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

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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.

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EXECUTIVE SUMMARY

BACKGROUND

Venous thromboembolic (VTE) events are important causes of morbidity in elective total hip replacement (THR) and total knee replacement (TKR) procedures. Current guidelines recommend thromboprophylaxis in patients undergoing THR or TKR, although the American Academy of Orthopaedic Surgeons (AAOS) guidelines suggest individual assessment of patients when choosing the specific thromboprophylaxis strategy. Low molecular weight heparin (LMWH) and adjusted-dose warfarin are the most commonly used anticoagulants for thromboprophylaxis in the United States, but a number of other treatment options are available, including unfractionated heparin, aspirin, mechanical devices, and newer oral anticoagulants.

Prior to 1980, rates of symptomatic VTE were 15 to 30 percent. However, improved surgical care and techniques 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.

Pharmacological thromboprophylaxis for THR or TKR surgery decreases VTE by approximately 50 percent but with the tradeoff of increased bleeding. The risk of bleeding is a concern because bleeding can lead to infections, reoperation, delayed wound healing, and extended hospital stay. The choice of which antithrombotic thus becomes pivotal for balancing the prevention of thromboembolism with the risk of bleeding. Newer oral anticoagulants have been developed with the goal of overcoming the limitations of warfarin and the available parenteral agents. These newer anticoagulants belong to two drug classes, based on their target coagulation protein: factor Xa (FXa) inhibitors and direct thrombin inhibitors (DTIs). These drugs 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 the lack of specific antidotes to reverse their anticoagulant effect in a timely fashion in case of bleeding, and drug costs.

Given the emerging data on new oral anticoagulants, this report was commissioned by the VA to examine the following key questions (KQs):

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?

METHODS

During the topic development phase of this study, we identified a number of published high-quality systematic reviews that addressed our KQs. We conducted a synthesis of these reviews as they pertained to the KQs and the Veteran population and followed a standard protocol for all steps of this review. 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 2009 through September 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.

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. Select data from published reports were then abstracted into the final abstraction form by a trained reviewer. All data abstractions were confirmed by a second reviewer. We also abstracted data necessary for assessing the quality of systematic reviews, adapted from the AMSTAR criteria. Based on these criteria, systematic reviews were categorized as good, fair, or poor quality. Poor-quality reviews were excluded.

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 the quality of methodological designs, more complete drug comparisons, and detailed information about population, specific drug intervention, 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 these estimates, 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.

Our synthesis focused on 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, inclusion/exclusion criteria, differences in outcome definition, analytic approach, and conflict of interest. Because total hip and knee replacement have distinct primary endpoints, we examined the groups of studies as they pertained to these diagnoses separately.

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. In brief, this approach requires assessment of four domains: risk of bias,

consistency, directness, and precision. For risk of bias, we considered study design using the quality assessments of the primary literature reported in the systematic reviews. We used results from meta-analyses when evaluating consistency, precision, strength of association, and whether publication bias was detected. Optimal information size and consideration of whether the confidence interval crossed the clinical decision threshold for a therapy were also used when evaluating precision.

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 the appendix, which elucidates how each comment was considered in the final report.

RESULTS

Our search for systematic reviews (SRs) identified 182 unique citations from a combined search of MEDLINE via PubMed, Embase, the Cochrane Database of Systematic Reviews, and bibliographies of key articles. After applying inclusion and exclusion criteria at both the title-and-abstract and full-text review levels, the final set of articles used in this evidence report consisted of six recently published, high-quality systematic reviews.

All of the SRs compared newer oral anticoagulants with other drug classes used for thromboprophylaxis in THR or TKR (KQ 1), but specific strategies varied. Two SRs used random-effects meta-analyses to compare drug classes as a whole (e.g., FXa inhibitors versus LMWH) while the other four SRs compared individual drugs, some analyzing THR and TKR studies separately. 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. Only one SR compared a pharmacological agent plus mechanical modality versus pharmacologic prophylaxis alone (KQ 2).

All reviews assessed the quality of included trials, and overall quality was judged to be good. Publication bias was assessed and did not indicate bias that would favor newer oral anticoagulants. Three of the SRs were unfunded and reported no conflicts of interest. One SR was unfunded but did report a conflict of interest for one author. Two SRs were funded by government agencies.

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 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?

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.

FXa inhibitors. Rivaroxaban and apixaban are the most commonly studied FXa inhibitors, and rivaroxaban is the only FXa inhibitor marketed in the United States. The risk of symptomatic DVT was reduced with FXa inhibitors compared with LMWH, while the risks of nonfatal PE and mortality were 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 receiving thromboprophylaxis with FXa inhibitors over 5 weeks. Higher doses of FXa inhibitors, but not intermediate or low doses, were associated with increased major bleeding. 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. No reviews identified trials comparing oral FXa inhibitors with warfarin, unfractionated heparin, 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. No reviews identified trials comparing oral DTIs with warfarin, unfractionated heparin, or oral antiplatelet agents. Table 1 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 1. 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	TKR RR=1.06 (0.36 to 3.12) RD=0 (2 fewer to 6 more) events/1000 patients THR RR=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

[a]Data from Neumann, 2012.
[b]Risk 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

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 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.

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 alone. The evidence was insufficient for all other outcomes.

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 THR or TKR.
- 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.

Only indirect comparisons of rivaroxaban, apixaban, and dabigatran were performed through common comparison with LMWH. 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 2 summarizes the findings and strength of evidence for between-drug comparisons of newer oral anticoagulants in patients undergoing THR or TKR.

Table 2. Summary of the strength of evidence for KQ 3

Outcome	Domains Pertaining to SOE				Effect Estimate (95% CI)	SOE
	Number of Studies (Subjects)	Study Design/ Quality	Consistency Directness	Precision Publication Bias		
Apixaban, rivaroxaban, dabigatran[a]						
Mortality	NR	NA	NA	NA	Outcome not reported	Insufficient
Symptomatic DVT	NR	NA	NA	NA	Outcome not reported	Insufficient
Nonfatal PE	NR	NA	NA	NA	Outcome not reported	Insufficient
Symptomatic VTE	16 (38,747)	RCT/Good	NA Indirect	Imprecise None detected	Rivaroxaban vs. dabigatran RR=0.68 (0.21 to 2.23) RD=3 fewer (11 fewer to 4 more) events/1000 patients Rivaroxaban vs. apixaban RR=0.59 (0.26 to 1.33) RD=4 fewer (9 fewer to 1 more)/1000 patients Apixaban vs. dabigatran RR=1.16 (0.31 to 4.28) RD=1 more (7 fewer to 8 more)/1000 patients	Low Low Low
Major bleeding	16 (38,747)	RCT/Good	NA Indirect	Imprecise None detected	Rivaroxaban vs. dabigatran RR=1.37 (0.21 to 2.23); RD=4 more (2 fewer to 11 more) events/1000 patients Rivaroxaban vs. apixaban RR=1.59 (0.84 to 3.02); RD=5 more (2 fewer to 12 more)/1000 patients Apixaban vs. dabigatran RR=1.16 (0.31 to 4.28); RD=0 (8 fewer to 7 more)/1000 patients	Low Low Low

[a]Data from Gómez-Outes, 2012.

Abbreviations: DVT=deep vein thrombosis; NA=not applicable; NR=not reported; PE=pulmonary embolism; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio; SOE=strength of evidence; VTE=venous thromboembolism

RECOMMENDATIONS FOR FUTURE RESEARCH

We used a structured framework to identify gaps in evidence and classify why these gaps exist (Table 3).

Table 3. 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 or mechanical 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

Abbreviation: 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.

ABBREVIATIONS TABLE

CI	confidence interval
DTI	direct thrombin inhibitor
DVT	deep vein thrombosis
FDA	U.S. Food and Drug Administration
FXa	factor Xa inhibitor
INR	international normalized ratio
KQ	key question
LMWH	low molecular weight heparin
MeSH	medical subject heading
NA	not applicable
NR	not reported
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
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
VKA	vitamin K antagonist
VTE	venous thromboembolism