Summary Review

Newer Oral Anticoagulant Drugs

Final Original Report

January 2013

The Agency for Healthcare Research and
Quality has not yet seen or approved this report

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Susan Carson, MPH
Shelley Selph, MD
Sujata Thakurta, MPA:HA
Marian McDonagh, PharmD

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

Copyright © 2013 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.

STRUCTURED ABSTRACT

Purpose

To compare the effectiveness and safety of newer oral anticoagulant drugs in patients with atrial fibrillation, patients undergoing orthopedic surgery, or patients who are medically ill to inform policy decisions by the participating organizations of the Drug Effectiveness Review Project. Lacking direct evidence, comparisons of the newer agents with warfarin or heparins are reported.

Data Sources

We searched Ovid MEDLINE®, the Cochrane Database of Systematic Reviews®, Health Technology Assessments database, and Database of Abstracts of Reviews of Effects, up to August 2012 and Websites of health technology assessment entities including the Agency for Healthcare Research and Quality Effective Healthcare Program, Canadian Agency for Drugs and Technologies in Health, Veterans Affairs-Evidence Synthesis Program, and the National Institute of Clinical Excellence.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard review methods established by the Drug Effectiveness Review Project.

Results and Conclusion

Although the quality (internal validity) and consistency of the evidence available for this report was good, a major limitation was the lack of available direct evidence. Conclusions were based on indirect evidence, which limited our ratings to low or moderate strength of evidence.

In patients undergoing orthopedic surgery, apixaban, rivaroxaban, and dabigatran did not differ in preventing symptomatic venous thromboembolic events or in net clinical benefit. Clinically relevant bleeding was less likely with apixaban. Better efficacy with dabigatran compared with enoxaparin on some outcomes was associated with a greater incidence of harms.

In non-valvular atrial fibrillation patients, network analyses indicates that there is a tradeoff with each medication between clotting and bleeding. For instance, compared with warfarin or the newer oral anticoagulants, rivaroxaban is more likely to prevent myocardial infarction, but is also more likely to lead to intracranial hemorrhage. Compared with the newer oral anticoagulants, warfarin, however, is likely less effective for the prevention of all-cause mortality in this patient population.

Evidence for prevention of venous thromboembolic events in medically ill patients is insufficient. Evidence for treatment in medical patients with venous thromboembolic events is limited and non-comparative for the new drugs, but shows no difference in benefit compared with warfarin. Differences between the new oral drugs and warfarin in bleeding may exist but require further study.

A major concern with these drugs compared with older drugs is that there is no known antidote for use in the case of serious bleeding or overdose. Appropriate dosing of rivaroxaban in patients with impaired kidney function may also be a safety issue. Finally, the newer anticoagulants may have unknown adverse effects and may result in lower patient compliance relative to warfarin due to the lack of a need for regular contact for international normalized ratio monitoring, and the cost to the patient may be increased compared with older anticoagulants.

TABLE OF CONTENTS

INTRODUCTION **6**
Purpose of a Summary Review 8
Scope and Key Questions 8
METHODS **9**
Inclusion Criteria 9
Literature Search 10
Study Selection 10
Data Abstraction 10
Validity Assessment 10
Data Synthesis 11
Peer Review 11
Public Comment 12
RESULTS **12**
Overview 12
Key Question 1. What is the evidence from existing comparative effectiveness systematic reviews on the efficacy and effectiveness of the newer anticoagulant drugs in adults with atrial fibrillation or for prevention or treatment of thromboembolic events in adults who are medically ill or venous thromboembolic events in adults who have undergone orthopedic surgery? 13
Summary of findings 13
Detailed assessment: Prevention of venous thromboembolic events in patients who have undergone orthopedic surgery 14
Detailed assessment: Patients with atrial fibrillation 19
Detailed assessment: Medically ill patients 22
Key Question 2. What is the evidence from existing comparative effectiveness systematic reviews on the harms of the newer anticoagulant drugs in adults with atrial fibrillation or for prevention or treatment of thromboembolic events in adults who are medically ill or venous thromboembolic events in adults who have undergone orthopedic surgery? 23
Summary of findings 23
Detailed assessment: Patients undergoing orthopedic surgery 25
Detailed assessment: Atrial fibrillation 26
Detailed assessment: Medically ill patients 28
Key Question 3. What is the evidence from existing comparative effectiveness systematic reviews 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 newer anticoagulant drug is more effective or associated with fewer harms? 29
Summary of findings 29
Detailed assessment: Patients undergoing orthopedic surgery 30
Detailed assessment: Atrial fibrillation 30
Detailed assessment: Medically ill patients 32
SUMMARY **32**
Strength of Evidence 32
Limitations of this Report 32
CONCLUSION **33**
REFERENCES **34**

TABLES

Table 1. Included drugs 7
Table 2. Definitions of the grades of overall strength of evidence 11
Table 3. Overview of included systematic reviews of newer anticoagulant drugs in patients undergoing surgery 15
Table 4. Characteristics of trials included in systematic reviews of newer anticoagulant drugs 16
Table 5. Effectiveness outcomes in systematic reviews of newer anticoagulant drugs (adapted from Gomez-Outes 2012 and Falck-Ytter 2012) 18
Table 6. Indirect comparisons between rivaroxaban, dabigatran, and apixaban (adapted from Gomez-Outes 2012) 18
Table 7. Trial characteristics of studies included in reviews 20
Table 8. Bayesian network analysis of newer oral anticoagulants for atrial fibrillation 21
Table 9. Prevention of venous thromboembolic events in medically ill patients with newer oral anticoagulants 23
Table 10. Safety outcomes in systematic reviews of newer oral anticoagulant drugs in patients undergoing orthopedic surgery 25
Table 11. Indirect comparisons between rivaroxaban, dabigatran, and apixaban (adapted from Gomez-Outes 2012) 26
Table 12. Summary of safety results from network meta-analyses 27
Table 13. Adverse events with newer oral anticoagulants compared with warfarin 29
Table 14. Net clinical endpoint[a] by type of surgery (adapted from Gomez-Outes 2012) 30
Table 15. Trials not included in systematic reviews (published after review search dates) 33

FIGURES

Figure 1. Results of literature search 12

APPENDIXES

Published in a separate document.

EVIDENCE TABLES

Published in a separate document.

Acknowledgments
We thank Leah Williams, our publications editor, for putting this report into its present form.

Suggested Citation
Carson S, Selph S, Thakurta S, McDonagh M. Summary Review: Newer oral anticoagulant drugs. Final original report. Prepared by the RTI-UNC Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Health & Science University. Portland, OR. 2013. Available at http://derp.ohsu.edu/about/final-document-display.cfm.

Funding
The Drug Effectiveness Review Project, composed of 9 state Medicaid agencies, commissioned and funded this report. These organizations selected the topic of the report and had input into its Key Questions. The content and conclusions of the report were entirely determined by the Evidence-based Practice Center researchers. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in this report.

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 preventing further blood loss and possible death. This 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 summary of systematic reviews is concerned with the prevention and treatment of inappropriate blood clotting.

Inappropriate clotting can result in deep vein thrombosis, pulmonary embolism, heart attack, and stroke, causing significant morbidity and mortality. The burden of disease due to inappropriate clotting in the United States is high. Each year approximately 300,000 to 600,000 individuals in the United States develop a venous thromboembolism (deep vein thrombosis or pulmonary embolism),[1] 935,000 individuals have a heart attack,[2] and 795,000 have a stroke,[2] leaving over half a million Americans dead each year from thrombotic or thromboembolic events.[1-3] Blood clots within the venous system include deep vein thrombosis and pulmonary embolisms. Acquired risk factors for deep vein thrombosis and pulmonary embolisms include immobilization (e.g., long plane flight and major orthopedic surgery), cancer, pregnancy, oral contraceptives, and smoking. A deep vein thrombosis typically occurs when blood flow back to the heart from the legs is sluggish, such as when sitting for a long time, or when other factors like smoking, cancer, or surgery predisposes one to form clots easily. A clot in the deep veins of the legs can break off and travel and, when it does, will often lodge in the vasculature of the lungs where it is known as a pulmonary embolism and can cause death.

Blood clots within the arterial system can cause heart attacks and strokes. Risk factors include having atrial fibrillation or atherosclerosis (hardening of the arteries). Heart attacks can occur when a cholesterol plaque breaks off from the inner wall of a coronary artery causing a clot to form at the site of the plaque. A thromboembolic stroke can occur when the left atrium of the heart is fibrillating or quivering, rather than experiencing normal contractions, causing the blood within the left atrium to pool and form a clot. If this clot exits the heart, it could eventually occlude a cerebral artery supplying oxygenated blood to the brain, killing brain cells (stroke). A widely used instrument to predict thromboembolic risk in atrial fibrillation patients is the $CHADS_2$ score.[4] The $CHADS_2$ score can range from 0-6 with 0 indicating the least risk of stroke and 6 the greatest risk of stroke. A $CHADS_2$ score of 0 indicates an annual adjusted rate of stroke of approximately 1.9 in 100 patient-years of follow-up (95% CI, 1.2 to 3.0) whereas a score of 6 indicates an approximate annual stroke rate of 18.2 (95% CI, 10.5 to 27.4).

Recent recommendations from the American College of Chest Physicians include treating certain higher-risk patients with atrial fibrillation with dabigatran over warfarin and to not treat low-risk patients with a $CHADS_2$ score of 0.[5] The American College of Chest Physicians guideline panel chose to only consider those newer oral anticoagulants approved for atrial fibrillation which, at the time, included only dabigatran. Since the publication of these guidelines, rivaroxaban and apixaban have been approved for stroke prophylaxis in patients with non-valvular atrial fibrillation.[6, 7]

Prevention and treatment of inappropriate clotting can target any of several locations within the clotting cascade.[8] This summary of reviews compares the effectiveness of several new oral anticoagulant pharmacotherapies with each other: 3 oral factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) and a direct thrombin inhibitor (dabigatran) (Table 1) in patients with non-valvular atrial fibrillation, in patients undergoing hip or knee replacement surgery, and

in medically ill patients. Advantages of these agents over the 2 conventional medications to prevent blood clots, heparin and warfarin, are that these are oral agents (vs. subcutaneous or intravenous heparin) and do not require frequent blood work for dose monitoring and adjustment (warfarin, IV heparin). Potential concerns with the use of these newer anticoagulants include lack of a known antidote (dabigatran) and drug clearance in patients with impairment of kidney function (rivaroxaban).

Rivaroxaban, dabigatran, and apixaban are approved for use in the United States. Currently, edoxaban is licensed only in Japan (see Table 1 for indications). See Appendix A for boxed warning.

Table 1. Included drugs

Drug	Trade name(s), form	FDA approval status	Labeled indications	Mechanism of action
Apixaban[9]	Eliquis® Oral tablets	Approved on December 28, 2012	Reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation	Apixaban is an oral, reversible, and selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. It inhibits free and clot-bound factor Xa, and prothrombinase activity. It has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin.
Dabigatran[10]	Pradaxa® Oral capsule	Approved on October 19, 2010	Reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation	Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.
Rivaroxaban[11]	Xarelto® Oral tablet	10mg approved on July 1, 2011 15, 20mg approved on Nov 4, 2011	1. Reduction of risk of stroke and systemic embolism in non-valvular atrial fibrillation 2. Treatment of DVT/PE 3. Reduction in the risk of recurrence of DVT and of PE 4. Prophylaxis of DVT following hip/ knee replacement surgery	XARELTO is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity. Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation.
Edoxaban[a]	Lixiana® Oral tablet	Not yet approved, phase 3 trials to be completed in Spring 2013	Prevention of VTE in adult patients with elective hip or knee replacement surgery[a]	Edoxaban is a oral, reversible competitive inhibitor of factor Xa.

Abbreviations: DVT, deep vein thrombosis; FDA, US Food and Drug Administration; PE, pulmonary embolism; VTE, venous thromboembolic events.
[a] Edoxaban (Lixiana®) not currently approved in US; indication is for approval in Japan.

Purpose of a Summary Review

A Summary Review uses the best evidence available from existing comparative systematic reviews to provide information on the benefits and harms of drug products in specific patient populations. These reviews focus on drug classes that are likely to have recent, good-quality systematic reviews available (e.g., those that have new drug approvals in the past 2-3 years, but not within the last 6 months), limited indications, and significant questions on how they compare with one another. In addition to summarizing existing review findings, the summary review also itemizes studies published since the review inclusion dates and identifies gaps in the review literature relevant to the Drug Effectiveness Review Project participants.

Scope and Key Questions

The purpose of this report is to compare the effectiveness and safety of newer oral anticoagulant drugs in patients with atrial fibrillation, patients undergoing orthopedic surgery, or patients who are medically ill and to inform policy decisions by the participating organizations of the Drug Effectiveness Review Project. Lacking direct evidence, comparisons of the newer agents with warfarin or heparins are also reported. A thorough and systematic comparison of the benefits and harms of the newer anticoagulant drugs relative to warfarin or heparins is beyond the scope of this report. 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. The draft was reviewed and revised by representatives of the organizations participating in the Drug Effectiveness Review Project. Revision took into consideration 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 this review:

1. What is the evidence from existing comparative effectiveness systematic reviews on the efficacy and effectiveness of the newer anticoagulant drugs in adults with atrial fibrillation or for prevention or treatment of thromboembolic events in adults who are medically ill or venous thromboembolic events in adults who have undergone orthopedic surgery?

2. What is the evidence from existing comparative effectiveness systematic reviews on the harms of the newer anticoagulant drugs in adults with atrial fibrillation or for prevention or treatment of thromboembolic events in adults who are medically ill or venous thromboembolic events in adults who have undergone orthopedic surgery?

3. What is the evidence from existing comparative effectiveness systematic reviews 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 newer anticoagulant drug is more effective or associated with fewer harms?

METHODS

Inclusion Criteria

Populations

Adults with:

- Atrial fibrillation
- Prevention or treatment of thromboembolic events in medically ill patients
- Prevention or treatment of venous thromboembolic events in patients who have undergone orthopedic surgery.

Drugs

Apixaban (Eliquis®), dabigatran (Pradaxa®), rivaroxaban (Xarelto®), edoxaban (Lixiana®)

Comparators

The primary comparison was of the newer oral anticoagulants with each other.

Other comparators:

- Vitamin K antagonists (e.g., warfarin)
- Unfractionated heparin or low molecular weight heparins.

Effectiveness outcomes

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

Harms outcomes

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

Study designs

We included comparative systematic reviews that addressed questions similar to the Drug Effectiveness Review Project Summary Review questions. The review must directly address questions that are similar enough to the Drug Effectiveness Review Project key questions to provide useful information. Reviews that only examine a class effect were not likely to be useful and were not considered, but both direct and indirect comparisons were considered. Three

additional criteria for inclusion were applied. To be considered "systematic", the reviews had to include a comprehensive search for evidence from multiple sources of information (electronic databases, reference lists, etc.), describe the terms used in the search, and use dual review of studies for inclusion. Second, the searches had to be conducted on or after September 2010. Third, the review had to include at least 2 of the newer anticoagulant drugs.

Literature Search

To identify systematic reviews, we searched Ovid MEDLINE® and Ovid OLDMEDLINE (1946 to September Week 1 2012), the Cochrane Database of Systematic Reviews® (2005 to August 2012), EBM Reviews-Health Technology Assessments (3rd Quarter 2012), Database of Abstracts of Reviews of Effects (DARE 3rd Quarter 2012), and ACP Journal Club (1991 to August 2012) using included drugs, indications, and study designs as search terms. (See Appendix B for complete search strategies). We attempted to identify additional systematic reviews by searching the review registry PROSPERO. We searched Websites of health technology assessment entities, including the Agency for Healthcare Research and Quality Effective Healthcare Program, Canadian Agency for Drugs and Technologies in Health, Veterans Affairs-Evidence Synthesis Program, National Institute of Clinical Excellence, and others. We hand searched reference lists of included reviews. All citations were imported into an electronic database (Endnote® version X3, Thomson Reuters).

Study Selection

Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using the criteria described above. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by both reviewers. Disagreements were resolved by consensus.

Data Abstraction

For systematic reviews, we abstracted information on aims, time period covered, eligibility criteria, subject enrollment, characteristics of study designs, populations and interventions from identified articles, results for efficacy, effectiveness, harms, and subgroups. Data were abstracted by 1 reviewer and checked by another.

Validity Assessment

We rated the internal validity of included systematic reviews 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. Studies were categorized as good when all criteria were met.[12] Two reviewers independently assessed each study and differences were resolved by consensus.

Grading the Strength of Evidence

When available, we used strength of evidence grades reported in included systematic reviews. When strength of evidence grades were not available from existing reviews, 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.[13] 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 the newer oral anticoagulant drugs. Grades do not refer to the general efficacy or effectiveness. Strength of evidence is graded for each key outcome measure and is limited to head-to-head comparisons except where a case can be made for assessing the strength of indirect evidence.

Table 2. Definitions of the grades of overall strength of evidence[14]

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis

We constructed evidence tables showing the review characteristics, quality ratings, and results for all included systematic reviews. We reviewed reviews using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question addressed. For example if 2 reviews were included that both evaluate drug A and drug B, but 1 is fair quality and the other is good quality, then we focused on the good-quality review. In such situations, the fair-quality review was used to determine if the findings are concordant in general. If not, we explored reasons for the discrepancy, as in a sensitivity analysis. Reviews that included studies that evaluated 1 newer oral anticoagulant drug against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data were the primary focus. To synthesize evidence, we used quantitative analyses that were reported in systematic reviews. When meta-analyses were conducted, we assessed whether studies were combined appropriately from clinical and statistical standpoints.[15] When meta-analysis was not performed, the data were summarized qualitatively.

Peer Review

We requested and received peer review of the report from 3 experts. Their comments were reviewed and, where possible, incorporated into the final document. All comments and the authors' proposed actions were reviewed by representatives of the participating organizations of the Drug Effectiveness Review Project before finalization of the report. Names of peer reviewers for the Drug Effectiveness Review Project are listed at http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/index.cfm.

Public Comment

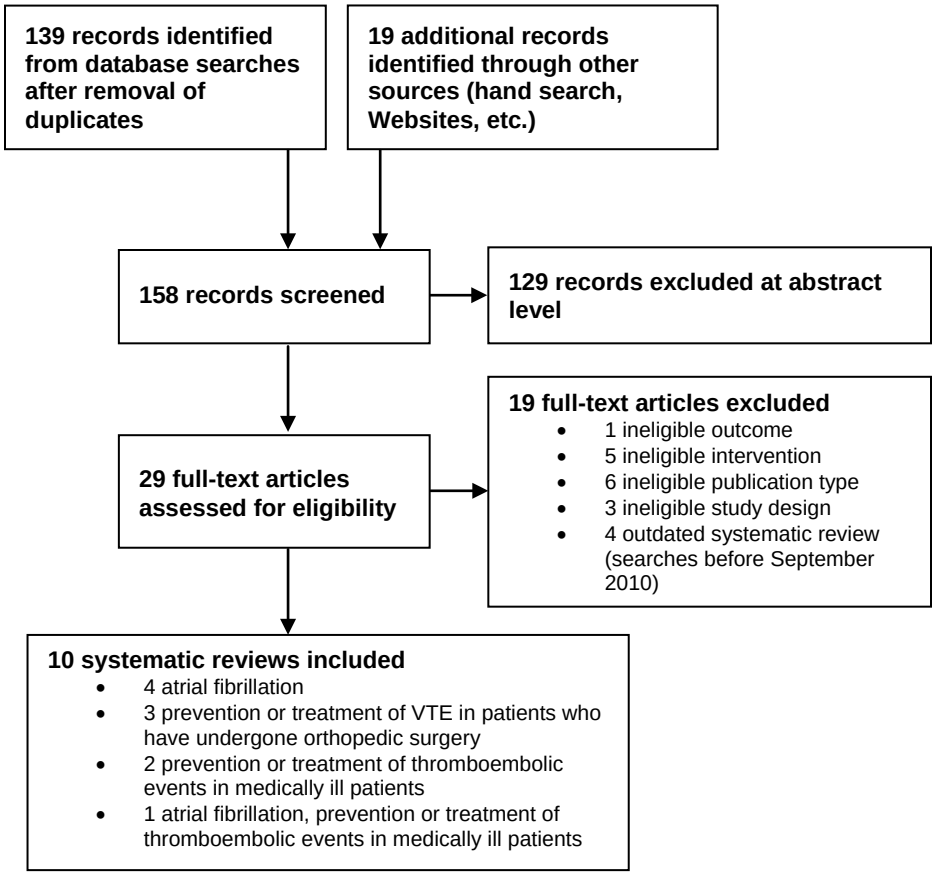
This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 2 pharmaceutical companies.

RESULTS

Overview

Literature searches identified 158 citations. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 29 citations. After reapplying the criteria for inclusion, we ultimately included 10 unique reviews. See Appendix C for a list of excluded reviews and reasons for exclusion at this stage. Figure 1 shows the flow of study selection.

Figure 1. Results of literature search[a]



Abbreviations: VTE, venous thromboembolic event.
[a] The Drug Effectiveness Review Project uses a modified PRISMA flow diagram.[16]

Key Question 1. What is the evidence from existing comparative effectiveness systematic reviews on the efficacy and effectiveness of the newer anticoagulant drugs in adults with atrial fibrillation or for prevention or treatment of thromboembolic events in adults who are medically ill or venous thromboembolic events in adults who have undergone orthopedic surgery?

Summary of findings

- There was no direct evidence comparing 1 newer anticoagulant drug with another.
- In patients undergoing orthopedic surgery:
  - There were no systematic reviews that included edoxaban (strength of evidence: insufficient)
  - In indirect meta-analyses, there was no significant difference between apixaban, rivaroxaban, and dabigatran in preventing symptomatic venous thromboembolic events in patients undergoing orthopedic surgery (strength of evidence: low)
    - Rivaroxaban compared with dabigatran: RR, 0.68 (95% CI, 0.21 to 2.23); risk difference per 1000 patients treated −3 (95% CI, −11 to 4)
    - Rivaroxaban compared with apixaban: RR, 0.59 (95% CI, 0.26 to 1.33); risk difference per 1000 patients treated −4 (95% CI, −9 to 1)
    - Apixaban compared with dabigatran: RR, 1.16 (95% CI, 0.31 to 4.28); risk difference 1 (95% CI, −7 to 8)
  - There was moderate- to high-strength evidence that, compared with enoxaparin in preventing symptomatic venous thromboembolic events in patients undergoing orthopedic surgery:
    - The risk of symptomatic venous thromboembolic events was lower with rivaroxaban (RR, 0.48; 95% CI, 0.31 to 0.75)
    - The risk of symptomatic deep vein thrombosis was lower with apixaban (RR, 0.41; 95% CI, 0.18 to 0.95) and rivaroxaban (RR, 0.40; 95% CI, 0.22 to 0.72) but not dabigatran (RR, 0.82; 95% CI, 0.17 to 3.99)
    - There was no significant difference between the newer oral anticoagulants and enoxaparin in the risk of all-cause mortality or symptomatic pulmonary embolism.
- In patients with non-valvular atrial fibrillation, indirect meta-analysis found:
  - No difference between apixaban, rivaroxaban, and dabigatran in all-cause mortality (strength of evidence: low-moderate)
  - There was moderate-strength evidence that:
    - Rivaroxaban was associated with more all-cause strokes/systemic embolism than dabigatran 150 mg (OR, 1.35; 95% CrI, 1.03 to 1.79)
    - Rivaroxaban was associated with fewer myocardial infarctions than dabigatran 150 mg (OR, 0.63; 95% CrI, 0.42 to 0.93)
    - Apixaban was associated with less risk of all-cause stroke/systemic embolism or systemic embolism (OR, 0.80; 96% CrI, 0.66 to 0.95) and all-cause mortality when compared with warfarin (OR, 0.90; 95% CrI, 0.80 to 0.998)
  - There was moderate- to high-strength evidence that:
    - Dabigatran 150 mg was associated with less risk of all-cause stroke/systemic embolism compared with warfarin (OR, 0.65; 95% CrI, 0.52 to 0.81).

- In medically ill patients:
  - There was no evidence from systematic reviews on the newer oral anticoagulant drugs in preventing venous thromboembolic events in medical patients at risk
  - Limited moderate-strength evidence suggested no difference between dabigatran and rivaroxaban compared with warfarin in longer-term treatment of venous thromboembolic events (6 to 12 months duration). Outcomes assessed included mortality and recurrence of venous thromboembolic events.

Detailed assessment: Prevention of venous thromboembolic events in patients who have undergone orthopedic surgery

For evidence of comparative effectiveness in patients undergoing orthopedic surgery, we included 3 systematic reviews (Table 3).[17, 18] One met all quality criteria and was rated good quality.[17] Another was rated fair quality because of a lack of detail in its reporting of inclusion criteria and validity assessment process.[18] One additional good-quality review aimed to include quality-of-life outcomes, but found no evidence.[19]

Together the reviews included 18 randomized controlled trials (4 apixaban, 5 dabigatran, and 9 rivaroxaban). No studies of edoxaban were included. A fourth review,[20] which we excluded, included 4 trials of edoxaban but they were either meeting abstracts, dose-ranging studies with no active comparator, or included a comparator (dalteparin) not included in any other trials. Additionally, analyses combined data from the edoxaban trials with data from trials of other, non-included drugs, so this review did not provide any useful comparative evidence.

Table 3. Overview of included systematic reviews of newer anticoagulant drugs in patients undergoing surgery

	Gomez-Outes[18]	Falck-Ytter[17]
Aims	To analyze clinical outcomes with new oral anticoagulants for prophylaxis against venous thromboembolism after total hip or knee replacement.	To provide guidelines for optimal prophylaxis to reduce postoperative PE and DVT.
End date of searches	April 2011	December 2010
Eligible Populations	Patients undergoing total hip or knee replacement.	Patients undergoing major orthopedic surgery (total hip replacement, total knee replacement, hip fracture surgery)
Eligible Interventions (newer anticoagulants only)	Rivaroxaban Dabigatran Apixaban	Rivaroxaban Dabigatran Apixaban
Eligible Outcomes	Primary: Symptomatic VTE (symptomatic DVT or symptomatic PE). Primary safety outcome: Clinically relevant bleeding (major bleeding or clinically relevant non-major bleeding)	Non-fatal, symptomatic PE; symptomatic DVT; major bleeding requiring re-operation; major, non-fatal bleeding; total mortality
Eligible study designs	Randomized controlled trials comparing any of the approved new oral anticoagulants with enoxaparin.	Systematic reviews; additional analyses from RCTs and observational studies if evidence from systematic reviews not available
Characteristics of included studies	16 RCTs Dabigatran (n=4) Rivaroxaban (n=8) Apixaban (n=4) 8 hip replacement, 8 knee replacement Total N=38,747 Age ranges 61-68 years, predominance of women, body weight between 75 and 84 kg	Rivaroxaban (7 RCTs, 10,941 patients) Dabigatran 220 mg (4 RCTs, 7377 patients) Dabigatran 150 mg (3 RCTs, 5453 patients) Apixaban (4 RCTs, 11,964 patients) All compared with LMWH
Quality rating	Fair	Good

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low-molecular-weight heparin; RCT, randomized controlled trial; VTE, venous thromboembolic events.

Direct evidence

We identified no direct comparative evidence.

Indirect evidence

We relied primarily on the most recent systematic review because of its search dates and inclusion of an indirect meta-analysis comparing the newer oral anticoagulants to each other.[18] Table 4 shows the characteristics of trials included in the review and meta-analysis. Sixteen trials were included (4 apixaban, 4 dabigatran, and 8 rivaroxaban), all with the enoxaparin as the comparator. Eight trials were conducted in patients undergoing hip replacement surgery and 8 in

patients undergoing knee replacement surgery. Follow-up periods ranged from 35 to 100 days. The Jadad score was used to assess quality of the included trials; all but 1[21] received a score of 5 out of 5. In addition to meta-analyses of each drug compared with enoxaparin, adjusted indirect comparison meta-analyses were conducted to compare the newer oral anticoagulants to each other on the primary outcomes.

We supplemented this evidence with information from a systematic review and meta-analysis conducted for the American College of Chest Physicians.[17, 22] This review included the same trials as the primary review above, but provided some additional outcomes and used GRADE criteria to rate the strength of the evidence for each drug compared with enoxaparin. Results of the 2 reviews were consistent.

Table 4. Characteristics of trials included in systematic reviews of newer anticoagulant drugs

Trial	Drug, dose, duration (comparator)	Population	N	Duration of follow-up (days)
RE-MODEL[21]	Dabigatran 220 mg or 150 mg 6-10 days (enoxaparin 40 mg once daily)	Total knee replacement	2101	90
RE-NOVATE[23]	Dabigatran 220 mg or 150 mg 28-35 days (enoxaparin 40 mg once daily)	Total hip replacement	3493	94
RE-MOBILIZE[24]	Dabigatran 220 mg or 150 mg 12-15 days (enoxaparin 30 mg twice daily)	Total knee replacement	2615	90
RE-NOVATE II[25]	Dabigatran 220 mg 28-35 days (enoxaparin 40 mg once daily)	Total hip replacement	2055	90
RECORD1[26]	Rivaroxaban 10 mg 35 days (enoxaparin 40 mg once daily)	Total hip replacement	4541	66-71
RECORD2[27]	Rivaroxaban 10 mg 31-39 days (enoxaparin 40 mg once daily)	Total hip replacement	2509	62-75
RECORD3[28]	Rivaroxaban 10 mg 10-14 days (enoxaparin 40 mg once daily)	Total knee replacement	2531	41-50
RECORD4[29]	Rivaroxaban 10 mg 10-14 days (enoxaparin 30 mg twice daily)	Total knee replacement	3148	40-49
PROOF OF CONCEPT[21]	Rivaroxaban 2.5, 5, 10, 20 , or 30 mg twice daily, 30 mg once daily 5-9 days (enoxaparin 40 mg once daily)	Total hip replacement	641	38-68
ODIXA KNEE[30]	Rivaroxaban 2.5, 5, 10, 20 , or 30 mg twice daily 5-9 days (enoxaparin 30 mg twice daily)	Total knee replacement	621	37-67

Trial	Drug, dose, duration (comparator)	Population	N	Duration of follow-up (days)
ODIXA HIP[31] (twice daily)	Rivaroxaban 2.5, 5, 10, 20 , or 30 mg twice daily 5-9 days (enoxaparin 40 mg once daily)	Total hip replacement	722	38-68
ODIXA HIP[32] (once daily)	Rivaroxaban 2.5, 5, 10, 20 , or 30 mg once daily 5-9 days (enoxaparin 40 mg once daily)	Total hip replacement	873	35-69
ADVANCE-1[33]	Apixaban 2.5 mg twice daily 10-14 days (enoxaparin 30 mg twice daily)	Total knee replacement	3195	70-84
ADVANCE-2[34]	Apixaban 2.5 mg twice daily 10-14 days (enoxaparin 40 mg once daily)	Total knee replacement	3057	70-84
ADVANCE-3[35]	Apixaban 2.5 mg twice daily 35 days (enoxaparin 40 mg once daily)	Total hip replacement	5407	90-100
APROPOS[36]	Apixaban 5, 10, or 20 mg once daily, 2.5, 5, or 10 mg twice daily 10-14 days (enoxaparin 30 mg twice daily)	Total knee replacement	1238	42

Meta-analyses were conducted for the comparison of each drug to enoxaparin (Table 5). The primary outcome measure was the incidence of symptomatic venous thromboembolic events. For this outcome, only rivaroxaban showed a reduction in risk compared with enoxaparin. There was no difference in all-cause mortality, symptomatic pulmonary embolism, fatal pulmonary embolism, or the net clinical endpoint (composite of symptomatic venous thromboembolic events, major bleeding, and death) for any of the newer drugs compared with enoxaparin. The risk of symptomatic deep vein thrombosis was lower with apixaban and rivaroxaban but not dabigatran.

Table 5. Effectiveness outcomes in systematic reviews of newer anticoagulant drugs (adapted from Gomez-Outes 2012[18] and Falck-Ytter 2012[17])

Outcome	Apixaban	Dabigatran	Rivaroxaban
		Relative risk (95% CI) vs. enoxaparin	
Symptomatic VTE (Primary outcome)	0.82 (0.41 to 1.64)	0.71 (0.23 to 2.12)[a]	**0.48 (0.31 to 0.75)**
All-cause mortality	1.71 (0.56 to 5.26)	1.54 (0.38 to 6.33) 150 mg: 2.58 (0.47 to 14.00)	0.58 (0.24 to 1.38)[18] 0.84 (0.31 to 2.27)[17]
Symptomatic DVT	**0.41 (0.18 to 0.95)**	Overall: 0.82 (0.17 to 3.99) 150 mg: 1.52 (0.45 to 5.05) 250 mg: 0.70 (0.12 to 3.91)	**0.40 (0.22 to 0.72)**
Symptomatic PE	1.25 (0.38 to 4.15)	0.69 (0.31 to 1.54)	0.89 (0.30 to 2.67)
Non-fatal PE (Falck-Ytter)	1.09 (0.31 to 3.88)	150 mg: 0.31 (0.04 to 2.48)	1.34 (0.39 to 4.60)
Total VTE and/or all cause mortality (composite)	**0.63 (0.42 to 0.95)**	1.08 (0.93 to 1.25)	**0.56 (0.39 to 0.80)**
Major VTE and/or VTE related mortality (composite)	0.61 (0.32 to 1.14)	0.89 (0.63 to 1.25)	**0.42 (0.21 to 0.86)**
Net clinical benefit (composite of symptomatic VTE, major bleeding, and death)	0.92 (0.68 to 1.23)	0.93 (0.63 to 1.37)	0.88 (0.70 to 1.12)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolic events.
[a] Statistical heterogeneity among trials.
Statistically significant results are shown in boldface.

Adjusted indirect meta-analysis comparing rivaroxaban, dabigatran, and apixaban on the primary outcome (Table 6) showed no difference between the drugs in the incidence of symptomatic venous thromboembolic events.

Table 6. Indirect comparisons between rivaroxaban, dabigatran, and apixaban (adapted from Gomez-Outes 2012)[18]

Outcomes	Rivaroxaban vs. dabigatran	Rivaroxaban vs. apixaban	Apixaban vs. dabigatran
	Relative risk (95% CI) Risk difference (95% CI) per 1000 patients treated		
Symptomatic VTE	0.68 (0.21 to 2.23) −3 (−11 to 4)	0.59 (0.26 to 1.33) −4 (−9 to 1)	1.16 (0.31 to 4.28) 1 (−7 to 8)

Abbreviations: VTE, venous thromboembolic events.

Detailed assessment: Patients with atrial fibrillation

For evidence of comparative effectiveness in patients with non-valvular atrial fibrillation, we identified 5 good- or fair-quality systematic reviews (Evidence Table 1).[5, 37-40] Together these reviews included 7 randomized controlled trials (3 apixaban, 2 dabigatran, 1 rivaroxaban, and 1 edoxaban).

Direct evidence

We identified no direct comparative evidence from systematic reviews of 1 newer anticoagulant drug compared with another.

Indirect evidence

We relied primarily on 1 recent, good-quality systematic review and network analysis prepared for the Canadian Agency for Drugs and Technologies in Health (CADTH).[39] Table 7 shows the characteristics of the 5 trials included in the CADTH review (1 apixaban, 2 rivaroxaban, and 2 dabigatran). Two trials also included study arms with different doses of the dabigatran. Follow-up periods ranged from 12 weeks to 4 years. Two methods of quality assessment were used – the Scottish Intercollegiate Guidelines Network (SIGN 50) and the Cochrane Collaboration risk of bias tool.[41, 42] The target international normalized ratio for warfarin was 2.0 to 3.0 in all trials.

Table 7. Trial characteristics of studies included in reviews

Trial	Drug	N	Duration of follow-up	Country	Quality rating
Connolly, 2009 ***RE-LY***	Dabigatran 110 mg bid Dabigatran 150 mg bid warfarin **Total**	6015 6076 6022 **18,113**	Maximum: 3 years Median: 2 years	44 countries 951 sites	Good (CADTH)
Patel, 2011 ***ROCKET-AF***	Rivaroxaban 20 mg qd warfarin **Total**	7.131 7133 **14,264**	Maximum: 4 years Median: 1.9 years	45 countries 1178 sites	Very Good (CADTH)
Granger, 2011 ***ARISTOTLE***	Apixaban 5 mg bid or matching placebo warfarin **Total**	9120 9081 **18,201**	Maximum: 4 years Median: 1.8 years	39 countries 1034 sites	Good (CADTH)
Ogawa, 2011 ***ARISTOTLE-J***	Apixaban 5 mg bid Apixaban 2.5 mg bid warfarin **Total**	74 74 74 **222**	Maximum: 12 weeks Median duration of treatment: 85 days	Single country: Japan 23 sites	Very Good (CADTH)
Ezekowitz, 2007 ***PETRO***	Dabigatran 150 mg bid warfarin **Total**	166 70 **502**[a]	Maximum: 12 weeks	4 countries 53 sites	Very Good (CADTH)
Weitz, 2010	Edoxaban 30 mg qd Edoxaban 20 mg bid Edoxaban 60 mg qd Edoxaban 60 mg bid warfarin **Total**	235 245 235 180 251 **1146**	Maximum: 12 weeks	Multinational Multicenter	Good (AHRQ)
Connolly, 2011 **AVERROES**	Apixaban 5mg bid Aspirin 81-324 mg **Total**	2808 2791 **5599**	Mean 1.1 years; study terminated early due to benefit	36 countries 522 sites	Good (AHRQ)

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; bid, twice daily; CADTH, Canadian Agency for Drugs and Technologies in Health; qd, once daily.
[a] Results do not include 236 patients assigned to the 50 and 300mg dose groups.

A Bayesian network meta-analysis including the 3 largest trials was conducted for the comparison of the newer oral anticoagulants, with adjusted dose warfarin as the reference group (Table 8). Only the 3 largest trials were used in this analysis as the 2 smaller studies had no events in both arms for many of the outcomes. When compared with warfarin, use of apixaban and higher dose dabigatran resulted in fewer strokes or systematic embolism. Use of apixaban also resulted in fewer deaths due to all causes than did warfarin. When different doses of dabigatran were compared, the higher dose (150 mg twice daily) resulted in fewer strokes than the lower dose (110 mg twice daily). When the newer anticoagulants were compared with each other, use of dabigatran 150 mg resulted in fewer strokes than rivaroxaban, but more myocardial infarctions. No other comparisons were significant. One other review conducted an indirect analysis and had similar findings to the CADTH review.[38]

Table 8. Bayesian network analysis of newer oral anticoagulants for atrial fibrillation

Comparison	Stroke/systemic embolism	All-cause mortality	Myocardial infarction
		Odds ratio (95% CrI)	
Apixaban vs. warfarin	**0.80** **(0.66 to 0.95)**	**0.90** **(0.80 to 0.998)**	0.88 (0.66 to 1.17)
ARR per 1000 patients treated each year	**3 fewer** **(1 fewer-5 fewer)**	**4 fewer** **(0 fewer-8 fewer)**	1 fewer (1 more, 2 fewer)
Dabigatran 110 mg vs. warfarin	0.91 (0.74 to 1.11)	0.91 (0.80 to 1.05)	1.32 (0.98 to 1.79)
ARR per 1000 patients treated each year	2 fewer (2 more, 4 fewer)	3 fewer (2 more, 8 fewer)	2 more (5 more, 0 more)
Dabigatran 150 mg vs. warfarin	**0.65** **(0.52 to 0.81)**	0.89 (0.78 to 1.01)	1.29 0.96 to 1.75)
ARR per 1000 patients treated each year	**6 fewer** **(3 fewer, 8 fewer)**	4 fewer (0 more, 9 fewer)	2 more (5 more, 0 more)
Rivaroxaban vs. Warfarin	0.88 (0.74 to 1.04)	0.93 (0.83 to 1.04)	0.80 (0.62 to 1.05)
ARR per 1000 patients treated each year	3 fewer (1 more, 6 fewer)	4 fewer (2 more, 8 fewer)	2 fewer (1 more, 4 fewer)
Dabigatran 110 mg vs. apixaban	1.15 (0.87 to 1.51)	1.03 (0.86 to 1.22)	1.50 (0.99 to 2.28)
Dabigatran 150 mg vs. apixaban	0.82 (0.62 to 1.1)	1.00 0.84 to 1.19)	1.47 (0.97 to 2.23)
Rivaroxaban vs. apixaban	1.11 (0.87 to 1.42)	1.04 (0.89 to 1.23)	0.92 (0.62 to 1.35)
Dabigatran 150 mg vs. dabigatran 110 mg	**0.72** **(0.58 to 0.90)**	0.97 (0.85 to 1.12)	0.98 (0.74 to 1.31)
Rivaroxaban vs. dabigatran 110 mg	0.97 (0.75 to 1.26)	1.02 (0.86 to 1.21)	**0.61** **(0.41 to 0.91)**
Rivaroxaban vs. dabigatran 150 mg	**1.35** **(1.03 to 1.79)**	1.05 (0.88 to 1.26)	**0.63** **(0.42 to 0.93)**

Abbreviations: ARR, absolute risk reduction.
Statistically significant results are shown in boldface.

Other reviews

A draft comparative effectiveness review on stroke prevention in atrial fibrillation prepared for the Agency for Healthcare Research and Quality included 2 good-quality trials not in the CADTH review.[40] The first trial of patients with atrial fibrillation compared 3 different total daily doses of edoxaban and 2 dosing schedules (edoxaban 30 mg once daily, 30 mg twice daily, 60 mg once daily, and 60 mg twice daily) to warfarin and found no difference in the rate of stroke, transient ischemic attack, or systemic embolism between the 2 treatments but events were few (7/897 for any stroke, transient ischemic attack, and/or systemic embolism in the edoxaban groups combined compared with 4/250 in the warfarin group).

The second trial included only atrial fibrillation patients for whom a vitamin K antagonist was not appropriate. Reasons why patients were not prescribed warfarin included: an assessment that international normalized ratio could not or was unlikely to be measured at requested intervals (43%), patient refusal to take warfarin (37%), $CHADS_2$ score of 1 and vitamin K

antagonist therapy not recommended by physician (21%), assessment that international normalized ratio could not be maintained in therapeutic range (17%), and multiple reasons (52%), among others. This trial compared apixaban 5 mg twice daily to aspirin 81-324 mg once daily and found that apixaban reduced the risk of ischemic stroke (HR, 0.46; 95% CI, 0.33 to 0.65) and systemic embolism (HR, 0.15; 95% CI, 0.03 to 0.68) compared with aspirin.

The Agency for Healthcare Research and Quality review did not conduct indirect comparison meta-analyses to investigate comparisons of 1 newer anticoagulant with another.

Detailed assessment: Medically ill patients

Prevention

We found 2 good-quality systematic reviews addressing the prevention or treatment of venous thromboembolic events in patients who were medically ill (i.e., non-surgical and non-atrial fibrillation patients).[37, 43] In a review conducted to support a guideline for the American College of Chest Physicians, prophylaxis of venous thromboembolic events was evaluated for patients in the following groups: Hospitalized acutely ill medical patients, patients with cancer, patients receiving cancer treatment in outpatient setting, patients with indwelling central venous catheters, and chronically immobilized patients (e.g., nursing home or rehab residents and immobilized persons living at home). No evidence was found regarding the use of newer oral anticoagulant drugs at the time of the searches (December 2010).

Treatment

In a good-quality review conducted for the Department of Veterans Affairs, extended-duration (6 to 12 months) treatment of venous thromboembolic events with newer oral anticoagulants in medical patients was evaluated (deep vein thrombosis or pulmonary embolism etiologies: idiopathic/unprovoked, cancer or a prior deep vein thrombosis). This review included only dabigatran, rivaroxaban, and ximelagatran (a drug removed from the market). While the key results combine the findings of dabigatran and rivaroxaban in a meta-analyses (a single good-quality trial each), the results for each were reported here separately. Neither dabigatran nor rivaroxaban were found statistically significantly different to warfarin in preventing all-cause mortality, death due to a thromboembolic event, or recurrence of deep vein thrombosis or pulmonary embolism (Table 9). A second good-quality systematic review conducted to support a guideline for the American College of Chest Physicians included these same 2 trials and came to similar conclusions, although they presented hazard rations rather than relative risks. This review noted that these studies included few cancer patients and rated this evidence as moderate strength based on the GRADE method.

Table 9. Prevention of venous thromboembolic events in medically ill patients with newer oral anticoagulants

Study	Drug	All-cause mortality	Death–thromboembolic Event	Recurrent DVT/PE
		Relative risk (95% CI)		
Schulman, 2009 (RECOVER) N = 2564 Good	Dabigatran 150 mg vs. Warfarin 6 months duration	0.99 (0.55 to 1.81)	0.33 (0.03 to 3.18)	1.10 (0.66 to 1.84)
Bauersachs,2005 (EINSTEINDVT) n = 3449 Good	Rivaroxaban 20 mg vs. warfarin 6 to 12 months duration	0.77 (0.51 to 1.17)	0.66 (0.19 to 2.34)	0.70 (0.46 to 1.07)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

Key Question 2. What is the evidence from existing comparative effectiveness systematic reviews on the harms of the newer anticoagulant drugs in adults with atrial fibrillation or for prevention or treatment of thromboembolic events in adults who are medically ill or venous thromboembolic events in adults who have undergone orthopedic surgery?

Summary of findings

- There was no direct evidence comparing the harms of 1 newer anticoagulant drug with another.
- In patients undergoing orthopedic surgery:
  - There were no systematic reviews that included edoxaban
  - In indirect meta-analyses, there were no differences among the newer oral anticoagulant drugs in the risk of major bleeding (strength of evidence: low)
    - Rivaroxaban compared with dabigatran: RR, 1.37 (95% CI, 0.79 to 2.39); risk difference per 1000 patients treated, 4 (95% CI, −2 to 11)
    - Rivaroxaban compared with. apixaban: RR, 1.59 (95% CI, 0.84 to 3.02); risk difference per 1000 patients treated, 5 (95% CI, −2 to 12)
    - Apixaban compared with dabigatran: RR, 0.86 (95% CI, 0.41 to 1.83); risk difference per 1000 patients treated, 0 (95% CI, −8 to 7)
  - On the composite outcome clinically relevant bleeding (either major bleeding or clinically relevant minor bleeding):
    - Indirect meta-analysis showed higher risk with rivaroxaban compared with apixaban (moderate strength evidence); RR, 1.52 (95% CI, 1.19 to 1.95); risk difference per 1000 patients treated, 18 (95% CI, 7 to 28)
    - Lower risk with apixaban compared with dabigatran (moderate strength evidence); RR 0.73 (95% CI, 0.57 to 0.94); risk difference per 1000 patients treated, −13 (95% CI, −24 to −2)

        - No difference between rivaroxaban and dabigatran (low strength evidence due to imprecision of the estimate); RR, 1.37 (95% CI, 0.79 to 2.39); risk difference per 1000 patients treated, −13 (95% CI, −2 to 11)
    - Compared with enoxaparin, moderate- to high-strength evidence showed:
        - The risk of clinically relevant bleeding was lower with apixaban (RR, 0.82; 95% CI, 0.69 to 0.98) and higher with rivaroxaban (RR, 1.25; 95% CI, 1.05 to 1.49); there was no difference compared with dabigatran (RR, 1.12; 95% CI, 0.94 to 1.35)
        - There was no difference in risk for any of the newer oral anticoagulants compared with enoxaparin on the outcomes bleeding requiring re-operation, major bleeding, major non-fatal bleeding, or clinically relevant minor bleeding.
- In patients with non-valvular atrial fibrillation, indirect meta-analysis found moderate strength evidence that:
    - Dabigatran 150 mg was associated with increased risk of major bleeding (OR, 1.35; 95% CrI, 1.11 to 1.66) and major gastrointestinal bleeding (OR, 1.65; 95% CrI, 1.16 to 2.38) compared with apixaban
    - Rivaroxaban was associated with increased risk of major bleeding (OR, 1.48; 95% CrI, 1.21 to 1.82) and major gastrointestinal bleeding (OR, 1.83; 95% CrI, 1.30 to 2.57) compared with apixaban
    - Rivaroxaban was associated with increased risk of major bleeding (OR, 1.28; 95% CrI, 1.04 to 1.58) intracranial bleeding (OR, 2.22; 95% CrI, 1.29 to 3.89) and major gastrointestinal bleeding (OR, 1.49; 95% CrI, 1.07 to 2.09) compared with dabigatran 110 mg.
- There was moderate-high strength evidence that:
    - Dabigatran 150 mg was associated with increased major bleeding (OR, 1.17; 95% CrI, 1.01 to 1.36) and major gastrointestinal bleeding (OR, 1.35; 95% CrI, 1.07 to 1.72) compared with dabigatran 110 mg
    - Apixaban was associated with reduced risk of major bleeding (OR, 0.70; 95% CrI, 0.61 to 0.81) and intracranial bleeding (OR, 0.42; 95% CrI, 0.30 to 0.58) compared with warfarin
    - Dabigatran 110 mg was associated with reduced risk of major bleeding (OR, 0.81; 95% CrI, 070 to 0.93) and intracranial bleeding (OR, 0.30; 95% CrI, 0.19 to 0.45) compared with warfarin
    - Dabigatran 150 mg was associated with reduced risk of intracranial bleeding (OR, 0.42; 95% CrI, 0.28 to 0.60) but increased risk of major gastrointestinal bleeding (OR, 1.45; 95% CrI, 1.14 to 1.86) compared with warfarin
    - Rivaroxaban was associated with decreased risk of intracranial bleeding (OR, 0.66; 95% CrI, 0.47 to 0.92) but increased risk of major gastrointestinal bleeding (OR, 1.61; 95% CrI, 1.30 to 1.99) compared with warfarin.
- No evidence was found in systematic reviews on prevention of venous thromboembolic events in medically ill patients with newer oral anticoagulant drugs.
- In medically ill patients, comparisons of dabigatran and rivaroxaban to warfarin found very limited differences in adverse events (moderate-strength evidence)
    - No difference was found in major bleeding, fatal bleeding, myocardial infarction, and discontinuations due to adverse events

- Liver dysfunction occurred less frequently with rivaroxaban than with warfarin (RR, 0.40; 95% CI, 0.25 to 0.63)
- Gastrointestinal bleeding occurred more frequently with dabigatran that warfarin but was not statistically significant (RR, 1.51; 95% CI, 0.99 to 2.29).

Detailed assessment: Patients undergoing orthopedic surgery

Direct evidence

We identified no direct comparative evidence in systematic reviews.

Indirect evidence

For evidence of comparative harms of the newer anticoagulant drugs, we again relied primarily on a recent fair-quality systematic review and meta-analysis,[18] supplemented by a review and meta-analysis conducted for American College of Chest Physicians guidelines.[17] In the main review, the primary safety outcome was the risk of clinically relevant bleeding, defined as either major bleeding or clinically relevant minor bleeding. Secondary outcomes were the components of the primary outcome. The American College of Chest Physicians review also reported bleeding requiring re-operation and major non-fatal bleeding. Meta-analysis results are shown in Table 10.

Table 10. Safety outcomes in systematic reviews of newer oral anticoagulant drugs in patients undergoing orthopedic surgery

Outcome	Apixaban	Dabigatran	Rivaroxaban
	Relative risk (95% CI) vs. enoxaparin		
Clinically relevant bleeding (primary outcome)	**0.82 (0.69 to 0.98)**	1.12 (0.94 to 1.35)	**1.25 (1.05 to 1.49)**
Bleeding requiring re-operation[17]	0.82 (0.15 to 4.58)	150 mg: 0.83 (0.23 to 2.97) 250 mg: 0.98 (0.27 to 3.54)	2.03 (0.86 to 4.83)
Major bleeding	0.81 (0.45 to 1.43)	0.94 (0.58 to 1.52)	1.29 (0.98 to 1.69)
Major non-fatal bleeding[17]	0.76 (0.44 to 1.32)	150 mg: 0.71 (0.42 to 1.19) 250 mg: 1.06 (0.66 to 1.72)	1.58 (0.84 to 2.97)
Clinically relevant minor bleeding	0.83 (0.68 to 1.00)	1.19 (0.96 to 1.48)	1.21 (0.98 to 1.50)

Statistically significant results are shown in boldface.

Clinically relevant bleeding was less likely in patients taking apixaban compared with enoxaparin and more likely in patients taking rivaroxaban compared with enoxaparin. Indirect meta-analysis showed a 52% increased risk of clinically relevant bleeding with rivaroxaban compared with apixaban (Table 11). This translates to an absolute risk of 18 more patients per 1000 experiencing clinically relevant bleeding with rivaroxaban compared with apixaban (95% CI, 7 to 98). On other safety outcomes, there were no statistically significant differences.

Table 11. Indirect comparisons between rivaroxaban, dabigatran, and apixaban (adapted from Gomez-Outes 2012[18])

Outcomes	Rivaroxaban vs. dabigatran	Rivaroxaban vs. apixaban	Apixaban vs. dabigatran
	Relative risk (95% CI) Risk difference (95% CI) per 1000 patients treated		
Clinically relevant bleeding	1.12 (0.87 to 1.44) 5 (−7 to 16)	**1.52 (1.19 to 1.95)** **18 (7 to 28)**	**0.73 (0.57 to 0.94)** **−13 (−24 to −2)**
Major bleeding	1.37 (0.79 to 2.39) 4 (−2 to 11)	1.59 (0.84 to 3.02) 5 (−2 to 12)	0.86 (0.41 to 1.83) 0 (−8 to 7)

Statistically significant results are shown in boldface.

Detailed assessment: Atrial fibrillation

Direct evidence

We identified no direct comparative evidence in systematic reviews of 1 newer oral anticoagulant drug compared with another.

Indirect evidence

For evidence of comparative harms of the newer anticoagulant drugs, we relied primarily on the CADTH systematic review and network meta-analysis (Table 12).[39] The primary safety outcome of this review was the risk of clinically relevant bleeding which included major bleeding as defined by the International Society of Thrombosis and Hemostasis (fatal bleeding, symptomatic bleeding in a critical area or organ, and/or bleeding causing a fall in hemoglobin level of 20 g/L or leading to a transfusion of 2 or more units of whole blood or red cells).

Table 12. Summary of safety results from network meta-analyses

Comparison	Major bleeding	Intracranial bleeding	Major gastrointestinal bleeding
	OR (95% Credible interval)		
Apixaban vs. warfarin	**0.70**	**0.42**	0.88
	(0.61 to 0.81)	**(0.30 to 0.58)**	(0.68 to 1.15)
ARR per 1000 patients	**8 fewer**	**4 fewer**	1 fewer
treated each year	**(6 fewer, 11 fewer)**	**(3 fewer, 5 fewer)**	(1 more, 2 fewer)
Dabigatran 110 mg vs. warfarin	**0.81**	**0.30**	1.08
	(0.70 to 0.93)	**(0.19 to 0.45)**	(0.84 to 1.40)
ARR per 1000 patients	**7 fewer**	**5 fewer**	1 more
treated each year	**(2 fewer, 11 fewer)**	**(4 fewer, 6 fewer)**	(4 more, 1 fewer)
Dabigatran 150 mg	0.94	**0.42**	**1.45**
vs. warfarin	0.82 -1.08)	**(0.28 to 0.60)**	**(1.14 to 1.86)**
ARR per 1000 patients	2 fewer	**4 fewer**	**4 more**
treated each year	(3 more, 6 fewer)	**(3 fewer, 5 fewer)**	**(8 more, 1 more)**
Rivaroxaban vs.	1.03	**0.66**	**1.61**
Warfarin	(0.89 to 1.19)	**(0.47 to 0.92)**	**(1.30 to 1.99)**
ARR per 1000 patients	1 more	**3 fewer**	**8 more**
treated each year	(6 more, 3 fewer)	**(1 fewer, 4 fewer)**	**(13 more, 4 more)**
Dabigatran 110 mg vs. apixaban	1.16	0.71	1.23
	(0.95 -1.43)	(0.41 to 1.21)	(0.85 to 1.78)
Dabigatran 150 mg	**1.35**	0.99	**1.65**
vs. apixaban	**(1.11 to 1.66)**	(0.60 to 1.62)	**(1.16 to 2.38)**
Rivaroxaban vs. apixaban	**1.48**	1.56	**1.83**
	(1.21 to 1.82)	(0.97 to 2.50)	**(1.30 to 2.57)**
Dabigatran 150 mg vs.	**1.17**	1.41	**1.35**
dabigatran 110 mg	**(1.01 to 1.36)**	(0.86 to 2.33)	**(1.07 to 1.72)**
Rivaroxaban vs. dabigatran 110	**1.28**	**2.22**	**1.49**
mg	**(1.04 to 1.58)**	**(1.29 to 3.89)**	**(1.07 to 2.09)**
Rivaroxaban vs. dabigatran 150	1.10	1.58	1.11
mg	(0.90 to 1.35)	(0.95 to 2.66)	(0.80 to 1.53)

Abbreviations: ARR, absolute risk reduction.
Statistically significant results are shown in boldface.

When compared with warfarin, use of apixaban and dabigatran resulted in less major bleeding overall, while use of apixaban, dabigatran, and rivaroxaban resulted in fewer intracranial bleeds. However, use of dabigatran 150 mg and rivaroxaban increased the incidence of major gastrointestinal bleeding compared with warfarin. When different doses of dabigatran were compared, the higher dose resulted in increased gastrointestinal bleeding and increased major bleeding overall compared with the lower dose. When the newer anticoagulants were compared with each other using indirect meta-analysis, use of apixaban resulted in fewer major gastrointestinal bleeds and episodes of major bleeding than either dabigatran 150 mg or rivaroxaban; use of dabigatran 110 mg resulted in fewer episodes of major gastrointestinal bleeding, intracranial bleeding, and major bleeding overall than rivaroxaban. Dabigatran 150 mg and rivaroxaban had similar rates of bleeding as did dabigatran 110 mg and apixaban.

Other reviews

A draft comparative effectiveness review on stroke prevention in atrial fibrillation prepared for the Agency for Healthcare Research and Quality also included 2 good-quality trials not in the CADTH review.[40] A trial of edoxaban compared with warfarin found that edoxaban when dosed twice daily (either 30 or 60 mg twice daily) was associated with increased incidence of major bleeding compared with warfarin but was similar to warfarin when daily dosing was employed (30 or 60 mg once daily). The second trial compared apixaban with aspirin in patients in whom warfarin therapy was not suitable and found no difference between apixaban and aspirin on the rates of hemorrhagic stroke, major bleeding, or intracranial bleeding.

Additionally, a review prepared for the Department of Veterans Affairs reported a recent analysis of the RE-LY trial that examined rates of myocardial ischemic events, including silent myocardial infarctions (the first report of the RE-LY trial included only clinically evident myocardial infarctions), and found that dabigatran was associated with a non-significant increase in myocardial infarction (HR, 1.29; 95% CI, 0.96 to 1.75 for dabigatran 110 mg; HR, 1.27; 95% CI, 0.94 to 1.71 for dabigatran 150 mg) relative to warfarin, but unstable angina, cardiac arrest, or cardiac death showed no increased risk.[37]

The Agency for Healthcare Research and Quality review also reported that only 2 trials provided the rate of overall study adverse events. In the ARISTOTLE trial, there were similar rates of adverse events (81.5% in the apixaban group compared with 83.1% in the warfarin group). In the second trial, the percent of adverse events in with edoxaban was dose-dependent, with the highest dose having a rate similar to warfarin: edoxaban 30 mg once daily (11.1%), edoxaban 30 mg twice daily (13.5%), edoxaban 60 mg once daily (11.5%), edoxaban 60 mg twice daily (22.2%), and warfarin (18.4%). When serious treatment emergent adverse events were compared, the results were similar (5.9% across edoxaban groups compared with 4.4% in the warfarin group).

Detailed assessment: Medically ill patients

Prevention

As reported for Key Question 1, we found no evidence on prevention of venous thromboembolic events in medically ill patients with the newer oral anticoagulant drugs.[43]

Treatment

We found 2 good-quality systematic reviews addressing the treatment of venous thromboembolic events in patients who were medically ill (i.e., non-surgical and non-atrial fibrillation patients).[37, 44] Both reviews include the same 2 trials, 1 using rivaroxaban and 1 using dabigatran, both for longer-term treatment of venous thromboembolic events in medical patients compared with warfarin. This evidence is rated moderate strength of evidence. The types of events reported differed slightly between trials, but commonly-reported adverse events are listed in Table 13 below. The only statistically significant difference between the newer drugs and warfarin was the incidence on liver dysfunction, which was significantly lower with rivaroxaban compared with warfarin.

Table 13. Adverse events with newer oral anticoagulants compared with warfarin

Outcome	Dabigatran vs. warfarin	Rivaroxaban vs. warfarin
	Relative risk (95% CI)	
Major bleeding	0.83 (0.46 to 1.49)	0.70 (0.35 to 1.38)
Fatal bleeding	0.99 (0.06 to 15.88)	0.40 (0.08 to 2.05)
Gastrointestinal bleeding	1.51 (0.99 to 2.29)	--
Myocardial Infarction	1.99 (0.36 to 10.84)	4.98 (0.58 to 42.58)
Liver dysfunction	0.90 (0.60 to 1.35)	**0.40 (0.25 to 0.63)**
Discontinued due to adverse events	1.33 (1.02 to 1.74)	1.04 (0.77 to 1.40)

Statistically significant results are shown in boldface.

Key Question 3. What is the evidence from existing comparative effectiveness systematic reviews 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 newer anticoagulant drug is more effective or associated with fewer harms?

Summary of findings

- For non-valvular atrial fibrillation patients there was low- to moderate-strength evidence that compared with warfarin:
  - The newer oral anticoagulants were not superior to warfarin when the international normalized ratio for warfarin was therapeutic at least 66% of the time.
  - Age ≥ 75 compared with <75 affected risk of stroke and risk of bleeding with the newer oral anticoagulants. In older patients, apixaban, dabigatran 150 mg, and rivaroxaban reduced stroke/systemic embolism risk compared with warfarin while only apixaban reduced the risk of major bleeding. In younger patients, only dabigatran 150 mg was associated with fewer strokes than warfarin while apixaban and dabigatran 110 mg and 150 mg were associated with reduced risk of major bleeding.
  - In individuals with a $CHADS_2$ score ≥ 2 apixaban and dabigatran 150 mg reduced the incidence of stroke/systemic embolism compared with warfarin but only apixaban reduced the risk of major bleeding. In individuals with less comorbidity ($CHADS_2$ score <2) dabigatran 150 mg was associated with reduced risk of stroke compared with warfarin while apixaban and dabigatran 110 mg reduced the risk of major bleeding.
  - Apixaban was better than aspirin in reducing risk of stroke in patients who had a history of prior stroke or transient ischemic attack (HR, 0.29; 95% CI, 0.15 to 0.60) with no difference in risk of major bleeding in this population.
  - In patients with renal impairment, a reduced dose of rivaroxaban was not different from warfarin in rates of all cause stroke/systemic embolism, intracranial bleeding, and fatal bleeding.
- Evidence on the use of newer oral anticoagulant drugs in subgroups of medically ill patients was insufficient to make conclusions.

Detailed assessment: Patients undergoing orthopedic surgery

Direct evidence

We identified no direct evidence about comparative effectiveness and safety of the newer anticoagulants in subgroups.

Indirect evidence

Subgroup analyses of the main efficacy and safety outcomes by type of surgery (total hip or knee replacement) in the primary systematic review found no statistically significant interactions.[18] Overall, the net clinical endpoint (composite of symptomatic venous thromboembolic events, major bleeding, and death) was better in total knee replacement surgery than in total hip replacement surgery for all of the newer oral anticoagulant drugs (Table 14).

Table 14. Net clinical endpoint[a] by type of surgery (adapted from Gomez-Outes 2012[18])

	Number of events/number in group		Relative risk (95% CI)	*P* value
	New anticoagulant	Enoxaparin		
Dabigatran				
Hip	81/3367	38/2181	1.26 (0.80 to 1.98)	0.06
Knee	58/3141	41/1575	0.71 (0.48 to 1.05)	
Rivaroxaban				
Hip	86/3888	94/3990	0.92 (0.60 to 1.41)	0.76
Knee	71/2940	84/2946	0.85 (0.60 to 1.19)	
Apixaban				
Hip	29/2708	29/2699	1.00 (0.60 to 1.66)	0.70
Knee	58/3437	62/3277	0.88 (0.62 to 1.26)	

[a] Composite of symptomatic venous thromboembolic events, major bleeding, and death.

Detailed assessment: Atrial fibrillation

Direct evidence

We identified no direct evidence about comparative effectiveness and safety of the newer anticoagulants in subgroups.

Indirect evidence

For evidence of comparative effectiveness and harms on subgroups of patients, we relied primarily on the CADTH systematic review and network meta-analysis.[39] Due to clinical and methodological heterogeneity across trials, several subgroup analyses were performed.

When the international normalized ratio for warfarin was within the therapeutic range (2-3) ≥ 66% of the time. There was no benefit of the newer oral anticoagulants on stroke/systemic embolism prevention compared with warfarin. Apixaban 5 mg was less likely to be associated with major bleeding (OR, 0.82; 95% CrI, 0.67 to 0.99) and rivaroxaban 20 mg was more likely to be associated with major bleeding (OR, 1.30; 95% CrI, 1.01 to 1.69) compared with warfarin.

When individuals were ≥ 75 years of age. Apixaban, dabigatran 150 mg, and rivaroxaban were associated with reduced stroke/systemic embolism (OR, 0.72; 95% CrI, 0.53 to 0.96; OR, 0.67; 95% CrI, 0.49 to 0.90; and OR, 0.66; 95% CrI, 0.49 to 0.87, respectively) but only apixaban was associated with fewer episodes of major bleeding compared with warfarin (OR, 0.65; 95% CrI, 0.53 to 0.81). *In patients under 75 years of age*, only dabigatran 150 mg was associated with fewer strokes/systemic embolisms (OR, 0.64; 95% CrI, 0.46 to 0.87), while apixaban, dabigatran 110 mg, and dabigatran 150 mg were associated with fewer episodes of major bleeding compared with warfarin (OR, 0.73; 95% CrI, 0.60 to 0.89; OR, 0.62; 95% CrI, 0.50 to 0.77; and OR, 0.70; 95% CrI, 0.57 to 0.87, respectively).

In individuals with a $CHADS_2$ Score ≥ 2 (≥ 4% chance of thromboembolism annually). Apixaban 5 mg and dabigatran 150 mg reduced the incidence of stroke/systemic embolism (OR, 0.78; 95% CrI, 0.64 to 0.96 and OR, 0.67; 95% CrI, 0.52 to 0.85, respectively) but only apixaban reduced the risk of major bleeding compared with warfarin (OR, 0.74; 95% CrI, 0.62 to 0.87). *In individuals with a $CHADS_2$ Score <2*, dabigatran 150 mg reduced the risk of stroke/systemic embolism (OR, 0.61; 95% CrI, 0.37 to 0.997) while apixaban 5 mg and dabigatran 110 mg were associated with fewer episodes of major bleeding compared with warfarin (OR, 0.59; 95% CrI, 0.44 to 0.79 and OR, 0.65 and 95% CrI, 0.48 to 0.89, respectively).

Patients with a prior stroke or transient ischemic attack. The draft comparative effectiveness review prepared for the Agency for Healthcare Research and Quality included subgroup analyses of patients with atrial fibrillation who had already had a stroke or transient ischemic attack.[40] Based on a single trial each there were no differences in risk of stroke or systemic embolism when apixaban, dabigatran, or rivaroxaban was compared with warfarin in direct comparisons. In the trial of apixaban compared with aspirin, however, the risk of stroke, systemic embolism, ischemic stroke, and disabling or fatal stroke was significantly reduced with apixaban when compared with aspirin (HR, 0.29; 95% CI, 0.15 to 0.60) in patients receiving secondary prophylaxis.

For these patients, the rate of major bleeding was reduced with dabigatran 110 mg and apixaban compared with warfarin (RR, 0.66; 95% CI, 0.48 to 0.90 and HR, 0.37; 95% CI, 0.21 to 0.67, respectively). However, this was not different from the effects of dabigatran and apixaban on patients without a prior history of stroke or transient ischemic attack. The Agency for Healthcare Research and Quality subgroup analysis found no difference between rivaroxaban compared with warfarin on patients with and without previous stroke or transient ischemic attack in the risk of major and non-major but clinically relevant bleeding. There was also no difference in risk for major bleeding between apixaban and aspirin.

Patients with renal impairment. The draft comparative effectiveness review prepared for the Agency for Healthcare Research and Quality also reported a substudy of the ROCKET-AF trial of rivaroxaban 15 mg (instead of 20 mg daily) in patients with a creatinine clearance 30 to 49 mL/min on risk of stroke/systemic embolism which occurred in 2.32 per 100 patient-years compared with 2.77 with warfarin (HR, 0.86; 95% CI, 0.63 to 1.17). Risk of intracranial bleeding (0.71 vs. 0.88 per 100 patient-years) and fatal bleeding (0.28 vs. 0.74 per 100 patient-years) were also non-significantly reduced with rivaroxaban relative to warfarin.

Detailed assessment: Medically ill patients

Prevention

No evidence was found for prevention of venous thromboembolic events in medically ill patients with newer oral anticoagulants.

Treatment

Evidence on dabigatran and rivaroxaban for treatment of venous thromboembolic events in medical patients is limited to a single study each. Systematic reviews evaluating these studies note that very few cancer patients were included in these trials, such that evidence in this subgroup is insufficient.

SUMMARY

Strength of Evidence

Our ratings of the strength of evidence for each population and key question are shown in Appendix D. For comparisons of the newer oral anticoagulants to each other, the strength of the evidence for most outcomes was low, due to indirectness of the comparisons and imprecision of the estimates.

Limitations of this Report

As with other types of research, the limitations of this summary review are important to recognize. The main limitation was the dependence on published systematic reviews that were not conducted specifically for the Drug Effectiveness Review Project. The aims and methodology may not have been ideally suited to our purposes and therefore it is possible that issues important to the Project were not examined in these reviews. Other potential methodological limitations included the exclusion of reviews published in languages other than English and not being able to search additional electronic databases.

Additionally, depending on published reviews may mean that recently-reported studies relevant to this topic were not included in the reviews or trials relevant to the Drug Effectiveness Review Project were not included in the review for various reasons. We have provided a list of trials published since the search end date of included systematic reviews in the table below (Table 15), and trials known to have been excluded from reviews (see Appendix E for abstracts of these trials).

Table 15. Trials not included in systematic reviews (published after review search dates)

Author, year	N	Study drug	Comparator	Population details
Weitz, 2010	1146	Edoxaban 30 mg qd, 30 mg bid, 60 mg qd, or 60 mg bid	Warfarin	Non-valvular atrial fibrillation; 12 weeks double-blind to edoxaban dose, but open-label to warfarin
RE-LY Trial publications (subgroups and additional outcomes): Atrial fibrillation				
Healey, 2012 RE-LY	4591	Dabigatran 110 mg Dabigatran 150 mg	Warfarin	Examined bleeding risk in patients who had an invasive procedure (e.g., cataract removal, colonoscopy, joint replacement, or pacemaker)
Hori, 2011 RE-LY	326	Dabigatran 110 mg Dabigatran 150 mg	Warfarin	Japanese patients
Hart, 2012 RE-LY	18,113	Dabigatran 110 mg Dabigatran 150 mg	Warfarin	Intracranial hemorrhage incidence over 2 years

Abbreviations: bid, twice daily.

CONCLUSION

Although the quality (internal validity) and consistency of the evidence available for this report was good, a major limitation was the lack of available direct evidence. Conclusions were based on indirect evidence, which limited our ratings to low or moderate strength of evidence.

In patients undergoing orthopedic surgery, apixaban, rivaroxaban, and dabigatran did not differ in preventing symptomatic venous thromboembolic events or in net clinical benefit. Clinically relevant bleeding was less likely with apixaban. Better efficacy with dabigatran compared with enoxaparin on some outcomes was associated with a greater incidence of harms.

In non-valvular atrial fibrillation patients, network analyses indicates that there is a tradeoff with each medication between clotting and bleeding. For instance, compared with warfarin or the newer oral anticoagulants, rivaroxaban is more likely to prevent myocardial infarction, but is also more likely to lead to intracranial hemorrhage. Compared with the newer oral anticoagulants, warfarin, however, is likely less effective for the prevention of all-cause mortality in this patient population.

Evidence for prevention of venous thromboembolic events in medically ill patients is insufficient. Evidence for treatment in medical patients with venous thromboembolic events is limited and non-comparative for the new drugs, but shows no difference in benefit compared with warfarin. Differences between the new oral drugs and warfarin in bleeding may exist but require further study.

A major concern with these drugs compared with older drugs is that there is no known antidote for use in the case of serious bleeding or overdose. Appropriate dosing of rivaroxaban in patients with impaired kidney function may also be a safety issue. Finally, the newer anticoagulants may have unknown adverse effects and may result in lower patient compliance relative to warfarin due to the lack of a need for regular contact for international normalized ratio monitoring, and the cost to the patient may be increased compared with older anticoagulants.

REFERENCES

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. *Am J Prev Med.* Apr 2010;38(4 Suppl):S495-501.

2. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation.* Jan 3 2012;125(1):e2-e220.

3. Kochanek KD, Xu J, Murphy SL, Minino AM, Kung H-C. *Deaths: Preliminary Data for 2009.* Hyattsville, MD: National Center for Health Statistics;2011.

4. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA.* Jun 13 2001;285(22):2864-2870.

5. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* Feb 2012;141(2 Suppl):e531S-575S.

6. FDA approves Xarelto to prevent stroke in people with common type of abnormal heart rhythm. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm278646.htm. Accessed 12.28, 2012.

7. FDA approval letter for apixaban. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/202155Orig1s000ltr.pdf. Accessed Jan 4, 2013.

8. Adams RL, Bird RJ. Review article: Coagulation cascade and therapeutics update: relevance to nephrology. Part 1: Overview of coagulation, thrombophilias and history of anticoagulants. *Nephrology (Carlton).* Aug 2009;14(5):462-470.

9. Eliquis (Apixaban) Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf. Accessed Jan 3, 2013.

10. Pradaxa (dabigatran etexilate mesylate) Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022512s014lbl.pdf. Accessed Nov 16, 2012.

11. Xarelto Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022406s001s002s003lbl.pdf. Accessed Nov 16, 2012.

12. McDonagh MS, Jonas DE, Gartlehner G, et al. Methods for the Drug Effectiveness Review Project. *BMC Med Res Methodol.* Sep 12 2012;12(1):140.

13. Owens DK, Lohr KN, Atkins D. Grading the strength of a body of evidence when comparing medical interventions. *Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews*. Rockville, MD2009.

14. Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. *J Clin Epidemiol.* 2010;63(5):513-523.

15. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the effective healthcare program (Article in Press). *Journal of Clinical Epidemiology.* 2011.

16. Liberati A, Altman D, Tetzlaff J, Mulrow C, al. e. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals of Internal Medicine.* 2009;151(4):W65-W94.

17. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* Feb 2012;141(2 Suppl):e278S-325S.

18. Gomez-Outes A, Terleira-Fernandez AI, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *Bmj.* 2012;344:e3675.

19. Ringerike T, Hamidi V, Hagen G, Reikvam A, Klemp M. *Health technology assessment of thromboprophylactic treatment with rivaroxaban or dabigatran compared with enoxaparin or dalteparin in patients undergoing elective hip- or knee replacement surgery.* Oslo: Norwegian Knowledge Centre for the Health Services;2011.

20. Neumann I, Rada G, Claro J, et al. Oral direct factor Xa inhibitors versus low-molecular-weight heparin to prevent venous thromboembolism in patients undergoing total hip or knee replacement: a systematic review and meta-analysis *Annals of Internal Medicine.* 2012;156(10):710-719.

21. Eriksson BI, Borris LC, Dahl OE, et al. Dose-escalation study of rivaroxaban (BAY 59-7939)--an oral, direct Factor Xa inhibitor--for the prevention of venous thromboembolism in patients undergoing total hip replacement. *Thromb Res.* 2007;120(5):685-693.

22. Guyatt GH, Norris SL, Schulman S, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* Feb 2012;141(2 Suppl):53S-70S.

23. Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial.[Erratum appears in Lancet. 2007 Dec 15;370(9604):2004]. *Lancet.* Sep 15 2007;370(9591):949-956.

24. Committee R-MW, Ginsberg JS, Davidson BL, et al. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty.* Jan 2009;24(1):1-9.

25. Eriksson BI, Dahl OE, Huo MH, et al. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. *Thromb Haemost.* Apr 2011;105(4):721-729.

26. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med.* Jun 26 2008;358(26):2765-2775.

27. Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet.* Jul 5 2008;372(9632):31-39.

28. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med.* Jun 26 2008;358(26):2776-2786.

29. Turpie AGG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet.* May 16 2009;373(9676):1673-1680.

30. Turpie AGG, Fisher WD, Bauer KA, et al. BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. *J Thromb Haemost.* Nov 2005;3(11):2479-2486.

31. Eriksson BI, Borris L, Dahl OE, et al. Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost.* Jan 2006;4(1):121-128.

32. Eriksson BI, Borris LC, Dahl OE, et al. A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. *Circulation.* Nov 28 2006;114(22):2374-2381.

33. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement.[Erratum appears in N Engl J Med. 2009 Oct 29;361(18):1814]. *N Engl J Med.* Aug 6 2009;361(6):594-604.

34. Lassen MR, Raskob GE, Gallus A, et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet.* Mar 6 2010;375(9717):807-815.

35. Lassen MR, Gallus A, Raskob GE, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med.* Dec 23 2010;363(26):2487-2498.

36. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost.* Dec 2007;5(12):2368-2375.

37. Adam SS, McDuffie JR, Ortel TL, Nagi A, Williams JWJ. Comparative Effectiveness of Warfarin and Newer Oral Anticoagulants for the Long-term Prevention and Treatment of Arterial and Venous Thromboembolism. VA-ESP Project #09-010. 2012.

38. Testa L, Agnifili M, Latini RA, et al. Adjusted indirect comparison of new oral anticoagulants for stroke prevention in atrial fibrillation. *QJM.* Oct 2012;105(10):949-957.

39. Wells G, Coyle D, Cameron C, et al. Safety, effectiveness, and cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation. 2012.

40. Agency for Healthcare Research and Quality. *Stroke Prevention in Atrial Fibrillation (Draft Report).* Rockville, MD 2012.

41. Higgins JPT, Altman D. Assessing risk of bias in included studies. In: higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions.* Vol 8. West Sussex, U.K.: John Wiley & Sons Ltd.; 2008.

42. NHS Quality Improvemen Scotland (NHS QIS). Sign 50. A guideline developer's handbook: Edinburgh Scottish Intercollegiate Guidelines Network: http://www.sign.ac.uk/pdf/sign50.pdf. Accessed November 27, 2012.

43. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* Feb 2012;141(2 Suppl):e195S-226S.

44. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* Feb 2012;141(2 Suppl):e419S-494S.