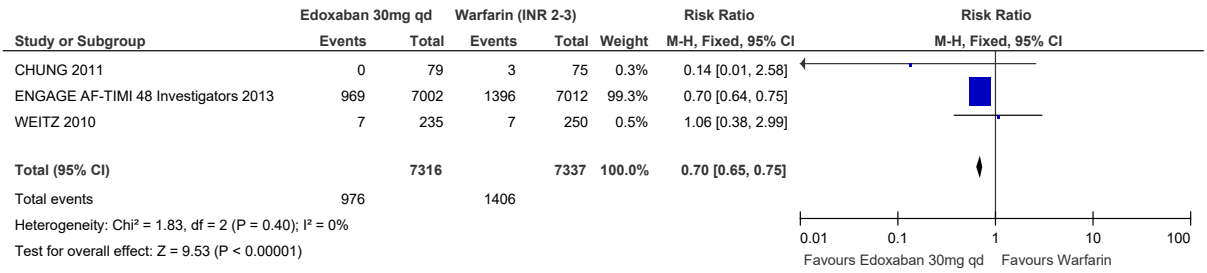


Figure 89: Minor bleeding

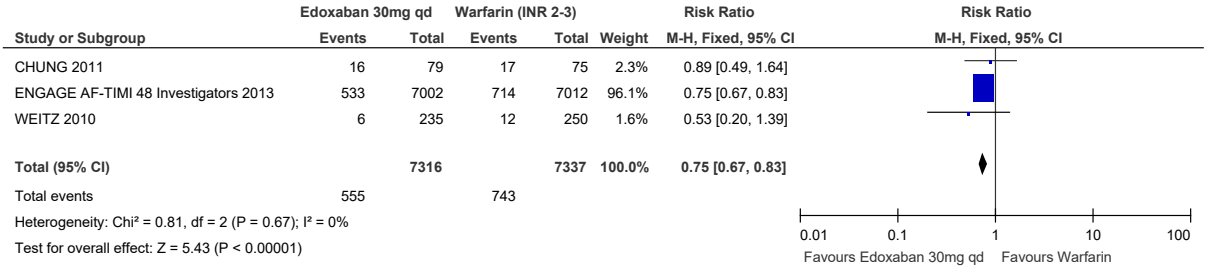


Figure 90: Major bleeding

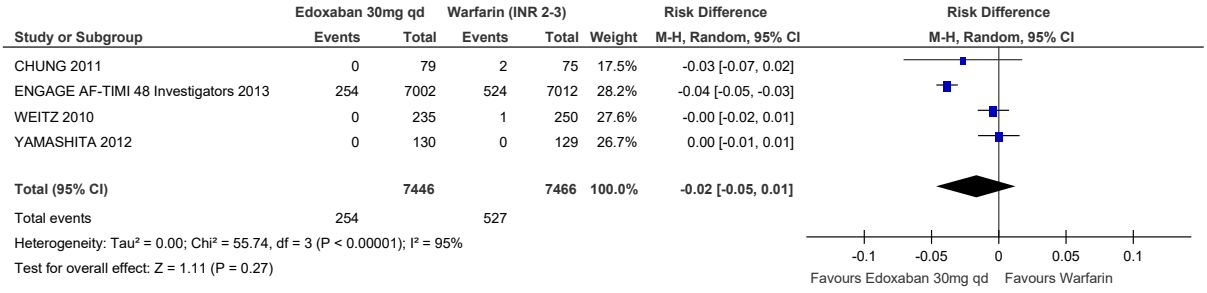


Figure 91: Intracranial bleeding

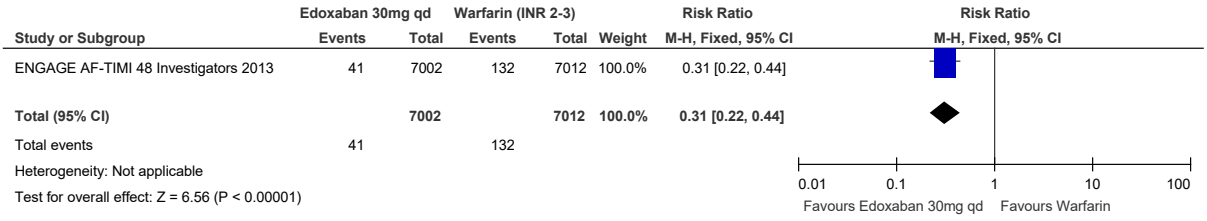
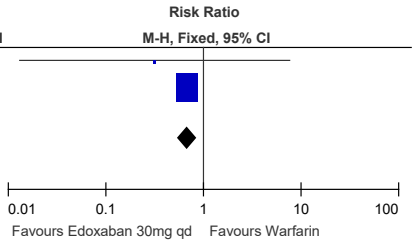


Figure 92: Gastrointestinal bleeding

Study or Subgroup	Edoxaban 30mg qd Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHUNG 2011	0	79	1	75	0.8%	0.32 [0.01, 7.65]
ENGAGE AF-TIMI 48 Investigators 2013	129	7002	190	7012	99.2%	0.68 [0.55, 0.85]
Total (95% CI)		**7081**		**7087**	**100.0%**	**0.68 [0.54, 0.84]**
Total events	129		191			

Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 3.47 (P = 0.0005)



Edoxaban 60mg versus Warfarin

Figure 93: Health related quality of life

Study or Subgroup	Edoxaban 60mg qd Mean	SD	Total	Warfarin (INR 2-3) Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

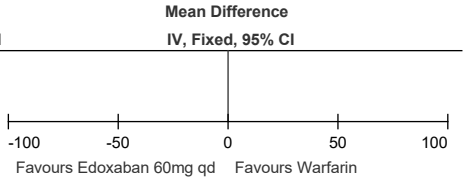


Figure 94: All stroke and systemic embolism

Study or Subgroup	Edoxaban 60mg qd Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
ENGAGE AF-TIMI 48 Investigators 2013	296	7035	337	7036	95.0%	-0.01 [-0.01, 0.00]
WEITZ 2010	1	234	4	250	3.3%	-0.01 [-0.03, 0.01]
YAMASHITA 2012	0	130	0	129	1.7%	0.00 [-0.01, 0.01]
Total (95% CI)		**7399**		**7415**	**100.0%**	**-0.01 [-0.01, 0.00]**
Total events	297		341			

Heterogeneity: Chi² = 1.01, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)

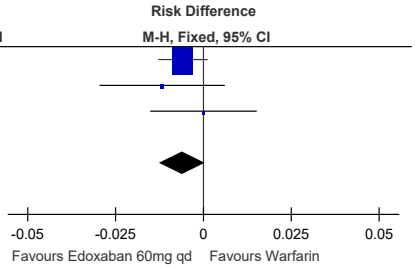


Figure 95: All cause mortality

Study or Subgroup	Edoxaban 60mg qd Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHUNG 2011	0	80	2	75	0.3%	0.19 [0.01, 3.85]
ENGAGE AF-TIMI 48 Investigators 2013	773	7035	839	7036	99.3%	0.92 [0.84, 1.01]
WEITZ 2010	0	234	2	250	0.3%	0.21 [0.01, 4.43]
YAMASHITA 2012	1	130	1	129	0.1%	0.99 [0.06, 15.70]
Total (95% CI)		**7479**		**7490**	**100.0%**	**0.92 [0.84, 1.01]**
Total events	774		844			

Heterogeneity: Chi² = 1.96, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.84 (P = 0.07)

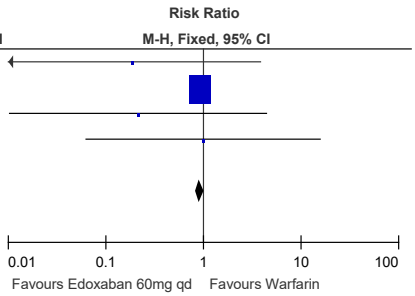


Figure 96: Myocardial infarction

Study or Subgroup	Edoxaban 60mg qd Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ENGAGE AF-TIMI 48 Investigators 2013	133	7035	141	7036	99.7%	0.94 [0.75, 1.19]
WEITZ 2010	2	234	0	250	0.3%	5.34 [0.26, 110.66]
Total (95% CI)		**7269**		**7286**	**100.0%**	**0.96 [0.76, 1.21]**
Total events	135		141			

Heterogeneity: Chi² = 1.25, df = 1 (P = 0.26); I² = 20%

Test for overall effect: Z = 0.36 (P = 0.72)

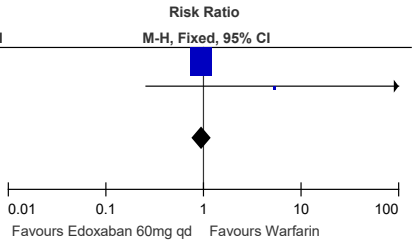


Figure 97: Clinically relevant non major bleeding

Study or Subgroup	Edoxaban 60mg qd Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHUNG 2011	6	80	3	75	0.2%	1.88 [0.49, 7.23]
ENGAGE AF-TIMI 48 Investigators 2013	1214	7012	1396	7012	99.3%	0.87 [0.81, 0.93]
WEITZ 2010	8	234	7	250	0.5%	1.22 [0.45, 3.31]
Total (95% CI)		**7326**		**7337**	**100.0%**	**0.87 [0.82, 0.94]**
Total events	1228		1406			

Heterogeneity: Chi² = 1.68, df = 2 (P = 0.43); I² = 0%

Test for overall effect: Z = 3.83 (P = 0.0001)

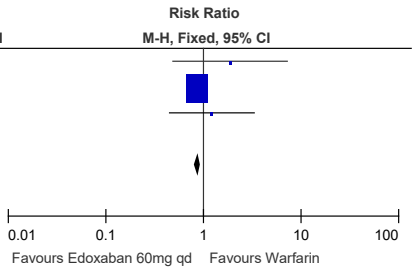


Figure 98: Minor bleeding

Study or Subgroup	Edoxaban 60mg qd Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHUNG 2011	15	80	17	75	2.4%	0.83 [0.45, 1.54]
ENGAGE AF-TIMI 48 Investigators 2013	604	7012	714	7012	96.1%	0.85 [0.76, 0.94]
WEITZ 2010	8	234	12	250	1.6%	0.71 [0.30, 1.71]
Total (95% CI)		**7326**		**7337**	**100.0%**	**0.84 [0.76, 0.93]**
Total events	627		743			

Heterogeneity: Chi² = 0.15, df = 2 (P = 0.93); I² = 0%

Test for overall effect: Z = 3.30 (P = 0.0010)

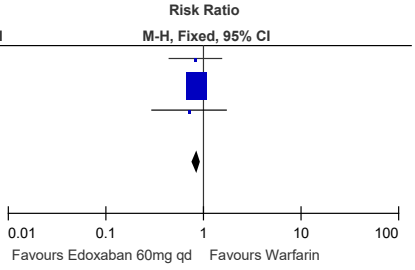


Figure 99: Major bleeding

Study or Subgroup	Edoxaban 60mg qd Events	Total	Warfarin (INR 2-3) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHUNG 2011	0	80	2	75	0.5%	0.19 [0.01, 3.85]
ENGAGE AF-TIMI 48 Investigators 2013	418	7012	524	7012	99.2%	0.80 [0.70, 0.90]
WEITZ 2010	1	234	1	250	0.2%	1.07 [0.07, 16.98]
YAMASHITA 2012	2	130	0	125	0.1%	4.81 [0.23, 99.19]
Total (95% CI)		**7456**		**7462**	**100.0%**	**0.80 [0.71, 0.90]**
Total events	421		527			

Heterogeneity: Chi² = 2.28, df = 3 (P = 0.52); I² = 0%

Test for overall effect: Z = 3.55 (P = 0.0004)

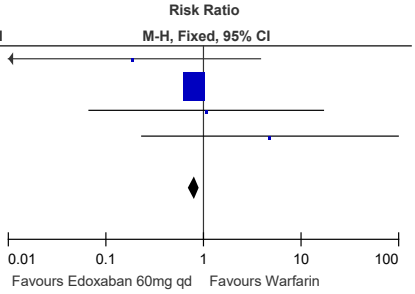


Figure 100: Intracranial bleeding

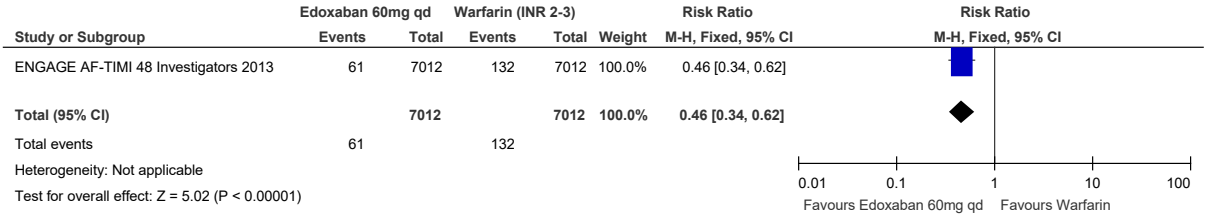
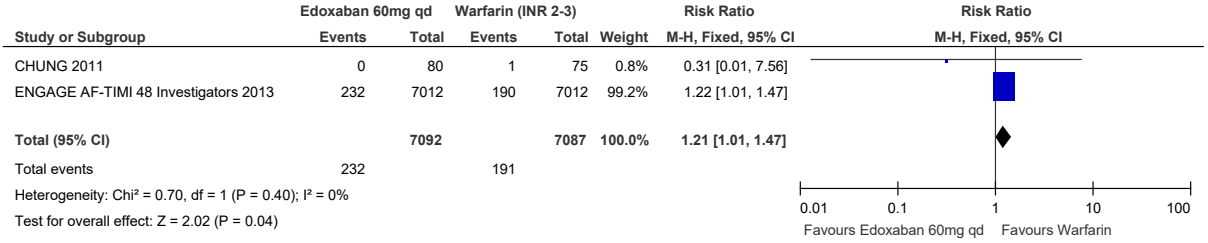


Figure 101: Gastrointestinal bleeding



Apixaban 5mg versus antiplatelets

Figure 102: Health related quality of life

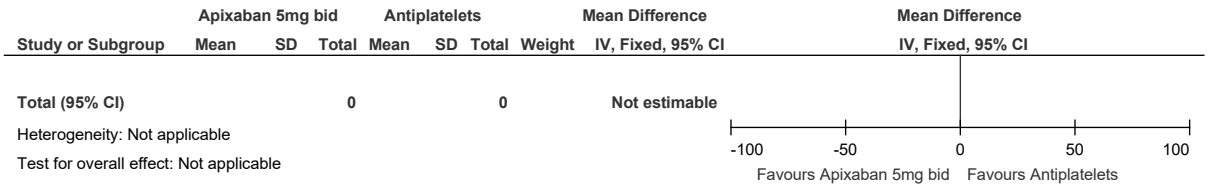


Figure 103: All stroke and systemic embolism

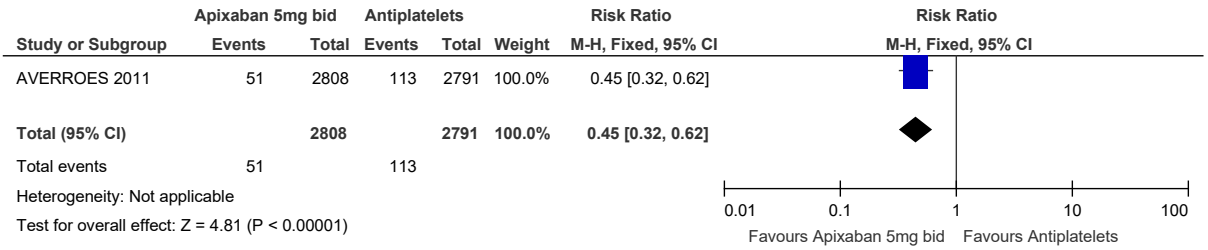


Figure 104: All cause mortality

Study or Subgroup	Apixaban 5mg bid Events	Total	Antiplatelets Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AVERROES 2011	111	2808	140	2791	100.0%	0.79 [0.62, 1.01]
Total (95% CI)		**2808**		**2791**	**100.0%**	**0.79 [0.62, 1.01]**
Total events	111		140			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.92 (P = 0.06)

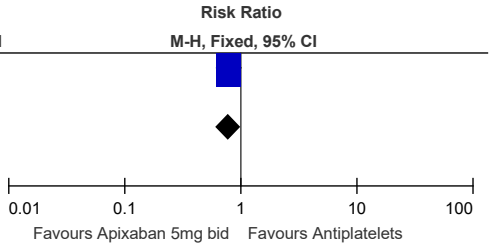


Figure 105: Myocardial infarction

Study or Subgroup	Apixaban 5mg bid Events	Total	Antiplatelets Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AVERROES 2011	24	2808	28	2791	100.0%	0.85 [0.50, 1.47]
Total (95% CI)		**2808**		**2791**	**100.0%**	**0.85 [0.50, 1.47]**
Total events	24		28			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

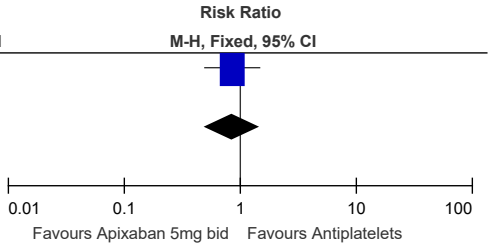


Figure 106: Clinically relevant non major bleeding

Study or Subgroup	Apixaban 5mg bid Events	Total	Antiplatelets Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AVERROES 2011	96	2808	84	2791	100.0%	1.14 [0.85, 1.52]
Total (95% CI)		**2808**		**2791**	**100.0%**	**1.14 [0.85, 1.52]**
Total events	96		84			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.39)

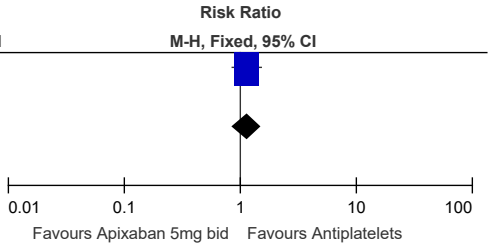


Figure 107: Minor bleeding

Study or Subgroup	Apixaban 5mg bid Events	Total	Antiplatelets Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AVERROES 2011	188	2808	153	2791	100.0%	1.22 [0.99, 1.50]
Total (95% CI)		**2808**		**2791**	**100.0%**	**1.22 [0.99, 1.50]**
Total events	188		153			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.89 (P = 0.06)

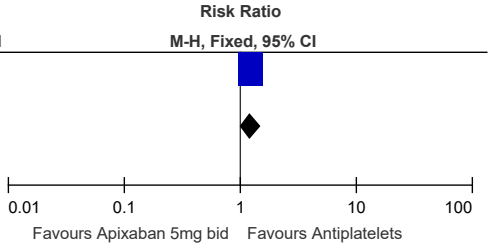


Figure 108: Major bleeding

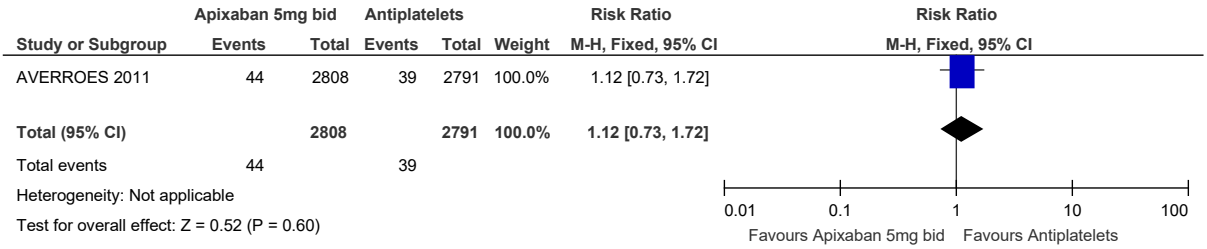


Figure 109: Intracranial bleeding

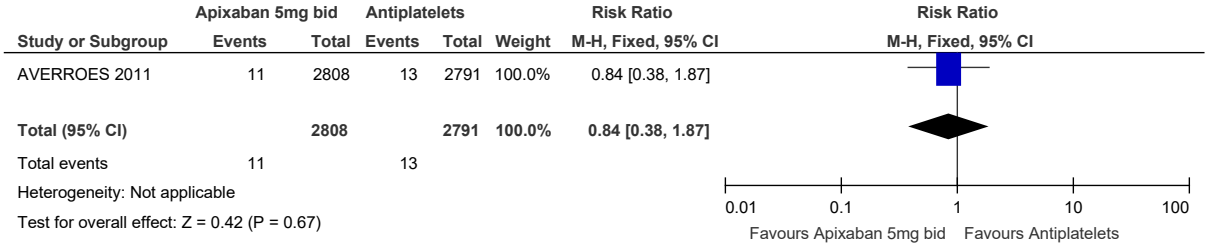
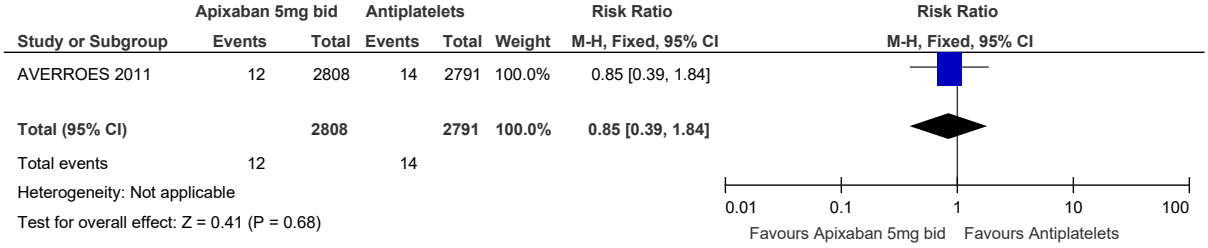


Figure 110: Gastrointestinal bleeding



Placebo versus Warfarin INR 3-4

Figure 111: Health related quality of life

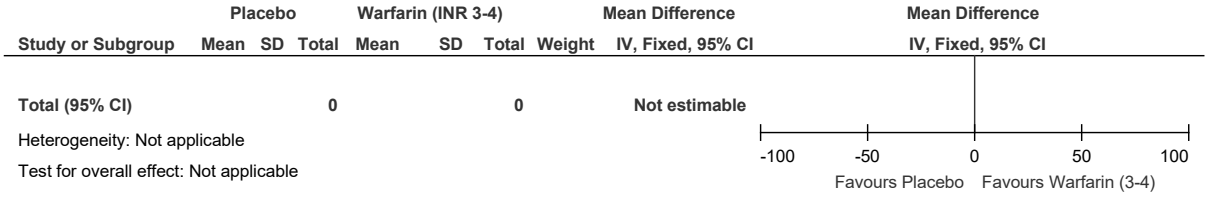


Figure 112: All stroke and systemic embolism

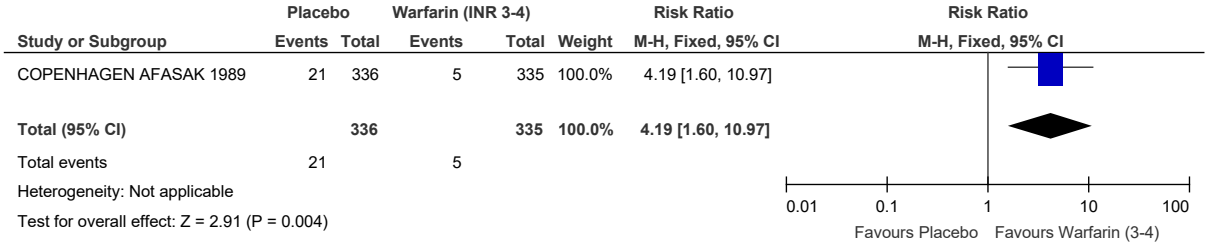


Figure 113: All cause mortality

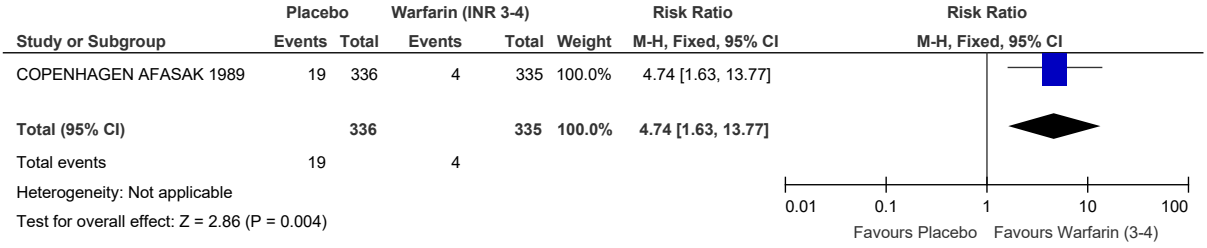


Figure 114: Myocardial infarction

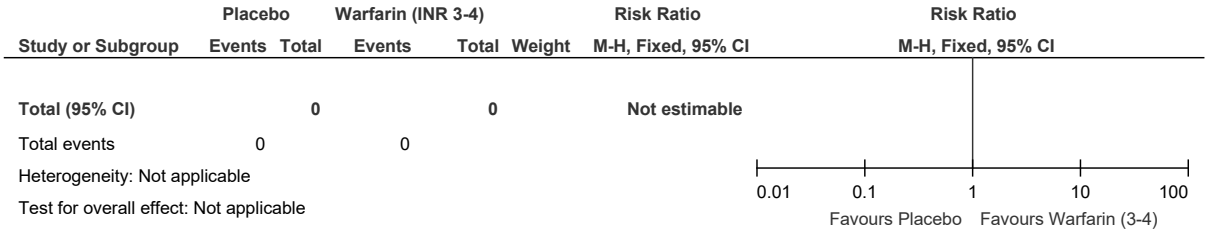


Figure 115: Clinically relevant non major bleeding

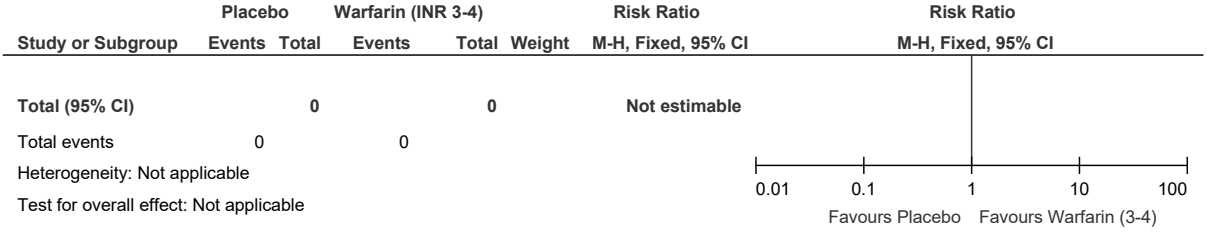


Figure 116: Minor bleeding

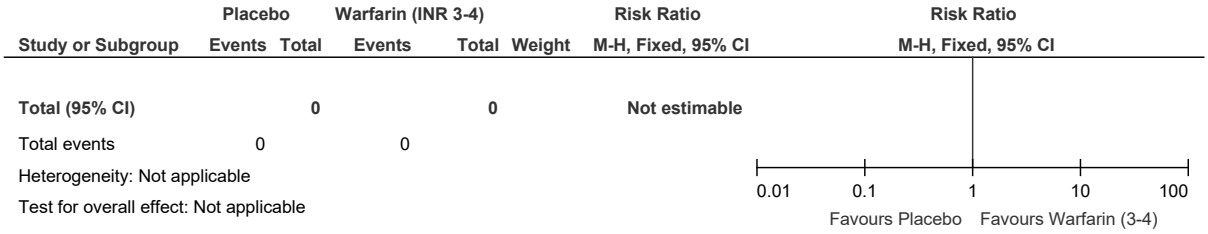


Figure 117: Major bleeding

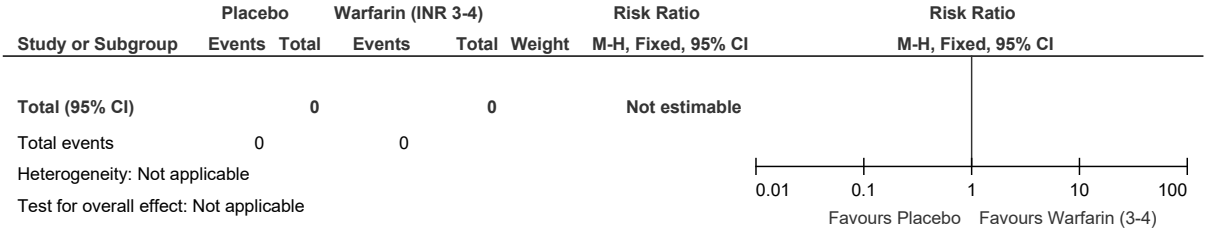


Figure 118: Intracranial bleeding

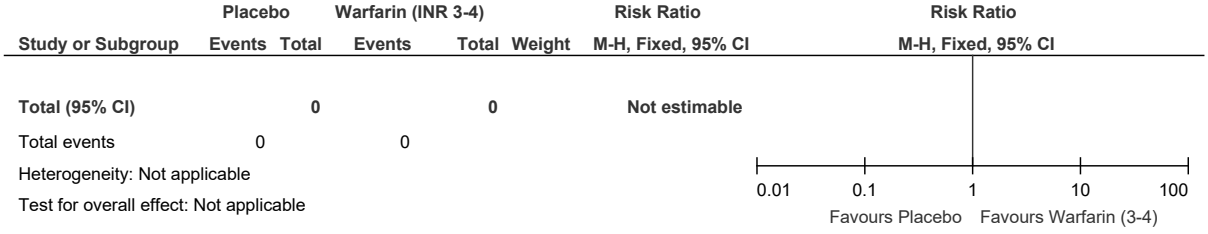
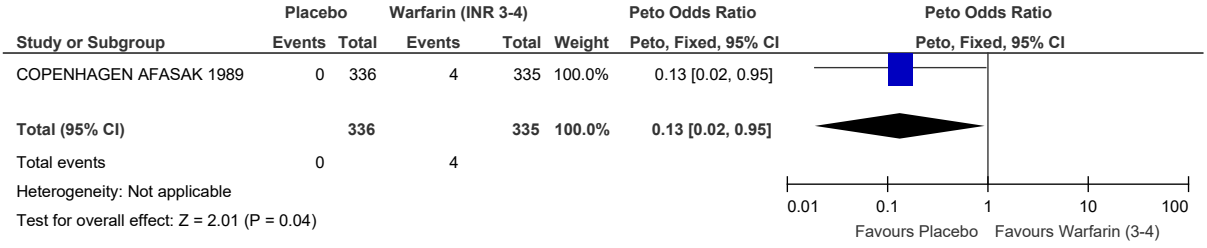


Figure 119: Gastrointestinal bleeding



Antiplatelets versus Warfarin INR 3-4

Figure 120: Health related quality of life

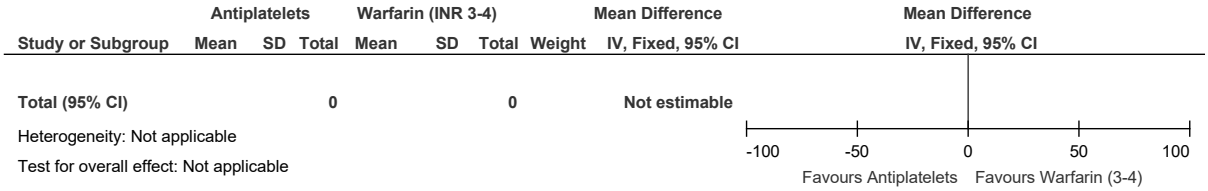


Figure 121: All stroke and systemic embolism

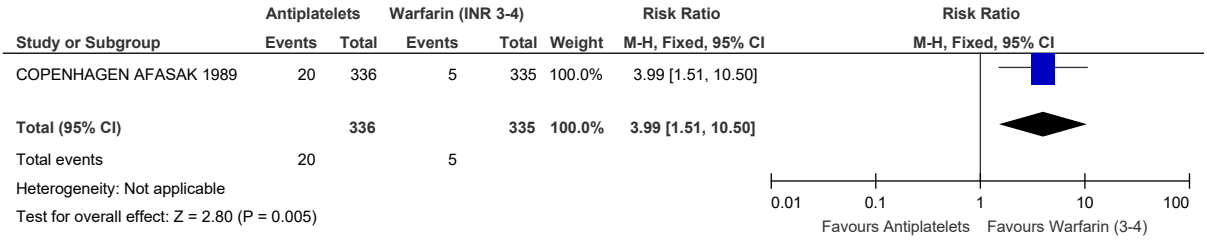


Figure 122: All cause mortality

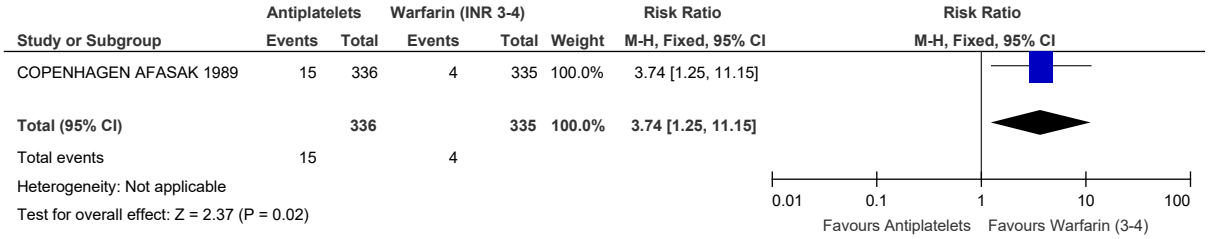


Figure 123: Clinically relevant non major bleeding

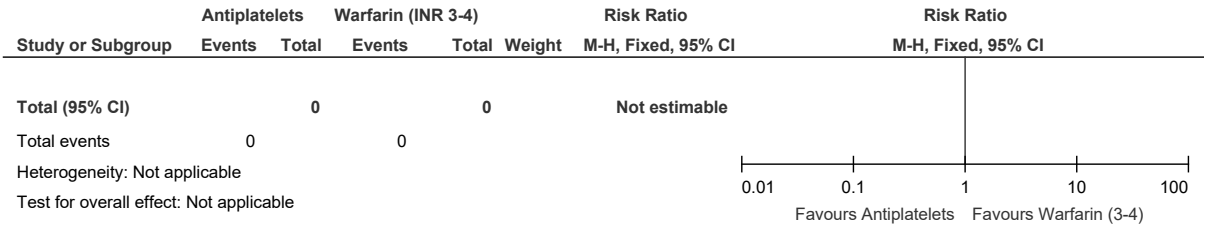


Figure 124: Myocardial infarction

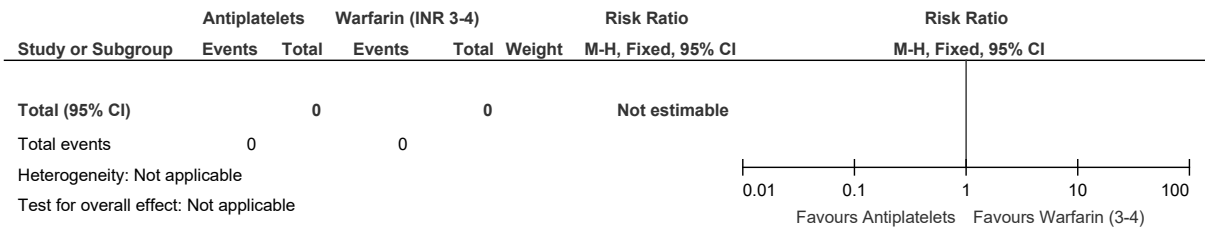


Figure 125: Minor bleeding

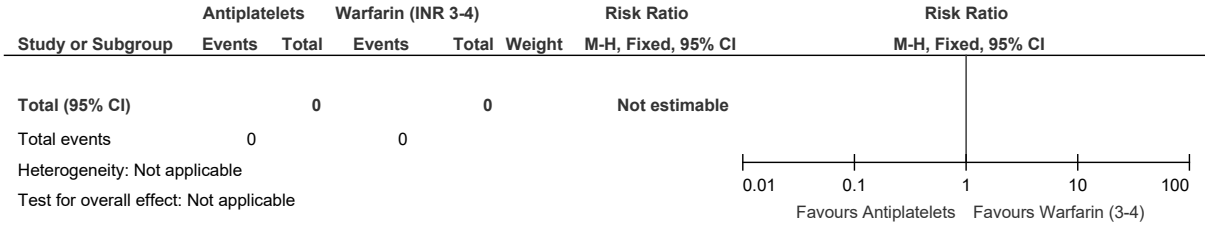


Figure 126: Major bleeding

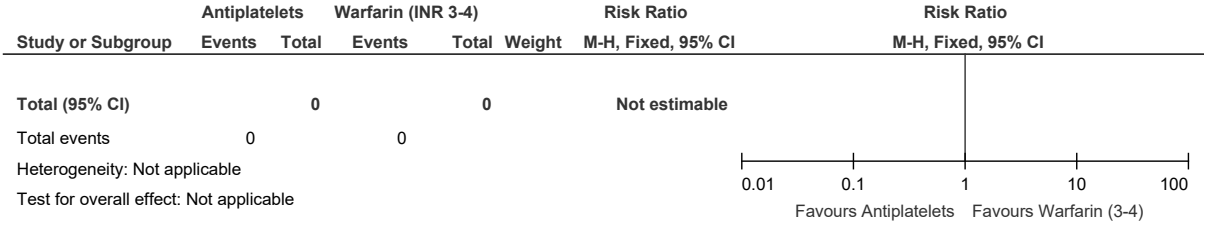


Figure 127: Intracranial bleeding

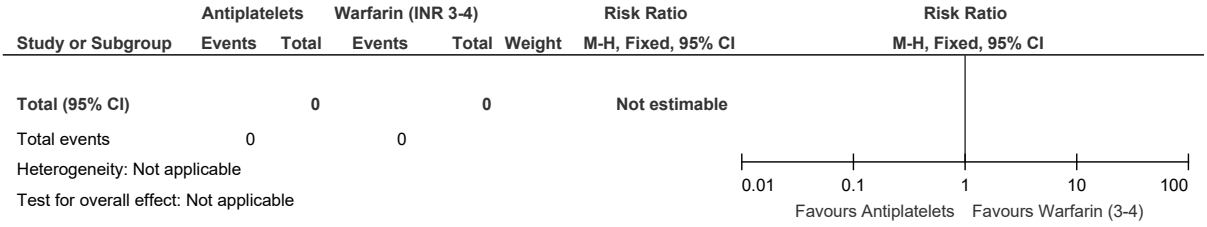
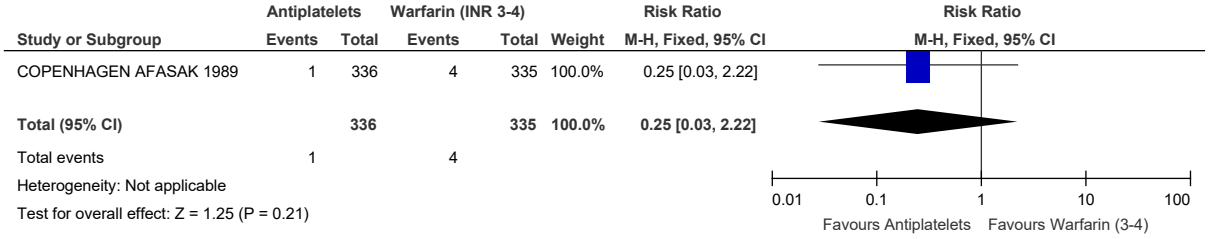


Figure 128: Gastrointestinal bleeding



GRADE tables

Table 35: Clinical evidence profile: Dabigatran 150mg bd versus Rivaroxaban 15mg qd for preventing stroke and thromboembolic events in people with AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dabigatran 150mg bd versus Rivaroxaban 15mg qd	Control	Relative (95% CI)	Absolute		
Health-related quality of life												
0	No evidence available					none	-	0%	not pooled	not pooled	-	CRITICAL
All stroke and systemic thromboembolism												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/62 (0%)	0%	RD 0.00(-0.03 to 0.03)	0 more per 1000 (from 30 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
All cause mortality												
0	No evidence available					none	-	0%	not pooled	not pooled	-	CRITICAL
Myocardial Infarction												

0	No evidence available					none	-	0%	not pooled	not pooled	-	CRITICAL
Clinically relevant non-major bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled	-	CRITICAL
Minor bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled	-	CRITICAL
major bleeding												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Very serious[3]	none	5/62 (8.1%)	5.5%	RR 1.48 (0.37 to 5.9)	26 more per 1000 (from 35 fewer to 270 more)	⊕OOO VERY LOW	CRITICAL
Intracranial bleeding												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/62 (0%)	0%	RD 0.00(-0.03 to 0.03)	0 more per 1000 (from 30 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
GI bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled	-	CRITICAL

[1] Very serious risk of bias due to unclear allocation concealment and very serious attrition
[2] Very serious imprecision because the sample size did not reach the optimum information size
[3] very serious risk of imprecision because the 95% Cis crossed both MIDS

Table 36: Clinical evidence profile: Antiplatelets versus warfarin for preventing stroke and thromboembolic events in people with AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelets	Warfarin	Relative (95% CI)	Absolute		
Health-related quality of life												
0	No evidence available					none	0	-	-	not pooled		
All stroke and systemic thromboembolism												
8	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[4]	No serious risk of imprecision	none	266/5088 (5.2%)	3.8%	RR 1.78 (1.47 to 2.17)	30 more per 1000 (from 18 more to 44 more)	VERY LOW	CRITICAL
All cause mortality												
8	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[4]	No serious risk of imprecision	none	377/5088 (7.4%)	6.9%	RR 1.04 (0.91 to 1.19)	3 more per 1000 (from 6 fewer to 13 more)	VERY LOW	CRITICAL
Myocardial infarction												
6	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[4]	serious risk of imprecision[2]	none	78/4848 (1.6%)	2.2%	RR 1.28 (0.92 to 1.78)	6 more per 1000 (from 2 fewer to 17 more)	VERY LOW	CRITICAL

Clinically relevant non-major bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled	-	CRITICAL
Minor bleeding												
5	RCT	Very serious risk of bias[1]	Very serious risk of inconsistency[3]	Serious risk of indirectness[4]	Serious risk of imprecision[2]	none	613/3917 (15.6%)	14.3%	Random effects RR 0.63 (0.36 to 1.1)	53 fewer per 1000 (from 92 fewer to 14 more)	VERY LOW	CRITICAL
major bleeding												
8	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[4]	Serious risk of imprecision[2]	none	160/5088 (3.1%)	2.8%	RR 0.92 (0.74 to 1.13)	2 fewer per 1000 (from 7 fewer to 4 more)	VERY LOW	CRITICAL
Intracranial bleeding												
2	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	6/714 (0.84%)	1.8%	RR 0.41 (0.16 to 1.04)	11 fewer per 1000 (from 15 fewer to 1 more)	VERY LOW	CRITICAL
GI bleeding												
3	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	12/978 (1.2%)	2.3%	RR 0.52 (0.26 to 1.04)	11 fewer per 1000 (from 17 fewer to 1 more)	VERY LOW	CRITICAL

[1] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.

[2] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given.
[3]I2 was >75%. Sub-grouping using the 4 pre-specified strategies was attempted but none resolved heterogeneity, so random effects model was used.
[4]Downgraded for indirectness, resulting from the ACTIVE W trial using a non-warfarin VKA and combining aspirin with clopidogrel.

Table 37: Clinical evidence profile: Placebo versus warfarin for preventing stroke and thromboembolic events in people with AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	Warfarin	Relative (95% CI)	Absolute		
Health-related quality of life												
0	No evidence available	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	0	-	-	not pooled	-	CRITICAL
All stroke and systemic thromboembolism												
2	RCT	Serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[3]	Serious risk of imprecision[2]	none	31/402 (7.7%)	4%	RR 1.92 (1.07 to 3.45)	37 more per 1000 (from 3 more to 98 more)	VERY LOW	CRITICAL
All-cause mortality												
2	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	16/402 (4%)	4.1%	RR 0.99 (0.5 to 1.94)	0 fewer per 1000 (from 20 fewer to 39 more)	VERY LOW	CRITICAL
Myocardial infarction												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	2/211 (0.95%)	1%	RR 1 (0.14 to 7)	0 fewer per 1000 (from 9 fewer to 60 more)	VERY LOW	CRITICAL
Clinically relevant non-major bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled	-	CRITICAL
Minor bleeding												

1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	18/191 (9.4%)	16%	RR 0.59 (0.34 to 1.02)	66 fewer per 1000 (from 106 fewer to 3 more)	LOW	CRITICAL
major bleeding												
2	RCT	Serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[3]	Very serious risk of imprecision[2]	none	5/402 (1.2%)	2.3%	RR 0.55 (0.19 to 1.62)	10 fewer per 1000 (from 19 fewer to 14 more)	VERY LOW	CRITICAL
Intracranial bleeding												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0/191 (0%)	0.5%	RR 0.33 (0.01 to 7.96)	3 fewer per 1000 (from 5 fewer to 35 more)	VERY LOW	CRITICAL
GI bleeding												
0	No evidence available	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	-	0%	not pooled	not pooled	-	CRITICAL

[1] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.
[2] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious)
[3]For SSE, the CAFA trial only looked at stroke and not SE, and for major bleeding the SPAF trial used an outcome that was not strictly defined as major bleeding (but was very similar)

Table 38: Clinical evidence profile: Apixaban 2.5mg bid versus warfarin for preventing stroke and thromboembolic events in people with AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Apixaban 2.5mg bid**	**Warfarin**	**Relative (95% CI)**	**Absolute**		
Health-related quality of life												
0	No evidence available					none	0	-	-	not pooled		

All stroke and systemic thromboembolism												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	0/72 (0%)	5.4%	Peto OR 0.13 (0.02 to 0.97)	48 fewer per 1000 (from 53 fewer to 58 more)	VERY LOW	CRITICAL
All-cause mortality												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0/72 (0%)	0%	RD 0.00 (-0.03 to 0.03)	O fewer per 1000 (from 30 fewer to 30 more)	VERY LOW	CRITICAL
Myocardial infarction												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0/72 (0%)	0%	RD 0.00 (-0.03 to 0.03)	O fewer per 1000 (from 30 fewer to 30 more)	VERY LOW	CRITICAL
Clinically relevant non-major bleeding												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	1/72 (1.4%)	4%	RR 0.35 (0.04 to 3.26)	26 fewer per 1000 (from 38 fewer to 90 more)	VERY LOW	CRITICAL
Minor bleeding												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	8/72 (11.1%)	13.3%	RR 0.83 (0.35 to 1.99)	23 fewer per 1000 (from 86 fewer to 132 more)	VERY LOW	CRITICAL
major bleeding												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0/72 (0%)	1.3%	Peto OR 0.14 (0.00 to 7.10)	8 fewer per 1000 (from 13 fewer to 96 more)	VERY LOW	CRITICAL
Intracranial bleeding												
0	No evidence available					none	-	-	not pooled	not pooled		
GI bleeding												

0	No evidence available					none	-	-	not pooled	not pooled		

[1] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.
[2] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious

Table 39: Clinical evidence profile: Apixaban 5mg bid versus warfarin for preventing stroke and thromboembolic events in people with AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Apixaban 5mg bid**	**Warfarin**	**Relative (95% CI)**	**Absolute**		
Health related quality of life												
0	No evidence available	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	0	-	-	not pooled	-	CRITICAL
All stroke and systemic thromboembolism												
2	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	212/9191 (2.3%)	4.1%	RR 0.79 (0.66 to 0.94)	9 fewer per 1000 (from 2 fewer to 14 fewer)	LOW	CRITICAL
All-cause mortality												
2	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	603/9191 (6.6%)	7.3%	RD -0.01 (-0.01 to 0.00)	10 fewer per 1000 (from 10 fewer to 0 more)	VERY LOW	CRITICAL
Myocardial infarction												
2	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	90/9191 (0.98%)	1.1%	RD 0.00 (0.00 to 0.00)	0 fewer per 1000 (from 0 fewer to 0 more)	VERY LOW	CRITICAL
Clinically relevant non-major bleeding												

1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	1/71 (1.4%)	4%	RR 0.35 (0.04 to 3.31)	26 fewer per 1000 (from 38 fewer to 92 more)	VERY LOW	CRITICAL
Minor bleeding												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	17/71 (23.9%)	13.3%	RR 1.8 (0.88 to 3.65)	106 more per 1000 (from 16 fewer to 352 more)	VERY LOW	CRITICAL
major bleeding												
2	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	327/9159 (3.6%)	3.2%	RR 0.7 (0.61 to 0.81)	10 fewer per 1000 (from 6 fewer to 12 fewer)	LOW	CRITICAL
Intracranial bleeding												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	52/9088 (0.57%)	1.4%	RR 0.42 (0.31 to 0.59)	8 fewer per 1000 (from 6 fewer to 10 fewer)	MOD	CRITICAL
GI bleeding												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	105/9088 (1.2%)	1.3%	RR 0.88 (0.68 to 1.14)	2 fewer per 1000 (from 4 fewer to 2 more)	LOW	CRITICAL

[1] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.
[2] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious

Table 40: Clinical evidence profile: Dabigatran 110mg bid versus warfarin for preventing stroke and thromboembolic events in people with AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dabigatran 110mg bid**	**Warfarin**	**Relative (95% CI)**	**Absolute**		

Health related quality of life												
0	No evidence available					none	0	-	-	not pooled		
All stroke and systemic thromboembolism												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	183/6015 (3%)	3.4%	RR 0.91 (0.74 to 1.1)	3 fewer per 1000 (from 9 fewer to 3 more)	LOW	CRITICAL
All-cause mortality												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	446/6015 (7.4%)	8.1%	RR 0.92 (0.81 to 1.04)	6 fewer per 1000 (from 15 fewer to 3 more)	MOD	CRITICAL
Myocardial infarction												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	98/6015 (1.6%)	1.3%	RR 1.31 (0.97 to 1.76)	4 more per 1000 (from 0 fewer to 10 more)	LOW	CRITICAL
Clinically relevant non-major bleeding												
0	No evidence available	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	-	0%	not pooled	not pooled		
Minor bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
major bleeding												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	342/6015 (5.7%)	7%	RR 0.81 (0.71 to 0.93)	13 fewer per 1000 (from 5 fewer to 20 fewer)	LOW	CRITICAL
Intracranial bleeding												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision[2]	none	27/6015 (0.45%)	1.4%	RR 0.31 (0.2 to 0.48)	10 fewer per 1000 (from 7 fewer to 11 fewer)	MOD	CRITICAL

GI bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled	-	CRITICAL

[1] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.
[2] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given.

Table 41: Clinical evidence profile: Dabigatran 150mg bid versus warfarin for preventing stroke and thromboembolic events in people with AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dabigatran 150mg bid**	**Warfarin**	**Relative (95% CI)**	**Absolute**		
Health related quality of life												
0	No evidence available					none	0	-	-	not pooled		
All stroke and systemic thromboembolism												
2	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	134/6176 (2.2%)	3.3%	RD -0.01 (-0.02 to -0.01)	10 fewer per 1000 (from 20 fewer to 10 more)	MODERATE	CRITICAL
All-cause mortality												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	438/6076 (7.2%)	8.1%	RR 0.89 (0.79 to 1.01)	9 fewer per 1000 (from 17 fewer to 1 more)	LOW	CRITICAL
Myocardial infarction												

1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	97/6076 (1.6%)	1.3%	RR 1.28 (0.95 to 1.73)	4 more per 1000 (from 1 fewer to 9 more)	LOW	CRITICAL
Clinically relevant non-major bleeding												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	9/100 (9%)	5.7%	RR 1.57 (0.5 to 4.91)	33 more per 1000 (from 28 fewer to 223 more)	VERY LOW	CRITICAL
Minor bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
major bleeding												
2	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	399/6176 (6.5%)	6.9%	RD 0.00 (-0.01 to 0.00)	0 fewer per 1000 (from 10 fewer to 0 more)	VERY LOW	CRITICAL
Intracranial bleeding												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision[2]	none	36/6076 (0.59%)	1.4%	RR 0.41 (0.28 to 0.6)	8 fewer per 1000 (from 6 fewer to 10 fewer)	MOD	CRITICAL
GI bleeding												
0	No evidence available					none	-	-	not pooled	not pooled		

[1] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.
[2] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious

Table 42: Clinical evidence profile: Rivaroxaban 20mg qd versus warfarin for preventing stroke and thromboembolic events in people with AF

Quality assessment						No of patients		Effect		Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rivaroxaban 20mg qd**	**Warfarin**	**Relative (95% CI)**	**Absolute**		
Health related quality of life												
0	No evidence available					none	0	-	-	not pooled		
All stroke and systemic thromboembolism												
4	RCT	No serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	276/7328 (3.8%)	4.3%	RD -0.01 (-0.01 to 0.00)	5 fewer per 1000 (from 10 fewer to 0 more)	MOD	CRITICAL
All-cause mortality												
3	RCT	No serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	584/7288 (8%)	8.6%	RD -0.01 (-0.02 to 0.00)	10 fewer per 1000 (from 20 fewer to 0 more)	LOW	CRITICAL
Myocardial infarction												
1	RCT	No serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	101/7111 (1.4%)	1.8%	RR 0.8 (0.62 to 1.04)	4 fewer per 1000 (from 7 fewer to 1 more)	MOD	CRITICAL
Clinically relevant non-major bleeding												
2	RCT	No serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	1190/7141 (16.7%)	21.4%	RR 1.03 (0.96 to 1.11)	6 more per 1000 (from 9 fewer to 24 more)	HIGH	CRITICAL
Minor bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
major bleeding												

3	RCT	No serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	407/7328 (5.6%)	5.4%	RD 0.00 (-0.01 to 0.01)	2 more per 1000 (from 10 fewer to 10 more)	HIGH	CRITICAL
Intracranial bleeding												
3	RCT	No serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	56/7318 (0.77%)	1.7%	RR 0.63 (0.45 to 0.88)	6 fewer per 1000 (from 2 fewer to 9 fewer)	MOD	CRITICAL
GI bleeding												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	8/177 (4.5%)	0.6%	RR 7.95 (1.01 to 62.94)	42 more per 1000 (from 0 more to 372 more)	LOW	CRITICAL

[1] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.
[2] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given.

Table 43: Clinical evidence profile: Rivaroxaban 15mg qd versus warfarin for preventing stroke and thromboembolic events in people with AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rivaroxaban 15mg qd**	**Warfarin**	**Relative (95% CI)**	**Absolute**		
Health related quality of life												
0	No evidence available					none	0	-	-	not pooled		
All stroke and systemic thromboembolism												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	11/637 (1.7%)	3.5%	RR 0.5 (0.24 to 1.02)	18 fewer per 1000 (from 27 fewer to 1 more)	LOW	CRITICAL
All-cause mortality												

1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	7/637 (1.1%)	0.8%	RR 1.4 (0.45 to 4.39)	3 more per 1000 (from 4 fewer to 27 more)	VERY LOW	CRITICAL
Myocardial infarction												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	3/637 (0.47%)	0.2%	RR 3 (0.31 to 28.76)	4 more per 1000 (from 1 fewer to 56 more)	VERY LOW	CRITICAL
Clinically relevant non-major bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
Minor bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
major bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
Intracranial bleeding												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	5/639 (0.78%)	1.6%	RR 0.5 (0.17 to 1.45)	8 fewer per 1000 (from 13 fewer to 7 more)	VERY LOW	CRITICAL
GI bleeding												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	6/639 (0.94%)	1.9%	RR 0.5 (0.19 to 1.32)	9 fewer per 1000 (from 15 fewer to 6 more)	VERY LOW	CRITICAL

[1] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.
[2] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given.

Table 44: Clinical evidence profile: Edoxaban 30mg qd versus warfarin for preventing stroke and thromboembolic events in people with AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Edoxaban 30mg qd	Warfarin	Relative (95% CI)	Absolute		
Health related quality of life												
0	No evidence available					none	0	-	-	not pooled		
All stroke and systemic thromboembolism												
3	RCT	No serious risk of bias	Serious risk of inconsistency[3]	No serious risk of indirectness	Very serious risk of imprecision[2]	none	384/7399 (5.2%)	4.6%	RD 0.00 (-0.01 to 0.01)	0 fewer per 1000 (from 10 fewer to 10 more)	VERY LOW	CRITICAL
All-cause mortality												
4	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision[2]	none	739/7478 (9.9%)	1.7%	RR 0.88 (0.8 to 0.96)	2 fewer per 1000 (from 1 fewer to 3 fewer)	HIGH	CRITICAL
Myocardial infarction												
2	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	171/7269 (2.4%)	1%	RR 1.21 (0.97 to 1.51)	2 more per 1000 (from 0 fewer to 5 more)	MOD	CRITICAL
Clinically relevant non-major bleeding												
3	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	976/7316 (13.3%)	4%	RR 0.7 (0.65 to 0.75)	12 fewer per 1000 (from 10 fewer to 14 fewer)	HIGH	CRITICAL
Minor bleeding												

3	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	555/7316 (7.6%)	10.2%	RR 0.75 (0.67 to 0.83)	25 fewer per 1000 (from 17 fewer to 34 fewer)	LOW	CRITICAL
major bleeding												
4	RCT	Serious risk of bias[1]	Very serious risk of inconsistency[3]	No serious risk of indirectness	No serious risk of imprecision	none	254/7446 (3.4%)	7.1%	RD -0.02 (-0.05 to 0.01)	20 fewer per 1000 (from 50 fewer to 10 more)	VERY LOW	CRITICAL
Intracranial bleeding												
1	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	41/7002 (0.59%)	1.9%	RR 0.31 (0.22 to 0.44)	13 fewer per 1000 (from 11 fewer to 15 fewer)	HIGH	CRITICAL
GI bleeding												
2	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	129/7081 (1.8%)	2%	RR 0.68 (0.54 to 0.84)	6 fewer per 1000 (from 3 fewer to 9 fewer)	MOD	CRITICAL

[1] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.
[2] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious
[3]Inconsistency was rated as serious if I^2 was 50-74% and very serious if I^2 was 75% or higher.

Table 45: Clinical evidence profile: Edoxaban 60mg qd versus warfarin for preventing stroke and thromboembolic events in people with AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Edoxaban 60mg qd versus warfarin**	**Control**	**Relative (95% CI)**	**Absolute**		
Health related quality of life												

0	No evidence available					none	0	-	-	not pooled		
All stroke and systemic thromboembolism												
3	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[1]	none	297/7399 (4%)	4.6%	RD -0.01 (-0.01 to 0.00)	10 fewer per 1000 (from 10 fewer to 0 more)	LOW	CRITICAL
All-cause mortality												
4	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	774/7479 (10.3%)	1.7%	RR 0.92 (0.84 to 1.01)	1 fewer per 1000 (from 3 fewer to 0 more)	HIGH	CRITICAL
Myocardial infarction												
2	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[1]	none	135/7269 (1.9%)	1%	RR 0.96 (0.76 to 1.21)	0 fewer per 1000 (from 2 fewer to 2 more)	MOD	CRITICAL
Clinically relevant non-major bleeding												
3	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision[1]	none	1228/7326 (16.8%)	4%	RR 0.87 (0.82 to 0.94)	5 fewer per 1000 (from 2 fewer to 7 fewer)	HIGH	CRITICAL
Minor bleeding												
3	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[1]	none	627/7326 (8.6%)	10.2%	RR 0.84 (0.76 to 0.93)	16 fewer per 1000 (from 7 fewer to 24 fewer)	MOD	CRITICAL
major bleeding												
4	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[1]	none	421/7456 (5.6%)	1.5%	RR 0.8 (0.71 to 0.9)	3 fewer per 1000 (from 2 fewer to 4 fewer)	MOD	CRITICAL
Intracranial bleeding												
1	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	61/7012 (0.87%)	1.9%	RR 0.46 (0.34 to 0.62)	10 fewer per 1000 (from 7 fewer to 13 fewer)	HIGH	CRITICAL

GI bleeding												
2	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[1]	none	232/7092 (3.3%)	2%	RR 1.21 (1.01 to 1.47)	4 more per 1000 (from 0 more to 9 more)	MOD	CRITICAL
Health related quality of life (Better indicated by lower values)												

[1] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given.

Table 46: Clinical evidence profile: Apixaban 5mg bid versus aspirin for preventing stroke and thromboembolic events in people with AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Apixaban 5mg bid**	**Aspirin**	**Relative (95% CI)**	**Absolute**		
Health related quality of life												
0	No evidence available					none	0	-	-	not pooled		
All stroke and systemic thromboembolism												
1	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	51/2808 (1.8%)	4.1%	RR 0.45 (0.32 to 0.62)	23 fewer per 1000 (from 16 fewer to 28 fewer)	HIGH	CRITICAL
All-cause mortality												
1	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[1]	none	111/2808 (4%)	5%	RR 0.79 (0.62 to 1.01)	10 fewer per 1000 (from 19 fewer to 0 more)	MOD	CRITICAL
Myocardial infarction												

1	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[1]	none	24/2808 (0.85%)	1%	RR 0.85 (0.5 to 1.47)	1 fewer per 1000 (from 5 fewer to 5 more)	LOW	CRITICAL
Clinically relevant non-major bleeding												
1	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[1]	none	96/2808 (3.4%)	3%	RR 1.14 (0.85 to 1.52)	4 more per 1000 (from 4 fewer to 16 more)	MOD	CRITICAL
Minor bleeding												
1	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[1]	none	188/2808 (6.7%)	5.5%	RR 1.22 (0.99 to 1.5)	12 more per 1000 (from 1 fewer to 27 more)	MOD	CRITICAL
major bleeding												
1	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[1]	none	44/2808 (1.6%)	1.4%	RR 1.12 (0.73 to 1.72)	2 more per 1000 (from 4 fewer to 10 more)	LOW	CRITICAL
Intracranial bleeding												
1	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[1]	none	11/2808 (0.39%)	0.5%	RR 0.84 (0.38 to 1.87)	1 fewer per 1000 (from 3 fewer to 4 more)	LOW	CRITICAL
GI bleeding												
1	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[1]	none	12/2808 (0.43%)	0.5%	RR 0.85 (0.39 to 1.84)	1 fewer per 1000 (from 3 fewer to 4 more)	LOW	CRITICAL

[1] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given.

Table 47: Clinical evidence profile: Placebo versus warfarin INR 3-4 for preventing stroke and thromboembolic events in people with AF

Quality assessment							No of patients		Effect		Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	warfarin INR 3-4	Relative (95% CI)	Absolute		
Health related quality of life												
0	No evidence available					none	0	-	-	not pooled		
All stroke and systemic thromboembolism												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	21/336 (6.3%)	1.5%	RR 4.19 (1.6 to 10.97)	48 more per 1000 (from 9 more to 150 more)	LOW	CRITICAL
All-cause mortality												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[3]	No serious risk of imprecision	none	19/336 (5.7%)	1.2%	RR 4.74 (1.63 to 13.77)	45 more per 1000 (from 8 more to 153 more)	VERY LOW	CRITICAL
Myocardial infarction												
0	No evidence available					none	-	0%	not pooled	not pooled		
Clinically relevant non-major bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
Minor bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
major bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
Intracranial bleeding												

0	No evidence available					none	-	0%	not pooled	not pooled		
GI bleeding												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	0/336 (0%)	1.2%	Peto OR 0.13 (0.02 to 0.95)	11 fewer per 1000 (from 12 fewer to 13 more)	VERY LOW	CRITICAL

[1] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.
[2] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious)
[3]Mortality, but not all-cause mortality

Table 48: Clinical evidence profile: Antiplatelets versus warfarin INR 3-4 for preventing stroke and thromboembolic events in people with AF

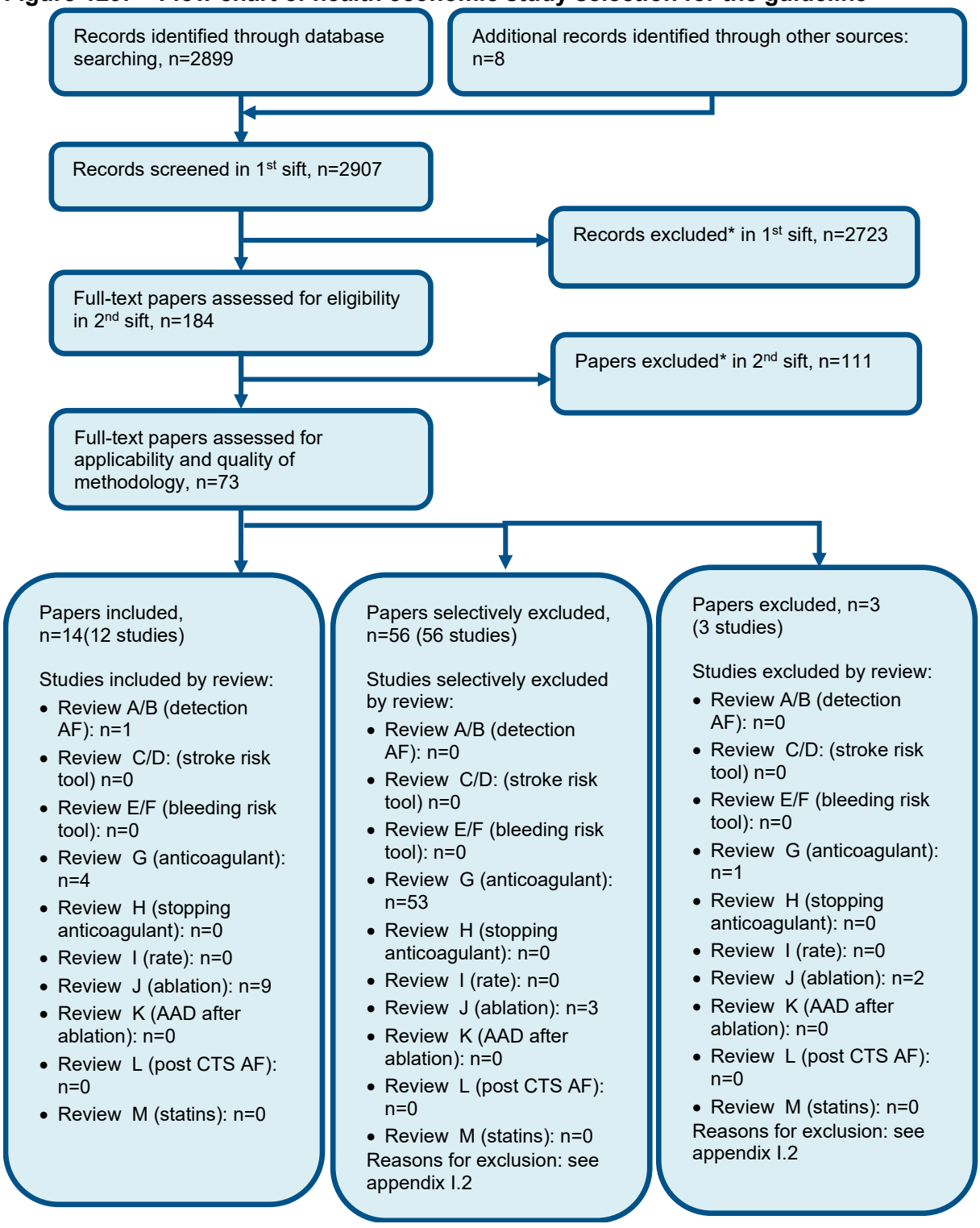
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aspirin**	**Warfarin INR 3-4l**	**Relative (95% CI)**	**Absolute**		
Health related quality of life												
0	No evidence available					none	0	-	-	not pooled		
All stroke and systemic thromboembolism												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	20/336 (6%)	1.5%	RR 3.99 (1.51 to 10.5)	45 more per 1000 (from 8 more to 142 more)	LOW	CRITICAL
All-cause mortality												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[3]	No serious risk of imprecision	none	15/336 (4.5%)	1.2%	RR 3.74 (1.25 to 11.15)	33 more per 1000 (from 3 more to 122 more)	VERY LOW	CRITICAL

Myocardial infarction												
0	No evidence available					none	-	0%	not pooled	not pooled		
Clinically relevant non-major bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
Minor bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
major bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
Intracranial bleeding												
0	No evidence available					none	-	0%	not pooled	not pooled		
GI bleeding												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	1/336 (0.3%)	1.2%	RR 0.25 (0.03 to 2.22)	9 fewer per 1000 (from 12 fewer to 15 more)	VERY LOW	CRITICAL

[1] If the majority of evidence was characterised by risk of bias due to poor reporting of allocation concealment then a rating of serious risk of bias was given. If the majority of evidence was characterised by poor reporting of allocation concealment and lack of patient/HCP blinding and/or risk of attrition bias then a rating of very serious bias was given.
[2] If the confidence intervals crossed ONE of the default MIDs (OR of 0.8 or OR of 1.25) then a rating of serious imprecision was given. If the confidence intervals crossed BOTH of the default MIDs then a rating of very serious imprecision was given. Where there were no data in either arm of a study, imprecision based on optimum information size (power<0.8=very serious; 0.8-0.9=serious)
[3]Mortality, but not all-cause mortality

Appendix F:Health economic evidence selection

Figure 129: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G: Health economic evidence tables

Study	Sterne 2017[160]/Lopez-Lopez 2017[113, 114]/Thom 2019[163]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model. Health states (17 in total) include: clinically relevant (extracranial) bleed, ICH, ischaemic stroke, MI, TIA, SE, discontinue or switch because of these events, death. Relative treatment effects for all events applied for each comparator. Memory states included to record a history of most important events (ischaemic stroke, ICH, other CRB and MI have long term consequences that are modelled).3 month	**Population:** Patients with non-valvular atrial fibrillation eligible for anticoagulation **Cohort settings:** Start age: 70 years Male: 60% **Intervention 1:** Warfarin, target INR 2-3, ongoing or until treatment switch/discontinuation **Intervention 2:** Apixaban, 5mg bd, ongoing or until treatment switch/discontinuation **Intervention 3:** Dabigatran, 150mg bd, ongoing or until treatment	**Total costs (mean per patient):** Intervention 1: £24,418 Intervention 2: £23,340 Intervention 3: £23,064 Intervention 4: £23,985 Intervention 5: £24,841 *For incremental analysis see cost effectiveness column* **Currency & cost year:** 2013-2014 UK pounds **Cost components incorporated:** Drug costs (including monitoring costs for warfarin), acute event costs (ischaemic stroke, ICH, SE (non-fatal),	**QALYs (mean per patient):** Intervention 1: 5.166 Intervention 2: 5.488 Intervention 3: 5.416 Intervention 4: 5.405 Intervention 5: 5.451 *For incremental analysis see cost effectiveness column*	**Full incremental analysis (pa):[(b)(c)]** Int | Cost | QALY | Inc cost | Inc QALY | ICER | % most CE at £20K[(d)]: 1 | £24,418 | 5.166 | Dominated by 3 | | | 0% 4 | £23,985 | 5.405 | Dominated by 3 | | | 5% 3 | £23,064 | 5.416 | Baseline | | | 25% 5 | £24,841 | 5.451 | Dominated by 2 | | | 10% 2 | £23,340 | 5.488 | £276 | 0.072 | £3,833 | 60% **Results presented as incremental net monetary benefit compared to warfarin at threshold of £20,000/QALY: (95%CI)** Intervention 1: baseline Intervention 2: £7,533 (£490 to £18,228) Intervention 3: £6,365 (-£168 to £17,039) Intervention 4: £5,212 (-£894 to £14,826) Intervention 5: £5,279 (-£1,097 to 15,180) Conclusions hold at threshold £30,000/QALY. **Analysis of uncertainty:**

cycle duration. Treatment switching may occur as a result if failure indicated by ischaemic stroke or serious AEs such as ICH. Assumed switch following MI for dabigatran patients only. Warfarin switch to no treatment and DOACs switch to warfarin or no treatment (depending on event) – see figure below for full switching algorithm. **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration:**[(a)] n/a **Discounting:** Costs: 3.5%; Outcomes: 3.5%	switch/discontinuation **Intervention 4:** Edoxaban, 60mg od, ongoing or until treatment switch/discontinuation **Intervention 5:** Rivaroxaban, 20mg od, ongoing or until treatment switch/discontinuation	TIA, clinically relevant bleed and MI), and chronic care costs (post ischaemic stroke [same assumed for ICH]: weighted average of non-disabling, moderately disabling, totally disabling). Unit cost of edoxaban not available at the time of publication and so assumed to be equal to dabigatran. Cost of reversal agents not explicitly mentioned but are likely to be included in the NHS reference costs (note the reversal agents for DOACs were not available when this model was conducted)		A number of scenario analyses were undertaken, the following scenarios did not change conclusions found in the base case (intervention 2 remains most cost effective): • No warfarin drug and monitoring costs • No effect of previous bleed/ICH on future risk of death • Switch to no treatment after ICH or MI (if on dabigatran) • All switch after ischaemic stroke or clinically relevant bleed, none after TIA or SE • Excluding 'no treatment control' studies from MA of warfarin vs. placebo trials • Change initial age of cohort (60 and 80 yrs respectively) • No difference in hazard of ICH between 'no treatment' and warfarin Two scenarios resulted in a change in results: • All switch after ischaemic stroke, bleed, SE and TIA as well as switch to no treatment after ICH or MI (if on dabigatran): intervention 1 most cost effective • Different doses for apixaban and dabigatran (2.5mg bd and 110mg bd, respectively): apixaban 2.5mg bd most likely to be cost effective but probability it is most cost effective at £20K is ~50% Key drivers of results noted by authors: • Lower rates of MI, ICH and other CRB for apixaban. • High cost and disutility of ICH has great influence on total costs, total QALYs and net benefits.
Data sources				
Health outcomes: Relative treatment effects applied to warfarin event rates (baseline). Hazards of events for warfarin taken from a model conducted using the warfarin arms of the studies identified in the systematic review undertaken in Sterne 2017. Relative efficacy of warfarin to no treatment (relevant for treatment switches) taken from most recently published meta-analysis of warfarin vs placebo/no treatment (Hart 2007). Effect of past health events and states on future event rates taken from other published sources such as a Swedish cohort study and Danish registry (Friberg 2012, Andreson 2007). Mortality using England and Wales life tables. Relative treatment effects taken from NMA conducted in Sterne 2017. This was a competing risk NMA				

model which jointly estimated log-HRs for the different events. This NMA included 18 of the 24 trials identified in our clinical review. They also included 5 we didn't include as they did not meet our protocol. Treatment switch rules and probabilities based on expert opinion. **Quality-of-life weights:** Taken from NICE TA submission for rivaroxaban which had conducted a systematic review of literature for EQ-5D data in health states related to AF. Unclear if selected EQ-5D values use UK tariff. Utility decrements applied for acute events (3 months) to stable AF value. Where there is no recovery from acute event utility values for chronic health states are used thereafter. Utility decrements adjusted for age to account for quality of life decreasing with age. Weighted averages used to account for gender. **Cost sources:** NHS reference costs, BNF, UK stroke registry.

Some model assumptions of note: no distinction between severity of ischaemic stroke; non-clinically relevant minor bleed events not included; SE assumed to be transient without long-term consequences; dose of apixiban and dabigatran do not reduce with age; no distinction between bleed locations (other than ICH)

Comments

Source of funding: NIHR **Limitations:** EQ-5D data identified via systematic review of literature, unclear however if all are from UK representative population. No stratification by stroke or bleeding risk. Seven studies identified in our systematic review of the evidence are not included in the NMA used in this model and so this may not reflect the full body of evidence. The cost of edoxaban is assumed to be the same as dabigatran. Reversal agents for DOACs not included in costs/effects of treating bleeds (not available at time of publication). **Other:**

Overall applicability:(e) Directly applicable **Overall quality:**(f) Minor limitations

Abbreviations: AEs= adverse events; bd= twice daily; 95% CI= 95% confidence interval; CRB = clinically relevant bleed; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; ICH= intracranial haemorrhage; IS= ischaemic stroke; MI= myocardial infarction; DOACs= novel anticoagulants; NR= not reported; n/a = not applicable; od= once daily; pa= probabilistic analysis; QALYs= quality-adjusted life years; SE= systemic embolism; TIA = transient ischaemic attack

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Intervention number in order of least to most effective (in terms of QALYs)

(c) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option

(d) Probability cost effective at threshold of £20,000 per QALY estimated from graph.

(e) Directly applicable / Partially applicable / Not applicable

(f) Minor limitations / Potentially serious limitations / Very serious limitations

Switching algorithm Sterne 2017:

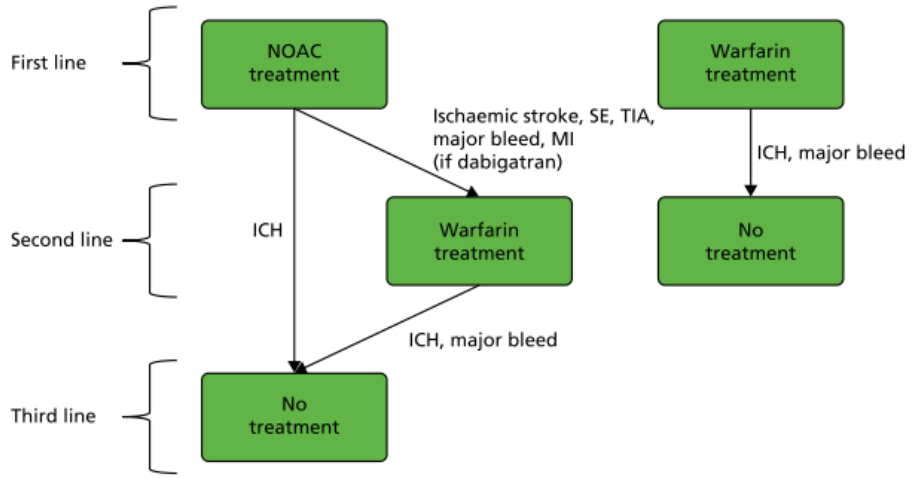


FIGURE 1 Treatment strategies and switching/discontinuation rules. The events that may lead to treatment switching are indicated next to the arrows between treatments.

Study	**NICE 2015[127]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov	**Population:** Patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥75years, diabetes mellitus, prior	**Total costs (mean per patient):** Intervention 1: £12,868 Intervention 2: £15,531 Intervention 3: £15,732	**QALYs (mean per patient):** Intervention 1:6.56 Intervention 2: 6.77 Intervention 3: 6.66	**Full incremental analysis (pa):[(b)(c)]** Int | Cost | QALY | Inc cost | Inc QALY | ICER | % most CE at £20K[(d)]: 1 | £12,868 | 6.56 | Baseline | | | 36.8% 6 | £16,313 | 6.65 | Dominated by 4 | | | ~1% 3 | £15,732 | 6.66 | Dominated by 4 | | | ~10% 5 | £15,471 | 6.72 | Dominated by 4 | | | 2.9%

model. Main states were: stable AF, HS, IS, SE, MI and dead. Stroke events (HS and IS) are divided into mild, moderate and severe categories. Health states (IS, HS, SE and MI) are further divided into acute events and long-term impacts. Following the acute stage of a thrombotic event, patients remain in the 'post-event' health state until they experience another event. The model reflects that patients are able to experience recurrent events. Other transitional clinical outcomes that are considered to have no long-term impact are also included in the model: ICH, non-ICH major bleeds, clinically relevant non-major bleeds, and TIA. Patients can experience one of these temporary events whilst in each (initial and post-event) health state of the

stroke or TIA. CHADS2>2

Cohort settings:

Start age: 71 years

Male: 62%

Intervention 1:

Warfarin, average daily dose 4.5mg od, ongoing or until treatment switch/discontinuation

Intervention 2:

Apixaban, 5mg bd, ongoing or until treatment switch/discontinuation

Intervention 3:

Dabigatran, 110mg bd, ongoing or until treatment switch/discontinuation

Intervention 4:

Dabigatran, 150mg bd until 80 years old, then reduced to 110mg bd, ongoing or until treatment switch/discontinuation

Intervention 5:

Intervention 4: £15,293

Intervention 5: £15,451

Intervention 6: £16,313

For incremental analysis see cost effectiveness column

Currency & cost year:

2013-2014 UK pounds

Cost components incorporated:

Drug costs (including monitoring costs for warfarin), acute event costs (IS and HS by severity, SE, MI, other ICH, TIA, non-ICH major bleed, clinically relevant non-major bleed, and death), and chronic care costs (post IS and HS by severity, SE, MI). Cost of reversal agents not explicitly costed (note the reversal agents for DOACs were not available when this model was conducted).

Intervention 4: 6.75

Intervention 5: 6.72

Intervention 6: 6.65

For incremental analysis see cost effectiveness column

4	£15,293	6.75	£2,425	0.185	Extendedly dominated by 2	~25%
2	£15,531	6.77	£2,662	0.204	£13,036	~25%

Analysis of uncertainty:

Deterministic and probabilistic sensitivity analyses conducted.

Base case presented deterministically by manufacturer: all interventions are dominated by intervention 4, ICER of intervention 4 vs. 1 £7,645 per QALY. ERG presented probabilistic full incremental analysis (reported here).

Deterministic and probabilistic results differ. The ERG considers that this is due to the very small differences in QALYs between dabigatran 150mg and apixaban in all analyses. In addition the results of the probabilistic analysis are not completely stable (repeated runs of the same analyses give slightly different results).

Analyses conducted by manufacturer:

- 14 pair-wise deterministic sensitivity analyses (intervention 5 vs. 1 and 5 vs. 4) each varying on of the following: starting age, risk adjustment factor per decade, other-cause mortality adjustment factor, acute mortality risk for all events, post-outcome mortality HR for all events, intervention cost per month for each drug, monitoring cost per month for each drug, acute cost of each event, post-outcome monthly cost of each event, cost of death, stable AF utility, acute disutility and post-outcome utility for each event and other cause discontinuation rates. Analyses sensitive to start age, cost of treatment and addition of monitoring cost for those receiving edoxaban.

model. Treatment discontinuation /switching (permanently or temporarily). Occurs only after ischaemic or haemorrhagic stroke. Following switch or discontinuation, transition probabilities for events do not change. **Perspective:** UK NHS **Time horizon:** 30 years (remaining lifetime) **Treatment effect duration:**[(a)] n/a **Discounting:** Costs: 3.5%; Outcomes: 3.5%	Edoxaban, 60md od, ongoing or until treatment switch/discontinuation **Intervention 6:** Rivaroxaban, 20mg od, ongoing or until treatment switch/discontinuation			• 4 scenario analyses: varying HR for TIA and clinically relevant non-major bleeding. Little impact on deterministic. • Subgroup analyses: ○ Higher risk of stroke (CHADS2≥3): Intervention 2 most cost effective (ICER £3,730 per QALY vs intervention 1). ○ cTTR on warfarin≥60%: Intervention 4 most cost effective (ICER £11,696 vs intervention 1) Sensitivity analyses conducted by ERG: The ERG made a number of adjustments to correct for methodological errors and to use alternative data sources. Most resulted in no change in the probabilistic results (intervention 2 remained the most cost effective). Some adjustments resulted in intervention 4 being most cost effective. These included adjustments such as: • Alternative method for switch in dabigatran 150mg to 110mg at 80 years • Change in age and gender distribution over time • Apply ENGAGE trial hazard rates for HS
Data sources				
Health outcomes: Warfarin event rates taken from ENGAGE trial in base case and from NMA in a sensitivity analysis, UK registry data used for recurrent stroke estimates, mortality for events taken from various published literature sources (including Italian registry, England and Wales life tables) and assumptions. Relative treatment effects taken from NMA conducted as part of this technology appraisal. This NMA included 4 (ENGAGE-AF, ARISTOTLE, RE-LY, ROCKET-AF) of the 24 trials identified in our clinical review. Only patients with CHADS score of 2 or more included in NMA. ERG noted serious concern regarding the NMA (violation of the proportional hazards assumption both within trials and across trials) and believes that these violations mean that the mathematics used to generate the output HRs has been fundamentally compromised and, therefore, reliable HR estimates have not been generated. Treatment switch/discontinuation based on clinical opinion. **Quality-of-life weights:** A systematic review of literature for EQ-5D data in health states related to AF. Utility values for stroke are based on hypothetical descriptions of health states. Other utility values are based on measurements using EQ-5D reported directly by patients. Although UK tariff applied some data based on non-UK patient populations and so may not be generalisable. ERG noted the source of data used to adjust utilities to reflect a reduction of HRQoL with increasing age are based on data from a US population and significantly underestimate this impact when compared with data from a UK population. **Cost sources:** Drug doses based on licenced doses and costs from BNF, including warfarin. Warfarin monitoring resource use based on those from rivaroxaban TA and unit cost from apixaban TA. All costs for IS, HS, and SE were based on UK costing study (Oxford Vascular Study). Other unit costs from NHS reference costs.				

Comments
Source of funding: Manufacturer of edoxaban (Daiichi Sankyo). Model adjustments made by NICE technology appraisal ERG. **Limitations:** EQ-5D data identified via systematic review of literature; however the source of data used to adjust utilities to reflect a reduction of HRQoL with increasing age are based on data from a US population to which a UK utility weight was applied, the ERG noted UK data would be more appropriate. ERG also identified an error in the application of the utility decrement which led to double counting. An addendum was submitted by the ERG and upon correction of the error and use of UK utility data source no significant change in the results was reported. The incremental analysis is based upon the company's NMA. Analysis by the ERG has shown that assumptions of proportional hazards required for this NMA do not hold. The results of the incremental analysis are therefore highly uncertain. Subgroup analyses were conducted to stratify by stroke risks, however as there was limited data available to inform these analyses, much of the data on relative effectiveness is the same as that used in the base case analysis. Therefore this assumes no differences in relative treatment effects between subgroups. Twenty studies identified in our systematic review of the evidence are not included in the NMA used in this model and so this may not reflect the full body of evidence. Reversal agents for DOACs not included in costs/effects of treating bleeds (not available at time of publication). Potential financial conflict of interest funded by manufacturers of edoxiban. **Other:**
Overall applicability:[e] Directly applicable **Overall quality:**[f] Potentially serious limitations

Abbreviations: bd = twice daily; cTTR= centre time in therapeutic range; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ERG= Evidence review group; HR= hazard ratio; HS= haemorrhagic stroke; ICER= incremental cost-effectiveness ratio; ICH= intracranial haemorrhage; IS= ischaemic stroke; MI= myocardial infarction; NMA= network meta-analysis; NR= not reported; od = once daily; pa= probabilistic analysis; QALYs= quality-adjusted life years; SE= systemic embolism; TA= technology appraisal; TIA = transient ischaemic attack.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Intervention number in order of least to most effective (in terms of QALYs)

(c) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option

(d) Probability cost effective at threshold of £20,000 per QALY estimated from graph (with exception of edoxaban and warfarin).

(e) Directly applicable / Partially applicable / Not applicable

(f) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix H: Health economic analysis

See ‘G2. Health economic Analysis Anticoagulation’ document

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 49: Studies excluded from the clinical review

Study	Exclusion reason
Al-Khatib 2013[4]	Secondary analysis from Aristotle trial looking at effects of type and duration of AF
Alexander 2014[5]	secondary analysis of concomitant aspirin vs no aspirin from ARISTOTLE study
Amini 2013[6]	Patients undergoing ablation; no protocol outcomes
Anonymous 1993[11]	Incorrect interventions
Anonymous 2012[10]	Review of a paper
Anonymous 2012[9]	No relevant outcome data reported
Bahit 2013[17]	sub-group analysis (CAD/no CAD) of ARISTOTLE trial
Barylski 2015[20]	Not in English
Beyth 2000[21]	warfarin management programme versus no program; all on warfarin
Boehringer Ingelheim 2014[23]	clinical trial webpage
Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990[24]	Incorrect interventions. INR 1.5 to 2.7
Brendel 2017[26]	Heparin; patients undergoing RFA; non-randomised
Calkins 2017[27]	patients undergoing ablation
Cappato 2014[28]	patients undergoing cardioversion
Christersson[32]	sub-analysis of ARISTOTLE trial - coagulation markers
Coleman, 2020[34]	propensity matched cohort study (non-randomised)
Collet 2018[35]	patients undergoing trans-aortic valve implantation for aortic stenosis
Connolly 2013[36]	Used Betrixoban
Desai[46]	Trial registration
Di pasquale 2014[47]	Non English

Diener 2012[48]	sub-group analysis of AVERROES trial (stroke vs no stroke)
Dinh 2011[50]	Baseline data only
Dinh 2014[49]	INR not stated; special population with Transoesophageal echo evidence of no aortic plaques
Easton 2012[52]	secondary sub-group analysis of ARISTOTLE trial (stroke/TIA or not)
Eikelboom 2010[54]	protocol for AVERROES trial
Eikelboom 2013[53]	patients with mechanical heart valves
Esprit study group 2007[57]	Not guideline condition
Ezekowitz 1992[58]	INR 1.4 to 2.8
Ezekowitz 2010[61]	comparing treatment effects in VKA naive and VKA experienced groups
Ezekowitz 2018[59]	patients undergoing cardioversion
Flaker 2013[63]	conference abstract
Fox 2011-1[64]	sub-group analysis of data already included
Garcia 2013[65]	Secondary subgroup analysis from Aristotle trial (warfarin naive or not)
Gibson 2015[66]	patients undergoing percutaneous coronary intervention
Granger 2015[70]	patients transitioning to warfarin from DOACs
Hankey 2012[73]	secondary subgroup analysis of ROCKET trial (stroke/TIA or not)
Hohnloser 2011[75]	conference abstract
Hohnloser 2012[78]	Secondary sub-group analysis from ARISTOTLE trial (renal function)
Hohnloser[76]	anticoagulation during ablation
Hohnloser[77]	anticoagulation during ablation
Hong 2017[79]	<3 months treatment period
Hori 2011[80]	sub-group analysis of RE-LY trial in Japanese subset
Hu 2006[83]	Non English
Hylek 2014[84]	ARISTOTLE trial secondary analysis

Jansson, 2019[85]	Non randomised
Kirchhof 2018[93]	undergoing ablation procedure
Koefoed 1997[95]	Secondary analysis of AFASAK study
Lavitola pde 2010[104]	patients with mitral valvulopathy
Lee 2017[106]	non-randomised
Lee 2018[105]	No protocol outcomes - study evaluating effects on atherosclerotic plaques
Lidell 2003[107]	Mixed treatments: warfarin + placebo vs warfarin + clopidogrel
Liu 2014[111]	INR 1.6-2.5
Lopes 2010[112]	protocol
Mahaffey 2013[115]	secondary sub-group analysis of ROCKET trial (VKA naive or not)
Mant 2008[117]	same data as Mant 2007
Mavaddat 2014[119]	Only cognitive outcomes assessed
McMurray 2013[120]	SEcondary analysis of ARISTOTLE trial
Nagao 2017[123]	No protocol outcomes - only physiological markers
Nin 2013[134]	periablation anticoagulation
Okcun 2009[138]	patients with cardioversion
Posada 1999[146]	aspirin v control
Rocket AF Study Investigators 2010[148]	Protocol
Rose, 2019[151]	Protocol
Ruff 2010[152]	protocol
Ruff 2014[153]	transition to open label study
Sairaku 2013[154]	patients undergoing ablation surgery
Sato 2006[155]	Aspirin v control
Shevelev 2015[156]	Non-English

Stroke Prevention in Atrial Fibrillation Study Group 1990[162]	No separation of results between warfarin and aspirin (same arm)
Van Latum 1994[165]	Non English
van Miert[166]	DOAC 'mostly apixaban' but no sub-grouping for different DOACs; letter
Verma 2018[167]	Patients after catheter ablation
Win[174]	no protocol outcomes
Yasuda[178]	rivaroxaban versus rivaroxaban plus antiplatelet (combination therapy)
Yoshimoto, 2020[179]	post-ablation
Zhu 2017[181]	After RF ablation

I.2 Excluded health economic studies

Studies that meet the review protocol population and interventions, and the economic study inclusion criteria but have not been included in the review based on applicability and/or methodological quality are summarised below with reasons for exclusion.

Table 50: Studies excluded from the health economic review

Reference	Reason for exclusion
Ademi 2017[2]	This study was partially applicable (Australian healthcare setting, a sub population of non-valvular AF, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, model structure may not adequately reflect nature of topic - MI not modelled, cycle length too long and time horizon may be too short, relative treatment effects based on single RCT, and may not reflect full body of evidence available, costs are from an Australian perspective). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Ademi 2015[3]	This study was partially applicable (Australian healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT, and may not reflect full body of evidence available, costs are from an Australian perspective, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Andrikopoulos 2013[7]	This study was partially applicable (Greek healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative

Reference	Reason for exclusion
	treatment effects not based on systematic reviews of the literature, and may not reflect full body of evidence available, costs are from a Greek perspective, potential financial conflict of interest: funded by manufacturer of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Athanasakis 2017[15]	This study was partially applicable (Greek healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on two RCT, and may not reflect full body of evidence available, costs are from a Greek perspective, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Athanasakis 2015[16]	This study was partially applicable (Greek healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on three RCTs, and may not reflect full body of evidence available, costs are from a Greek perspective, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Baron Esquivias 2015[19]	This study was partially applicable (Spanish healthcare setting and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT, and may not reflect full body of evidence available, costs are from a Spanish perspective, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Bowrin 2020[25]	This study was partially applicable (French healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (use of 'real-world' data for baseline and relative treatment effects, this wasnon-comparative evidence excluded from clinical review, costs are from a French perspective, potential financial conflict of interest: funded by manufacturer of rivoraxaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Chevalier 2014[31]	This study was partially applicable (French healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, and may not reflect full body of evidence available, costs are from a French perspective, potential financial conflict of interest: funded by manufacturer of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne

Reference	Reason for exclusion
	2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Coyle 2013[42]	This study was partially applicable (Canadian healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline effects based on a single study rather than systematic review of literature, Canadian costs which may not reflect costs to the NHS, assumptions made regarding costs of apixaban being equal to cost of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Davidson 2013[43]	This study was partially applicable (Swedish healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT, and may not reflect full body of evidence available, costs are from a Swedish perspective, potential financial conflict of interest: funded by manufacturer of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
De Jong[45]	This study was partially applicable (Dutch healthcare setting, incorrect discounting used and although it included all comparators, results were only available for pairwise comparisons to apixaban, rather than a full incremental analysis) and judged to have potentially serious limitations (baseline effects not based on systematic reviews of the literature, relative treatment effects based published NMA which was not as comprehensive as the one included in our clinical review, and may not reflect full body of evidence available, costs are from a Dutch perspective, potential financial conflict of interest: funded by manufacturers of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
De Jong[44]	This study was partially applicable (Dutch healthcare setting and did not include all comparators) and judged to have potentially serious limitations (baseline effects and relative treatment effects not based on systematic review of literature and used observational data, time horizon 1 year, costs are from a Dutch perspective, potential financial conflict of interest: funded by manufacturers of rivaroxaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Dorian 2014[51]	This study was partially applicable (did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on two RCTs, and may not reflect full body of evidence available, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.

Reference	Reason for exclusion
Faria 2013[62]	This summary of the dabigatran NICE technology appraisal was partially applicable (did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects based on single RCT and so may not reflect full body of evidence, cost of INR monitoring considered to be overestimated by Evidence Review Group, potential conflict of interest: funded by manufacturers of dabigatran). However, developers felt this study was superseded by a more recent NICE technology appraisal (TA 355, NICE 2015)[127] which included all the relevant comparators, and therefore was selectively excluded.
Gonzalez-Juanatey 2012[68]	This study was partially applicable (Spanish healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effect not based on systematic reviews of the literature and may not reflect full body of evidence available, costs are from a Spanish perspective, potential financial conflict of interest: funded by manufacturer of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Hallinen 2016[72]	This study was partially applicable (Finnish healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT, and may not reflect full body of evidence available, costs are from a Finnish perspective, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Hori 2019[82]	This study was partially applicable (Japanese healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (costs are from a Japanese perspective, potential financial conflict of interest: funded by manufacturer of rivaroxaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Janzic 2015[86]	This study was partially applicable (Slovenian healthcare setting and incorrect discounting used) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, treatment switching not modelled, costs are from a Slovenian perspective, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Jowett 2011[87]	This study was partially applicable (did not include all comparators) and judged to have potentially serious limitations (within trial analysis based on single RCT, and may not reflect full body of evidence available, short time horizon and drug costs not included). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.

Reference	Reason for exclusion
Kamae 2015[88]	This study was partially applicable (Japanese healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT, and may not reflect full body of evidence available, costs are from a Japanese perspective, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Kansal 2012[89]	This study was partially applicable (Canadian healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effect not based on systematic reviews of the literature and may not reflect full body of evidence available, costs are from a Canadian perspective, potential financial conflict of interest: funded by manufacturer of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Kansal 2012[90]	This study was partially applicable (did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effect not based on systematic reviews of the literature and may not reflect full body of evidence available, unit costs inflated, potential financial conflict of interest: funded by manufacturer of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Kleintjens 2013[94]	This study was partially applicable (Belgian healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT and may not reflect full body of evidence available, costs are from a Belgian perspective, potential financial conflict of interest: funded by manufacturer of rivaroxaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Kongnakorn 2015[96]	This study was partially applicable (Belgian healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline effect not based on systematic reviews of the literature, costs are from a Belgian perspective, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Kongnakorn 2014[97]	This study was partially applicable (Belgian healthcare setting, a sub population of non-valvular AF, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT, and may not reflect full body of evidence available, costs are from an Belgian perspective, potential financial conflict of interest: funded by manufacturer of apixaban).

Reference	Reason for exclusion
	However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Kourlaba 2014[98]	This study was partially applicable (Greek healthcare setting and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT and may not reflect full body of evidence available, costs are from a Greek perspective, potential financial conflict of interest: funded by manufacturer of rivaroxaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Krejczy 2014[99]	This study was partially applicable (German healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, discontinuation or switching not modelled, full incremental analysis not presented, costs are from a German perspective). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Krejczy 2015[100]	This study was partially applicable (German healthcare setting and incorrect discounting used) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on 4 RCTs, and may not reflect full body of evidence available, costs are from a German perspective). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Langkilde 2012[101]	This study was partially applicable (Danish healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effect not based on systematic reviews of the literature and may not reflect full body of evidence available, costs are from a Danish perspective, potential financial conflict of interest: funded by manufacturer of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Lanitis 2014[103]	Excluded as not applicable. Swedish societal perspective, which is a broader perspective than that stated in the NICE reference case and therefore deemed not applicable.
Lanitis 2014[102]	This study was partially applicable (French healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effect not based on systematic reviews of the literature, relative treatment effects based on two RCTs and may not reflect full body of evidence available, costs are from a French perspective, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.

Reference	Reason for exclusion
Lip 2014[108]	This study was partially applicable (did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on three RCTs, and may not reflect full body of evidence available, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Lip 2015[109]	This study was partially applicable (did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on two RCTs, and may not reflect full body of evidence available, assumptions made regarding cost of edoxaban being equal to apixaban, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Lip 2015[110]	This study was partially applicable (a sub population of non-valvular AF and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT, and may not reflect full body of evidence available, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Mensch 2015[121]	This study was partially applicable (German healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT, and may not reflect full body of evidence available, costs are from a German perspective). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Morais 2014[122]	This study was partially applicable (Portuguese healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT and may not reflect full body of evidence available, costs are from a Portuguese perspective). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
NICE 2012[131]	This NICE technology appraisal (TA256 – rivaroxaban) was partially applicable (did not include all comparators) and judged to have potentially serious limitations (baseline effects based on single study, relative treatment effects based on NMA which was heterogeneous, double counting of re-initiation costs of warfarin monitoring, analysis primarily focused on comparison of rivaroxaban to warfarin, comparison to other anticoagulants in

Reference	Reason for exclusion
	sensitivity analyses only, potential financial conflict of interest: funded by manufacturer of rivaroxaban). However, developers felt this study was superseded by a more recent NICE technology appraisal (TA 355, NICE 2015)[127] which included all the relevant comparators, and therefore was selectively excluded.
NICE 2013[129]	This NICE technology appraisal (TA275 – apixaban) was partially applicable (did not include all comparators) and judged to have potentially serious limitations (relative treatment effects based on NMA including only 3 RCT,and so may not reflect full body of evidence available, potential heterogeneity in model, TIA not included in model, potential financial conflict of interest: funded by manufacturer of apixaban).However, developers felt this study was superseded by a more recent NICE technology appraisal (TA 355, NICE 2015)[127] which included all the relevant comparators, and therefore was selectively excluded.
NICE 2012[130]	This NICE technology appraisal (TA249 – dabigatran) was partially applicable (did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects based on single RCT and so may not reflect full body of evidence, cost of INR monitoring considered to be overestimated by Evidence Review Group, potential conflict of interest: funded by manufacturers of dabigatran). However, developers felt this study was superseded by a more recent NICE technology appraisal (TA 355, NICE 2015)[127] which included all the relevant comparators, and therefore was selectively excluded.
Nshimyumukiza 2013[135]	This study was partially applicable (Canadian healthcare setting, incorrect discounting used, did not include all comparators and included a comparator outside of scope: genetic guided dosing of warfarin) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT, and may not reflect full body of evidence available, short time horizon may not account for full downstream effects, costs are from a Canadian perspective). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Oyaguez 2019[139]	This study was partially applicable (Spanish healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effect not based on systematic reviews of the literature and may not reflect full body of evidence available, costs are from a Spanish perspective, potential financial conflict of interest: funded by manufacturer of apixaban). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Pink 2011[143]	This study was partially applicable (did not include all comparators) and judged to have potentially serious limitations (Relative treatment effects for dabigatran from single RCT and may not reflect full body of evidence available, unit costs inflated). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Pink 2014[144]	This study was partially applicable (did not include all comparators and includes a comparator outside of scope: genetic guided dosing of warfarin) and judged to have potentially serious limitations

Reference	Reason for exclusion
	(relative treatment effects not based on systematic reviews of the literature; based on 3 RCTs, and may not reflect full body of evidence available). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Pletscher 2013[145]	This study was partially applicable (Swiss healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, and may not reflect full body of evidence available, costs are from a Swiss perspective, potential financial conflict of interest: funded by manufacturer of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Rognoni 2014[149]	This study was partially applicable (Italian NHS setting and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature. Costs are primarily based on Italian NHS costs and so may not reflect UK NHS setting and assumptions made regarding costs of DOACs in analysis being equal to cost of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Rognoni 2015[150]	This study was partially applicable (Italian healthcare setting and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT and may not reflect full body of evidence available, costs are from a Italian NHS perspective, assumptions made regarding cost of edoxaban being equal to dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Sorensen 2011[159]	This study was partially applicable (Canadian healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effect not based on systematic reviews of the literature and may not reflect full body of evidence available, costs are from a Canadian perspective, potential financial conflict of interest: funded by manufacturer of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Stevanovic 2014[161]	This study was partially applicable (Dutch healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on two RCTs, and may not reflect full body of evidence available, costs are from a Dutch perspective). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.

Reference	Reason for exclusion
van Hulst 2018[164]	This study was partially applicable (Dutch healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on single RCT, and may not reflect full body of evidence available, costs are from a Dutch perspective, potential financial conflict of interest: funded by manufacturer of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Walter 2020[170]	This study was partially applicable (Austrian healthcare setting and incorrect discounting used) and judged to have minor limitations (Austrian costs which may not reflect costs to the NHS). This study was an adaptation of Sterne 2017[160] for an Austrian healthcare perspective. The developers felt this study was superseded by Sterne 2017[160] which had a UK NHS perspective and therefore this study was selectively excluded.
Wells 2012[172]	This study was partially applicable (Canadian healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline effects based on a single study rather than systematic review of literature, Canadian costs which may not reflect costs to the NHS, assumptions made regarding costs of apixaban being equal to cost of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Wisloff 2014[175]	This study was partially applicable (Norwegian healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, relative treatment effects based on three RCT and may not reflect full body of evidence available, treatment discontinuation and switching not modelled, costs are from a Norwegian perspective). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Wouters 2013[176]	This study was partially applicable (Belgian healthcare setting, incorrect discounting used and did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, and may not reflect full body of evidence available, costs are from a Belgian perspective, potential financial conflict of interest: funded by manufacturer of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.
Zheng 2014[180]	This study was partially applicable (did not include all comparators) and judged to have potentially serious limitations (baseline and relative treatment effects not based on systematic reviews of the literature, potential financial conflict of interest: funded by manufacturer of dabigatran). However, developers felt this study was superseded by a comprehensive UK analysis by Sterne 2017[160], in terms of its applicability and methodological quality, and therefore this study was selectively excluded.