South African National Essential Medicine List
Primary Healthcare & Adult Hospital Level of Care Medication Review Process
Component: Cardiovascular conditions

MEDICINE REVIEW

Title: Evidence review of the clinical benefits and harms of Direct Oral Anticoagulants (DOACs) compared to warfarin for adult patients with chronic non-valvular atrial fibrillation (AF).

Date: 26 March 2022

Key findings

- We conducted a rapid review of evidence regarding the use of DOACs versus warfarin for adult patients with chronic non-valvular atrial fibrillation.
- We found one systematic review with meta-analysis (Jia[12] et al. which was deemed to be of critically low quality on the AMSTAR-2 rating see Figure 10 below), which included five randomized controlled trials (RCTs) that were mostly of good quality.
- Compared to warfarin, "higher dose" DOACs resulted in a reduced risk of stroke and systemic embolism (relative risk [RR] = 0.80; 95% CI, 0.71-0.91; Number needed to treat to benefit [NNT] =149 [95% CI: 103 to 331]). Low-dose DOACs had similar efficacy in reducing the risk of stroke and systemic embolism compared to warfarin (RR = 1.03; 95% CI, 0.84-1.27). Certainty of evidence: High
- DOACs reduced the risk of all-cause mortality, with a similar reduction noted whether a high dose (RR = 0.90; 95% CI, 0.85-0.95; NNT 177 [118 to 354]) or low dose DOAC regimen (RR = 0.89; 95% CI, 0.83-0.96; NNT 161 [95% CI: 104-442]) was used. Certainty of evidence: High
- Compared to warfarin, DOACs reduce the risk for major bleeding (RR = 0.86; 95% CI: 0.74-0.99; NNT 119 [95% CI: 64-1660]). Lower dose DOAC regimens probably also result in a reduced risk for major bleeding (RR = 0.63, 95% CI: 0.38-1.04). Certainty of evidence: High.
- The use of DOACs result in a lower risk of intracranial bleeding compared with warfarin use (RR = 0.48, [95% CI: 0.41-0.56]; NNT = 136 [95% CI: 120 to 161]). This reduction is more pronounced when a low dose regimen is used (RR = 0.31, [95% CI: 0.24-0.41]; NNT = 103 [95% CI: 93 to 120]). Certainty of evidence: High.
- The risk of gastrointestinal bleeding was significantly increased with the use of DOACs compared with warfarin (RR = 1.24 [95% CI: 1.10-1.39]; Number needed to harm = 224 [95% CI: 138 to 538]). This risk may be reduced with the use of low-dose DOAC regimens (RR = 0.85, [95% CI: 0.72-1.00]). Certainty of evidence: High.
- Overall, the combined results of efficacy and safety support use of the DOACs as an alternative to warfarin for the long-term prevention of stroke in patients with chronic atrial fibrillation.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			

Recommendation: The PHC/Adult Hospital Level Committee suggests that DOACs not be used for anticoagulation in atrial fibrillation.

Rationale: Direct oral anticoagulants (DOACs) have similar efficacy to warfarin in preventing ischaemic stroke and systemic embolism. They are associated with reduced mortality and lower rates of intracranial haemorrhage and major bleeding events. Despite these benefits, DOACs are not currently affordable. A rivaroxaban price reduction of at least 35% would be required for rivaroxaban to be considered as cost-effective using an ICER threshold of R100,000/QALY, while a price reduction of 75% would be required for cost-neutrality (Approximately R153.00 per patient per month).

Level of Evidence: High certainty evidence

Review indicator: Price reduction

NEMLC RECOMMENDATION (MEETING OF 31 MARCH 2022):

The medicine review and supporting economic analysis was done with consideration of the generic formulations of rivaroxaban. As the patent of the originator rivaroxaban formulation is currently still valid, the evidence review and

economic analysis needs to be updated and re-tabled at the next NEMLC meeting.

- *Medicine review – key findings:* It was recommended that the AMSTAR assessment of the critically low evidence to be added to the key findings.

NEMLC RECOMMENDATION (MEETING OF 8 DECEMBER 2022):

The Committee ratified the review and related costing analyses for DOACS for the management of AF for publication, pending editorial amendments to the costing analysis.

Monitoring and evaluation considerations
Research priorities

(Refer to the Evidence to decision framework – Appendix A)

1. Executive Summary

Date: 30 November 2021
Medicine (INN): Rivaroxaban, dabigatran, apixaban
Medicine (ATC): Antithrombotic agents B01A (B01AF01, B01AE07, B01AF02)
Indication (ICD10 code): Atrial fibrillation (I48.2)
Patient population: Adults with chronic non-valvular atrial fibrillation
Prevalence of condition: 0.5 – 3.0% in LMIC[1]
Level of Care: Primary and Adult Hospital Level
Prescriber Level: Nurse, Medical Doctor, Specialist
Current standard of Care: Warfarin
Efficacy and safety estimates:

Ischaemic stroke/Systemic embolism:

- **High dose regimen:** RR = 0.80 (95% CI 0.71-0.91); Absolute risk reduction (ARR): -0.67% (95% CI: -0.97% to -0.3%); NNT =149 (95% CI 103 to 331)
- **Low dose regimen:** RR = 1.03 (95% CI 0.84-1.27); ARR: 0.1% (95% CI -0.54% to 0.91%)

All-cause mortality:

- **High dose regimen:** RR = 0.90 (95% CI 0.85-0.95); ARR: -0.57% (95% CI -0.85% to -0.28%); NNT 177 (95%CI 118-354)
- **Low dose regimen:** RR = 0.89 (95% CI 0.83-0.96); ARR: -0.62% (95% CI -0.96% to -0.23%); NNT 161 (95% CI 104-442)

Major bleeding:

- **High dose regimen:** RR = 0.86 (95% CI 0.74-0.99); ARR: -0.84% (95% CI -1.57% to -0.06%); NNT 119 (95% CI 64 to 1660)
- **Low dose regimen:** RR = 0.63 (95% C, 0.38-1.04)

Intracranial bleeding:

- **High dose regimen:** RR = 0.48 (95% CI: 0.41-0.56); ARR: -0.74% (95% CI: -0.84% to -0.62%); NNT 136 (95% CI 120-161)
- **Low dose regimen:** RR = 0.31 (95% CI: 0.24-0.41); ARR: -0.98% (95% CI: -1.08% to -0.84%); NNT 103 (95% CI93-120)

Gastrointestinal bleeding:

- **High dose:** RR = 1.24 (95% CI: 1.10-1.39); ARR: 0.45% (95% CI: 0.19% to 0.73%); NNH 224 (9% CI 138-538)
- **Low dose:** RR = 0.85 (95% CI: 0.72-1.00); ARR: -0.28% (95% CI: -0.52% to 0%)

Motivator/reviewer name(s): Hannah May Gunter, Rephaim Mpofu, and Enkosi Mondleki
PTC affiliation: Enkosi Mondleki (Groote Schuur Hospital), Rephaim Mpofu (Red Cross War Memorial Children's Hospital)

2. Name of author(s)/motivator(s)

Hannah May Gunter, Rephaim Mpofu, Enkosi Mondleki, Tamara Kredo, Marc Blockman, Jacqui Miot, Trudy Leong

3. Author affiliation and conflict of interest details

- Hannah May Gunter, Rephaim Mpofu and Enkosi Mondleki: University of Cape Town, Groote Schuur Hospital, Department of Medicine, Division of Clinical Pharmacology
- Tamara Kredo: Cochrane South Africa, South African Medical Research Council and Division of Clinical Pharmacology, Department of Medicine, and Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University
- Marc Blockman: University of Cape Town, Groote Schuur Hospital, Adult Hospital Level Committee, National Department of Health, South Africa
- Jacqui Miot: Health Economics and Epidemiology Research Office (HE²RO), University of the Witwatersrand
- Trudy Leong: Essential Drugs Programme, Affordable Medicines Directorate, National Department of Health.

TK is partly supported by the Research, Evidence and Development Initiative (READ-It). READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies. HMB, RM, EM and MB have no conflicts of interest to declare pertaining to DOACs. JM is Chair of the clinical advisory board of Health Quality Assessment (HQA) and HE²RO receives grants from various organizations (not pertaining to DOACs for atrial fibrillation).

4. BACKGROUND

Atrial fibrillation (AF) is the most common clinically significant arrhythmia, and is characterised by uncoordinated atrial activation with consequent deterioration of atrial mechanical function.[1, 2] There is a wide variation in reported

prevalence of AF in low- and middle-income countries (LMIC), and it is uncertain whether this is due to poor surveillance, under-reporting, or a possible genetic predisposition.[3]

Patients with chronic atrial fibrillation are at risk of systemic emboli, ischaemic stroke and medication-related complications such as major bleeds, which affects morbidity and mortality. The main aims of management for patients with atrial fibrillation are that of reduction of stroke and systemic embolic risk, rate control, and the relief of symptoms attributed to atrial fibrillation.

The CHA_2DS_2-VASc score is used to stratify risk of stroke associated with non-valvular atrial fibrillation and may not be applicable to patients with atrial fibrillation and rheumatic mitral valve disease. A score of 2 or more is generally considered to be a risk of thromboembolism, and warfarin therapy is indicated. Anticoagulation can be considered for patients with a score of 1. The higher the score, the greater the risk of stroke and therefore the more compelling the use of effective anticoagulation.[4]

Warfarin, a vitamin K antagonist, is the anticoagulant recommended in the Adult Hospital level Standard Treatment Guideline and Essential Medicines List, 2019.[5] Anticoagulation is aimed at preventing thrombo-embolic events. Warfarin is usually prescribed at a starting oral dose of 5 mg, and the dose is adjusted according to the international normalised ratio (INR). Known difficulties with warfarin are that it has a narrow therapeutic index that requires frequent INR monitoring with dose adjustments, and is associated with many drug-drug and drug-food interactions.[6]

A motivation was received for the inclusion of the direct acting oral anticoagulants (DOACs) on the National Essential Medicines List for chronic non-valvular atrial fibrillation at secondary level of care. DOACs have been registered by the Medicines Control Council (now South African Health Products Regulatory Authority) and are available on the South African market. DOACs directly inhibit coagulation factors, with dabigatran inhibiting thrombin, and rivaroxaban and apixaban inhibiting factor Xa. As therapeutic alternatives to warfarin, DOACs have a more predictable pharmacokinetic profile, do not require frequent monitoring, have less reported drug-drug or drug-food interactions, and are easier to administer compared to warfarin.[7] They are also thought to result in less major bleeding overall, particularly intracranial bleeding. On the other hand, an increase in gastrointestinal (GI) bleeding has been reported with the use of DOACs compared to warfarin.[6] Additionally, unlike for warfarin, accessibility to reversal agents for DOACs that may be required in the event of over-anticoagulation or toxicity is limited.[8] These relative benefits and harms of DOACs will be important in the assessment of their overall efficacy and safety.

A review of the available evidence follows to compare the efficacy of warfarin to the direct acting oral anticoagulants (also known as new/novel oral anticoagulants) to prevent thromboembolic events in patients with non-valvular atrial fibrillation.

5. OBJECTIVE AND RESEARCH QUESTION:

Amongst adult patients with chronic non-valvular atrial fibrillation, are the direct acting oral anticoagulants (DOACs) more efficacious than warfarin in preventing ischaemic stroke, systemic embolism and mortality, and safer than warfarin with regards to major bleeds?

PICO framework of the technical review

- **Population:** Adults with non-valvular atrial fibrillation, otherwise unspecified
- **Intervention:** DOACs (rivaroxaban, apixaban, dabigatran) (therapeutic review). Where applicable, data were analysed by subgroup according to whether a high-, or low-dose regimen was used. High dose regimens included all data where the highest dose was used in the study, even if the study only had one intervention dose arm. The low dose subgroup was limited to studies that had intervention arms with multiple dosage regimens.
- **Comparison:** Warfarin

Outcome: Mortality, ischaemic stroke, systemic embolism, major bleeds. We also assessed intracranial and gastrointestinal bleeding separately due to their clinical importance as subgroups of major bleeding.

6. METHODS

PubMed, the Cochrane Database of Systematic Reviews, Epistemonikos databases were searched up to 12 October 2021, and references of systematic reviews were scanned. There was no restriction on date, language, or publication status. We also looked at the clinical guidelines such as National Institute for Health and Care Excellence, American College of Cardiology, Canadian Agency for Drugs and Technologies in Health, American Society of Hematology, and European Society of Cardiology. The search strategy was adapted for each database used (Appendix A). Included were systematic reviews of randomized controlled trials. We only included studies that had a direct comparison between DOACs (including edoxaban, not SAHPRA-registered) and warfarin.

The most up to date systematic review with the highest quality was then selected for further reporting. We cross checked that all trials reported in other reviews were also reported in the up to date, high quality review.

a. Excluded studies:

Most studies initially screened were excluded as they did not match the pre-specified PICO framework for the review. We also excluded trials, case reports, case series, and narrative reviews.

b. Data extraction

Three reviewers independently assessed the screened systematic reviews for eligibility. We determined the list of eligible systematic reviews based on their relevance by discussion and assessed their quality. Reviewers independently assessed the quality of the selected systematic review, and consensus was reached by discussion. The most appropriate systematic review was selected based its recency and quality.

Eligible trials information and outcome data were extracted from the eligible systematic review by a single reviewer and verified by the other 2 reviewers and were reported in Table 1. We extracted point estimates of effects and their respective 95% confidence interval bounds. Due to the presence of double counting in the reviewed meta-analysis, we reported point estimates and confidence intervals from subgroup analyses where applicable rather than the overall pooled estimates and corresponding confidence intervals. Numbers needed to treat to benefit (NNTB) or harm (NNTH) were obtained by using baseline risks of outcomes that were calculated from the extracted data with inverse variance weighting (Appendix Table 1).

We assessed the study quality of the potentially eligible systematic reviews using AMSTAR-2, a critical appraisal tool for systematic reviews that include randomised and non-randomised studies.[9] Risk of bias from individual studies was assessed using the modified Cochrane Collaboration risk of bias tool.[10] Certainty of evidence was assessed using the GRADE framework, and the summary of findings table was created in GRADEPro.[11]

Sensitivity analysis

Our literature search identified the meta-analysis by Jia[12] et al. as the most appropriate report for this review, however, it was still deemed to be of critically low quality on the AMSTAR-2 rating. Major concerns included the presence of double-counting of control groups in estimate pooling, the lack of *a priori* protocol formulation or reporting indicating a pre-specified analysis plan, and significant heterogeneity in the majority of pooled analyses without any reported attempt to investigate for potential causes. In addition, the meta-analysis included trials that assessed edoxaban, which was not part of the original PICO definition, and we wanted to assess whether the inclusion of these data would significantly affect the magnitude and/or direction of results. We therefore conducted a separate meta-analysis by extracting the data from the studies that were included in our primary review, namely RE-LY[13], ROCKET-AF[14], J-ROCKET-AF[15], ARISTOTLE[16], and ENGAGE-AF-TIMI 48[17]. The outcomes used were in accordance with the pre-specified PICO definition. In addition, we also analysed intracranial bleeding and major

gastrointestinal bleeding separately. Risk ratios were calculated to assess the measure of effect, as well as 95% confidence intervals for each of the pooled estimates. The inverse variance and random effects methods were used for this sensitivity analysis. Heterogeneity was assessed using the I^2 statistic. In order to prevent double counting of participants from control treatment arms and to assess potential differences in efficacy and safety between dosage regimens, 3 separate analyses were conducted to assess the outcomes, stratified by treatment regimen: 1) all dosage regimens, which included all studies and participants regardless of dosage administered, 2) low dosage regimens, which was limited to participants in studies that received a low dosage regimen in a multi-dose treatment trial, i.e. RE-LY[13] and ENGAGE-AF-TIMI 48[17], and 3) high dosage regimens, which only included participants in studies that received a high dosage regimen in a multi-dose treatment trial (RE-LY[13] and ENGAGE-AF-TIMI 48[17]). Finally, we assessed whether the inclusion of studies assessing edoxaban would significantly alter the magnitude and/or direction of effect by comparing the forest plots with, and without, these data.

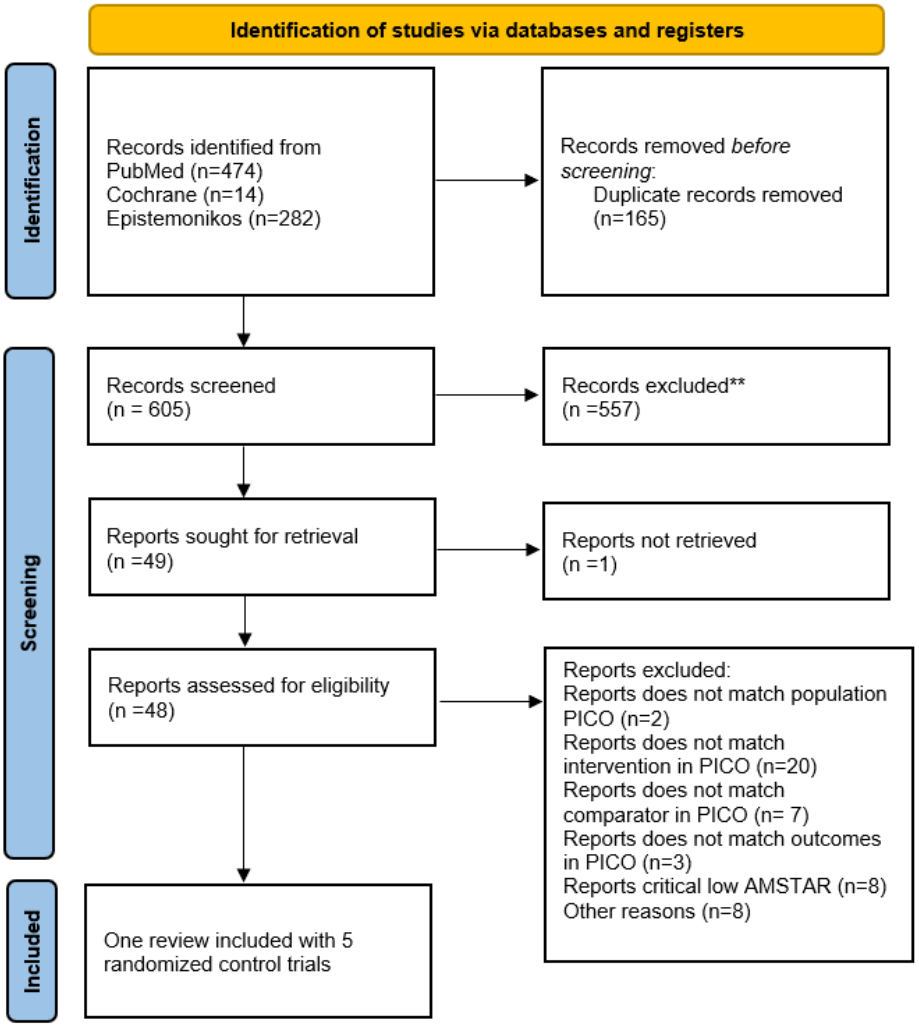

Figure 1. PRISMA flow-chart detailing study identification, selection, and exclusion

7. RESULTS

Table 1. Characteristics of the studies and treatments included in the systematic review by Jia et al (2014)

Characteristics	Dabigatran RE-LY[13]	Rivaroxaban ROCKET-AF[14]	Apixaban ARISTOTLE[16]	J–ROCKET-AF[15]	ENGAGE, AF-TIMI 48[17]
Number of participants (n)	18 113	14 264	18 201	1 278	21 105
Experimental Drug	Dabigatran 150 mg or 110 mg, twice daily	Rivaroxaban 20 mg or 15 mg (RDA), once daily	Apixaban 5 mg or 2,5 mg (RDA), twice daily	Rivaroxaban 15mg or 10mg (RDA), once daily	Edoxaban 60mg or 30mg, once daily
Experimental (n)	12 091	7 131	9 120	639	14 036
High dose	6 076	5 624	8 702	498	7 035
Low dose	6 015	1 597	428	141	7 034
Control drug	Warfarin dose-adjusted to INR 2-3, once daily	Warfarin dose-adjusted to INR 2-3, once daily	Warfarin dose-adjusted to INR 2-3, once daily	Warfarin dose-adjusted to INR 1.6-2.6 ≥ 70yrs; INR 2-3 <70yrs, once daily	Warfarin dose-adjusted to INR 2-3, once daily
Control (n)	6 022	7 133	9 081	639	7 036
Mean TTR (%)	64.4	55.2	62.2	44	64.9
Median TTR (%)	67	58	66	-	68.4
Trial Phase	III	III	III	III	III
Design of randomised control trial	Multicentre, PROBE†	Multicentre double-blind	Multicentre double-blind	Multicentre double- blind, double-dummy	Multicentre double-blind, double- dummy
Adjudicating committee & blinded adjudication of outcomes	Yes	Yes	Yes	Yes	Yes
Interim analysis (n)	2	1	1	1	1
Analysis type	Non-inferiority	Non-inferiority	Non-inferiority	Non-inferiority	Non-inferiority
Non-inferiority margin	Relative risk < 1.46	Relative risk < 1.46	Relative risk < 1.38	Relative risk < 2	Relative risk<1.38
Main efficacy outcome	Stroke and SEE	Stroke and SEE	Stroke and SEE	Stroke and SEE	Stroke and SEE
Main efficacy population	Intention-to-treat	Per protocol	Intention-to-treat	Intention-to-treat and Per protocol	Intention-to-treat
Main safety outcome	Major bleeding	Clinically relevant bleeding	Major bleeding	Major & non-major bleeding	Major bleeding
Main safety population	Safety population	Safety population	Safety population	Safety population	Safety population
Secondary efficacy outcomes	IS, HS, all-cause mortality, and MI Safety – ICB and GIT bleeding	IS, HS, all-cause mortality, and MI Safety – ICB and GIT bleeding	IS, HS, all-cause mortality, and MI Safety – ICB and GIT bleeding	IS, HS, all-cause mortality, and MI Safety – ICB and GIT bleeding	IS, HS, all-cause mortality, and MI Safety – ICB and GIT bleeding
Quality of evidence§	Poor	Good	Good	Good	Good
Median length follow-up (days)	730	707	657	584	907

*After treatment discontinuation

GIT: gastrointestinal; HS: haemorrhagic stroke; ICB: intracranial bleeding; INR: International normalized ratio; IS: ischaemic stroke;

†PROBE: prospective, open-label, blinded endpoint; RDA: renal dose adjusted, SEE: systemic embolic events; TTR: time in therapeutic range

§See Figure 11 for risk of bias summary

8. Evidence synthesis

a. Ischaemic stroke and systemic emboli

The pooled risk of stroke and systemic embolism in patients randomised to DOACs was 20% lower (RR = 0.80 95% CI, 0.71-0.91, Figure 2) than those randomised to warfarin (high certainty evidence). This benefit was mostly driven by the large reduction of haemorrhagic stroke (RR = 0.50; 95% CI, 0.41-0.62, Figure 3).

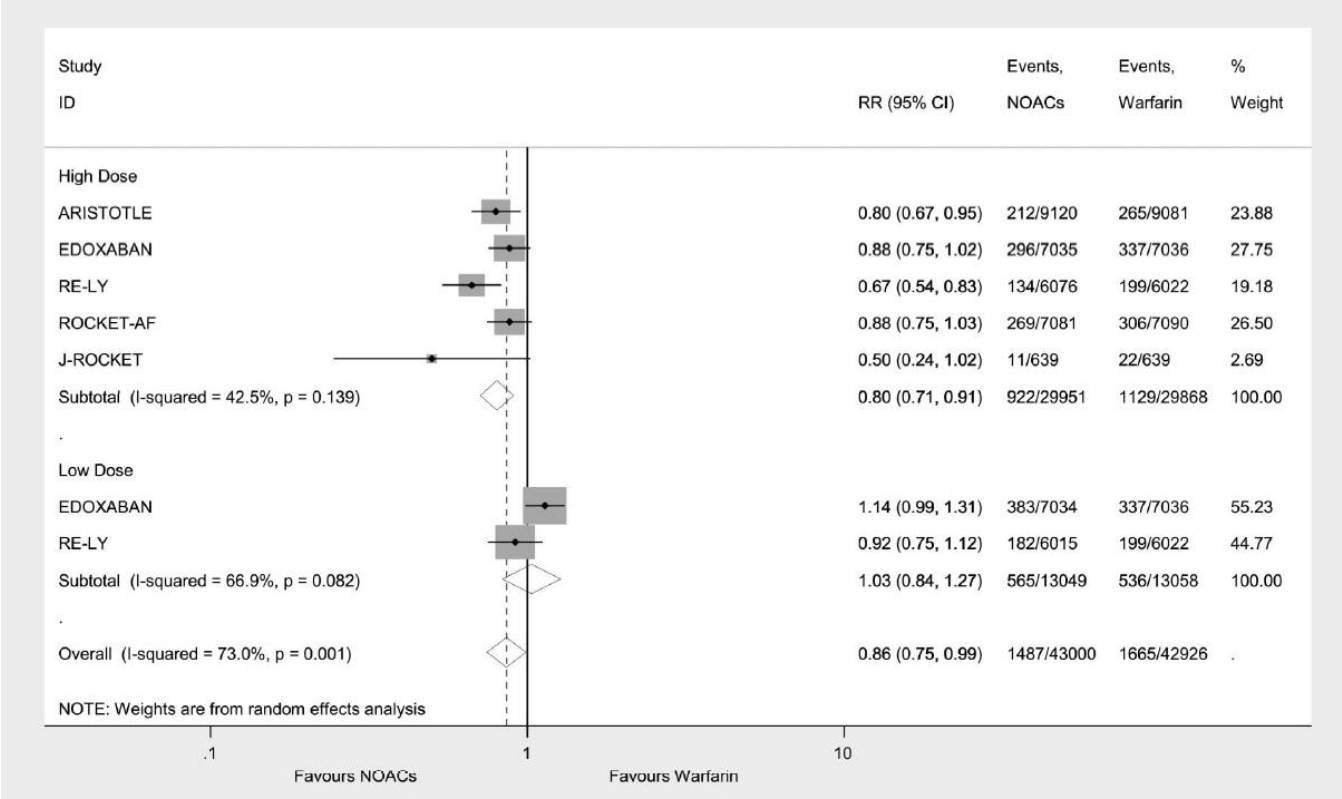

Figure 2. Meta-analysis of stroke and systemic embolism for high dose and low dose regimens, by Jia et al (2014).[12]

For low-dose regimens, DOACs demonstrated similar efficacy to warfarin for prevention of stroke and systemic emboli in each study (RR = 1.03; 95% CI, 0.84-1.27). If differentiated by stroke types, the large reduction in the risk of haemorrhagic stroke (RR = 0.33; CI, 0.23-0.46) was offset by the increase in ischaemic stroke (RR = 1.31; 95% CI, 1.14-1.49). The number needed to treat to prevent one additional ischaemic stroke or systemic embolism (NNTB) was 149 (95% CI: 103-331) for high dose regimens.

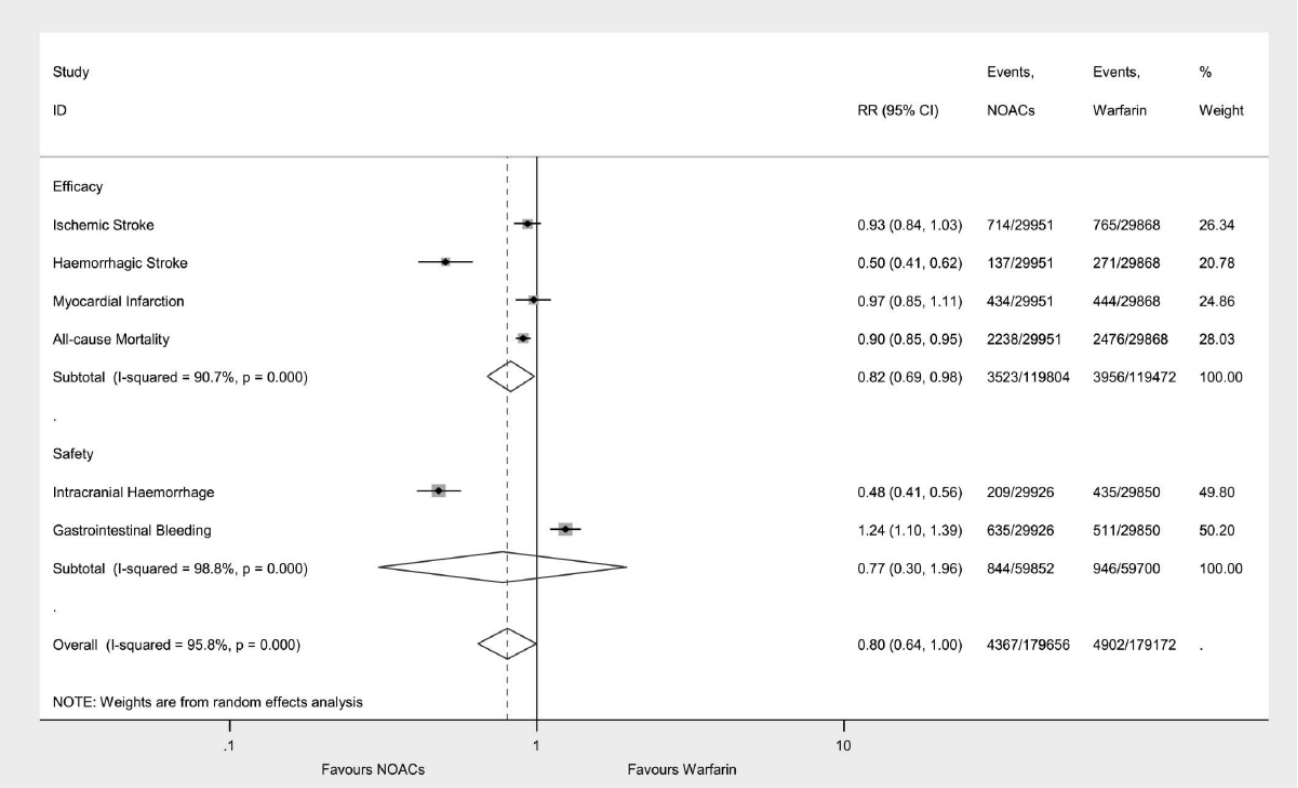

Figure 3. Forest plot of efficacy and safety for high-dose regimen, by Jia et al (2014).[12]

b. <u>All-cause mortality</u>

Compared with warfarin, DOACs were associated with a reduced risk for mortality The high dosage regimen was associated with a relative risk reduction of 10% (RR = 0.90 [95% CI: 0.85-0.95]), and the low dosage regimen was associated with a relative risk reduction of 11% (RR = 0.89 [95% CI: 0.83-0.96], Figure 4; Certainty of evidence: High). The numbers needed to treat to prevent one additional death (NNTB) were 177 (95% CI: 118-354) for the high dose regimen, and 161 (95% CI: 104-442) for the low dose regimen.

c. <u>Major bleeding</u>

Overall, the risks for major bleeding associated with the use of a high dose regimen of DOACs were lower compared with warfarin use (RR = 0.86 [95% CI: 0.74-0.99], Figure 5*;* Certainty of evidence: High). Lower dose DOAC regimens probably reduce major bleeding (RR = 0.63, 95% CI: 0.38-1.04). The number needed to treat with a high dose DOAC to prevent one major bleed is 119 (95% CI: 64-1660).

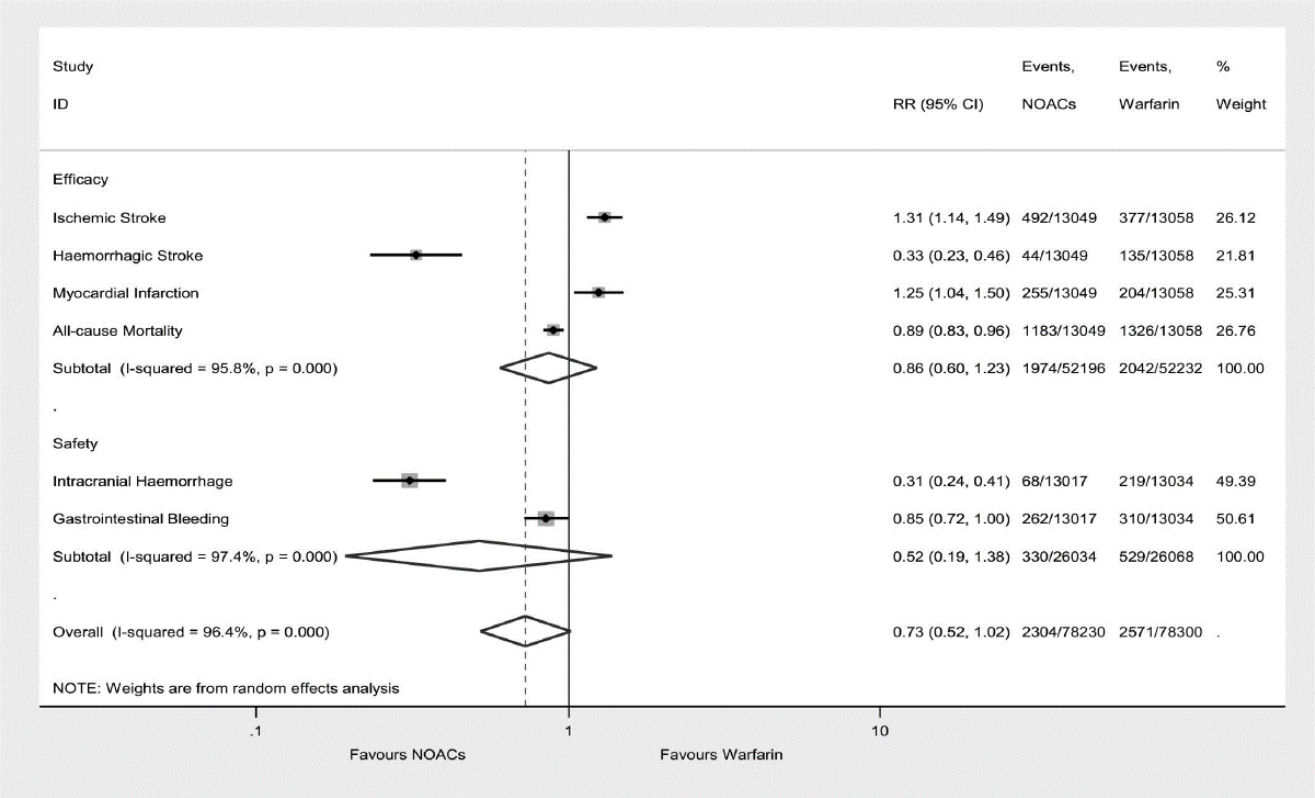

Figure 4. Forest plot of efficacy and safety for low-dose regimen by Jia et al (2014).[12]

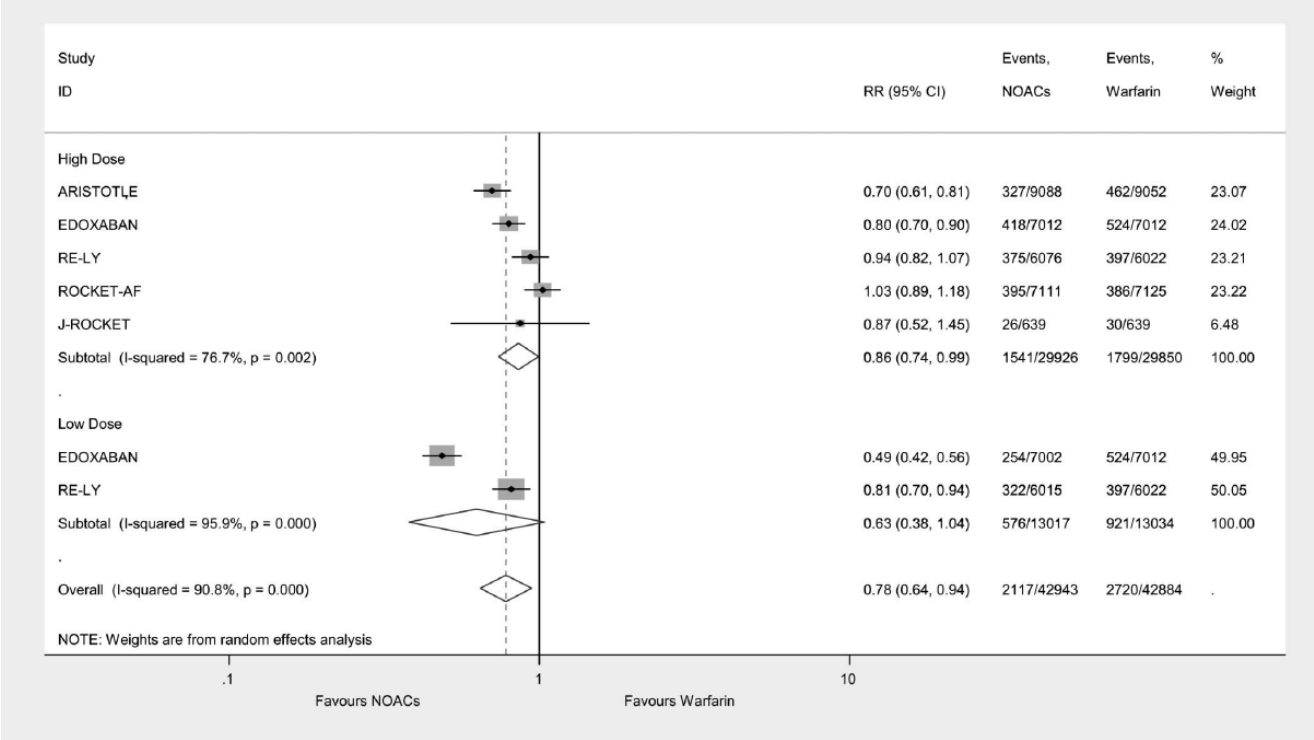

Figure 5. Forest plot of major bleeding for high-dose and low-dose regimen, Jia et al (2014).[12]

Intracranial bleeding

The use of DOACs resulted in a large reduction in intracranial bleeding risk, with a 69% relative decrease observed when a low dose regimen was compared with warfarin therapy (RR = 0.31, [95% CI: 0.24-0.41]; Figure 3), and a relative risk reduction of 52% when high dose DOAC regimens were compared with warfarin (RR = 0.48, [95% CI: 0.41-0.56]; Figure 4; Certainty of evidence: High). The numbers needed to treat to prevent one additional episode of intracranial haemorrhage (NNTB) were 136 (95% CI: 120-161) and 103 (95% CI: 93-120) using high-, and low-dose regimens respectively.

Gastrointestinal bleeding

There was an increased risk of gastrointestinal bleeding with high-dose DOAC regimens compared with warfarin (RR = 1.24 [95% CI: 1.10-1.39]; Certainty of evidence: High). However, this risk was reduced when low-dose DOAC regimens were used (RR = 0.85, [95% CI: 0.72-1.00]). The number needed to treat to cause (NNTH) one additional episode of GI bleeding with the high dose regimen was 224 (95% CI: 138-538).

9. Sensitivity analysis

Sensitivity analyses assessing outcomes that considered all dosage regimens with the exclusion of edoxaban-related trials (i.e. ENGAGE-AF-TIMI 48[17]) were similar in direction and magnitude (Figure 6) when compared with the data from the reviewed meta-analysis. When edoxaban data were excluded for the outcome of mortality, a minor change in risk ratio was noted from 0.90 (95% CI: 0.85-0.94) when edoxaban studies included, to 0.89 (95% CI: 0.83-0.96) without edoxaban studies. For the composite outcome of ischaemic stroke and systemic embolism, the risk ratio changed from 0.82 (95% CI: 0.74-0.90) to 0.85 (95% CI: 0.77-0.93). For the outcome of major bleeding, the risk ratio changed from 0.85 (95% CI: 0.69-1.03) to 0.91 (95% CI: 0.75-1.09). Similarly, the outcomes of intracranial bleeding and gastrointestinal bleeding also showed non-significant changes from 0.47 (95% CI: 0.34-0.63) to 0.44 (95% CI: 0.35-0.55) with, and without, edoxaban-related studies, and from 1.10 (95% CI: 0.81-1.50) to 1.07 (95% CI: 0.84-1.37) with, and without, edoxaban-related studies respectively. Therefore, the inclusion of edoxaban-related studies in the main evidence synthesis does not change the interpretation or outcomes of this therapeutic review. Other sensitivity analyses to assess the potential influence of double-counting noted in the main therapeutic review also showed a similar direction of effect, though the point estimates differed slightly. (Figure 7-9).

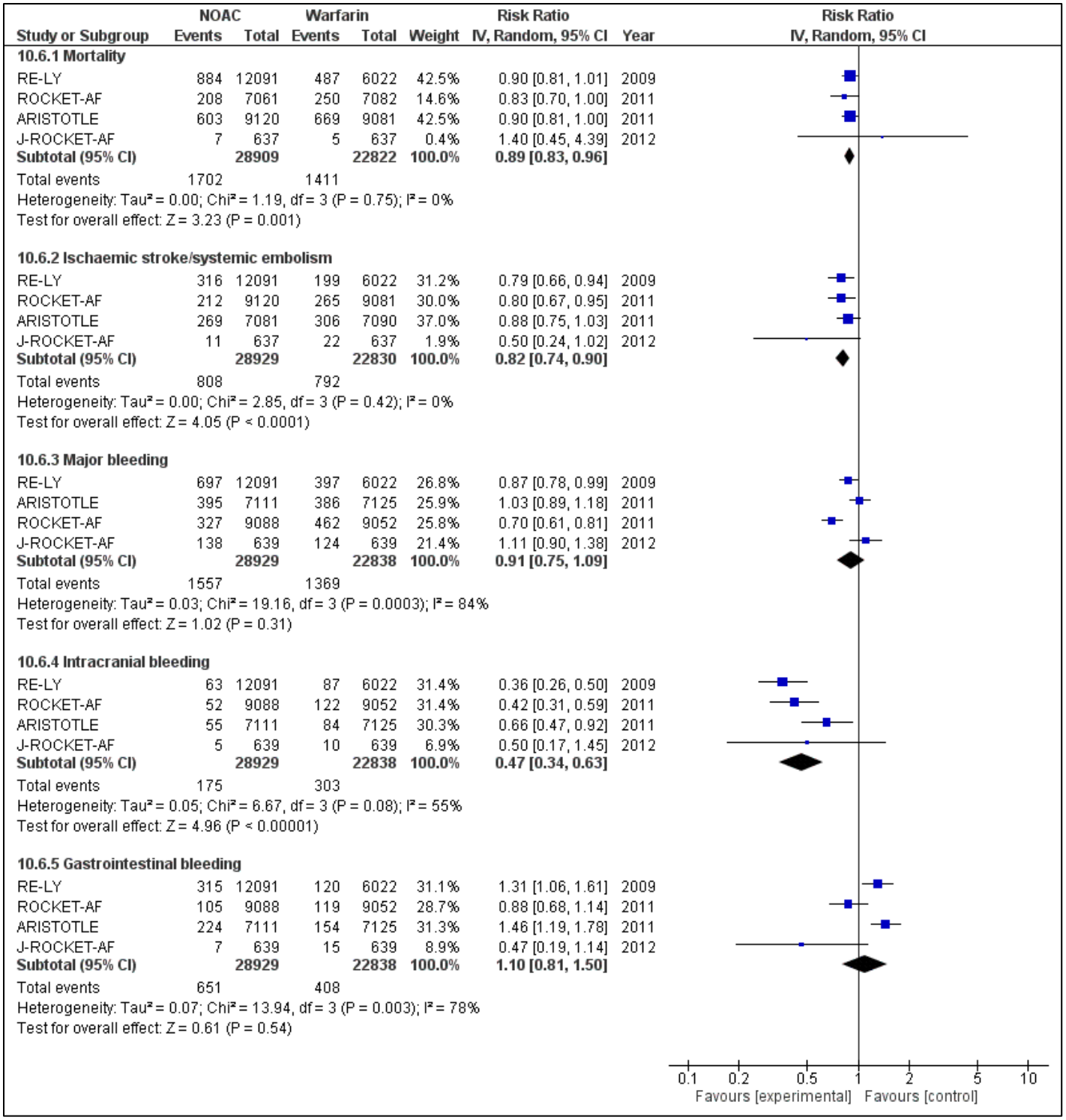

Figure 6. Sensitivity analysis forest plot assessing outcomes using all dosage regimens excluding edoxaban studies

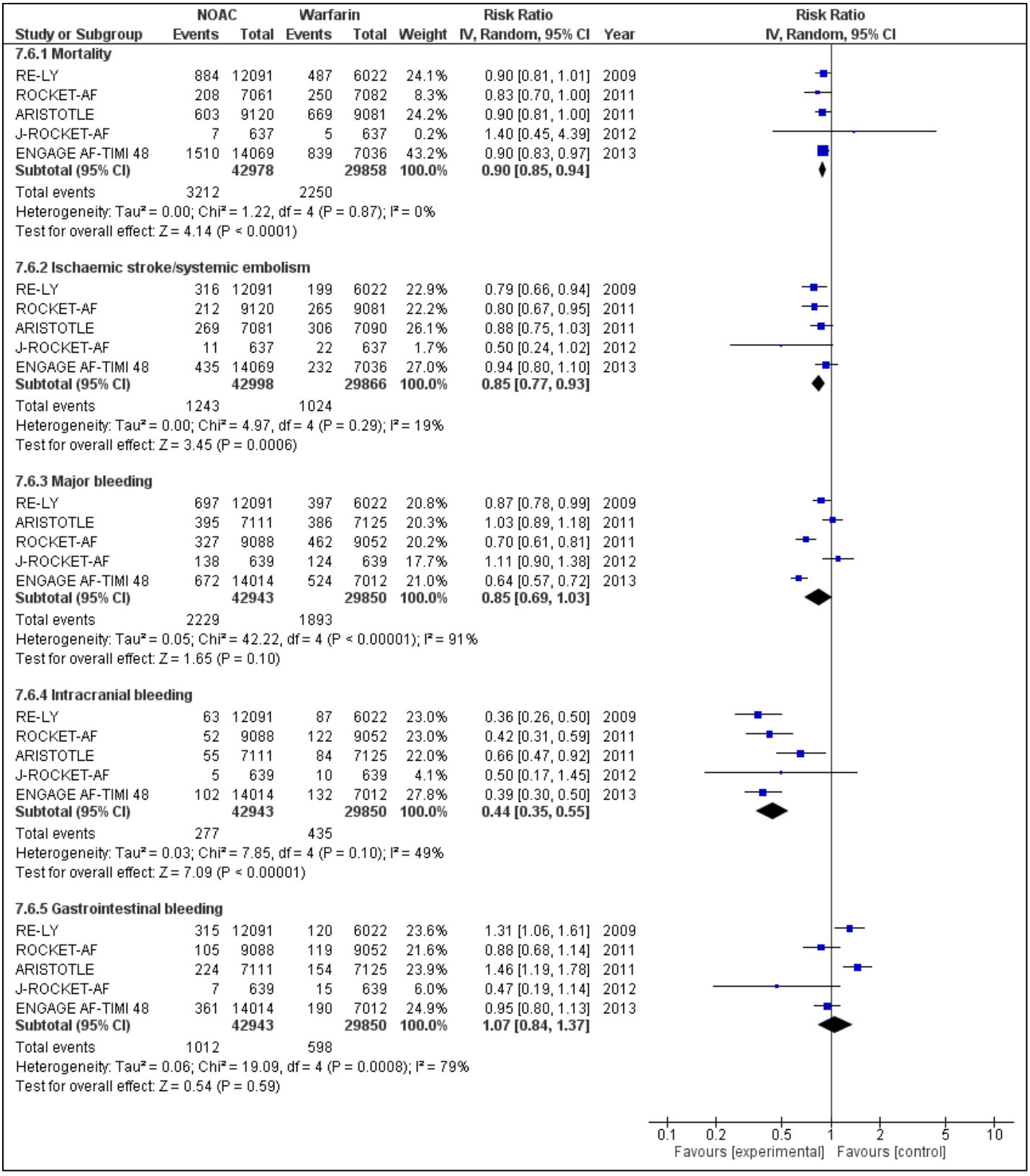

Figure 7. Sensitivity analysis forest plot assessing outcomes using all dosage regimens including edoxaban studies

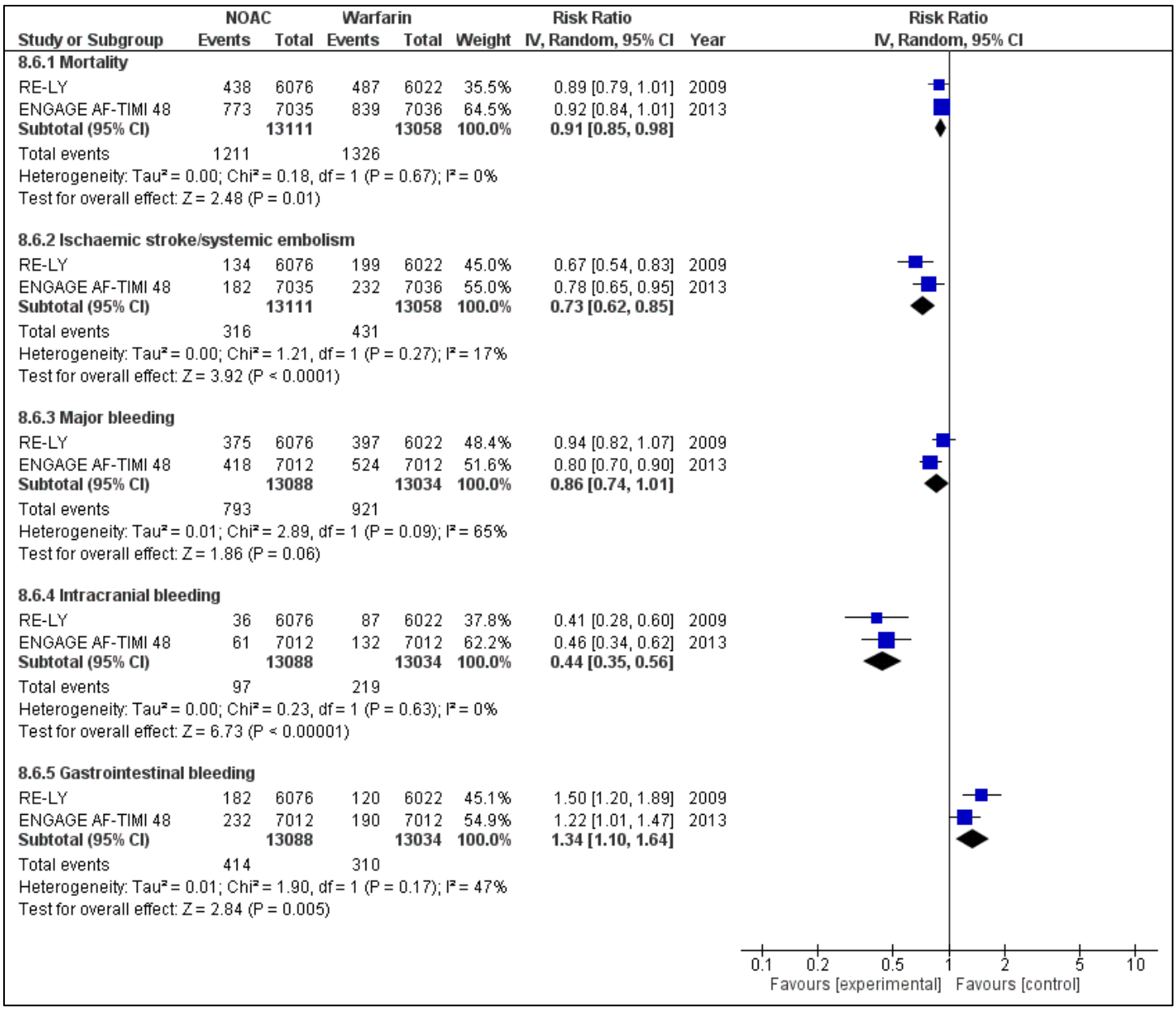

Figure 8. Sensitivity analysis forest plot assessing outcomes using high dosage regimens

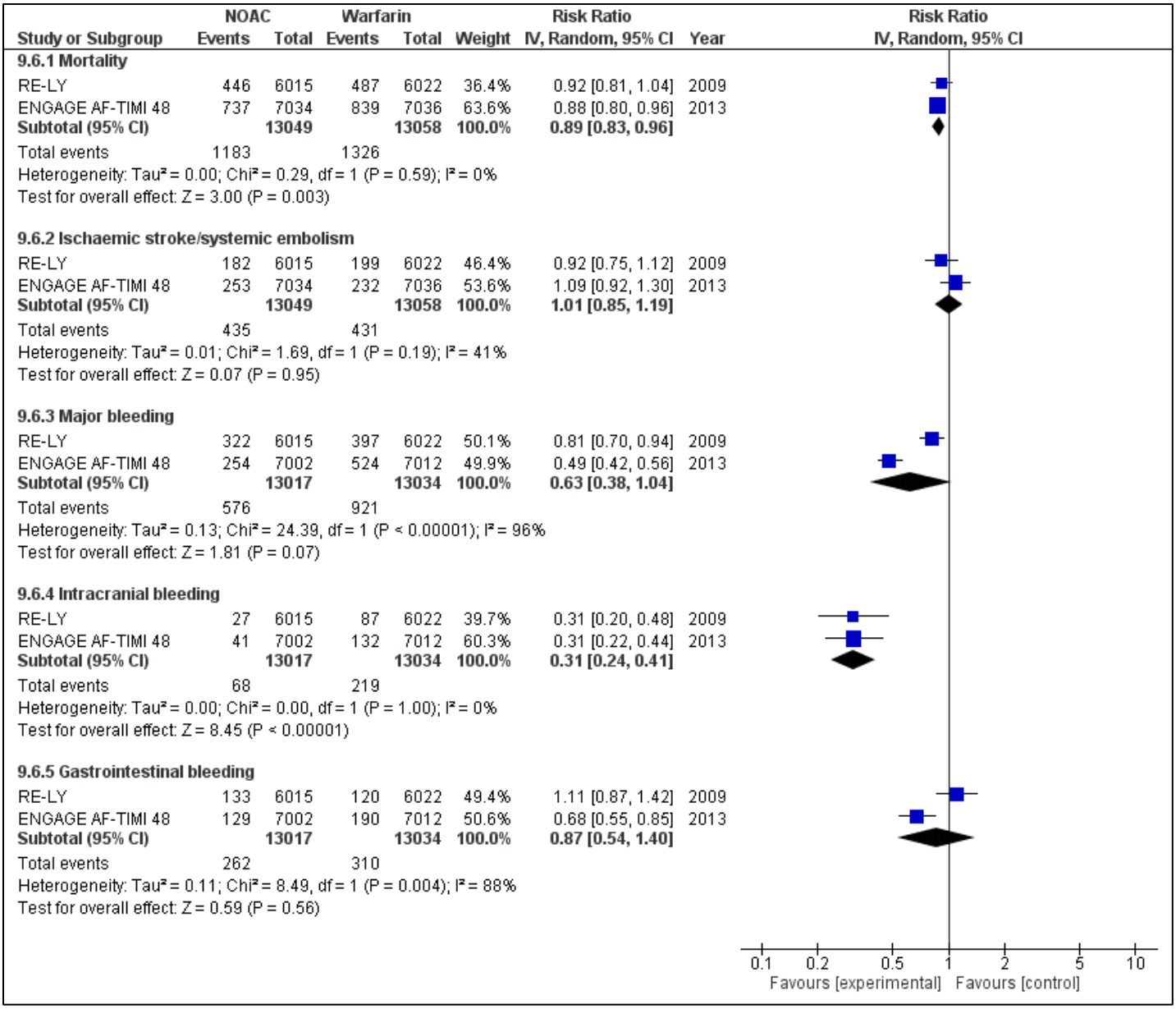

Figure 9. Sensitivity analysis forest plot forest plot assessing outcomes using low dosage regimens

Table 2. Excluded studies

Citation	Reference	Reason for exclusion
[18]	Adam, 2012	Critical low score on AMSTAR tool.
[19]	Almutairi, 2017	Population included those with DVT, not in keeping with PICO
[20]	Antza, 2019	Network meta-analysis with head-to-head comparisons
[21]	Bates, 2017	Outcomes and interventions not in keeping with PICO
[22]	Biondi-Zoccai, 2013	Network meta-analysis with head-to-head comparisons
[23]	Briere, 2019	No meta-analysis conducted
[24]	Caldeira, 2015	Edoxaban included in meta-analyses, not in keeping with PICO for this review
[25]	Canadian Agency for Drugs and Technologies in Health, 2012	Health technology appraisal summary, no new data synthesis included
[26]	Chai-Adisaksopha, 2014	Outcomes not in keeping with PICO
[27]	Chai-Adisaksopha, 2015	Population not in keeping with PICO
[7]	Capodanno, 2013	Critical low score on AMSTAR tool.

[28]	Coleman, 2019	Critical low score on AMSTAR tool.
[29]	Cope, 2015	Intervention not in keeping with PICO
[30]	Deitelzweig, 2017	No meta-analysis conducted
[31]	Deitelzweig, 2018	Network meta-analysis with head-to-head comparisons
[32]	Dogliotti, 2013	Interventions such as ximelagatran were included in the PICO definition
[33]	Dogliotti, 2014	Interventions such as aspirin and clopidogrel were included in the PICO definition
[34]	Escobar, 2018	Critical low score on AMSTAR tool, included Observational controlled studies
[35]	Fernandes, 2015	Unable to source full text
[36]	Gomez-Outes, 2013	Critical low score on AMSTAR tool.
[37]	Guo, 2017	Not in keeping with PICO for this review
[38]	Harenberg, 2012	Head-to-head comparisons conducted, not in keeping with PICO
[39]	Hicks, 2016	Phase 2 clinical trial data; edoxaban was included in the analysis
[40]	Hirschl, 2019	Vitamin K antagonists other than warfarin included in study
[41]	Kwong, 2014	Analysis included comparators other than warfarin
[42]	López-López, 2017	Intervention not in keeping with PICO
[43]	Lowernstern, 2018	Edoxaban included in meta-analyses, not in keeping with PICO for this review
[44]	Madzak, 2015	Customised composite endpoints used for their analysis, not in keeping with PICO for this review
[45]	Mendoza, 2017	Non-English manuscript, unable to obtain translated manuscript
[46]	Miller, 2012	Critical low score on AMSTAR tool.
[47]	Mitchell, 2013	Head-to-head comparisons conducted, not in keeping with PICO
[48]	Morimoto, 2015	Intervention not in keeping with PICO; study design
[49]	Ntaios, 2017	Vitamin K antagonists other than warfarin included in study
[50]	O'Dell, 2012	No meta-analysis conducted
[51]	Pirlog, 2019	Outcomes were not in keeping with PICO
[52]	Providência, 2014	Intervention not in keeping with PICO; study design
[53]	Rong, 2015	Methodological not in keeping with PICO for this review
[6]	Ruff, 2014	J-ROCKET not included in systematic review, , whilst was included in Jia et al (2014)
[54]	Siddiqui, 2019	Intervention not in keeping with PICO
[55]	Sun, 2019	Comparator not in keeping with PICO
[56]	Tahir, 2013	No meta-analysis conducted
[57]	Tereshchenko, 2016	Edoxaban and left atrial appendage occlusion interventions included in analysis
[58]	Testa, 2012	Critical low score on AMSTAR tool.
[59]	Verdecchia, 2015	Intervention only included apixaban
[60]	Wang, 2020	Edoxaban included in meta-analyses, methodology not in keeping with PICO for this review
[61]	Waranugraha, 2021	Edoxaban included in meta-analyses, methodology not in keeping with PICO for this review
[62]	Xu, 2021	Head-to-head comparisons; Comparator not in keeping with PICO

10. Evidence quality:

While the included meta-analysis was able to provide data to address the question, the overall confidence in data quality was assessed as critically low due to the presence of one or more critical errors and/or omissions according to the AMSTAR-2 critical appraisal tool (Figure 10). Study quality of the included RCTs were mostly of good quality (Figure 11-12).

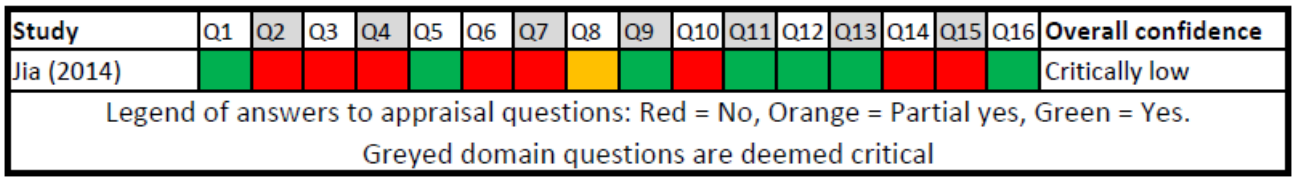

Figure 10. Overall confidence in study quality assessment with AMSTAR-2 appraisal tool

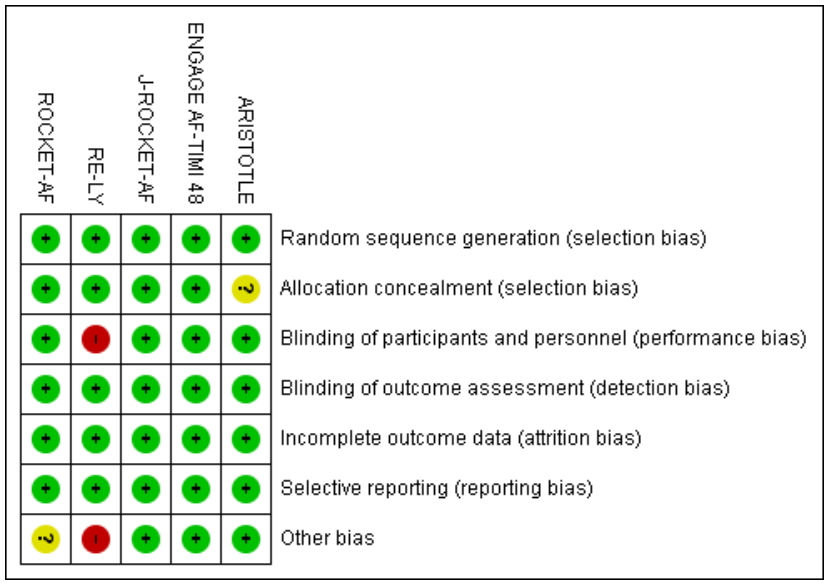

Figure 11. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

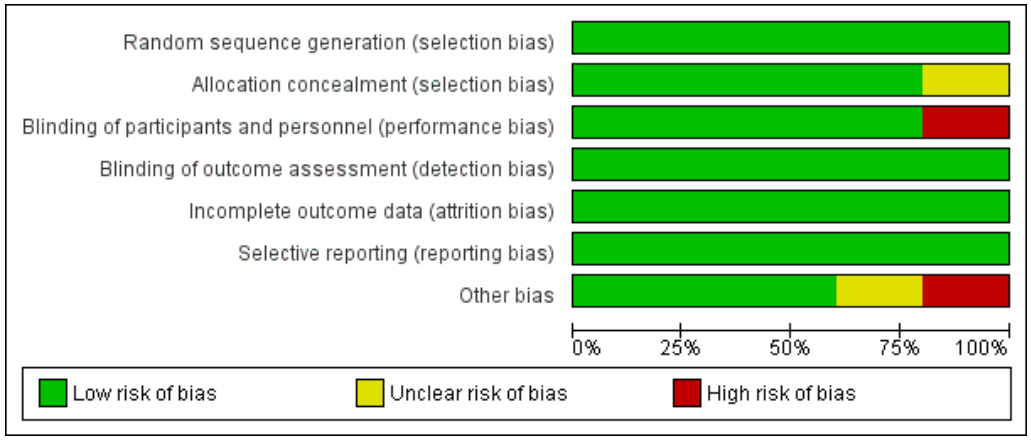

Figure 12. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Table 2: Summary of findings: DOACs compared to warfarin for anticoagulation in chronic non-valvular atrial fibrillation

DOACS compared to Warfarin for Chronic non-valvular atrial fibrillation

Patient or population: Chronic non-valvular atrial fibrillation
Intervention: DOACS
Comparison: Warfarin

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Warfarin	Risk difference with DOACS
Mortality	72836 (5 RCTs)	⊕⊕⊕⊕ High	**RR 0.90** (0.85 to 0.94)	75 per 1,000	**8 fewer per 1,000** (11 fewer to 5 fewer)
Ischaemic stroke/Systemic embolism	72864 (5 RCTs)	⊕⊕⊕⊕ High	**RR 0.85** (0.77 to 0.93)	34 per 1,000	**5 fewer per 1,000** (8 fewer to 2 fewer)
Major bleeding - All major bleeding	72793 (5 RCTs)	⊕⊕⊕⊕ High	**RR 0.85** (0.69 to 1.03)	63 per 1,000	**10 fewer per 1,000** (20 fewer to 2 more)
Major bleeding - Intracranial bleeding	72793 (5 RCTs)	⊕⊕⊕⊕ High	**RR 0.44** (0.35 to 0.55)	15 per 1,000	**8 fewer per 1,000** (9 fewer to 7 fewer)
Major bleeding - Gastrointestinal bleeding	72793 (5 RCTs)	⊕⊕⊕⊕ High	**RR 1.07** (0.84 to 1.37)	20 per 1,000	**1 more per 1,000** (3 fewer to 7 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CONCLUSION

Five phase III randomised controlled trials, namely ARISTOTLE[16], ENGAGE AF-TIMI 48[17], RE-LY[13], ROCKET-AF[14], and J-ROCKET-AF[15] were included in the meta-analysis that we selected for reporting in this therapeutic review. DOACs reduced the risk of stroke and systemic embolism compared with warfarin. The benefit was mainly driven by a substantial reduction in haemorrhagic stroke. Additionally, DOACs were associated with lower all-cause mortality compared to warfarin. For DOACs that assessed multiple dosage regimens, the lower dose appeared to reduce the risk of adverse bleeding, however, this was also associated with a reduction in the prevention of thromboembolic strokes and systemic emboli. Overall, when considering the balance of efficacy and safety DOACs are a viable alternative to warfarin for the long-term prevention of stroke in patients with chronic non valvular AF.

Besides potential therapeutic benefits, providing access to DOACs would eliminate the substantial burden to the health services of INR monitoring which is required with warfarin therapy which may be associated with healthcare access inequality.[18] The cost of DOACS needs to be considered as that be a potential barrier to adequate drug access: DOACs may be 4-8 fold more expensive when compared with warfarin, even when other associated treatment costs, e.g. monthly INR monitoring, are taken into account. It is possible that the additional benefits provided by DOACs may outweigh the incremental costs that would be incurred. To maximize feasibility, DOACs may potentially be considered for patients who have failed initial anticoagulation with warfarin (i.e. labile INRs, poor access to healthcare facilities, and adverse effects such as intracranial haemorrhage). Formal pharmacoeconomic assessments are needed.

Appendix A: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [x] Moderate [ ] Low [ ] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Randomised controlled trials Large sample size Despite the critically low assessment of the systematic review by Jia et al (2019), the GRADE assessments per outcome were generally graded as high certainty evidence (see below and the summary of findings table 2, above).
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [x] Small [ ] None [ ]	• Stroke/systemic embolism: RR 0.86 (95% CI: 0.75-0.99), *high certainty evidence* • Ischaemic stroke: RR 0.93 (95% CI: 0.84-1.03) • Haemorrhagic stroke: RR 0.50 (95% CI: 0.41-0.62), *high certainty evidence* • Mortality: - High dose regimen: RR 0.90 (95% CI: 0.85-0.95), *high certainty evidence* - Low dose regimen: RR 0.89 (95% CI: 0.83-0.96), *high certainty evidence*
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [x] Moderate [ ] Low [ ] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Randomised controlled trials Large sample size Despite the critically low assessment of the systematic review by Jia et al (2019), the GRADE assessments per outcome were generally graded as high certainty evidence (see below and the summary of findings table 2, above).
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [x] None [ ]	Overall, DOACs are safer and result in lower rates of major bleeding and intracranial haemorrhage compared to warfarin; however, the risk of gastrointestinal bleeding is increased, particularly when higher doses are used. **Major bleeding:** - High dose regimen: 0.86 (95% CI: 0.74-0.99), *high certainty* - Low dose regimen: 0.63 (95% CI: 0.38-1.04), *high certainty*

<table>
<tr><td></td><td></td><td>Intracranial bleeding:
- High dose regimen: 0.48 (95% CI: 0.41-0.56), high certainty
- Low dose regimen: 0.31 (95% CI: 0.24-0.41), high certainty

Gastrointestinal bleeding:
- High dose regimen: 1.24 (95% CI: 1.10-1.39), high certainty
- Low dose regimen: 0.85 (95% CI: 0.72-1.00), high certainty</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable harms?
Favours intervention [x] Favours control [ ] Intervention = Control or Uncertain [ ]</td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available?</td><td>n/a</td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [x] No [ ] Uncertain [ ]</td><td>DOACs may potentially be considered, noting that management with warfarin is more complex requiring INR-monitoring with respective dose adjustments.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [X] Less intensive [ ] Uncertain [ ]</td><td>Price of medicines – 30 days
<table>
<tr><th>Medicine (30 days)</th><th>SEP (ZAR)</th><th>60% of SEP</th></tr>
<tr><td>Dabigatran, 150 mg 12 hourly</td><td>1133.06</td><td>679.84</td></tr>
<tr><td>Dabigatran, 110 mg 12 hourly</td><td>1133.06</td><td>679.84</td></tr>
<tr><td>Rivaroxaban, 20 mg daily</td><td>637.50**</td><td>382.50</td></tr>
<tr><td>Apixaban, 5 mg 12 hourly</td><td>983.40</td><td>590.04</td></tr>
<tr><td>Warfarin, 5 mg daily</td><td>52.09</td><td>31.32</td></tr>
</table>
** generic price on SEP database

References:
SEP database, 24 December 2021
NHLS price list for public sector, 2021

Other resources:
*SEP of warfarin only; additional cost of R51.62 per INR test
Frequency of INR testing: every 2-3 days upon initiation for the first 2 weeks or until stability of INR, then weekly/as clinically indicated

Pharmacoeconomic and budget impact analysis (refer to the detailed report update by J Miot and TD Leong, 26 March 2022):
This economic analysis was conducted from the payer's perspective (i.e. Department of Health), using a discount rate of 5% for both cost and clinical inputs.

Incremental cost-effectiveness ratio:
Although numerous published cost-effectiveness analyses suggest that rivaroxaban is cost-effective in a long-term setting, the model assimilated on local costs (including generic rivaroxaban pricing) and population information produced an incremental cost-effectiveness ratio (ICER) of R188 000/QALY.

Sensitivity analysis:
In the current model, the cost of rivaroxaban, followed by stroke event rates with rivaroxaban and warfarin use had the largest impacts on cost effectiveness.

Reducing the price of rivaroxaban by 35% produced an ICER of R100 000/QALY, and a reduction of 74.5% resulted in cost neutrality (compared to warfarin).</td></tr>
</table>

		Reducing the stroke event rate by ≤ 20% on rivaroxaban decreased the ICER to R128 809/QALY, while increasing the stroke event rate by ≥20% while on warfarin decreased the ICER to R 124 512/QALY. ***Estimated budget impact:*** The incremental budget impact analysis for 2021 was estimated as R231 million (for generic rivaroxaban-use compared to warfarin-use), over a five-year period. Note that the prevalence figures for non-valvular AF in the public sector are simply estimates and it is challenging to predict what the actual budget impact is likely to be – very dependent on uptake and utilization.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	Committee expert opinion, as no local survey data is available.
EQUITY	**Would there be an impact on health inequity?** Yes [x] No [ ] Uncertain [ ]	Access to DOACs would reduce monitoring requirements of warfarin therapy, which are currently associated with healthcare access inequality.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	26 March 2022	HMG, RM, EM, TK, MB, JM, TL	DOACs not be used for anticoagulation in atrial fibrillation. DOACs have similar efficacy to warfarin in preventing ischaemic stroke and systemic embolism and are associated with reduced mortality and lower rates of intracranial haemorrhage and major bleeding events. However, DOACs are not currently affordable.

References

1.Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;123(10):e269-367.

2.Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129(8):837-47.

3.Santos IS, Goulart AC, Olmos RD, Thomas GN, Lip GYH, Lotufo PA, et al. Atrial fibrillation in low- and middle-income countries: a narrative review. Eur Heart J Suppl. 2020;22(Suppl O):O61-o77.

4.National Department of Health, South Africa. Essential Drugs Programme. Hospital level (Adults) Standard Treatment Guidelines and Essential Medicines List. 5th ed. 2019. Available from: https://www.knowledgehub.org.za/system/files/elibdownloads/2020-07/Hospital%20Level%20%28Adult%29%202019_v2.0.pdf.

5.National Department of Health, South Africa. Essential Drugs Programme. Hospital level (Adults) Standard Treatment Guidelines and Essential Medicines List. 5th ed. 2019. [cited Chapter 3: Cardiovascular system]. Available from: https://www.knowledgehub.org.za/system/files/elibdownloads/2020-07/Hospital%20Level%20%28Adult%29%202019_v2.0.pdf.

6.Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955-62.

7.Capodanno D, Di Maio M, Greco A, Bhatt DL, Gibson CM, Goette A, et al. Safety and Efficacy of Double Antithrombotic Therapy With Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. Journal of the American Heart Association. 2020;9(16):e017212.

8.Laäs DJ, Naidoo M. Oral anticoagulants and atrial fibrillation: A South African perspective. S Afr Med J. 2018;108(8):640-6.

9.Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Bmj. 2017;358:j4008.

10.Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

11.GRADEpro Guideline Development Tool. GRADEpro GDT. McMaster University and Evidence Prime; 2021.

12.Jia B, Lynn HS, Rong F, Zhang W. Meta-analysis of efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation. J Cardiovasc Pharmacol. 2014;64(4):368-74.

13.Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51.

14.Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-91.

15.Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation – the J-ROCKET AF study –. Circ J. 2012;76(9):2104-11.

16.Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-92.

17.Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093-104.

18.Adam SS, McDuffie JR, Ortel TL, Williams JW, Jr. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review. Ann Intern Med. 2012;157(11):796-807.

19.Almutairi AR, Zhou L, Gellad WF, Lee JK, Slack MK, Martin JR, et al. Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-Analyses. Clinical therapeutics. 2017;39(7):1456-.

20.Antza C, Doundoulakis I, Akrivos E, Economou FI, Vazakidis P, Haidich AB, et al. Non-vitamin K oral anticoagulants in nonvalvular atrial fibrillation: A network meta-analysis. Scandinavian cardiovascular journal : SCJ. 2019;53(2):1-22.

21.Bates ER. 2016 - Review: In AF, direct oral anticoagulants reduce all-cause and vascular mortality compared with warfarin. ACP Journal Club. 2017;166(6):1-.

22.Biondi-Zoccai G, Malavasi V, D'Ascenzo F, Abbate A, Agostoni P, Lotrionte M, et al. Comparative effectiveness of novel oral anticoagulants for atrial fibrillation: evidence from pair-wise and warfarin-controlled network meta-analyses. HSR proceedings in intensive care & cardiovascular anesthesia. 2013;5(1):40-54.

23.Briere JB, Bowrin K, Coleman C, Fauchier L, Levy P, Folkerts K, et al. Real-world clinical evidence on rivaroxaban, dabigatran, and apixaban compared with vitamin K antagonists in patients with non-valvular atrial fibrillation: a systematic literature review. Expert review of pharmacoeconomics & outcomes research. 2019;19(1):1-10.

24.Caldeira D, Barra M, Ferreira A, Rocha A, Augusto A, Pinto FJ, et al. Systematic review with meta-analysis: the risk of major gastrointestinal bleeding with non-vitamin K antagonist oral anticoagulants. Alimentary pharmacology & therapeutics. 2015;42(11-12):1239-49.

25.Wells G, Coyle D, Cameron C, Steiner S, Coyle K, Kelly S, et al. Safety, Effectiveness, and Cost-Effectiveness of New Oral Anticoagulants Compared with Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation2012 2012.

26.Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. Blood. 2014;124(15):2450-8.

27.Chai-Adisaksopha C, Hillis C, Monreal M, Witt DM, Crowther M. Thromboembolic events, recurrent bleeding and mortality after resuming anticoagulant following gastrointestinal bleeding. A meta-analysis. Thrombosis and haemostasis. 2015;114(4):819-25.

28.Coleman CI, Briere JB, Fauchier L, Levy P, Bowrin K, Toumi M, et al. Meta-analysis of real-world evidence comparing non-vitamin K antagonist oral anticoagulants with vitamin K antagonists for the treatment of patients with non-valvular atrial fibrillation. Journal of market access & health policy. 2019;7(1):1574541.

29.Cope S, Clemens A, Hammès F, Noack H, Jansen JP. Critical appraisal of network meta-analyses evaluating the efficacy and safety of new oral anticoagulants in atrial fibrillation stroke prevention trials. Value Health. 2015;18(2):234-49.
30.Deitelzweig S, Farmer C, Luo X, Vo L, Li X, Hamilton M, et al. Risk of major bleeding in patients with non-valvular atrial fibrillation treated with oral anticoagulants: a systematic review of real-world observational studies. Current medical research and opinion. 2017;33(9):1-21.
31.Deitelzweig S, Farmer C, Luo X, Li X, Vo L, Mardekian J, et al. Comparison of major bleeding risk in patients with non-valvular atrial fibrillation receiving direct oral anticoagulants in the real-world setting: a network meta-analysis. Current medical research and opinion. 2018;34(3):1-30.
32.Dogliotti A, Paolasso E, Giugliano RP. Novel oral anticoagulants in atrial fibrillation: a meta-analysis of large, randomized, controlled trials vs warfarin. Clin Cardiol. 2013;36(2):61-7.
33.Dogliotti A, Paolasso E, Giugliano RP. Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79 808 patients. Heart. 2014;100(5):396-405.
34.Escobar C, Martí-Almor J, Pérez Cabeza A, Martínez-Zapata MJ. Direct Oral Anticoagulants Versus Vitamin K Antagonists in Real-life Patients With Atrial Fibrillation. A Systematic Review and Meta-analysis. Revista espanola de cardiologia (English ed). 2019;72(4):305-16.
35.Fernandes ALC, Andrade AMdS, Cruz CMS, Oliveira EN. New oral anticoagulants (NOACs) in prevention of stroke brain and thromboembolic events in patients with atrial fibrillation. Rev Soc Bras Clín Méd. 2015;13(2).
36.Gómez-Outes A, Terleira-Fernández AI, Calvo-Rojas G, Suárez-Gea ML, Vargas-Castrillón E. Dabigatran, Rivaroxaban, or Apixaban versus Warfarin in Patients with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Subgroups. Thrombosis. 2013;2013:640723.
37.Guo L, Li S, Wang P, Zhong X, Hong Y. Comparative Efficacy of Clinical Events Prevention of Five Anticoagulants in Patients With Atrial Fibrillation (A Network Meta-Analysis). The American journal of cardiology. 2017;119(4):585-93.
38.Harenberg J, Marx S, Diener HC, Lip GY, Marder VJ, Wehling M, et al. Comparison of efficacy and safety of dabigatran, rivaroxaban and apixaban in patients with atrial fibrillation using network meta-analysis. International angiology : a journal of the International Union of Angiology. 2012;31(4):330-9.
39.Hicks T, Stewart F, Eisinga A. NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis. Open heart. 2016;3(1):e000279.
40.Hirschl M, Kundi M. Safety and efficacy of direct acting oral anticoagulants and vitamin K antagonists in nonvalvular atrial fibrillation - a network meta-analysis of real-world data. Vasa. 2019;48(2):134-47.
41.Kwong JS, Lam YY, Yan BP, Yu CM. Bleeding of new oral anticoagulants for stroke prevention in atrial fibrillation: a meta-analysis of randomized controlled trials. Cardiovasc Drugs Ther. 2013;27(1):23-35.
42.López-López JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ (Clinical research ed). 2017;359:j5058.
43.Lowenstern A, Al-Khatib SM, Sharan L, Chatterjee R, Allen LaPointe NM, Shah B, et al. Interventions for Preventing Thromboembolic Events in Patients With Atrial Fibrillation: A Systematic Review. Ann Intern Med. 2018;169(11):774-87.
44.Madzak A, Larsen TB, Lane DA, Lip GY, Nielsen PB. Composite end point analyses of non-vitamin K antagonist oral anticoagulants compared with warfarin in patients with atrial fibrillation. Expert Rev Cardiovasc Ther. 2015;13(10):1155-63.
45.Mendoza JA, Silva FA, Ortiz Castro CH, Rangel LM. Systematic review of new oral anticoagulants versus warfarin in non valvular atrial fibrillation. Acta neurol colomb. 2017;33(3):188-98.
46.Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. The American journal of cardiology. 2012;110(3):453-60.
47.Mitchell SA, Simon TA, Raza S, Jakouloff D, Orme ME, Lockhart I, et al. The efficacy and safety of oral anticoagulants in warfarin-suitable patients with nonvalvular atrial fibrillation: systematic review and meta-analysis. Clin Appl Thromb Hemost. 2013;19(6):619-31.
48.Morimoto T, Crawford B, Wada K, Ueda S. Comparative efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation: A network meta-analysis with the adjustment for the possible bias from open label studies. J Cardiol. 2015;66(6):466-74.
49.Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. Real-World Setting Comparison of Nonvitamin-K Antagonist Oral Anticoagulants Versus Vitamin-K Antagonists for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis. Stroke. 2017;48(9):2494-503.
50.O'Dell KM, Igawa D, Hsin J. New oral anticoagulants for atrial fibrillation: a review of clinical trials. Clin Ther. 2012;34(4):894-901.
51.Pirlog AM, Pirlog CD, Maghiar MA. DOACs vs Vitamin K Antagonists: a Comparison of Phase III Clinical Trials and a Prescriber Support Tool. Open Access Maced J Med Sci. 2019;7(7):1226-32.
52.Providência R, Grove EL, Husted S, Barra S, Boveda S, Morais J. A meta-analysis of phase III randomized controlled trials with novel oral anticoagulants in atrial fibrillation: comparisons between direct thrombin inhibitors vs. factor Xa inhibitors and different dosing regimens. Thromb Res. 2014;134(6):1253-64.
53.Rong F, Jia B, Huang P, Lynn HS, Zhang W. Safety of the direct-acting anticoagulants in patients with atrial fibrillation: a meta-analysis. Thromb Res. 2015;135(6):1117-23.
54.Siddiqui MU, Scalzitti D, Naeem Z. Apixaban in Comparison to Warfarin for Stroke Prevention in Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Observational Studies. Cardiology Research & Practice. 2019;2019:1-7.
55.Sun Z, Liu Y, Zhang Y, Guo X, Xu Y. Differences in safety and efficacy of oral anticoagulants in patients with non-valvular atrial fibrillation: A Bayesian analysis. International journal of clinical practice. 2019;73(4):e13308.
56.Tahir F, Riaz H, Riaz T, Badshah MB, Riaz IB, Hamza A, et al. The new oral anti-coagulants and the phase 3 clinical trials - a systematic review of the literature. Thrombosis journal. 2013;11(1):18.
57.Tereshchenko LG, Henrikson CA, Cigarroa J, Steinberg JS. Comparative Effectiveness of Interventions for Stroke Prevention in Atrial Fibrillation: A Network Meta-Analysis. J Am Heart Assoc. 2016;5(5).
58.Testa L, Agnifili M, Latini RA, Mattioli R, Lanotte S, De Marco F, et al. Adjusted indirect comparison of new oral anticoagulants for stroke prevention in atrial fibrillation. QJM : monthly journal of the Association of Physicians. 2012;105(10):949-57.

59.Verdecchia P, Angeli F, Bartolini C, De Filippo V, Aita A, Di Giacomo L, et al. Safety and efficacy of non-vitamin K oral anticoagulants in non-valvular atrial fibrillation: A Bayesian meta-analysis approach. Expert Opinion on Drug Safety. 2015;14(1):7-20.
60.Wang YP, Kehar R, Iansavitchene A, Lazo-Langner A. Bleeding Risk in Nonvalvular Atrial Fibrillation Patients Receiving Direct Oral Anticoagulants and Warfarin: A Systematic Review and Meta-Analysis of Observational Studies. TH open : companion journal to thrombosis and haemostasis. 2020;4(3):e145-e52.
61.Waranugraha Y, Rizal A, Syaban MFR, Faratisha IFD, Erwan NE, Yunita KC. Direct comparison of non-vitamin K antagonist oral anticoagulant versus warfarin for stroke prevention in non-valvular atrial fibrillation: a systematic review and meta-analysis of real-world evidences. The Egyptian heart journal : (EHJ) : official bulletin of the Egyptian Society of Cardiology. 2021;73(1):70.
62.Xu W, Lv M, Wu S, Jiang S, Zeng Z, Fang Z, et al. Severe Bleeding Risk of Direct Oral Anticoagulants Versus Vitamin K Antagonists for Stroke Prevention and Treatment in Patients with Atrial Fibrillation: A Systematic Review and Network Meta-Analysis. Cardiovasc Drugs Ther. 2021.

Appendix B: Search strategy

Database: PubMed
Date: 12 October 2021

Search	Query	Results
#1	(((Non-valvular atrial fibrillation) OR (atrial fibrillation) OR (NVAF) OR (Nonvalvular atrial))) AND ((warfarin) OR (vitamin K antagonist)) AND ((direct oral anticoagulant) OR (novel oral anticoagulant) OR (DOAC) OR (NOAC) OR (non-vitamin k oral anticoagulant*) OR (oral anticoagulant) OR (rivaroxaban) OR (dabigatran) OR (apixaban) OR (factor Xa inhibitor) OR (thrombin inhibitor))	N = 474

Database: Epistemonikos
Date: 12 October 2021

Search	Query	Results
#1	((title:(non-valvular atrial fibrillation) OR abstract:(non-valvular atrial fibrillation)) OR (title:(atrial fibrillation) OR abstract:(atrial fibrillation))) AND ((title:(warfarin) OR abstract:(warfarin)) OR (title:(vitamin k antagonist) OR abstract:(vitamin k antagonist))) AND ((title:(direct oral anticoagulant) OR abstract:(direct oral anticoagulant)) OR (title:(novel oral anticoagulant) OR abstract:(novel oral anticoagulant)) OR (title:(oral anticoagulant) OR abstract:(oral anticoagulant))	N = 282

Database: Cochrane Library
Date: 12 October 2021

Search	Query	Results
#1	((Non-valvular atrial fibrillation) OR (atrial fibrillation) OR (NVAF) OR (Nonvalvular atrial)) AND ((warfarin) OR (vitamin K antagonist)) AND ((direct oral anticoagulant) OR (novel oral anticoagulant) OR (DOAC) OR (NOAC) OR (non-vitamin k oral anticoagulant*) OR (oral anticoagulant) OR (rivaroxaban) OR (dabigatran) OR (apixaban) OR (factor Xa inhibitor) OR (thrombin inhibitor))	N = 14

Appendix C: Table with calculated numbers needed to treat to benefit/harm

Number needed to treat to benefit/harm (95% CI)					
		High dose regimen		Low dose regimen	
Outcome	Control event incidence	Absolute risk reduction	NNTB/H	Absolute risk reduction	NNTB/H
Mortality	*5.66% (95% CI: 5.05%-6.27%)*	-0.57% (95% CI: -0.85% to -0.28%)	NNTB 177 (118-354)	-0.62% (95% CI: -0.96% to -0.23%)	NNTB 161 (104-442)
Ischaemic stroke/systemic embolism	*3.36% (95% CI: 2.9%-3.82%)*	-0.67% (95% CI: -0.97% to -0.3%)	NNTB 149 (103-331)	0.1% (95% CI: -0.54% to 0.91%)	NNTH 993 (NNTB 187 to ∞ to NNTH 111)
Ischamic stroke	*2.35% (95% CI: 1.95%-2.75%)*	-1.17% (95% CI: -1.39% to -0.89%)	NNTB 609 (NNTB 267 to ∞ to NNTH 1420)	0.73% (95% CI: 0.33% to 1.15%)	NNTH 138 (87-305)
Systemic embolism	*0.25% (95% CI: 0.12%-0.37%)*	Not available	Not available	Not available	Not available
Major bleeding	*6.03% (95% CI: 5.32%-6.73%)*	-0.84% (95% CI: -1.57% to -0.06%)	NNTB 119 (NNTB 64-1660)	-2.23% (95% CI: -3.74% to 0.24%)	NNTB 45 (NNTB 27 to ∞ to NNTH 415)
Intracranial bleeding	*1.42% (95% CI: 1.11%-1.72%)*	-0.74% (95% CI: -0.84% to -0.62%)	NNTB 136 (120-161)	-0.98% (95% CI: -1.08% to -0.84%)	NNTB 103 (93-120)
Gastrointestinal bleeding	*1.86% (95% CI: 0.15%-2.22%)*	0.45% (95% CI: 0.19% to 0.73%)	NNTH 224 (138-538)	-0.28% (95% CI: -0.52% to 0%)	NNTB 359 (NNTB 192 to ∞ to NNTH ∞)

Notes: NNTB = Number needed to treat to benefit; NNTH = Number needed to harm.