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Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease (Review)

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[Intervention Review]

Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease

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ABSTRACT

Background

Chronic kidney disease (CKD) is an independent risk factor for atrial fibrillation (AF), which is more prevalent among CKD patients than the general population. AF causes stroke or systemic embolism, leading to increased mortality. The conventional antithrombotic prophylaxis agent warfarin is often prescribed for the prevention of stroke, but risk of bleeding necessitates regular therapeutic monitoring. Recently developed direct oral anticoagulants (DOAC) are expected to be useful as alternatives to warfarin.

Objectives

To assess the efficacy and safety of DOAC including apixaban, dabigatran, edoxaban, and rivaroxaban versus warfarin among AF patients with CKD.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register (up to 1 August 2017) through contact with the Information Specialist using search terms relevant to this review. Studies in the Specialised Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal, and ClinicalTrials.gov.

Selection criteria

We included all randomised controlled trials (RCTs) which directly compared the efficacy and safety of direct oral anticoagulants (direct thrombin inhibitors or factor Xa inhibitors) with dose-adjusted warfarin for preventing stroke and systemic embolic events in non-valvular AF patients with CKD, defined as creatinine clearance (CrCl) or eGFR between 15 and 60 mL/min (CKD stage G3 and G4).

Data collection and analysis

Two review authors independently selected studies, assessed quality, and extracted data. We calculated the risk ratio (RR) and 95% confidence intervals (95% CI) for the association between anticoagulant therapy and all strokes and systemic embolic events as the primary efficacy outcome and major bleeding events as the primary safety outcome. Confidence in the evidence was assessing using GRADE.

Main results

Our review included 12,545 AF participants with CKD from five studies. All participants were randomised to either DOAC (apixaban, dabigatran, edoxaban, and rivaroxaban) or dose-adjusted warfarin. Four studies used a central, interactive, automated response system for allocation concealment while the other did not specify concealment methods. Four studies were blinded while the other was partially open-label. However, given that all studies involved blinded evaluation of outcome events, we considered the risk of bias to be low. We were unable to create funnel plots due to the small number of studies, thwarting assessment of publication bias. Study duration ranged from 1.8 to 2.8 years. The large majority of participants included in this study were CKD stage G3 (12,155), and a small number were stage G4 (390). Of 12,545 participants from five studies, a total of 321 cases (2.56%) of the primary efficacy outcome occurred per year. Further, of 12,521 participants from five studies, a total of 617 cases (4.93%) of the primary safety outcome occurred per year. DOAC appeared to probably reduce the incidence of stroke and systemic embolism events (5 studies, 12,545 participants: RR 0.81, 95% CI 0.65 to 1.00; moderate certainty evidence) and to slightly reduce the incidence of major bleeding events (5 studies, 12,521 participants: RR 0.79, 95% CI 0.59 to 1.04; low certainty evidence) in comparison with warfarin.

Authors' conclusions

Our findings indicate that DOAC are as likely as warfarin to prevent all strokes and systemic embolic events without increasing risk of major bleeding events among AF patients with kidney impairment. These findings should encourage physicians to prescribe DOAC in AF patients with CKD without fear of bleeding. The major limitation is that the results of this study chiefly reflect CKD stage G3. Application of the results to CKD stage G4 patients requires additional investigation. Furthermore, we could not assess CKD stage G5 patients. Future reviews should assess participants at more advanced CKD stages. Additionally, we could not conduct detailed analyses of subgroups and sensitivity analyses due to lack of data.

PLAIN LANGUAGE SUMMARY

Direct oral anticoagulants for prevention of stroke in atrial fibrillation patients with chronic kidney disease

What is the issue?

Chronic kidney disease (CKD) patients have an increased risk of atrial fibrillation (AF), which can often lead to stroke or systemic embolism. The conventional therapy for preventive AF is dose-adjusted warfarin, but this can increase the risk of bleeding, which necessitates regular therapeutic monitoring. Recently, direct oral anticoagulants (DOAC) have been developed as alternatives to warfarin. We reviewed the evidence on DOAC compared to warfarin for preventing stroke and systemic embolic events in AF patients with CKD.

What did we do?

We found five studies that compared the effects of DOAC (apixaban, dabigatran, edoxaban, and rivaroxaban) and dose-adjusted warfarin. The 12,545 participants in these five studies had non-valvular AF and moderate kidney impairment. These studies presented data on all composite outcomes of stroke and systematic embolic events as the primary efficacy outcome, with major bleeding events as the primary safety outcome. The median follow-up period ranged from 1.8 to 2.8 years. The evidence is accurate as of August 2017.

What did we find?

DOAC probably reduced the incidence of stroke and systemic embolic events as a primary efficacy outcome, compared to warfarin. Further, DOAC might slightly reduce the incidence of major bleeding events as a primary safety outcome, compared to warfarin.

Conclusions

This review demonstrated that DOAC are as likely as warfarin to prevent all strokes and systemic embolic events without increasing major bleeding events among AF patients with CKD. According to GRADE, the quality of the evidence was moderate for the primary efficacy outcome because of concerns with imprecision and low for the primary safety outcome because of concerns with inconsistency and imprecision. The results of this study chiefly apply to CKD stage G3 patients, since we could not assess those with CKD stage G4 or G5.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Direct oral anticoagulants (DOAC) versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease (CKD)

DOAC versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with CKD

Patient or population: atrial fibrillation patients with CKD

Setting: Hospital-based setting

Intervention: DOAC

Comparison: Dose-adjusted warfarin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Warfarin	DOAC			
All strokes and systemic embolic events Follow up: 1.8 years to 2.8 years	29 per 1,000	23 per 1,000 (19 to 29)	RR 0.81 (0.65 to 1.00)	12,545 (5)	⊕⊕⊕⊖ [1] MODERATE
Major bleeding Follow up: 1.8 years to 2.8 years	55 per 1,000	43 per 1,000 (32 to 57)	RR 0.79 (0.59 to 1.04)	12,521 (5)	⊕⊕⊖⊖ [1] [2] LOW
Myocardial infarction Follow up: 2.8 years	11 per 1,000	10 per 1,000 (5 to 21)	RR 0.92 (0.45 to 1.90)	2,740 (1)	-
Minor bleeding Follow up: 2.5 years to 2.8 years	74 per 1,000	72 per 1,000 (43 to 119)	RR 0.97 (0.58 to 1.61)	3,012 (2)	⊕⊕⊖⊖ [1] [2] LOW
Gastrointestinal bleeding Follow up: 1.9 years to 2.8 years	17 per 1,000	24 per 1,000 (17 to 35)	RR 1.40 (0.97 to 2.01)	5,678 (2)	⊕⊕⊕⊖ [1] MODERATE
Intracranial haemorrhage Follow up: 1.8 years to 2.8 years	14 per 1,000	6 per 1,000 (4 to 9)	RR 0.43 (0.27 to 0.69)	12,521 (5)	⊕⊕⊕⊖ [1] MODERATE

All-cause mortality Follow up: 1.8 years to 2.8 years	78 per 1,000	71 per 1,000 (61 to 82)	RR 0.91 (0.78 to 1.05)	9,595 (4)	⊕⊕⊕⊖ [1] MODERATE

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

AF: atrial fibrillation; **CI:** confidence interval; **DOAC**: direct oral anticoagulants; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Some concerns with imprecision because of the uncertain effect estimate
[2] Some concerns with inconsistency because of medium heterogeneity

BACKGROUND

Description of the condition

Atrial fibrillation (AF) is the most common form of sustained arrhythmia and causes irregular and rapid heart rate. Common symptoms are palpitation and chest pain; some people also experience fainting spells.

Chronic kidney disease (CKD) is an independent risk factor for AF (Go 2009). It has been reported that AF prevalence among CKD patients is much higher than the 1% to 2% prevalence in the general population (Alonso 2011; Go 2001; Nelson 2012; Stewart 2001). A recent study demonstrated AF prevalence of 16% for patients with estimated glomerular filtration rate (eGFR) of 45 mL/min or more and 20.4% prevalence for those with eGFR < 45 mL/min (Soliman 2010). CKD is defined as kidney structure or function abnormality present for more than three months, with health implications. CKD is classified into stage 1 (eGFR ≥ 90 mL/min); stage 2 (60 to 89 mL/min); stage 3a (45 to 59 mL/min); stage 3b (30 to 44 mL/min); stage 4 (15 to 29 mL/min); and stage 5 (< 15 mL/min) (KDIGO 2012).

CKD and AF have several risk factors in common, such as increasing age, hypertension, diabetes mellitus and other pre-existing heart diseases. Once people suffer from CKD, further multiple factors are associated with AF such as activation of the renin-angiotensin-aldosterone system, chronic inflammation, vascular calcification, and left ventricular hypertrophy (Ng 2013). AF is associated with stroke or systemic embolism, leading to increased morbidity or mortality. Stroke due to AF are attributed to the poor contractile status of the left atrium and blood stasis in the atrium that leads to thrombus formation (Watson 2009). It has been shown that reduced eGFR and proteinuria were independently associated with the incidence of thromboembolism in patients with AF after adjusting for other stroke risk factors (Go 2009).

Description of the intervention

It has been reported that anticoagulation therapy reduces the risk of thromboembolic events in AF patients with normal kidney function. The conventional antithrombotic prophylaxis agent is a vitamin K antagonist such as warfarin. Efficacy of dose-adjusted warfarin for preventing AF-related stroke has been reported to be better (risk reduction of 60%) than aspirin (20% risk reduction) (Hart 2007). However, warfarin has some limitations: it has multiple dietary interactions, especially with vitamin K, and concomitant drugs; and takes two to three days to begin working. Because warfarin has a narrow therapeutic window, and inadequate control results in haemorrhage, guidelines suggest that warfarin levels should be controlled within the range of the international normalised ratio (INR) of 2.0 to 3.0 (EHRA-EACTS 2010). In people with CKD, further warfarin-related complications may arise because risk of haemorrhage is increased (Olsen 2012). Warfarin use for people with end-stage kidney disease is particularly challenging because of the risk of serious bleeding; however, people with CKD patients in earlier stages with AF may benefit from warfarin.

Recently, direct oral anticoagulants (DOAC) have been developed as alternatives to vitamin K agonists. It has been reported that DOAC such as direct thrombin inhibitors and factor Xa inhibitors are associated with lower risks of stroke and bleeding than vitamin K agonists in people with normal kidney function (Bruins Slot 2013; Miller 2012; Mitchell 2013). DOAC provide rapid onset of action and do not need regular monitoring because they do not interact with foods or other drugs (Eriksson 2011). Currently, major regulatory agencies (EMA 2014; FDA 2014; Health Canada 2017) have approved the DOAC for AF patients with CKD stage G3 or G4 (creatinine clearance (CrCl) or eGFR between 15 and 60 mL/min) (Table 1), but evidence supporting their use is limited (Reinecke 2013).

How the intervention might work

Warfarin indirectly interrupts the extrinsic coagulation cascade by inhibiting the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X. In contrast, factor Xa inhibitors including apixaban, edoxaban and rivaroxaban directly interrupt the activity of clotting factor Xa, which converts prothrombin to thrombin. In addition, direct thrombin inhibitors such as dabigatran also act by directly inhibiting thrombin.

Bruins Slot 2013 showed that DOAC significantly decreased the number of stroke and other systemic embolic events compared with dose-adjusted warfarin in AF patients regardless of kidney function (odds ratio (OR) 0.81, 95% confidence interval (CI) 0.72 to 0.91) and reduced major bleeding (OR 0.89, 95% CI 0.81 to 0.98).

Why it is important to do this review

The number of people with CKD and AF is rising annually. The risk for stroke or systemic thromboembolism due to AF in people with CKD is significantly higher than in those with normal kidney function (hazard ratio (HR) 1.49, 95% CI 1.38 to 1.59). All-cause mortality is also significantly higher among people with CKD (HR 2.37, 95% CI 2.30 to 2.44) (Olsen 2012) than the general population.

Although anticoagulants are frequently prescribed for CKD patients with AF to reduce the risk for stroke or systemic thromboembolic events, these agents tend to be used less often for this population than for people who do not have CKD (Olsen 2012). This finding is attributed to the fact that results of large clinical studies of anticoagulant therapy for AF among moderate to severe CKD patients are lacking, and clinicians are wary of risks of bleeding.

DOAC may be more effective and safer for people with CKD than warfarin; they show promise to reduce prevalence of stroke and systemic embolic events, and may reduce risk of bleeding.

OBJECTIVES

To assess the efficacy and safety of DOAC including apixaban, dabigatran, edoxaban, and rivaroxaban versus warfarin among AF patients with CKD.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) comparing DOAC with warfarin were obtained. Cluster RCTs were also included if the intra-cluster correlation coefficient was reported. Cross-over studies were not included to avoid carry-over effects.

Types of participants

Eligible participants were diagnosed with non-valvular AF and moderate kidney impairment, defined as CrCl or eGFR between 15 and 60 mL/min (CKD stage G3 and G4). Non-valvular AF was diagnosed with electrocardiography. Patients were excluded if they had valvular AF, recent stroke, and conditions associated with an increased risk for bleeding.

Types of interventions

We included studies that investigated DOAC. These include apixaban, dabigatran, edoxaban, and rivaroxaban as well as any other intervention classified as DOAC. We included any dose or regimen compared with warfarin. Warfarin was to be dose-adjusted using INR.

Types of outcome measures

Primary outcomes

- Composite of all strokes and systemic embolic events
  - All strokes: sudden focal neurologic deficit caused by cerebrovascular thrombosis, and categorised as ischaemic, haemorrhagic, or unspecific
  - Systemic embolic events: acute vascular occlusion of an extremity or organ
- Major bleeding: reduction in haemoglobin of at least 20 g/L, and transfusion of at least two units of blood, or symptomatic bleeding in a critical area or organ.

In our protocol, we intended to distinguish the effect of DOAC on two efficacy primary outcomes: all strokes and systemic embolic events. However, all included studies reported composite outcomes for all strokes, including ischaemic and haemorrhagic stroke and systemic embolic events; we therefore assessed these as one composite outcome.

Secondary outcomes

- Myocardial infarction (MI): diagnosis based on electrocardiographic changes, elevation of enzymes or confirmed during post-mortem examination
- Minor bleeding: non-major clinically relevant bleeding
- Gastrointestinal (GI) bleeding
- Intracranial haemorrhage: all intracerebral, subdural, epidural and subarachnoid haemorrhage
- All-cause mortality: death from any cause (vascular and non-vascular)
- Vascular death: death due to stroke (both ischaemic and haemorrhagic), heart disease, haemorrhage and sudden deaths of unknown causes.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register (up to 1 August 2017) through contact with the Information Specialist using search terms relevant to this review. The Cochrane kidney and Transplant Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register were identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, were available in the Specialised Register section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies, and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.
3. We also searched reference lists of the identified studies and contacted the pharmaceutical companies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that might be relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable; however, studies and reviews that might include relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts, and if necessary, the full text of these studies to determine which satisfy our inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English or non-Japanese language journals was translated before assessment. Where more than one publication of one study exists, reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions, these data were used. Any discrepancy between published versions was highlighted.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (detection bias)
  - Outcome assessors (performance bias)

- Were incomplete outcome data adequately addressed (attrition bias)?
- Were reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. stroke, bleeding), results were expressed as risk ratio (RR) with 95% CI. Where continuous scales of measurement were used to assess the effects of treatment, the mean difference (MD) were used, or the standardised mean difference (SMD) if different scales had been used.

Unit of analysis issues

RCTs with multiple intervention groups were included. Each intervention group was compared to the single control group.

Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing to corresponding authors) and any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat (ITT), as-treated and per-protocol (PP) population were carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

If possible, funnel plots were used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data were pooled using the random-effects model but the fixed-effects model was also be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity (e.g. participants, interventions and study quality). Heterogeneity among participants could be related to age, history of previous stroke and baseline stroke risk factors (assessed by $CHADS_2$ score) (Gage 2001). CKD stages were also assessed.

Heterogeneity in treatments could be related to dose and duration of therapy, subtype of DOAC, and concomitant use of antiplatelet therapy.

Where a variety of agents were used, adverse effects were tabulated and assessed with descriptive techniques, as they were likely to differ for the various agents. Where possible, the risk difference with 95% CI was calculated for each adverse effect.

Sensitivity analysis

We performed sensitivity analyses to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We presented the following outcomes in the 'Summary of findings' tables.

- All strokes and systemic embolic events
- Major bleeding
- Ischaemic stroke
- Haemorrhagic stroke
- MI
- Minor bleeding
- GI bleeding
- Intracranial haemorrhage
- All-cause mortality
- Vascular death

RESULTS

Description of studies

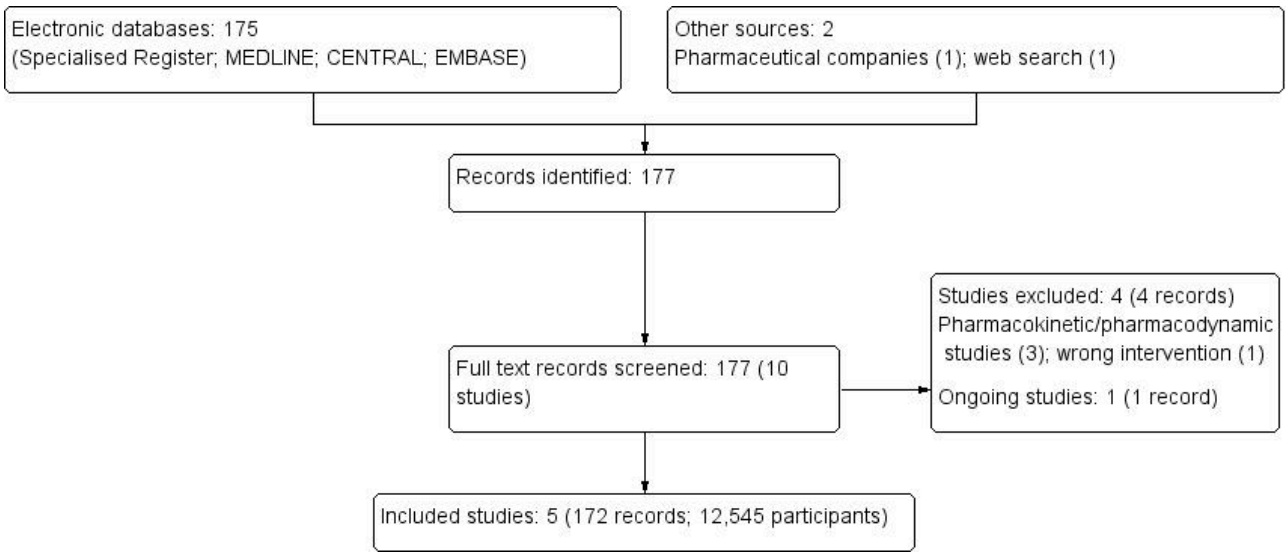
For detailed descriptions of the studies covered in this review, please see the following tables: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

After searching the Specialised Register, contacting pharmaceutical companies, and an additional web search, we identified 177 records. After full-text review, five studies (172 records) were included (ARISTOTLE Study 2010; ENGAGE AF-TIMI 48 Study 2013; J-ROCKET AF Study 2012; RE-LY Study 2009; ROCKET AF Study 2010) and four studies (four records) were excluded (Caluwé 2016;

Eriksson 2003a; Koretsune 2015; Murray 2004). One ongoing study was identified (X-NOAC Study 2015) and will be included in a future update of this review (Figure 1).

Figure 1. Study flow diagram.



Included studies

We identified a total of 172 records representing five large studies (ARISTOTLE Study 2010; ENGAGE AF-TIMI 48 Study 2013; J-ROCKET AF Study 2012; RE-LY Study 2009; ROCKET AF Study 2010). We sent enquiry requests to the relevant pharmaceutical companies about how they dealt with missing data (the ITT analysis or modified ITT analysis). All companies responded but only one provided additional unpublished information (ARISTOTLE Study 2010).

These five studies enrolled 12,545 G3 and G4 participants. The participants had non-valvular AF and moderate kidney impairment. All five studies used the Cockcroft-Gault equation to define CrCl as a marker of kidney function. ARISTOTLE Study 2010 defined moderate kidney impairment as CrCl of 25 to 50 mL/min, while the other studies defined it as CrCl of 30 to 50 mL/min. Although participants with severe kidney impairment were exclusionary in ENGAGE AF-TIMI 48 Study 2013, a few participants with CrCl < 30 mL/min were randomised and analysed as having moderate kidney impairment.

- ARISTOTLE Study 2010 included 2747 participants (91.1%) with CKD stage G3 and 270 participants (8.9%) with CKD stage G4
- ENGAGE AF-TIMI 48 Study 2013 included 2620 participants (95.6%) with CKD stage G3 and 120 participants (4.4%) with CKD stage G4
- J-ROCKET AF Study 2012 included 284 participants with CKD stage G3
- RE-LY Study 2009 included 3554 participants with CKD stage G3
- ROCKET AF Study 2010 included 2950 participants with CKD stage G3.

Therefore, the large majority of participants included in this review were CKD stage G3 rather than stage G4 (CKD stage G3: 12,155 participants; stage G4: 390 participants).

Of 172 records, ARISTOTLE Study 2010 had 43 records, ENGAGE AF-TIMI 48 Study 2013 had 27 records, J-ROCKET AF Study 2012 had 15 records, RE-LY Study 2009 had 25 records, and ROCKET AF Study 2010 had 62 records. They included original studies and various sub studies such as different research questions, different population focused on specific conditions (e.g. elderly patients, patients with high $CHADS_2$ score), and conference proceedings.

We used a subset of data from these five studies, which enrolled primarily AF patients with normal kidney function. The number of patients with CKD in each study was:

- ARISTOTLE Study 2010: 3,017/18,122 (17%)
- ENGAGE AF-TIMI 48 Study 2013: 2,740/14,071 (19.5%)
- J-ROCKET AF Study 2012: 284/1,278 (22.2%)
- RE-LY Study 2009: 3,554/17,951 (19.8%)
- ROCKET AF Study 2010: 2,950/14,264 (20.7%).

The extracted participants from each study were of an acceptable sample size. We determined that the patients with CKD represented a predefined subgroup in each of the original studies, because the balance of the allocated groups had been maintained.

All five studies were RCTs. We summarized the baseline characteristics of four studies that estimated kidney function by the Cockcroft-Gault equation (ARISTOTLE Study 2010; ENGAGE AF-TIMI 48 Study 2013; J-ROCKET AF Study 2012; ROCKET AF Study 2010). RE-LY Study 2009 estimated kidney function by CKD-EPI and while the characteristics of these patients were not likely to differ from the other four studies, the results of this study were excluded from the summary of the baseline characteristics.

Mean and median age of participants ranged between 78 and 79 years, and 53.5 % were female. Previous stroke history was 35.6%, mean $CHADS_2$ score ranged between 2.6 and 3.7, prior vitamin K use was 56.1%, and prevalence of aspirin use was 33.6%.

Patients excluded from the included studies had: reversible AF or AF due to heart valve disorder; experienced a stroke in the past seven days; a condition associated with an increased risk of bleeding; were contraindicated for warfarin treatment; severe anaemia; received an investigational drug or medical device within 30 days before the planned clinical trial; active liver disease; severe comorbidity and whose life expectancy fell within the planned study period; were pregnant; and were unfit or unwilling to comply with the study-related procedures, such as subjects with alcohol dependence or those who refused to supply written informed consent. All studies allowed participants to use concomitant anti-platelet agents containing less than 100 mg of acetylsalicylic acid and thienopyridine, but this was restricted to a single use.

The included studies compared warfarin against the following DOAC: apixaban 2.5 or 5.0 mg (ARISTOTLE Study 2010), dabigatran 110 or 150 mg (RE-LY Study 2009), edoxaban 30 mg (ENGAGE AF-TIMI 48 Study 2013), rivaroxaban 10 mg (J-ROCKET AF Study 2012) or 15 mg (ROCKET AF Study 2010). Apixaban and dabigatran are usually administered twice a day while edoxaban and rivaroxaban were administered once daily. All studies compared DOAC with dose-adjusted warfarin using INR. The target INR for four studies, excluding J-ROCKET AF Study 2012, was between 2.0 and 3.0 among all participants. In J-ROCKET AF Study 2012, the target INR in participants younger than 70 years was between 2.0 and 3.0, while that in those aged 70 years and older was between 1.6 and 2.5.

All five studies presented data on all composite outcomes of stroke and systematic thromboembolism as the primary efficacy outcome, with major bleeding events as the primary safety outcome. The median follow-up period ranged from 1.8 to 2.8 years.

Excluded studies

Four studies were excluded. Three studies where pharmacokinetic/pharmacodynamic studies of ximelagatran and metagatran (Eriksson 2003a), edoxaban (Koretsune 2015), and argatroban (Murray 2004), and one study compared rivaroxaban plus vitamin K2 versus vitamin K antagonist (Caluwé 2016).

Risk of bias in included studies

Figure 2 and Figure 3 summarize our assessment of risk of bias for the five included studies. Two authors independently assessed the included studies for each checklist item as having high, low, or unclear risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

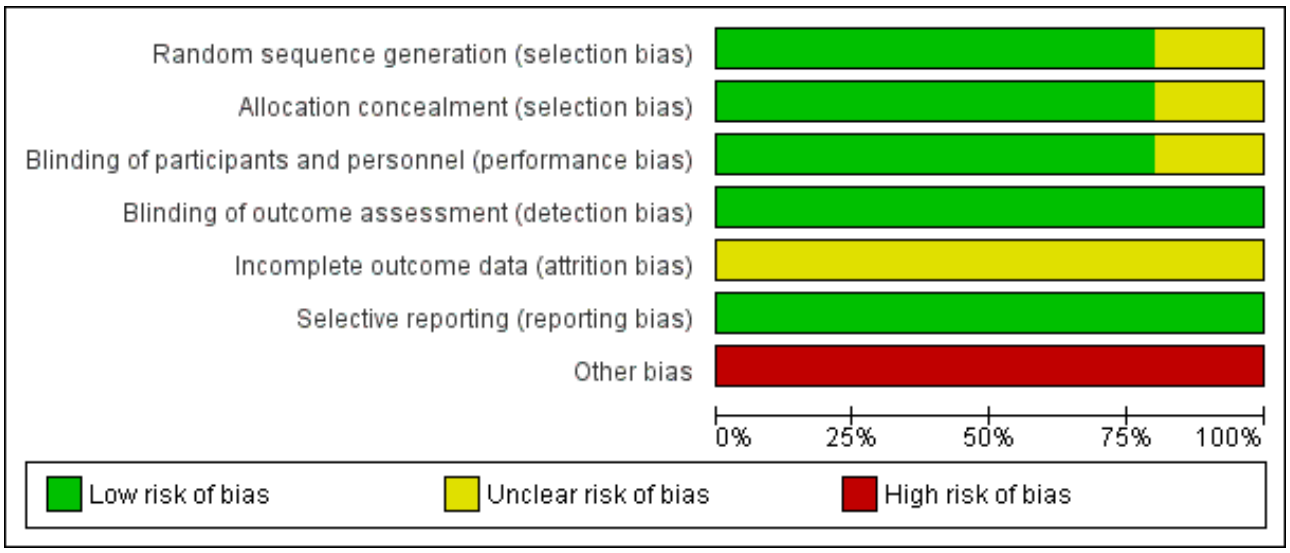
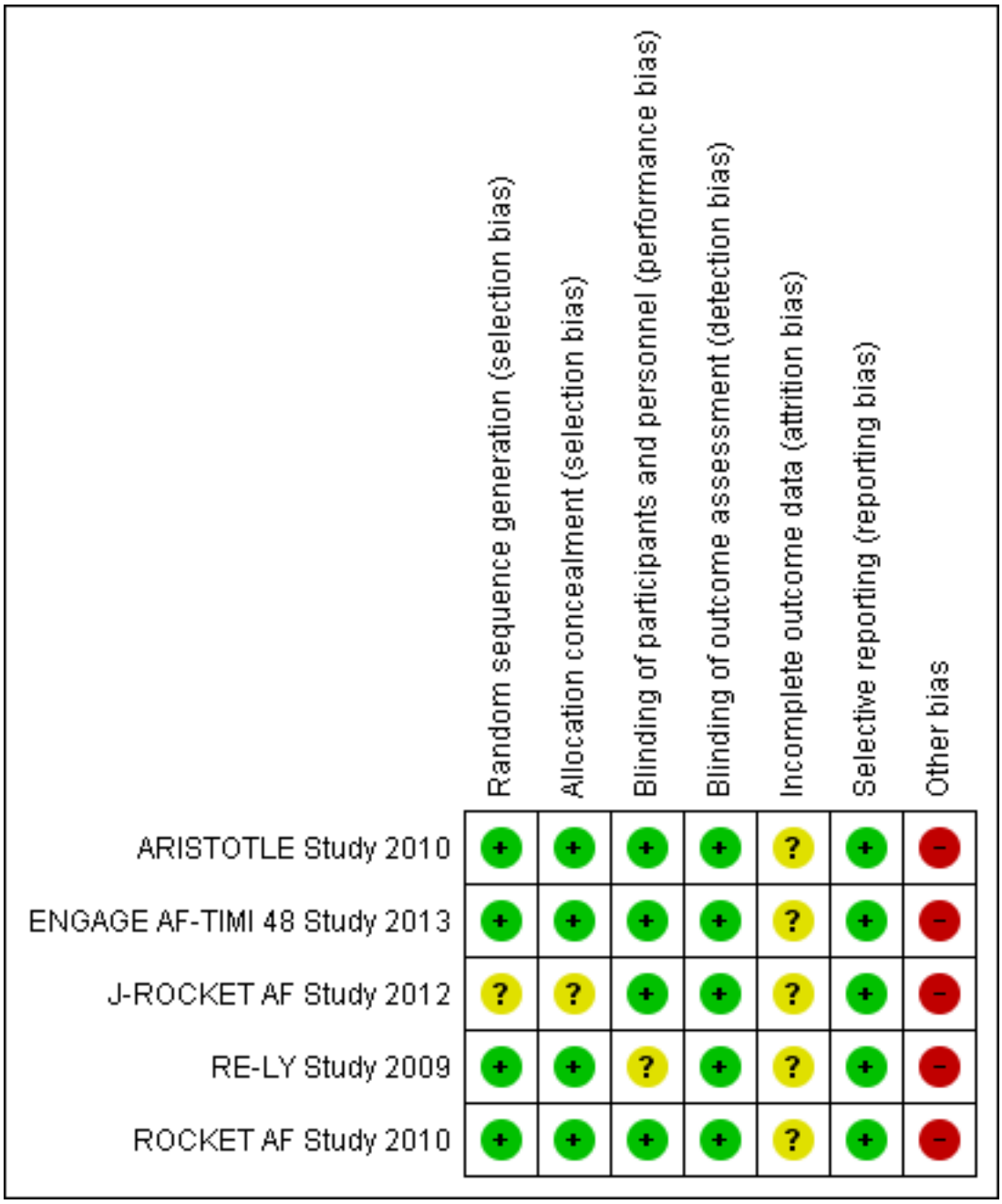


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Four studies used a central, interactive, automated response system for allocation concealment (ARISTOTLE Study 2010; ENGAGE AF-TIMI 48 Study 2013; RE-LY Study 2009; ROCKET AF Study 2010), while J-ROCKET AF Study 2012 did not specify randomisation or concealment methods. Therefore, we assessed the four studies to have a low risk of bias and J-ROCKET AF Study 2012 to have unclear risk of bias. We used subgroup analysis results from each large study but determined that the balance of the allocated groups had been maintained because the extracted participants from each study were of an acceptable sample size.

Blinding

Four studies had adequate double-blinding procedures (ARISTOTLE Study 2010; ENGAGE AF-TIMI 48 Study 2013; J-ROCKET AF Study 2012; ROCKET AF Study 2010). Further, independent, centralized clinical end-point committees who were blind to treatment assessed outcomes based on agreed-upon definitions. RE-LY Study 2009 had incomplete blinding, as while dabigatran was administered in a blinded fashion, warfarin was administered in an open-label fashion, and INR was adjusted at least monthly. This incomplete blinding may have led to performance bias. However, we considered that any risk of performance bias would be reduced by a predetermined equal interval of follow-up. Further, we

assessed the risk of detection bias to be low because the outcomes were objective measures and outcome assessors were blinded.

Incomplete outcome data

For the primary efficacy outcome of all strokes and systematic thromboembolic events, two studies (ARISTOTLE Study 2010; RE-LY Study 2009) reported results from ITT analyses; ENGAGE AF-TIMI 48 Study 2013 reported results based on both ITT and modified ITT analyses; ROCKET AF Study 2010 reported results based on ITT, modified ITT, and PP analyses; and J-ROCKET AF Study 2012 reported results from modified ITT and PP analyses. For the primary safety outcome of major bleeding events, only RE-LY Study 2009 reported results from ITT analyses, while the other four provided results from modified ITT analyses, which included all randomised participants who had received at least one dose of the study drug during the follow-up period.

Selective reporting

We found no evidence of selective reporting bias in any of the five studies, and all predefined primary efficacy and safety outcomes in the protocols were reported in the published manuscripts.

Other potential sources of bias

All of the studies examined were sponsored by pharmaceutical companies.

Effects of interventions

See: **Summary of findings for the main comparison** Direct oral anticoagulants (DOAC) versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease (CKD)

See: Summary of findings for the main comparison for the main comparisons.

In the original protocol, we aimed to distinguish two primary efficacy outcomes: all strokes and systemic embolic events. However, all included studies reported composite outcomes of all strokes, including both ischaemic and haemorrhagic stroke and systemic embolic events; therefore we examined them as one composite outcome.

For both primary and secondary efficacy outcomes, including all strokes and systemic embolic events, MI, and all-cause mortality, we included the results that used the conventional ITT analyses for the four studies (ARISTOTLE Study 2010; ENGAGE AF-TIMI 48 Study 2013; RE-LY Study 2009; ROCKET AF Study 2010) and the results that used the modified ITT analyses for one study (J-ROCKET AF Study 2012). Vascular death was not reported in any of the included studies.

For primary and secondary safety outcomes, including major bleeding, minor bleeding, GI bleeding, and intracranial haemorrhage, we included the results that used modified ITT analyses for four studies (ARISTOTLE Study 2010; ENGAGE AF-TIMI 48 Study 2013; J-ROCKET AF Study 2012; ROCKET AF Study 2010) and the result that used the conventional ITT analyses for one study (RE-LY Study 2009).

Primary outcomes

All strokes and systemic embolic events

A total of 12,545 participants from all five studies were included in this analysis. We used the random-effects model to assess the association between anticoagulants and the primary efficacy outcome. DOAC probably reduced the incidence of composite outcomes in comparison with warfarin (Analysis 1.1 (5 studies, 12,545 participants): RR 0.81, 95% CI 0.65 to 1.00; moderate certainty evidence). There was no heterogeneity (I^2 = 0%). We assessed the quality of evidence for the primary efficacy outcome to be moderate by GRADE because of concerns with imprecision. In addition, four studies (ARISTOTLE Study 2010; ENGAGE AF-TIMI 48 Study 2013; J-ROCKET AF Study 2012; ROCKET AF Study 2010) reported the RR of ischaemic stroke or haemorrhagic stroke. DOAC probably made little difference to the incidence of ischaemic stroke in comparison with warfarin (Analysis 1.2 (4 studies, 8,991 participants): RR 1.01, 95% CI 0.75 to 1.36; moderate certainty evidence). There was no heterogeneity (I^2 = 0%). In contrast, DOAC probably reduced the incidence of haemorrhagic stroke in comparison with warfarin (Analysis 1.3 (4 studies, 8,991 participants): RR 0.52, 95% CI 0.28 to 0.97; moderate certainty evidence). There was no heterogeneity (I^2 = 0%). We assessed the quality of evidence concerning both ischaemic and haemorrhagic strokes to be moderate because of concerns with imprecision.

Major bleeding

A total of 12,521 participants from all five studies reported major bleeding events, defined as a reduction in at least 20 g/L of haemoglobin, transfusion of at least two units of blood, symptomatic bleeding in a critical area or organ, or death due to major bleeding, according to the ISTH criteria. DOAC might slightly reduce the incidence of major bleeding events in comparison with warfarin (Analysis 1.4 (5 studies, 12,521 participants): RR 0.79, 95% CI 0.59 to 1.04; low certainty evidence). There was medium heterogeneity (I^2 = 63%). We assessed the quality of evidence for the primary safety outcome to be low by GRADE because of concerns with inconsistency and imprecision.

Secondary outcomes

Myocardial infarction

ENGAGE AF-TIMI 48 Study 2013 reported no difference in the incidence of MI between DOAC compared to warfarin (Analysis 1.5 (1 study, 2,740 participants): RR 0.92, 95% CI 0.45 to 1.90). Although the other four studies (ARISTOTLE Study 2010; J-ROCKET AF Study 2012; RE-LY Study 2009; ROCKET AF Study 2010) indicated that they would assess the incidence of MI in their protocol, ARISTOTLE Study 2010 and J-ROCKET AF Study 2012 did not report on the results, while RE-LY Study 2009 and ROCKET AF Study 2010 reported the composite outcomes for stroke, systemic embolic events, MI and others, but not separately for these items.

Minor bleeding

Two studies (ENGAGE AF-TIMI 48 Study 2013; J-ROCKET AF Study 2012) reported that DOAC might make little difference to minor bleeding events in comparison with warfarin (Analysis 1.6 (2 studies, 3,012 participants): RR 0.97, 95% CI 0.58 to 1.61; low certainty evidence). There was substantial heterogeneity (I^2 = 70%). We assessed the quality of evidence to be low because of concerns with inconsistency and imprecision. No data was available for the

other three studies (ARISTOTLE Study 2010; RE-LY Study 2009; ROCKET AF Study 2010).

Gastrointestinal bleeding

Two studies (ENGAGE AF-TIMI 48 Study 2013; ROCKET AF Study 2010) reported that DOAC probably leaded to slightly more GI bleeding events in comparison with warfarin (Analysis 1.7 (2 studies, 5,678 participants): RR 1.40, 95% CI 0.97 to 2.01; moderate certainty evidence). There was no heterogeneity (I^2 = 0%). We assessed the quality of evidence to be moderate because of concerns with imprecision. No data was available for the other three studies (ARISTOTLE Study 2010; J-ROCKET AF Study 2012; RE-LY Study 2009).

Intracranial haemorrhage

All five studies reported that DOAC probably reduced intracranial haemorrhage events in comparison with warfarin (Analysis 1.8 (5 studies, 12,521 participants): RR 0.43, 95% CI 0.27 to 0.69; moderate certainty evidence). There was low heterogeneity (I^2 = 25%). We assessed the quality of evidence to be moderate because of concerns with imprecision.

All-cause mortality

Four studies (ARISTOTLE Study 2010; ENGAGE AF-TIMI 48 Study 2013; J-ROCKET AF Study 2012; RE-LY Study 2009) reported that DOAC probably make little difference to all-cause mortality in comparison with warfarin (Analysis 1.9 (4 studies, 9,595 participants): RR 0.91, 95% CI 0.78 to 1.05; moderate certainty evidence). There was no heterogeneity (I^2 = 0%). We assessed the quality of evidence to be moderate because of concerns with imprecision. Although ROCKET AF Study 2010 also indicated the assessment of all-cause mortality in their protocol, the results were not reported.

Vascular death

We could not obtain the results for vascular death from any of the included studies.

Subgroup analyses

We conducted several pre-defined subgroup analyses for both the primary efficacy outcome and primary safety outcome to explore the heterogeneity of treatment effects.

CKD stages

ARISTOTLE Study 2010 and ENGAGE AF-TIMI 48 Study 2013 included several participants with CrCl < 30 mL/min. In the original articles, these participants were analysed as having moderate kidney impairment. However, an FDA report for ENGAGE AF-TIMI 48 Study 2013 and a report from the pharmaceutical company for ARISTOTLE Study 2010 categorised the data differently, as CKD stage 3 (CrCl 30 to 50 mL/min) and CKD stage 4 (CrCl 15 to 30 mL/min), respectively. Therefore, we re-analysed the primary outcomes according to CKD stage, categorising 12,155 participants as CKD stage G3 and 390 participants as stage G4.

DOAC probably slightly reduced the composite efficacy outcomes of all strokes and systemic embolic events in comparison with warfarin for participants with CKD stage 3 (Analysis 2.1 (5 studies, 12,155 participants): RR 0.82, 95% CI 0.66 to 1.02; moderate certainty evidence). There was no heterogeneity (I^2 = 0%). Likewise, DOAC might slightly reduce the composite efficacy outcomes in comparison with warfarin for participants with CKD stage G4 (Analysis 3.1 (2 studies, 390 participants): RR 0.68, 95% CI 0.23 to 2.00; low certainty evidence). There was no heterogeneity (I^2 = 0%). These results were consistent with the overall results.

DOAC probably slightly reduced major bleeding events in comparison with warfarin for participants with CKD stage G3 (Analysis 2.2 (5 studies, 12,132 participants): RR 0.80, 95% CI 0.62 to 1.03; moderate certainty evidence). There was moderate heterogeneity (I^2 = 53%). Only one study (ARISTOTLE Study 2010) of 268 participants with CKD stage G4 reported that DOAC might improve major bleeding events in comparison with warfarin (Analysis 3.2 (1 studies, 268 participants): RR 0.30, 95% CI 0.11 to 0.80).

Other baseline characteristics

No data were available for subgroup analyses of other participant characteristics such as age, history of stroke and risk factors of baseline stroke ($CHADS_2$ score). Additional assessments are required once more information is published.

How to prescribe anticoagulants

Dose and duration of therapy per day

Participants in RE-LY Study 2009 were randomly assigned to receive either 110 mg or 150 mg of dabigatran twice a day. Participants in ARISTOTLE Study 2010 were prescribed either 2.5 mg or 5 mg of apixaban twice a day, with dosage determined according to whether participants satisfied two or more of the following criteria: (i) age ≥ 80 years; (ii) body weight ≤ 60 kg; or (iii) SCr ≥ 1.5 mg/dL (133 µmol/L). Participants in the other three studies were administered single doses (ENGAGE AF-TIMI 48 Study 2013: 30 mg edoxaban once a day; ROCKET AF Study 2010: 15 mg rivaroxaban once a day; J-ROCKET AF Study 2012: 10 mg rivaroxaban once a day).

We conducted subgroup analyses to assess the different dosages of DOAC. In RE-LY Study 2009, the patients were randomised in a 1:1:1 fashion, 110 mg of dabigatran, 150 mg of dabigatran or dose-adjusted warfarin, and the results of analyses were separately shown for dabigatran 110 mg versus warfarin and for dabigatran 150 mg versus warfarin. However, we could not obtain the results for different dosages of apixaban (ARISTOTLE Study 2010). We entered two comparisons of dabigatran (dabigatran 110 mg versus warfarin, and dabigatran 150 mg versus warfarin) into the meta-analysis. Participants on DOAC probably reduced the composite primary efficacy outcomes of all strokes and systemic embolic events in comparison with warfarin (Analysis 4.1 (5 studies, 12,545 participants): RR 0.81, 95% CI 0.65 to 1.00; moderate certainty evidence). There was no heterogeneity (I^2 = 0%). Likewise, DOAC probably made little difference to all-cause mortality as the secondary efficacy outcome in comparison with warfarin (Analysis 4.3 (4 studies, 9,595 participants): RR 0.91, 95% CI 0.78 to 1.05; moderate certainty evidence). There was no heterogeneity (I^2 = 0%). Further, DOAC might slightly reduce the incidence of major bleeding in comparison with warfarin (Analysis 4.2 (5 studies, 12,521 participants): RR 0.81, 95% CI 0.63 to 1.03; low certainty evidence). There was moderate heterogeneity (I^2 = 54%). These results were mostly consistent with the original results.

No data were available for the comparison of the duration of each therapy.

Subtype of DOAC

Rivaroxaban was studied in two studies (ROCKET AF Study 2010; J-ROCKET AF Study 2012). However, the sample size of J-ROCKET AF Study 2012 was smaller than ROCKET AF Study 2010, and the prescribed doses were different between the studies. Therefore, it was difficult to perform subtype analysis. All other drugs were examined by a single study respectively, so we could not assess differences in DOAC subtypes.

Concomitant use of antiplatelet therapy

All studies allowed the use of less than 100 mg or 165 mg of aspirin, and all but one study (ENGAGE AF-TIMI 48 Study 2013) permitted the use of antiplatelet agents such as thienopyridine. However, no data were available for subgroup analysis.

Adverse events

Several adverse events were assessed for rivaroxaban (ROCKET AF Study 2010; J-ROCKET AF Study 2012). Rivaroxaban might make little difference to any adverse effects in comparison with warfarin (see results; Analysis 5).

Sensitivity analysis

We planned several pre-defined sensitivity analyses for both the primary efficacy outcome and primary safety outcome to explore the influence on effect size.

We did not carry out the sensitivity analysis for repeating the analysis excluding unpublished studies, because our study did not include unpublished studies. We did not carry out the sensitivity analysis for repeating the analysis taking into account risk of bias, because we considered the risk of bias to be low. We did not carry out the sensitivity analysis for repeating the analysis excluding any very long or large studies to establish how much they dominate the results, because the sample size of J-ROCKET AF Study 2012 was small, and other studies had similar weight. We also did not the sensitivity analysis for repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country. The criteria for kidney impairment and warfarin dosage were previously described and similar, and other criteria were similar. All included publications were written in English. All studies were supported by pharmaceutical research companies. Various western or Asian countries were involved in all studies except for J-ROCKET AF Study 2012, which targeted Japanese participants only.

Analysis using fixed effects model

We performed sensitivity analyses using the fixed-effect model. DOAC probably slightly reduced the incidence of composite outcomes in comparison with warfarin (Analysis 6.1 (5 studies, 12,545 participants): RR 0.81, 95% CI 0.65 to 1.01; moderate certainty evidence). There was no heterogeneity (I^2 = 0%). Further, DOAC probably reduced the incidence of major bleeding in comparison with warfarin (Analysis 6.2 (5 studies, 12,521 participants): RR 0.79, 95% CI 0.67 to 0.92; low certainty evidence). There was medium heterogeneity (I^2 = 63%). The results obtained using the fixed-effects model were mostly consistent with those obtained using the random-effects model even though the point estimates and 95% CIs were slightly different.

DISCUSSION

Summary of main results

We analysed 12,545 AF patients with moderate to severe kidney impairment in five RCTs that examined the efficacy and safety of four DOAC: apixaban, dabigatran, edoxaban, and rivaroxaban.

Included studies directly compared the association between DOAC and dose-adjusted warfarin for the composite outcomes of all strokes and systemic embolic events as the primary efficacy outcome, and major bleeding as the primary safety outcome. AF patients with CKD on DOAC probably reduced the incidence of all strokes and systemic embolic events in comparison with warfarin. Further, participants on DOAC might slightly reduce the incidence of major bleeding events.

This was the subset of data from five large studies, which enrolled primarily AF patients regardless of kidney function. The incidence of all strokes and systemic embolic events among patients with CKD was probably slightly consistent with among all participants from the original studies (Bruins Slot 2013). Further, the point estimates for the incidence of major bleeding among participants with CKD were lower than those among patients without kidney impairment, although 95% CI was larger because of the smaller sample size.

The results of subgroup analyses according to CKD stage G3 and G4 were mostly consistent with the overall results. The only point of difference was that CKD stage G4 (ARISTOTLE Study 2010) DOAC might reduce major bleeding events in comparison with warfarin, but the number of participants categorised into CKD stage G4 was small, so we could not assess the association with sufficient power.

These findings indicate that DOAC are more or similarly effective and similarly safe for AF patients with CKD as dose-adjusted warfarin, at least in stage 3 CKD. Physicians can therefore feel more confident in prescribing DOAC to AF patients with CKD without the burden of regular monitoring that is necessary for warfarin.

Overall completeness and applicability of evidence

Currently, major regulatory agencies (EMA 2014; FDA 2014; Health Canada 2017) have approved DOAC for use by AF patients with CKD stage G3 or G4, but evidence supporting their use is limited (Reinecke 2013).

We systematically reviewed the studies that re-analysed the subgroups; that is, participants with kidney impairment, of the five large RCTs targeting AF participants. The sample size of each subgroup study was large and the balance and comparability of randomised baseline characteristics was retained in these subgroups.

All participants in the intervention and control groups had non-valvular AF and CKD, and other baseline characteristics were similar across the studies. Warfarin was controlled within the range of the INR of 2.0 to 3.0 for four studies, excluding J-ROCKET AF Study 2012, and the conditions for comparisons were consistent across studies. In J-ROCKET AF Study 2012, the target INR range was 2.0 to 3.0 for participants younger than 70 years and 1.6 to 2.5 for those aged 70 years and older.

Each study also included participants from western and Asian countries, indicating that the data were higher generalizable.

This systematic review had several limitations. First, ARISTOTLE Study 2010 and ENGAGE AF-TIMI 48 Study 2013 included participants with severe kidney impairment (CrCl < 30 mL/min). However, as shown in the subgroup analyses, our results chiefly apply to CKD stage G3 patients, so further studies are required to determine the efficacy and safety of DOAC on patients with CKD stage G4. Additionally, we could not examine the effects on CKD stage G5 patients. Although recent meta-analyses showed that warfarin may not be beneficial for patients with end-stage kidney disease, the effect of DOAC on these patients is unclear (Dahal 2016; Liu 2015). Future reviews should assess participants with more advanced CKD stages. Second, kidney function can be measured using several parameters and equations, such as CrCl, estimated by Cockcroft-Gault equation; and eGFR, estimated by the Modification of Diet in Renal Disease (MDRD) equation or CKD-EPI. GFR as estimated by MDRD or CKD-EPI may be more precise than CrCl (Levey 2006; Levey 2009). However, we could not estimate GFR using MDRD or CKD-EPI because the number of participants within each group were not indicated. We used CrCl estimated by the Cockcroft-Gault equation because it is widely used and all RCTs included in this review estimated kidney function using this method. Third, we could not perform some subgroup or sensitivity analyses due to lack of available data. In particular, it is important to assess subtypes or different dosages of DOAC to explore possible sources of heterogeneity. Such analyses should be conducted once more RCT results have been obtained, and the analyses in this study repeated after the publication of more data.

Quality of the evidence

Only RE-LY Study 2009 was conducted in single blinded fashion; however, since the outcome assessors were blinded, we concluded that this analysis method did not have adverse effects on the results. We assessed the risk of bias for both the primary efficacy and primary safety outcomes to be low. However, this study did not report important secondary outcomes such as MI and all-cause mortality even though they were predefined in the protocol; therefore, outcome reporting bias was suspected.

We could not assess differences in the types or dosages of DOAC sufficiently. We could not obtain the results for different dosages of apixaban. It is possible that higher doses caused more serious bleeding than lower doses, but this information is hidden by combining the dosages.

To assess publication of incomplete outcome data, which is related to attrition bias, we basically adopted the ITT principle for the primary efficacy outcome and the modified ITT principle for the primary safety outcome. The ITT principle for the efficacy outcomes maintains the balance of random allocation and is generally conservative by accepting the results of noncompliance and dropouts. In contrast, safety outcomes should not be diluted by noncompliance or dropouts, making the modified ITT principle more appropriate. J-ROCKET AF Study 2012 used modified ITT for efficacy outcomes and RE-LY Study 2009 used conventional ITT for safety outcomes. We expected that the relative measure (RR) was probably similar in conventional ITT and modified ITT analyses because this review adapted an active comparator. Therefore, we considered that adherence was likely to be similar in both groups and not to be related to the efficacy and the safety.

Funding biases can also affect the results of studies. Since all of the included studies followed the pre-defined protocol, we considered that the impact, if any, was small.

Using the GRADE system, we assessed the primary efficacy outcome to be of moderate quality due to concerns with imprecision and the primary safety outcome to be of low certainty due to concerns with inconsistency and imprecision. For the secondary outcomes, we assessed the results for minor bleeding to be of low certainty due to concerns with inconsistency and imprecision, GI bleeding, intracranial haemorrhage, and all-cause mortality to be of moderate certainty due to concerns with imprecision, respectively.

Potential biases in the review process

We performed a comprehensive search using several different databases but we cannot rule out the possibility that we may have missed several smaller studies. Further, we contacted the sponsors and performed web searches to collect data that we could not obtain from the Cochrane Kidney and Transplant Specialised Register, but there may still be a possibility that we missed some data.

Agreements and disagreements with other studies or reviews

A previous systematic review reported that DOAC were more effective than warfarin in preventing stroke and systemic embolism among AF patients regardless of kidney function, but the evidence among patients with kidney impairment were not established. Since CKD patients have an increased risk of stroke compared to the general population, preventive strategies for stroke are necessary for these patients (Lau 2016; Marinigh 2011; Masson 2015). However, clinicians hesitate to prescribe anticoagulants to CKD patients due to concerns about bleeding risks (Lau 2016). For example, dabigatran is predominantly excreted from the kidneys (Stangier 2008), so there is a risk that blood concentrations of the drug may rise.

The included original RCTs were all designed as non-inferiority studies and the data from a smaller group of participants in this review showed consistent results. Moreover, the point estimates among CKD participants were lower than among those without kidney impairment; variability (by 95% CI) was larger because of the smaller sample size.

AUTHORS' CONCLUSIONS

Implications for practice

DOAC are as likely as warfarin to prevent all strokes and systemic embolic events without increasing risk of major bleeding events among AF patients with kidney impairment. These findings should encourage physicians to prescribe DOAC to AF patients with CKD. Additionally, prescription of DOAC may improve quality of life because, unlike warfarin, they do not require regular monitoring or restrictions on foods or other drugs.

Implications for research

Several concerns remain and future studies should address the following points.

1. This study could not assess the effectiveness or safety of DOAC among patients with severe kidney dysfunction, such as those with CrCl < 30 mL/min, especially haemodialysis patients; it is important to establish the recommendations for these patients.
2. Other subgroup analyses using baseline characteristics such as age, history of previous stroke, and stroke risk factors (assessed by $CHADS_2$ score) should be conducted. Further, future studies should assess the impact of concomitant use of antiplatelet agents and DOAC.
3. We could not sufficiently assess the effect of DOAC on important secondary outcomes such as MI, minor bleeding and vascular death because of lack of available data. Therefore, these analyses should be repeated after the publication of more data.
4. The included studies had a maximum follow up period of 2.8 years. Future studies should assess the long-term effectiveness and safety of DOAC use.
5. Future studies should compare subtypes dosages of DOAC so as to provide clinicians with the comparative effectiveness of available alternatives.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ARISTOTLE Study 2010

Methods	• Study design: double-blind, double-dummy RCT • Study duration: 19 December to 2 April 2010 • Median duration of study follow-up: 1.8 years
Participants	• Countries: Australia, China, Hong Kong, India, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Netherlands, Norway, Poland, Romania, Russia, South Africa, Spain, Sweden, Switzerland, Turkey, UK, Ukraine, Argentina, Brazil, Chile, Colombia, Mexico, Peru, Puerto Rico, Canada, USA • Setting: multicentre • Patients with non-valvular AF; moderate kidney impairment (25≤ CrCl < 50 mL/min); aged ≥ 21 years, and at least one additional risk factors for stroke; age ≥ 75 years; previous stroke, TIA or systemic embolic event; symptomatic heart failure within previous 3 months or left ventricular ejection fraction of no more than 40%; DM; hypertension requiring pharmacologic treatment • Number: treatment group (1502); control group (1515) • Relevant health status: participants • Mean age ± SD: 77.6 ± 7.1 years • Sex (M/F): 1408/1609 • Exclusion criteria: AF due to a reversible cause; moderate or severe mitral stenosis; conditions other than AF that required anticoagulation (e.g. a prosthetic heart valve); stroke within the previous 7 days; need for aspirin at a dose of > 165 mg/d or for both aspirin and clopidogrel; severe kidney insufficiency (SCr > 221 µmol/L or calculated CrCl < 25 mL/min)
Interventions	Treatment group • Oral apixaban: either 2.5 mg or 5 mg twice/d, with dosage determined according to whether participants satisfied two or more of the following criteria: (i) age of at least 80 years; (ii) body weight of no more than 60 kg; or (iii) SCr ≥ 133 µmol/ L Control group • Oral warfarin: dose-adjusted (target INR 2.0 to 3.0)
Outcomes	• All strokes and systemic embolic events • All-cause mortality • Major bleeding • Intracranial haemorrhage
Notes	• Funding sources: Bristol-Myers Squibb and Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to treatment groups according to the stratification by clinical site and prior VKA use, and the possibility that this method give the influence on the results was low
Allocation concealment (selection bias)	Low risk	Allocation was concealed because participants were assigned to each group using the Interactive Voice Response System

ARISTOTLE Study 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Efficacy and safety outcomes were adjudicated on the basis of prespecified criteria by a clinical events committee whose members were unaware of study group assignments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Primary efficacy outcome was analysed in ITT population. Primary safety outcome was analysed in modified ITT population including all randomised patients who received least one dose of the study drug and included all events from receipt of the study drug until 2 days after the last dose of the drug. It has unclear risk because the number of participants that discontinued during study was reported, but the reason was unclear
Selective reporting (reporting bias)	Low risk	All predefined efficacy and safety outcomes were reported
Other bias	High risk	The study was funded by Bristol-Myers Squibb and Pfizer

ENGAGE AF-TIMI 48 Study 2013

Methods	• Study design: double-blind, double-dummy RCT • Study duration: 19 November 2008 to 22 November 2010 • Median duration of study follow-up: 2.8 years
Participants	• Countries: USA, Canada, Argentina, Brazil, Chile, Colombia, Mexico, Peru, Guatemala, Belgium, Finland, France, Germany, Greece, Israel, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, UK, Denmark, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Poland, Romania, Russia, Serbia and Montenegro, Slovakia, Ukraine, Australia, China, India, Korea, New Zealand, Philippines, South Africa, Taiwan, Thailand, Japan • Relevant health status: participants aged ≥ 21 years with non-valvular AF, moderate kidney impairment (30≤ CrCl <50 mL/min); a score of 2 or higher on the $CHADS_2$ risk assessment • Setting: multicentre • Number: treatment group (1379); control group (1361) • Median age (IQR): 79 years (75 to 83) • Sex(M/F): 1260/1480 • Exclusion criteria: AF due to a reversible disorder; an estimated CrCl < 30 mL/min; a high risk of bleeding; use of dual antiplatelet therapy; moderate-to severe mitral stenosis; other indications for anticoagulation therapy; acute coronary syndromes, coronary revascularization, or stroke within 30 days before randomisation; an inability to adhere to study procedures
Interventions	Treatment group • Oral edoxaban: 30 mg/d Control group • Oral warfarin: dose-adjusted (target INR 2.0 to 3.0)
Outcomes	• All strokes and systemic embolic events • MI • All-cause mortality • Major bleeding

ENGAGE AF-TIMI 48 Study 2013 *(Continued)*

	• Minor bleeding • GI bleeding • Intracranial haemorrhage
Notes	• Funding source: Daiichi Sankyo Pharma Development

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to treatment groups with the use of a central, 24-horur, interactive, computerized response system
Allocation concealment (selection bias)	Low risk	Allocation was concealed because participants were assigned to each group using a central, 24-horur, interactive, computerized response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Efficacy and safety outcomes were adjudicated by an independent clinical end-point committee whose members were not aware of study group assignments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Primary efficacy outcome was reported in both ITT and modified ITT population. Primary safety outcome was analysed in modified ITT population. The number of participants that discontinued during study was reported, but the reason was unclear
Selective reporting (reporting bias)	Low risk	All predefined efficacy and safety outcomes were reported
Other bias	High risk	The study was funded by Daiichi Sankyo Pharma Development

J-ROCKET AF Study 2012

Methods	• Study design: double-blind, double-dummy RCT • Study duration: 8 June 8 2007 to 19 January 2010 • Median duration of study follow-up: 2.5 years
Participants	• Country: Japan • Setting: Multicentre • Participants with non-valvular AF, moderate kidney impairment (30≤ CrCl < 50 mL/min); aged ≥ 20 years, and at least one additional risk factors: a history of prior ischaemic stroke, TIA, or non-CNS systemic embolism, or had ≥ 2 of the following risk factors for thromboembolism, congestive heart failure and/or left ventricular ejection fraction ≤ 35%, hypertension, age ≥75 years, or DM • Number: treatment group (141); control group (143) • Median age, IQR (years): treatment group (78, 74 to 81), control group (78, 75 to 82) • Sex(M/F): treatment group (105/36); control group (95/48) • Exclusion criteria: CrCl < 30 mL/min
Interventions	Treatment group • Oral rivaroxaban: 10 mg/d

J-ROCKET AF Study 2012 *(Continued)*

	Control group • Oral warfarin: dose-adjusted (target INR 2.0 to 3.0 for age < 70 and 1.6 to 2.6 to patients for age ≥ 70)
Outcomes	• All strokes and systemic embolic events (not shown because of the result from modified ITT analysis) • Major bleeding • Minor bleeding • Intracranial haemorrhage
Notes	• Funding source: the Bayer Healthcare Pharmaceuticals Japanese subsidiary, Bayer Yakuhin

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Efficacy and safety outcomes were adjudicated on the basis of prespecified criteria by an independent clinical endpoint committee whose members were unaware of study group assignments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Primary efficacy endpoints were analysed in the per-protocol population whose were ITT patients with no major protocol violation. Primary safety endpoints were analysed in modified ITT population. The number of participants that discontinued during study was reported, but the reason was unclear
Selective reporting (reporting bias)	Low risk	All predefined efficacy and safety outcomes were reported
Other bias	High risk	The study was funded by the Bayer Healthcare Pharmaceuticals Japanese subsidiary, Bayer Yakuhin

RE-LY Study 2009

Methods	• Study design: parallel RCT • Study duration: 22 December 2005 to 15 March 2009 • Median duration of study follow-up: 2.0 years
Participants	• Country: Taiwan, Colombia, Mexico, Peru, Romania, India, Russia, Brazil, China, Korea, Greece, Thailand, Malaysia, Poland, Japan, South Africa, France, Slovakia, Portugal, Israel, Czech Republic, Philippines, Bulgaria, Hungary, Hong Kong, Turkey, Belgium, Austria, USA, Spain, Germany, Switzerland, Singapore, Argentina, Netherlands, Norway, Canada, Italy, Ukraine, UK, Denmark, Australia, Finland, Sweden • Setting: multicentre • Relevant health status: participants with non-valvular AF, moderate kidney impairment (30 ≤ CrCl < 50 mL/min); aged ≥ 18 years, and at least one of the following risk factors for stroke; previous stroke or TIA, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher

RE-LY Study 2009 *(Continued)*

	heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74 years plus DM, hypertension, or coronary artery disease • Number: treatment group (2428); control group (1126) • Mean age ± SD: 75.2 ± 7.2 years • Sex (M/F): 1803/1571 • Exclusion criteria: presence of a severe heart-valve disorder; stroke within 14 days or severe stroke within 6 months before screening; a condition that increased the risk of haemorrhage; CrCl < 30 mL/min; active liver disease; pregnancy
Interventions	Treatment group • Oral dabigatran: 110 mg or 150 mg twice daily Control group • Oral warfarin: dose-adjusted (target INR 2.0 to 3.0)
Outcomes	• All strokes and systemic embolic events • All-cause mortality • Major bleeding (not included in this review because of the result from conventional ITT analysis) • Intracranial haemorrhage (not included in this review because of the result from conventional ITT analysis)
Notes	• Funding source: Boehringer Ingelheim Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to treatment groups with means of a central, interactive, automated telephone system
Allocation concealment (selection bias)	Low risk	Allocation was concealed because participants were assigned to each group using a central, interactive, automated telephone system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Dabigatran was administered in a blinded fashion, but warfarin was administered in an unblinded fashion. But we judged that incomplete blinding didn't give influence for the outcomes, because the outcomes were objective measures and the outcome assessors were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Each primary and secondary outcome event was adjudicated by two independent investigators who were unaware of the treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All outcomes were analyses in the ITT population. The information about discontinuation during study was unclear
Selective reporting (reporting bias)	Low risk	All predefined efficacy and safety outcomes were reported
Other bias	High risk	The study was funded by Boehringer Ingelheim Pharmaceuticals

ROCKET AF Study 2010

Methods	• Study design: double-blind, double-dummy RCT

ROCKET AF Study 2010 *(Continued)*

	• Study duration: 18 December 2006 to 17 June 2009 • Median duration of study follow-up: 1.9 years
Participants	• Countries: Australia, China, Hong Kong, India, Korea, Malaysia, New Zealand, Philippines, Singapore, Taiwan, Thailand, Bulgaria, Czech Republic, Greece, Hungary, Lithuania, Poland, Romania, Russia, Turkey, Ukraine, Argentina, Brazil, Chile, Colombia, Mexico, Panama, Peru, Venezuela, Canada, USA, Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, South Africa, Spain, Sweden, Switzerland, UK • Setting: multicentre • Participants with non-valvular AF, moderate kidney impairment (30≤ CrCl < 50 mL/min); aged ≥ 18 years, and a score of 2 or higher on the $CHADS_2$ risk assessment • Number: treatment group (1474); control group (1476) • Median age, IQR (years): treatment group (79; 75 to 82); control group (79, 75 to 83) • Sex (M/F): treatment group (663/811); control group (651/825) • Exclusion criteria: cardiovascular-related conditions; haemorrhage risk-related criteria; any stroke within 14 days before randomisation; TIA within 3 days before randomisation; indication for anticoagulant therapy for a condition other than AF; anaemia at the screening visit; pregnancy or breastfeeding; calculated CrCl < 30 mL/min; known significant liver disease
Interventions	Treatment group • Oral rivaroxaban: 15 mg/d Control group • Oral warfarin: dose-adjusted (target INR 2.0 to 3.0)
Outcomes	• All strokes and systemic embolic events • Major bleeding • GI bleeding • Intracranial haemorrhage
Notes	• Funding sources: Johnson & Johnson Pharmaceutical Research & Development L.L.C. (Raritan, NJ) and Bayer HealthCare Pharmaceuticals (Berlin, Germany)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to treatment groups with the use of a central 24-hour, computerized, automated voice-response system
Allocation concealment (selection bias)	Low risk	Allocation was concealed because participants were assigned to each group using a central 24-hour, computerised, automated voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Efficacy and safety outcomes were adjudicated by an independent clinical end-point committee whose members were unaware of study group assignments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Primary efficacy outcome was reported in both ITT and modified ITT population. Primary and secondary safety outcome was analysed in the modified ITT population

ROCKET AF Study 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes were analyses in the ITT population. The number of participants that discontinued during study was reported, but the reason was unclear
Other bias	High risk	The study was funded by Johnson & Johnson Pharmaceutical Research & Development L.L.C. (Raritan, NJ) and Bayer HealthCare Pharmaceuticals (Berlin, Germany)

AF - atrial fibrillation; CNS - central nervous system; CrCl - creatinine clearance; DM - diabetes mellitus; GI - gastrointestinal; INR - international normalised ratio; IQR - interquartile range; ITT - intention to treat; M/F - male/female; RCT - randomised controlled trial; SCr - serum creatinine; SD - standard deviation; TIA - transient ischaemic attack

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Caluwé 2016	Wrong intervention: rivaroxaban versus rivaroxaban plus vitamin K2 versus vitamin K antagonist
Eriksson 2003a	Pharmacokinetic/pharmacodynamic RCT of ximelagatran and melagatran
Koretsune 2015	Pharmacokinetic/pharmacodynamic RCT of 3 treatment regimens of edoxaban
Murray 2004	Pharmacokinetic/pharmacodynamic cross-over RCT of 3 treatment regimens of argatroban

RCT - randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

X-NOAC Study 2015

Trial name or title	Efficacy of rivaroxaban on renal function in patients with non-valvular atrial fibrillation and chronic kidney disease: The X-NOAC study
Methods	• Parallel RCT (1:1)
Participants	• Non-valvular AF patients with eGFR < 30 and < 89 mL/min/1.73 m^2 • Randomisation factors were age (< 75 years or ≥ 75 years), gender, anticoagulation pretreatment (none or warfarin), and the $CHADS_2$ score (< 2 or ≥ 2). The total sample size is 160 patients
Interventions	Treatment group • Oral rivaroxaban: 15 mg once daily after a meal. In addition, in cases where the CrCl was 30 to 49 mL/min, 10 mg was given orally once daily after a meal Control group • Warfarin: dose was adjusted such that PT-INR would become 2.0 to 3.0 in patients aged < 70 years or 1.6 to 2.6 in those aged ≥ 70 years
Outcomes	• The primary endpoint is the change in urinary albumin excretion, and the secondary endpoints are changes in endothelial cell function, blood coagulation/fibrinolysis, inflammation, and kidney function three months after registration
Starting date	• Not reported
Contact information	Makoto Suzuki, Department of Cardiology, Kameda Medical centre, 929 Higashi-chou, Kamogawa-city, Chiba 296-8602, Japan.

X-NOAC Study 2015 *(Continued)*

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Notes

AF - atrial fibrillation; eGFR - estimated glomerular filtration rate; RCT - randomised controlled trial

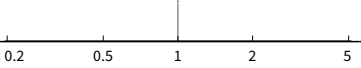
DATA AND ANALYSES

Comparison 1. Direct oral anticoagulants versus warfarin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All strokes and systemic embolic events	5	12545	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.65, 1.00]
2 Ischaemic stroke	4	8991	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.75, 1.36]
3 Haemorrhagic stroke	4	8991	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.97]
4 Major bleeding	5	12521	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.59, 1.04]
5 Myocardial infarction	1	2740	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.45, 1.90]
6 Minor bleeding	2	3012	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.58, 1.61]
7 Gastrointestinal bleeding	2	5678	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.97, 2.01]
8 Intracranial haemorrhage	5	12521	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.27, 0.69]
9 All-cause mortality	4	9595	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.05]

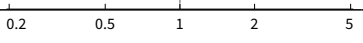
Analysis 1.1. Comparison 1 Direct oral anticoagulants versus warfarin, Outcome 1 All strokes and systemic embolic events.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE Study 2010	32/1502	40/1515		22.49%	0.81[0.51,1.28]
ENGAGE AF-TIMI 48 Study 2013	32/1379	37/1361		21.74%	0.85[0.53,1.36]
J-ROCKET AF Study 2012	4/141	5/143		2.83%	0.81[0.22,2.96]
RE-LY Study 2009	47/2428	30/1126		23.17%	0.73[0.46,1.14]
ROCKET AF Study 2010	43/1474	51/1476		29.76%	0.84[0.57,1.26]
Total (95% CI)	**6924**	**5621**		**100%**	**0.81[0.65,1]**
Total events: 158 (DOAC), 163 (Warfarin)					
Heterogeneity: Tau^2=0; Chi^2=0.31, df=4(P=0.99); I^2=0%					
Test for overall effect: Z=1.92(P=0.06)					



Analysis 1.2. Comparison 1 Direct oral anticoagulants versus warfarin, Outcome 2 Ischaemic stroke.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE Study 2010	26/1502	25/1515		29.43%	1.05[0.61,1.81]
ENGAGE AF-TIMI 48 Study 2013	25/1379	24/1361		28.3%	1.03[0.59,1.79]
J-ROCKET AF Study 2012	2/141	3/143		2.77%	0.68[0.11,3.99]
ROCKET AF Study 2010	34/1474	34/1476		39.5%	1[0.63,1.6]
Total (95% CI)	**4496**	**4495**		**100%**	**1.01[0.75,1.36]**
Total events: 87 (DOAC), 86 (Warfarin)					
Heterogeneity: Tau^2=0; Chi^2=0.22, df=3(P=0.97); I^2=0%					
Test for overall effect: Z=0.08(P=0.94)					

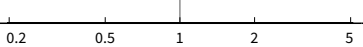


Analysis 1.3. Comparison 1 Direct oral anticoagulants versus warfarin, Outcome 3 Haemorrhagic stroke.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE Study 2010	4/1502	13/1515		30.5%	0.31[0.1,0.95]
ENGAGE AF-TIMI 48 Study 2013	6/1379	10/1361		37.45%	0.59[0.22,1.62]
J-ROCKET AF Study 2012	2/141	1/143		6.68%	2.03[0.19,22.12]
ROCKET AF Study 2010	4/1474	7/1476		25.37%	0.57[0.17,1.95]
Total (95% CI)	**4496**	**4495**		**100%**	**0.52[0.28,0.97]**
Total events: 16 (DOAC), 31 (Warfarin)					
Heterogeneity: Tau^2=0; Chi^2=2.15, df=3(P=0.54); I^2=0%					
Test for overall effect: Z=2.05(P=0.04)					

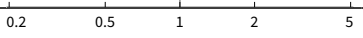
Analysis 1.4. Comparison 1 Direct oral anticoagulants versus warfarin, Outcome 4 Major bleeding.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE Study 2010	48/1493	97/1512		22.81%	0.5[0.36,0.7]
ENGAGE AF-TIMI 48 Study 2013	55/1372	72/1356		22.61%	0.75[0.54,1.06]
J-ROCKET AF Study 2012	7/141	8/143		6.5%	0.89[0.33,2.38]
RE-LY Study 2009	133/2428	62/1126		24.89%	0.99[0.74,1.33]
ROCKET AF Study 2010	66/1474	69/1476		23.2%	0.96[0.69,1.33]
Total (95% CI)	**6908**	**5613**		**100%**	**0.79[0.59,1.04]**
Total events: 309 (DOAC), 308 (Warfarin)					
Heterogeneity: Tau^2=0.06; Chi^2=10.76, df=4(P=0.03); I^2=62.84%					
Test for overall effect: Z=1.68(P=0.09)					



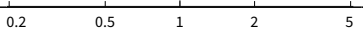
Analysis 1.5. Comparison 1 Direct oral anticoagulants versus warfarin, Outcome 5 Myocardial infarction.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ENGAGE AF-TIMI 48 Study 2013	14/1379	15/1361		100%	0.92[0.45,1.9]
Total (95% CI)	**1379**	**1361**		**100%**	**0.92[0.45,1.9]**
Total events: 14 (DOAC), 15 (Warfarin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.22(P=0.82)					



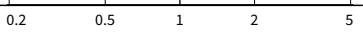
Analysis 1.6. Comparison 1 Direct oral anticoagulants versus warfarin, Outcome 6 Minor bleeding.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ENGAGE AF-TIMI 48 Study 2013	67/1372	86/1356		55.85%	0.77[0.56,1.05]
J-ROCKET AF Study 2012	32/141	25/143		44.15%	1.3[0.81,2.07]
Total (95% CI)	**1513**	**1499**		**100%**	**0.97[0.58,1.61]**
Total events: 99 (DOAC), 111 (Warfarin)					
Heterogeneity: Tau^2=0.1; Chi^2=3.33, df=1(P=0.07); I^2=70%					
Test for overall effect: Z=0.12(P=0.91)					



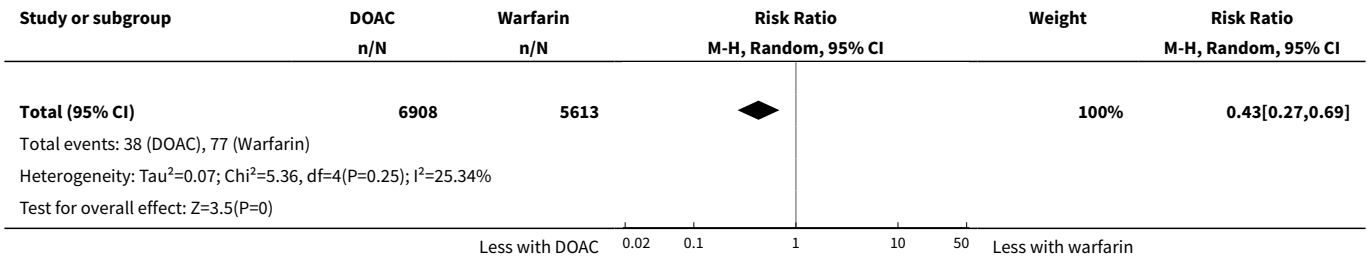
Analysis 1.7. Comparison 1 Direct oral anticoagulants versus warfarin, Outcome 7 Gastrointestinal bleeding.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ENGAGE AF-TIMI 48 Study 2013	27/1372	23/1356		43.52%	1.16[0.67,2.01]
ROCKET AF Study 2010	42/1474	26/1476		56.48%	1.62[1,2.62]
Total (95% CI)	**2846**	**2832**		**100%**	**1.4[0.97,2.01]**
Total events: 69 (DOAC), 49 (Warfarin)					
Heterogeneity: Tau^2=0; Chi^2=0.79, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=1.81(P=0.07)					

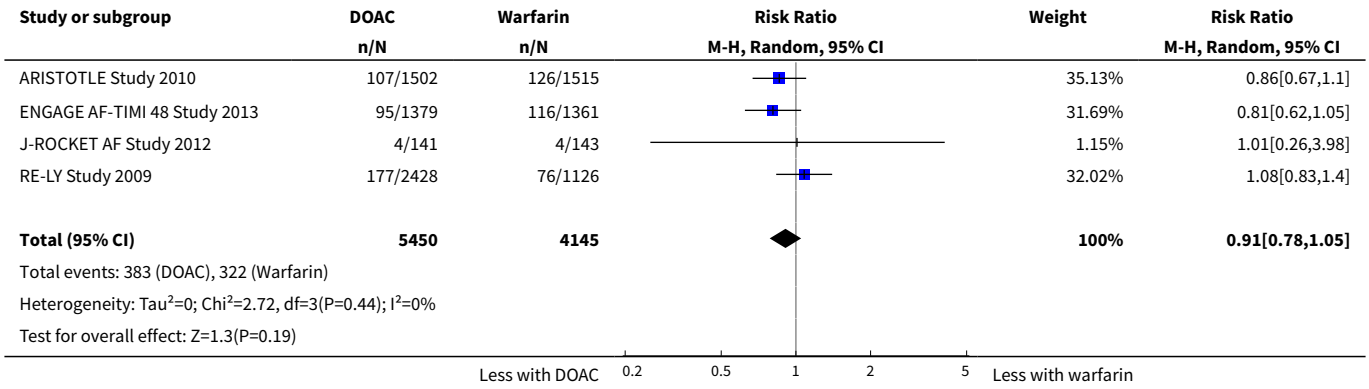


Analysis 1.8. Comparison 1 Direct oral anticoagulants versus warfarin, Outcome 8 Intracranial haemorrhage.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE Study 2010	5/1493	27/1512		18.8%	0.19[0.07,0.49]
ENGAGE AF-TIMI 48 Study 2013	10/1372	19/1356		25.88%	0.52[0.24,1.11]
J-ROCKET AF Study 2012	2/141	4/143		7.18%	0.51[0.09,2.72]
RE-LY Study 2009	11/2428	14/1126		24.79%	0.36[0.17,0.8]
ROCKET AF Study 2010	10/1474	13/1476		23.34%	0.77[0.34,1.75]



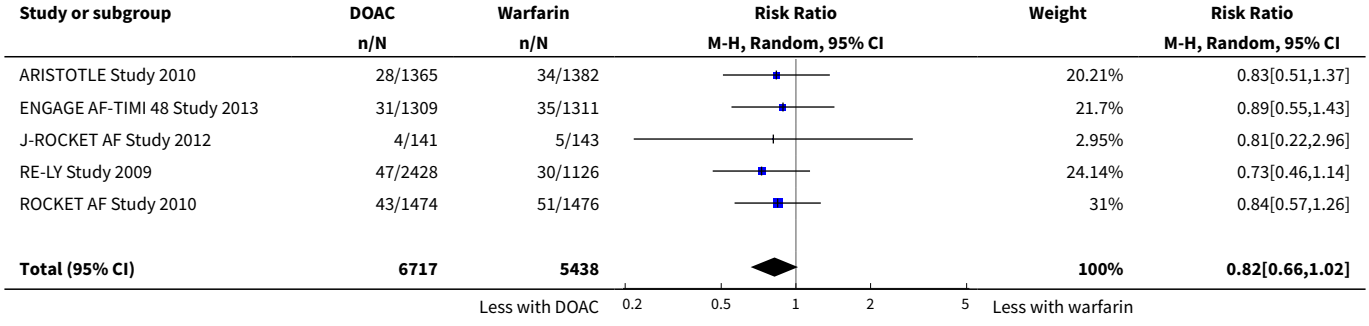
Analysis 1.9. Comparison 1 Direct oral anticoagulants versus warfarin, Outcome 9 All-cause mortality.

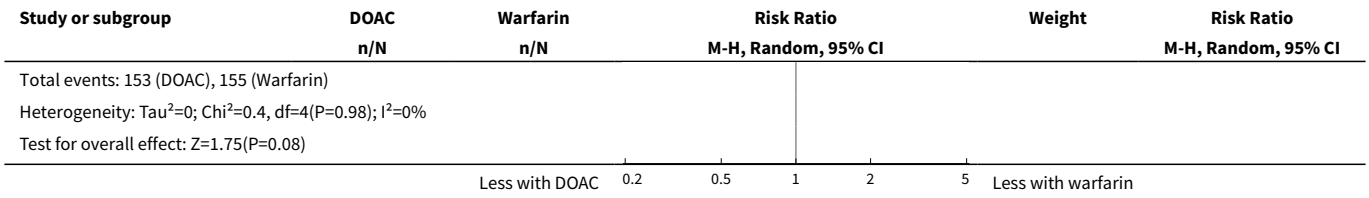


Comparison 2. Direct oral anticoagulants versus warfarin: subgroup analysis for participants with CrCl 30 to 50 mL/min

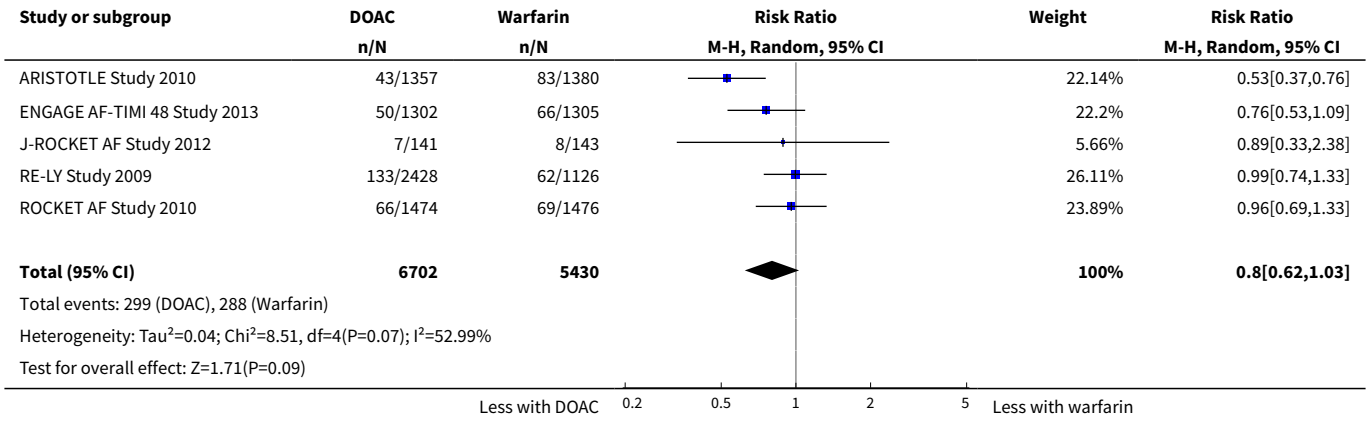
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All strokes and systemic embolic events	5	12155	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.66, 1.02]
2 Major bleeding	5	12132	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.03]

Analysis 2.1. Comparison 2 Direct oral anticoagulants versus warfarin: subgroup analysis for participants with CrCl 30 to 50 mL/min, Outcome 1 All strokes and systemic embolic events.





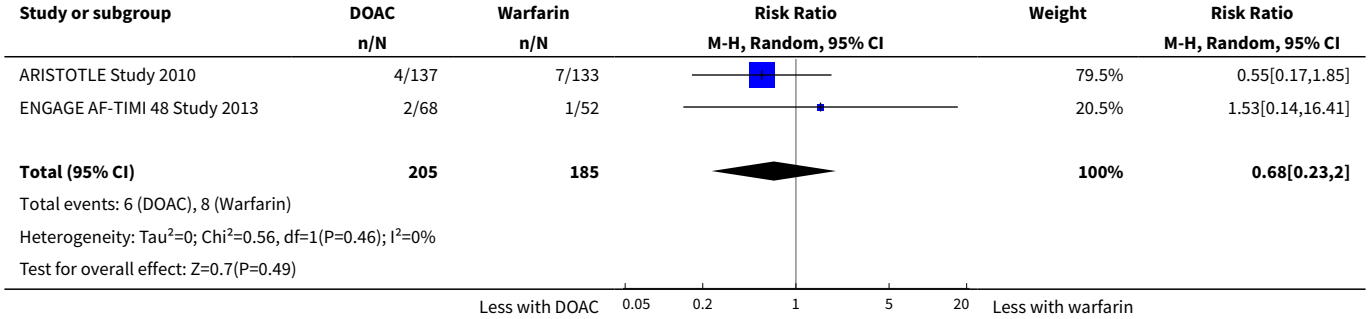
Analysis 2.2. Comparison 2 Direct oral anticoagulants versus warfarin: subgroup analysis for participants with CrCl 30 to 50 mL/min, Outcome 2 Major bleeding.



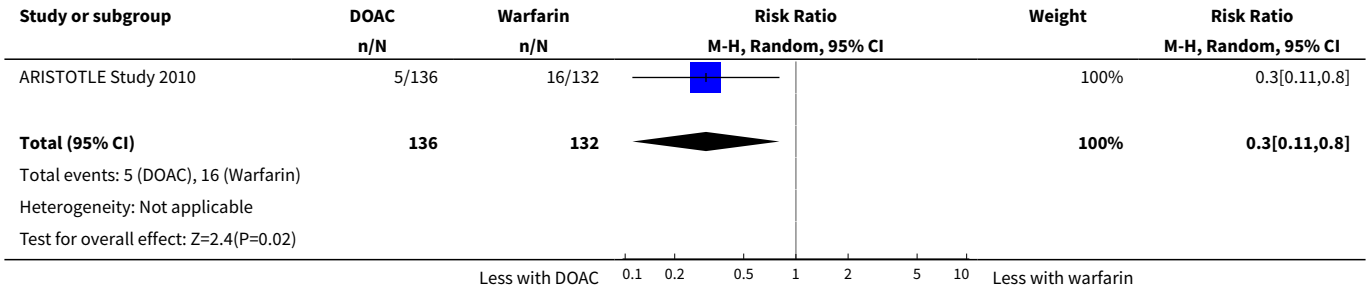
Comparison 3. Direct oral anticoagulants versus warfarin: subgroup analysis for participants with CrCl 15 to 30 mL/min

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All strokes and systemic embolic events	2	390	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.23, 2.00]
2 Major bleeding	1	268	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.11, 0.80]

Analysis 3.1. Comparison 3 Direct oral anticoagulants versus warfarin: subgroup analysis for participants with CrCl 15 to 30 mL/min, Outcome 1 All strokes and systemic embolic events.



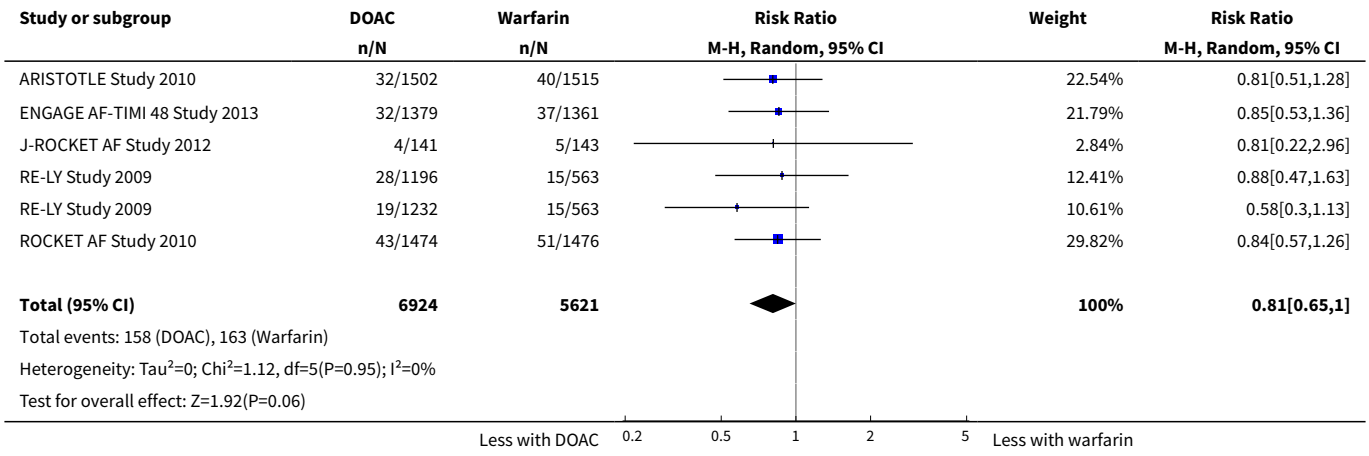
Analysis 3.2. Comparison 3 Direct oral anticoagulants versus warfarin: subgroup analysis for participants with CrCl 15 to 30 mL/min, Outcome 2 Major bleeding.



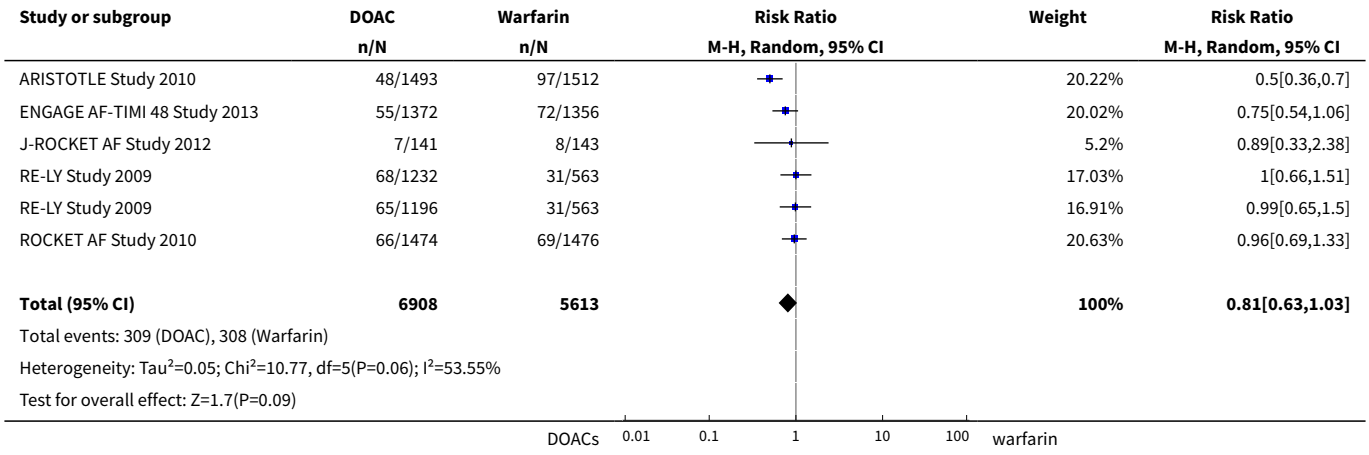
Comparison 4. Direct oral anticoagulants versus warfarin: subgroup analysis for different doses of DOAC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All strokes and systemic embolic events	5	12545	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.65, 1.00]
2 Major bleeding	5	12521	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.63, 1.03]
3 All-cause mortality	4	9595	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.05]

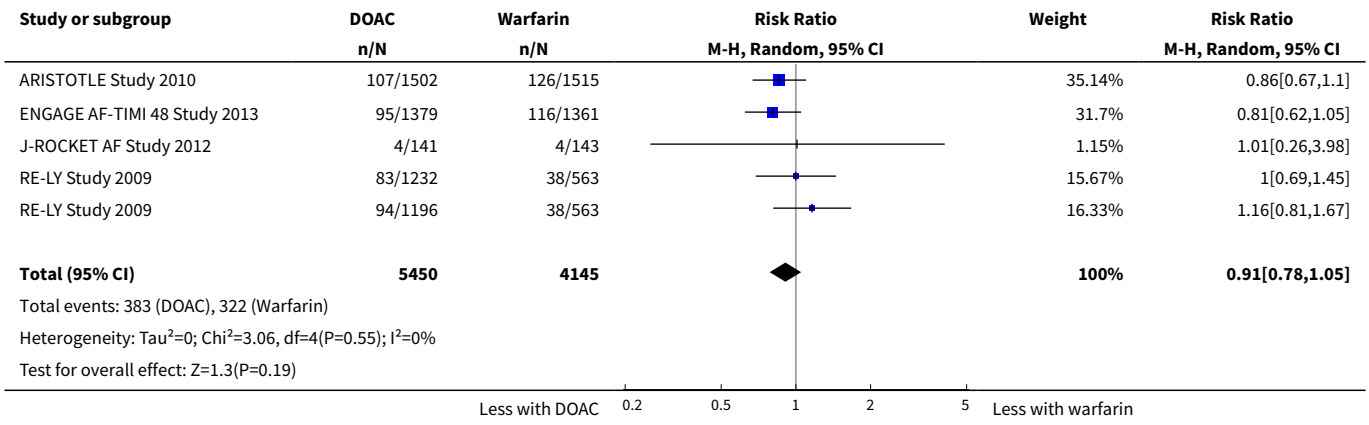
Analysis 4.1. Comparison 4 Direct oral anticoagulants versus warfarin: subgroup analysis for different doses of DOAC, Outcome 1 All strokes and systemic embolic events.



Analysis 4.2. Comparison 4 Direct oral anticoagulants versus warfarin: subgroup analysis for different doses of DOAC, Outcome 2 Major bleeding.



Analysis 4.3. Comparison 4 Direct oral anticoagulants versus warfarin: subgroup analysis for different doses of DOAC, Outcome 3 All-cause mortality.

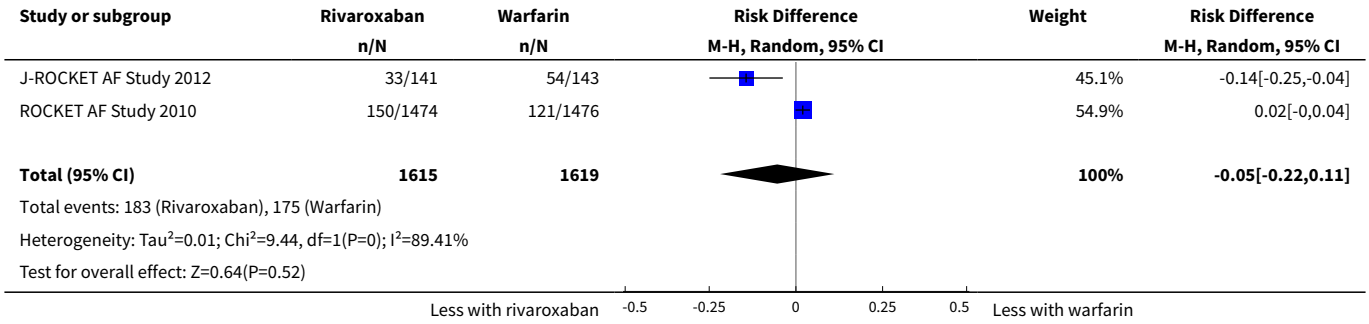


Comparison 5. Direct oral anticoagulants versus warfarin: adverse events

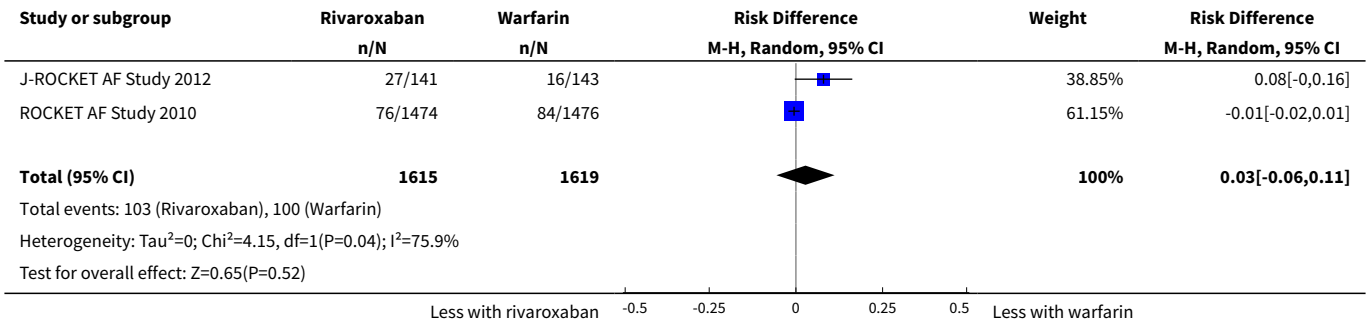
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Epistaxis	2	3234	Risk Difference (M-H, Random, 95% CI)	-0.05 [-0.22, 0.11]
2 Nasopharyngitis	2	3234	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.06, 0.11]
3 Diarrhoea	2	3234	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.04, 0.06]
4 Upper respiratory tract inflammation	2	3234	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.02, 0.01]
5 Back pain	2	3234	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.05, 0.01]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
6 Cardiac failure	2	3234	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.03, 0.01]

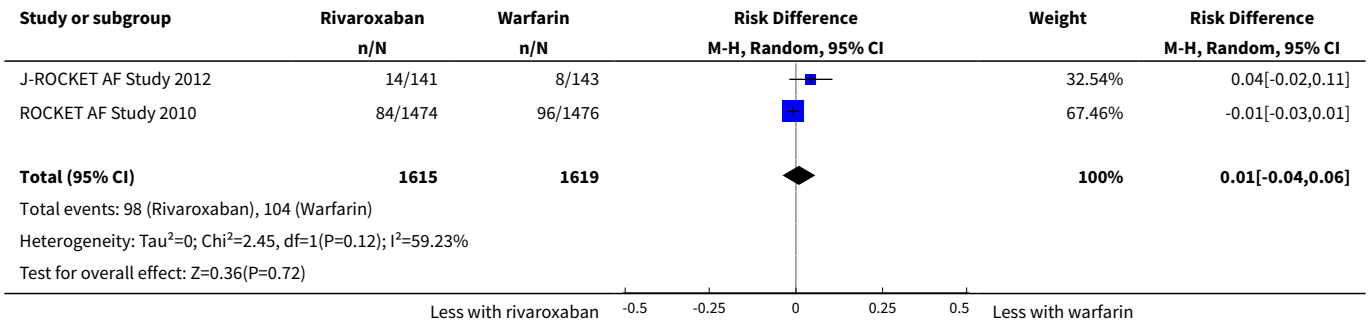
Analysis 5.1. Comparison 5 Direct oral anticoagulants versus warfarin: adverse events, Outcome 1 Epistaxis.



Analysis 5.2. Comparison 5 Direct oral anticoagulants versus warfarin: adverse events, Outcome 2 Nasopharyngitis.



Analysis 5.3. Comparison 5 Direct oral anticoagulants versus warfarin: adverse events, Outcome 3 Diarrhoea.



Analysis 5.4. Comparison 5 Direct oral anticoagulants versus warfarin: adverse events, Outcome 4 Upper respiratory tract inflammation.

Study or subgroup	Rivaroxaban n/N	Warfarin n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
J-ROCKET AF Study 2012	12/141	15/143		4.57%	-0.02[-0.09,0.05]
ROCKET AF Study 2010	62/1474	70/1476		95.43%	-0.01[-0.02,0.01]
Total (95% CI)	**1615**	**1619**		**100%**	**-0.01[-0.02,0.01]**
Total events: 74 (Rivaroxaban), 85 (Warfarin)					
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%					
Test for overall effect: Z=0.81(P=0.42)					

Analysis 5.5. Comparison 5 Direct oral anticoagulants versus warfarin: adverse events, Outcome 5 Back pain.

Study or subgroup	Rivaroxaban n/N	Warfarin n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
J-ROCKET AF Study 2012	13/141	21/143		15.66%	-0.05[-0.13,0.02]
ROCKET AF Study 2010	58/1474	74/1476		84.34%	-0.01[-0.03,0]
Total (95% CI)	**1615**	**1619**		**100%**	**-0.02[-0.05,0.01]**
Total events: 71 (Rivaroxaban), 95 (Warfarin)					
Heterogeneity: Tau^2=0; Chi^2=1.35, df=1(P=0.25); I^2=25.69%					
Test for overall effect: Z=1.07(P=0.28)					

Analysis 5.6. Comparison 5 Direct oral anticoagulants versus warfarin: adverse events, Outcome 6 Cardiac failure.

Study or subgroup	Rivaroxaban n/N	Warfarin n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
J-ROCKET AF Study 2012	20/141	17/143		5.62%	0.02[-0.06,0.1]
ROCKET AF Study 2010	104/1474	120/1476		94.38%	-0.01[-0.03,0.01]
Total (95% CI)	**1615**	**1619**		**100%**	**-0.01[-0.03,0.01]**
Total events: 124 (Rivaroxaban), 137 (Warfarin)					
Heterogeneity: Tau^2=0; Chi^2=0.68, df=1(P=0.41); I^2=0%					
Test for overall effect: Z=0.93(P=0.35)					

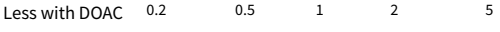
Comparison 6. Direct oral anticoagulants versus warfarin: fixed-effect model

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All strokes and systemic embolic events	5	12545	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.65, 1.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Major bleeding	5	12521	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.67, 0.92]

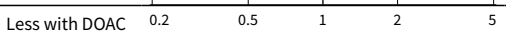
Analysis 6.1. Comparison 6 Direct oral anticoagulants versus warfarin: fixed-effect model, Outcome 1 All strokes and systemic embolic events.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ARISTOTLE Study 2010	32/1502	40/1515		22.89%	0.81[0.51,1.28]
ENGAGE AF-TIMI 48 Study 2013	32/1379	37/1361		21.41%	0.85[0.53,1.36]
J-ROCKET AF Study 2012	4/141	5/143		2.85%	0.81[0.22,2.96]
RE-LY Study 2009	47/2428	30/1126		23.56%	0.73[0.46,1.14]
ROCKET AF Study 2010	43/1474	51/1476		29.29%	0.84[0.57,1.26]
Total (95% CI)	**6924**	**5621**		**100%**	**0.81[0.65,1.01]**
Total events: 158 (DOAC), 163 (Warfarin)					
Heterogeneity: Tau^2=0; Chi^2=0.31, df=4(P=0.99); I^2=0%					
Test for overall effect: Z=1.91(P=0.06)					



Analysis 6.2. Comparison 6 Direct oral anticoagulants versus warfarin: fixed-effect model, Outcome 2 Major bleeding.

Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ARISTOTLE Study 2010	48/1493	97/1512		29.17%	0.5[0.36,0.7]
ENGAGE AF-TIMI 48 Study 2013	55/1372	72/1356		21.92%	0.75[0.54,1.06]
J-ROCKET AF Study 2012	7/141	8/143		2.4%	0.89[0.33,2.38]
RE-LY Study 2009	133/2428	62/1126		25.64%	0.99[0.74,1.33]
ROCKET AF Study 2010	66/1474	69/1476		20.87%	0.96[0.69,1.33]
Total (95% CI)	**6908**	**5613**		**100%**	**0.79[0.67,0.92]**
Total events: 309 (DOAC), 308 (Warfarin)					
Heterogeneity: Tau^2=0; Chi^2=10.76, df=4(P=0.03); I^2=62.84%					
Test for overall effect: Z=2.95(P=0)					



ADDITIONAL TABLES

Table 1. Recommendation of major regulatory agencies

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
EMA 2014	150 mg twice daily for CKD stage G3 (CrCl 30 to 50 mL/min)	2.5 mg twice daily in patients with at least two of the following characteristics:	15 mg daily for CKD stage G3 and G4 (CrCl 15 to 50 mL/min)	30 mg once daily for CKD stage G3

Table 1. Recommendation of major regulatory agencies *(Continued)*

	No recommendation for CKD stage G4	- age ≥ 80 years - body weight ≤ 60 kg - SCr > 1.5 mg/dL		and G4 (CrCl 15 to 50 mL/min)
FDA 2014	150 mg twice daily for CKD stage G3 (CrCl > 30 mL/min) 75 mg twice daily for CKD stage G4 (CrCl 15 to 30 mL/min)	2.5 mg twice daily in patients with at least two of the following characteristics: - age ≥ 80 years - body weight ≤ 60 kg - SCr > 1.5 mg/dL	15 mg daily for CKD stage G3 and G4 (CrCl 15 to 50 mL/min)	30 mg once daily for CKD stage G3 and G4 (CrCl 15 to 50 mL/min)
Health Canada 2017	110 or 150 mg twice daily for CKD stage G3 (CrCl 30 to 50 mL/min) No recommendation for CKD stage G4	2.5 mg twice daily in patients with at least two of the following characteristics: - age ≥ 80 years - body weight ≤ 60 kg - SCr > 1.5 mg/dL	15 mg daily for CKD stage G3 (CrCl 30 to 50 mL/min) No recommendation for CKD stage G4	30 mg once daily for CKD stage G3 (CrCl 30 to 50 mL/min)

CKD - chronic kidney disease; CrCl - creatinine clearance; SCr - serum creatinine

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. "atrial fibrillation":ti,ab,kw 2. "auricular fibrillation":ti,ab,kw 3. {or #1-#2} 4. (new near/3 anticoagulant*):ti,ab 5. dabigatran:ti,ab,kw 6. apixaban:ti,ab,kw 7. rivaroxaban:ti,ab,kw 8. edoxaban:ti,ab,kw 9. (thrombin next inhibit*):ti,ab,kw 10.((factor next xa next inhibit*) or (factor next 10a next inhibit*)):ti,ab,kw 11.MeSH descriptor: [Anticoagulants] this term only 12.MeSH descriptor: [Factor Xa] this term only 13.#11 and #12 14.MeSH descriptor: [Factor Xa] explode all trees and with qualifiers: [Antagonists & inhibitors - AI] 15.{or #4-#10, #13-#14} 16.{and #3, #15}
MEDLINE	1. Atrial Fibrillation/ 2. atrial fibrillation.tw. 3. auricular fibrillation

(Continued)

	4. or/1-3 5. (new adj3 anticoagulant*).tw. 6. dabigatran.tw,rn. 7. apixaban.tw,rn. 8. rivaroxaban.tw,rn. 9. edoxaban.tw,rn. 10.direct thrombin inhibit*.tw. 11.Anticoagulants/ and Factor Xa/ 12.factor xa inhibit*.tw. 13.Factor Xa/ai 14.or/5-13 15.and/4,14
EMBASE	1. exp heart atrium fibrillation/ 2. atrial fibrillation.tw. 3. auricular fibrillation.tw. 4. or/1-3 5. (new adj3 anticoagulant*).tw. 6. dabigatran/ 7. apixaban/ 8. rivaroxaban/ 9. edoxaban/ 10.dabigatran.tw. 11.apixaban.tw. 12.rivaroxaban.tw. 13.edoxaban.tw. 14.exp blood clotting factor 10a inhibitor/ 15.exp thrombin inhibitor/ 16.direct thrombin inhibit*.tw. 17.factor Xa inhibit*.tw. 18.or/5-17 19.and/4,18

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequential-

(Continued)

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	ly numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse

(Continued)

	effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias -Funding bias	*Low risk of bias:* The trial was independently funded by a government organization or universities etc.
	High risk of bias: The trial was funded by the commercial support and we are sure that there is an important risk of bias.
	*Unclear: T*he trial did not declare its funding source, or the trial was funded by the commercial support and we are not sure whether there is an important risk of bias.

CONTRIBUTIONS OF AUTHORS

1. Drafted the protocol: MK, TAF, KK, YG, S Fukuhara
2. Study selection: MK, KK, YG
3. Extracted data from studies: MK, KK, YG
4. Entered data into RevMan: MK, KK
5. Carried out the analysis: MK, KK, YG
6. Interpreted the analysis: MK TAF, KK, YG, S Fukuma, S Fukuhara
7. Drafted the final review: MK, TAF, KK, YG,
8. Disagreement resolution: MK, TAF
9. Updated the review: MK

DECLARATIONS OF INTEREST

- Miho Kimachi: none known
- Toshiaki Furukawa has received lecture fees from Eli Lilly, Janssen, Meiji, Mitsubishi-Tanabe, MSD and Pfizer. He has received royalties from Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mitsubishi-Tanabe and Mochida. These funds are not related to the production of this review.
- Kimihiko Kimachi: none known
- Yoshihito Goto: none known
- Shingo Fukuma: none known
- Shunichi Fukuhara: none known

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the terms "NOACs (New oral anticoagulants)" to "DOAC (direct oral anticoagulants)" in accordance with the recommendation of the International Society on Thrombosis and Haemostasis (ISTH). In the original protocol, we intended to distinguish the effect of DOAC on two efficacy primary outcomes: all strokes and systemic embolic events. However, all included studies reported composite outcomes for all strokes, including ischaemic and haemorrhagic stroke and systemic embolic events; we therefore assessed these as one composite outcome.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anticoagulants [adverse effects] [*therapeutic use]; Antithrombins [adverse effects] [therapeutic use]; Atrial Fibrillation [*complications]; Dabigatran [adverse effects] [therapeutic use]; Embolism [*prevention & control]; Hemorrhage [chemically induced] [epidemiology]; Pyrazoles [adverse effects] [therapeutic use]; Pyridines [adverse effects] [therapeutic use]; Pyridones [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Renal Insufficiency, Chronic [*complications]; Rivaroxaban [adverse effects] [therapeutic use]; Stroke [*prevention & control]; Thiazoles [adverse effects] [therapeutic use]; Warfarin [adverse effects] [therapeutic use]

MeSH check words

Humans