



Comparative Effectiveness of Newer Oral Anticoagulants and Standard Anticoagulant Regimens for Thromboprophylaxis in Patients Undergoing Total Hip or Knee Replacement

December 2012

Prepared for:

Department of Veterans Affairs
Veterans Health Administration
Quality Enhancement Research Initiative
Health Services Research & Development Service
Washington, DC 20420

Prepared by:

Evidence-based Synthesis Program (ESP) Center
Durham Veterans Affairs Healthcare System
Durham, NC
John W. Williams Jr., M.D., M.H.Sc., Director

Investigators:

Principal Investigator:
Soheir S. Adam, M.D.

Co-Investigators:
Jennifer R. McDuffie, Ph.D.
Paul F. Lachiewicz, M.D.
Thomas L. Ortel, M.D., Ph.D.
John W. Williams Jr., M.D., M.H.Sc.

Research Associate:
Avishek Nagi, M.S.

Medical Editor:
Liz Wing, M.A.



VA
HEALTH CARE | Defining
EXCELLENCE
in the 21st Century

PREFACE

Quality Enhancement Research Initiative's (QUERI's) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

Recommended citation: Adam SS, McDuffie JR, Lachiewicz PF, Ortel TL, Williams JW Jr. Comparative Effectiveness of Newer Oral Anticoagulants and Standard Anticoagulant Regimens for Thromboprophylaxis in Patients Undergoing Total Hip or Knee Replacement. VA ESP Project #09-010; 2012.

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the Durham VA Medical Center, Durham, NC, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. Potential conflicts of interest: Dr. Ortel: *Grants*—GlaxoSmithKline, Eisai, Daichi Sankyo, Pfizer, Instrumentation Laboratory; *Consultancy*—Boehringer Ingelheim, Pfizer, Instrumentation Laboratory. No other investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report. To limit conflict of interest, Dr. Ortel participated in the design and critical review of the report but did not participate in data abstraction or drafting of the report.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Background.....	1
Methods.....	2
Data Synthesis.....	2
Rating the Body of Evidence.....	2
Peer Review.....	3
Results.....	3
Recommendations for Future Research.....	9
Conclusion.....	9
Abbreviations Table.....	10

INTRODUCTION

Pharmacological Treatment Options for VTE Thromboprophylaxis.....	11
---	----

METHODS

Topic Development.....	13
Analytic Framework.....	13
Search Strategy.....	14
Study Selection.....	14
Data Abstraction.....	15
Quality Assessment.....	16
Data Synthesis.....	16
Rating the Body of Evidence.....	17
Peer Review.....	18

RESULTS

Literature Search.....	19
Study Characteristics.....	20
Participant Characteristics.....	22
KQ 1. Comparative effectiveness of newer oral anticoagulants and standard drug classes.....	23
KQ 2. Comparative effects of combined pharmacological and mechanical modalities.....	27
KQ 3. Comparative efficacy of newer oral anticoagulants.....	28

SUMMARY AND DISCUSSION

Summary of Evidence by Key Question.....	30
Clinical and Policy Implications.....	34
Applicability.....	36
Strengths and Limitations.....	36
Recommendations for Future Research.....	36
Conclusion.....	37

REFERENCES.....	38
------------------------	-----------

APPENDIX A	SEARCH STRATEGIES	42
APPENDIX B	EXCLUDED STUDIES	43
APPENDIX C	SAMPLE DATA ABSTRACTION FORM	46
APPENDIX D	CRITERIA USED IN QUALITY ASSESSMENT OF SYSTEMATIC REVIEWS	49
APPENDIX E	PEER REVIEW COMMENTS	52
APPENDIX F	GLOSSARY	56

FIGURES

Figure 1.	Analytic framework for the comparative effectiveness of newer oral anticoagulants.....	13
Figure 2.	Literature flow diagram.....	19

TABLES

Table 1.	Summary of the strength of evidence for KQ 1	5
Table 2.	Summary of the strength of evidence for KQ 3	8
Table 3.	Evidence gaps and future research.....	9
Table 4.	Summary of inclusion and exclusion criteria.....	15
Table 5.	Characteristics of included systematic reviews.....	21
Table 6.	Characteristics of patient samples.....	22
Table 7.	Summary of the strength of evidence for KQ 1	31
Table 8.	Summary of the strength of evidence for KQ 3	33
Table 9.	U.S. guideline recommendations related to specific thromboprophylaxis strategies.....	35
Table 10.	Evidence gaps and future research.....	37

EVIDENCE REPORT

INTRODUCTION

Venous thromboembolic (VTE) events are important causes of morbidity in elective total hip replacement (THR) and total knee replacement (TKR) procedures, which are being performed with increasing frequency in an aging population. Because of the substantial risk of VTE, current guidelines recommend thromboprophylaxis in patients undergoing THR or TKR.¹⁻³ Low molecular weight heparin (LMWH) and adjusted-dose warfarin are the most commonly used anticoagulants for thromboprophylaxis in the United States,⁴ but a number of pharmacological treatment options are available including unfractionated heparin, aspirin, and newer oral anticoagulants. These drug classes differ in practical applications such as a predictable dose-response and the need for laboratory monitoring, oral versus injection administration, dosing frequency, drug-drug interactions, and the availability of an appropriate reversal mechanism in case of over anticoagulation. In addition, mechanical thromboprophylaxis, most frequently used in combination with anticoagulants, is commonly used in the United States.

Risk factors for VTE include venous stasis, endothelial injury, and hypercoagulability. Venous stasis can result from the positioning of the limb, localized postoperative swelling, or limited mobility in the postoperative period.^{5,6} Endothelial injury can result from positioning and manipulation of the limb.^{5,7} Markers of thrombin generation, indicating hypercoagulability, have been shown to be elevated in total hip arthroplasty.⁸ Prior to 1980, rates of symptomatic VTE were 15 to 30 percent. However, changes in surgical care, including earlier ambulation, and changes to surgical technique that are less invasive and possibly less thrombogenic have decreased the rate of symptomatic VTE. A recent analysis that incorporated data from trials and observational studies estimated the contemporary 35-day rate of symptomatic VTE without thromboprophylaxis at 4.3 percent.¹

Pharmacological thromboprophylaxis for THR or TKR surgery decreases VTE by approximately 50 percent but with the tradeoff of increased bleeding.⁹ Surgical procedures may also increase bleeding risk; major bleeding is estimated to occur in 1.5 percent of patients undergoing THR or TKR, even without thromboprophylaxis.¹ The risk of bleeding is a concern because bleeding can lead to infections, reoperation, delayed wound healing, and extended hospital stay.¹⁰ Considering both benefits and risks, guideline panels have issued moderate to strong recommendations for thromboprophylaxis in patients without a contraindication.¹⁻³ The choice of which antithrombotic thus becomes pivotal for balancing the prevention of thromboembolism with the risk of bleeding.

PHARMACOLOGICAL TREATMENT OPTIONS FOR VTE THROMBOPROPHYLAXIS

The most commonly used anticoagulants are LMWH, fondaparinux, and warfarin.^{4,11,12} Unfractionated heparin and antiplatelet agents are rarely used. The efficacy and safety of LMWH for postoperative thromboprophylaxis has been established in more than 30 studies.^{3,9,13} LMWH binds to antithrombin and accelerates the inhibition of thrombin and factor X. LMWH has a long half-life, which allows a once-daily dosing schedule and good bioavailability after subcutaneous

injection. Disadvantages of LMWH include the need for parenteral administration, high drug cost, and a small risk of heparin-induced thrombocytopenia.¹⁴ Similarly, fondaparinux has good bioavailability when given once daily subcutaneously. Due to the length of the molecule, fondaparinux mainly acts by catalyzing the inhibition of factor Xa (FXa) with essentially no inhibition of thrombin.¹⁵

For nearly 50 years, warfarin has been successfully used for prophylaxis and treatment of VTE. Warfarin is administered orally once daily and is inexpensive. However, it has several disadvantages, including the need for regular monitoring with international normalized ratio (INR) and numerous interactions with a host of drugs, herbs, and dietary products. Its delayed onset of action can leave patients unprotected in the early postoperative period. In fact, registry data show that surgeons using warfarin are less likely to meet guideline recommendations than with other agents due to failure to meet the target INR.⁴

Newer oral anticoagulants have been developed with the goal to overcome the limitations of warfarin and the available parenteral agents. These new anticoagulants belong to two drug classes, based on their target coagulation protein: FXa inhibitors and direct thrombin inhibitors (DTIs). These are given as fixed oral doses and have the advantage of a more predictable anticoagulant effect, eliminating the need for monitoring when used for short term thromboprophylaxis. Disadvantages of newer oral anticoagulants include drug costs and the lack of specific antidotes to reverse their anticoagulant effect in a timely fashion in case of bleeding. Rivaroxaban, an oral FXa inhibitor, was approved on July 1, 2011, by the U.S. Food and Drug Administration (FDA) for prophylaxis of VTE in adults undergoing orthopedic surgery. Other oral FXa inhibitors that are currently under clinical development include apixaban, edoxaban, and betrixaban. Apixaban is under FDA review for thromboprophylaxis in orthopedic surgery. Dabigatran etexilate is an oral DTI that has been approved in the United States for stroke prevention in atrial fibrillation. Renal excretion is the predominant elimination pathway for dabigatran, with more than 80 percent of systemically available dabigatran eliminated unchanged.¹⁶ Dabigatran has a better drug interaction profile compared with warfarin and is currently under review for FDA approval in patients undergoing elective orthopedic surgery.

Given the emerging data on new oral anticoagulants, this report was commissioned by the VA to assess the comparative effectiveness of newer oral anticoagulants and standard thromboprophylaxis regimens in total hip and knee replacement surgery.

METHODS

TOPIC DEVELOPMENT

This review was commissioned by the VA’s Evidence-based Synthesis Program. The topic was nominated after a topic refinement process that included a preliminary review of published peer-reviewed literature, consultation with internal partners and investigators, and consultation with key stakeholders. We further developed and refined the key questions (KQs) based on a preliminary review of published peer-reviewed literature in consultation with VA and non-VA experts.

The final KQs were:

KQ 1. For patients undergoing total hip or total knee replacement, what is the comparative effectiveness of newer oral anticoagulants and standard drug classes (low molecular weight heparin, injectable factor Xa inhibitors, unfractionated heparin, warfarin, aspirin) on the incidence of symptomatic, objectively confirmed venous thromboembolism (VTE), other VTE events, total mortality, and bleeding outcomes?

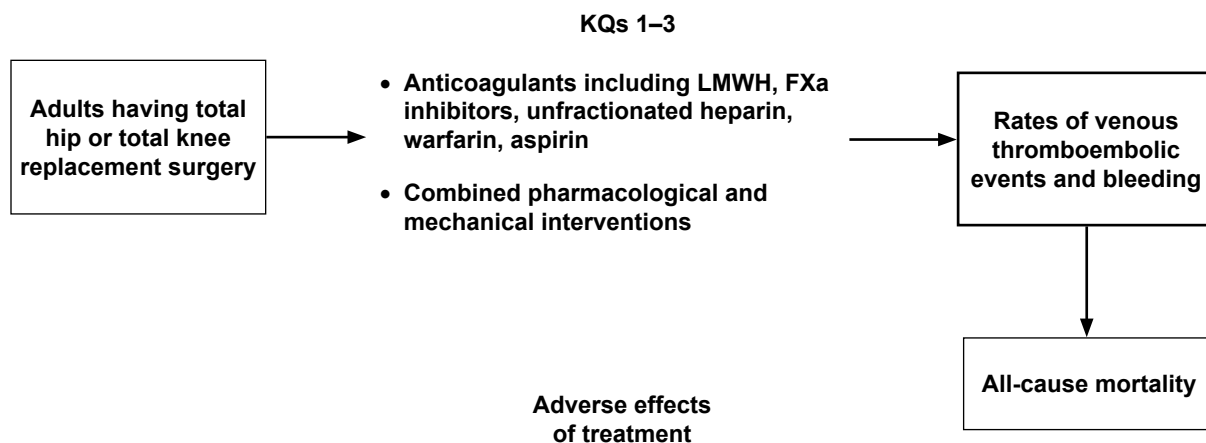
KQ 2. For patients undergoing total hip or total knee replacement, what are the effects of combined pharmacological and mechanical modalities versus pharmacological treatment alone on the incidence of symptomatic, objectively confirmed VTE, other VTE events, total mortality, and bleeding outcomes?

KQ 3. For patients undergoing total hip or total knee replacement, what is the comparative efficacy of individual newer oral anticoagulants on the incidence of symptomatic, objectively confirmed VTE, other VTE events, total mortality, and bleeding outcomes?

ANALYTIC FRAMEWORK

We followed a standard protocol for all steps of this review; certain methods map to the PRISMA checklist.¹⁷ Our approach was guided by the analytic framework shown in Figure 1.

Figure 1. Analytic framework for the comparative effectiveness of newer oral anticoagulants



Abbreviations: FXa=factor Xa; KQs=key questions; LMWH=low molecular weight heparin

SEARCH STRATEGY

During the topic development phase of this study, we identified a number of published high-quality systematic reviews that addressed our KQs. We concluded that a synthesis of these reviews as they pertained to the KQs and the Veteran population would be the most effective approach to summarizing the evidence. This approach is particularly useful when different intervention options or outcomes are evaluated in multiple recent reviews and when the audience is policymakers. We searched MEDLINE® (via PubMed®), Embase®, and the Cochrane Database of Systematic Reviews for systematic review publications comparing the newer oral anticoagulants to other types of anticoagulation (aspirin, warfarin, LMWH, unfractionated heparin, etc.) from January 1, 2009, through May 30, 2012. Our search strategy used the National Library of Medicine’s medical subject headings (MeSH) keyword nomenclature and text words for newer oral anticoagulants, the conditions of interest, and validated search terms for systematic reviews.^{18,19}

Our final search terms included new or novel oral anticoagulants; DTIs, including dabigatran, FXa inhibitors, including edoxaban, rivaroxaban, apixaban, betrixaban, YM150; the MeSH descriptor “orthopedic procedures”; and terms for the specific procedures of interest, total knee replacement or total hip replacement surgery. We limited the search to systematic reviews and meta-analyses and articles published in the English language involving human subjects 18 years of age and older. The full search strategy is provided in Appendix A. We supplemented the electronic searches with a manual search of citations from a set of key systematic reviews²⁰⁻²³ and clinical guidelines.^{1,24} We developed our search strategy in consultation with an experienced search librarian and updated the search during the course of analysis so as not to miss any recent, pertinent reviews; the last update was conducted September 2012. A supplementary search of the primary literature was conducted in September 2012 to identify relevant trials published since May 2012. All citations were imported into an electronic database (DistillerSR; Evidence Partners, Inc., Manotick, ON, Canada) for citation screening.

STUDY SELECTION

Using prespecified inclusion and exclusion criteria, two reviewers assessed titles and abstracts for relevance to the KQs. Full-text systematic reviews identified by either reviewer as potentially relevant were retrieved for further review. Each article retrieved was examined by two reviewers against the eligibility criteria. Disagreements on inclusion, exclusion, or major reason for exclusion were resolved by discussion or by a third reviewer.

The criteria to screen articles for inclusion or exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 4. Studies excluded at the full-text review stage are listed with the reasons for exclusion in Appendix B.

Table 4. Summary of inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	Adults (≥18 years) of age undergoing elective orthopedic surgery for total hip or total knee replacement	Pregnant women
Intervention	KQ 1: Newer oral anticoagulants: Direct thrombin inhibitors and factor Xa inhibitors KQ 2: Combined pharmacological and mechanical modalities KQ 3: Newer oral anticoagulants	Newer anticoagulants requiring intravenous or subcutaneous administration
Comparator	KQ 1: Warfarin, low molecular weight heparin, unfractionated heparin, aspirin KQ 2: Pharmacological treatment alone KQ 3: Within-class or between-class comparison with another newer oral anticoagulant	Comparators other than those specified by the KQ inclusion criteria
Outcome	Primary outcomes: Symptomatic, objectively confirmed deep vein thrombosis or pulmonary embolism Secondary outcomes: Major bleeding, surgical-site bleeding, or mortality	No relevant outcomes
Timing	Outcomes reported >1 week postoperatively	Less than 1 week postoperatively
Setting	Inpatient surgical settings	None
Study design	Systematic reviews that evaluated randomized controlled trials (RCTs) or secondary data analysis from an RCT	Not an SR of at least fair or good quality
Publications	English-language only Published from 2009 to present Peer-reviewed article	Non-English language publication Published before 2009

Abbreviations: KQ=key question; RCT=randomized controlled trial

DATA ABSTRACTION

Before general use, the abstraction form templates designed specifically for this report were pilot-tested on a sample of included articles and revised to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors. Select data from published reports were then abstracted into the final abstraction form by a trained reviewer (Appendix C). All data abstractions were confirmed by a second reviewer. Disagreements were resolved by consensus or by obtaining a third reviewer’s opinion when consensus could not be reached. We abstracted the following key information for each included study:

- Systematic review design features
 - Databases used in searches and dates of searches
 - Inclusion/exclusion criteria
 - Number of primary studies that apply to each KQ
 - Method of analysis
 - Types of comparisons
 - Tests for heterogeneity
 - Assessment of publication bias

- Characteristics of the included studies
 - Average or range of ages included
 - Average or range of sex distribution
 - Inclusion of Veteran Health Care Facilities
 - Indication for anticoagulation
 - Baseline bleeding risk or factors associated with increased risk (e.g., creatinine >1.5, history of gastrointestinal bleeding), if given
 - Countries included in primary studies
 - Study drug and comparator, route of administration, and dosage
 - Length of treatment and followup duration
 - Funding source
- Results of the systematic review
 - Number of studies and subjects and completion rates
 - Quality of the primary literature and strength of evidence, if given
 - Outcomes (including definition of outcome, if given)
 - Results from subgroup or sensitivity analyses
 - Author conclusions

In addition, we examined included articles for subgroup analyses of particular relevance to the population served by Veterans Health Administration. Data on the inclusion of Veteran Health Care Facilities was not provided at the systematic review level; therefore, we returned to the primary literature to abstract this information.

QUALITY ASSESSMENT

We also abstracted data necessary for assessing the quality of systematic reviews, adapted from the AMSTAR criteria.²⁵⁻²⁷ These key quality criteria consist of (1) search methods are adequate for replication and are comprehensive, (2) selection bias is avoided, (3) data are abstracted reliably, (4) characteristics of primary literature are reported and quality is assessed appropriately, (5) results are synthesized using appropriate methods, (6) publication bias is assessed, (7) conflict of interest is reported, and (8) conclusions are supported by results. We supplemented these criteria for studies that used multiple treatment comparisons based on the guidance by Mills et al.²⁸ Based on these criteria, systematic reviews were categorized as good, fair, or poor quality (Appendix D). Poor-quality reviews were excluded. The criteria were applied for each study by the reviewer abstracting the article; this initial assessment was then overread by a second reviewer. Disagreements were resolved between the two reviewers or, when needed, by arbitration from a third reviewer.

DATA SYNTHESIS

We categorized each systematic review by the key research questions they addressed and critically analyzed them to compare their characteristics, methods, and findings. We summarized the key findings and conclusions from each included review and produced summary tables for comparison across reviews. We prioritized the evidence from these reviews by higher quality of methodological designs, more complete drug comparisons (e.g., by class and drug rather than

by drug only), and more detailed information about population, specific drug intervention (e.g., dosage), and definitions of outcomes. In addition to summary measures of relative effects (e.g., risk ratios), we report absolute risk differences in the summary strength of evidence tables. For FXa inhibitors, we used the risk differences reported by Neumann et al.²⁰ To standardize the reporting of risk differences, which are dependent on the baseline risk of events, we adopted the approach used by Neumann et al. for other drugs. Risk difference was estimated by using the baseline risk from the control group and the risk ratio from the relevant meta-analysis. Baseline risk for patients treated with LMWH, the common comparator for newer anticoagulants, was estimated for each major outcome as symptomatic deep vein thrombosis (DVT), 9 per 1000 patients; nonfatal pulmonary embolism (PE), 3 per 1000 patients; mortality, 3 per 1000 patients; and major bleeding, 7 per 1000 patients.²⁰

Our synthesis focused on documenting and identifying patterns in efficacy and safety of the different drugs. To determine the consistency of results and conclusions, we then compared each additional review that addressed the same key question. If findings or conclusions differed importantly across reviews, we analyzed potential reasons for discrepancies such as the primary literature included (both the type of studies and the dates of the searches), review inclusion/exclusion criteria, differences in outcome definition, analytic approach, and conflict of interest.

In the event that our supplemental search of the primary literature identified additional eligible studies, we planned a qualitative summary of these studies to determine if the outcomes observed were consistent with the results from the systematic reviews. However, our search did not identify any additional relevant RCTs.

RATING THE BODY OF EVIDENCE

In addition to rating the quality of individual studies, we evaluated the overall quality of the evidence for each KQ as described in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.²⁹ In brief, this approach requires assessment of four domains: risk of bias, consistency, directness, and precision. For risk of bias, we considered basic (e.g., RCT) and detailed study design (e.g., adequate randomization) using the quality assessments of the primary literature reported in the systematic reviews. We used results from meta-analyses when evaluating consistency (forest plots, tests for heterogeneity), precision (confidence intervals), strength of association (odds ratio), and whether publication bias was detected (e.g., funnel plots or Begg's test). Optimal information size and consideration of whether the confidence interval crossed the clinical decision threshold for a therapy were also used when evaluating precision.³⁰

These domains were considered qualitatively, and a summary rating of high, moderate, low, or insufficient strength of evidence was assigned after discussion by two reviewers. This four-level rating scale consists of the following definitions:

- **High**—Further research is very unlikely to change our confidence on the estimate of effect.
- **Moderate**—Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low**—Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

- **Insufficient**—Evidence on an outcome is absent or too weak, sparse, or inconsistent to estimate an effect.

When a rating of high, moderate, or low was not possible or was imprudent to make, a grade of insufficient was assigned.³¹

PEER REVIEW

A draft version of the report was reviewed by technical experts and clinical leadership. A transcript of their comments can be found in Appendix E, which elucidates how each comment was considered in the final report.

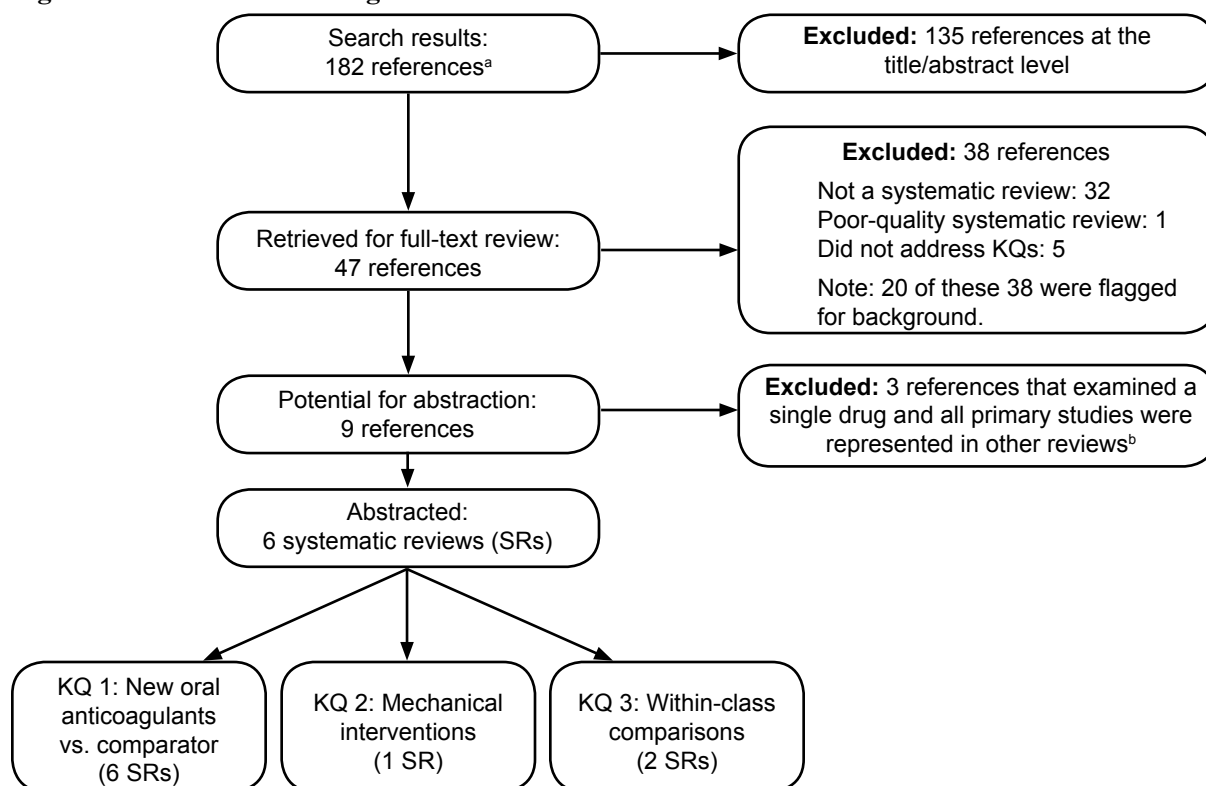
RESULTS

LITERATURE SEARCH

The flow of articles through the literature search and screening process is illustrated in Figure 2. Our search for systematic reviews (SRs) identified 162 unique citations from a combined search of MEDLINE via PubMed (n=117), Embase (n=42), and the Cochrane Database of Systematic Reviews (n=3). Manual searching of included study bibliographies and review articles added 20 more citations for a total of 182 unique citations. After applying inclusion and exclusion criteria at the title-and-abstract level, 47 full-text articles were retrieved and screened. Of these, 38 were excluded at the full-text screening stage, leaving 9 articles (representing 9 unique studies) for data abstraction. After further review, we excluded three systematic reviews³²⁻³⁴ because they reviewed only one drug of interest and all of the primary studies included in these systematic reviews were already represented in another, more comprehensive included review. Thus, the final set of articles used in this evidence report comprises six systematic reviews.

Appendix B provides a complete listing of published articles excluded at the full-text screening stage, with reasons for exclusion. We did not search www.clinicaltrials.gov for randomized controlled trials (RCTs) currently underway, as we relied on methods in the included systematic reviews to ascertain publication bias. We grouped the studies by key question (Figure 2).

Figure 2. Literature flow diagram



^aSearch results for systematic reviews from PubMed (117), Embase (42), Cochrane (3), previous database (14), and manual (6) were combined.

^bCao, 2010; Huang, 2011; and Turun, 2011.

Note: The reference list of this report includes additional references cited for background and methods plus Web sites relevant to the key questions.

Abbreviations: KQ=key question; SR=systematic review

STUDY CHARACTERISTICS

We identified six recent, good-quality SRs^{9,20-23,35} that were relevant to our KQs (Table 5). All of the SRs compared newer oral anticoagulants with other drug classes used for thromboprophylaxis in THR or TKR (KQ 1), although one considered only safety outcomes such as major bleeding.³⁵ Two of the six SRs compared one newer oral anticoagulant with another (KQ 3) though all results were based on indirect comparisons; i.e., through common comparison with enoxaparin.^{21,23} Only one SR⁹ compared a pharmacological agent plus mechanical modality versus mechanical modality alone (KQ 2). Five of the six SRs included trials examining thromboprophylaxis for both THR and TKR, while one also included hip fracture surgery.⁹ Characteristics of the SRs are summarized in Table 5; detailed quality assessments are presented in Appendix D.

Search dates ranged from May 2009 to December 2011. All literature search strategies included MEDLINE, and all but one²¹ included some aspect of the Cochrane Library. Other databases or sources of information were meeting abstracts (5), Embase (3), regulatory Web sites (4), clinical trial registries (3), and the Center for Reviews and Dissemination (1). Four studies^{9,20-22} also involved a manual search of the bibliographies of exemplary primary articles. The searches were limited only to RCTs in four of the SRs. One included SRs,²² and one included observational studies of more than 750 subjects⁹ in addition to RCTs. Language limits were used in only two of the studies.

All reviews assessed the quality of included trials. Overall trial quality was judged to be good, with the most common quality problems being unclear allocation concealment and incomplete reporting of outcome data. Publication bias was assessed most commonly with funnel plots, which did not indicate any publication bias that would favor newer oral anticoagulants. All studies conducted random-effects meta-analyses, but specific strategies varied. Two SRs compared drug classes as a whole (for example, FXa inhibitors versus LMWH^{9,20}), while the other four SRs compared individual drugs, some analyzing THR and TKR studies separately. All of the SRs performed meta-analysis using direct comparisons, and two also provided indirect comparisons.^{21,23} Every SR except one²¹ evaluated major bleeding using the same definition: bleeding that was fatal, involved a critical organ, required reoperation, or where bleeding was associated with a fall in hemoglobin level of at least 2 g/dL or required infusion of 2 or more units of whole blood or packed cells. Our other prespecified primary outcomes—all-cause mortality, symptomatic DVT, and nonfatal PE—were reported in three of the SRs.^{9,20,22} It was difficult to evaluate the other SRs^{21,23,35} due to the individuality of the definitions given for the outcomes reported, many of which were composite outcomes. For example, in the study by Loke et al.,²¹ the authors state the composite primary outcome as “total VTE” and define it as “DVT, non-fatal PE and all-cause mortality” (emphasis added). The study also reports bleeding as a combination of major bleeding (using the standard definition given above) and “clinically relevant non-major bleeding.”

Three of the SRs were unfunded and reported no conflicts of interest.^{21,23,35} One SR was unfunded but did report a conflict of interest for one author.²⁰ Two SRs were funded by government agencies.^{9,22}

Table 5. Characteristics of included systematic reviews

Study	Neumann, 2012 ²⁰	Sobieraj, 2012 ⁹	Gómez-Outes, 2012 ²³	Loke, 2011 ²¹	Ringerike, 2011 ²²	Alves, 2011 ³⁵
Quality	Good	Good	Good	Good	Good	Good
Applicable KQ^a	KQ 1	KQs 1, 2	KQs 1, 3	KQs 1, 3	KQ 1	KQ 1 (safety only)
Orthopedic procedures	THR, TKR	THR, TKR, HFS	THR, TKR	THR, TKR	THR, TKR	THR, TKR
Intervention and comparator for direct comparisons	As drug classes: - FXa vs. LMWH (LMWH/warfarin in one of 22 studies)	As drug classes: - FXa vs. LMWH - DTI vs. LMWH - DTI vs. UFH	As individual drugs vs. LMWH: - Apixaban - Dabigatran - Rivaroxaban	As individual drugs vs. LMWH: - Dabigatran - Rivaroxaban	As individual drugs vs. LMWH: - Dabigatran - Rivaroxaban	As individual drugs vs. LMWH: - Apixaban - Rivaroxaban
Databases	MEDLINE, Embase, CCRCT, meeting abstracts	MEDLINE, CCRCT, Scopus, clinical trial registries, meeting abstracts, regulatory Web sites	MEDLINE, CCRCT, clinical trial registries, meeting abstracts, regulatory Web sites	MEDLINE, Embase, clinical trial registries, regulatory Web sites	MEDLINE, Embase, Cochrane Library and Center for Reviews and Dissemination	MEDLINE, Cochrane Library; meeting abstracts, regulatory Web sites
Search date	December 2011	May 2011	April 2011	May 2009	September 2010	June 2011
Language limits	None	None	None	None	English, Scandinavian	None
Study designs	RCTs	RCTs, observational if more than 750 subjects	RCTs	RCTs	RCTs, SRs	RCTs
Analytic approach	Meta-analysis, direct, subgroup by dosage	Meta-analysis, direct, indirect, network MA	Meta-analysis, direct, indirect, subgroup by surgery type	Meta-analysis, direct, indirect, subgroup by protocol	Meta-analysis, subgroup by type of surgery	Meta-analysis, direct, subgroup by surgery type
Major outcomes analyzed (included in most studies)	Mortality, symptomatic DVT, nonfatal PE, major bleeding	Mortality, symptomatic DVT, nonfatal PE, major bleeding	Symptomatic DVT, nonfatal PE, major bleeding	None included	Mortality, symptomatic DVT, nonfatal PE, major bleeding	Major bleeding
Other outcomes of interest	Intracranial bleeding, bleeding leading to reoperation	Symptomatic VTE, major VTE, PE, surgical site bleeding, readmission	Total VTE or mortality, symptomatic VTE, clinically relevant bleeding	Total VTE (mortality + DVT + nonfatal PE), bleeding (major + clinically relevant nonmajor)	None	Safety variables: Other types of bleeding, adverse events
Source of funding	None	Government	None	None	Government	None
Conflict of interest?	Yes, disclosed	No	No	No	NR	No

^aKQ 1=between-class comparisons; KQ 2=combined pharmacological and mechanical vs. pharmacological monotherapy; KQ 3=within-class comparisons of newer oral anticoagulants, all of which are indirect via an LWMH

Abbreviations: CCRCT=Cochrane Central Registry of Controlled Trials; CINAHL=Cumulative Index of Nursing and Allied Health Literature; COI=conflict of interest; DTI=direct thrombin inhibitor; DVT=deep vein thrombosis; FXa=factor Xa inhibitor; HFS=hip fracture surgery; KQ=key question; LMWH=low molecular weight heparin; MA=meta-analysis; NR=not reported; PE=pulmonary embolism; RCT=randomized controlled trial; SR=systematic review; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin; VTE=venous thromboembolism

PARTICIPANT CHARACTERISTICS

Information on the populations studied was very limited in all of the included SRs (Table 6). The number of primary articles included ranged from 5 to 45; total sample size ranged from just over 19,000 to almost 240,000, but two articles did not report the total number of subjects. Females made up approximately 50 to 75 percent of the population when reported. Mean age ranged from 55 to 68 years in the 5 studies reporting age. Weight or body mass index was reported in four studies and indicated most subjects were moderately overweight to slightly obese. Risk factors for VTE were limited to a prior history of VTE (two studies) or history of cancer (one study); only a small proportion of patients had one of these risk factors. No other risk profiles or population characteristics were reported, and no study reported whether or not Veterans were included in the sample. However, our review of the primary studies found that no studies specifically included Veterans or were conducted at VA medical centers.

Table 6. Characteristics of patient samples

Study	Neumann, 2012 ²⁰	Sobieraj, 2012 ⁹	Gómez-Outes, 2012 ²³	Loke, 2011 ²¹	Ringerike, 2011 ²²	Alves, 2011 ³⁵
Studies (N patients)^a	22 (32,159)	45 (36,152)	16 (38,747)	9 (19,218)	5 (NR)	12 (28,483)
Female (% range)	44.6 to 72.5	RCTs 36.05–84.1% observational 63–65%	50 to 74	55 to 70	NR ^b	51 to 71
Mean age (range)	57.8 to 67.6	RCTs 52.4 to 78.3; observational 66.4 to 71	61 to 68	63.2 to 67.7	NR ^b	60.6 to 67.6
Weight (kg range)	26.5 to 32.7 ^c	RCTs 64.2 to 89 kg; observational NR	75 to 89	76 to 89	NR	NR
Veterans?	No	No	No	No	No	No
Risk factors: History of VTE	NR	0 to 14.5%	1 to 4% (9 studies)	NR	NR	NR
History of cancer	NR	0 to 12.4%				
Risk factors^d	NR	NR	NR	NR	NR	NR

^aNumbers are for RCTs, with the exception of Ringerike et al., which reviewed three RCTs and two SRs. Sobieraj et al. also reviewed three observational studies including over 239,000 participants.

^bRingerike et al. did not give demographics on study populations but did give national statistics on who had these surgeries performed in Sweden: average age is 69.1 and 69.4 yrs and % female is 68.4 and 67.4% on average for THR and TKR, respectively.

^cValue is in BMI units (kg/m²).

^dRisk factors sought were prior gastrointestinal bleeding, anemia, chronic kidney disease, and diabetes mellitus.

Abbreviations: kg=kilogram; NR=not reported; RCT=randomized controlled trial; VTE=venous thromboembolism

KEY QUESTION 1. For patients undergoing total hip or total knee replacement, what is the comparative effectiveness of newer oral anticoagulants and standard drug classes (low molecular weight heparin, injectable FXa inhibitors, unfractionated heparin, warfarin, aspirin) on the incidence of symptomatic, objectively confirmed venous thromboembolism (VTE), other VTE events, total mortality, and bleeding outcomes?

Key Points

- For all-cause mortality and nonfatal PE, there were no important differences between oral FXa inhibitors and LMWH (high strength of evidence). Using a base rate of 9 events per 1000 patients with LMWH, FXa inhibitors were associated with lower symptomatic DVT (4 fewer events per 1000 patients; 95% CI, 3 to 6). Overall, FXa inhibitors were associated with an increased risk of major bleeding, but major bleeding did not differ importantly at low to moderate doses (moderate strength of evidence). Based on subgroup analyses, there was not a consistent pattern of differences in treatment effects for THR and TKR.
- There were fewer studies evaluating oral DTIs than oral FXa inhibitors; all trials compared dabigatran with enoxaparin. Although estimates of effect were often imprecise, there were no significant differences between oral DTIs and enoxaparin for any major outcome.
- Neither oral FXa inhibitors nor DTIs have been compared directly with adjusted-dose warfarin, oral antiplatelet drugs, or unfractionated heparin in existing SRs.

We identified six good-quality SRs^{9,20-23,35} that evaluated thromboprophylaxis using newer oral anticoagulants versus LMWH. For each comparison, we focus our discussion on the review having the most recent search date and comprehensive analysis, and which reported our prespecified outcomes of interest. Other reviews are described briefly when findings differed importantly or additional analyses provided relevant results.

Effects of Oral FXa Inhibitors Compared With Low Molecular Weight Heparin

A good-quality SR²⁰ (search date December 2011) included 22 RCTs and a total of 32,159 patients that compared FXa inhibitors with LMWH for surgical thromboprophylaxis. Eleven of the included studies were on hip replacement, 10 were on knee replacement, and 1 was on either procedure. FXa inhibitors included apixaban (four studies), rivaroxaban (eight studies), edoxaban (four studies), YM150 (two studies), and LY1517717, TAK442, razaxaban, and betrixaban (one study each). Of these drugs, only rivaroxaban is currently available in the United States. In the majority of trials, the European-approved dose of enoxaparin, 40 mg daily, was the comparator instead of the U.S.-approved dose, 30 mg twice daily. The duration of thromboprophylaxis was 14 days or less in all but 4 trials. Patients were followed for less than 14 days in 9 trials, 30 to 70 days in 12 trials, and up to 90 days in one trial. In addition to a random-effects meta-analysis of drug class comparisons, this sophisticated review performed a multiple-treatment-comparison meta-analysis to evaluate effects of FXa dose, and sensitivity analyses to examine the effects of missing outcomes. Pooled estimates of effect were presented as summary odds ratios and

summary risk differences. In addition, risk differences were estimated by applying the relative risk reduction from meta-analysis to the baseline risk estimated from a large cohort study.

This SR by Neumann et al.²⁰ found high strength of evidence suggesting no important difference between oral FXa inhibitors and LMWH for all-cause mortality (OR 0.95; 95% CI, 0.55 to 1.63; $I^2=43\%$) and nonfatal PE (OR 1.07; CI, 0.65 to 1.73; $I^2=35\%$) in patients undergoing THR or TKR. However, high strength of evidence indicated that the risk of symptomatic DVT is decreased by 4 events for every 1000 patients treated using FXa thromboprophylaxis compared with LMWH (OR 0.46; CI, 0.30 to 0.70; $I^2=0\%$). There was moderate strength of evidence because of inconsistency, suggesting that the risk of major bleeding may be increased with oral FXa inhibitors compared with LMWH (OR 1.27; CI, 0.98 to 1.65; $I^2=55\%$). This finding represents an increase of 2 major bleeding events per 1000 patients treated with FXa, for 1 to 5 weeks compared with LMWH. The pooled effect estimate of bleeding that led to reoperation also was increased (OR 1.62; CI, 0.82 to 3.19; $I^2=1\%$), but the confidence interval included the possibility of a chance association.

In a subgroup analysis, higher doses of FXa inhibitors, but not intermediate or lower doses, were associated with increased risk of bleeding (OR 2.50; 95% CI, 1.38 to 4.53; $p=0.02$). The authors did not report the drug doses used for this subgroup analysis. Total daily doses were reported for the primary studies and ranged from 5 to 20 mg for apixaban and 5 to 60 mg for rivaroxaban. In an analysis that adjusted for FXa dose, there was no significant difference in thrombotic or bleeding outcomes for different FXa inhibitors. Sensitivity analyses that accounted for missing outcomes did not differ appreciably from the main analyses. Thus this SR concluded that while there is no important difference between low-dose oral FXa inhibitors and LMWH for the outcomes of all-cause mortality, nonfatal PE, and major bleeding, there is a small absolute reduction in symptomatic DVT events (4 fewer events per 1000 patients treated). However, most studies included in this SR reported bleeding as a composite outcome and did not include details; this introduces uncertainty about the importance of the reported bleeding events. Other limitations of the included trials in this SR were (1) missing outcomes for 3 to 41 percent of randomized patients, (2) the short duration of followup in many trials, (3) the nonstandard dosing of enoxaparin, and (4) the short duration of prophylaxis in patients undergoing THR.

The other SRs^{9,21-23,35} were generally in agreement with the results and conclusions of Neumann et al. Where disagreements occurred, they were mainly due to different outcomes (e.g., composite outcomes), differences in approach to data analysis (separate analyses for each drug), and fewer included studies due to earlier search dates and more restrictive inclusion criteria (e.g., only FDA-approved drugs). Also, most SRs reported on outcomes by individual new oral anticoagulants, whereas those by Neumann et al. and Sobieraj et al. reported on outcomes by drug class.

We summarize below the notable findings from these other SRs:

- In a good-quality review²³ that separately analyzed the effects of apixaban (4 trials) and rivaroxaban (8 trials), both drugs were associated with lower symptomatic DVT than enoxaparin (apixaban, RR 0.41; 95% CI, 0.18 to 0.95, and rivaroxaban, RR 0.40; CI, 0.22 to 0.72). Symptomatic VTE (DVT or PE) was decreased with rivaroxaban (RR 0.48; CI, 0.31 to 0.75; $I^2=5\%$) but not apixaban (RR 0.82; CI, 0.41 to 1.64; $I^2=40\%$). All-cause

mortality was not reported as a separate outcome. Symptomatic PE and major bleeding did not differ significantly from LMWH, but confidence intervals for these estimates were wide and included the potential for clinically important differences. Notably, to increase the consistency of outcome definitions and results, major bleeding rates for the RECORD studies of rivaroxaban³⁶⁻³⁹ were analyzed using data reported to the FDA—a definition that included wound bleeding. Subgroup analyses showed no differences in treatment effect by type of surgery (THR vs. TKR) for symptomatic VTE or clinically relevant bleeding.

- In a review limited by the exclusion of rivaroxaban,⁹ the pooled effect from four RCTs comparing LMWH with FXa inhibitors did not show a significant difference in major bleeding leading to reoperation (OR 0.67; 95% CI, 0.28 to 1.61).
- In a review limited by the exclusion of apixaban,²¹ the risk of hemorrhage (major and clinically relevant nonmajor bleeding) did not differ significantly for rivaroxaban compared with LMWH (RR 1.26; 95% CI, 0.94 to 1.69; $I^2=28\%$). Hemorrhage was defined as major bleeding leading to death, reoperation, blood transfusion of two or more units, a drop in hemoglobin level of more than two g/dL, or bleeding into a critical organ. In contrast to the review by Gómez-Outes et al., published rates of bleeding rather than rates reported to the FDA (that included wound bleeding) were used for these analyses.
- A report on adverse outcomes by type of surgery compared two oral FXa inhibitors with enoxaparin.³⁵ There was a lower risk of major bleeding with apixaban compared with LMWH in TKR (RR 0.56; 95% CI, 0.32 to 0.96) but not in THR (RR 1.22; 95% CI, 0.65 to 2.26). Major bleeding events were not different with rivaroxaban treatment compared with LMWH in both types of surgeries. Subgroup analysis showed an increased risk of bleeding with the 30-mg twice-daily dosing regimen of LMWH compared with the 40-mg once-daily dose.

Effects of Direct Thrombin Inhibitors Compared with Low Molecular Weight Heparin

Only four SRs^{9,21-23} included comparisons of dabigatran—the only available DTI—with standard thromboprophylaxis using LMWH. A good-quality SR (search date April 2011) included 4 trials involving 12,897 patients that compared dabigatran with enoxaparin for thromboprophylaxis of THR or TKR.²³ The surgical procedure was THR and TKR in two trials each. In three trials, the comparator was enoxaparin at 40 mg daily, and in one trial the dose was 30 mg twice daily. The duration of thromboprophylaxis was 15 days or less in the two TKR studies and 28 to 35 days in the two THR studies. The duration of followup was approximately 3 months. Three studies used a three-arm design; the dabigatran 150 mg and dabigatran 220 mg treatment arms were combined for meta-analysis. The two-arm trial evaluated dabigatran 220 mg, a dose that is not approved by the FDA. All-cause mortality was not reported as a separate outcome.

In a random-effects meta-analysis, the risk of symptomatic PE (RR 0.69; 95% CI, 0.31 to 1.54; $I^2=NR$) and symptomatic DVT (RR 0.82; CI, 0.17 to 3.99; $I^2=NR$) did not differ between dabigatran and enoxaparin.²³ Similarly, there was no statistically significant difference in symptomatic VTE (DVT and PE), but treatment effects differed substantially across studies ($I^2=73\%$). Clinically relevant bleeding events (major bleeding and clinically relevant nonmajor bleeding) were not different with dabigatran treatment (RR 0.94; CI, 0.58 to 1.52; $p=0.79$). In subgroup analyses, there was no statistically significant interaction between type of surgery and effects on symptomatic VTE or clinically relevant bleeding.

Three other SRs^{9,21,22} reported additional outcomes, including mortality, major bleeding, and bleeding leading to rehospitalization, summarized below:

- The SR by Ringerike et al.²² included an additional study (BISTRO-II)⁴⁰ of patients undergoing either THR or TKR, but anticoagulation was given for 7 days only. The SR by Sobieraj et al.⁹ evaluated an injectable DTI (desirudin) but did not include the most recent trial of oral DTI,⁴⁰ which was also omitted in the SR by Loke et al.²¹ Despite these differences in approach, mortality did not differ significantly for DTIs compared with enoxaparin in any of these analyses. Consistent with the findings by Gómez-Outes et al.²³ for clinically relevant bleeding, major bleeding did not differ between drug classes when analyzed by surgical procedure²² or in aggregate.^{9,21}
- Sobieraj et al.⁹ found no significant difference between LMWH and dabigatran for bleeding leading to rehospitalization (RR 1.27; 95% CI, 0.43 to 3.75; moderate strength of evidence).

Other Comparisons of Interest

Only one good-quality SR by Sobieraj et al.⁹ (search date May 2011) addressed drug class comparisons between older antithrombotics. We summarize results for key drug class comparisons and outcomes below.

Low molecular weight heparin versus vitamin K antagonists. Sobieraj et al.⁹ reported on the comparative effects of LMWH thromboprophylaxis versus adjusted-dose warfarin. LMWHs included enoxaparin (30 mg every 12 hours) and logiparin. Other details such as duration of treatment and duration of followup were not reported uniformly for the included trials. Depending on outcomes, 3 to 7 trials were included in the meta-analyses. There was no significant difference in mortality (OR 0.79; 95% CI, 0.42 to 1.50; I²=0%), nonfatal PE (OR 1.00; CI, 0.20 to 4.95; I²=NR), or symptomatic DVT (OR 0.87; CI, 0.61 to 1.24; I²=28.4%). The risk of major bleeding was significantly higher in the LMWH treatment group (OR 1.92; CI, 1.27 to 2.91; I²=0; high strength of evidence).

Oral FXa inhibitors versus unfractionated heparin. Sobieraj et al.⁹ reported on the comparative effects of oral FXa inhibitors versus unfractionated heparin. There were no RCTs comparing oral or injectable FXa inhibitors with unfractionated heparin. One observational study compared an injectable FXa inhibitor (fondaparinux) with unfractionated heparin; drug doses were not reported. The injectable FXa inhibitor was associated with lower mortality compared with unfractionated heparin. The risk of major bleeding was found to be increased in the unfractionated heparin treatment group compared with the injectable FXa inhibitor group (OR 1.27; 95% CI, 1.06 to 1.52). Effects on symptomatic DVT and nonfatal PE were not reported.

Low molecular weight heparin versus oral antiplatelet agents. Sobieraj et al.⁹ reported on the comparative effects of LMWH versus oral antiplatelet agents but identified no studies comparing these drug classes.

Antiplatelet agents versus vitamin K antagonists. Sobieraj et al.⁹ reported on the comparative effects of antiplatelet agents versus vitamin K antagonists, identifying a single RCT. Among patients undergoing hip fracture surgery, the risk of mortality was similar in both treatment arms (RR 0.98; 95% CI, 0.32 to 3.05). Nonfatal PE was evaluated, but there were no events

in either treatment arm. The risk of major bleeding was also reported in this trial and did not show a statistically significant difference (RR 0.20; CI 0.03 to 1.23). In addition to this RCT, two observational studies compared aspirin prophylaxis with vitamin K antagonists in patients undergoing THR or TKR. One study showed higher mortality with aspirin prophylaxis (0.3 percent vs. 0 percent; $p=0.013$); the other study found no significant difference in mortality. There were no reports on symptomatic DVT or symptomatic VTE.

KEY QUESTION 2. For patients undergoing total hip or total knee replacement, what are the effects of combined pharmacological and mechanical modalities versus pharmacological treatment alone on the incidence of symptomatic, objectively confirmed VTE, other VTE events, total mortality, and bleeding outcomes?

Key Points

- In the included SRs, no studies were identified that compared the combination of newer oral anticoagulants and mechanical thromboprophylaxis with pharmacological treatment alone.
- Few studies have compared older antithrombotics (LMWH, oral antiplatelet agents, or unfractionated heparin) combined with mechanical prophylaxis to pharmacological or mechanical prophylaxis alone.
- The strength of evidence is insufficient to determine the comparative effectiveness for combined pharmacological and mechanical prophylaxis compared with pharmacological prophylaxis alone for all major outcomes prioritized for this report.

One good-quality SR⁹ (search date May 2011) included 6 trials and a total of 995 patients that compared a combined-modality thromboprophylaxis (pharmacological and mechanical agents) with a single modality and found a paucity of data. Four of the included studies were on hip replacement, one was on knee replacement, and one included both surgeries. No trial evaluated the combination of a newer oral anticoagulant together with mechanical prophylaxis. Combination treatments included LMWH, aspirin, or unfractionated heparin together with mechanical prophylaxis. Of the six trials, the comparator was pharmacologic prophylaxis alone (4 trials), mechanical prophylaxis alone (1 trial), and both pharmacological and mechanical comparators (1 trial). Duration of followup ranged from the postoperative period to 90 days.

Three trials reported effects on mortality, but treatment effects were not pooled. Two of these trials had no mortality events; the third trial comparing the combination of aspirin plus pneumatic compression to aspirin alone found no effects on mortality (OR 7.72; 95% CI, 0.15 to 389.59), but the trial was underpowered for clinically significant differences. Two trials evaluated the effects on nonfatal PE, but there were no events in either trial. A single older trial evaluated the effects of sequential unfractionated heparin for 3 days, then aspirin together with a venous foot pump versus sequential pharmacologic prophylaxis alone or a venous foot pump alone. The combined modality had a lower risk of symptomatic DVT compared with pharmacologic prophylaxis only (RR 0.14; 95% CI, 0.01 to 1.42), but there were few events, and the confidence interval included no effect. Only one trial reported the effects of combined

thromboprophylaxis (aspirin plus venous foot pump) compared with aspirin alone for major bleeding. However, there were no major bleeding events in either treatment arm. The authors concluded that there was insufficient evidence for all outcomes when comparing pharmacologic plus mechanical prophylaxis to pharmacologic prophylaxis alone, with the exception of overall DVT (including asymptomatic DVT). For overall DVT, combined treatment was more effective than pharmacologic prophylaxis alone.

KEY QUESTION 3. For patients undergoing total hip or total knee replacement, what is the comparative efficacy of individual newer oral anticoagulants on the incidence of symptomatic, objectively confirmed VTE, other VTE events, total mortality, and bleeding outcomes?

Key Points

- No clinical trials directly compared newer oral anticoagulants with each other for thromboprophylaxis of TKR or THR.
- The included SRs did not estimate the comparative efficacy of newer oral anticoagulants for symptomatic DVT, nonfatal PE, all-cause mortality, or surgical site bleeding.
- Based on indirect comparisons, there were few differences between newer oral anticoagulants for the outcomes examined. Rivaroxaban was associated with more major bleeding than apixaban (RR 1.59; 95% CI, 0.84 to 3.02). In contrast, the risk of symptomatic VTE was lower for rivaroxaban than apixaban or dabigatran, but confidence intervals included the possibility of a chance association.

In the absence of direct comparisons between the newer oral anticoagulants, two good-quality SRs used indirect comparisons^{21,23} to analyze these drugs.

A good-quality comprehensive review²³ (search date April 2011) evaluated apixaban (4 trials), dabigatran (4 trials), and rivaroxaban (8 trials) against a common comparator (enoxaparin). These indirect comparisons utilized pooled risk ratios and yielded an unbiased estimate of effect “when there is no interaction between covariates defining subgroups of patients (reflected, for instance, in different inclusion criteria in different studies) and the magnitude of the treatment effect.”⁴¹ Of the 16 trials (total of 38,747 patients), 8 were of total hip replacement and 8 of total knee replacement. Outcomes reported in the indirect comparisons included symptomatic venous thromboembolism (DVT or PE), clinically relevant bleeding (major bleeding or clinically relevant nonmajor bleeding), major bleeding, and a net clinical endpoint—defined as a composite of symptomatic VTE, major bleeding, and all-cause death. Overall, the primary trials were rated low risk of bias. Individual drug comparisons across these 4 outcomes (12 comparisons) showed only one statistically significant difference: rivaroxaban resulted in more clinically relevant bleeding compared with apixaban (RR 1.52; 95% CI, 1.19 to 1.95). The risk of major bleeding was also increased with rivaroxaban compared with apixaban (RR 1.59; CI, 0.84 to 3.02), but the difference was not statistically significant. Rivaroxaban was associated with lowest risk of symptomatic VTE compared with dabigatran (RR 0.68; CI, 0.21 to 2.23) and apixaban (RR 0.59; CI, 0.26 to 1.33), but neither comparison was statistically significant. Overall, differences in the

number of VTE events were offset by the number of major bleeding episodes. Thus, there was no difference on the net clinical endpoint among apixaban, dabigatran, and rivaroxaban. The review concluded that “higher efficacy of new anticoagulants was generally associated with higher bleeding tendency. The new anticoagulants did not differ significantly for efficacy and safety.”²³

The other SR provided few additional relevant findings. Similar to the review described above, Loke et al.²¹ (search date May 2009) used indirect analysis methods but excluded studies of apixaban, yielding a less informative analysis. In addition, a dabigatran trial published after 2009 and three rivaroxaban studies were excluded due to more restrictive eligibility criteria. Despite these differences, findings regarding rivaroxaban compared with dabigatran were generally similar. The authors concluded that rivaroxaban was superior to dabigatran in preventing VTE (RR 0.50; 95% CI, 0.37 to 0.68) although with an increased risk of bleeding (RR 1.14; CI, 0.80 to 1.64). The decreased risk of VTE with rivaroxaban was consistent across different doses of dabigatran (150 mg vs. 220 mg), different dosing regimens of enoxaparin in the control groups (30 mg twice daily vs. 40 mg once daily), and the type of surgery (THR vs. TKR).

SUMMARY AND DISCUSSION

We identified six good-quality SRs that evaluated thromboprophylaxis using newer oral anticoagulants versus LMWH. One SR evaluated additional drug classes, including unfractionated heparin, aspirin, and vitamin K antagonists. Although we identified no direct comparisons of newer oral anticoagulants, two good-quality SRs indirectly compared one newer oral anticoagulant with another through common comparison to enoxaparin.^{21,23} Only one SR compared combined pharmacologic and mechanical thromboprophylaxis to either method alone.⁹ FXa inhibitors have been studied more extensively than DTIs. In the absence of head-to-head comparisons between newer oral anticoagulants, it is difficult to draw strong conclusions on inter- or intra-drug class differences. The main findings and strength of evidence from our literature synthesis are summarized by key question in the section that follows.

SUMMARY OF EVIDENCE BY KEY QUESTION

KQ 1: Newer Oral Anticoagulants Versus Standard Treatments

FXa inhibitors. Rivaroxaban and apixaban are the most commonly studied FXa inhibitors. The risk of symptomatic DVT was reduced with FXa inhibitors thromboprophylaxis compared with LMWH, while the risk of nonfatal PE and mortality was not significantly different (all high strength of evidence). The estimated absolute risk difference was 4 fewer symptomatic DVT events for each 1000 patients receiving thromboprophylaxis with FXa inhibitors over 5 weeks compared with LMWH. However, these benefits were offset by an increase in major bleeding (moderate strength of evidence). The absolute risk difference was 2 more major bleeding events per 1000 patients on FXa thromboprophylaxis over a period of 5 weeks. Higher doses of FXa inhibitors but not intermediate or low doses were associated with increased major bleeding.²⁰ Subgroup analysis by specific drug and type of surgery showed a reduced risk of bleeding with apixaban compared with LMWH in TKR but not in THR; risk of major bleeding with rivaroxaban did not differ significantly for either surgery.³⁵ No reviews identified trials comparing oral FXa inhibitors with warfarin, UFH, or oral antiplatelet agents.

Direct thrombin inhibitors. Dabigatran is the only FDA-approved oral DTI, and the only DTI evaluated in existing SRs. Compared with LMWH, dabigatran was not associated with significant differences for any outcome examined. The strength of evidence was low for most outcomes due to few events and imprecise estimates of effect; also, effects on mortality varied substantially across studies. In addition to the major outcomes, a subgroup analysis in one SR found no significant difference between both treatment groups on bleeding requiring rehospitalization.⁹ No reviews identified trials comparing oral DTIs with warfarin, unfractionated heparin, or oral antiplatelet agents.

Table 7 summarizes the findings and strength of evidence for the effects of newer oral anticoagulant drug classes compared with enoxaparin in patients undergoing THR or TKR surgery.

Table 7. Summary of the strength of evidence for KQ 1

Outcome	Domains Pertaining to SOE				Effect Estimate (95% CI)	SOE
	Number of Studies (Subjects)	Study Design/Quality	Consistency Directness	Precision Publication Bias		
FXa vs. LMWH^a						
Mortality (up to 10 weeks)	11 (22,838)	RCT/Good	Consistent Direct	Precise None detected	OR=0.95 (0.55 to 1.63) RD=0 (2 fewer to 1 more) deaths/1000 patients	High
Symptomatic DVT (up to 5 weeks)	18 (22,877)	RCT/Good	Consistent Direct	Precise None detected	OR=0.46 (0.30 to 0.70) RD=4 fewer (3 to 6 fewer) events/1000 patients	High
Nonfatal PE (up to 5 weeks)	20 (26,998)	RCT/Good	Consistent Direct	Precise None detected	OR=1.07 (0.65 to 1.73) RD=0 (1 fewer to 2 more) events/1000 patients	High
Major bleeding (up to 5 weeks)	21 (31,424)	RCT/Good	Inconsistent Direct	Precise None detected	OR=1.27 (0.98 to 1.65) RD=2 more (0 to 4 more) events/1000 patients	Moderate
LMWH vs. DTI^b						
Mortality (up to 13 weeks)	4 (10,080)	RCT/Good	Inconsistent Direct	Imprecise None detected	RR OR=1.06 (0.36 to 3.12) RD=0 (2 fewer to 6 more) events/1000 patients RR OR=1.17 (0.04 to 36.52) RD=0 (3 fewer to 107 more) events/1000 patients	Low
Symptomatic DVT (up to 5 weeks)	4 (10,264)	RCT/Good	Consistent Direct	Imprecise None detected	RR=0.82 (0.17 to 3.99) RD=2 fewer (7 fewer to 27 more) events/1000 patients	Low
Symptomatic PE (up to 5 weeks)	4 (10,264)	RCT/Good	Consistent Direct	Imprecise None detected	OR=0.69 (0.31 to 1.54) RD=1 fewer (2 fewer to 2 more) events/1000 patients	Low
Major bleeding (up to 5 weeks)	4 (10,264)	RCT/Good	Consistent Direct	Imprecise None detected	RR=0.94 (0.58 to 1.52) RD=0 (3 fewer to 3 more) events/1000 patients	Moderate
FXa or DTI vs. other antithrombotics						
All outcomes	0	NA	NA	NA	Not estimable	Insufficient

^aData from Neumann, 2012.

^bRisk ratio data from Ringerike, 2012, and Gómez-Outes, 2012; risk difference calculated; SOE ratings from Sobieraj, 2012.

Notes: Outcomes are short-term; there may be some differences for hip versus knee replacement (different baseline risk and different duration of anticoagulation in existing studies); there is some evidence that FXa inhibitors at higher doses increase risk of bleeding.

Abbreviations: CI=confidence interval; DVT=deep vein thrombosis; DTI=direct thrombin inhibitor; FXa=factor X inhibitor; LMWH=low molecular weight heparin; NA=not applicable; OR=odds ratio; PE=pulmonary embolism; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio; SOE=strength of evidence; THR=total hip replacement; TKR=total knee replacement

KQ 2: Combined Pharmacological and Mechanical Prophylaxis

No reviews identified trials comparing newer oral anticoagulants combined with mechanical prophylaxis to pharmacological prophylaxis alone. Even when considering standard treatments, very little data are available comparing combined-modality thromboprophylaxis and pharmacologic prophylaxis only. One SR found moderate strength of evidence that combined-modality thromboprophylaxis was associated with a decreased risk of overall DVT (including asymptomatic events) compared with pharmacologic prophylaxis only.⁹ The evidence was insufficient for all other outcomes.

KQ 3: Comparisons of Individual Newer Oral Anticoagulants

Only indirect comparisons of rivaroxaban, apixaban, and dabigatran were performed through common comparison with LMWH.^{23,35} These comparisons were made for only two of our major outcomes—symptomatic VTE (DVT or PE) and major bleeding. There were no significant differences in treatment effect for symptomatic VTE or major bleeding. Because these indirect comparisons are subject to confounding and the treatment effects were imprecise, we considered the strength of evidence low. Other outcomes reported included clinically relevant bleeding and net clinical endpoints. Rivaroxaban was found to be associated with an increased risk of clinically relevant bleeding, but there was no significant difference in net clinical endpoints (symptomatic VTE, major bleeding and death). Table 8 summarizes the findings and strength of evidence for between-drug comparisons of newer oral anticoagulants in patients undergoing THR or TKR.

CLINICAL AND POLICY IMPLICATIONS

Patients undergoing total knee replacement or total hip replacement are at a significant risk for VTE. The precise risk for VTE in contemporary orthopedic surgery is difficult to estimate because of changes in surgical management, the paucity of recent trials comparing thromboprophylaxis to placebo, and the high frequency of thromboprophylaxis in routine practice, making observational studies of natural history difficult to conduct. A recent, careful analysis estimated the prevalence of symptomatic VTE without thromboprophylaxis at 2.8 percent for the initial 14 days and 4.3 percent at 35 days following major orthopedic surgery.¹ Appropriate use of perioperative thromboprophylaxis significantly reduces the risk of postoperative proximal VTE, but the evidence is much more limited for effects on symptomatic DVT, PE, and mortality.^{1,9}

Our evidence synthesis primarily addresses the comparative effectiveness of newer oral anticoagulants compared with standard antithrombotic agents for VTE prophylaxis. These newer drugs have been compared only to LMWH and show similar effects on most major clinical outcomes, although the strength of evidence varies by drug class and specific drug. In evaluating whether to add these newer agents to the VA formulary and whether to promote a specific thromboprophylaxis strategy, consideration should be given to the evidence of effectiveness and the importance and variability of patient values and preferences, costs, and health care system resources for successfully implementing competing strategies. In the following section, we summarize recommendations from the two major U.S. clinical guideline panels that have addressed this issue.

Guidelines

Both the American College of Chest Physicians (ACCP) and the American Academy of Orthopaedic Surgeons (AAOS) have recently issued guidelines on thromboprophylaxis in patients undergoing TKR or THR.^{1,2,24} The ACCP recommends antithrombotic prophylaxis over no prophylaxis for patients undergoing TKR or THR. The AAOS guidelines suggest individual assessment of patients for thromboprophylaxis. For patients at average risk, the guidelines do not include a recommendation for a specific thromboprophylactic strategy, considering the evidence for comparative effectiveness to be inconclusive. In contrast, the ACCP guidelines make recommendations for specific strategies and include the following options: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin, adjusted-dose vitamin K antagonists, aspirin, or an intermittent pneumatic compression device. However, in the absence of elevated bleeding risk, LMWH is recommended in preference to other agents. Factors identified as increasing the risk of bleeding include previous major bleeding, severe renal failure, concomitant antiplatelet use, and a history of or difficult-to-control surgical bleeding during the current operative procedure, extensive surgical dissection, and revision surgery.¹ For patients with increased bleeding risk, ACCP recommends intermittent pneumatic compression device or no prophylaxis.

In making recommendations, both guideline panels considered benefits and potential harms but had different approaches to considering costs. The AAOS did not conduct cost analyses and instructed guideline members to consider costs only when the impact was likely to be substantial. The ACCP process considered costs when it was plausible that resource use might change

the direction or strength of recommendation and when high-quality economic analyses were available; it is not stated whether costs were considered in the recommendations pertaining to major orthopedic surgery. Guideline recommendations regarding choice of thromboprophylaxis are summarized in Table 9. Finally, we note that these guidelines address other clinical management issues, including duration and timing of thromboprophylaxis and use of routine DVT screening, which are not summarized here since they are not directly germane to our key questions.

Table 9. U.S. guideline recommendations related to specific thromboprophylaxis strategies

ACCP 2012 ^a	AAOS 2011 ^b
In patients undergoing THR or TKR, we recommend use of one of the following for minimum of 10–14 days rather than no antithrombotic prophylaxis: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban low-dose unfractionated heparin (LDUH), adjusted-dose VKA, aspirin (all Grade 1B) or an intermittent pneumatic compression device (IPCD) (Grade 1C).	We suggest the use of pharmacologic agents and/or mechanical compressive devices for the prevention of VTE in patients undergoing elective hip or knee arthroplasty, and who are not at elevated risk beyond that of the surgery itself for venous thromboembolism or bleeding. Grade: Moderate
In patients undergoing THR or TKR, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban low-dose unfractionated heparin (LDUH) (all Grade 1B), adjusted-dose VKA, aspirin (all Grade 2C).	Current evidence is unclear about which prophylactic strategy is optimal or suboptimal. Therefore, we are unable to recommend for or against specific prophylactics in these patients. Grade: Inconclusive
In patients undergoing major orthopedic surgery, we suggest using dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay (Grade 2C).	In the absence of reliable evidence, patients who have had a previous VTE should receive pharmacologic prophylaxis and mechanical compressive devices. Grade: Consensus
In patients undergoing major orthopedic surgery and increased risk of bleeding, we suggest using an IPCD or no prophylaxis rather than pharmacologic treatment (Grade 2C).	In the absence of reliable evidence, patients with a known bleeding disorder and/or active liver disease should use mechanical compressive devices for preventing VTE. Grade: Consensus
In patients undergoing major orthopedic surgery and who decline or are uncooperative with injections or an IPCD, we recommend using apixaban or dabigatran (alternatively, rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable) rather than other forms of prophylaxis (Grade 1B).	In the absence of reliable evidence about how long to employ these prophylactic strategies, it is the opinion of this work group that patients discuss the duration of prophylaxis with their treating physicians. Grade: Consensus

^aACCP evidence grading of evidence was as follows: grade 1 recommendations are strong and indicate that the benefits do or do not outweigh risks, burden, and costs, while grade 2 suggestions imply that individual patient values may lead to different choices. Furthermore, level A indicates consistent results from RCTs or observational studies with very strong association and secure generalization (high), B indicates inconsistent results from RCTs or RCTs with methodological limitations (moderate), C indicates unbiased observational studies (low), and D indicates other observational studies (e.g. case series) (very low).

^bAAOS grading was as follows: strong when good-quality evidence, moderate when fair-quality evidence, weak when poor-quality evidence, inconclusive when insufficient or conflicting evidence, or consensus in the absence of reliable evidence. Abbreviations: IPCD=intermittent pneumatic compression device; LDUH=low-dose unfractionated heparin; LMWH=low molecular weight heparin; THR=total hip replacement; TKR=total knee replacement; VKA=vitamin K antagonist; VTE=venous thromboembolism

APPLICABILITY

We think these results are likely to apply to Veteran populations, but recommend some caution when applying trial data to standard clinical practice. There were strict exclusion criteria for patients enrolled in these studies, including severe renal or hepatic impairment or high risk of bleeding. Patients enrolled in trials are often more adherent to treatment plans and are monitored more closely than patients in routine clinical care. As a result, treatment effects in standard clinical practice may differ from those observed in clinical trials. Furthermore, the definition of bleeding was not consistent across studies, and it did not always include surgical site bleeding, which can lead to infection, dehiscence, and reoperation. Another limitation is the treatments compared. Newer anticoagulants were compared exclusively with LMWH, an appropriate and widely used comparator, but there were no direct comparisons to other treatment options recommended by guideline panels. Finally, none of these studies included patients from the VA health care system. Compared to patients with private sector insurance, VA patients on average have a greater burden of chronic disease, which would likely increase bleeding risk. If the comparative treatment effects vary by the presence of certain comorbid conditions, these results may not be reproducible in VA settings.

STRENGTHS AND LIMITATIONS

Our study has a number of strengths, including a protocol-driven review, a comprehensive search, and careful quality assessment. Another strength is the opportunity for meta-synthesis from existing systematic reviews and the opportunity to carefully evaluate reasons for different findings or conclusions across published reviews. Limitations include the lack of head-to-head comparisons of the newer oral anticoagulants, which precludes strong conclusions on their comparative effectiveness. Further, the length of experience with these new anticoagulants is too short to allow identification of longer term adverse events that may only emerge with more widespread use.

RECOMMENDATIONS FOR FUTURE RESEARCH

We used the framework recommended by Robinson et al.⁴² to identify gaps in evidence and classify why these gaps exist (Table 10).

This approach considers PICOTS (population, intervention, comparator, outcomes, timing, and setting) to identify gaps and classifies them as due to: (1) insufficient or imprecise information, (2) biased information, (3) inconsistency or unknown consistency, and (4) not the right information. VA and other health care systems should consider their clinical and policy needs when deciding whether to invest in research to address gaps in evidence. Specific research questions can be evaluated quantitatively, using value-of-information analysis, which uses Bayesian methods to estimate the potential benefits of gathering further information through research.⁴³

Table 10. Evidence gaps and future research

Evidence Gap	Reason	Type of Studies to Consider
Absence of direct comparisons between newer anticoagulant drugs	Insufficient information	Multicenter RCTs High-quality network meta-analyses Observational comparative effectiveness studies
Absence of direct comparisons between newer anticoagulants and agents other than LMWH	Insufficient information	Multicenter RCTs Observational comparative effectiveness studies
Absence of comparisons between combined treatment with newer anticoagulants and mechanical thromboprophylaxis to pharmacological thromboprophylaxis alone	Insufficient information	Multicenter RCTs Observational comparative effectiveness studies
Adverse effects with long-term use and in usual clinical practice	Insufficient information	Observational studies

Abbreviations: LMWH=low molecular weight heparin; RCT=randomized controlled trial

CONCLUSION

For THR or TKR, the 35-day rate of symptomatic VTE without thromboprophylaxis is estimated to be 4.3 percent. Pharmacological thromboprophylaxis decreases VTE by approximately 50 percent but with the tradeoff of increased bleeding. Newer oral anticoagulants have a more convenient route of administration compared with LMWH, and unlike adjusted dose warfarin, they do not require regular laboratory monitoring. Compared with LMWH, FXa inhibitors are associated with a reduced risk of symptomatic DVT, but mortality and nonfatal PE are not significantly different, and the risk of major bleeding episodes is increased.

There are no available studies on head-to-head comparisons of these novel anticoagulants. Longer clinical experience and direct drug-drug comparisons are needed to better assess the risk-to-benefit ratio of newer oral anticoagulants for surgical thromboprophylaxis. Based on current evidence, newer anticoagulants—particularly FXa inhibitors—are a reasonable option for thromboprophylaxis in patients undergoing total hip replacement or total knee replacement.

REFERENCES

1. 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*. 2012;141(2 Suppl):e278S-325S.
2. Mont MA, Jacobs JJ, Boggio LN, et al. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. *J Am Acad Orthop Surg*. 2011;19(12):768-76.
3. Hill J, Treasure T. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients having surgery: summary of NICE guidance. *BMJ*. 2007;334(7602):1053-4.
4. Friedman RJ, Gallus A, Gil-Garay E, et al. Practice patterns in the use of venous thromboembolism prophylaxis after total joint arthroplasty—insights from the Multinational Global Orthopaedic Registry (GLORY). *Am J Orthop (Belle Mead NJ)*. 2010;39(9 Suppl):14-21.
5. Binns M, Pho R. Femoral vein occlusion during hip arthroplasty. *Clin Orthop Relat Res*. 1990(255):168-72.
6. Clark C, Cotton LT. Blood-flow in deep veins of leg. Recording technique and evaluation of methods to increase flow during operation. *Br J Surg*. 1968;55(3):211-4.
7. Planes A, Vochelle N, Fagola M. Total hip replacement and deep vein thrombosis. A venographic and necropsy study. *J Bone Joint Surg Br*. 1990;72(1):9-13.
8. Sharrock NE, Go G, Harpel PC, et al. The John Charnley Award. Thrombogenesis during total hip arthroplasty. *Clin Orthop Relat Res*. 1995(319):16-27.
9. Sobieraj DM, Coleman CI, Tongbram V, et al. Venous Thromboembolism in Orthopedic Surgery. Comparative Effectiveness Review No. 49. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) AHRQ Publication No. 12-EHC020-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2012. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed November 7, 2012.
10. Lieberman JR, Hsu WK. Prevention of venous thromboembolic disease after total hip and knee arthroplasty. *J Bone Joint Surg Am*. 2005;87(9):2097-112.
11. Molnar RB, Jenkin DE, Millar MJ, et al. The Australian arthroplasty thromboprophylaxis survey. *J Arthroplasty*. 2012;27(2):173-9.
12. Ettema HB, Mulder MC, Nurmohamed MT, et al. Dutch orthopedic thromboprophylaxis: a 5-year follow-up survey. *Acta Orthop*. 2009;80(1):109-12.
13. Hirsh J, Levine MN. Low molecular weight heparin: laboratory properties and clinical evaluation. A review. *Eur J Surg Suppl*. 1994(571):9-22.

14. Weitz JI. Low-molecular-weight heparins. *N Engl J Med*. 1997;337(10):688-98.
15. Turpie AG. Pentasaccharide Org31540/SR90107A clinical trials update: lessons for practice. *Am Heart J*. 2001;142(2 Suppl):S9-15.
16. Fareed J, Thethi I, Hoppensteadt D. Old versus new oral anticoagulants: focus on pharmacology. *Annu Rev Pharmacol Toxicol*. 2012;52:79-99.
17. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-12.
18. Montori VM, Wilczynski NL, Morgan D, et al. Optimal search strategies for retrieving systematic reviews from MEDLINE: analytical survey. *BMJ*. 2005;330(7482):68.
19. Shojania KG, Bero LA. Taking advantage of the explosion of systematic reviews: an efficient MEDLINE search strategy. *Eff Clin Pract*. 2001;4(4):157-62.
20. Neumann I, Rada G, Claro JC, 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. *Ann Intern Med*. 2012;156(10):710-719.
21. Loke YK, Kwok CS. Dabigatran and rivaroxaban for prevention of venous thromboembolism--systematic review and adjusted indirect comparison. *J Clin Pharm Ther*. 2011;36(1):111-24.
22. Ringerike T, Hamidi V, Hagen G, et al. Thromboprophylactic treatment with rivaroxaban or dabigatran compared with enoxaparin or dalteparin in patients undergoing elective hip- or knee replacement surgery. Report from NOKC nr 13 - 2011. *Health Technology Assessment (HTA)*. 2011.
23. Gómez-Outes A, Terleira-Fernández AI, Suárez-Gea ML, et al. 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.
24. Jacobs JJ, Mont MA, Bozic KJ, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. *J Bone Joint Surg Am*. 2012;94(8):746-7.
25. Marinopoulos SS, Dorman T, Ratanawongsa N, et al. Effectiveness of continuing medical education. *Evid Rep Technol Assess (Full Rep)*. 2007(149):1-69.
26. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet*. 1999;354(9193):1896-900.
27. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7:10.

28. Mills EJ, Ioannidis JP, Thorlund K, et al. How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA*. 2012;308(12):1246-53.
29. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. Available at: www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&mp=1&productID=318. Accessed August 1, 2012.
30. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol*. 2011;64(12):1283-93.
31. Schunemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ*. 2008;336(7653):1106-10.
32. Cao YB, Zhang JD, Shen H, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total hip or knee arthroplasty: a meta-analysis of randomized controlled trials. *Eur J Clin Pharmacol*. 2010;66(11):1099-108.
33. Huang J, Cao Y, Liao C, et al. Apixaban versus enoxaparin in patients with total knee arthroplasty. A meta-analysis of randomised trials. *Thromb Haemost*. 2011;105(2):245-53.
34. Turun S, Banghua L, Yuan Y, et al. A systematic review of rivaroxaban versus enoxaparin in the prevention of venous thromboembolism after hip or knee replacement. *Thromb Res*. 2011;127(6):525-34.
35. Alves C, Batel-Marques F, Macedo AF. Apixaban and Rivaroxaban Safety After Hip and Knee Arthroplasty: A Meta-Analysis. *J Cardiovasc Pharmacol Ther*. 2011.
36. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med*. 2008;358(26):2765-75.
37. 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*. 2008;372(9632):31-9.
38. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*. 2008;358(26):2776-86.
39. Turpie AG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet*. 2009;373(9676):1673-80.
40. Eriksson BI, Dahl OE, Buller HR, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost*. 2005;3(1):103-11.

41. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol*. 1997;50(6):683-91.
42. Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for Determining Research Gaps During Systematic Reviews. Methods Future Research Needs Report No. 2. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHS A 290-2007-10061-I.) AHRQ Publication No. 11-EHC043-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed May 22, 2012.
43. Myers E, McBroom AJ, Shen L, et al. Value-of-Information Analysis for Patient-Centered Outcomes Research Prioritization. Report prepared by the Duke Evidence-based Practice Center. Patient-Centered Outcomes Research Institute. March 2012.