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Eds versionTitle

Benefits and Harms of Oral Anticoagulant Therapy in Chronic Kidney Disease: A Systematic Review and Meta-Analysis

Short title

Oral anticoagulant therapy in kidney disease

Authors

Jeffrey T Ha, MBBS; Brendon L Neuen, MBBS(Hons); Lap P Cheng, MBBS; Min Jun, PhD; Tadashi Toyama, PhD; Martin P Gallagher, PhD; Meg J Jardine, PhD; Manish M Sood, MD; Amit X Garg, PhD; Suetonia C Palmer, PhD; Patrick B Mark, PhD; David C Wheeler, MD; Vivekanand Jha, MD; Ben Freedman, PhD; David W Johnson, PhD; Vlado Perkovic, PhD; Sunil V Badve, PhD

Author affiliations

The George Institute for Global Health, UNSW Medicine, Sydney, NSW, Australia (J.T.H., B.L.N., L.P.C., M.J., T.T., M.P.G., M.J.J., V.P., S.V.B.); Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan (T.T.); Department of Renal Medicine, St. George Hospital, Sydney, NSW, Australia (J.T.H., L.P.C., S.V.B); Concord Repatriation General Hospital, Sydney, NSW, Australia (M.P.G., M.J.J., B.F.); Institute for Clinical Evaluative Sciences, Toronto, Canada (A.X.G., M.M.S.); Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada (M.M.S.); Lilibeth Caberto Kidney Clinical Research Unit, London Health Sciences Centre, London, Canada (A.X.G.); Division of Nephrology, Western University, London, Canada (A.X.G.); Department of Medicine, University of Otago, Christchurch, New Zealand (S.C.P.); Institute for Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK (P.B.M.); Department of Renal Medicine, University College London, London, UK (D.C.W.); The George Institute for Global Health, New Delhi, India (V.J.); University of Oxford, Oxford, UK (V.J.); University of New South Wales, Sydney, NSW, Australia (V.J.); Heart Research Institute, Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia (B.F.); Department of Nephrology, Princess Alexandra Hospital, Brisbane, Australia (D.W.J.); Translational Research Institute, Brisbane, Australia (D.W.J.); Australasian Kidney Trials Network, University of Queensland, Brisbane, Australia (D.W.J.)

Corresponding Author

Sunil V. Badve

Renal and Metabolic Division, The George Institute for Global Health,

Level 5, 1 King Street, Newtown, NSW 2042, Australia

Ph: +61 (2) 8052 4300; Fax: +61 (2) 8052 4301 Email: sbadve@georgeinstitute.org.au

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ABSTRACT

Background: The effects of oral anticoagulation in chronic kidney disease (CKD) are uncertain.

Purpose: To evaluate benefits and harms of vitamin K antagonists (VKA) and non-vitamin K oral anticoagulants (NOAC) in patients with CKD stages 3 to 5, including those with dialysis-dependent end-stage kidney disease (ESKD).

Data Sources: Medline, EMBASE, and Cochrane databases from inception to February 2019 with English language restriction; bibliographies of reviews; Clinicaltrials.gov (February 25, 2019)

Study selection: Randomized controlled trials evaluating VKA or NOAC in adult CKD patients for any indication, and reported efficacy and/or bleeding outcomes.

Data Extraction: Two authors independently extracted data, performed risk of bias assessment, and rated certainty of evidence.

Data Synthesis: Forty-five trials, involving 34,082 participants anticoagulated for atrial fibrillation ([AF] (eleven trials), venous thromboembolism ([VTE] eleven trials), thromboprophylaxis (six trials), prevention of dialysis-access thrombosis (eight trials), and cardiovascular disease other than AF (nine trials) were included. All but the eight trials involving ESKD patients excluded participants with creatinine clearance <20 mL/min or estimated glomerular filtration rate <15 mL/min/1.73 m^2. In AF, compared with VKA, NOAC reduced the risks of stroke or systemic embolism (risk ratio 0.79, 95%CI 0.66–0.93; high certainty evidence), and hemorrhagic stroke (0.48, 0.30–0.76; moderate certainty evidence). Compared with VKA, NOAC effects on recurrent VTE or VTE-related death were uncertain (0.72, 0.44–1.17; low certainty evidence). In all trials combined, NOAC reduced major bleeding risk compared to VKA, though the finding was not statistically significant (0.75, 0.56–1.01; low certainty evidence).

Limitation: Scant evidence among patients with advanced CKD stages or ESKD, data mostly extracted from subgroup analyses of large trials.

Conclusion: In early stages of CKD, NOAC had a benefit-risk profile superior to VKA with a clear reduction in the risk of stroke or systemic embolism in AF, and reduction in overall major bleeding risk that was not statistically significant. There is insufficient evidence to conclude whether patients with advanced CKD stages or ESKD derive benefit from VKA or NOAC.

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INTRODUCTION

Chronic kidney disease (CKD) is a pro-thrombotic state, associated with substantially increased risks of arterial and venous thromboembolism (VTE) (1). In addition, atrial fibrillation is highly prevalent in this population, affecting 18% of patients with CKD (2), and 12-25% of patients with dialysis-dependent end-stage kidney disease (ESKD) (3, 4). The presence of CKD increases the risks of stroke or systemic embolism, congestive heart failure, myocardial infarction, and all-cause death among patients with atrial fibrillation (5, 6). Compared with people with normal kidney function, the risk of VTE is almost two-fold greater among those with estimated glomerular filtration rate (eGFR) between 15 and 59 mL/min/1.73 m^2) (7), and three-fold greater in patients with dialysis-dependent ESKD (8). VTE in ESKD is also associated with increased risks of bleeding and all-cause death (8). Other common clinical manifestations of increased thrombotic risk in CKD include acute coronary syndrome, stroke, peripheral arterial occlusion, and dialysis access thrombosis (1, 9).

Anticoagulant therapy is an important intervention in the prevention of cardiovascular thrombotic and VTE events. Evidence-based treatment guidelines recommend anticoagulation for the prevention of stroke in patients with nonvalvular atrial fibrillation and a CHA_2DS_2-VASc score ≥2 in men or ≥3 in women (10, 11), VTE in major orthopedic or non-orthopedic surgical patients or hospitalized acutely ill medical patients (12), and recurrent VTE in patients with VTE disease (13).

Patients with advanced stages of CKD and ESKD with atrial fibrillation are prescribed oral anticoagulant therapy less frequently than those with normal kidney function (3, 14). The use of warfarin in patients on dialysis who have atrial fibrillation varies considerably, ranging from as low as 2% in Germany to 37% in Canada (3). The low rates of anticoagulant therapy use in advanced CKD and ESKD may be due to the increased risk of bleeding, uncertainty regarding potential benefits in this population, warfarin-associated calciphylaxis, and warfarin-related nephropathy (15, 16). In CKD, the risk of major bleeding increases linearly with declining eGFR (17). In patients with dialysis-dependent ESKD, the bleeding risk is further increased with the incremental use of antithrombotic agents such as warfarin and antiplatelet agents (18). The exclusion of CKD patients from nearly 90% of trials evaluating anticoagulant interventions has contributed to uncertainty on the role of anticoagulant therapy in CKD (19).

The aim of the current systematic review was to evaluate the benefits and harms of oral anticoagulant (OAC) therapy for a range of clinical indications in patients with CKD stages 3 to 5, including those receiving dialysis.

METHODS

The systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (20). The protocol of this review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; December 4, 2017) and can be accessed at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=79709

Data Sources and Searches

Relevant studies were identified by searching Medline (inception to February 2019), Embase (inception to February 2019), and the Cochrane Central Register of Controlled Trials (January 2019) with English language restriction using search strategy described in **Appendix Table 1**. In addition, reference lists of relevant systematic reviews were searched. Online trial registry Clinicaltrials.gov was searched (February 25, 2019) using the following terms: chronic kidney disease, renal dialysis, atrial fibrillation and anticoagulation.

Study Selection and Outcomes

Studies were eligible for inclusion if they (i) were randomized controlled trials; (ii) included adults with CKD (creatinine clearance [CrCl] <60 mL/min or eGFR <60 mL/min/1.73 m^2), or dialysis-dependent ESKD; (iii) compared vitamin K antagonist (VKA) or non-vitamin K oral anticoagulant (NOAC) to another oral anticoagulant, placebo, low-molecular weight heparin (LMWH), aspirin, or no study medication; and (iv) reported efficacy and/or bleeding outcomes. All indications for anticoagulation were eligible for inclusion. Two authors (J.T.H. and B.L.N.) independently reviewed each title and abstract, and performed full-text review of shortlisted studies. Disagreements about study eligibility were resolved via consultation with two other authors (S.V.B. and V.P.). If multiple secondary publications of the same trial were identified, the publication with the most complete data was used and additional data from secondary sources were extracted. Incomplete, or unpublished data from trials were requested from the investigators.

The outcomes of this systematic review were: stroke or systemic embolism in atrial fibrillation, non-hemorrhagic stroke, hemorrhagic stroke, all-cause or cardiovascular death, VTE or VTE-related death, myocardial infarction, composite cardiovascular events (cardiovascular or all-cause death, nonfatal myocardial infarction, or stroke), dialysis access thrombotic events, major bleeding, major or non-major clinically relevant bleeding, and intracranial hemorrhage.

Data Extraction and Quality Assessment

Data extraction was carried out independently by two authors (J.T.H. and B.L.N.). Disagreements were resolved via consultation with two other authors (S.V.B. and V.P.). The following data were extracted using a standardized form: patient demographic details, study design and conduct, indication for anticoagulation, dose of drug, non-randomized co-interventions, follow-up duration, and outcome and bleeding events. The methodological quality of each study included was assessed at the outcome level independently by two authors (J.T.H. and B.L.N.) using the risk of bias assessment tool developed by the Cochrane Bias Methods Group (21).

Data Synthesis and Analysis

The results were expressed as risk ratios (RR) with 95% confidence intervals (CI). A treatment arm continuity correction was used if there were zero events in one arm in a trial. For trials with three arms comparing two different doses of NOAC with VKA, similar to a previous meta-analysis (22), data from only the high dose NOAC arm were used for the main analyses to avoid potentially uninterpretable results by merging of the benefits and harms of different doses. Additional analyses were conducted by combining data from both high and low dose arms of NOAC. Summary estimates were obtained by random-effects model using the Paule-Mandel method (23). If data on the number of events and participants were not reported, generic inverse variance meta-analysis was performed by calculating log hazard ratio and its standard error from the reported hazard ratio and respective CI. Evidence of statistical heterogeneity across the studies was estimated using the I^2 test. I^2 values of 25%, 50%, and 75% were considered to correspond to low, moderate, and high levels of heterogeneity (24). Statistical analyses were performed using Stata/MP, version 15.1 (StataCorp College Station, Texas), and R statistical software, version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Certainty in the evidence was summarized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, considering the following domains: (1) within-study risk of bias, (2) indirectness of evidence, (3) unexplained heterogeneity or inconsistency of results, and (4) imprecision of results by three authors (J.T.H., B.L.N., and L.P.C.) and disagreements were resolved via consultation with two other authors (S.V.B. and M.J.) (25). Because all meta-analyses involved fewer than 10 trials, small study effects (publication bias) was not assessed and publication bias was not included in rating certainty of evidence (26).

Role of the Funding Source

There was no funding source for this study.

RESULTS

Selection and Description of Studies

Forty-five trials involving 34,082 participants (median sample size 276 [range 10-4,168], median follow-up 12 [range 1-36] months) evaluating VKA or NOAC were included in the systematic review (**Figure 1**). Of these trials, eight included 685 participants with dialysis-dependent ESKD (median sample size 91 [range 18-174], median follow-up 12 [range 3-36] months) evaluating VKA for the prevention of dialysis access thrombosis in seven trials and one evaluated the effect of VKA on hemostatic factors. The remaining 37 trials included 33,397 participants with CKD, who were not receiving dialysis (defined as CrCl 20-60 mL/min, eGFR 15-60 mL/min/1.73 m^2, or serum creatinine level ≥1.5 mg/dL; median sample size 380 [range 10-4,168], median follow-up 12 [range 1-36] months). Eleven trials included 16,787 participants with atrial fibrillation (median sample size 516 [range 12-4,074], median follow-up 14 [range 3-34] months); eleven trials included 2,975 participants with acute VTE (median sample size 162 [range 72-657], median follow-up 12 [range 6-36] months), six trials included 3,908 medically ill or peri-operative patients requiring anticoagulation for thromboprophylaxis (median sample size 380 [range 42-2,197] median follow-up 2 [range 1-6] months); and the remaining nine trials included 9,727 participants with cardiovascular disease other than atrial fibrillation (median sample size 331 [range 72-2197] median follow-up 9 [range 1-36] months). Data from the 37 trials involving patients with non-dialysis CKD were obtained exclusively from CKD subgroup analyses of large trials. Details of included trials are described in **Appendix Table 2**.

NOAC was compared with VKA (15 trials, 16,495 participants), placebo (ten trials, 11,683 participants), LMWH (five trials, 1,720 participants), and aspirin (four trials, 2,690 participants); and VKA was compared with placebo (four trials, 408 participants), no study medication (four trials, 277 participants), LMWH (two trials, 293 participants), and aspirin (one trial, 516 participants). The interventional agents were: rivaroxaban (13 trials), dabigatran (eight trials), apixaban (seven trials), edoxaban (five trials), betrixaban (one trial), fixed-dose [1 or 2 mg] or low-intensity [target international normalized ratio (INR) 1.4-1.9] warfarin (six trials), and adjusted-dose (target INR 1.5-2.5, or 2-3) warfarin or acenocoumarol (five trials).

Source of funding was not reported in four trials. Thirty-nine of the remaining 41 (95%) trials were sponsored by pharmaceutical companies.

Risk of bias

Risk of bias assessment at outcome level is described in **Appendix Table 3**. Random sequence generation and allocation concealment were reported using low risk methods in 80% of trials reporting the outcomes of stroke or systemic embolism, and major bleeding in trials involving participants with atrial fibrillation. Random sequence generation and allocation concealment were reported using low risk methods in all trials reporting the outcome of VTE or VTE-related death in participants with acute VTE or those requiring thromboprophylaxis, and major adverse cardiovascular events in participants with cardiovascular disease other than atrial fibrillation. Trials involving participants with dialysis-dependent ESKD reporting the outcomes of hemodialysis access thrombosis or malfunction, all-cause death, and major bleeding were generally at high or unclear risk of bias in the domains of random sequence generation and allocation concealment.

Effects of interventions

Trials involving participants with atrial fibrillation

None of the eleven trials involving participants with atrial fibrillation included patients with dialysis-dependent ESKD. Anticoagulation was used for the prevention of stroke or systemic embolism in seven trials, acute coronary syndrome or percutaneous coronary intervention in two trials, and for periprocedural anticoagulation in participants undergoing cardioversion, or catheter ablation, in one trial each. No trial tested a treatment strategy of comparing an OAC to no anticoagulation in atrial fibrillation. Compared with

VKA, high dose NOAC reduced the risks of stroke or systemic embolism (RR 0.79, 95% CI 0.66–0.93), hemorrhagic stroke (RR 0.48, 95% CI 0.30–0.76), and all-cause death (RR 0.88, 95% CI 0.78–0.99); and had no clear effect on non-hemorrhagic stroke though confidence bounds were wide (RR 1.04, 95% CI 0.83–1.30) (**Figure 2**, **Appendix Figures 1 to 4**). Compared with aspirin, any OAC (VKA or NOAC) reduced the risk of stroke or systemic embolism (RR 0.30, 95% CI 0.19–0.48). Compared with VKA, high dose NOAC reduced the risk of major bleeding (RR 0.80, 95% CI 0.61–1.04), although this finding was not statistically significant (**Appendix Figure 5**). Compared to VKA, the effect of high dose NOAC on the risk of major or non-major clinically relevant bleeding was uncertain (RR 0.97, 95% CI 0.76–1.23) (**Appendix Figure 6**). Additional analyses after the inclusion of both high and low doses of NOAC showed that, compared with VKA, NOAC reduced the risks of stroke or systemic embolism (RR 0.87, 95% CI 0.74–1.02), and major bleeding (RR 0.74, 95% CI 0.55–1.00), though these findings were not statistically significant as their respective upper limits of confidence intervals crossed 1(**Appendix Figures 1 and 5**).

Trials involving participants with acute VTE

NOAC reduced the risk of recurrent VTE or VTE-related death when compared with placebo (RR 0.14, 95% CI 0.04–0.48); but had an uncertain effect when compared with VKA (RR 0.72, 95% CI 0.44–1.17) (**Figure 3**, **Appendix Figure 7**). There was no difference in the risk of recurrent VTE or VTE-related death between any OAC and LMWH (RR 2.10, 95% CI 0.72–6.15) (**Appendix Figure 7**). None of the NOAC trials reported data on all-cause death. There was no difference in the risk of all-cause death between VKA and LMWH (RR 1.01, 95% CI 0.79–1.31). There were no differences in the risk of major bleeding between NOAC and VKA (RR 0.54, 95% CI 0.21–1.43), VKA and LMWH (RR 1.03, 95% CI 0.43–2.51), and any OAC and LMWH (RR 1.24, 95% CI 0.54–2.88) (**Appendix Figure 8**). There was no difference in the risk of major or non-major clinically relevant bleeding between NOAC and VKA (RR 0.84, 95% CI 0.63–1.11) (**Appendix Figure 9**).

Trials involving participants requiring anticoagulation for thromboprophylaxis

There were no clear differences between NOAC and LMWH in the risks of VTE or VTE-related death (RR 0.85, 95% CI 0.40–1.83), major bleeding (RR 3.72, 95% CI 0.79–17.54), and major or non-major clinically relevant bleeding (RR 1.09, 95% CI 0.64–1.85) (**Appendix Figure 10**). There was no difference in the risk of VTE or VTE-related death (RR 0.98, 95% CI 0.53–1.82) between NOAC and placebo.

Trials involving participants with dialysis-dependent ESKD

None of the eight trials involving participants with dialysis-dependent ESKD evaluated NOAC (**Appendix Figure 11**). There was no clear difference in the risk of dialysis access thrombosis or catheter malfunction between fixed-dose/low-intensity warfarin and placebo/no study medication (RR 1.04, 95% CI 0.85–1.28) (**Appendix Figure 12**). Compared with no study medication, adjusted-dose warfarin reduced the risk of dialysis access thrombosis or catheter malfunction (RR 0.28, 95% CI 0.16–0.47) (**Appendix Figure 12**). Compared with placebo or no study medication, the effect of fixed-dose or low-intensity warfarin on all-cause death (RR 0.65, 95% CI 0.34–1.24), and major bleeding (RR 2.66, 95% CI 0.39–18.19) were uncertain (**Appendix Figures 13 and 14**).

Participants with cardiovascular disease other than atrial fibrillation

Compared with placebo, NOAC reduced the risk of major adverse cardiovascular events (defined as a composite of cardiovascular or all-cause death, non-fatal myocardial infarction or stroke), though this finding was not statistically significant as the upper limit of confidence intervals crossed 1 (RR 0.88, 95% CI 0.75–1.04) (**Appendix Figures 15 and 16**). In a single trial involving 4,168 participants with stable coronary or peripheral arterial disease, the risk of major adverse cardiovascular events with low dose NOAC was lower than placebo (RR 0.77, 95% CI 0.62–0.95). Compared with placebo, NOAC significantly increased the risk of major bleeding (2.18, 95% CI 1.10–4.32) (**Appendix Figure 17**). Additional analyses with the inclusion of trials comparing only the low dose NOAC with placebo showed that NOAC reduced the risk of major adverse cardiovascular events (RR 0.89, 95% CI 0.77–1.04) although the upper limit of confidence intervals crossed 1, with no difference in major bleeding risk (RR 2.29, 95% CI 0.57–9.18) (**Appendix Figures 16 and 17**).

Bleeding outcomes from all trials combined

Compared with VKA, high dose NOAC reduced the risk of major bleeding (RR 0.75, 95% CI 0.56–1.01), though this finding was not statistically significant as the upper limit of confidence intervals crossed 1 (**Figure 4**, **Appendix Figure 18**). There was no significant interaction of major bleeding risk by indication for anticoagulation (p=0.84). There was no clear difference in the risk of major or non-major clinically relevant bleeding (RR 0.95, 95% CI 0.83–1.07) between the NOAC and VKA groups (**Appendix Figure 19**). Compared with VKA, high dose NOAC reduced the risk of intracranial hemorrhage (RR 0.49, 95% CI 0.30–0.80) (**Appendix Figure 20**). Compared with placebo, NOAC increased the risks of major bleeding (RR 2.27, 95% CI 1.21–4.26), and major or non-major clinically relevant bleeding (RR 4.03, 95% CI 1.62–10.03). Compared to LMWH, NOAC increased the risk of major bleeding (RR 3.67, 95% CI 1.05–12.89), but not major or non-major clinically relevant bleeding (RR 1.09, 95% CI 0.64–1.85). Additional analysis after the inclusion of high and low doses of NOAC showed clear reduction in major bleeding risk with NOAC compared with VKA (RR 0.71, 95% CI 0.52–0.96) (**Appendix Figure 18**).

DISCUSSION

This review provides a comprehensive overview of the available data describing the effects of anticoagulation for people with kidney disease and a range of co-morbidities or other risk factors. It identifies some clear findings that can be used to guide treatment decisions, but also a number of areas where the available data are inadequate and further studies are urgently required. A key finding is that in patients with atrial fibrillation and early stage CKD, NOAC were superior to VKA, with 21%, 52% and 51% relative risk reductions in stroke or systemic embolism, hemorrhagic stroke and intracranial hemorrhage, respectively. However, NOAC did not reduce the risk of non-hemorrhagic stroke in atrial fibrillation. In AF, NOAC reduced the risk of major bleeding, though this finding was not statistically significant. Compared with placebo, NOAC reduced the risk of recurrent VTE or VTE-related death in patients with CKD receiving acute VTE treatment; but when compared with VKA, this effect was uncertain. These data suggest that NOAC may be a reasonable option in people with CKD who develop VTE, but further data would be helpful. In all trials combined, compared with VKA, high dose NOAC reduced the risk of major bleeding, though this result was not statistically significant. In contrast, for people with advanced stages of CKD (CrCl <25 mL/min), including dialysis-dependent ESKD, there were no data available regarding the effects of VKA or NOAC on the prevention of stroke or systemic embolism in atrial fibrillation, or on VTE and VTE-related death.

Although the rates of ischemic and hemorrhagic stroke, and intracranial hemorrhage were not reported in all trials involving participants with atrial fibrillation, it is possible that the benefit of reduced stroke or systemic embolism with NOAC was mainly driven by a reduction in hemorrhagic stroke. A similar finding was reported in the previously reported systematic review of four randomized trials comparing NOAC with VKA (22). The excess burden of atrial fibrillation, cardiovascular thrombotic events and VTE in patients with advanced CKD contributes to their poor survival (5, 6, 8). Given the greater rates of arterial and venous thrombotic in patients with advanced CKD than those with normal kidney function, the absolute risk reduction with anticoagulation treatment in this population may be greater, but this systematic review highlights the absence of evidence in patients with advanced stages of CKD and ESKD, specifically for the prevention of stroke or systemic embolism in atrial fibrillation, and recurrent VTE or VTE-related death. The potential benefit of anticoagulation treatment needs to be balanced against the risk of bleeding in this population. The rates of major bleeding with apixaban and warfarin in patients with hemodialysis-dependent ESKD (19.7 and 22.9 per 100 person-years, respectively) (27) are substantially greater than those with normal or mildly decreased kidney function (2.13 and 3.09 per 100 person-years, respectively) (28). Furthermore, 60-75% of patients with ESKD discontinue oral anticoagulation within one year, possibly due to bleeding (27, 29). Despite the absence of specific evidence, current guidelines suggest warfarin with target INR 2.0-3.0 or apixaban (recommendation class: IIa, evidence level: B-NR) (11) and time in therapeutic range >65-70% (ungraded consensus-based statements) (10) in patients CrCl <15 mL/min or dialysis-dependent ESKD with a CHA_2DS_2-VASc score ≥ 2 in men or ≥ 3 in women (11). The lack of evidence-based guidelines strongly suggests that adequately-powered randomized trials are required to address the unmet need in this population.

Leveraging their favourable benefit-harm profile, NOAC are now being evaluated for new cardiovascular indications. In early stage CKD, although NOAC did not reduce major cardiovascular events after acute coronary syndrome, the combination of low dose rivaroxaban and aspirin was beneficial for this primary outcome in patients with stable coronary or peripheral arterial disease in a single trial (30). A dose of rivaroxaban far below that required for full anticoagulation may be particularly valuable in patients with advanced CKD and ESKD, who also have an elevated bleeding risk. However, the exclusion of patients with eGFR <15 mL/min/1.73 m^2 in this trial mandates the testing of this strategy in randomized trials specifically in patients with advanced CKD and ESKD.

In contrast to the other recent systematic reviews identified by searching Medline to February 2019, this systematic review demonstrates superiority of NOAC over VKA in reducing the risk of stroke or systemic embolism in atrial fibrillation (31, 32). Furthermore, the broad scope of clinical settings of the present review allows a more comprehensive understanding of effects. Other strengths of this systematic review include inclusion of a large number of participants, robust evaluation of efficacy and bleeding outcomes, and use of the GRADE approach to assess the body of evidence. These strengths should be balanced against its limitations, which are largely due to the limitations of the underlying literature. These include exclusion of patients with dialysis-dependent ESKD and advanced non-dialysis CKD, limited information on demographic characteristics of the CKD subgroup, under-reporting of organ-specific bleeding data (especially gastrointestinal bleeding), lack of individual patient data and suboptimal methodological quality of trials involving participants with dialysis-dependent ESKD. Data on patients with CKD from trials of NOAC were obtained exclusively from subgroup analyses of large trials. The current review was not designed to assess differences between individual NOAC.

There are two ongoing trials comparing apixaban to VKA in participants with hemodialysis-dependent ESKD and atrial fibrillation (RENAL-AF trial: NCT02942407 and AXADIA trial: NCT02933697) (33). Another ongoing trial will compare VKA to no oral anticoagulation in participants with hemodialysis-dependent ESKD and atrial fibrillation (AVKDIAL: NCT02886962). Future trials should include not only participants with dialysis-dependent ESKD but also those with creatinine clearance <25 mL/min. Since no trial has evaluated a treatment strategy for comparing an OAC to no anticoagulation in atrial fibrillation, future trials should compare NOAC to placebo.

In summary, this systematic review demonstrates that NOAC had a benefit-risk profile superior to VKA in people with early stages of CKD, with significant reductions in stroke or systemic embolism and hemorrhagic stroke in atrial fibrillation, and also reduction in overall major bleeding risk in all trials combined that was not statistically significant, suggesting that these individuals will derive similar or greater benefit than those who do not have CKD. However, there is insufficient evidence to recommend widespread use of VKA or NOAC to improve clinical outcomes in patients with advanced CKD and dialysis-dependent ESKD. Adequately-powered randomized trials are required to evaluate the benefits and harms of anticoagulant therapy in this patient population.

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Author Contributions

Concept and design: J.T.H., L.P.C., V.P., S.V.B.

Literature search, data extraction and risk of bias assessment: J.T.H., B.L.N.

GRADE assessment: J.T.H., B.L.N., L.P.C., M.J.

Data analysis: J.T.H., T.T.

Data interpretation: J.T.H., L.P.C., T.T., M.J.J., M.P.G., M.J., M.M.S., A.X.G., P.B.M., D.C.W., S.C.P., V.J., B.F., D.W.J., V.P., S.V.B.
Drafting of the manuscript: J.T.H., L.P.C., S.C.P., S.V.B.
Critical review of the manuscript: All authors.
Supervision: V.P., S.V.B.
All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis.

Disclosures

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Reproducible Research Statement

Study protocol: Available from PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=79709)

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Mailing addresses of all authors

Drs Jeffrey T. Ha, Brendon L Neuen, Lap P. Cheng, Meg Jardine, Martin P. Gallagher, Min Jun, Vlado Perkovic, Sunil V. Badve

Renal and Metabolic Division, The George Institute for Global Health, Level 5, 1 King Street, Newtown, NSW 2042, Australia

Dr Tadashi Toyama

Department of Nephrology and Laboratory Medicine, Kanazawa University Hospital, Kanazawa, 920-8641, Japan

Dr Manish Sood

Ottawa Hospital Research Institute, Civic Campus, 2-014 Administrative Services Building, 1053 Carling Avenue, Box 693, Ottawa, Ontario K1Y 4E9, Canada

Dr Amit Garg

Institute for Clinical Evaluative Sciences Western Facility (ICES Western), 800 Commissioners Road, Victoria Hospital, Room ELL-215, London, ON N6A 5W9, Canada

Dr Suetonia Palmer

Department of Medicine, University of Otago Christchurch, 2 Riccarton Ave, Christchurch 8140 New Zealand

Dr Patrick Mark

Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK

Dr David Wheeler

Centre for Nephrology, University College London, Rowland Hill Street, London, NW3 2PF, UK

Dr Vivekanand Jha

The George Institute for Global Health, 310–11 Splendor Forum, Jasola, New Delhi 110025, India

Dr Ben Freedman

Heart Research Institute, Charles Perkins Centre, Building D17, Level 3, Room 3114, University of Sydney, Camperdown NSW 2006 Australia

Dr David Johnson

Ambulatory Renal and Transplant Services (ARTS) Building, 199 Ipswich Road, Woolloongabba QLD 4102 Australia

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FIGURE LEGENDS

Figure 1. PRISMA flow diagram showing selection of studies

PRISMA flow diagram showing selection of studies.

Abbreviations: CAD, coronary artery disease; ESKD, end-stage kidney disease; PAD: peripheral artery disease; RCT, randomized controlled trial; VTE, venous thromboembolism.

Figure 2. Summary of treatment effects in trials involving participants with atrial fibrillation

Forest plot showing treatment effects in trials involving participants with atrial fibrillation on stroke or systemic embolism, non-hemorrhagic stroke, hemorrhagic stroke, myocardial infarction, all-cause death, and bleeding outcomes.

Abbreviations: ASA, aspirin; CI, confidence intervals; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NOAC, non-vitamin K oral anticoagulants; OAC, oral anticoagulants; RR, risk ratio; VKA, vitamin K antagonists.

Figure 3. Summary of treatment effects in trials involving participants with acute VTE

Forest plot showing treatment effects in trials involving participants with acute VTE on recurrent VTE or VTE-related death, all-cause death, and bleeding outcomes.

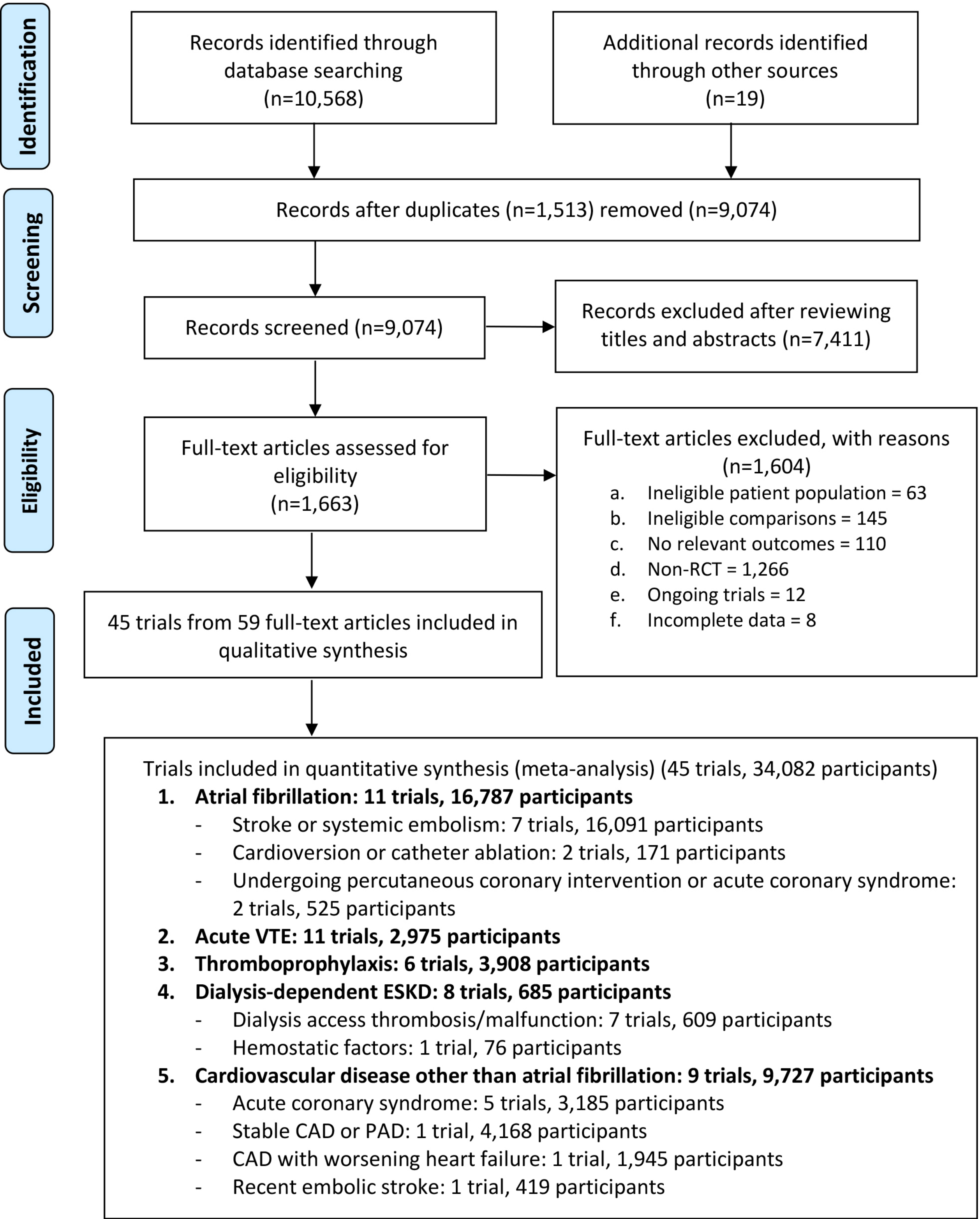
Abbreviations: ASA, aspirin; CI, confidence intervals; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LMWH, low molecular weight heparin; NOAC, non-vitamin K oral anticoagulants; OAC, oral anticoagulants; RR, risk ratio; VKA, vitamin K antagonists; VTE, venous thromboembolism.

Figure 4. Summary of treatment effects on bleeding outcomes in all trials combined

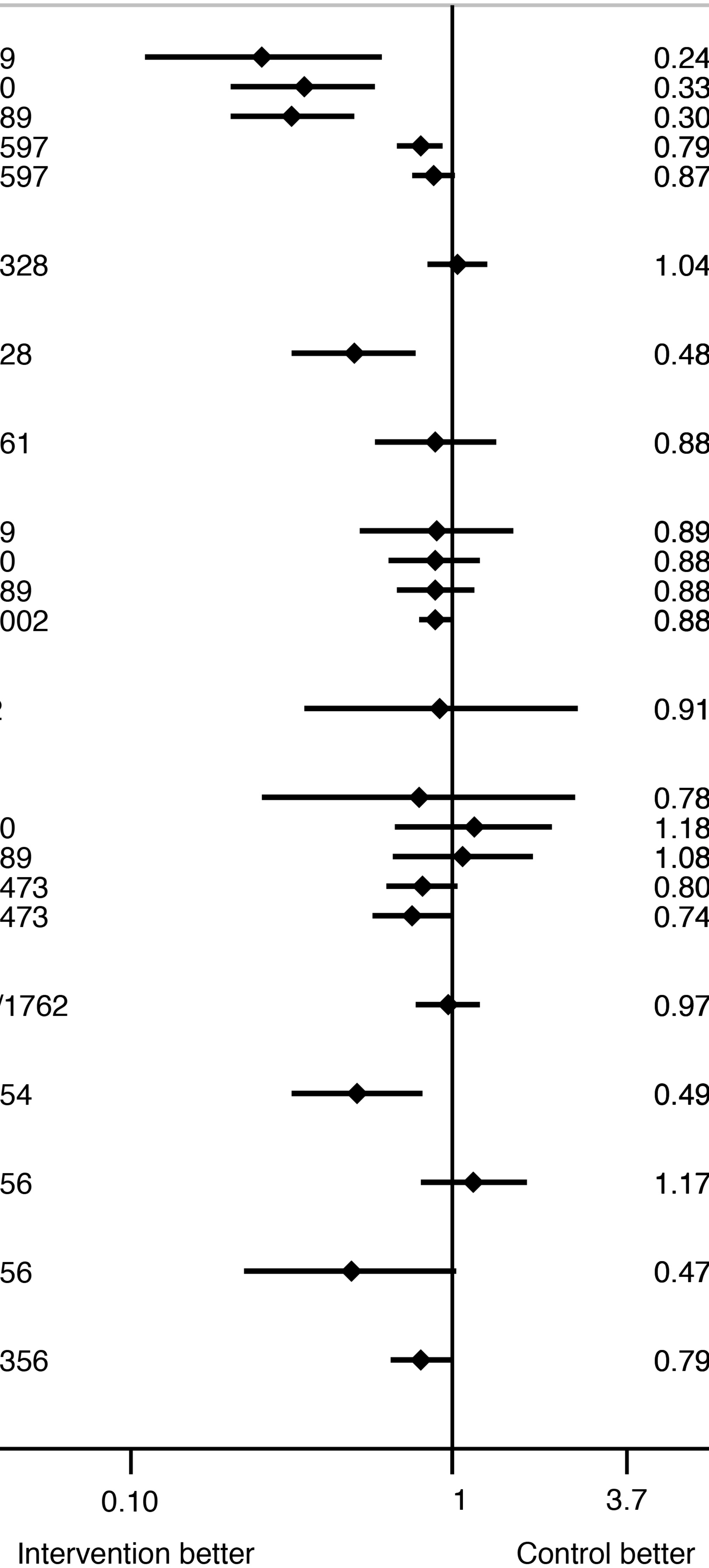
Forest plot showing treatment effects in all trials combined on major bleeding, major or non-major clinically relevant bleeding, and intracranial hemorrhage.

* The number of events were not reported in one trial; hence generic inverse variance meta-analysis was performed.

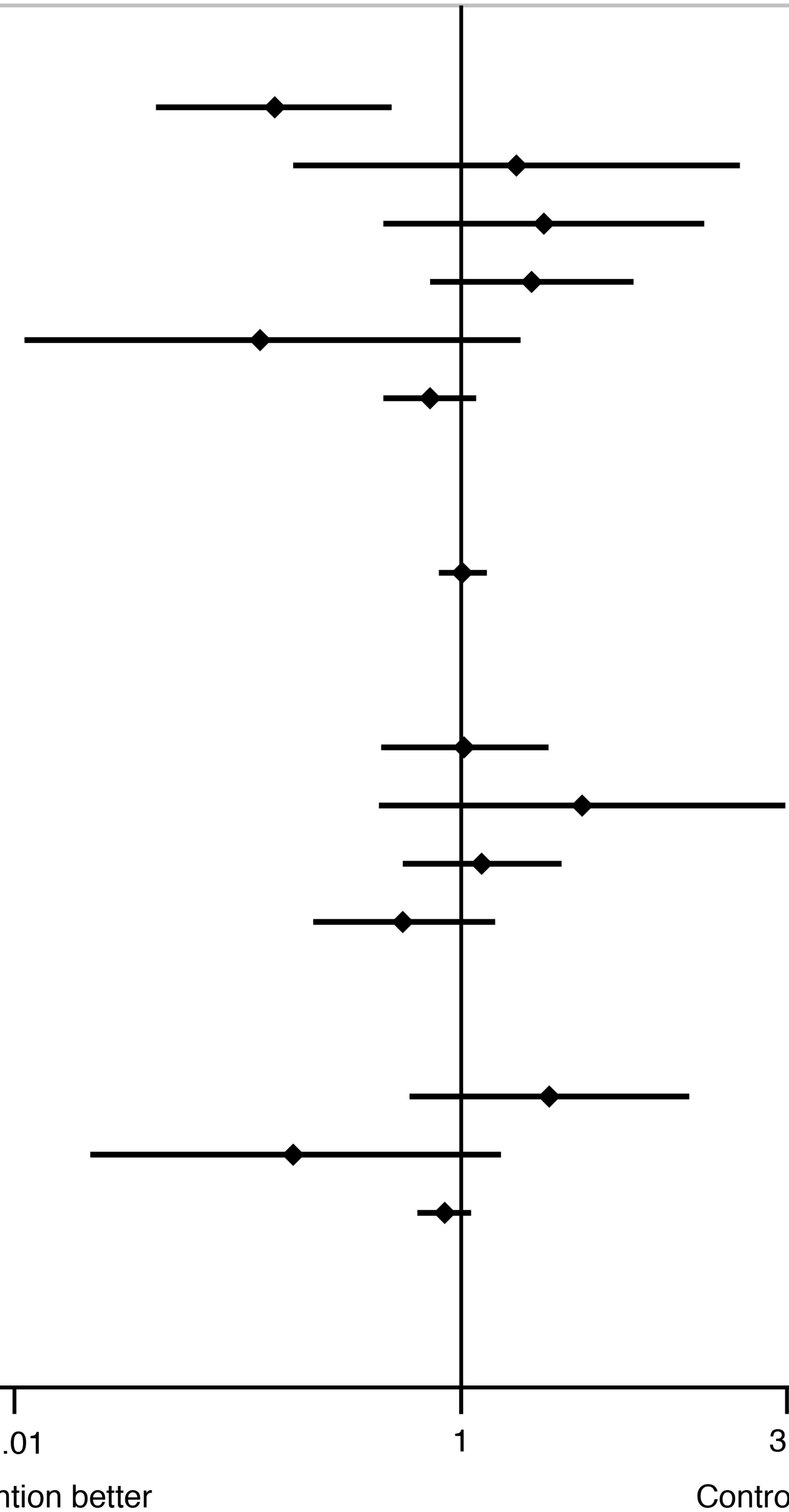
Abbreviations: ASA, aspirin; CI, confidence intervals; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LMWH, low molecular weight heparin; NOAC, non-vitamin K oral anticoagulants; RR, risk ratio; VKA, vitamin K antagonists.


Identification
Screening
Eligibility
Included
Records identified through database searching (n=10,568)
Additional records identified through other sources (n=19)
Records after duplicates (n=1,513) removed (n=9,074)
Records screened (n=9,074)
Records excluded after reviewing titles and abstracts (n=7,411)
Full-text articles assessed for eligibility (n=1,663)
Full-text articles excluded, with reasons (n=1,604)
a. Ineligible patient population = 63
b. Ineligible comparisons = 145
c. No relevant outcomes = 110
d. Non-RCT = 1,266
e. Ongoing trials = 12
f. Incomplete data = 8
45 trials from 59 full-text articles included in qualitative synthesis
Trials included in quantitative synthesis (meta-analysis) (45 trials, 34,082 participants)
1. Atrial fibrillation: 11 trials, 16,787 participants
- Stroke or systemic embolism: 7 trials, 16,091 participants
- Cardioversion or catheter ablation: 2 trials, 171 participants
- Undergoing percutaneous coronary intervention or acute coronary syndrome: 2 trials, 525 participants
2. Acute VTE: 11 trials, 2,975 participants
3. Thromboprophylaxis: 6 trials, 3,908 participants
4. Dialysis-dependent ESKD: 8 trials, 685 participants
- Dialysis access thrombosis/malfunction: 7 trials, 609 participants
- Hemostatic factors: 1 trial, 76 participants
5. Cardiovascular disease other than atrial fibrillation: 9 trials, 9,727 participants
- Acute coronary syndrome: 5 trials, 3,185 participants
- Stable CAD or PAD: 1 trial, 4,168 participants
- CAD with worsening heart failure: 1 trial, 1,945 participants
- Recent embolic stroke: 1 trial, 419 participants

Outcome Comparison	Trials	Events, Intervention	Events, Control	RR (95% CI)	I^2 %	GRADE certainty of evidence
Stroke or systemic embolism						
VKA vs ASA	1	6/267	23/249	0.24 (0.10, 0.59)	NA	Very low
NOAC vs ASA	1	17/857	51/840	0.33 (0.19, 0.56)	NA	Very low
Any OAC vs ASA	2	23/1124	74/1089	0.30 (0.19, 0.48)	0	Moderate
High dose NOAC vs VKA	5	227/5735	283/5597	0.79 (0.66, 0.93)	0	High
High and low dose NOAC vs VKA	5	389/8265	283/5597	0.87 (0.74, 1.02)	8	High
Non-hemorrhagic stroke						
High dose NOAC vs VKA	3	151/4362	144/4328	1.04 (0.83, 1.30)	0	Moderate
Hemorrhagic stroke						
High dose NOAC vs VKA	3	27/4362	57/4328	0.48 (0.30, 0.76)	0	Moderate
Myocardial infarction						
High dose NOAC vs VKA	1	34/1379	38/1361	0.88 (0.56, 1.39)	NA	Very low
All-cause death						
VKA vs ASA	1	21/267	22/249	0.89 (0.50, 1.58)	NA	Very low
NOAC vs ASA	1	59/857	66/840	0.88 (0.62, 1.23)	NA	Very low
Any OAC vs ASA	2	80/1124	88/1089	0.88 (0.66, 1.18)	0	Low
High dose NOAC vs VKA	3	598/4113	664/4002	0.88 (0.78, 0.99)	22	Moderate
Death or ischemic event after PCI/ACS						
High dose NOAC vs VKA	2	* 13/73	* 8/72	0.91 (0.33, 2.56)	75	Very low
Major bleeding						
VKA vs ASA	1	5/267	6/249	0.78 (0.24, 2.51)	NA	Very low
NOAC vs ASA	1	24/857	20/840	1.18 (0.65, 2.11)	NA	Very low
Any OAC vs ASA	2	29/1124	26/1089	1.08 (0.64, 1.83)	0	Low
High dose NOAC vs VKA	5	402/5600	491/5473	0.80 (0.61, 1.04)	75	Low
High and low dose NOAC vs VKA	5	574/8121	491/5473	0.74 (0.55, 1.00)	83	Low
Major or non-major clinically relevant bleeding						
High dose NOAC vs VKA	5	* 401/1792	* 396/1762	0.97 (0.76, 1.23)	28	Low
Intracranial hemorrhage						
High dose NOAC vs VKA	3	41/4102	81/3954	0.49 (0.30, 0.80)	36	Moderate
Gastrointestinal bleeding						
High dose NOAC vs VKA	1	51/1372	43/1356	1.17 (0.79, 1.75)	NA	Very low
Fatal bleeding						
High dose NOAC vs VKA	1	9/1372	19/1356	0.47 (0.21, 1.03)	NA	Very low
Minor bleeding						
High dose NOAC vs VKA	1	120/1372	150/1356	0.79 (0.63, 0.99)	NA	Very low



Outcome Comparison	Trials	Events, Intervention	Events, Control	RR (95% CI)	I^2 %	GRADE certainty of evidence
VTE or VTE-related death						
NOAC vs placebo	2	3/298	18/245	0.14 (0.04, 0.48)	0	Low
NOAC vs LMWH	1	2/38	1/34	1.79 (0.17, 18.87)	NA	Very low
VKA vs LMWH	2	24/150	11/143	2.39 (0.44, 12.96)	76	Very low
Any OAC vs LMWH	3	26/188	12/177	2.10 (0.72, 6.15)	51	Very low
NOAC vs ASA	1	0/92	3/64	0.12 (0.01, 1.87)	NA	Very low
NOAC vs VKA	5	27/942	40/925	0.72 (0.44, 1.17)	0	Low
All-cause death						
VKA vs LMWH	2	66/144	61/137	1.01 (0.79, 1.31)	0	Very low
Major bleeding						
VKA vs LMWH	2	11/149	10/143	1.03 (0.43, 2.51)	10	Very low
NOAC vs LMWH	1	4/38	1/34	3.58 (0.42, 30.48)	NA	Very low
Any OAC vs LMWH	3	15/187	11/177	1.24 (0.54, 2.88)	11	Very low
NOAC vs VKA	3	14/610	27/598	0.54 (0.21, 1.43)	51	Very low
Major or non-major clinically relevant bleeding						
NOAC vs placebo	1	10/91	2/46	2.53 (0.58, 11.06)	NA	Very low
NOAC vs ASA	1	1/92	4/64	0.17 (0.02, 1.52)	NA	Very low
NOAC vs VKA	3	79/703	95/708	0.84 (0.63, 1.11)	0	Low



Outcome Comparison	Trials	Events, Intervention	Events, Control	RR (95% CI)	I[2] %	GRADE certainty of evidence
Major bleeding						
High dose NOAC vs VKA	9	416/6215	518/6076	0.75 (0.56, 1.01)	67	Low
High and low dose NOAC vs VKA	9	588/8736	518/6076	0.71 (0.52, 0.96)	76	Low
NOAC vs placebo	4	126/4480	68/4230	2.27 (1.21, 4.26)	50	Low
NOAC vs ASA	1	24/857	20/840	1.18 (0.65, 2.11)	NA	Very low
NOAC vs LMWH	4	12/443	3/420	3.67 (1.05, 12.89)	0	Very low
VKA vs ASA	1	5/267	6/249	0.78 (0.24, 2.51)	NA	Very low
VKA vs LMWH	2	11/149	10/143	1.03 (0.43, 2.51)	10	Very low
Low-intensity VKA vs placebo	2	16/184	7/182	2.66 (0.39, 18.19)	48	Very low
Major or non-major clinically relevant bleeding						
High dose NOAC vs VKA	8	* 480/2495	* 491/2470	0.95 (0.83, 1.07)	4	Low
NOAC vs placebo	3	48/397	5/177	4.03 (1.62, 10.03)	0	Very low
NOAC vs ASA	2	* 1/92	* 4/64	0.54 (0.12, 2.36)	47	Very low
NOAC vs LMWH	3	27/640	26/674	1.09 (0.64, 1.85)	0	Very low
Low-intensity VKA vs placebo	1	26/87	18/87	1.44 (0.86, 2.44)	NA	Very low
Intracranial haemorrhage						
High dose NOAC vs VKA	3	41/4102	81/3954	0.49 (0.30, 0.80)	36	Moderate