Drug Class Review

Newer Oral Anticoagulant Drugs

Draft Original Report

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STRUCTURED ABSTRACT

Purpose. The goal of this report is to compare the benefits and harms of novel direct-acting oral anticoagulants (NOACs) with each other in patients with venous thromboembolism (VTE), patients at risk of recurrence of VTE, and prophylaxis against VTE in patients with atrial fibrillation or undergoing orthopedic surgery.

Data Sources. We searched Ovid MEDLINE® (1946 to September 24, 2015), the Cochrane Database of Systematic Reviews® (2005 to September 24, 2015), and the Cochrane Central Register of Controlled Trials® (to September 24, 2015) using included drugs, indications, and study designs as search terms. We also searched dossiers submitted by manufacturers and FDA documents.

Review Methods. We included randomized controlled trials (RCTs), of the included NOACs that reported health outcomes (e.g., mortality, cardiovascular events, and embolism), and harms, particularly bleeding outcomes. Priority was given to head-to-head comparisons. Study identification, assessment, and synthesis of evidence were carried out according to standard Drug Effectiveness Review Project methods. We conducted network meta-analyses or used pre-existing network analyses where possible.

Results. We included 53 studies comparing NOACs with placebo, warfarin, heparins, or aspirin; 44 RCTs, 4 observational studies, and 5 systematic reviews. Studies were good or fair quality. In patients treated for VTE, network meta-analyses of 6 RCTs suggests no statistically significant differences in VTE recurrence, deep vein thrombosis, and pulmonary embolism for any comparison. There was low-strength evidence of lower risk of major bleeding for apixaban 5 mg twice daily compared to edoxaban 30 or 60 mg once daily (HR 0.37, 95% CI 0.15 to 0.89) and dabigatran 150 mg twice daily (HR 0.42, 95% CI 0.17 to 0.99). In patients given extended treatment for prevention of recurrent VTE, indirect-comparison meta-analyses of 3 RCTs found no statistically significant differences in VTE recurrence, all-cause mortality, acute coronary syndrome (ACS), or major bleeding for apixaban 2.5 mg or 5 mg twice daily, rivaroxaban 20 mg once daily, and dabigatran 150 mg twice daily. However, there was low-strength evidence of lower risk of clinically-relevant non-major bleeding for apixaban 2.5 mg or 5 mg twice daily versus rivaroxaban 20 mg once daily and apixaban 2.5 mg twice daily versus dabigatran 150 twice daily.

In patients with non-valvular atrial fibrillation, network meta-analyses of 10 trials comparing a NOAC to warfarin suggest the following low-strength evidence of statistically significant differences. For stroke or systemic embolism (composite outcome): edoxaban 30 mg results in statistically significantly higher risk than apixaban 5 mg (OR 1.38, 95% CI 1.07 to 1.80), rivaroxaban 15 mg (OR 2.24, 95% CI 1.07 to 4.93), or dabigatran 150 mg (OR 1.64, 95% CI 1.23 to 2.20); rivaroxaban 20 mg resulted in statistically significantly higher risk than dabigatran 150 mg (OR 1.32, 95% CI 1.01 to 1.74). The risk for ischemic stroke (alone) was not increased significantly (OR 1.31, 95% CI 0.94 to 1.77) while the risk for hemorrhagic stroke was significantly increased (OR 2.45, 95% CI 1.05 to 5.17). For myocardial infarction (MI): apixaban 5 mg (OR 0.62, 95% CI 0.40 to 0.95), edoxaban 60 mg (OR 0.68, 95% CI 0.46 to 1.01), and rivaroxaban 20 mg (OR 0.56, 95% CI 0.37 to 0.86) had significantly lower risk than dabigatran 150 mg; apixaban 5 mg (OR 0.64, 95% CI 0.41 to 0.99) and rivaroxaban 20 mg (OR 0.58, 95%

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CI 0.38 to 0.88) had statistically significantly lower risk than dabigatran 110 mg; and edoxaban 30 mg had a statistically significantly greater risk than edoxaban 60 mg (OR 1.27, 95% CI 1.01 to 1.60). For major bleeding: apixaban 5 mg resulted in statistically significantly lower risk than dabigatran 150 mg (OR 0.74, 95% CI 0.60 to 0.91) and rivaroxaban 20 mg (OR 0.67, 0.55 to 0.83); edoxaban 30 mg resulted in lower risk than apixaban 5 mg (OR 0.67, 95% CI 0.54 to 0.83), dabigatran 110 mg (OR 0.58, 0.46 to 0.72) or 150 mg (OR 0.50, 95% CI 0.40 to 0.61), and rivaroxaban 20 mg (OR 0.45, 95% CI 0.37 to 0.56); edoxaban 60 mg had lower risk than rivaroxaban 20 mg (OR 0.77, 95% CI 0.63 to 0.94); rivaroxaban 20 mg had higher risk than dabigatran 110 mg (OR 1.28, 95% CI 1.04 to 1.58); and edoxaban 30 mg resulted in 41% lower risk of major bleeding than the higher dose, 60 mg (OR 0.59, 95% CI 0.50 to 0.69). Differences in all-cause mortality were not found between drugs or between doses.

In patients undergoing orthopedic surgery, network meta-analyses of 21 trials of NOACs versus heparins and warfarin suggest the following low-strength evidence of statistically significant differences. For total venous thromboembolism and all-cause mortality (composite outcome): apixaban 2.5 mg twice daily resulted in significantly lower risk compared to dabigatran 150 mg twice daily (OR 0.52, 95% CI 0.33 to 0.84) and dabigatran 220 mg twice daily (OR 0.63, 95% CI 0.40 to 0.99); rivaroxaban 10 mg once daily resulted in significantly lower risk compared to dabigatran 150 mg twice daily (OR 0.38, 95% CI 0.24 to 0.61) and dabigatran 220 mg twice daily (OR 0.46, 95% CI 0.29 to 0.72); rivaroxaban 20 mg once daily resulted in significantly lower risk compared to dabigatran 150 mg twice daily (OR 0.29, 95% CI 0.12 to 0.71) and dabigatran 220 mg twice daily (OR 0.35, 95% CI 0.14 to 0.85); and rivaroxaban 20 mg once daily resulted in significantly lower risk compared to twice daily administration (OR 0.38, 95% CI 0.15 to 0.99). For major bleeding: apixaban 2.5 mg twice daily resulted in significantly lower risk compared to rivaroxaban 20 mg once daily (OR 0.25, 95% CI 0.07 to 0.98) and twice daily (OR 0.28, 95% CI 0.09 to 0.90); rivaroxaban 20 mg once daily and twice daily resulted in significantly increased risk compared to dabigatran 150 mg twice daily (OR 4.07, 95% CI 1.04 to 16.02 and OR 3.71, 95% CI 1.12 to 12.25, respectively). Differences in all-cause mortality and symptomatic deep vein thrombosis were not found between drugs or between doses, and this evidence was insufficient to draw conclusions.

Conclusion. Evidence directly comparing NOACs is unavailable; current evidence is limited to indirect comparisons. Low-strength evidence suggests apixaban and rivaroxaban had lower risk of VTE and mortality in orthopedic patients. In atrial fibrillation, edoxaban 30 mg had a higher risk of stroke or embolism, and rivaroxaban had higher risk than dabigatran (higher-dose). Differences in effectiveness were not found among the drugs in initial or extended treatment for VTE. Apixaban, edoxaban, and lower-dose dabigatran have lower rates of major bleeding. Evidence on other comparisons and outcomes were insufficient to draw conclusions.

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INTRODUCTION

Threat of hemorrhage, perhaps through a cut blood vessel in a finger, activates the body's complex coagulation cascade causing a blood clot to form at the site of injury. This prevents further blood loss and possible death, which is an appropriate response to vascular injury. However, sometimes clots form inappropriately, not in response to a cut blood vessel, but in response to other acquired or inherited factors. This review is concerned with the prevention and treatment of inappropriate blood clotting.

Inappropriate clotting can result in deep vein thrombosis (DVT) and pulmonary embolism (PE) in the venous system and heart attack and ischemic stroke in the arterial system, causing significant morbidity and mortality. The burden of disease due to inappropriate clotting in the United States is high. Risk factors for DVT and PE include immobilization (e.g., long plane flights and major orthopedic surgery), cancer, pregnancy, oral contraceptives, and smoking. The Centers for Disease Control and Prevention (CDC) estimates that as many as 900,000 people (1 to 2 per 1,000) could be affected by DVT/PE each year in the United States.[1] An estimated 60,000 to 100,000 Americans die of venous thromboembolism (DVT/PE), with 10% to 30% of people dying within 1 month of diagnosis.[1] It is estimated that among people who have a DVT, approximately 50% will have long-term complications, and approximately 33% of people with DVT/PE will have a recurrence within 10 years.[1] Risk factors for ischemic stroke and myocardial infarction include having nonvalvular atrial fibrillation or atherosclerosis. The CDC estimates that 2.7 to 6.1 million people in the United States have atrial fibrillation and approximately 735,000 Americans experience a myocardial infarction each year.[2,3] More than 795,000 people in the United States experience a stroke and nearly 130,000 Americans die from strokes annually.[4]

Historically, medications to treat or prevent blood clots were primarily low-molecular weight heparins and warfarin. These drugs inhibit clotting through indirect mechanisms and require injection (in the case of heparins) and laboratory monitoring for dose adjustment and have multiple drug-drug interactions (in the case of warfarin). Several "novel" direct-acting oral anticoagulant pharmacotherapies (NOACs) have been developed in recent years that have the theoretical advantages of oral administration, not requiring laboratory monitoring for dose adjustment, and not having numerous drug-drug interactions. These are 3 oral factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) and a direct thrombin inhibitor (dabigatran) (Table 1). Known concerns with NOACs include reduced drug clearance in patients with impairment of kidney function requiring lower doses for some drugs, and lack of a reversal agent for cases of over-anticoagulation or need for quick reversal (e.g., emergency surgery). In October 2015, the U.S. Food and Drug Administration granted accelerated approval to idarucizumab, a reversal agent for use in patients who are taking dabigatran, an anticoagulant for which a reversal agent had previously been unavailable.[5] This review compares the effectiveness and harms of NOACs with each other and focuses on the uses of these drugs for the treatment of thromboembolic events in adults, for extended treatment to prevent recurrence of thromboembolic events in adults at increased risk, and for the prevention of thromboembolic events in adults with atrial fibrillation or venous thromboembolic events in adults who have undergone orthopedic surgery.

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Scope and Key Questions

The goal of this report is to compare the benefits and harms of newer oral anticoagulant drugs. The Pacific Northwest Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, outcomes of interest, and, based on these, eligibility criteria for studies. A draft of these questions and inclusion and exclusion criteria were posted on the Drug Effectiveness Review Project website for public comment. The draft was reviewed and revised by representatives of the organizations participating in the Drug Effectiveness Review Project. Revision took into consideration input from the public and the organizations' desire for the key questions to reflect populations, drugs, and outcome measures of interest to clinicians and patients. These organizations approved the following key questions to guide the review for this report:

1. What is the evidence on the effectiveness and harms of the direct-acting oral anticoagulants compared with each other or with other anticoagulants for treatment of a thromboembolic event in adults?
2. What is the evidence on the effectiveness and harms of the direct-acting oral anticoagulants compared with each other or with other anticoagulants for extended treatment to prevent recurrence of thromboembolic events in adults at increased risk?
3. What is the evidence on the effectiveness and harms of the direct-acting oral anticoagulants compared with each other or with other anticoagulants for prevention of thromboembolic events in adults with atrial fibrillation or venous thromboembolic events (VTE) in adults who have undergone orthopedic surgery?
4. What is the evidence on whether there are subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one direct-acting oral anticoagulant is more effective or associated with fewer harms than another direct-acting oral anticoagulants or other anticoagulants?

METHODS

Inclusion Criteria

Populations

Adult populations for:

1. Treatment of distal venous thrombosis (DVT) or pulmonary embolism (PE)
2. Extension of treatment for DVT or PE, to prevent recurrence in patients at increased risk (as defined by study, or according to guidelines[1])
3. Prophylaxis to prevent venous thromboembolic events (VTE) in patients undergoing orthopedic surgery
4. Prophylaxis in patents with atrial fibrillation (valvular or non-valvular), to prevent thromboembolic events

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Interventions

Table 1. Interventions

Generic name	Trade name(s)	Forms
Direct Thrombin (Factor IIa) Inhibitors		
Dabigatran	Pradaxa®	Oral capsule
Direct Factor Xa Inhibitors		
Apixaban	Eliquis®	Oral tablet
Rivaroxaban	Xarelto®	Oral tablet
Edoxaban	Savaysa™ (US), Lixiana® (Japan)	Oral tablet

Comparators

- Other Factor Xa inhibitors
- Other anticoagulants (oral or injectable; including, but not limited to, warfarin, unfractionated heparin, low molecular weight heparins)
- Aspirin for patients unable to take warfarin

Outcomes

Effectiveness outcomes

- Mortality (all-cause and cardiovascular)
- Symptomatic thromboembolic event (ischemic stroke, recurrent/initial deep vein thrombosis or pulmonary embolism)
- Cardiovascular events (including, but not limited to, myocardial infarction)
- Functional capacity (e.g., return to work, ability to work)
- Quality of life (e.g., SF-36)

Harms outcomes

- Overall adverse events reported
- Overall withdrawals due to adverse events
- Major adverse events (including, but not limited to, major bleeding, intracranial bleeding [including intracerebral hemorrhage] readmission, reoperation,)
- Specific adverse events or withdrawals due to specific adverse events (including, but not limited to, any bleeding, gastrointestinal symptoms, hypersensitivity reactions, etc.)

Study Designs

- Efficacy/effectiveness: head-to-head or active-controlled randomized trials and good-quality systematic reviews
- Harms: head-to-head or active-controlled randomized trials, good-quality systematic reviews, as well as cohort or case-control observational studies

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Literature Search

We searched Ovid MEDLINE® (1946 to September 24, 2015), the Cochrane Database of Systematic Reviews® (2005 to September 24, 2015), and the Cochrane Central Register of Controlled Trials® (to September 24, 2015) using included drugs, indications, and study designs as search terms. See Appendix C for complete search strategies. We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. We searched the US Food and Drug Administration's Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® X7, Thomson Reuters).

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Titles and abstracts of citations identified through literature searches were first assessed for inclusion by one reviewer using the eligibility criteria above and a second reviewer checked all citations excluded by the first reviewer. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Results published only in abstract form were not included because inadequate details were available for quality assessment. We only included abstracts when they provided additional data on subgroups and outcomes of interest for an included study.

Data Abstraction

We abstracted information on population characteristics, interventions, subject enrollment, and discontinuation and results for efficacy, effectiveness, and harms outcomes for trials, observational studies, and systematic reviews. We recorded intent-to-treat results when reported. If true intent-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intent-to-treat results. In cases where only per protocol results were reported, we calculated intent-to-treat results if the data for these calculations were available. Data abstraction was performed by one reviewer and independently checked by a second reviewer and differences were resolved by consensus.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria of the Drug Effectiveness Review Project.[6] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intent-to-treat analysis. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category is broad, studies

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with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are likely to be valid, while others are only possibly valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist. A particular randomized trial might receive 2 different ratings, one for effectiveness and another for adverse events.

The criteria used to rate observational studies of adverse events reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair quality if they met 3 to 5 criteria, and poor quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality. We rated the internal validity based a clear statement of the questions(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies. Again, these studies were categorized as good when all criteria were met.

Two reviewers independently assessed the quality of each study and differences were resolved by consensus.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. For example, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes. While direct comparisons (one NOAC compared with another) were preferred over indirect comparison (one NOAC compared with a non-NOAC [e.g., warfarin]), there are no direct comparisons of the NOACs available for any population, and only indirect comparisons were available. Indirect comparisons can be difficult to interpret for a number of reasons, primarily heterogeneity of trial populations, interventions, and outcomes assessment. Data from indirect comparisons should be interpreted with caution.

We conducted network meta-analyses of data from trials of NOACs compared with warfarin in patients with nonvalvular atrial fibrillation, and indirect comparison meta-analyses of data from trials of NOACs compared with enoxaparin in patients undergoing orthopedic surgery. We combined only studies that were homogeneous enough that combining their results could be justified. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively.

For network meta-analyses of patients with atrial fibrillation, data were analyzed using the GeMTC package for R (gemtc version 0.7-1, R version 3.2.2). GeMTC implements a Bayesian network meta-analysis using Just Another Gibbs Sampler (JAGS) for Markov Chain Monte Carlo (MCMC) simulation. For each analysis, a total of 10,000 samples were simulated. Full details are available at http://dx.doi.org/10.5281/zenodo.47532.[7] Sensitivity analyses were conducted for the outcome of major bleeding to evaluate the sensitivity of the model to potential problems with a study of rivaroxaban that could affect bleeding outcomes. Other sensitivity

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analyses were not possible due to few studies per drug. For network meta-analyses of patients treated with NOACs to prevent VTE in patients undergoing orthopedic surgery, we used a frequentist approach, using the "mvmeta" command in Stata (version 14.0).[8]

Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.[9] Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. Table 2 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy and harms of newer oral anticoagulant drugs. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals, but rather the strength of the evidence supporting the result. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus.

Strength of evidence is graded for key outcome measures. For atrial fibrillation, these were all-cause mortality, the composite outcome of stroke and systemic embolism (the common primary outcome of trials), myocardial infarction and major bleeding. For treatment of VTE the prioritized outcomes were all-cause mortality, recurrent VTE, acute coronary syndrome, major bleeding and clinically relevant bleeding. For the prevention of VTE in orthopedic surgery patients, the key outcomes were All-cause mortality, symptomatic VTE, total VTE + all-cause mortality (primary composite outcome of many studies), and Major bleeding. For SOE ratings based on network meta-analyses where there were no studies directly comparing drugs head to head as a part of the network, the maximum rating was low.

Table 2. Definitions of the grades of overall strength of evidence[9]

Grade	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome**. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

RESULTS

Overview

We identified 1,806 citations from database searches and 151 citations from other sources, including dossiers from pharmaceutical companies, preliminary update scans, the topic brief, and

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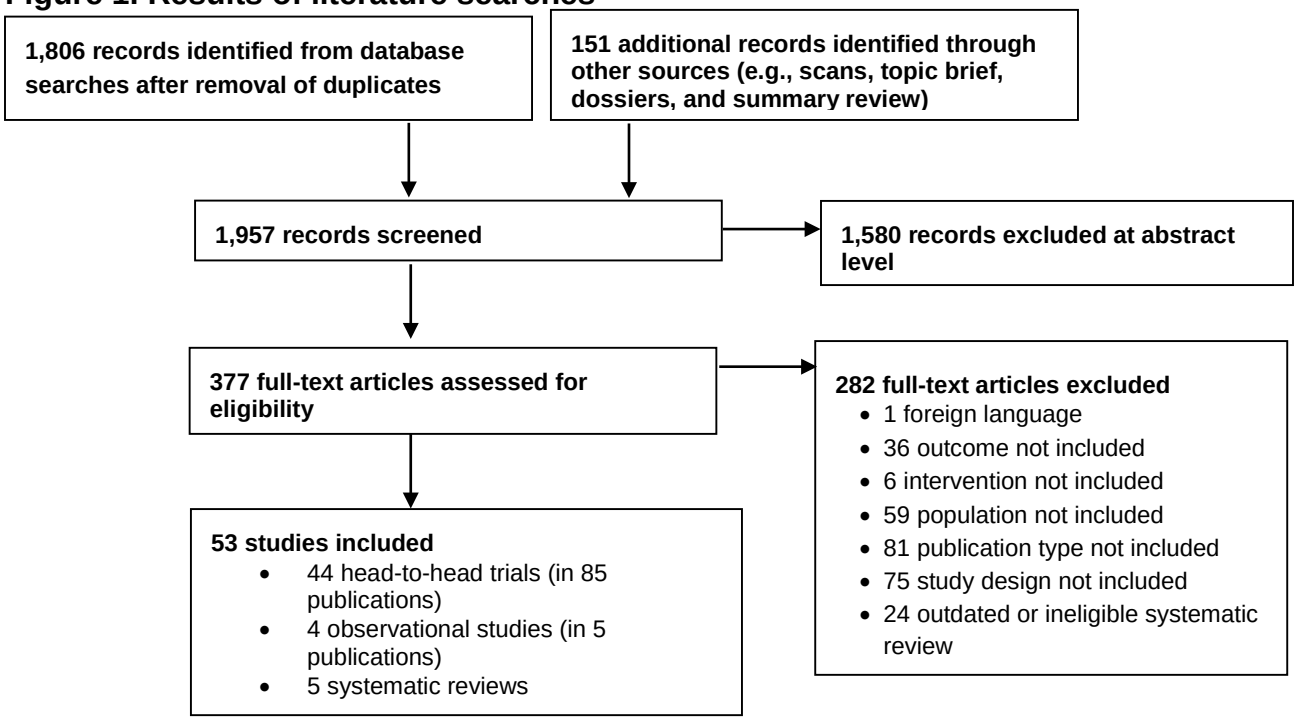
the prior summary review. Ultimately, our literature searches yielded 1,957 citations, 377 of which were evaluated for eligibility at the full-text level. Of these publications, we included 53 studies: 44 studies[10-53] (in 85 publications)[10-94] were randomized controlled trials, 4 studies[95-98] (in 5 publications)[95-99] were observational in design, and 5 were systematic reviews.[100-104] We received dossiers from 3 pharmaceutical companies, and we included 13 studies suggested to us through the dossier solicitation process. Figure 1 illustrates the flow of studies through the selection process. A list of studies excluded after full-text review and reasons for exclusion is provided in Appendix D. Study quality was fair to good, with none rated poor quality. Study quality ratings can be seen in Evidence Tables 2, 4, and 6.

Figure 1. Results of literature searches[a]



[a] The Drug Effectiveness Review Project uses a modified PRISMA flow diagram.[105]

Key Question 1. What is the evidence on the effectiveness and harms of the direct-acting oral anticoagulants compared with each other or with other anticoagulants for treatment of a thromboembolic event in adults?

Summary of Findings

- Based on network meta-analyses in a good-quality systematic review of 6 RCTs:
  - There were no statistically significance differences in VTE recurrence, any deep vein thrombosis, or any pulmonary embolism for the following comparisons: edoxaban 30 or 60 mg once daily versus apixaban 5 mg twice daily, edoxaban 30 or 60 mg once daily versus rivaroxaban 15 mg twice daily, edoxaban 30 or 60 mg once daily versus dabigatran 150 mg twice daily (VTE recurrence only), apixaban 5 mg twice daily versus rivaroxaban 15 mg twice daily, apixaban 5 mg twice daily versus dabigatran 150 mg twice daily (VTE recurrence only), and

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rivaroxaban 15 mg twice daily versus dabigatran 150 mg twice daily (VTE recurrence only). This evidence is insufficient to draw conclusions due to indirectness and imprecision.

- There was low-strength evidence of lower risk of major bleeding for apixaban 5 mg twice daily compared to edoxaban 30 or 60 mg once daily (HR 0.37, 95% CI 0.15 to 0.89) and dabigatran 150 mg twice daily (HR 0.42, 95% CI 0.17 to 0.99). Evidence on major bleeding for other comparisons found no statistically significant differences but was insufficient to draw conclusions. Evidence for other harms outcomes was also insufficient.

Detailed Assessment

We included one good-quality systematic review comparing the effectiveness and harms of NOACs in patients being treated for thromboembolic events.[101] The review conducted searches through February 2014 and identified six trials of NOACs (total N = 27,023 patients) (Table 3). Two of the included trials assessed dabigatran 150 mg twice daily (RE-COVER 1[24] and RE-COVER 2[23]), two trials assessed rivaroxaban 15 mg twice daily (EINSTEIN-DVT[30] and EINSTEIN-PE[106]), one assessed edoxaban 30 or 60 mg once daily (HOKUSAI[18]), and one assessed apixaban 5 mg twice daily (AMPLIFY[10]); all compared to heparin and warfarin. Median treatment duration of the included trials ranged from 6 to 8.2 months. All of the included studies of NOACs were rated as good quality. This review conducted a network meta-analysis across the included drugs, using heparin and/or warfarin as the common comparator.

We also included two fair-quality trials published since the systematic review (Table 3).[22,27] One of these trials (AMPLIFY-J[22]) assessed apixaban 10 mg twice daily, and the other (J-EINSTEIN[27]) assessed rivaroxaban 10-15 mg twice daily. Treatment duration was 6 months for AMPLIFY-J and 12 months for J-EINSTEIN. The AMPLIFY-J (N = 80) and J-EINSTEIN (N = 100) trials were small Japanese replications of earlier trials.

Table 3. Characteristics of trials of NOAC treatment for venous thromboembolism

Trial	Comparison(s)	Population	N	Duration of follow-up (months)
In Systematic Review [101]				
EINSTEIN-DVT[30]	Rivaroxaban 15 mg bid LMWH+Warfarin	Age >18 years old. Had acute symptomatic deep-vein thrombosis, with or without symptomatic pulmonary embolism.	3,449	6
EINSTEIN-PE[106]	Rivaroxaban 15 mg bid LMWH+Warfarin	Age >18 years old. Had acute symptomatic pulmonary embolism with or without symptomatic deep-vein thrombosis.	4,832	6
RE-COVER 1[24]	Dabigatran 150 mg bid LMWH+Warfarin	Age > 18 years old. Had objectively confirmed, symptomatic, proximal deep vein thrombosis or pulmonary embolism that had already been treated with approved anticoagulant for 6 to 12 months	2,539	6
RE-COVER 2[23]	Dabigatran 150 mg bid LMWH+Warfarin	Age > 18 years old. Had objectively confirmed, symptomatic, proximal deep vein thrombosis or pulmonary embolism that had already been treated with approved anticoagulant	2,568	6

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Trial	Comparison(s)	Population	N	Duration of follow-up (months)
		for 6 to 12 months		
HOKUSAI[18]	Edoxaban 60 mg qd Edoxaban 30 mg qd LMWH or UFH+Warfarin	Age > 18 years old. Had objectively confirmed, symptomatic, proximal deep vein thrombosis or pulmonary embolism that had already been treated with approved anticoagulant for 6 to 18 months	8,240	3-12
AMPLIFY[10]	Apixaban 5 mg bid LMWH+Warfarin	Age > 18 years old. Had objectively confirmed, symptomatic, proximal deep vein thrombosis or pulmonary embolism.	5,395	6
Published since systematic review				
J-EINSTEIN[27]	Rivaroxaban 10-15 mg bid UFH+Warfarin	Adults ≥20 y with acute, objectively confirmed symptomatic DVT and/or PE.	100	12
AMPLIFY-J[22]	Apixaban 5 mg bid UFH+Warfarin	Adults ≥20 y with acute pulmonary embolism/deep vein thrombosis.	80	6

Abbreviations: bid, twice daily; LMWH, low-molecular-weight heparin; n, sample size; qd, once daily; UFH, unfractionated heparin.

Comparative Efficacy and Effectiveness

Based on a network meta-analysis, the systematic review found no significant differences between any of the NOACs on the outcomes of VTE recurrence, any DVT, or any PE. This evidence is insufficient to draw conclusions based on indirectness, unknown consistency, and imprecision of estimates. Mortality was not assessed in the network meta-analysis.

In evidence from 2 trials not included in the network meta-analysis, a trial of apixaban reported no statistically significant difference in recurrent PE or recurrent VTE/VTE-related death between apixaban and unfractionated heparin/warfarin.[22] Similarly, statistically significant differences were not found between rivaroxaban and unfractionated heparin/warfarin (J-EINSTEIN[27]) in VTE, DVT, or PE.

Comparative Harms

For harms, the systematic review's network meta-analysis found low-strength evidence that there was a significantly lower risk of major bleeding with apixaban 5 mg than edoxaban 30 mg (HR 0.37, 95% CI 0.15 to 0.89) and dabigatran 150 mg (HR 0.42, 95% CI 0.17 to 0.99). No differences in major bleeding were reported for edoxaban versus rivaroxaban or dabigatran; apixaban versus rivaroxaban; or rivaroxaban versus dabigatran. This evidence is insufficient due to unknown consistency, indirectness, and imprecise estimates. Other harms outcomes were not assessed in the network meta-analysis.

The AMPLIFY-J trial found that apixaban resulted in lower risk of overall bleeding (RR 0.40, 95% CI 0.19 to 0.86) and composite major bleeding/clinically-relevant non-major bleeding (RR 0.27, 95% CI 0.08 to 0.88) compared to unfractionated heparin/warfarin, but the trial did not find significant differences in major bleeding, clinically-relevant non-major bleeding, overall adverse events, or withdrawal due to adverse events.[22] The J-EINSTEIN[27] trial reported no significant differences between rivaroxaban and unfractionated heparin/warfarin in withdrawal due to adverse events or any bleeding outcome.

Finally, we included a good-quality population-based retrospective cohort study using a health plan claims database of prescribing information from managed care plans and other sources (including Medicare and Medicaid) to assess rates of gastrointestinal bleeding associated

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with use of NOACs for any indication. The large (N = 46,163) database study reported no significant differences in rates of gastrointestinal bleeding between dabigatran and warfarin (HR 1.21, 95% CI 0.96 to 1.53) or rivaroxaban or warfarin (HR 0.98, 95% CI 0.36 to 2.69) in patients receiving a prescription for an NOAC.[96]

Key Question 2. What is the evidence on the effectiveness and harms of the direct-acting oral anticoagulants compared with each other or with other anticoagulants for extended treatment to prevent recurrence of thromboembolic events in adults at increased risk?

Summary of Findings

- Based on indirect-comparison meta-analyses from a good-quality systematic review of 3 RCTs:
    - Statistically significant differences in VTE recurrence, all-cause mortality, or acute coronary syndrome (ACS) were not found for the following comparisons: apixaban 2.5 mg or 5 mg twice daily versus rivaroxaban 20 mg once daily, apixaban 2.5 mg or 5 mg twice daily versus dabigatran 150 mg twice daily, and rivaroxaban 20 mg once daily versus dabigatran 150 twice daily. This evidence is insufficient to draw conclusions.
    - Statistically significant differences in major bleeding were not found between apixaban 2.5 mg or 5 mg twice daily, rivaroxaban 20 mg once daily, or dabigatran 150 mg twice daily. This evidence is insufficient to draw conclusions.
    - There was low-strength evidence of lower risk of clinically-relevant non-major bleeding for apixaban 2.5 mg or 5 mg twice daily versus rivaroxaban 20 mg once daily (OR 0.23, 95% CI 0.08 to 0.62 and OR 0.31, 95% CI 0.11 to 0.82, respectively) and apixaban 2.5 mg twice daily versus dabigatran 150 twice daily (OR 0.40, 95% CI 0.17 to 0.97).

Detailed Assessment

For evidence of comparative effectiveness and harms in adult patients undergoing extended treatment for VTE as prophylaxis against recurrence of VTE, we included 1 good-quality systematic review.[100] This review included 3 placebo-controlled RCTs (N = 5,036); 1 trial of dabigatran 150 mg twice daily versus placebo (RE-SONATE),[25] 1 trial of rivaroxaban 20 mg once daily versus placebo (EINSTEIN-EXT),[107] and 1 trial of apixaban 2.5 mg twice daily versus apixaban 5 mg twice daily versus placebo (AMPLIFY-EXT).[108] An additional trial, the RE-MEDY trial, was not included in the review because the population was considered at higher risk of recurrence, and the control group was treated with warfarin (goal INR 2.0 to 3.0). This was a fair-quality trial of extended of treatment with dabigatran 150 mg twice daily or warfarin for patients previously enrolled in the RECOVER 1 or 2 VTE treatment trials.[25] It was published with the results of the placebo-controlled RE-SONATE trial, which was included in the systematic review.[100]

The review included an indirect-comparison meta-analysis for the comparative effectiveness and harms of dabigatran, rivaroxaban, and apixaban in adult patients undergoing extended treatment to prevent recurrence of VTE using SPSS, with the METCARDIO meta-

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analysis tool. The following indirect comparisons were reported: apixaban 2.5 mg or 5 mg twice daily versus rivaroxaban 20 mg once daily, apixaban 2.5 mg or 5 mg twice daily versus dabigatran 150 mg twice daily, and rivaroxaban 20 mg once daily versus dabigatran 150 twice daily. Populations included adults with objectively confirmed, symptomatic, proximal DVT or PE that had been treated with an anticoagulant for 6 to 12 months (2 studies) or 6 to 18 months (2 studies). Please see Table 4 for additional study characteristics. NOAC extended treatment ranged from 6 to 36 months across the studies, with longer treatment in the RE-MEDY study of higher risk patients.

Table 4. Characteristics of trials of extended NOAC treatment to prevent venous thromboembolism recurrence

Trial	Comparison(s)	N	Duration of Treatment (months)
Placebo-controlled trials			
RE-SONATE[25]	Dabigatran 150 mg bid Placebo	1,353	6 (mean 5.5)
EINSTEIN-EXT[107]	Rivaroxaban 20 mg qd Placebo	1,197	6 to 12
AMPLIFY-EXT[108]	Apixaban 2.5 mg bid Apixaban 5 mg bid Placebo	2,486	12
Warfarin-controlled trial			
RE-MEDY[25]	Dabigatran 150 mg bid Warfarin	2,866	6 to 36 (mean 15.7)

Abbreviations: bid, twice daily; n, sample size; qd, once daily

Comparative Efficacy and Effectiveness

The primary efficacy endpoint for the studies included in this systematic review was recurrent VTE. All-cause mortality and ACS (myocardial infarction and unstable or stable angina) were also studied. The indirect comparison meta-analyses did not find statistically significant differences in VTE recurrence, all-cause mortality, and ACS for any comparison (Table 5). This evidence is insufficient to draw conclusions due to unknown consistency, indirectness, and imprecision of estimates.

Table 5. Efficacy and effectiveness results of indirect meta-analyses of extended treatment of venous thromboembolism[100]

	Recurrent VTE	All-cause mortality	ACS (MI, stable/unstable angina)
Apixaban 2.5 mg bid vs. Rivaroxaban 20 mg qd	OR 1.10 (95% CI 0.43 to 2.82)	OR 0.99 (95% CI 0.076 to 13)	OR 0.12 (95% CI 0.007 to 1.99)
Apixaban 5 mg bid vs. Rivaroxaban 20 mg qd	OR 1.068 (95% CI 0.41 to 2.76)	OR 0.58 (95% CI 0.05 to 37.8)	OR 0.192 (95% CI 0.013 to 2.7)
Apixaban 2.5 mg bid vs. Dabigatran 150 mg bid	OR 2.45 (95% CI 0.63 to 9.6)	OR 2.52 (95% CI 0.11 to 60)	OR 0.5 (95% CI 0.02 to 13.1)
Apixaban 5 mg bid vs. Dabigatran 150 mg bid	OR 2.4 (95% CI 0.6 to 9.3)	OR 1.48 (95% CI 0.05 to 37.8)	OR 0.78 (95% CI 0.03 to 18.4)
Rivaroxaban 20 mg qd vs. Dabigatran 150 mg bid	OR 2.23 (95% CI 0.5 to 9.6)	OR 2.54 (95% CI 0.05 to 122.2)	OR 4.0 (95% CI 0.012 to 140)

Abbreviations: bid, twice daily; CI, confidence interval; mg, milligram; OR, odds ratio; qd, once daily

The RE-MEDY trial of dabigatran 150 mg versus warfarin, which was not included in the network meta-analysis, included patients considered at higher risk of VTE recurrence and found

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no differences in all-cause mortality, recurrent or fatal VTE, symptomatic DVT, symptomatic non-fatal PE, VTE-related death, or all-cause death between dabigatran and warfarin.[25] However, this trial reported an increased risk of ACS during treatment with dabigatran compared with warfarin (RR 4.32, 95% CI 1.23 to 15.13).

Comparative Harms

The indirect comparison meta-analyses did not find statistically significant differences in major bleeding for any comparison (Table 6). This evidence is insufficient to draw conclusions due to unknown consistency, indirectness, and the imprecision of the effect measures. This imprecision indicates that future studies could alter the findings of this systematic review.

This review provided low-strength evidence that apixaban has lower risk of clinically relevant non-major bleeding than rivaroxaban or dabigatran, depending on dose comparisons. In comparison with rivaroxaban 20 mg once daily, both apixaban 2.5 mg twice daily (OR 0.23, 95% CI 0.08 to 0.62) and apixaban 5 mg twice daily (OR 0.31, 95% CI 0.11 to 0.82) had lower risk, and apixaban 2.5 mg twice daily had lower risk than dabigatran 150 twice daily (OR 0.40, 95% CI 0.17 to 0.97). Statistically significant differences in clinically relevant non-major bleeding were not found for apixaban 5 mg twice daily or rivaroxaban 20 mg once daily compared with dabigatran 150 mg twice daily (Table 6). Clinically-relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but requiring medical intervention, unscheduled contact with a physician, interruption of discontinuation of the study drug, or discomfort or impairment of activities of daily living.[100]

Table 6. Harms results of indirect meta-analyses of extended treatment of venous thromboembolism[100]

	Major bleeding	Clinically-relevant non-major bleeding
Apixaban 2.5 mg bid vs. Rivaroxaban 20 mg qd	OR 0.12 (95% CI 0.007 to 1.99)	**OR 0.23 (95% CI 0.084 to 0.62)**
Apixaban 5 mg bid vs. Rivaroxaban 20 mg qd	OR 0.064 (95% CI 0.003 to 1.426)	**OR 0.31 (95% CI 0.11 to 0.82)**
Apixaban 2.5 mg bid vs. Dabigatran 150 mg bid	OR 0.10 (95% CI 0.003 to 3.3)	**OR 0.40 (95% CI 0.168 to 0.97)**
Apixaban 5 mg bid vs. Dabigatran 150 mg bid	OR 0.05 (95% CI 0.001 to 2.2)	OR 0.54 (95% CI 0.233 to 1.3)
Rivaroxaban 20 mg qd vs. Dabigatran 150 mg bid	OR 0.81 (95% CI 0.019 to 34.5)	OR 1.76 (95% CI 0.61 to 5.0)

Abbreviations: bid, twice daily; CI, confidence interval; mg, milligram; OR, odds ratio; qd, once daily
*Statistically significant findings are bolded.

The RE-MEDY trial, which was not included in the network meta-analysis and included patients who had previously completed the RECOVER 1 or RECOVER 2 trials, reported less overall bleeding (HR 0.71, 95% CI 0.61 to 0.83) and major bleeding/clinically-relevant non-major bleeding (HR 0.54, 95% CI 0.41 to 0.71) with dabigatran compared to warfarin.[25] For the comparison of dabigatran versus warfarin, the results of the RE-MEDY trial for major bleeding (HR 0.54, 95% CI 0.41 to 0.71) were generally consistent with the pooled results of the meta-analysis (HR 0.64, 95% CI 0.35 to 1.14).

Key Question 3. What is the evidence on the effectiveness and harms of the direct-acting oral anticoagulants compared with each other or with other anticoagulants for prevention of thromboembolic events in adults with atrial

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fibrillation or venous thromboembolic events (VTE) in adults who have undergone orthopedic surgery?

Summary of Findings

Atrial Fibrillation

- Ten trials compared a NOAC to warfarin, and comparisons across NOACs were made using a network meta-analysis. All findings are low strength of evidence, with the exception of comparisons to rivaroxaban 15 mg, which were insufficient to draw conclusions. Differences in all-cause mortality were not found between drugs or between doses.
- Stroke or systemic embolism:
    - Edoxaban 30 mg results in statistically significantly higher risk than apixaban 5 mg (OR 1.38, 95% CI 1.07 to 1.80), rivaroxaban 15 mg (OR 2.24, 95% CI 1.07 to 4.93), or dabigatran 150 mg (OR 1.64, 95% CI 1.23 to 2.20).
    - Rivaroxaban 20 mg resulted in statistically significantly higher risk than dabigatran 150 mg (OR 1.32, 95% CI 1.01 to 1.74); the risk for ischemic stroke (alone) was not increased significantly (OR 1.31, 95% CI 0.94 to 1.77) while the risk for hemorrhagic stroke was significantly increased (OR 2.45, 95% CI 1.05 to 5.17).
- Myocardial infarction:
    - Apixaban 5 mg (OR 0.62, 95% CI 0.40 to 0.95), edoxaban 60 mg (OR 0.68, 95% CI 0.46 to 1.01) and rivaroxaban 20 mg (OR 0.56, 95% CI 0.37 to 0.86) had significantly lower risk than dabigatran 150 mg.
    - Apixaban 5 mg (OR 0.64, 95% CI 0.41 to 0.99) and rivaroxaban 20 mg (OR 0.58, 95% CI 0.38 to 0.88) had statistically significantly lower risk than dabigatran 110 mg.
    - Edoxaban 30 mg had a statistically significantly greater risk than edoxaban 60 mg (OR 1.27, 95% CI 1.01 to 1.60).
- Major bleeding:
    - Apixaban 5 mg resulted in statistically significantly lower risk than dabigatran 150 mg (OR 0.74, 95% CI 0.60 to 0.91) and rivaroxaban 20 mg (OR 0.67, 0.55 to 0.83).
    - Edoxaban 30 mg resulted in lower risk than apixaban 5 mg (OR 0.67, 95% CI 0.54 to 0.83), dabigatran 110 mg (OR 0.58, 0.46 to 0.72) or 150 mg (OR 0.50, 95% CI 0.40 to 0.61), and rivaroxaban 20 mg (OR 0.45, 95% CI 0.37 to 0.56).
    - Edoxaban 60 mg had lower risk than rivaroxaban 20 mg (OR 0.77, 95% CI 0.63 to 0.94).
    - Rivaroxaban 20 mg had higher risk than dabigatran 110 mg (OR 1.28, 95% CI 1.04 to 1.58).
    - Edoxaban 30 mg resulted in 41% lower risk of major bleeding than the higher dose, 60 mg (OR 0.59, 95% CI 0.50 to 0.69).

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Orthopedic Surgery

- 21 trials compared an NOAC to enoxaparin, and comparisons across NOACs were made using a network meta-analysis. The strength of evidence based on this analysis was low or insufficient; low-strength findings are listed below for the composite outcome of total venous thromboembolism and all-cause mortality and for major bleeding. The strength of evidence for these outcomes was insufficient for other comparisons. Differences in all-cause mortality and symptomatic deep vein thrombosis were not found between drugs or between doses, and this evidence was insufficient to draw conclusions.
- Total venous thromboembolism and all-cause mortality:
  - Apixaban 2.5 mg twice daily resulted in significantly lower risk compared to dabigatran 150 mg twice daily (OR 0.52, 95% CI 0.33 to 0.84) and dabigatran 220 mg twice daily (OR 0.63, 95% CI 0.40 to 0.99).
  - Rivaroxaban 10 mg once daily resulted in significantly lower risk compared to dabigatran 150 mg twice daily (OR 0.38, 95% CI 0.24 to 0.61) and dabigatran 220 mg twice daily (OR 0.46, 95% CI 0.29 to 0.72).
  - Rivaroxaban 20 mg once daily resulted in significantly lower risk compared to dabigatran 150 mg twice daily (OR 0.29, 95% CI 0.12 to 0.71) and dabigatran 220 mg twice daily (OR 0.35, 95% CI 0.14 to 0.85). Rivaroxaban 20 mg once daily resulted in significantly lower risk compared to twice daily administration (OR 0.38, 95% CI 0.15 to 0.99).
- Major bleeding:
  - Apixaban 2.5 mg twice daily resulted in significantly lower risk compared to rivaroxaban 20 mg once daily (OR 0.25, 95% CI 0.07 to 0.98) and twice daily (OR 0.28, 95% CI 0.09 to 0.90).
  - Rivaroxaban 20 mg once daily and twice daily resulted in significantly increased risk compared to dabigatran 150 mg twice daily (OR 4.07, 95% CI 1.04 to 16.02 and OR 3.71, 95% CI 1.12 to 12.25, respectively).

Detailed Assessment

Atrial Fibrillation

Comparative Effectiveness

Eleven RCTs assessed a NOAC drug to prevent ischemic stroke in patients with non-valvular atrial fibrillation (2 of dabigatran, 3 each of rivaroxaban, apixaban and edoxaban).[17,19,20,26,28,47-52] The studies enrolled patients at increased risk of an ischemic event (e.g., prior stroke/TIA, CHADS2 score of 2 or more), with 10 comparing a NOAC to warfarin and one comparing a NOAC (apixaban) to aspirin in patients with documented reasons for not taking warfarin. Study characteristics are presented in Table 7, below. Each of the drugs has at least one study with at more than a year duration, and in total over 80,000 patients were studied (range 222 to 21,105). Most of these studies (7 of 11) reported a primary composite outcome of any stroke (ischemic or hemorrhagic) or systemic embolism, while the rest, which were smaller studies, were intended to evaluate bleeding. Warfarin dosing was managed using either point-of-care or traditional laboratory testing, with doses adjusted to achieve an International Normalized Ratio (INR) in the range of 2-3. An exception was that patients over 70 years in Japanese studies used a reduced

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INR range of 2-2.6, according to national guideline recommendations. The 4 large trials have resulted in numerous additional publications, mainly presenting the results by various subgroups of the population, such as patients with or without diabetes.[55,56,58,62,64-66,68-72,77,78,80-87,89-92,94] Edoxaban and rivaroxaban are given once daily, while apixaban and dabigatran are given twice daily. In the text below, we refer to the dose given per capsule or tablet.

The Japanese study of rivaroxaban (J-ROCEKT AF) used a lower dose (15 mg daily) for all patients because pharmacokinetic modeling suggested higher peak and AUC drug levels with the 20 mg dose. Patients with reduced renal function , > 80 years, or < 60 kg received lower doses of apixaban in all studies, and studies of rivaroxaban used reduced dosing (15 mg daily) in patients with reduced renal function. Two smaller, early studies of dabigatran and edoxaban included doses that are not recommended for use now (i.e. too low or too high), and these doses were not included in our results.[26,48]

The quality of the studies varied from good (4 trials) to the lower end of fair. The ROCKET-AF study of rivaroxaban is rated good quality for cardiovascular outcomes, but fair for bleeding outcomes, with recent developments drawing into question the accuracy of the point-of-care INR test results used to adjust warfarin doses (the device was removed from the US market due to inaccurate readings).[109] All three rivaroxaban studies used some type of point-of-care device to test INRs, neither study of dabigatran reported the method, the larger study of apixaban used a point-of-care test while the smaller Japanese study did not, and the largest study of edoxaban used a point-of-care test while a smaller study used laboratory testing and a third smaller study did not report the method. The implications of the use of these various point-of-care tests on study results, including ROCKET-AF, are not entirely clear, but for ROCKET-AF some proportion of patients on warfarin had erroneously low INRs reported. This may have resulted in unnecessary upward dose adjustments, which could have resulted in higher than normal bleeding rates in the warfarin group. Implications for benefit outcomes, such as ischemic stroke, are less clear.

Table 7. Characteristics of RCTs of NOACs for atrial fibrillation

	Trial	Drug	Sample Size # Countries	Follow-up	INR Test	Primary Outcome
Comparisons with warfarin						
Dabigatran	Connolly, 2009 ***RE-LY*** (Good)	Dabigatran 110 mg bid Dabigatran 150 mg bid warfarin	18,113 44 countries	Median: 2 years	NR	Stroke/ embolism
	Ezekowitz, 2007 ***PETRO*** (Fair)	Dabigatran 150 mg bid warfarin	502 4 countries	Maximum: 12 weeks	NR	Major bleeding
Rivaroxaban	Patel, 2011 ***ROCKET-AF*** (Fair)	Rivaroxaban 20 mg qd warfarin	14,264 45 countries	Median: 1.9 years	POC	Stroke/ embolism
	Hori, 2012 **J -ROCKET-AF** (Good)	Rivaroxaban 15 mg qd warfarin	2801 1: Japan	Maximum 30 months	POC	Stroke/ embolism
	Mao, 2014 (Fair)	Rivaroxaban 20 mg Rivaroxaban 15 mg qd warfarin	353 1:China	Unclear	POC	Stroke/embolism
Apixaban	Granger, 2011 ***ARISTOTLE*** (Good)	Apixaban 5 mg bid Apixaban 2.5 mg bid warfarin	18,201 39 countries	Median: 1.8 years	POC	Stroke/ embolism
	Ogawa, 2011 ***ARISTOTLE-J*** (Good)	Apixaban 5 mg bid Apixaban 2.5 mg bid warfarin	222 1: Japan	Median: 85 days	Lab	Major bleeding

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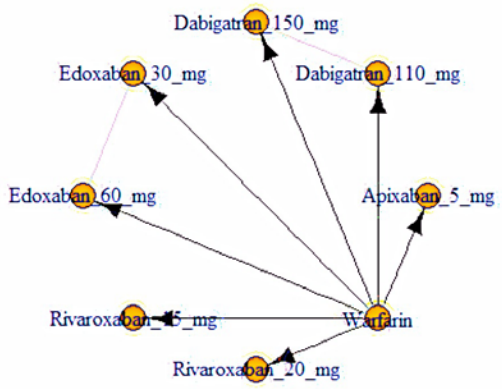
	Trial	Drug	Sample Size # Countries	Follow-up	INR Test	Primary Outcome
Edoxaban	Giugliano, 2013 **ENGAGE-TIMI 48** (Good)	Edoxaban 60 mg qd Edoxaban 30 mg qd warfarin	21,105 46 countries	Median 2.8 years	POC	Stroke/ embolism
	Yamashita, 2012 (Fair)	Edoxaban 30 mg qd Edoxaban 60 mg qd warfarin	536 1 country: Japan	12 weeks	NR	Major bleeding
	Weitz, 2010 (Fair)	Edoxaban 30 mg qd Edoxaban 60 mg qd warfarin	1146 Multinational	Maximum: 12 weeks	Lab	Major bleeding
Comparisons with Aspirin						
	Connolly, 2011 **AVERROES** (Fair)	Apixaban 5mg bid Apixaban 2.5 mg bid Aspirin 81-324 mg qd	5599 36 countries	Mean 1.1 years[a]	NA	Stroke/ embolism

Abbreviations: qd, once daily; bid, twice daily; NR, not reported; NA, not applicable; POC, point-of-care test; Lab, laboratory test
[a] Study terminated early due to benefit

Comparisons with warfarin

We conducted a network meta-analysis of three key benefit outcomes for NOACs in patients with non-valvular atrial fibrillation, using data from all 10 trials. The diagram for the network for the outcome of stroke or systemic embolism (composite outcome) is shown in Figure 2, below. Diagrams for other outcomes are available upon request. Because all drugs have so far been compared only with warfarin (and not to each other), the network is anchored by comparisons with warfarin, with only dose comparisons across drugs. This is a Bayesian network analysis, such that the variance around the point estimate is reported as the 95% credible interval, rather than the 95% confidence interval. We compare our results to the findings of the large trials as well as to a previous network meta-analysis conducted using only these 4 trials.[102]

Figure 2. Diagram of network for analysis



The results of our network meta-analysis are presented in Table 8 below.

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Table 8. NOAC Network Meta-analysis Results: Cardiovascular Outcomes

Comparison	Stroke/Embolism	All-cause Mortality	Myocardial Infarction
Drug vs. Drug (by dose)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Apixaban 5 mg vs. Dabigatran 110 mg	0.86 (0.65, 1.12)	0.98 (0.82, 1.17)	**0.64 (0.41, 0.99)**
Apixaban 5 mg vs. Dabigatran 150 mg	1.19 (0.89, 1.58)	1.01 (0.85, 1.21)	**0.62 (0.40, 0.95)**
Edoxaban 30 mg vs. Apixaban 5 mg	**1.38 (1.07, 1.80)**	0.97 (0.83, 1.13)	1.40 (0.96, 1.99)
Edoxaban 60 mg vs. Apixaban 5 mg	0.98 (0.76, 1.29)	1.02 (0.87, 1.19)	1.10 (0.75, 1.58)
Apixaban 5 mg vs. Rivaroxaban 15 mg	1.61 (0.76, 3.58)	0.62 (0.17, 2.07)	0.22 (0.01, 2.10)
Apixaban 5 mg vs. Rivaroxaban 20 mg	0.90 (0.70, 1.15)	1.08 (0.87, 1.34)	1.10 (0.74, 1.63)
Edoxaban 30 mg vs. Dabigatran 110 mg	1.18 (0.90, 1.55)	0.95 (0.80, 1.12)	0.89 (0.60, 1.32)
Edoxaban 60 mg vs. Dabigatran 110 mg	0.84 (0.63, 1.12)	1.00 (0.85, 1.18)	0.70 (0.47, 1.04)
Edoxaban 30 mg vs. Dabigatran 150 mg	**1.64 (1.23, 2.20)**	0.98 (0.82, 1.16)	0.87 (0.58, 1.28)
Edoxaban 60 mg vs. Dabigatran 150 mg	1.17 (0.87, 1.58)	1.03 (0.87, 1.22)	0.68 (0.46, 1.01)
Rivaroxaban 15 mg vs. Dabigatran 110 mg	0.53 (0.24, 1.11)	1.57 (0.48, 5.66)	2.83 (0.30, 96.44)
Rivaroxaban 20 mg vs. Dabigatran 110 mg	0.96 (0.73, 1.24)	0.91 (0.73, 1.14)	**0.58 (0.38, 0.88)**
Rivaroxaban 15 mg vs. Dabigatran 150 mg	0.74 (0.33, 1.55)	1.61 (0.50, 5.81)	2.76 (0.30, 97.17)
Rivaroxaban 20 mg vs. Dabigatran 150 mg	**1.32 (1.01, 1.74)**	0.94 (0.75, 1.18)	**0.56 (0.37, 0.86)**
Edoxaban 30 mg vs. Rivaroxaban 15 mg	**2.24 (1.07, 4.93)**	0.60 (0.17, 1.99)	0.31 (0.01, 2.87)
Edoxaban 30 mg vs. Rivaroxaban 20 mg	1.24 (0.97, 1.59)	1.05 (0.84, 1.30)	1.54 (1.08, 2.18)
Edoxaban 60 mg vs. Rivaroxaban 15 mg	1.59 (0.76, 3.48)	0.64 (0.18, 2.09)	0.24 (0.01, 2.26)
Edoxaban 60 mg vs. Rivaroxaban 20 mg	0.88 (0.68, 1.14)	1.10 (0.89, 1.36)	1.21 (0.84, 1.72)
Dose Comparisons			
Dabigatran 110 mg vs. 150 mg	**1.38 (1.11, 1.74)**	1.03 (0.90, 1.18)	0.97 (0.72, 1.31)
Edoxaban 30 mg vs. 60 mg	**1.40 (1.16, 1.72)**	0.95 (0.85, 1.06)	**1.27 (1.01, 1.60)**
Rivaroxaban 15 mg vs. 20 mg	0.56 (0.25, 1.16)	1.72 (0.52, 6.22)	4.95 (0.52, 158.60)
Comparisons with Warfarin			
Apixaban 5 mg vs. Warfarin	**0.78 (0.65, 0.93)**	0.89 (0.79, 1.00)	0.88 (0.66, 1.17)
Dabigatran 110 mg vs. Warfarin	0.91 (0.75, 1.12)	0.91 (0.80, 1.04)	1.37 (0.99, 1.91)
Dabigatran 150 mg vs. Warfarin	**0.66 (0.53, 0.82)**	0.88 (0.77, 1.01)	**1.41 (1.02, 1.97)**
Edoxaban 30 mg vs. Warfarin	1.08 (0.90, 1.30)	**0.86 (0.78, 0.96)**	1.22 (0.98, 1.53)
Edoxaban 60 mg vs. Warfarin	**0.77 (0.63, 0.94)**	0.91 (0.82, 1.01)	0.96 (0.76, 1.21)
Rivaroxaban 15 mg vs. Warfarin	**0.49 (0.22, 0.99)**	1.43 (0.44, 5.05)	3.92 (0.43, 130.90)
Rivaroxaban 20 mg vs. Warfarin	0.87 (0.74, 1.03)	0.83 (0.69, 1.00)	0.79 (0.61, 1.03)

Abbreviations: mg, milligrams; OR, odds ratio; 95% CI, 95% Credible Interval

All-cause mortality

For all-cause mortality, which includes death from ischemic stroke or systemic embolism as well as deaths due to bleeding, the drugs were not significantly different to each other and no differences were found between doses of edoxaban, rivaroxaban, or dabigatran. Compared with warfarin, the analyses indicate no differences, with the exception of edoxaban 30 mg, with an odds ratio of 0.86 (95% credible interval 0.78 to 0.96), indicating the pooled analysis shows edoxaban to be superior in reducing mortality by 14%. The strength of this evidence was low for all comparisons, except for comparisons with the low dose of rivaroxaban studied in Japan (15 mg per day), which was insufficient. Our findings are similar to the prior network meta-analysis in comparisons across NOACs, but their analysis found warfarin to have a slightly higher, but statistically significant, risk of all-cause mortality than apixaban 5 mg, while our analysis does not, likely reflecting the addition of data from ARISTOTLE-J.[102]

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Stroke or systemic embolism

The composite outcome of "stroke or systemic embolism" was the primary outcome for all of the large trials and 2 of the smaller trials. A disadvantage of this outcome, however, is that it includes ischemic and hemorrhagic strokes. Ascertainment of the etiology of stroke (e.g., using imaging) was not consistently applied in all cases for any study.

Our analysis finds that edoxaban 30 mg results in statistically significantly higher risk of stroke or systemic embolism than apixaban 5 mg (OR 1.38, 95% CI 1.07 to 1.80), rivaroxaban 15 mg (OR 2.24, 95% CI 1.07 to 4.93), or dabigatran 150 mg (OR 1.64, 95% CI 1.23 to 2.20) and that rivaroxaban 20 mg resulted in statistically significantly higher risk of stroke or systemic embolism than dabigatran 150 mg (OR 1.32, 95% CI 1.01 to 1.74). These findings are similar to that of the prior network meta-analysis, with the exception of the comparison to rivaroxaban 15 mg, which was not included in the prior analysis.[102] In considering strength of evidence for this outcome, we assumed a 30% reduction in risk was required for a clinically important difference compared with warfarin. Because these results are based indirect comparisons, the strength of this evidence was low for all comparisons, except for apixaban 5 mg and edoxaban 60 mg versus rivaroxaban 15 mg, which we rated insufficient due to greater imprecision in the estimate of effect (see Table 8 above).

The prior network meta-analysis also reported results for other outcomes.[102] For the comparison of rivaroxaban 20 mg and dabigatran 150 mg, as we found, the composite outcome was significantly increased. Looking at ischemic and hemorrhagic stroke separately, they found that the risk for ischemic stroke (alone) was not increased significantly (OR 1.31, 95% CI 0.94 to 1.77), while the risk for hemorrhagic stroke was significantly increased (OR 2.45, 95% CI 1.05 to 5.17).

Our analysis finds dabigatran 150 mg, apixaban 5 mg, rivaroxaban 15 mg and edoxaban 60 mg to result in statistically significantly fewer events than warfarin. These findings are consistent with the findings of the large trials of the drugs, with the RE-LY trial of dabigatran and the ARISTOTLE trial of apixaban also finding lower risk with the NOAC, a non-inferiority finding for rivaroxaban in the ROCKET AF trial, and confirming a trend seen in the intention-to-treat analysis of the ENGAGE AF-TIMI 48 trial of edoxaban. Similarly, our analysis finds the lower doses of dabigatran and edoxaban to result in greater risk of this outcome than the higher doses, which is also consistent with the large trial findings.

Myocardial infarction (MI)

In addition to being a key cardiovascular endpoint, there has been some concern over potentially increased risk of MI with dabigatran. All of the large studies provided definitions for and used adjudication committees to determine MI outcomes.

Our analysis finds that apixaban 5 mg (OR 0.62, 95% CI 0.40 to 0.95), edoxaban 60 mg (OR 0.68, 95% CI 0.46 to 1.01), and rivaroxaban 20 mg (OR 0.56, 95% CI 0.37 to 0.86) had significantly lower risk than dabigatran 150 mg. These findings are consistent with the findings of the prior network meta-analysis.[102] New findings from our analysis are that apixaban 5 mg (OR 0.64, 95% CI 0.41 to 0.99) and rivaroxaban 20 mg (OR 0.58, 95% CI 0.38 to 0.88) also had statistically significantly lower risk of MI than dabigatran 110 mg. Additionally, edoxaban 30 mg had a statistically significantly greater risk than edoxaban 60 mg (OR 1.27, 95% CI 1.01 to 1.60). The strength of this evidence was low for all comparisons, except for comparisons with the low dose of rivaroxaban studied in Japan (15 mg per day), which was insufficient. Similar to

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previous findings, the risk with dabigatran 150 mg was greater than with warfarin (OR 1.41, 95% CI 1.02 to 1.97).

Comparative Harms

Major Bleeding

The definitions for Major bleeding was consistent with the criteria established by the International Society on Thrombosis and Haemostasis in 2005[110] for all studies except the small study from China.[20] The ROCKET AF definition also added permanent disability associated with bleeding as part of the definition.

The results of our network meta-analysis of major bleeding are presented in Table 9 below. This analysis finds that apixaban 5 mg resulted in statistically significantly lower risk of major bleeding than dabigatran 150 mg (OR 0.74, 95% CI 0.60 to 0.91) and rivaroxaban 20 mg (OR 0.67, 0.55 to 0.83). Further, edoxaban 30 mg resulted in lower risk of major bleeding than apixaban 5 mg (OR 0.67, 95% CI 0.54 to 0.83), dabigatran 110 mg (OR 0.58, 0.46 to 0.72) or 150 mg (OR 0.50, 95% CI 0.40 to 0.61), and rivaroxaban 20 mg (OR 0.45, 95% CI 0.37 to 0.56). Edoxaban 60 mg also had lower risk of major bleeding than rivaroxaban 20 mg (OR 0.77, 95% CI 0.63 to 0.94). Comparisons between doses of the same drug showed that edoxaban 30 mg resulted in 41% lower risk of major bleeding than the higher dose, 60 mg (OR 0.59, 95% CI 0.50 to 0.69). Rivaroxaban 20 mg had higher risk than dabigatran 110 mg (OR 1.25, 95% CI 1.02 to 1.53), but similar to dabigatran 150 mg. Comparisons with warfarin resulted in significantly lower risk with all of the NOACs at all doses, except for rivaroxaban 20 mg. We have no data on the 15 mg dose of rivaroxaban for this outcome. These findings are consistent with the findings of the prior network meta-analysis.[102]

Because of recent concerns with the validity of data on bleeding outcomes with rivaroxaban (due to potentially inaccurate point-of-care INR test results used to adjust warfarin doses), we conducted two sensitivity analyses to test the robustness of our findings. The results are resented in Table 9, below. Sensitivity Analysis 1 is the analyses with the results of ROCKET AF removed. The results for the other statistically significant findings were unaffected by this simple analysis, mainly because the network depends almost entirely on comparisons with warfarin (i.e. there are no NOAC vs. NOAC comparison arms in the network that would be affected by removal of these data). In sensitivity analysis 2, the bleeding rate for warfarin was adjusted to be equivalent to that of rivaroxaban 20 mg. This would remove any potential increase in bleeding introduced by the inaccurate INR readings. Here the results are again almost identical to the primary analysis. The results for apixaban 5 mg and edoxaban 30 mg or 60 mg changed slightly in the direct of a smaller difference between the drugs, but still results in lower risk of major bleeding with apixaban or edoxaban. Comparisons with dabigatran shifted slightly, towards less of a difference with apixaban and edoxaban and slightly larger difference compared with rivaroxaban. However, no changes in statistical significance were found.

Table 9. NOAC Network Meta-analysis Results: Major Bleeding

Comparison	Original Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
Drug vs. Drug (by dose)			
Apixaban 5 mg vs. Dabigatran 110 mg	0.86 (0.70, 1.06)	0.87 (0.70, 1.06)	0.87 (0.70, 1.07)
Apixaban 5 mg vs. Dabigatran 150 mg	**0.74 (0.60, 0.91)**	**0.74 (0.61, 0.91)**	**0.74 (0.61, 0.92)**
Edoxaban 30 mg vs. Apixaban 5 mg	**0.67 (0.54, 0.83)**	**0.67 (0.54, 0.82)**	**0.67 (0.54, 0.83)**
Edoxaban 60 mg vs. Apixaban 5 mg	1.14 (0.94, 1.38)	1.14 (0.93, 1.38)	1.14 (0.94, 1.39)
Apixaban 5 mg vs. Rivaroxaban 20 mg	**0.67 (0.55, 0.83)**	--	**0.69 (0.56, 0.85)**

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Comparison	Original Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
Edoxaban 30 mg vs. Dabigatran 110 mg	**0.58 (0.46, 0.72)**	**0.58 (0.47, 0.72)**	**0.58 (0.47, 0.72)**
Edoxaban 60 mg vs. Dabigatran 110 mg	0.98 (0.80, 1.20)	0.98 (0.81, 1.20)	0.99 (0.80, 1.21)
Edoxaban 30 mg vs. Dabigatran 150 mg	**0.50 (0.40, 0.61)**	**0.50 (0.40, 0.61)**	**0.50 (0.40, 0.62)**
Edoxaban 60 mg vs. Dabigatran 150 mg	0.85 (0.69, 1.03)	0.85 (0.70, 1.03)	0.85 (0.70, 1.03)
Rivaroxaban 20 mg vs. Dabigatran 110 mg	**1.28 (1.04, 1.58)**	--	**1.25 (1.02, 1.53)**
Rivaroxaban 20 mg vs. Dabigatran 150 mg	1.10 (0.90, 1.35)	--	1.07 (0.88, 1.32)
Edoxaban 30 mg vs. Rivaroxaban 20 mg	**0.45 (0.37, 0.56)**	**--**	**0.47 (0.38, 0.57)**
Edoxaban 60 mg vs. Rivaroxaban 20 mg	**0.77 (0.63, 0.94)**	--	**0.79 (0.65, 0.96)**
Dose Comparisons			
Dabigatran 110 mg vs. 150 mg	0.86 (0.74, 1.00)	0.86 (0.74, 1.00)	0.86 (0.74, 1.00)
Edoxaban 30 mg vs. 60 mg	**0.59 (0.50, 0.69)**	**0.59 (0.50, 0.69)**	**0.59 (0.50, 0.69)**
Comparisons with Warfarin			
Apixaban 5 mg vs. Warfarin	**0.69 (0.60, 0.80)**	**0.69 (0.60, 0.80)**	**0.69 (0.60, 0.80)**
Dabigatran 110 mg vs. Warfarin	**0.80 (0.69, 0.93)**	**0.80 (0.69, 0.93)**	**0.80 (0.69, 0.93)**
Dabigatran 150 mg vs. Warfarin	0.93 (0.81, 1.08)	0.93 (0.80, 1.08)	0.93 (0.80, 1.08)
Edoxaban 30 mg vs. Warfarin	**0.46 (0.40, 0.54)**	**0.46 (0.40, 0.54)**	**0.46 (0.40, 0.54)**
Edoxaban 60 mg vs. Warfarin	**0.79 (0.69, 0.90)**	**0.79 (0.69, 0.90)**	**0.79 (0.69, 0.90)**
Rivaroxaban 20 mg vs. Warfarin	1.03 (0.89, 1.19)	--	1.00 (0.87, 1.15)

As another way to check the potential for erroneously high bleeding rates in the warfarin group in the ROCKET AF trial, we compared major bleeding rates across the trials (Table 10). Unadjusted rates increase across the trials according to the median duration of followup, but the rate in the ROCKET AF trial does not appear to be an outlier, particularly for the duration range of 1.8 to 2 years. It is not clear if there may be issues with the point-of-care tests used in other trials, but there does not appear to be a pattern according to whether the test was conducted in a standard laboratory or using a point-of-care test.

Table 10. Comparison of major bleeding rates in across trials

Study	NOAC	INR test method	Duration of followup	Rate in warfarin group
Giugliano, 2013; ENGAGE-TIMI 48	Edoxaban	POC	2.8 years median	7.45%
Connolly, 2009; RE-LY	Dabigatran	NR	2 years median	6.59%
Patel, 2011; ROCKET-AF	Rivaroxaban	POC	1.9 years median	5.44%
Granger, 2011; ARISTOTLE	Apixaban	POC	1.8 years median	5.10%
Ogawa, 2011; ARISTOTLE-J	Apixaban	Lab	12 weeks median	1.35%
Weitz, 2010	Edoxaban	Lab	12 weeks maximum; median NR	0.4%
Ezekowitz, 2007; PETRO	Dabigatran	NR	12 weeks maximum; median NR	0
Yamashita, 2012	Edoxaban	NR	12 weeks maximum; median NR	0

Abbreviations: NR, not reported; POC, point-of-care test for INR; Lab, laboratory test for INR; NOAC, novel oral anticoagulant drug

The good-quality network meta-analysis that included only the 4 major trials of NOACs reported additional outcomes.[102] This analysis found that there was an increased risk of intracranial hemorrhage with rivaroxaban 20 mg compared with dabigatran 100 mg (OR 2.23, 95% CI 1.23 to 3.90), while edoxaban 30 mg had a lower risk compared with rivaroxaban 20 mg (OR 0.48, 95% CI 0.28 to 0.75). Additionally, apixaban 5 mg had a lower risk than dabigatran 150 mg (OR 0.59, 95% CI 0.41 to 0.82).

For gastrointestinal bleeding, edoxaban 30 mg again had lower risk than dabigatran 110 (OR 0.61, 0.42 to 0.86), dabigatran 150 mg (OR 0.45, 95% CI 0.32 to 0.60) or rivaroxaban 20 mg (OR 0.46, 95% CI 0.33 to 0.61). Similarly, edoxaban 60 mg had a higher risk than the lower dose (OR 1.85, 95% CI 1.37 to 2.54) and rivaroxaban 20 mg had a higher risk than apixaban 5 mg (OR 1.70, 95% CI 1.16 to 2.31). Three small, fair quality retrospective cohort studies evaluated gastrointestinal bleeding associated with dabigatran and rivaroxaban.[95,96,98] These

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studies indicated that compared to rivaroxaban, the duration of use of dabigatran was much longer and patients were older, and only 2 controlled for these confounders.[96,98] However, these studies made their comparisons of each NOAC with warfarin and not with each other. Neither study found statistically significant differences.

Adverse event outcomes

The proportions of patients reporting treatment-emergent adverse effects were generally high across the trials, but not different between doses or compared with warfarin on a per-study basis. The range was 24% in J-ROCKET AF with 15 mg rivaroxaban or warfarin (2.5 years) to 84% with edoxaban 30 mg or 60 mg or warfarin in ENGAGE-TIMI 48 (2.8 years). Withdrawals due to adverse events were also not different between doses or compared with warfarin, and the incidence increased with duration of study; 4-5% for shorter studies, and 16% in the longest study (ENGAGE-TIMI 48, 2.8 years).

Comparisons with aspirin

The AVERROES study enrolled 5,599 patients with atrial fibrillation at increased risk of stroke, but for whom warfarin therapy had been ruled out.[47] Although multiple reasons could be given, the 2 most common single reasons were the expectation that the patient would not comply with INR testing according to schedule and patient refusal to take warfarin. At baseline, these patients appeared similar to patients enrolled in the other studies (above). The dose of aspirin was selected by the local investigator – and could range from 82 mg to 324 mg per day; most patients (64%) took 81 mg, and only 7% took 324 mg. This study was discontinued early (after mean patient follow-up of 1.1 years) by an independent data and safety monitoring committee, due to a large difference in outcomes favoring apixaban. For the primary outcome measure, stroke or systemic embolism, the hazard ratio was 0.45 (95% CI 0.32 to 0.62). The results for the other 2 outcomes reported in this report were not statistically significantly different; the hazard ratio was 0.79 (95% CI 0.62 to 1.02) for all-cause mortality and 0.86 (95% CI 0.50 to 1.48) for MI. The risk of major bleeding was 1.13 (95% CI 0.74 to 1.75). Because the study was stopped early for benefit (as opposed to for harm), we rated this study fair quality and find the evidence insufficient to draw conclusions.

Orthopedic Surgery

Comparative Effectiveness

Twenty-one RCTs evaluated the use of NOACs in patients undergoing orthopedic surgery.[14,21,29,31-46,111,112] Three trials assessed edoxaban,[14,111,112] four assessed apixaban,[41-43,46] nine assessed rivaroxaban,[29,31-34,39,40,44,45] and five assessed dabigatran;[21,35-38] all compared to enoxaparin. A total of 39,754 patients were included, with sample sizes of individual trials ranging from 90 to 5,407 patients. Trials enrolled adults undergoing knee arthroplasty (11 trials), hip arthroplasty (9 trials), or surgery for inner or outer femoral neck fracture (1 trial). Treatment duration ranged from 5 to 42 days, and followup ranged from 30 to 90 days. Mean ages ranged from 60 to 76 years, and the proportion of female patients ranged from 29% to 85% (all but one trial predominately enrolled women). Ethnicity was infrequently reported, and trials that did report ethnicity predominately enrolled white participants, with the exception of the three STARS trials,[14,111,112] which were conducted in Japan and predominately enrolled Japanese participants. The most common outcome reported (19 of 21 trials) was a composite of any deep

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vein thrombosis; non-fatal, symptomatic, objectively confirmed pulmonary embolism; and all-cause mortality. The 2 trials that did not report this composite outcome were small (N = 90 and 324) studies conducted in Iran and China.[21,29]

Table 11. Characteristics of RCTs of NOACs in orthopedic surgery patients

	Trial	Drug	Sample Size # Countries	Follow-up	Primary Outcome
Dabigatran	Eriksson, 2007 **RE-MODEL** (Fair)	Dabigatran 150 mg bid Dabigatran 220 mg bid Enoxaparin	2,076 105 centers (countries NR)	90 days	Composite VTE and mortality
	Eriksson, 2007 **RE-NOVATE** (Good)	Dabigatran 150 mg bid Dabigatran 220 mg bid Enoxaparin	3,463 19 countries	90 days	Composite VTE and mortality
	Eriksson, 2011 **RE-NOVATE II** (Fair)	Dabigatran 220 mg bid Enoxaparin	2,013 19 countries	90 days	Composite VTE and mortality
	Ginsberg, 2009 **RE-MOBILIZE** (Good)	Dabigatran 150 mg bid Dabigatran 220 mg bid Enoxaparin	2,615 4 countries	90 days	Composite VTE and mortality
	Mirdamadi, 2014 (Fair)	Dabigatran 225 mg bid Enoxaparin	90 1 country: Iran	90 days	Major bleeding
Rivaroxaban	Eriksson, 2006 **ODIXA-HIP (once daily)** (Fair)	Rivaroxaban 5 mg, 10 mg, 20 mg, 30 mg or 40 mg qd Enoxaparin	845 11 countries	30 days	Composite VTE and mortality
	Eriksson, 2006 **ODIXA-HIP (twice daily)** (Fair)	Rivaroxaban 2.5 mg, 5 mg, 10 mg, 20 mg and 30 mg bid Enoxaparin	548 12 countries	30 days	Composite VTE and mortality
	Turpie, 2005 **ODIXA-KNEE** (Fair)	Rivaroxaban 2.5 mg Rivaroxaban 2.5 mg, 5 mg, 10 mg, 20 mg and 30 mg bid Enoxaparin	613 2 countries	30 days	Composite VTE and mortality
	Eriksson, 2007 (Good)	Rivaroxaban 2.5 mg, 5 mg, 10 mg, 20 mg and 30 mg bid Rivaroxaban 30 mg qd Enoxaparin	625 10 countries	30-60 days	Composite VTE and mortality
	Eriksson, 2008 **RECORD 1** (Fair)	Rivaroxaban 1 mg qd Enoxaparin	4,433 27 countries	30-42 days	Composite VTE and mortality
	Kakkar, 2008 **RECORD 2** (Fair)	Rivaroxaban 10 mg qd Enoxaparin	2,509 21 countries	30-42 days	Composite VTE and mortality
	Lassen, 2008 **RECORD 3** (Fair)	Rivaroxaban 10 mg qd Enoxaparin	2,531 19 countries	14-17 days	Composite VTE and mortality
	Turpie, 2009 **RECORD 4** (Fair)	Rivaroxaban 10 mg qd Enoxaparin	3,148 12 countries	17 days	Composite VTE and mortality
	Zou, 2014 (Fair)	Rivaroxaban 10 mg qd Enoxaparin Aspirin	324 1 country: China	30 days	Deep vein thrombosis
Apixaban	Lassen, 2007 **APROPOS** (Good)	Apixaban 5 mg, 10 mg, or 20 mg qd Apixaban 2.5 mg, 5 mg or 10 mg bid Enoxaparin	1,238 8 countries	30 days	Composite VTE and mortality
	Lassen, 2009 **ADVANCE-1**	Apixaban 2.5 mg bid Enoxaparin	3,195 22 countries	60 days	Composite VTE and mortality

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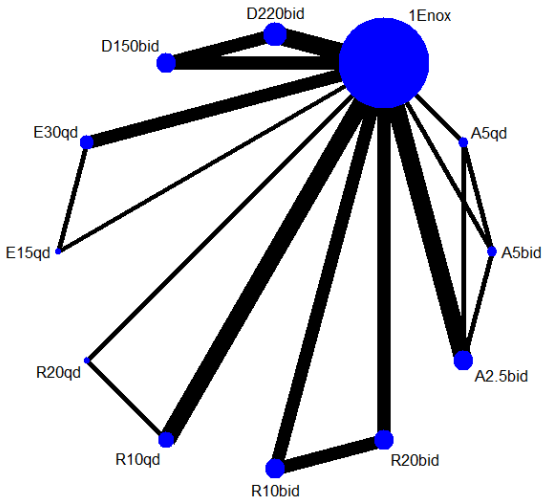
	Trial	Drug	Sample Size # Countries	Follow-up	Primary Outcome
	(Good)				
	Lassen, 2010 **ADVANCE-2** (Good)	Apixaban 2.5 mg bid Enoxaparin	3,009 22 countries	60 days	Composite VTE and mortality
	Lassen, 2010 **ADVANCE-3** (Good)	Apixaban 2.5 mg bid Enoxaparin	5,407 22 countries	60 days	Composite VTE and mortality
Edoxaban	Fuji, 2014 **STARS J2** (Fair)	Edoxaban 30 mg qd Enoxaparin	92 1 country: Japan	25-35 days	Composite VTE and mortality
	Fuji, 2014 **STARS J4** (Fair)	Edoxaban 15 mg qd Edoxaban 30 mg qd Enoxaparin	264 2 countries; Japan/Taiwan	25-35 days	Composite VTE and mortality
	Fuji, 2014 **STARS E3** (Good)	Edoxaban 30 mg qd Enoxaparin	716 2 countries; Japan/Taiwan	25-35 days	Composite VTE and mortality

Comparison to Enoxaparin

We conducted a network meta-analysis of 4 key benefit outcomes for NOACs in patients undergoing orthopedic surgery, using data from all 21 trials. The diagram of the network for the primary outcome (the composite of total venous thromboembolism and all-cause mortality) is shown in Figure 3; diagrams of the networks for other outcomes are available upon request. Because all drugs have so far been compared only with enoxaparin, the network is anchored by the enoxaparin comparison group, with dose comparisons across drugs. Study arms using dosages of NOACs that are not approved in the United States were excluded from analysis. Pooled results showed significant benefits on the composite outcome of VTE and mortality for apixaban 2.5 mg twice daily (OR 0.63, 95% CI 0.44 to 0.89), rivaroxaban 10 mg once daily (OR 0.45, 95% CI 0.32 to 0.64), and rivaroxaban 20 mg once daily (OR 0.35, 95% CI 0.15 to 0.80) compared to enoxaparin.

Figure 3. Network map for the composite outcome of total venous thromboembolism and all-cause mortality



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Abbreviations: 1Enox, enoxaparin; A2.5bid, apixaban 2.5 mg twice daily; A5bid, apixaban 5 mg twice daily; A5qd, apixaban 5 mg once daily; D150bid, dabigatran 150 mg twice daily; D220bid, dabigatran 220 mg twice daily; E15qd, edoxaban 15 mg once daily; E30qd, edoxaban 30 mg once daily; R10bid, rivaroxaban 10 mg twice daily; R10qd, rivaroxaban 10 mg once daily; R20bid, rivaroxaban 20 mg twice daily; R20qd, rivaroxaban 20 mg once daily.

Total venous thromboembolism and mortality

The composite of deep vein thrombosis, pulmonary embolism, and all-cause mortality was reported in 19 trials. The results of our network meta-analysis are presented in Table 12. Apixaban 2.5 mg twice daily was associated with a reduction in the composite outcome compared to dabigatran 150 mg twice daily (OR 0.52, 95% CI 0.33 to 0.84) and dabigatran 220 mg twice daily (OR 0.63, 95% CI 0.40 to 0.99). Rivaroxaban 10 mg once daily and 20 mg once daily were also superior to dabigatran 150 mg twice daily (rivaroxaban 10 mg once daily: OR 0.38, 95% CI 0.24 to 0.61; rivaroxaban 20 mg once daily: OR 0.29, 95% CI 0.12 to 0.71) and dabigatran 220 mg twice daily (rivaroxaban 10 mg once daily: OR 0.46, 95% CI 0.29 to 0.72; rivaroxaban 20 mg once daily: OR 0.35, 95% CI 0.14 to 0.85). Rivaroxaban 20 mg once daily was also associated with lower risk compared to twice daily administration (OR 0.38, 95% CI 0.15 to 0.99). The reason for this finding is unclear; despite similarities in population and timing and methods of outcome assessment in the once-daily and twice-daily ODIXA-HIP trials, the proportion of patients experiencing the primary outcome differed between the two studies (once daily: 8.5% vs. twice daily: 18.2%). The strength of the evidence for these findings was low. There were no significant differences for other drug-drug or drug-dose comparisons, and the evidence was judged to be insufficient to draw conclusions.

Symptomatic deep vein thrombosis

Symptomatic deep vein thrombosis was reported in 15 trials. In our network analysis, there were no significant differences in rates of symptomatic deep vein thrombosis for any drug-dose comparison (Table 12). Estimates were extremely imprecise due to the small numbers of events in the included trials, as a result the evidence is insufficient for drawing conclusions.

All-cause mortality

All-cause mortality was reported in 19 trials. Similar to the results for symptomatic deep vein thrombosis, our network analysis found no significant differences in rates of all-cause mortality for any drug-dose comparison, with highly imprecise estimates due to the small number of deaths. Again, we rated this evidence as insufficient to draw conclusions.

Table 12. NOAC Network Meta-analysis Results: Effectiveness outcomes

Comparison	Total VTE + mortality	All-cause Mortality	Symptomatic DVT
Drug vs. Drug (by dose)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Edoxaban 15 mg qd vs. Apixaban 2.5 mg bid	1.84 (0.05,61.57)	0.50 (0.01,22.82)	2.75 (0.07,110.13)
Edoxaban 15 mg qd vs. Apixaban 5 mg qd	2.59 (0.05,122.39)	0.22 (0.00,19.45)	2.95 (0.05,184.31)
Edoxaban 15 mg qd vs. Apixaban 5 mg bid	1.71 (0.04,74.35)	0.66 (0.00,99.21)	8.78 (0.08,977.68)
Edoxaban 15 mg qd vs. Rivaroxaban 10 mg qd	2.54 (0.08,85.08)	1.90 (0.04,85.52)	2.24 (0.05,100.59)
Edoxaban 15 mg qd vs. Rivaroxaban 10 mg bid	1.57 (0.05,53.44)	0.62 (0.01,45.62)	2.54 (0.03,190.05)
Edoxaban 15 mg qd vs. Rivaroxaban 20 mg qd	3.33 (0.09,121.24)	1.21 (0.01,181.46)	-
Edoxaban 15 mg qd vs. Rivaroxaban 20 mg bid	1.27 (0.04,43.15)	0.40 (0.01,26.51)	1.61 (0.03,92.33)
Edoxaban 15 mg qd vs. Dabigatran 150 mg bid	0.96 (0.03,32.19)	0.52 (0.01,27.18)	1.43 (0.04,57.26)
Edoxaban 15 mg qd vs. Dabigatran 220 mg bid	1.16 (0.03,38.62)	0.48 (0.01,23.80)	1.76 (0.04,69.90)
Edoxaban 30 mg qd vs. Apixaban 2.5 mg bid	2.41 (0.52,11.17)	0.47 (0.02,9.27)	4.20 (0.55,31.80)

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Comparison	Total VTE + mortality	All-cause Mortality	Symptomatic DVT
Edoxaban 30 mg qd vs. Apixaban 5 mg qd	3.40 (0.37,30.96)	0.21 (0.00,9.15)	4.50 (0.29,70.82)
Edoxaban 30 mg qd vs. Apixaban 5 mg bid	2.24 (0.29,17.60)	0.62 (0.01,50.87)	13.39 (0.38,473.46)
Edoxaban 30 mg qd vs. Rivaroxaban 10 mg qd	3.33 (0.72,15.42)	1.79 (0.09,34.50)	3.42 (0.37,31.63)
Edoxaban 30 mg qd vs. Rivaroxaban 10 mg bid	2.06 (0.43,9.88)	0.59 (0.02,20.71)	3.87 (0.19,79.33)
Edoxaban 30 mg qd vs. Rivaroxaban 20 mg qd	4.37 (0.79,24.25)	1.14 (0.01,92.98)	**-**
Edoxaban 30 mg qd vs. Rivaroxaban 20 mg bid	1.67 (0.35,7.94)	0.38 (0.01,11.80)	2.46 (0.18,33.86)
Edoxaban 30 mg qd vs. Dabigatran 150 mg bid	1.26 (0.27,5.82)	0.49 (0.02,11.41)	2.18 (0.29,16.61)
Edoxaban 30 mg qd vs. Dabigatran 220 mg bid	1.52 (0.33,6.96)	0.45 (0.02,9.86)	2.68 (0.36,20.02)
Apixaban 2.5 mg bid vs. Rivaroxaban 10 mg qd	1.38 (0.85,2.24)	3.84 (0.80,18.37)	0.82 (0.17,3.99)
Apixaban 2.5 mg bid vs. Rivaroxaban 10 mg bid	0.86 (0.47,1.54)	1.26 (0.10,15.78)	0.92 (0.07,12.21)
Apixaban 2.5 mg bid vs. Rivaroxaban 20 mg qd	1.81 (0.73,4.50)	2.44 (0.07,90.72)	-
Apixaban 2.5 mg bid vs. Rivaroxaban 20 mg bid	0.69 (0.39,1.22)	0.80 (0.08,8.55)	0.59 (0.07,4.80)
Apixaban 2.5 mg bid vs. Dabigatran 150 mg bid	**0.52 (0.33,0.84)**	1.06 (0.16,6.99)	0.52 (0.14,1.88)
Apixaban 2.5 mg bid vs. Dabigatran 220 mg bid	**0.63 (0.40,0.99)**	0.97 (0.16,5.78)	0.64 (0.18,2.30)
Apixaban 5 mg qd vs. Rivaroxaban 10 mg qd	0.98 (0.19,5.17)	8.58 (0.52,140.57)	0.76 (0.07,8.80)
Apixaban 5 mg qd vs. Rivaroxaban 10 mg bid	0.61 (0.11,3.30)	2.81 (0.09,86.84)	0.86 (0.04,20.76)
Apixaban 5 mg qd vs. Rivaroxaban 20 mg qd	1.29 (0.21,8.03)	5.46 (0.07,400.00)	-
Apixaban 5 mg qd vs. Rivaroxaban 20 mg bid	0.49 (0.09,2.66)	1.80 (0.07,49.24)	0.55 (0.03,9.06)
Apixaban 5 mg qd vs. Dabigatran 150 mg bid	0.37 (0.07,1.95)	2.36 (0.12,46.94)	0.48 (0.05,4.64)
Apixaban 5 mg qd vs. Dabigatran 220 mg bid	0.45 (0.09,2.34)	2.17 (0.12,40.43)	0.59 (0.06,5.73)
Apixaban 5 mg bid vs. Rivaroxaban 10 mg qd	1.48 (0.35,6.38)	2.89 (0.08,105.34)	0.26 (0.01,7.17)
Apixaban 5 mg bid vs. Rivaroxaban 10 mg bid	0.92 (0.21,4.09)	0.95 (0.02,57.61)	0.29 (0.01,14.38)
Apixaban 5 mg bid vs. Rivaroxaban 20 mg qd	1.95 (0.37,10.11)	1.84 (0.01,235.51)	-
Apixaban 5 mg bid vs. Rivaroxaban 20 mg bid	0.74 (0.17,3.29)	0.60 (0.01,33.33)	0.18 (0.00,6.77)
Apixaban 5 mg bid vs. Dabigatran 150 mg bid	0.56 (0.13,2.41)	0.79 (0.02,33.75)	0.16 (0.01,3.99)
Apixaban 5 mg bid vs. Dabigatran 220 mg bid	0.68 (0.16,2.88)	0.73 (0.02,29.47)	0.20 (0.01,4.92)
Rivaroxaban 10 mg qd vs. Dabigatran 150 mg bid	**0.38 (0.24,0.61)**	0.28 (0.04,1.74)	0.64 (0.13,3.12)
Rivaroxaban 10 mg qd vs. Dabigatran 220 mg bid	**0.46 (0.29,0.72)**	0.25 (0.04,1.43)	0.78 (0.16,3.81)
Rivaroxaban 10 mg bid vs. Dabigatran 150 mg bid	0.61 (0.35,1.09)	0.84 (0.06,12.63)	0.56 (0.04,7.44)
Rivaroxaban 10 mg bid vs. Dabigatran 220 mg bid	0.74 (0.42,1.29)	0.77 (0.06,10.80)	0.69 (0.05,9.15)
Rivaroxaban 20 mg qd vs. Dabigatran 150 mg bid	**0.29 (0.12,0.71)**	0.43 (0.01,18.26)	-
Rivaroxaban 20 mg qd vs. Dabigatran 220 mg bid	**0.35 (0.14,0.85)**	0.40 (0.01,15.94)	-
Rivaroxaban 20 mg bid vs. Dabigatran 150 mg bid	0.76 (0.44,1.31)	1.31 (0.10,16.95)	0.89 (0.11,7.24)
Rivaroxaban 20 mg bid vs. Dabigatran 220 mg bid	0.91 (0.53,1.56)	1.21 (0.10,14.43)	1.09 (0.13,8.91)
Dose Comparisons			
Edoxaban 15 mg qd vs. 30 mg qd	0.76 (0.02,25.13)	1.06 (0.03,40.92)	0.66 (0.02,23.36)
Apixaban 2.5 mg bid vs. 5 mg bid	0.93 (0.22,3.91)	1.33 (0.04,41.24)	3.19 (0.15,66.60)
Apixaban 2.5 mg bid vs. 5 mg qd	1.41 (0.27,7.29)	0.45 (0.03,5.92)	1.07 (0.14,8.15)
Apixaban 5 mg qd vs. 5 mg bid	0.66 (0.10,4.19)	2.97 (0.12,72.20)	2.97 (0.11,80.12)
Rivaroxaban 10 mg qd vs. 10 mg bid	0.62 (0.34,1.11)	0.33 (0.03,3.97)	1.13 (0.07,17.61)
Rivaroxaban 10 mg qd vs. 20 mg qd	1.31 (0.56,3.09)	0.64 (0.02,19.62)	-
Rivaroxaban 10 mg bid vs. 20 mg qd	2.12 (0.81,5.56)	1.94 (0.03,117.75)	-
Rivaroxaban 20 mg qd vs. 20 mg bid	**0.38 (0.15,0.99)**	0.33 (0.01,18.04)	-
Dabigatran 150 mg bid vs. 220 mg bid	1.20 (0.87,1.66)	0.92 (0.31,2.71)	1.23 (0.51,2.95)
Comparisons with Enoxaparin			
Edoxaban 15 mg qd vs. Enoxaparin	1.15 (0.03,37.97)	0.83 (0.02,31.98)	1.34 (0.04,47.69)
Edoxaban 30 mg qd vs. Enoxaparin	1.51 (0.34,6.73)	0.78 (0.05,12.31)	2.04 (0.34,12.40)
Apixaban 2.5 mg bid vs. Enoxaparin	**0.63 (0.44,0.89)**	1.67 (0.53,5.26)	0.49 (0.20,1.21)
Apixaban 5 mg qd vs. Enoxaparin	0.44 (0.09,2.27)	3.74 (0.28,49.56)	0.45 (0.06,3.61)
Apixaban 5 mg bid vs. Enoxaparin	0.67 (0.16,2.78)	1.26 (0.04,39.03)	0.15 (0.01,3.29)
Rivaroxaban 10 mg qd vs. Enoxaparin	**0.45 (0.32,0.64)**	0.44 (0.15,1.27)	0.60 (0.16,2.19)
Rivaroxaban 10 mg bid vs. Enoxaparin	0.73 (0.46,1.18)	1.33 (0.14,12.69)	0.53 (0.05,5.92)

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Comparison	Total VTE + mortality	All-cause Mortality	Symptomatic DVT
Rivaroxaban 20 mg qd vs. Enoxaparin	**0.35 (0.15,0.80)**	0.68 (0.02,21.11)	-
Rivaroxaban 20 mg bid vs. Enoxaparin	0.91 (0.58,1.42)	2.08 (0.26,16.47)	0.83 (0.12,5.53)
Dabigatran 150 mg bid vs. Enoxaparin	1.20 (0.87,1.65)	1.58 (0.35,7.12)	0.94 (0.38,2.33)
Dabigatran 220 mg bid vs. Enoxaparin	1.00 (0.74,1.34)	1.72 (0.44,6.75)	0.76 (0.31,1.87)

Abbreviations: bid, twice daily; CI, confidence interval; OR, odds ratio; VTE, venous thromboembolism; qd, once daily.

Comparative Harms

Major bleeding

Major bleeding was reported in 19 trials. Our network meta-analysis found that apixaban 2.5 mg twice daily was superior to rivaroxaban 20 mg once daily (OR 0.25, 95% CI 0.07 to 0.98) and rivaroxaban 20 mg twice daily (OR 0.28, 95% CI 0.09 to 0.90). Rivaroxaban 20 mg once daily and 20 mg twice daily were also associated with more major bleeding than dabigatran 150 mg twice daily (OR 4.07, 95% CI 1.04 to 16.02 and OR 3.71, 95% CI 1.12 to 12.25, respectively). The strength of the evidence for these findings was low. There were no significant differences in major bleeding for other comparisons, and the evidence was judged to be insufficient to draw conclusions (Table 13).

Table 13. NOAC Network Meta-analysis Results: Major bleeding

Comparison	Major bleeding
Drug vs. Drug (by dose)	**OR (95% CI)**
Edoxaban 15 mg qd vs. Apixaban 2.5 mg bid	0.88 (0.03,24.38)
Edoxaban 15 mg qd vs. Apixaban 5 mg qd	1.90 (0.02,176.88)
Edoxaban 15 mg qd vs. Apixaban 5 mg bid	0.21 (0.01,8.53)
Edoxaban 15 mg qd vs. Rivaroxaban 10 mg qd	0.51 (0.02,14.85)
Edoxaban 15 mg qd vs. Rivaroxaban 10 mg bid	0.41 (0.01,13.57)
Edoxaban 15 mg qd vs. Rivaroxaban 20 mg qd	0.22 (0.01,7.62)
Edoxaban 15 mg qd vs. Rivaroxaban 20 mg bid	0.24 (0.01,7.85)
Edoxaban 15 mg qd vs. Dabigatran 150 mg bid	0.90 (0.03,25.32)
Edoxaban 15 mg qd vs. Dabigatran 220 mg bid	0.63 (0.02,17.44)
Edoxaban 30 mg qd vs. Apixaban 2.5 mg bid	2.48 (0.52,11.95)
Edoxaban 30 mg qd vs. Apixaban 5 mg qd	5.36 (0.17,171.16)
Edoxaban 30 mg qd vs. Apixaban 5 mg bid	0.59 (0.06,5.75)
Edoxaban 30 mg qd vs. Rivaroxaban 10 mg qd	1.43 (0.27,7.70)
Edoxaban 30 mg qd vs. Rivaroxaban 10 mg bid	1.15 (0.17,7.89)
Edoxaban 30 mg qd vs. Rivaroxaban 20 mg qd	0.63 (0.09,4.55)
Edoxaban 30 mg qd vs. Rivaroxaban 20 mg bid	0.69 (0.11,4.45)
Edoxaban 30 mg qd vs. Dabigatran 150 mg bid	2.56 (0.52,12.52)
Edoxaban 30 mg qd vs. Dabigatran 220 mg bid	1.78 (0.37,8.52)
Apixaban 2.5 mg bid vs. Rivaroxaban 10 mg qd	0.58 (0.25,1.35)
Apixaban 2.5 mg bid vs. Rivaroxaban 10 mg bid	0.47 (0.13,1.64)
Apixaban 2.5 mg bid vs. Rivaroxaban 20 mg qd	**0.25 (0.07,0.98)**
Apixaban 2.5 mg bid vs. Rivaroxaban 20 mg bid	**0.28 (0.09,0.90)**
Apixaban 2.5 mg bid vs. Dabigatran 150 mg bid	1.03 (0.54,1.97)
Apixaban 2.5 mg bid vs. Dabigatran 220 mg bid	0.72 (0.40,1.29)
Apixaban 5 mg qd vs. Rivaroxaban 10 mg qd	0.27 (0.01,6.57)
Apixaban 5 mg qd vs. Rivaroxaban 10 mg bid	0.22 (0.01,6.05)
Apixaban 5 mg qd vs. Rivaroxaban 20 mg qd	0.12 (0.00,3.40)
Apixaban 5 mg qd vs. Rivaroxaban 20 mg bid	0.13 (0.00,3.49)
Apixaban 5 mg qd vs. Dabigatran 150 mg bid	0.48 (0.02,11.18)

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Comparison	Major bleeding
Apixaban 5 mg qd vs. Dabigatran 220 mg bid	0.33 (0.01,7.70)
Apixaban 5 mg bid vs. Rivaroxaban 10 mg qd	2.42 (0.38,15.41)
Apixaban 5 mg bid vs. Rivaroxaban 10 mg bid	1.95 (0.25,15.48)
Apixaban 5 mg bid vs. Rivaroxaban 20 mg qd	1.06 (0.13,8.89)
Apixaban 5 mg bid vs. Rivaroxaban 20 mg bid	1.16 (0.15,8.76)
Apixaban 5 mg bid vs. Dabigatran 150 mg bid	4.32 (0.74,25.27)
Apixaban 5 mg bid vs. Dabigatran 220 mg bid	3.01 (0.53,17.24)
Rivaroxaban 10 mg qd vs. Dabigatran 150 mg bid	1.78 (0.74,4.31)
Rivaroxaban 10 mg qd vs. Dabigatran 220 mg bid	1.24 (0.54,2.88)
Rivaroxaban 10 mg bid vs. Dabigatran 150 mg bid	2.21 (0.61,7.98)
Rivaroxaban 10 mg bid vs. Dabigatran 220 mg bid	1.54 (0.44,5.41)
Rivaroxaban 20 mg qd vs. Dabigatran 150 mg bid	**4.07 (1.04,16.02)**
Rivaroxaban 20 mg qd vs. Dabigatran 220 mg bid	2.84 (0.74,10.87)
Rivaroxaban 20 mg bid vs. Dabigatran 150 mg bid	**3.71 (1.12,12.25)**
Rivaroxaban 20 mg bid vs. Dabigatran 220 mg bid	2.58 (0.81,8.29)
Dose comparisons	
Edoxaban 15 mg qd vs. 30 mg qd	0.35 (0.02,7.99)
Apixaban 2.5 mg bid vs. 5 mg bid	4.20 (0.79,22.30)
Apixaban 2.5 mg bid vs. 5 mg qd	0.46 (0.02,10.30)
Apixaban 5 mg qd vs. 5 mg bid	9.06 (0.49,168.38)
Rivaroxaban 10 mg qd vs. 10 mg bid	1.24 (0.31,5.02)
Rivaroxaban 10 mg qd vs. 20 mg qd	2.28 (0.57,9.09)
Rivaroxaban 10 mg bid vs. 20 mg qd	1.84 (0.32,10.52)
Rivaroxaban 20 mg qd vs. 20 mg bid	0.91 (0.17,4.89)
Dabigatran 150 mg bid vs. 220 mg bid	1.44 (0.88,2.34)
Comparisons with Enoxaparin	
Edoxaban 15 mg qd vs. Enoxaparin	0.70 (0.03,18.84)
Edoxaban 30 mg qd vs. Enoxaparin	1.97 (0.43,8.95)
Apixaban 2.5 mg bid vs. Enoxaparin	0.79 (0.52,1.22)
Apixaban 5 mg qd vs. Enoxaparin	0.37 (0.02,8.30)
Apixaban 5 mg bid vs. Enoxaparin	3.33 (0.61,18.21)
Rivaroxaban 10 mg qd vs. Enoxaparin	1.38 (0.66,2.88)
Rivaroxaban 10 mg bid vs. Enoxaparin	1.71 (0.52,5.59)
Rivaroxaban 20 mg qd vs. Enoxaparin	3.14 (0.87,11.29)
Rivaroxaban 20 mg bid vs. Enoxaparin	2.86 (0.96,8.52)
Dabigatran 150 mg bid vs. Enoxaparin	0.77 (0.47,1.26)
Dabigatran 220 mg bid vs. Enoxaparin	1.11 (0.74,1.67)

Other adverse events

Rates of overall adverse events were generally high (range: 45% to 89%) but did not differ between NOAC doses or in comparison to enoxaparin. Rates of withdrawal due to adverse events ranged from 2.2% to 9.1% and also did not significantly differ between NOAC doses or in comparison to enoxaparin.

Key Question 4. What is the evidence on whether there are subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one direct-acting oral anticoagulant is more effective or associated with fewer harms than another direct-acting oral anticoagulants or other anticoagulants?

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Summary of Findings

Treatment of venous thromboembolism: based on a subgroup analysis of 1 trial

- Cancer: Bleeding outcomes are similar in patients with active cancer, a history of cancer, and no active cancer or history of cancer.

Atrial fibrillation: Based primarily on subgroup analyses of large RCTs (strength of evidence is insufficient):

- Age: Outcomes are similar in older patients with rivaroxaban, apixaban, or dabigatran.
- Sex: The effects of apixaban on ischemic stroke and bleeding compared with aspirin were similar between men and women.
- Race or Ethnicity: In Asian patients, there were no differences in primary or bleeding outcomes for dabigatran, rivaroxaban, and apixaban versus warfarin.
- Co-morbidities:
    - Diabetes: Findings are similar in patients with diabetes with rivaroxaban and apixaban in patients. Findings with dabigatran suggest greater benefit on stroke or systemic embolism but slightly greater risk of major bleeding.
    - Heart failure: Similar findings with rivaroxaban, apixaban and dabigatran.
    - Hypertension: No difference in outcomes with rivaroxaban.
    - Coronary Artery Disease: No difference in outcomes with apixaban.
    - Renal Dysfunction: Observational evidence suggests increased risk of hospitalization or death due to bleeding with rivaroxaban and dabigatran compared with warfarin in patients on hemodialysis. No difference in outcomes in patients with mild to moderate dysfunction for rivaroxaban, dabigatran and apixaban.
- Co-interventions:
    - Antiarrhythmic Drugs: Patients taking rivaroxaban and amiodarone had a higher risk of stroke or systemic embolism and major bleeding compared to warfarin Subgroup analysis of patients taking apixaban and amiodarone found no impact on outcomes.
    - Antiplatelet Drugs: Dabigatran 150 mg had greater risk of stroke or systemic embolism and time-dependent major bleeding in those also taking an antiplatelet drug. These effects were not seen with dabigatran 110 mg. Taking apixaban and aspirin concomitantly did not show significant impact on outcomes, but further study is warranted.

Detailed Assessment

Age

In patients with nonvalvular atrial fibrillation, two subgroup analyses of bleeding rates by age from the ROCKET AF and the J-ROCEKT AF trials come to different conclusions.[72,82] The larger ROCKET AF trial found no difference between rivaroxaban and warfarin in older (≥ 75 years) versus younger patients. The smaller J ROCKET AF trial analyses found that while there were no differences between the drugs by age in cardiovascular outcomes, the incidence of major or non-major clinically relevant bleeding was greater with rivaroxaban than warfarin in patients 75 years or older and lower in younger patients (test for interaction P = 0.04). This difference

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may be due to the lower dose of rivaroxaban (15 mg vs. 20 mg) and the lower target INR for patients > 70 assigned to warfarin.

In meta-analyses of trial data for any indication in patients > 75 years, the risk of clinically relevant bleeding was not statistically significantly different with rivaroxaban, apixaban, or dabigatran and the control anticoagulant.[103] Results for stroke or systemic embolism in patients > 75 years were similar to the findings for the total study populations.

Sex

In patients with atrial fibrillation, a subgroup analyses from the AVERROES study found that while women had higher ischemic stroke rates compared with men, the effects of apixaban on ischemic stroke and bleeding compared with aspirin were similar between men and women.[85]

Race or Ethnicity

In patients with nonvalvular atrial fibrillation, subgroup analyses of the patients from East Asian countries in the RE-LY, ROCKET AF, and ARISTOTLE trials found no differences in results in the primary outcomes or bleeding outcomes for dabigatran, rivaroxaban, and apixaban versus warfarin, respectively.[71,81,94]

Co-morbidities

Cancer

In patients being treated for acute VTE, the AMPLIFY trial of apixaban 5 mg daily reported lower risk of major bleeding (RR 0.32, 95% CI 0.09 to 0.16 for patients with active cancer or a history of cancer and RR 0.30, 95% CI 0.16 to 0.58 for patients without a history of cancer or active cancer) or composite major bleeding/clinically-relevant non-major bleeding (RR 0.40, 95% CI 0.20 to 0.78 for patients with cancer history but without active cancer; RR 0.47, 95% CI 0.29 to 0.75 for patients with active cancer and cancer history; and RR 0.43, 95% CI 0.34 to 0.55 for patients with no history of cancer or active cancer) compared to enoxaparin/warfarin.[54]

Diabetes

In patients with nonvalvular atrial fibrillation, subgroup analyses indicated similar findings with rivaroxaban (ROCKET AF) and apixaban (ARISTOTLE) in patients with and without diabetes, compared to warfarin.[53,85]With dabigatran, subgroup analyses from the RE-LY trial suggest that the reduction in stroke or systemic embolism was greater compared with warfarin in patients with diabetes than for those without diabetes (absolute reduction dabigatran 110 mg 0.59% vs 0.05% and dabigatran 150 mg 0.89% vs 0.51%; %'s per year). However, the findings also show slight increases in the risk of major bleeding for both doses compared with warfarin in patients with diabetes.[59]

Heart failure

In patients with heart failure, subgroup analyses indicated similar findings with rivaroxaban (ROCKET AF), apixaban (ARISTOTLE), and dabigatran (RE-LY) compared to warfarin to those without heart failure.[68,88,92]

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Hypertension

In patients with nonvalvular atrial fibrillation, a subgroup analysis of the J-ROCKET AF trial found no difference in outcomes in patients with hypertension.[87]

Coronary Artery Disease

In patients with nonvalvular atrial fibrillation, a subgroup analysis of the ARISTOTLE study found no difference in outcomes with apixaban in patients with known prior coronary artery disease.[58]

Renal Dysfunction

While patients with renal dysfunction are known to have higher risk for cardiovascular outcomes, subgroup analyses from large trials of rivaroxaban, dabigatran, and apixaban in patients with atrial fibrillation,[65,77,78,83] and a meta-analysis of trial subgroups[104] did not find important differences in results in patients with mild to moderate dysfunction. However, a small, fair quality retrospective cohort study found that there was an increased risk of hospitalization or death due to bleeding with rivaroxaban and dabigatran compared with warfarin in patients on hemodialysis. The risk of hospitalization or death from bleeding was relative risk 1.48 (95% CI 1.21 to 1.81) with dabigatran and 1.38 (95% CI 1.03 to 1.83) with rivaroxaban. The risk of death from hemorrhagic bleeding was also increased for dabigatran (RR 1.78, 95% CI 1.18 to 2.68) and rivaroxaban (RR 1.71, 95% CI 0.94 to 3.12).

Co-interventions

Antiarrhythmic Drugs

In patients with nonvalvular atrial fibrillation, the impacts of antiarrhythmic drugs, particularly amiodarone, were studies in subgroup analyses of large trials of rivaroxaban and apixaban. [69,90] With rivaroxaban, patients taking amiodarone had a higher risk of stroke or systemic embolism compared to warfarin (HR 1.72, 95% CI 0.80 to 3.65) than those not taking any antiarrhythmic drug (HR 0.82, 95% CI 0.68 to 0.98; P value for interaction = 0.063).[90] Similarly, the risk of major bleeding was also greater with amiodarone (HR 2.20, 95% CI 0.98 to 4.91) than with no antiarrhythmic drug (HR 0.61, 95% CI 0.42 to 0.88; P for interaction 0.16). In a subgroup analysis of ARISTOTLE, patients taking amiodarone had rates of stroke or embolism that were similar to patients not taking amiodarone (HR 0.68, 95% CI 0.40 to 1.15 and HR 0.82, 95% CI 0.68 to 1.00, respectively).[69] Similar results were found for all-cause mortality and major bleeding.

Antiplatelet Drugs

In patients with atrial fibrillation, subgroup analyses of the impact of antiplatelet drugs were conducted from the RE-LY trial of dabigatran and the ARISTOTLE trial of apixaban.[55,62] With dabigatran 110 mg, the concomitant use of aspirin or clopidogrel did not alter the findings significantly to the overall trial results.[62] For dabigatran 150 mg, the risk of stroke or systemic embolism was higher in those also taking an antiplatelet drug (HR 0.80 versus 0.52; P-value for interaction = 0.058). While the risk of major bleeding was not significantly different in the overall analysis, a time-dependent analysis indicated greater risk for those taking an antiplatelet

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drug (HR 1.60, 95% CI 1.42 to 1.82, and using 2 antiplatelet drugs increased the risk to HR 2.31, 95% CI 1.79 to 2.98).

In the subgroup analysis of concomitant aspirin (only) with apixaban, while the P-value for interaction between the hazard ratios is not statistically significant (P = 0.10), the hazard ratio for stroke or systemic embolism was lower, and statistically significant, with concomitant aspirin use (0.58, 95% CI 0.39 to 0.85) than without (0.84, 95% CI 0.66 to 1.07). The risk of major bleeding, comparing apixaban and warfarin, was similar between those taking and not taking aspirin.

Pre-existing Disease

In patients with atrial fibrillation, subgroup analyses from ROCKET AF (rivaroxaban) and ARISTOTLE (apixaban) did not indicate different results for patients with prior stroke or transient ischemic attacks.[64] Subgroup analyses based on variations in the type of atrial fibrillation (paroxysmal or persistent) or the presence of underlying native mitral or aortic valve disease did not indicate differing results from the overall study populations for rivaroxaban or apixaban.[56,80,91]

SUMMARY

Strength of Evidence

In this report, although the studies were fair to good quality, the evidence is so far entirely indirect in that the NOACs are not compared directly with each other. As such, the evidence is only low strength at best. Much of the indirect comparisons were rated insufficient to draw conclusions due to not only indirectness but also to lack of ability to truly judge consistency of findings when using a network meta-analysis to create the direct comparisons, and, importantly, the imprecision of estimates. in situations where the estimates are precise, we rated the evidence as low strength, and those findings are highlighted in the summary table. These limitations mean that the findings of this report could easily change if and when direct evidence becomes available.

Limitations of this Report

As with other types of research, the limitations of this systematic review are important to recognize. Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and not being able to search additional electronic databases. While the search of the US Food and Drug Administration documents and request for information from the manufacturers of the drugs is an important step in searching for unpublished studies and supplemental data, another possible limitation is the lack of a specific search for gray literature. As noted above, the lack of direct head-to-head comparisons seriously limits the ability to draw solid conclusions.

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Table 14. Summary of the evidence by key question for benefits and harms of newer oral anticoagulant drugs

Comparison	Population	Strength of evidence	Conclusions
Key Question 1. Comparative effectiveness and harms of treatment of VTE in adults			
VTE recurrence, DVT, and PE			
Indirect comparisons of edoxaban 30 or 60 mg qd or bid, apixaban 5 mg bid, rivaroxaban 15 mg bid, and dabigatran 150 mg bid	Treatment for VTE	Insufficient	No statistically significant difference.
Major bleeding			
Indirect comparisons of edoxaban 30 or 60 mg qd, apixaban 5 mg bid, and dabigatran 150 mg bid	Treatment for VTE	Low	Significantly lower risk with apixaban 5 mg bid compared to edoxaban 30 or 60 mg qd (HR 0.37, 95% CI 0.15 to 0.89) and dabigatran 150 mg bid (HR 0.42, 95% CI 0.17 to 0.99)
Key Question 2. Comparative effectiveness and harms of extended treatment to prevent recurrence of VTE			
VTE recurrence, All-cause mortality, Acute coronary syndrome (individual outcomes)			
Indirect comparisons of apixaban 2.5 mg or 5 mg bid , rivaroxaban 20 mg qd, and dabigatran 150 mg bid	Extended treatment for VTE	Insufficient	No statistically significant difference.
Major bleeding			
Indirect comparisons of apixaban 2.5 mg or 5 mg bid , rivaroxaban 20 mg qd, and dabigatran 150 mg bid	Extended treatment for VTE	Insufficient	No statistically significant difference.
Clinically-relevant non-major bleeding			
Indirect comparisons of: Apixaban 2.5 mg and 5 mg bid , rivaroxaban 20 mg qd, dabigatran 150 bid	Extended treatment for VTE	Low	Significantly lower risk with apixaban 2.5 mg (OR 0.23, 95% CI 0.084 to 0.62) or 5 mg (OR 0.31, 95% CI 0.11 to 0.82) compared with rivaroxaban 20 mg
			Significantly lower risk with apixaban 2.5 mg than dabigatran 150 mg (OR 0.40, 95% CI 0.168 to 0.97).
Indirect comparisons of apixaban 5 mg bid, rivaroxaban 20 mg qd, and dabigatran 150 mg twice daily.		Insufficient	No statistically significant difference.
Key Question 3. Comparative effectiveness and harms in atrial fibrillation and orthopedic surgery			
Stroke or systemic embolism (composite outcome)			
Indirect comparisons of edoxaban 30 mg and 60 mg, apixaban 5 mg, rivaroxaban 15 mg and 20 mg, and dabigatran 110 mg and 150 mg	Atrial fibrillation (non-valvular)	Low	Edoxaban 30 mg results in statistically significantly higher risk than apixaban 5 mg (OR 1.38; 95% CI 1.07 to 1.80), rivaroxaban 15 mg (OR 2.24; 95% CI 1.07 to 4.93), or dabigatran 150 mg (OR 1.64; 95% CI 1.23 to 2.20).
			Rivaroxaban 20 mg resulted in statistically significantly higher risk than dabigatran 150 mg (OR 1.32; 95% CI 1.01 to 1.74); the risk for ischemic stroke (alone) was not increased significantly (1.31, 95% CI 0.94 to 1.77) while the risk for hemorrhagic stroke was significantly

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Comparison	Population	Strength of evidence	Conclusions
			increased (2.45, 95% CI 1.05 to 5.17).
All other comparisons		Insufficient	No statistically significant difference.
Myocardial Infarction (MI):			
Indirect comparisons of edoxaban 30 mg and 60 mg, apixaban 5 mg, rivaroxaban 15 mg and 20 mg, and dabigatran 110 mg and 150 mg	Atrial fibrillation (non-valvular)	Low	Apixaban 5 mg (OR 0.62; 95% CI 0.40 to 0.95), edoxaban 60 mg (OR 0.68; 95% CI 0.46 to 1.01) and rivaroxaban 20 mg (OR 0.56; 95% CI 0.37 to 0.86) had significantly lower risk than dabigatran 150 mg.
			Apixaban 5 mg (OR 0.64; 95% CI 0.41 to 0.99) and rivaroxaban 20 mg (OR 0.58; 95% CI 0.38 to 0.88) had statistically significantly lower risk than dabigatran 110 mg
			Edoxaban 30 mg had a statistically significantly greater risk than edoxaban 60 mg (OR 1.27; 95% CI 1.01 to 1.60).
All other comparisons		Insufficient	No statistically significant difference.
Major bleeding			
Indirect comparisons of edoxaban 30 mg and 60 mg, apixaban 5 mg, rivaroxaban 15 mg and 20 mg, and dabigatran 110 mg and 150 mg	Atrial fibrillation (non-valvular)	Low	Apixaban 5 mg resulted in statistically significantly lower risk than dabigatran 150 mg (OR 0.74, 95% CI 0.60 to 0.91) and rivaroxaban 20 mg (OR 0.67, 0.55 to 0.83).
			Edoxaban 30 mg resulted in lower risk than apixaban 5 mg (OR 0.67, 95% CI 0.54 to 0.83), dabigatran 110 mg (OR 0.58, 0.46 to 0.72) or 150 mg (OR 0.50, 95% CI 0.40 to 0.61), and rivaroxaban 20 mg (OR 0.45, 95% CI 0.37 to 0.56).
			Edoxaban 60 mg had lower risk than rivaroxaban 20 mg (OR 0.77, 95% CI 0.63 to 0.94).
			Rivaroxaban 20 mg had higher risk than dabigatran 110 mg (OR 1.28, 95% CI 1.04, 1.58).
			Edoxaban 30 mg resulted in 41% lower risk of major bleeding than the higher dose, 60 mg (OR 0.59, 95% CI 0.50 to 0.69).
All other comparisons		Insufficient	No statistically significant difference.
Total VTE and all-cause mortality (composite outcome)			
Indirect comparisons of apixaban 2.5 mg bid or rivaroxaban 10 mg or 20 mg qd vs. dabigatran 150 mg bid or 220 mg bid	Orthopedic surgery	Low	Significantly lower risk with apixaban 2.5 mg bid (OR 0.52, 95% CI 0.33 to 0.84), rivaroxaban 10 mg qd (OR 0.38, 95% CI 0.24 to 0.61), and rivaroxaban 20 mg qd (OR 0.29, 95% CI 0.12 to 0.71) compared to dabigatran 150 mg bid.
			Significantly lower risk with apixaban 2.5 mg bid (OR 0.63, 95% CI 0.40 to 0.99), rivaroxaban 10 mg qd (OR 0.46, 95% CI 0.29 to 0.72), and rivaroxaban 20 mg qd (OR 0.35, 95% CI 0.14 to 0.85) compared to dabigatran 220 mg bid
Indirect comparison of	Orthopedic surgery	Insufficient	No statistically significant differences.

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Comparison	Population	Strength of evidence	Conclusions
other drugs and doses			
Symptomatic DVT and all-cause mortality (individual outcomes)			
Indirect comparisons of NOACs	Orthopedic surgery	Insufficient	No statistically significant differences.
Major bleeding			
Indirect comparisons of apixaban 2.5 mg or 5 mg bid , rivaroxaban 20 mg qd, and dabigatran 150 mg bid	Orthopedic surgery	Low	Significantly lower risk with apixaban 2.5 mg bid compared to rivaroxaban 20 mg qd (OR 0.25, 95% CI 0.07 to 098) or bid (OR 0.28, 95% CI 0.09 to 0.90).
			Significantly higher risk with rivaroxaban 20 mg qd (OR 4.07, 95% CI 1.04 to 16.02) and bid (OR 3.71, 95% CI 1.12 to 12.25) compared to dabigatran 150 mg bid
Indirect comparison of other drugs and doses	Orthopedic surgery	Insufficient	No statistically significant differences.
Key Question 4. Comparative effectiveness and harms in subgroups			
Sub-group analyses of large RCTs of individual NOACs compared with warfarin (except Edoxaban – no studies)	Majority of evidence in atrial fibrillation patients	Insufficient	No comparative evidence. Findings on age, sex, ethnicity similar to findings in overall studies populations. Findings in patients with diabetes taking dabigatran, patients on hemodialysis taking rivaroxaban or dabigatran (observational study), patients taking rivaroxaban and amiodarone, and patients taking dabigatran and an antiplatelet drug suggest further study is needed.

CONCLUSIONS

Evidence directly comparing NOACs is unavailable; current evidence is limited to indirect comparisons. Low-strength evidence suggests apixaban and rivaroxaban had lower risk of VTE and mortality in orthopedic patients. In atrial fibrillation, edoxaban 30 mg had a higher risk of stroke or embolism, and rivaroxaban had higher risk than dabigatran (higher-dose). Differences in effectiveness were not found among the drugs in initial or extended treatment of VTE. Apixaban, edoxaban, and lower-dose dabigatran have lower rates of major bleeding. Evidence on other comparisons and outcomes was insufficient to draw conclusions.

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