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Comparative Effectiveness of Warfarin and Newer Oral Anticoagulants for the Long-term Prevention and Treatment of Arterial and Venous Thromboembolism

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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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TABLE OF CONTENTS

FIGURES

Return to Contents

TABLES

Return to Contents

EXECUTIVE SUMMARY

BACKGROUND

Thromboembolic diseases represent a major public health burden and are associated with significant morbidity and mortality. For over 50 years, vitamin K antagonists (VKAs) have been the mainstay of treatment and prophylaxis of thromboembolism. There are many indications for VKA, including primary prevention of systemic embolism in nonvalvular atrial fibrillation (AF) and mechanical prosthetic heart valves. Other indications include secondary prophylaxis following venous thromboembolism (VTE) and preventing stroke in patients with a mural thrombus following myocardial infarction.

In North America, warfarin is the most widely used VKA. In 2004, more than 30 million prescriptions for warfarin were written in the United States. Warfarin significantly reduces the risk for thromboembolic complications in AF, mechanical heart valves, and VTE. However, warfarin therapy has several disadvantages, including its narrow therapeutic window and wide interindividual and intraindividual variability in anticoagulant effect. This variability dictates the need for continuous and regular monitoring, using the international normalized ratio (INR), to maintain patients within the desired therapeutic range. Even with regular monitoring, 30 to 50 percent of INR values fall outside the target range. Furthermore, patients find repeated venipuncture for INR monitoring tedious, and health care providers find it costly.

Over the past decade, several novel oral anticoagulants have emerged. These anticoagulants fall under two drug classes: (1) factor Xa (FXa) inhibitors and (2) direct thrombin inhibitors (DTIs). These drugs characteristically have a predictable anticoagulant effect, eliminating the need for routine monitoring. Moreover they have a faster onset of action, and there is no need to overlap with a parenteral agent when starting thromboprophylaxis—as is the case with warfarin. Warfarin reversal is necessary in some cases of overanticoagulation, which can be achieved using specific products and according to established guidelines. Despite the shorter half-life of new oral anticoagulants compared with warfarin, there are well-founded concerns over the lack of specific antidotes to reverse their anticoagulant effect in a timely fashion in case of bleeding or in preparation for a procedure. These concerns are more pronounced in elderly patients and those with renal impairment. Furthermore, drug acquisition costs are much higher for the newer anticoagulants than for warfarin.

This review was commissioned by the Evidence-based Synthesis Program of the Department of Veterans Affairs (VA) to evaluate newer anticoagulants compared with warfarin. 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 following key questions (KQs) based on the review of published peer-reviewed literature in consultation with VA and non-VA experts:

Key Question 1. For patients with chronic nonvalvular AF, what is the comparative effectiveness of long-term anticoagulation using newer oral anticoagulants versus warfarin on stroke incidence, mortality, health-related quality of life (HRQOL), and patient treatment experience?

Key Question 2. For patients with venous thromboembolism, are there differential effects of newer oral anticoagulants versus warfarin or low molecular weight heparins on recurrent thromboembolism, mortality, HRQOL, and patient treatment experience?

Key Question 3. For patients with mechanical heart valves, what is the comparative effectiveness of newer oral anticoagulants versus warfarin on the incidence of thromboembolic complications, mortality, HRQOL, and patient treatment experience?

Key Question 4. When used for long-term anticoagulation treatment, what is the nature and frequency of adverse effects for newer oral anticoagulants versus warfarin?

METHODS

We searched MEDLINE® (via PubMed®), Embase®, and the Cochrane Library of Systematic Reviews for peer-reviewed publications comparing the newer oral anticoagulants to standard care (usually VKAs) from January 2001 (the year newer oral anticoagulants were introduced) through May 2011. Our search strategy used the National Library of Medicineís medical subject headings (MeSH) keyword nomenclature and text words for newer anticoagulants and the conditions of interest. Our final search terms included new or novel anticoagulants; direct thrombin inhibitors, including dabigatran, and ximelagatran; factor Xa inhibitors, including edoxaban, rivaroxaban, apixaban, betrixaban, YM150; and the names of the conditions of interestóatrial fibrillation, venous thromboembolism, and mechanical heart valve. We limited the search to articles involving human subjects 18 years of age and older and published in the English language. Based on the recommendations of our reviewers, we searched for observational studies that documented adverse effects and updated the original search through February 2012 via PubMed® only. We also searched the Food and Drug Administration (FDA) databases for documentation of adverse effects. We developed our search strategy in consultation with an experienced search librarian. To assess publication bias, we searched www.clinicaltrials.gov for completed but unpublished studies.

DATA SYNTHESIS

We critically analyzed studies to compare their characteristics, methods, and findings. We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis) by exploring the volume of relevant literature, the completeness of the results reporting, and the conceptual homogeneity of the studies. When a meta-analysis was appropriate, we used random-effects models to synthesize the available evidence quantitatively. For three-arm studies that included more than one dose of the newer anticoagulant, we used data from the treatment arm using the standard FDA-approved dose. We conducted sensitivity analyses by including the studies that (1) evaluated ximelagatran, a newer anticoagulant (no longer available) and (2) used the other dose of the newer anticoagulant in three-arm studies. Heterogeneity was examined among the studies using graphical displays and test statistics (Cochran's Q and I^2). The I^2 describes the percentage of total variation across studies due to heterogeneity rather than to chance. Heterogeneity was categorized as low, moderate, or high based on I^2 values of 25 percent, 50 percent, and 75 percent respectively.

The outcomes for this report were binary; therefore we summarized these outcomes by a weighted-effect measure for proportions (e.g., risk ratio). We present summary estimates and 95 percent confidence intervals (CIs). When there were statistically significant treatment differences, we estimated the absolute treatment effect by calculating the risk difference. Risk difference was calculated using the median event rate from the control treatments and the summary risk ratio. For KQ 4 (adverse effects), analyses were compared for consistency across conditions, and a sensitivity analysis was performed to examine the effect of ximelagatran (withdrawn from the market due to liver toxicity).

RATING THE BODY OF EVIDENCE

In addition to rating the quality of individual studies, we evaluated the overall strength of evidence (SOE) for each KQ by assessing the following domains: risk of bias, consistency, directness, precision, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, low, or insufficient SOE was assigned after discussion by two reviewers.

PEER REVIEW

The draft version of the report was reviewed by technical experts and clinical leadership. A transcript of their comments is in an appendix of the full report, which elucidates how each comment was considered in the final report.

RESULTS

We identified 594 unique citations from a combined search of MEDLINE (via PubMed, n = 338), Embase (n = 178), and the Cochrane Database of Systematic Reviews (n = 78). Manual searching of included study bibliographies and review articles identified an additional 17 citations for a total of 611 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 80 full-text articles were retrieved and screened. Of these, 56 were excluded at the full-text screening stage, leaving 24 articles (representing 8 unique studies) for data abstraction. All studies compared newer anticoagulants to adjusted-dose warfarin; there were no direct comparisons between newer anticoagulants. Our search of www.clinicaltrials.gov did not suggest publication bias. A separate search of the observational study literature yielded 369 references. Manual searches and reviewer suggestions added an additional 8 articles. After applying our eligibility criteria, 28 articles were retrieved and screened at the full-text level. Of these, 10 articles (including 7 unique studies) were retained for data abstraction.

Key Question 1. For patients with chronic nonvalvular AF, what is the comparative effectiveness of long-term anticoagulation using newer oral anticoagulants versus warfarin on stroke incidence, mortality, health-related quality of life (HRQOL), and patient treatment experience?

Five good-quality studies, involving 57,908 patients compared newer anticoagulants (FXa, two studies; DTI, three studies) with adjusted-dose warfarin. The mean age of participants was over 70 years; about 55 percent were men and CHADS2 scores averaged from 2.1 to 3.5. Key exclusion

criteria were marked renal impairment, aspirin use of more than 100 to 165 mg, uncontrolled hypertension, prior stroke, significant anemia, and platelet count lower than 90,000 to 100,000. In the control groups, the percentage of time in the INR target range was 55 to 68 percent (median 66%).

Table ES-1 summarizes the findings and SOE for each major outcome. In brief, newer anticoagulants were associated with a lower rate of all-cause mortality compared with warfarin (high SOE). Newer anticoagulants were also associated with fewer hemorrhagic strokes (moderate SOE). For these outcomes, we estimated the absolute risk difference to be 8 fewer deaths and 4 fewer hemorrhagic strokes for every 1000 patients treated with the newer anticoagulants compared with adjusted-dose warfarin over approximately 2 years of treatment. The difference in bleeding-related outcomes is dependent in part on the quality of adjusted-dose warfarin treatment; these studies reported rates of time in therapeutic range that were similar to those observed in the Veterans Health Administration (VHA). Except for discontinuations due to adverse effects, other outcomes also favored newer anticoagulants; however, they were not statistically significant. No studies reported effects on patient experience or HRQOL.

In addition to these findings, we evaluated subgroup analyses from the primary trials. These analyses showed no differential effects on stroke prevention (interaction effects) for individuals with a history of cerebrovascular accidents, impaired renal function, or older age. However, these analyses suggest that some bleeding complications with dabigatran compared with warfarin may be increased in patients older than age 75 and at centers with high-quality warfarin treatment. The effects of impaired renal function were mixed, showing no interaction effect in one analysis and a differential risk of gastrointestinal bleeding with rivaroxaban in another analysis.

Table ES-1. Summary of the strength of evidence for KQ 1—chronic AF

Number of Studies (Subjects)	Domains Pertaining to SOE				SOE
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
All-cause mortality					**High SOE**
3 (44,442)	RCT/Good	Consistent	Direct	Precise	RR = 0.88 (0.82 to 0.95) RD = 8 (3 to 11) fewer deaths/1000
VTE-related mortality					**Moderate SOE**
2 (30,299)	RCT/Good	Some inconsistency	Direct	Some imprecision	RR = 0.77 (0.57 to 1.02)
Ischemic stroke					**Moderate SOE**
3 (44,442)	RCT/Good	Consistent	Direct	Some imprecision	RR = 0.89 (0.78 to 1.02)
Hemorrhagic stroke					**Moderate SOE**
3 (44,442)	RCT/Good	Some inconsistency	Direct	Some imprecision	RR = 0.46 (0.31 to 0.68) RD = 4 (2 to 5) fewer hemorrhagic strokes/1000
Discontinuation due to adverse effects					**Low SOE**
3 (44,502)	RCT/Good	Important inconsistency	Direct	Important imprecision	RR = 1.26 (0.86 to 1.84)
Major bleeding					**Low SOE**
3 (44,474)	RCT/Good	Important inconsistency	Direct	Some imprecision	RR = 0.88 (0.70 to 1.09)

Abbreviations: CI = confidence interval; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; SOE = strength of evidence

Key Question 2. For patients with venous thromboembolism, are there differential effects of newer oral anticoagulants versus warfarin or low molecular weight heparins on recurrent thromboembolism, mortality, HRQOL, and patient treatment experience?

Three good-quality studies, involving 8,477 patients compared newer anticoagulants (FXa, one study; DTI, two studies) to adjusted-dose warfarin. The average age of participants was 50 to 55 years; about 56 percent were men. Key exclusion criteria were marked renal impairment and, less commonly, prior stroke or low platelet count. In the control groups, the percentage of time in the INR target range was 58 to 61 percent (median 60%).

Table ES-2 summarizes the findings and SOE for each major outcome. In comparison with the chronic AF studies, there were fewer studies and patients enrolled as well as shorter duration of followup for this population. The summary risk ratio favored newer anticoagulants for all-cause mortality, VTE-related mortality, recurrent VTE, and major bleeding, but in each instance the CI included no effect. Overall, these results support the conclusion that newer anticoagulants are no worse than adjusted-dose warfarin for major clinical outcomes. No studies reported effects on patient experience or HRQOL.

Table ES-2. Summary of the strength of evidence for KQ 2—venous thromboembolism

Number of Studies (Subjects)	Domains Pertaining to SOE				SOE
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
All-cause mortality					**Moderate SOE**
2 (5988)	RCT/Good	Consistent	Direct	Some imprecision	RR = 0.83 (0.59 to 1.18)
VTE-related mortality					**Low SOE**
2 (5988)	RCT/Good	Consistent	Direct	Important imprecision	RR = 0.56 (0.19 to 1.69)
Recurrent DVT/PE					**Moderate SOE**
2 (5988)	RCT/Good	Some inconsistency	Direct	Some imprecision	RR = 0.85 (0.54 to 1.33)
Discontinuation due to adverse effects					**Moderate SOE**
2 (5988)	RCT/Good	Consistent	Direct	Some imprecision	RR = 1.19 (0.93 to 1.51)
Major bleeding					**Moderate SOE**
2 (5988)	RCT/Good	Consistent	Direct	Some imprecision	RR = 0.77 (0.49 to 1.20)

Abbreviations: CI = confidence interval; NA = not applicable; NR = not reported; RCT = randomized controlled trial; RR = risk ratio; SOE = strength of evidence

Key Question 3. For patients with mechanical heart valves, what is the comparative effectiveness of newer oral anticoagulants versus warfarin on the incidence of thromboembolic complications, mortality, HRQOL, and patient treatment experience?

We did not identify any published studies that compared newer anticoagulants to adjusted-dose warfarin in patients with mechanical heart valves. We identified one ongoing, Phase II trial of dabigatran from our search of www.clinicaltrials.gov.

Key Question 4. When used for long-term anticoagulation treatment, what is the nature and frequency of adverse effects for newer oral anticoagulants versus warfarin?

The adverse effects of newer oral anticoagulants compared with adjusted-dose warfarin were generally consistent across treatment indications. After excluding the ximelagatran studies, the summary risk ratio for discontinuation due to adverse effects was higher for newer anticoagulants, but this result was not statistically significant. The effects on bleeding rates are complex. *Fatal bleeding* was significantly lower for newer oral anticoagulants, an effect that was consistent across drug classes. *Major bleeding* was lower for newer oral anticoagulants, but this effect was not statistically significant and varied greatly across studies. In contrast, *gastrointestinal bleeding* was increased with newer oral anticoagulants. Gastrointestinal bleeding was significantly increased in patients treated with dabigatran and rivaroxaban compared with warfarin. The efflux of dabigatran by p-glycoprotein transporters into the gastrointestinal tract may be a mechanism for this finding. Subgroup analyses from clinical trials and FDA reports suggest that bleeding risk may be increased in older adults and in those with impaired renal function. Further, the differential bleeding risk may be related to the quality of warfarin anticoagulation.

Another potential adverse effect is myocardial infarction. We found no increased risk when combining results from all studies. However, for dabigatran alone, we found an elevated risk (RR = 1.35) that approached statistical significance. A separate meta-analysis, primarily of short-term trials, found a statistically significant increase in myocardial infarction or acute coronary syndrome (OR 1.33; 95% CI, 1.03 to 1.71). Liver dysfunction was substantially higher for ximelagatran, a drug withdrawn from the market due to this adverse effect. Elevated rates of liver dysfunction have not been seen with the other newer oral anticoagulants. The SOE was low for several outcomes because CIs included clinically important differences, and there was unexplained variability in treatment effects (Table ES-3).

Table ES-3. Summary of findings for KQ 4—adverse effects

Outcome	Strength of Evidence	Summary
Drug discontinuation due to adverse effects	Low	Across all indications, discontinuation due to adverse effects was higher with newer oral anticoagulants (RR 1.23; 95% CI, 0.94 to 1.61), but the 95-percent CI was large and included no effect. In subgroup analysis, rates of discontinuation were higher for dabigatran compared with FXa inhibitors. A clinically important increase in drug discontinuation compared with warfarin cannot be excluded.
Major bleeding	Low	Across all indications, the risk of major bleeding was lower with newer oral anticoagulants (RR 0.86; 95% CI, 0.71 to 1.04), but the 95-percent CI was large and included no effect. A clinically important decrease in major bleeding compared with warfarin cannot be excluded. In December 2011, the FDA issued a notice that it was evaluating reports of serious bleeding with dabigatran.
Fatal bleeding	Moderate	Across all indications, the risk of fatal bleeding was lower with newer oral anticoagulants (RR 0.59; 95% CI, 0.46 to 0.77). Risk difference was 1 fewer death per 1000 patients.
Gastrointestinal bleeding	Moderate	Across all indications, the risk of gastrointestinal bleeding was increased with newer oral anticoagulants (RR 1.30; 95% CI, 1.17 to 1.49). Risk difference was 1 additional gastrointestinal bleed per 1000 patients.

Outcome	Strength of Evidence	Summary
Myocardial infarction	Low	Across all indications, the risk of myocardial infarction was not different with newer oral anticoagulants (RR 1.02; 95% CI, 0.76 to 1.39). In a subgroup analysis, the risk was increased with dabigatran (RR 1.35; CI, 0.99 to 1.85) compared with FXa inhibitors (RR 0.86; CI, 0.66 to 1.11); p = 0.03 for between-group comparison.
Liver dysfunction	Moderate	Across all indications, the risk of liver dysfunction was not different with newer oral anticoagulants (RR 0.82; 95% CI, 0.61 to 1.11).

RECOMMENDATIONS FOR FUTURE RESEARCH

We used a structured framework to identify gaps in evidence and classify why these gaps exist (Table ES-4).

Table ES-4. Evidence gaps and future research

Evidence Gap	Reason	Type of Studies to Consider
Absence of data for patients with mechanical heart valves	Insufficient information	Multicenter RCTs
Uncertain effects on patient experience and health-related quality of life	Insufficient information	Multicenter RCTs and/or qualitative studies
Uncertain relative benefits across and within newer anticoagulant drug classes	Insufficient information	Multicenter RCTs comparing newer anticoagulants to each other and network meta-analyses
Uncertain effects on health system costs	Insufficient information	Budget impact analysis
Effects on thrombosis and systemic embolism when newer anticoagulants are stopped prior to invasive procedures	Insufficient information	Pharmacokinetic studies; observational studies
Management of patients on newer anticoagulants with bleeding complications	Insufficient information	RCTs; observational studies
Adverse effects with long-term use and in usual clinical practice	Insufficient information	Observational studies

Abbreviation: RCT = randomized controlled trial

CONCLUSION

Our review shows that the newer oral anticoagulants are a viable option for long-term anticoagulation. DTIs and FXa inhibitors have the advantage of more predictable anticoagulation, fewer drugñdrug interactions, and equivalent or better mortality and vascular outcomes compared with warfarin. However, the treatment benefits compared with warfarin are small and vary depending on the quality of warfarin anticoagulation. Also, no studies have evaluated these drugs in patients with mechanical heart valves, the drugs are costly, and the FDA is evaluating numerous reports of bleeding complications, particularly in older adults and those with severely impaired renal function. Because there are no head-to-head comparisons of newer anticoagulants, we were unable to determine if effects varied across drugs, and we had limited ability to test for differences between DTI and FXa drug classes.

ABBREVIATIONS TABLE

AF	atrial fibrillation
CI	confidence interval
FDA	U.S. Food and Drug Administration
FXa	factor Xa inhibitor
HRQOL	health-related quality of life
INR	international normalized ratio
KQ	key question
MeSH	medical subject headings
NA	not applicable
NR	not reported
RCT	randomized controlled trial
RD	risk difference
RR	risk ratio
SOE	strength of evidence
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
VKA	vitamin K antagonist
VTE	venous thromboembolism

EVIDENCE REPORT

INTRODUCTION

Thromboembolic diseases represent a major public health burden and are associated with significant morbidity and mortality. For more than 50 years, vitamin K antagonists (VKAs) have been the mainstay of treatment and prophylaxis of thromboembolism. There are many indications for VKAs, including primary prevention of systemic embolism in nonvalvular atrial fibrillation (AF) and mechanical prosthetic heart valves. Other indications include secondary prophylaxis following venous thromboembolism (VTE) and preventing stroke in patients with a mural thrombus following myocardial infarction.

In North America, the most widely recognized VKA is warfarin. In 2004, more than 30 million prescriptions for warfarin were written in the United States.[1] The advent of warfarin has resulted in significant risk reduction for thromboembolic complications in AF,[2] mechanical heart valves,[3-5] and VTE.[6]

CHRONIC ATRIAL FIBRILLATION AND STROKE

Chronic AF affects 2.2 million adults in the United States[7] and is associated with older age, hypertension, and heart disease—characteristics prevalent in the VA population. In patients with AF, the annual risk of stroke without prophylactic anticoagulation is 5 percent and increases to 7 percent if transient ischemic attacks and silent stroke are taken into account.[8] Furthermore, the rising incidence of AF and the increasing age of the population are projected to increase the stroke burden from 38 million disability-affected life-years in 1990 to 60 million disability-affected life-years in 2020.[9] The use of anticoagulants significantly reduces the risk of stroke or death from AF-related stroke.[10,11] Despite long experience with warfarin, it is underutilized. Warfarin is currently being prescribed for only 48 to 65 percent of suitable patients with AF.[12-14]

Guidelines on the management of AF from the American College of Cardiology/American Heart Association/ recommend treatment with aspirin or warfarin according to the degree of stroke risk, which can be estimated by the CHADS2 scoring system.[15] CHADS2 is a clinical score ranging from 0 to 6 used to predict the annual risk of stroke in individuals with chronic nonvalvular AF. Guidelines recommend aspirin for patients with a CHADS2 score of 0, aspirin or warfarin for those with a score of 1, and warfarin for those with a score greater than or equal to 2. In high-risk AF, VKAs decreased the risk of stroke by 80 percent while increasing the risk of minor bleeding by 3 percent per year.[16]

VENOUS THROMBOEMBOLISM

The incidence of VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE) is 1 in 1000 per year in the general population.[17,18] In the United States, the incidence of DVT is comparable to the incidence of fatal and nonfatal stroke or myocardial infarction.[19,20] DVT is associated with an increased risk for PE and postphlebitic syndrome, a condition characterized by chronic pain, swelling, and ulceration.[21] Untreated PE is associated with a hospital mortality

rate of 5.4 to 15 percent.[22,23] Furthermore, the cumulative incidence of chronic thromboembolic pulmonary hypertension 2 years after the diagnosis of PE is 4 percent.[24] Anticoagulation lowers the risk of recurrent DVT and PE, postphlebitic syndrome, chronic pulmonary hypertension, and death.

Current guidelines of the American College of Chest Physicians recommend the treatment of acute DVT/PE with heparin or low molecular weight heparin, overlapping with an oral VKA for at least 3 months. In unprovoked proximal DVT, recurrent DVT, or PE—and in the absence of significant risk factors for bleeding—it is recommended that VKAs be continued for 6 months or longer.[25]

MECHANICAL HEART VALVES AND THROMBOSIS

Aortic stenosis and mitral regurgitation are the most common valvular disorders in older adults. The prevalence of at least moderate aortic stenosis in the general population increases from 2.5 percent at age 75 to 8.1 percent at age 85.[26] Aortic valve replacement is the most common heart valve operation, accounting for 60 to 70 percent of all valve surgery performed in the elderly. Mitral valve regurgitation affects approximately 2.3 percent of adults aged 60 to 69 and 5.5 percent of adults older than age 70.[27] It is the second most common reason for valve surgery in older adults. Mechanical valves have longer durability than bioprosthetic valves but are associated with the risks of valvular thrombosis and systemic emboli. Thus, patients with mechanical valves require lifelong anticoagulation. Because of their longer durability, mechanical heart valves are recommended for younger patients (< 65 years of age) who are willing to take oral anticoagulants (e.g., warfarin) and comply with continuous anticoagulation monitoring.[28]

THERAPEUTIC OPTIONS FOR ANTICOAGULATION

The pharmacological properties of anticoagulants considered in this report are summarized in Table 1. The conventional management of acute VTE requires the use of a parenteral anticoagulant for 5 to 7 days, overlapping with longer term warfarin. Parenteral anticoagulants used in conjunction with warfarin include unfractionated heparin administered intravenously, low molecular weight heparin administered subcutaneously, and fondaparinux administered subcutaneously.[25] Unfractionated heparin requires hospital admission and continuous monitoring and carries the risk of heparin-induced thrombocytopenia. The advantages of low molecular weight heparin include longer half-life, better bioavailability, a predictable dose-response that minimizes the need for laboratory monitoring, and a decreased risk of heparin-induced thrombocytopenia.[29] The disadvantages of low molecular weight heparin include the need for subcutaneous administration once or twice daily, which patients find painful and inconvenient. Further, protamine sulfate only partially reverses heparin's anticoagulant effect.[30]

There is much experience with warfarin treatment among patients and care providers alike and, although bleeding remains a concern,[31] protocols and guidelines are available for reversal of overanticoagulation using vitamin K and blood products.[32-35] However, warfarin therapy has several disadvantages, including its narrow therapeutic window and wide interindividual and intraindividual variability in anticoagulant effect. This variability dictates the need for continuous

and regular monitoring to maintain patients within the desired therapeutic range. Monitoring warfarin therapy is achieved through measurement of the international normalized ratio (INR), which is dependent on the prothrombin clotting time. However, despite regular monitoring, 30 to 50 percent of INR values fall outside target range.[36] Furthermore, patients find repeated venipuncture for dose monitoring tedious, and health care providers find it costly.[37]

Warfarin also interacts with a long list of food, herbal medicines, vitamins, and drugs; and the list of drugs is continuously expanding.[38] This list should be taken into consideration every time there is a change in the patient's medications. In addition, patients on long-term warfarin therapy may need bridging with heparin before a planned procedure. Depending on the procedure, this may entail admission to the hospital preoperatively, which is costly and inconvenient for patients.

Newer Oral Anticoagulants

The search has been ongoing for novel oral anticoagulants with equal efficacy, a wider therapeutic range, and less complex pharmacodynamics, thus precluding the need for routine laboratory monitoring. Over the past decade, several newer oral anticoagulants have emerged. These anticoagulants fall under two drug classes: (1) factor Xa (FXa) inhibitors and (2) direct thrombin inhibitors (DTIs). These drugs characteristically have a predictable anticoagulant effect, eliminating the need for routine monitoring. However, patients on newer oral anticoagulants should still be monitored for any adverse effects, including bleeding. Bleeding risk is increased with concurrent use of antiplatelet medications, older age, and renal impairment since most of these drugs are eliminated through the kidneys.[39,40] Newer anticoagulants have a faster onset of action, so there is no need to overlap with a parenteral agent when starting thromboprophylaxis—as is the case with warfarin. While the reversal of warfarin is necessary in some cases of overanticoagulation, oral anticoagulants from these two classes have a shorter half-life, thus minimizing the need for an antidote (Table 1). However, there are valid concerns about the lack of specific antidotes for newer oral anticoagulants that would prevent the timely reversal of their anticoagulant effect in a bleeding patient. This is especially worrisome in elderly patients and those with renal disease, where drug clearance may be longer and the anticoagulant effects prolonged.

Factor Xa inhibitors

The coagulation cascade consists of two intertwined pathways—the intrinsic and extrinsic—which, when activated, result in a fibrin clot that stops bleeding. Both the intrinsic and extrinsic pathways converge in FX activation, making activated FX (FXa) an obvious target for anticoagulant therapy. Several FXa inhibitors have been developed for clinical use, including rivaroxaban and apixaban. Rivaroxaban was approved in Canada and the European Union for thromboprophylaxis after orthopedic surgery. It was approved in July 2011 by the U.S. Food and Drug Administration (FDA) for prophylaxis of venous thromboembolism in adults undergoing orthopedic surgery. In November 2011, the FDA approved rivaroxaban for stroke prophylaxis in patients with AF. Apixaban has also shown promise in clinical trials, and is currently under priority review by the FDA.[41] Other FXa inhibitors that are currently under clinical development include edoxaban and betrixaban. Edoxaban is being evaluated in a large Phase III trial, ENGAGE AF TIMI (Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48), comparing two different doses

of edoxaban with warfarin for prevention of stroke in patients with AF.[42] The study has finished recruitment and is projected to be completed in March 2012. Another ongoing trial is evaluating edoxaban for the treatment of VTE. (NCT00986154; see Appendix F, Table F-2)

Direct thrombin inhibitors

DTIs are another class of oral anticoagulants rapidly emerging in the clinical arena. Ximelagatran was the first DTI to be used clinically but is currently no longer available due to liver toxicity. Dabigatran etexilate is an oral, reversible DTI that was approved by the FDA in October 2010 for stroke prevention in AF. Renal excretion is the predominant elimination pathway for dabigatran, with more than 80 percent of systemically available dabigatran eliminated unchanged.[43] This capability may prove significant in the AF patient population since renal function declines with age, increasing the potential for prolonged elimination in older adults and greater anticoagulant effect.[44] In contrast to warfarin, dabigatran is not metabolized by the liver's cytochrome P 450 (CYP) enzyme system, yielding a better drug interaction profile.[43] Dabigatran acts as a substrate for the p-glycoprotein transporter system, which makes it more prone to drug-drug interactions. Coadministration of dabigatran with other p-glycoprotein substrate drugs, while affecting the pharmacokinetics, has not been shown to result in significant changes in coagulation parameters, including prothrombin time, activated prothrombin time, and ecarin clotting time.[45] Despite this lack of change in standard coagulation parameters, bleeding risk may be increased. ZD 0837 is another oral DTI under development in Phase II clinical trials.

Although these two newer classes of oral anticoagulants have the advantage of a predictable anticoagulant effect, drug acquisition costs are substantially higher than for warfarin. The cost of dabigatran therapy is approximately $3000 per year. This is substantially more than the price of warfarin, which is approximately $48 per year, even after adding the modest expense of INR testing and provider visits to adjust the dose.[46]

Return to Contents

Table 1. Characteristics of oral anticoagulants

	Vitamin K Antagonists	FXa Inhibitors			Direct Thrombin Inhibitors	
	Warfarin	**Rivaroxaban**	**Apixaban**	**Edoxaban**	**Dabigatran**	**Ximelagatran**
Mode of action	Inhibition of hepatic synthesis of vitamin K-dependent coagulation factors	Direct inhibition of FXa	Direct inhibition of FXa	Direct inhibition of FXa	Direct inhibition of clot-bound and free thrombin (FIIa)	Direct inhibition of thrombin (FII)
Time to peak effect (hours)	72–96	0.5–3	3	1.5	2–3	1.6–1.9
Half-life hours	20–60	5–9 (9–13 in elderly)	8–13	9–11	14–17	4–5
Bioavailability %	100	80	66	50	6.5	20
Recommended therapeutic dose and frequency	Adjusted-dose based on INR; once daily	20 mg; once daily	5 mg; twice daily	30 mg or 60 mg; once daily	150 mg; twice daily	Not available in the U.S.
Monitoring	Required using INR	Not required In case of hemorrhage or renal impairment, FXa-dependent assays may be used[47]	Not required due to predictable pharmacokinetics In hemorrhage or renal impairment, FXa-dependent assays may be used[47]	Not required due to predictable pharmacokinetics	Not required except in subgroups such as patients with renal impairment [48] Ecarin clotting time can be used if needed[49]	Not required
Renal excretion[39]	1% excreted unchanged in the urine	66% renal elimination	50% renal elimination	45% renal elimination	80% renal elimination	Main route of elimination
Interactions	CYP2C9, CYP1A2, CYP3A4 inhibitors Dietary vitamin K[50]	Potent CYP3A4 inhibitors and P-glycoprotein inhibitors[50]	Potent CYP3A4 inhibitors[50]	P-glycoprotein inhibitors[43]	P-glycoprotein inhibitors Proton pump inhibitors[38]	NA
Drug reversal	Vitamin K, fresh frozen plasma, prothrombin complex concentrate, recombinant FVIIa[51]	FVIIa partially reverses rivaroxaban anticoagulant effect[52] Prothrombin complex concentrate completely reverses its anticoagulant effect[53]	No available antidote	No available antidote	It is partially dialyzable[54]	NA
Precautions	Severe active bleeding, pregnancy, breast feeding, documented hypersensitivity[55] Severe renal impairment (glomerular filtration rate <30 mL/min/1.73m^2)[39]	Severe active bleeding; severe renal impairment[39]	Severe active bleeding; severe renal impairment	Severe active bleeding; severe renal impairment	Severe active bleeding, severe renal impairment[39]	NA

	Vitamin K Antagonists	FXa Inhibitors			Direct Thrombin Inhibitors	
	Warfarin	**Rivaroxaban**	**Apixaban**	**Edoxaban**	**Dabigatran**	**Ximelagatran**
FDA indications	1. Prophylaxis and treatment of thromboembolic complications associated with AF and or cardiac valve replacement 2. Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism 3. Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction	Prevention of VTE in patients undergoing orthopedic surgery and prevention of stroke in AF	None	None	Prevention of stroke in AF	None

Abbreviations: AF = atrial fibrillation; CYP = cytochrome P450; INR = international normalized ratio; NA = not applicable; VTE = venous thromboembolism

Return to Contents

OBJECTIVE OF THIS REPORT

The Veterans Health Administration (VHA) System serves a largely older, male population with a high prevalence of chronic AF and VTE. Many veterans with chronic AF have risk profiles for stroke that, according to current clinical guidelines, place them in a risk group where chronic anticoagulation is recommended. Adjusted-dose warfarin has been the preferred approach to chronic anticoagulation in the VHA, and in many VHA settings, specialized therapeutic drug-monitoring services provide high-quality warfarin treatment. However, the advent of newer anticoagulants with the promise of simplified long-term anticoagulation requires reconsideration of current treatment practices. The purpose of this systematic review was to study the comparative effectiveness of warfarin and the newer oral anticoagulants used for the long-term prevention and treatment of arterial and venous thromboembolism. An evaluation of newer oral anticoagulants for VTE prophylaxis in the perioperative period will be the subject of a later report.

Return to Contents

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 key questions (KQs) were:

Key Question 1. For patients with chronic nonvalvular AF, what is the comparative effectiveness of long-term anticoagulation using newer oral anticoagulants versus warfarin on stroke incidence, mortality, health-related quality of life (HRQOL), and patient treatment experience?

Key Question 2. For patients with venous thromboembolism, are there differential effects of newer oral anticoagulants versus warfarin or low molecular weight heparins on recurrent thromboembolism, mortality, HRQOL, and patient treatment experience?

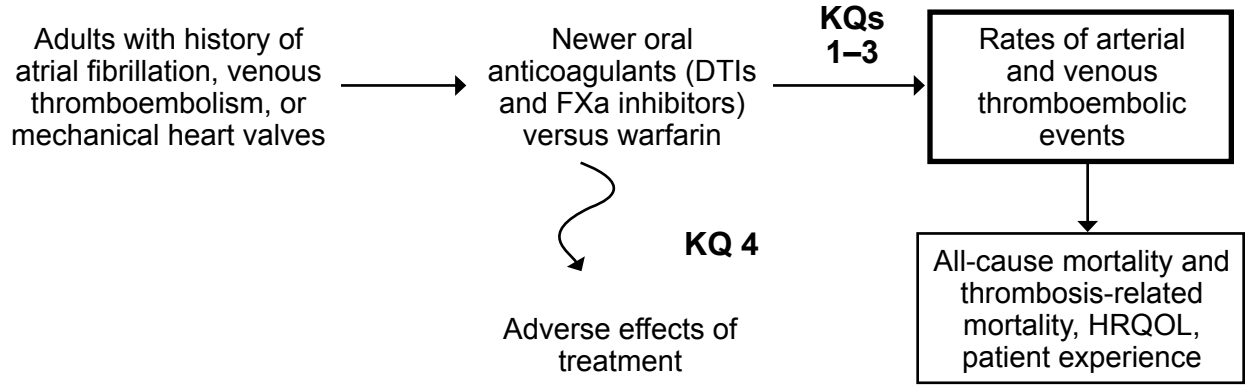
Key Question 3. For patients with mechanical heart valves, what is the comparative effectiveness of newer oral anticoagulants versus warfarin on the incidence of thromboembolic complications, mortality, HRQOL, and patient treatment experience?

Key Question 4. When used for long-term anticoagulation treatment, what is the nature and frequency of adverse effects for newer oral anticoagulants versus warfarin?

ANALYTIC FRAMEWORK

We followed a standard protocol for all steps of this review; certain methods map to the PRISMA checklist.[56] 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: DTI = direct thrombin inhibitors; FXa = factor X inhibitors; HRQOL = health-related quality of life; KQ = key question

SEARCH STRATEGY

We searched MEDLINE® (via PubMed®), Embase®, and the Cochrane Database of Systematic Reviews for peer-reviewed publications comparing the newer oral anticoagulants to standard care (usually VKAs) from January 2001 (the year newer oral anticoagulants were introduced) through May 2011. 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 randomized controlled trials.[57] Our final search terms included new or novel oral anticoagulants; DTIs, including dabigatran, and ximelagatran; FXa inhibitors, including edoxaban, rivaroxaban, apixaban, betrixaban, YM150; and the names of the conditions of interest—atrial fibrillation, venous thromboembolism, and mechanical heart valves. We limited the search to articles published in the English language involving human subjects 18 years of age and older. The full search strategy is provided in Appendix A. Following peer review of the draft report, we conducted a supplemental search of PubMed to identify observational studies or systematic reviews that addressed adverse effects of the newer oral anticoagulants. We also examined the FDA Web site, Drugs@FDA, to identify safety concerns. These included Drug Alerts and Statements (www.fda.gov/Drugs/DrugSafety/ucm215175.htm) and Drug Safety Communications (www.fda.gov/Drugs/DrugSafety/ucm199082.htm) in addition to the Advisory Committee Briefing Documents, the Center for Drug Evaluation and Research Summary Review, and the medical and statistical summary reports on the two newer oral anticoagulants (dabigatran and rivaroxaban) that have been FDA-approved. These supplemental searches along with an updated search for RCTs in PubMed were conducted in February 2012. We developed our search strategy in consultation with an experienced search librarian.

We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles.[58-70] The reference list for identified pivotal articles was manually hand-searched and cross-referenced against our library in order to retrieve additional manuscripts. All citations were imported into two electronic databases (EndNote® Version X5; Thomson Reuters, Philadelphia, PA, for referencing and DistillerSR for data abstraction). As a mechanism to assess the risk of publication bias, we searched www.clinicaltrials.gov for completed but unpublished studies.

STUDY SELECTION

Using prespecified inclusion and exclusion criteria, two reviewers assessed titles and abstracts for relevance to the KQs. Full-text articles identified by either reviewer as potentially relevant were retrieved for further review. Each article retrieved was examined by two reviewers against the eligibility criteria (Appendix B). 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 2. We modified these criteria for observational studies of adverse effects to include noncomparative studies (i.e., case reports, case series), nonrandomized comparative studies (i.e., cohort studies, case-control studies, controlled pre–post studies), and studies of any treatment duration. Studies excluded at the full-text review stage are listed with the reasons for exclusion in Appendix C.

Table 2. Summary of inclusion and exclusion criteria

Study characteristic	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years) of age with a history of chronic nonvalvular atrial fibrillation, venous thromboembolism, or mechanical heart valve replacement	Pregnant women
Intervention	Newer oral anticoagulants: direct thrombin inhibitors and factor Xa inhibitors	Newer anticoagulants requiring intravenous or subcutaneous administration
Comparator	Warfarin or low molecular weight heparin	None
Outcome	Any of the following: symptomatic thrombo-embolic event, mortality, health-related quality of life, adverse effects, patient experience	No relevant outcomes
Timing	• KQ 1 and KQ 3: ≥ 12 months • KQ 2: ≥ 6 months	< 6 months anticoagulation
Setting	Outpatient settings; may include initial hospitalization for acute anticoagulation	None
Study design	KQs 1–4: Randomized controlled trials (RCTs) or secondary data analysis from an RCT KQ 4: Observational studies including noncomparative and nonrandomized comparative studies	• Cross-sectional studies • Phase I clinical trials • Sample size < 50
Publications	• English-language only • Published from 2001 to present • Peer-reviewed article	• Non-English language publication • Published before 2001[a]

[a]Newer oral anticoagulants were first introduced in 2001.
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 (sample form is in Appendix D) by one trained reviewer. 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:

- age
- sex
- indication for anticoagulation
- baseline bleeding risk or factors associated with increased risk (e.g., creatinine >1.5, history of gastrointestinal bleeding)
- study drug and dosage
- comparator and quality of INR control
- length of treatment
- study design
- number of subjects and retention data
- outcomes/adverse effects
- for case studies, the sequence of clinical events

In addition, we examined included articles for subgroup analyses of particular relevance to the population served by VHA.

QUALITY ASSESSMENT

Data necessary for assessing quality and applicability, as described in the Agency for Healthcare Research and Quality's (AHRQ's) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,[71] also were abstracted. For RCTs, these key quality criteria consisted of (1) adequacy of randomization and allocation concealment, (2) comparability of groups at baseline, (3) blinding, (4) completeness of follow up and differential loss to follow up, (5) whether incomplete data were addressed appropriately, (6) validity of outcome measures, and (7) conflicts of interest. Using these quality criteria, we assigned a summary quality score (good, fair, poor) to individual RCTs studies as defined by the AHRQ *Methods Guide*.[71] The criteria were applied for each study by the reviewer abstracting the article; this initial assessment was then over-read by a second reviewer. Disagreements were resolved between the two reviewers or, when needed, by arbitration from a third reviewer. Observational studies consisted only of case studies and were not quality rated.

DATA SYNTHESIS

We critically analyzed studies to compare their characteristics, methods, and findings. We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis) by exploring the volume of relevant literature, the completeness of the results reporting and the conceptual homogeneity of the studies. When a meta-analysis was appropriate, we used random-effects models to synthesize the available evidence quantitatively. For three-arm studies that included more than one dose of the newer oral anticoagulant, we used data from the treatment arm using the standard FDA-approved dose. We conducted sensitivity analyses by (1) including the studies that evaluated ximelagatran, a newer anticoagulant that is not available, (2) using the other dose of the newer anticoagulant in three-arm studies, and (3) using revised data on adverse effects from the trial by Eikelboom et al.[72] When there were sufficient studies, we conducted a mixed-effects analysis to compare treatment effects by drug class. These later analyses should be considered hypothesis-generating because they consist of indirect comparisons (across studies that may differ in ways other than the drug class) and thus are subject to confounding. Heterogeneity was examined among the studies using graphical displays and test statistics (Cochran's Q and I^2); the I^2 describes the percentage of total variation across studies due to heterogeneity rather than to chance.[73] Heterogeneity was categorized as low, moderate, or high based on I^2 values of 25 percent, 50 percent, and 75 percent respectively.

The outcomes for this report were binary; we therefore summarized these outcomes by a weighted-effect measure for proportions (e.g., risk ratio). We present summary estimates and 95 percent confidence intervals (CIs). When there were statistically significant treatment differences, we estimated the absolute treatment effect by calculating the risk difference. Risk difference was calculated using the median event rate from the control treatments and the summary risk ratio.[74] These results are presented in the strength of evidence tables (in the Summary and Discussion section).

Because AF, venous thromboembolism, and mechanical heart valve replacement are distinct clinical entities with distinct primary endpoints, we examined the groups of studies as they pertained to these diagnoses separately. For KQ 4 (adverse effects), we analyzed common

outcomes (e.g., death, major bleeding) across treatment indications. All analyses were conducted using Review Manager (RevMan) 5.1.4. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

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*.[71] In brief, this approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains considered were strength of association (magnitude of effect) and publication bias. For risk of bias, we considered basic (e.g., RCT) and detailed study design (e.g., adequate randomization). We used results from meta-analyses when evaluating consistency (forest plots, tests for heterogeneity), precision (CIs), strength of association (odds ratio [OR]), and publication bias (www.clinicaltrials.gov survey). Optimal information size and consideration of whether the CI crossed the clinical decision threshold using a therapy were also used when evaluating precision.[75] 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.[76] We also considered the risk of publication bias. Publication bias was addressed through a careful search of www.clinicaltrials.gov (March 2012) for identification of any study completed but unpublished or ongoing. We did not use graphical (e.g., funnel plots) or test statistics (e.g., Beggs test) because these methods do not perform well with fewer than 10 studies.

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 Figures 2 and 3. Our search for RCTs (Figure 2) identified 594 unique citations from a combined search of MEDLINE via PubMed (n = 338), Embase (n = 178), and the Cochrane Database of Systematic Reviews (n = 78). Manual searching of included study bibliographies and review articles identified an additional 17 citations for a total of 611 unique citations. After applying inclusion and exclusion criteria at the title-and-abstract level, 80 full-text articles were retrieved and screened. Of these, 56 were excluded at the full-text screening stage, leaving 24 articles (representing 8 unique studies) for data abstraction.

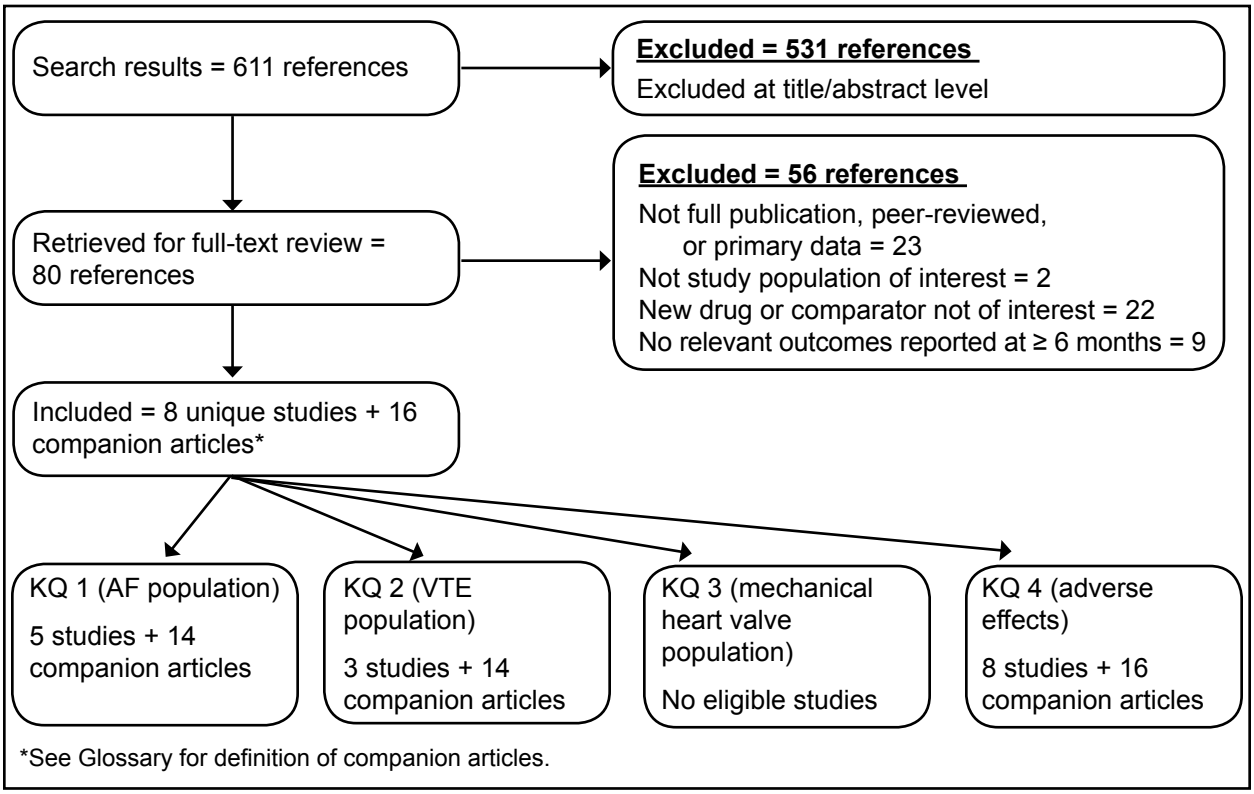
Our search of the observational literature including systematic reviews via PubMed (Figure 3) identified 369 unique citations. An additional 8 citations were identified from personal communications of experts and bibliographies of included studies for a total of 377 unique citations. After applying inclusion and exclusion criteria specifically for observational designs at the title-and-abstract level, 28 full-text articles were retrieved and screened. Of these, 10 contained new data and were abstracted either as unique studies (n = 7)[70,77-82] or as additional analyses from earlier trials (n = 3).[72,83,84]

Appendix C provides a complete listing of published articles excluded at the full-text screening stage, with reasons for exclusion.

Our search of the FDA website, Drugs@FDA, identified two MedWatch reports of adverse events with dabigatran (QuarterWatch 10/6/2011 and 1/12/2012) and one FDA Drug Safety Communication on dabigatran. We also examined the FDA Advisory Committee Briefing Reports, FDA Summary Reviews, and the medical and statistical reviews on dabigatran and rivaroxaban. These reports are detailed under KQ 4.

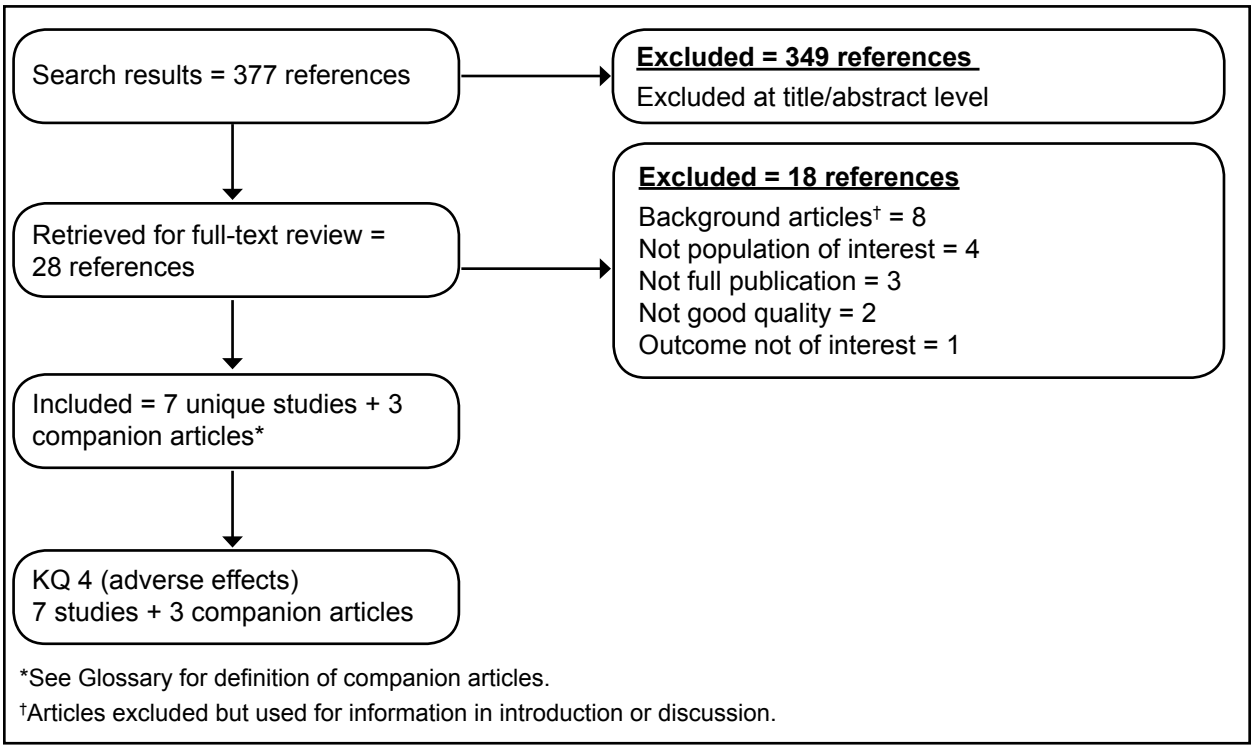
Finally, we searched www.clinicaltrials.gov, which revealed nine unpublished studies that met our eligibility criteria (Appendix F). Of these, four are ongoing trials and two have completed data collection within the last 6 months. The other three trials (NCT00645853, NCT00448214, NCT00329238) were scheduled for completion more than a year ago (between 2008 and 2010). Of these, two examined chronic AF and one examined venous thromboembolism. When the sponsors were contacted, we received the following information: (1) A 5-year RCT of AZD0837 in patients with chronic AF (NCT00645853) was terminated early due to "a limitation in the long-term stability of the AZD0837 drug product"; (2) development of darexaban maleate (YM150, examined in NCT00448214) was stopped for financial reasons prior to Phase III trials; and (3) an abstract reporting longer term outcomes (NCT00329238) from the dabigatran RECOVER study[85] was presented at the 2011 International Symposium on Hemostasis and Thrombosis in Kyoto, Japan.

Figure 2. Literature flow diagram for RCTs



Abbreviations: AF = atrial fibrillation; VTE = venous thromboembolism; KQ = key question

Figure 3. Literature flow diagram for observational studies and systematic reviews



Abbreviations: KQ = key question

STUDY CHARACTERISTICS

Randomized Controlled Trials

We identified 8 randomized studies involving 66,449 subjects.[85-92] Five studies evaluated newer oral anticoagulants for chronic AF, and three studies examined the treatment of venous thromboembolism; no study evaluated newer oral anticoagulants for patients with mechanical heart valves. All studies compared newer oral anticoagulants to adjusted-dose warfarin; there were no direct comparisons between newer oral anticoagulants.

Seven studies were conducted in multisite trials that included U.S. sites and one study was conducted outside the United States. None of the studies were conducted in VA settings. All studies were judged good quality (Appendix G), although there were design features that may have affected the findings: (1) patients not blinded to treatment assignment (seven of eight studies), (2) uncertainty whether outcomes assessors were blinded to treatment status (one study),[87] and (3) uncertainty whether all outcomes were reported (one study).[89]

For the five studies conducted in patients with chronic AF, key exclusion criteria were marked renal impairment (5 studies), aspirin use of more than 100 mg (4 studies) or more than 165 mg daily (1 study), uncontrolled hypertension (4 studies), prior stroke (4 studies), significant anemia (4 studies), and platelet count lower than 90,000 to 100,000 (4 studies). Exclusion criteria were somewhat less stringent for the VTE studies. For the three VTE studies, key exclusion criteria were marked renal impairment (3 studies), uncontrolled hypertension (1 study), prior stroke (1 study), and low platelet count (1 study). Table 3 presents an overview of study characteristics of the included studies, and Table 4 provides further details.

Table 3. Overview of study characteristics for included RCTs

Study Characteristic	Chronic Atrial Fibrillation Number of studies (patients)	Venous Thromboembolism Number of studies (patients)[a]
Studies	5 (57,908)	3 (8541)
Factor Xa inhibitors		
Apixaban	1 (18,201)	–
Rivaroxaban	1 (14,262)	1 (3449)
Direct thrombin inhibitors		
Dabigatran	1 (18,113)	1 (2564)
Ximelagatran	2 (7332)	1 (2528)
Study country		
Multiple countries (with U.S.)	4	3
Multiple countries (without U.S.)	1	–
Study duration		
6 months	–	2 (5092)
6–12 months	–	1 (3449)
>12 months–2 years	5 (57,908)	–
Mean age		
Age 50–59	–	3 (8541)
Age 60–69	–	–
Age 70–75	5 (57,908)	–
Funding source		
Industry	5	3
Government	–	–

Study Characteristic	Chronic Atrial Fibrillation Number of studies (patients)	Venous Thromboembolism Number of studies (patients)[a]
Outcomes reported		
Mortality	5	3
Thromboembolic-related mortality	4	3
Thromboembolic events	5	3
Major bleeding	5	3
Adverse effects	5	3
Health-related quality of life	–	–
Patient treatment experience	–	–
Study quality		
Good	5	3

[a]Represents number of patients randomized but does not include the third treatment arm (110 mg dabigatran) from Connolly et al., 2009.

Table 4. Details of study characteristics

Study	RCT n	Quality[a]	Intervention vs. Comparator	Outcome Measures[b]	Adverse Effects
Chronic nonvalvular AF: KQ 1 and KQ 4					
Albers et al., 2005[88] (SPORTIF V study)	n = 3922	Good	Ximelagatran (DTI) 36 mg vs. warfarin	All-cause mortality Death–thromboembolic event Stroke–ischemic Stroke–hemorrhage Peripheral embolism	Serious adverse events
Connolly et al., 2009[87] (RELY study)	n = 18113	Good	Dabigatran (DTI) 150 mg vs. warfarin	All-cause mortality Death–thromboembolic event Stroke–hemorrhage Combined stroke Peripheral embolism	Major bleeding Fatal bleeding Myocardial infarction Intracranial bleeding
Granger et al., 2011[92] (ARISTOTLE study)	n = 18201	Good	Apixaban (FXa) 5 mg vs. warfarin	All-cause mortality Death–thromboembolic event Stroke–ischemic Stroke–hemorrhage Combined stroke Peripheral embolism	Adverse effects drug discontinuation Major bleeding Major bleeding requiring transfusion Myocardial infarction Intracranial bleeding
Olsson et al., 2003[90] (SPORTIF III study)	n = 3410	Good	Ximelagatran (DTI) 36 mg vs. warfarin	All-cause mortality Death–thromboembolic event Stroke–ischemic Stroke–hemorrhage Peripheral embolism	NR
Patel et al., 2011[91] (ROCKET-AF study)	n = 14264	Good	Rivaroxaban (FXa) 20 mg vs. warfarin	All-cause mortality Stroke–ischemic Stroke–hemorrhage Combined stroke	Major bleeding Fatal bleeding Major bleeding requiring transfusion Myocardial infarction Intracranial bleeding
Venous thromboembolism: KQ 2 and KQ 4					
Bauersachs et al., 2005[86] (EINSTEIN-DVT study)	n = 3449	Good	Rivaroxaban (FXa) 20 mg vs. warfarin	All-cause mortality Death–thromboembolic event Recurrent DVT PE Recurrent DVT/PE	Major bleeding

Study	RCT n	Quality[a]	Intervention vs. Comparator	Outcome Measures[b]	Adverse Effects
Fiessinger et al., 2005[89] (THRIVE study)	n = 2528	Good	Ximelagatran (DTI) 36 mg vs. warfarin	All-cause mortality Recurrent DVT PE Recurrent DVT/PE	Major bleeding
Schulman et al., 2009[85] (RECOVER study)	n = 2564	Good	Dabigatran (DTI) 150 mg vs. warfarin	All-cause mortality Death–thromboembolic event Recurrent DVT PE	All adverse effects Serious adverse events Adverse effects drug discontinuation Major bleeding Myocardial infarction

[a]Study quality assessed using key quality criteria described in *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*
[b]Outcomes limited to those with direct relevance to KQs 1, 2, and 4 (i.e., chronic AF, venous thromboembolism, adverse effects).
Abbreviations: DTI= direct thrombin inhibitors; DVT = deep venous thrombosis; FXa = factor Xa inhibitor; PE = pulmonary embolism

KEY QUESTION 1: For patients with chronic nonvalvular AF, what is the comparative effectiveness of long-term anticoagulation using newer oral anticoagulants versus warfarin on stroke incidence, mortality, health-related quality of life (HRQOL), and patient treatment experience?

We identified five good-quality studies relevant to KQ 1, which involved 57,908 patients. All studies were funded by the pharmaceutical industry. These studies compared apixaban,[92] dabigatran,[87] rivaroxaban,[91] and ximelagatran[88,90] to adjusted-dose warfarin. Two studies[91,92] modified the drug dose for patients with impaired renal function. In the study by Granger et al.,[92] this was due to older age (>80 years), lower weight (<60 kg), or high creatinine (>1.5 mg/dl). In the study by Patel et al.,[91] this was due to creatinine clearance less that 30 mL/minute. The mean age of participants in all studies was over 70 years; about 55 percent were men. CHADS2 stroke risk scores averaged approximately 2.1 in the studies evaluating dabigatran and apixaban[87,92] and 3.5 in the study evaluating rivaroxaban;[91] two studies did not report CHADS2 scores.[88,90] Average adherence to the intervention drugs was greater than 90 percent for two studies[88,90] and in another study, 79 percent of participants took at least 80 percent of prescribed medication doses[87]; two studies did not report adherence.[91,92] In the control groups, the percentage of time in the INR target range was 55 to 68 percent (median 66%). All studies planned outcomes assessment over 24 months; none reported effects on HRQOL or patient experience. Study characteristics are summarized in Table 5.

Return to Contents

Table 5. Summary table for KQ 1—chronic atrial fibrillation

Study Characteristic	Number of Studies (Patients)[a]
Total number of studies (patients)	5 studies (57,908)
Factor Xa inhibitors, dose	
Apixaban, 5 mg twice daily	1 (18,201)
Rivaroxaban, 20 mg daily	1 (14,262)
Direct thrombin inhibitors, dose	
Dabigatran, 150 mg twice daily	1 (18,113)
Ximelagatran, 36 mg twice daily	2 (7,332)
Mean age	
50–60 years	–
60–70 years	–
≥70 years	5 (57,908)
Sex[b]	
Men	5 (33107)
Women	5 (18785)
Baseline CHADS2 stroke risk score[c]	
≤1	3 (10,207)
2	3 (12,742)
≥3	3 (20,822)
NR	2
Adjusted-dose warfarin range	
Time above range (%)	1 (12%), 4 NR
Time in range (%)	5 (median 66%, range: 55–68%)
Time below range (%)	1 (20%), 4 NR

[a]Does not include the third treatment arm (110 mg dabigatran) from Connolly et al., 2009.
[b]Does not match randomized total because some patient characteristics were reported only for those subjects analyzed.
[c]CHADS2 is a clinical score ranging from 0 to 6 used to predict the annual risk of stroke in individuals with chronic nonvalvular AF.
Abbreviations: NR = not reported

Meta-Analyses for KQ 1

We used random-effects model meta-analyses to evaluate the effects of newer oral anticoagulants compared with adjusted-dose warfarin on mortality, risk of ischemic and hemorrhagic stroke, major bleeding, fatal bleeding, myocardial infarction, liver dysfunction, and drug discontinuation due to an adverse event (Table 6, Figures 4–9). For our primary analyses, we excluded the studies using ximelagatran since this drug is not available in the U.S. All-cause mortality (summary RR 0.88; 95% CI, 0.82 to 0.95), hemorrhagic stroke (RR 0.46; CI, 0.31 to 0.68), hemorrhagic or ischemic stroke (RR 0.77; CI, 0.67 to 0.88), and fatal bleeding (RR 0.55; CI, 0.41 to 0.76) were lower with the newer oral anticoagulants. Tests for heterogeneity suggest important variability in treatment effects across studies for death due to thromboembolism, hemorrhagic stroke, drug discontinuation due to adverse effects, major bleeding, and myocardial infarction.

There were too few studies to conduct quantitative analyses for factors that may be associated with variable treatment effects. However, a qualitative inspection shows differences in the study eligibility criteria that may contribute to differential treatment effects. The study by Patel et al.[91] found the greatest effect on mortality and enrolled an older patient population with higher CHADS2 scores than the other studies.[9] Older age is a risk factor for both thrombosis and bleeding,[22,93] and a higher CHADS2 score is associated with a higher risk of stroke, systemic embolism, and death.[94] Variation in effects may also be related to different definitions for outcomes. For example, adverse effects leading to drug discontinuation include liver disease and bleeding. Liver disease was defined in two of three included AF studies as liver enzymes

elevated to twice the upper limit of normal,[87,92] while one study defined it as three or more times the upper limit of normal.[91]

We conducted two sensitivity analyses, first by including studies of ximelagatran and second by using the data from the dabigatran 110 mg treatment arm instead of the 150 mg treatment arm in the study by Connolly et al.[87] When the two studies examining ximelagatran are included, results are similar except that drug discontinuation due to adverse effects and rates of liver dysfunction are significantly higher than rates with adjusted-dose warfarin. Using data from the dabigatran 110 mg treatment arm, risk ratios did not differ by more than 10 percent except for ischemic stroke (summary RR 1.0; 95% CI, 0.88 to 1.13) and peripheral emboli (RR 1.03; CI, 0.61 to 1.74). Summary risk ratios and tests for variability in treatment effects across studies are summarized in Table 6. There were too few studies to conduct meaningful analyses by drug class or statistical tests for publication bias. However, our search of www.clinicaltrials.gov did not suggest publication bias.

Table 6. Effects of newer oral anticoagulants compared with adjusted-dose warfarin for chronic AF

	Summary Risk Ratios (95% CI)	Test for Heterogeneity	Summary Risk Ratios (95% CI)	Test for Heterogeneity
Outcome	Non-ximelagatran studies (n = 3)		All studies (n = 5)	
All-cause mortality	0.88 (0.82 to 0.95)	Q = 0.49, I^2 = 0% p = 0.78	0.89 (0.83 to 0.96)	Q = 1.15, I^2 = 0% p = 0.89
Death–thromboembolic[a]	0.77 (0.57 to 1.03)	Q = 2.23, I^2 = 55% p = 0.14	0.91 (0.61 to 1.36)	Q = 7.85, I^2 = 62% **p = 0.05**
Stroke–ischemic	0.89 (0.78 to 1.02)	Q = 1.77, I^2 = 0% p = 0.41	0.90 (0.78 to 1.04)	Q = 5.30, I^2 = 25% p = 0.26
Stroke–hemorrhagic	0.45 (0.31 to 0.68)	Q = 4.18, I^2 = 52% p = 0.12	0.47 (0.35 to 0.64)	Q = 4.74, I^2 = 16% p = 0.31
Combined stroke	0.77 (0.67 to 0.88)	Q = 2.80, I^2 = 29% p = 0.25	NA	NA
Peripheral embolism[a]	1.17 (0.64 to 2.14)	Q = 1.38, I^2 = 28% p = 0.24	1.40 (0.78 to 2.51)	Q = 3.84, I^2 = 22% p = 0.28
Adverse Effect				
Discontinued due to adverse effects	1.26 (0.86 to 1.84)	Q = 56.27, I^2 = 96% p < 0.001	1.41 (1.05 to 1.89)	Q = 76.37, I^2 = 95% p < 0.001
Major bleeding	0.88 (0.70 to 1.09)	Q = 15.45, I^2 = 87% p < 0.001	0.84 (0.71 to 1.00)	Q = 16.44, I^2 = 82% p = 0.001
Fatal bleeding	0.55 (0.41 to 0.76)	Q = 0.49, I^2 = 0% p = 0.48	0.57 (0.42 to 0.77)	Q = 1.57, I^2 = 0% p = 0.67
Myocardial infarction	0.97 (0.72 to 1.30)	Q = 6.37, I^2 = 69% p = 0.04	0.99 (0.75 to 1.31)	Q = 11.52, I^2 = 65% p = 0.02
Liver dysfunction	0.97 (0.82 to 1.15)	Q = 1.61, I^2 = 0% p = 0.45	2.18 (0.96 to 4.95)	Q = 99.92, I^2 = 96% p < 0.001

[a]No data for Patel 2011.
Abbreviation: NA = not applicable

Return to Contents

Forest Plots for Studies Without Ximelagatran (Atrial Fibrillation)

Figure 4. AF: All-cause mortality without ximelagatran[a]

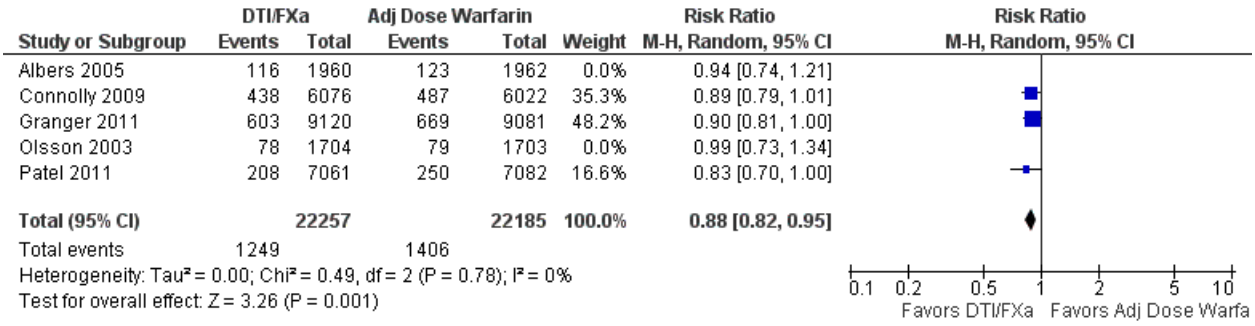


Figure 5. AF: Ischemic stroke without ximelagatran[a]

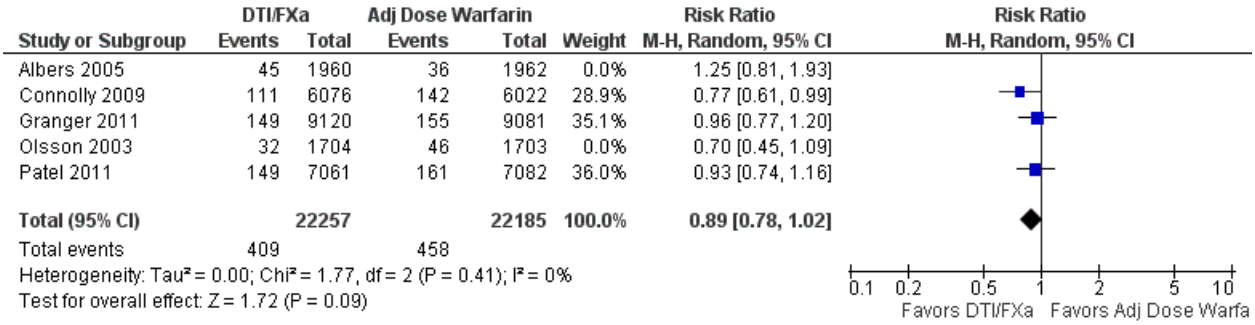
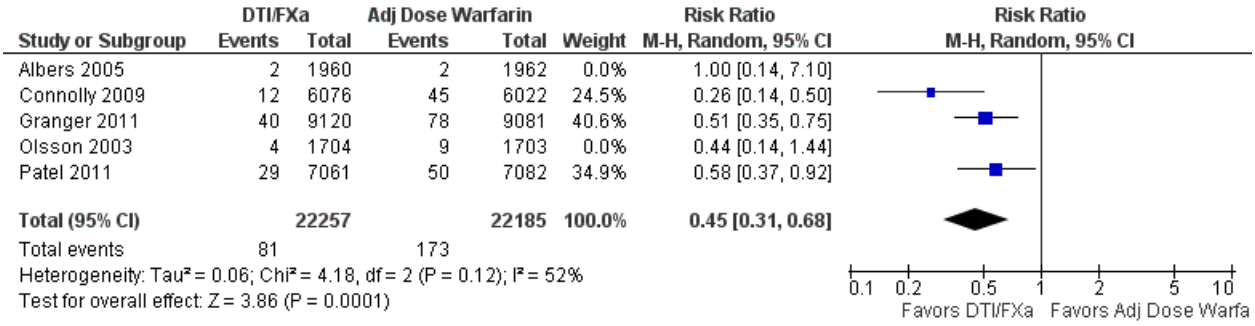


Figure 6. AF: Hemorrhagic stroke without ximelagatran[a]



[a]Studies evaluating ximelagatran are shown but not incorporated into the summary risk ratio in Figures 4, 5, and 6.

Forest Plots for Studies With Ximelagatran (Atrial Fibrillation)

Figure 7. AF: All-cause mortality with ximelagatran

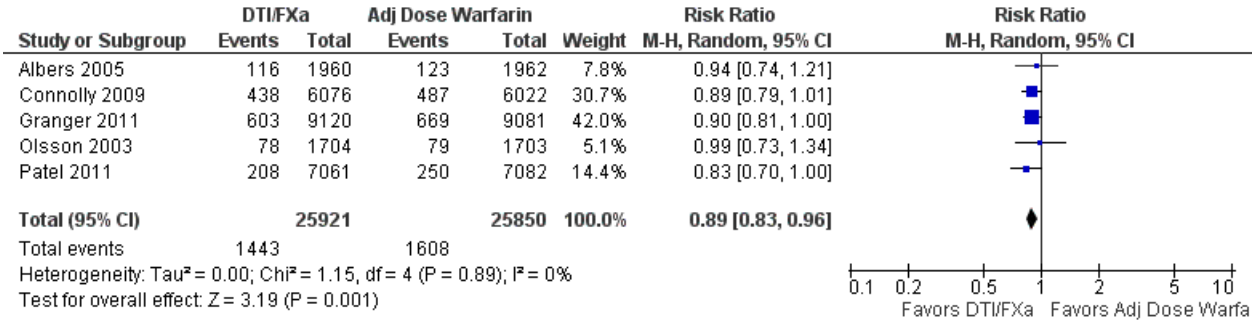


Figure 8. AF: Ischemic stroke with ximelagatran

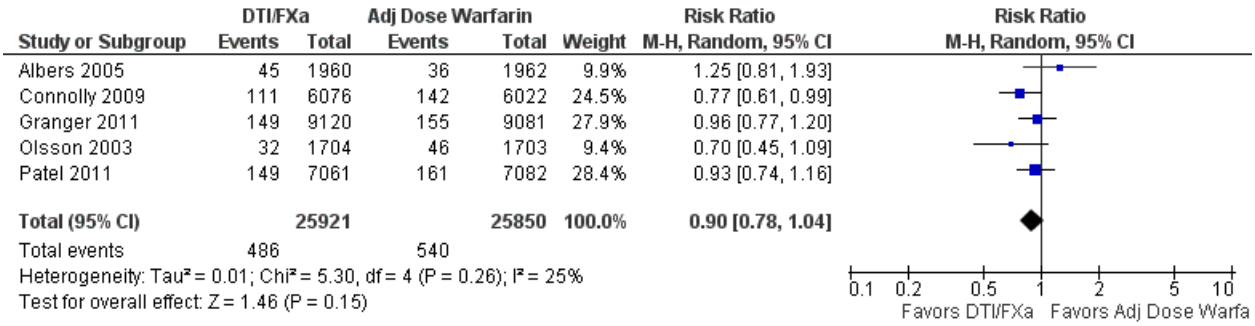
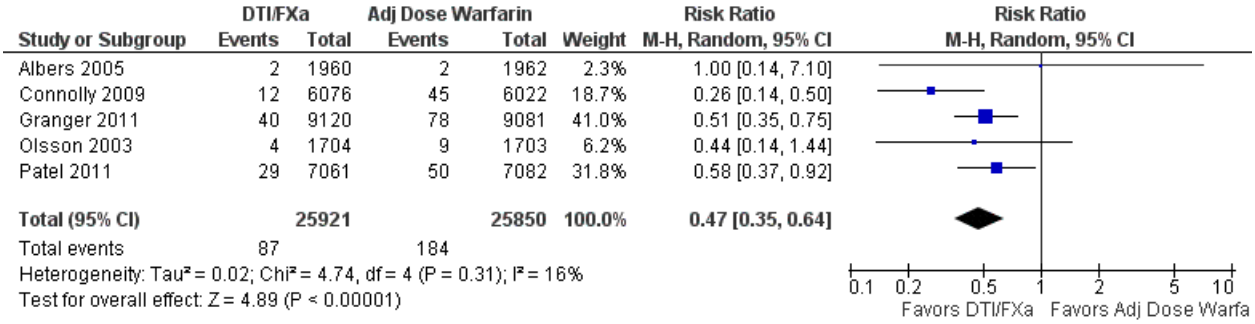


Figure 9. AF: Hemorrhagic stroke with ximelagatran



Subgroup Analyses From Primary Publications

SPORTIF III and V Trials (Ximelagatran Versus Warfarin)

In three industry-sponsored, pooled analyses on the combined sample (n = 7329) of the SPORTIF III and V trials, the following results were reported:

- There was no significant difference in the primary event rate (stroke or systemic embolism) for patients with a history of stroke or transient ischemic attack (TIA) compared with those without a prior history of stroke or TIA. Similarly, there was no difference between these groups in the incidence of cerebral hemorrhage.[95]
- Ximelagatran was comparable to warfarin for stroke prevention in adults under age 75 and those older than age 75. Risk of bleeding with ximelagatran was lower than warfarin in both the younger and older subgroups.[96]
- Patients with markers of heart failure compared to patients without markers of heart failure had a higher rate of stroke or systemic embolic events. Ximelagatran was comparable to warfarin for these outcomes in patients with or without markers of heart failure.[97]

Return to Contents

RE-LY Trial (Dabigatran Versus Warfarin)

In the RE-LY trial, the following results were reported:

- Diener et al. performed a subgroup analysis for the primary outcome, stroke or systemic embolism, and seven secondary outcomes in patients with and without a history of previous stroke or TIA.[98] Treatment effects did not differ significantly by subgroup except for the secondary outcome of vascular death. For this outcome, dabigatran 110 mg was more effective in the group with prior stroke or TIA compared with those without prior stroke or TIA (OR 0.63 versus 0.98, p = 0.038). However, this finding was not replicated in the dabigatran 150 mg treatment arm.

- Because therapeutic INR with warfarin anticoagulation control is key for stroke prevention, Walletin et al. performed a subgroup analysis to compare treatment effects by each sites average INR control level.[99] For the 18,024 patients at 906 sites, subgroup analyses were completed by grouping sites into quartiles of time in therapeutic range (TTR). Analyses were adjusted for differences in baseline characteristics across these groups. For the primary outcome of stroke or systemic embolism, there were no significant interactions between TTR and the comparative effects of dabigatran and warfarin. However, the risk of major bleeding was significantly lower for dabigatran 150 mg at sites with poor INR control (TTR <57.1%; test for interaction p = 0.03) but not significantly different from warfarin at sites with better INR control. In contrast, major gastrointestinal bleeding was approximately doubled with dabigatran 150 mg compared to warfarin at sites with better TTR (≥65.5%, p = 0.019). Dabigatran 150 mg was also *more effective* than warfarin at sites with poor INR control compared with those with good INR control for all vascular events (test for interaction, p = 0.006) and mortality (p = 0.05). In summary, these subgroup analyses suggest that the quality of adjusted-dose warfarin treatment is associated with the comparative effectiveness of dabigatran for several clinically important outcomes.

- In another subgroup analysis that focused on bleeding complications, the effects of dabigatran varied by age.[72] In patients under age 75, both doses of dabigatran were associated with a modestly lower risk of major bleeding in comparison to warfarin. In those over age 75, the risk of major bleeding was not significantly different for the 110 mg dose of dabigatran, but the risk approached a statistically significant higher rate for the 150 mg dose compared with warfarin (5.1 versus 4.4%, p = 0.07). Although the risk of bleeding increased with lower creatinine clearance (CrCl), there was no interaction effect between CrCl and the effect of dabigatran. The authors concluded that the observed age effects were not "simply a pharmacokinetic interaction" related to declining CrCl in older adults.

- In a separate analysis of data from the RE-LY study, rates of MI, unstable angina, cardiac arrest, and cardiac death were reported. In the treatment groups on dabigatran 110 mg, 150 mg, and adjusted-dose warfarin, myocardial infarction occurred at an annual rate of 0.82 percent, 0.81 percent, and 0.64 percent (HR 1.29; 95% CI, 0.96 to 1.75; p = 0.09 for dabigatran 110 mg and HR 1.27; CI, 0.94 to 1.71;p = 0.12 for dabigatran 150 mg).[84] In conclusion, there was a nonsignificant increase in myocardial infarction with dabigatran

treatment while other myocardial events were not increased. The relative effects of dabigatran versus warfarin on myocardial ischemic events were consistent in patients with or without a baseline history of myocardial infarction or coronary artery disease.

ROCKET-AF Trial (Rivaroxaban Versus Warfarin)

In the ROCKET-AF trial, the following results were reported:

- A secondary analysis of data from the ROCKET-AF trial evaluated the efficacy and safety of rivaroxaban compared to warfarin in patients with moderate renal dysfunction.[83] Around one-fifth of the enrolled population (20.7%) had moderate renal impairment at baseline (CrCl 30–49 mL/min). Compared to patients with CrCl ≥50 mL/min, patients with moderate renal impairment had higher CHADS2 scores and more cardiovascular disease. Patients with moderate renal impairment were treated with a lower dose of rivaroxaban (15 mg/day) than those with better renal function (20 mg/day). For patients with moderate renal dysfunction, the rates of stroke and systemic embolism were higher than in those with CrCl ≥ 50 mL/min, regardless of anticoagulant treatment received. Major bleeding and clinically relevant non–major bleeding occurred more frequently in those with renal insufficiency than in those without, regardless of randomized treatment assigned. Comparative treatment effects for rivaroxaban versus warfarin were similar for all major outcomes, including bleeding events, for those with and without renal insufficiency. When bleeding rates were analyzed further by site of bleeding, patients with impaired renal function who were treated with rivaroxaban had higher gastrointestinal bleeding rates than those treated with warfarin (4.1% versus 2.6%, p = 0.02).

In summary, subgroup analyses show no differential effects on stroke prevention (interaction effects) for individuals with a history of cerebrovascular accidents, impaired renal function, or older age. However, these analyses suggest that some bleeding complications with dabigatran compared with warfarin may be increased in those older than age 75 and at centers with high-quality warfarin treatment. Further, myocardial infarction—but not other myocardial ischemic events—showed a non–statistically significant increase with dabigatran. The effects of impaired renal function were mixed, showing no interaction effect in one analysis and a differential risk of gastrointestinal bleeding with rivaroxaban in another analysis.

KEY QUESTION 2: For patients with venous thromboembolism, are there differential effects of newer oral anticoagulants versus warfarin or low molecular weight heparins on recurrent thromboembolism, mortality, HRQOL, and patient treatment experience?

We identified three good-quality studies relevant to KQ 2, which involved 8541 patients; all studies were funded by the pharmaceutical industry. These studies evaluated dabigatran (n = 1),[85] rivaroxaban (n = 1),[89] and ximelagatran (n = 1)[86] versus adjusted-dose warfarin. The mean age of participants was between 50 and 55; approximately 56 percent were men. Almost 80 percent of participants had DVT alone, with most of the remainder having both DVT and PE. Average adherence to the intervention drugs was 98 percent in the study evaluating dabigatran,[85]

and in the study evaluating ximelagatran,[89] 93 percent of participants took at least 80 percent of prescribed doses. One study did not report adherence.[86] In the control groups, the percentage of time in the INR target range was 58 to 61 percent (median 60%). Two studies reported the proportion of time below range (21 to 24%) and above range (16 to 19%).[85,86] Studies assessed outcomes at 6 to 12 months; none reported effects on HRQOL or patient experience. Study characteristics are summarized in Table 7.

Table 7. Summary table for KQ 2—venous thromboembolism

Study Characteristic	Number of Studies (Patients)
Total number of studies (patients)	3 (8541)
Factor Xa inhibitor, dose	
Rivaroxaban, 20 mg daily	1 (3449)
Direct thrombin inhibitors, dose	
Dabigatran, 150 mg twice daily	1 (2564)
Ximelagatran, 36 mg twice daily	1 (2528)
Study duration:	
6 months	2 (5092)
12 months	1 (3449)
Mean age	
50–60 years	3 (8541)
60–70 years	–
Sex	
Men	3 (4763)
Women	3 (3714)
DVT/PE etiology[a]	
Idiopathic/unprovoked	1 (2138), 2 NR
Active cancer	3 (655)
Prior VTE	3 (1855)
Adjusted-dose warfarin range	
Time above range (%)	2 (16.2–19%), 1 NR
Time in range (%)	3 (57.7–61%)
Time below range (%)	2 (19–21%), 1 NR

[a]Some subjects may have had more than one risk factor.
Abbreviations: DVT = deep venous thrombosis; NR = not reported; PE = pulmonary embolism; VTE = venous thromboembolism

Meta-Analyses for KQ 2

We used random-effects model meta-analyses to evaluate the effects of newer oral anticoagulants compared with adjusted-dose warfarin on mortality, risk of recurrent DVT or PE, major bleeding, fatal bleeding, myocardial infarction, liver dysfunction, and drug discontinuation due to adverse effects. There was no statistically significant difference for any of these outcomes. For some outcomes, such as death due to thromboembolism, fatal bleeding, and myocardial infarction, the 95-percent CIs were particularly wide and include the potential for clinically important differences. Tests for heterogeneity suggest variability in treatment effects across studies for recurrent DVT/PE (moderate) and liver dysfunction (high).

There were too few studies to conduct quantitative analyses for factors that may be associated with variable treatment effects. However, a qualitative inspection shows differences across studies in patient characteristics, eligibility criteria, and interventions that may be related to differential treatment effects. Individuals with a previous history of VTE have a 25-percent risk of recurrence in the first 5 years.[100] A higher proportion of patients in the dabigatran study [85] had a history of previous VTE than patients in the rivaroxaban study (25 versus 19%).[86] The dabigatran

study also had a lower threshold to exclude patients for elevations in the alanine transaminase level than for the rivaroxaban study.[86] Furthermore, all patients in the dabigatran study received low molecular weight heparin or unfractionated heparin before starting dabigatran, while patients in the rivaroxaban study did not. Low molecular weight heparin and unfractionated heparin can cause liver enzyme elevation.[101,102]

When the study examining ximelagatran was included, results were similar except that drug discontinuation due to adverse effects was significantly higher than rates with adjusted-dose warfarin. This result appears to be related primarily to higher rates of liver dysfunction with ximelagatran. Summary risk ratios and tests for variability in treatment effects across studies are summarized in Table 8 (Figures 10–14). There were too few studies to conduct subgroup analyses by drug class or statistical tests for publication bias. However, our search of www.clinicalTrials.gov did not suggest publication bias.

Table 8. Effects of newer oral anticoagulants compared with adjusted-dose warfarin for venous thromboembolism

	Summary Risk Ratios (95% CI)	Test for Heterogeneity	Summary Risk Ratios (95% CI)	Test for Heterogeneity
Outcome	Non-ximelagatran studies (n = 2)		All studies (n = 3)	
All-cause mortality	0.84 (0.59 to 1.18)	Q = 0.47, I^2 = 0% p = 0.49	0.78 (0.59 to 1.02)	Q = 1.01, I^2 = 0% p = 0.60
Recurrent DVT	0.66 (0.37 to 1.15)	Q = 1.49, I^2 = 33% p = 0.22	0.72 (0.49 to 1.06)	Q = 2.02, I^2 = 1% p = 0.36
Death–thromboembolic[a]	0.56 (0.19 to 1.69)	Q = 0.28, I^2 = 0% p = 0.60	NA	NA
Recurrent DVT/PE	0.86 (0.55 to 1.33)	Q = 1.79, I^2 = 44% p = 0.18	0.91 (0.67 to 1.24)	Q = 2.43, I^2 = 18% p = 0.30
Adverse Effect				
Discontinued due to adverse effects	1.19 (0.93 to 1.51)	Q = 1.43, I^2 = 30% p = 0.23	1.24 (1.10 to 1.41)	Q = 1.73, I^2 = 0% p = 0.42
Major bleeding	0.77 (0.49 to 1.20)	Q = 0.14, I^2 = 0% p = 0.71	0.69 (0.48 to 0.99)	Q = 0.91, I^2 = 0% p = 0.63
Fatal bleeding	0.50 (0.12 to 2.06)	Q = 0.31, I^2 = 0% p = 0.58	0.41 (0.13 to 1.35)	Q = 0.59, I^2 = 0% p = 0.75
Myocardial infarction	2.83 (0.75 to 10.71)	Q = 0.44, I^2 = 0% p =0.51	3.46 (1.03 to 11.62)	Q = 0.98, I^2 = 0% p = 0.61
Liver dysfunction	0.60 (0.27 to 1.34)	Q = 6.80, I^2 = 85% p = 0.009	1.20 (0.29 to 4.98)	Q = 65.83, I^2 = 97% p < 0.001

[a]No data for ximelagatran group.
[b]Fiessenger 2005 did not report thromboembolic death
Abbreviations: DVT = deep venous thrombosis; NA = not applicable; PE = pulmonary embolism

Return to Contents

Forest Plots for Studies Without Ximelagatran (Venous Thromboembolism)

Figure 10. VTE: All-cause mortality without ximelagatran[a]

Figure 11. VTE: Death–thromboembolic without ximelagatran[a,b]

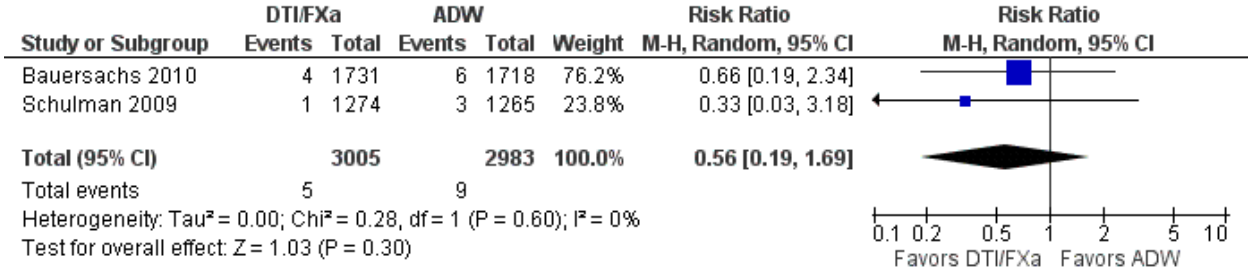
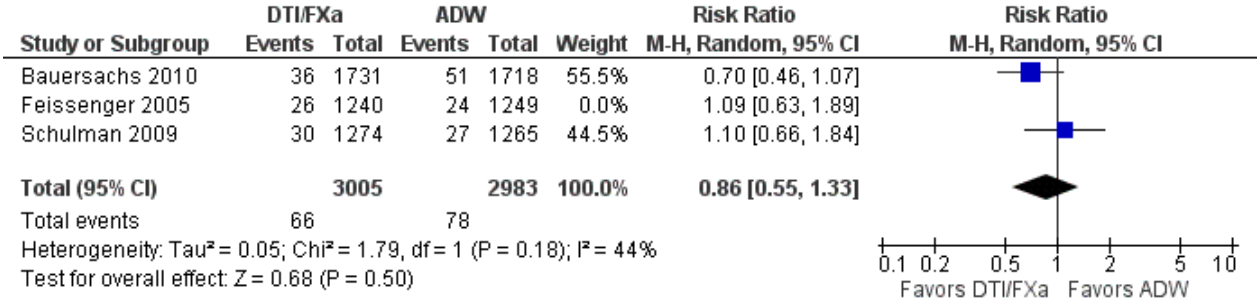


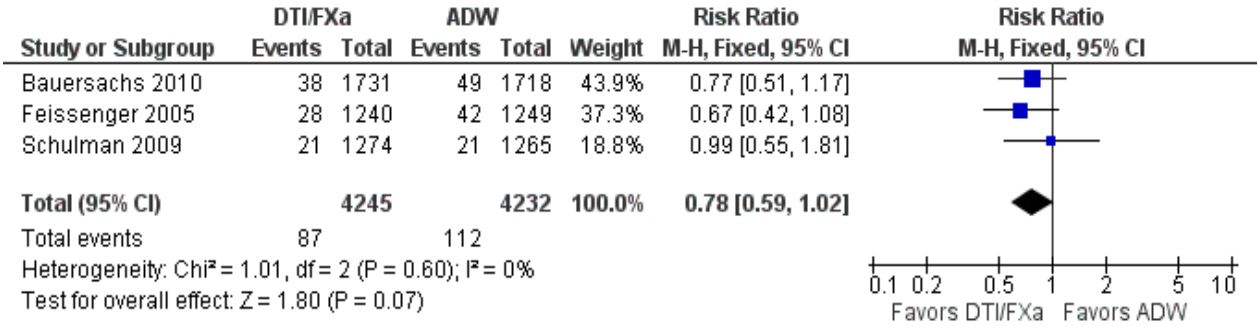
Figure 12. VTE: Recurrent DVT/PE without ximelagatran[a]



[a]The study evaluating ximelagatran is shown but not incorporated into the summary risk ratio in Figures 10, 11, and 12.
[b]Fiessenger 2005 did not report thromboembolic death.

Forest Plots for Studies With Ximelagatran (Venous Thromboembolism)

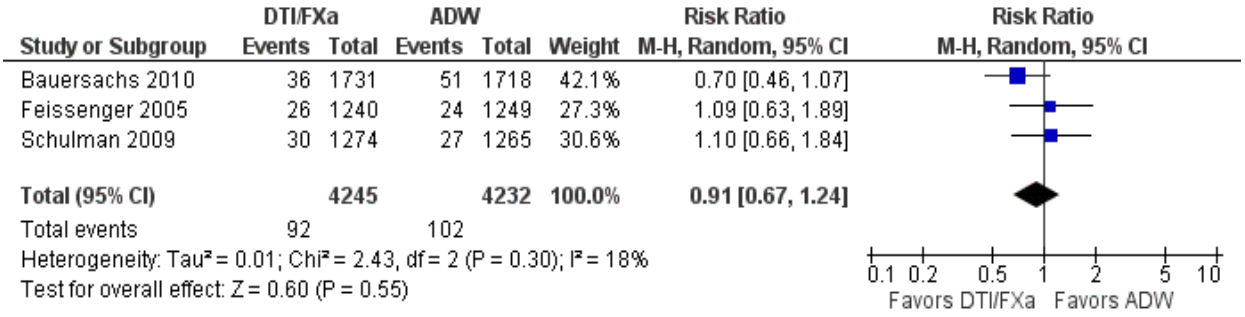
Figure 13. VTE: All-cause mortality with ximelagatran



NOTE: NO Forest Plot for VTE: Death–thromboembolic with ximelagatran.

There were no data on this outcome for the ximelagatran group.

Figure 14. VTE: Recurrent DVT/PE with ximelagatran



KEY QUESTION 3: For patients with mechanical heart valves, what is the comparative effectiveness of newer anticoagulants versus warfarin on the incidence of thromboembolic complications, mortality, HRQOL, and patient treatment experience?

We did not identify any published studies that compared newer anticoagulants to adjusted-dose warfarin in patients with mechanical heart valves. We identified one ongoing trial from our search of www.clinicaltrials.gov (Appendix F).

KEY QUESTION 4: When used for long-term anticoagulation treatment, what is the nature and frequency of adverse effects for newer anticoagulants versus warfarin?

We reported the risks of adverse effects separately in KQ 1 and KQ 2 for each treatment indication. In this section, we examine the risk of adverse effects for all included randomized controlled trials and supplement this by a review of observational studies and FDA alerts. For the analysis of trial data, we examined the summary risk ratios, first in all studies and then by drug class. We excluded studies of ximelagatran for this analysis because this drug has been withdrawn from the market due to adverse effects on liver function.

The range of adverse effect rates for newer oral anticoagulants in the chronic AF studies and VTE studies, respectively, were discontinued due to adverse effects (6.2% to 8.3%; 4.9% to 9.0%); major bleeding (3.6% to 6.2%; 0.8% to 1.6%); fatal bleeding (0.1% to 0.4%; 0.1% reported in one study); myocardial infarction (1.0% to 1.5%; 0.3% reported in one study); and liver dysfunction (0.5% to 1.9%; 1.5% to 3.4%). Compared with the VTE studies, the studies in patients with chronic AF included older patients who may have had more chronic medical conditions and concurrent medications, increasing the risk for adverse effects.[94] In addition, the treatment duration was longer for the chronic AF studies, which may also increase the absolute rates of adverse effects.

The newer oral anticoagulants were associated with a consistent decrease in mortality (0.88; 95% CI, 0.82 to 0.95), without significant variability across studies or differences between drug classes. Similarly, rates of fatal bleeding were consistently lower with newer oral anticoagulants (Table 9). There was a non–statistically significant reduction in major bleeding, but this effect

varied importantly across studies—variability that was not explained by drug class. The unexplained variability in effect for this outcome and others with similar findings suggests the possibility of important differences between individual drugs, even within drug class. The risk of gastrointestinal bleeding was increased with newer oral anticoagulants, with significant variability across studies that was not explained by drug class. Overall, the risk of myocardial infarction was not different from adjusted-dose warfarin. When analyzed by drug class, the risk of myocardial infarction was higher with DTIs than with FXa inhibitors. Drug discontinuation due to adverse effects showed a small, non–statistically significant increased risk ratio, but the risk of discontinuation varied substantially across studies. When analyzed by drug class, DTIs had a higher risk of drug discontinuation compared with FXa inhibitors. The risk of liver dysfunction, an adverse effect that led to the withdrawal of ximelagatran from the market, was not increased.

Table 9. Risk of mortality and adverse effects overall and by drug class

	All studies (n = 5)		Comparison by Drug Class	
Adverse Effect	**Summary Risk Ratios (95% CI)**	**Tests for Heterogeneity**	**Summary Risk Ratios (95% CI)**	**Test for differences between drug classes**
All-cause mortality	0.88 (0.82 to 0.95)	Q = 1.05, I^2 = 0% p < 0.90	DTI: 0.90 (0.79 to 1.01) FXa: 0.88 (0.80 to 0.96)	p = 0.77
Discontinued due to adverse effects	1.23 (0.94 to 1.61)	Q = 57.96, I^2 = 93% p < 0.001	DTI: 1.61 (1.14 to 2.27) FXa: 1.04 (0.84 to 1.28)	p = 0.03
Major bleeding	0.86 (0.71 to 1.04)	Q = 16.08, I^2 = 75% p = 0.003	DTI: 0.93 (0.82 to 1.06) FXa: 0.83 (0.60 to 1.14)	p = 0.49
Fatal bleeding	0.59 (0.46 to 0.77)	Q = 1.57, I^2 = 0% p = 0.81	DTI: 0.72 (0.45 to 1.16) FXa: 0.55 (0.40 to 0.75)	p = 0.35
Gastrointestinal bleeding	1.30 (1.01 to 1.68)	Q=12.04, I^2 = 75% p = 0.007	DTI: 1.50 (1.24 to 1.80) FXa: 1.14 (0.69 to 1.87)	p = 0.05
Myocardial infarction[a]	1.02 (0.76 to 1.39)	Q = 9.37, I^2 = 57% p = 0.05	DTI: 1.35 (0.99 to 1.85) FXa: 0.86 (0.66 to 1.11)	p = 0.03
Liver dysfunction	0.82 (0.61 to 1.11)	Q = 14.48, I^2 = 72% p = 0.006	DTI: 0.88 (0.72 to 1.09) FXa: 0.76 (0.41 to 1.42)	p = 0.65

[a]Only four studies reported this outcome.
Abbreviations: CI = confidence interval; NA = not applicable

Forest Plots for Studies Without Ximelagatran (Adverse Effects)

Figure 15. Adverse effects: All-cause mortality without ximelagatran

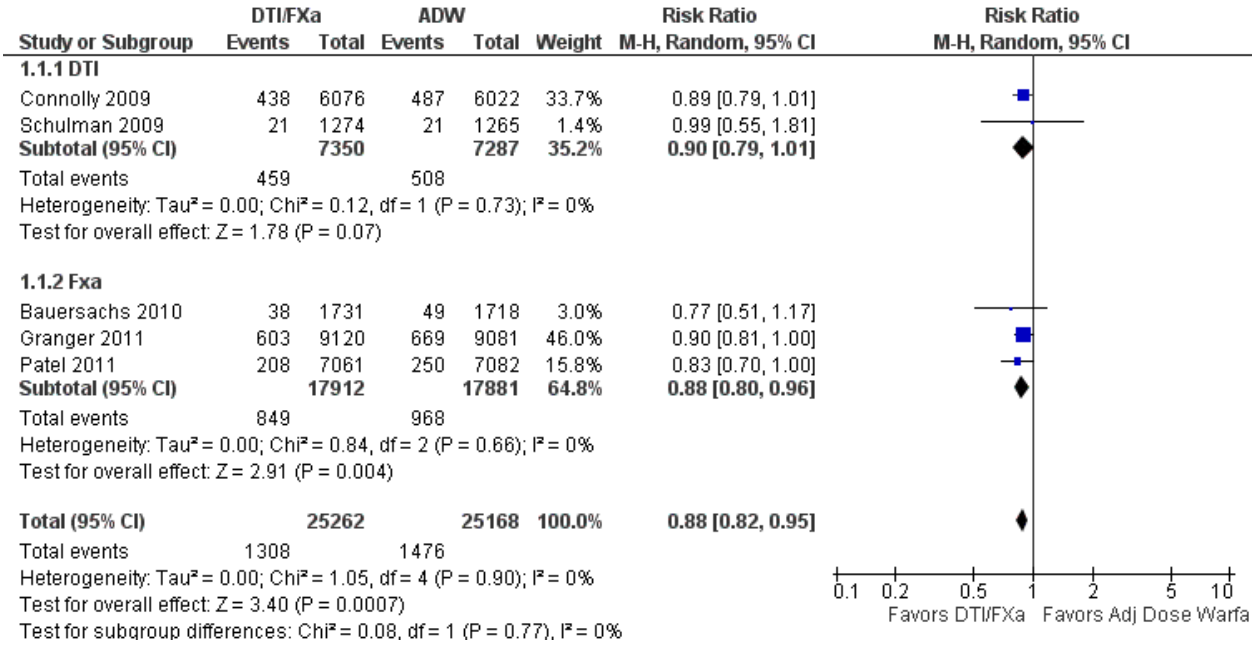


Figure 16. Adverse effects: Discontinued due to adverse effects without ximelagatran

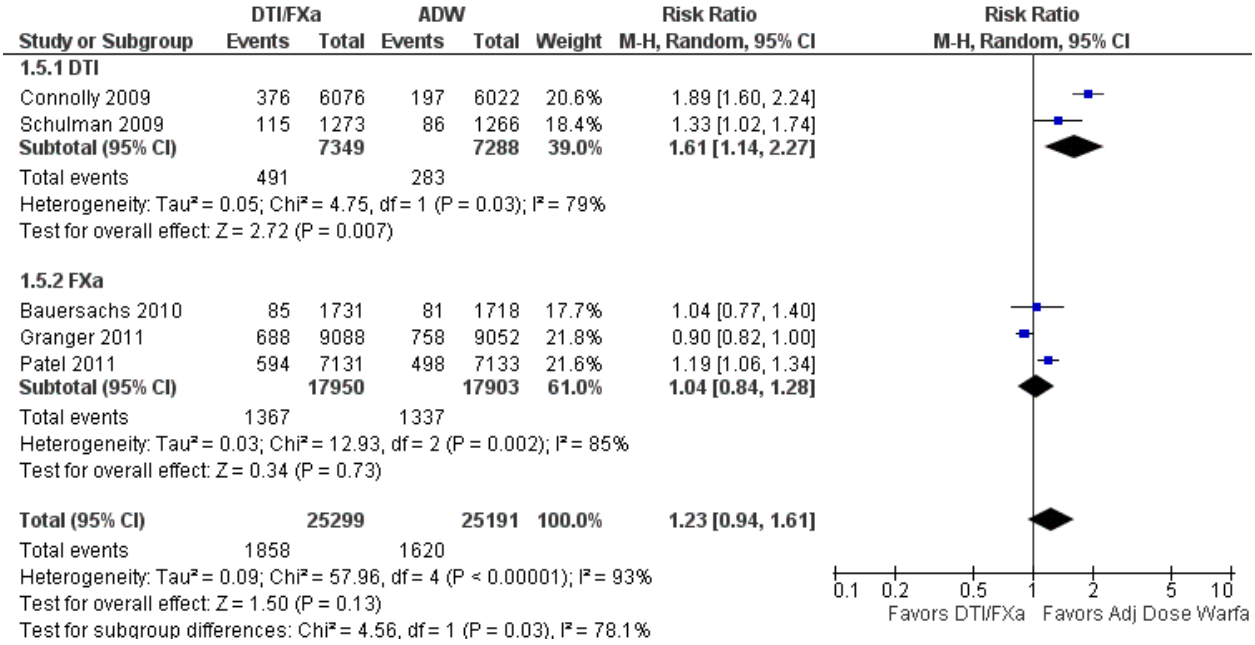


Figure 17. Adverse effects: Major bleeding without ximelagatran

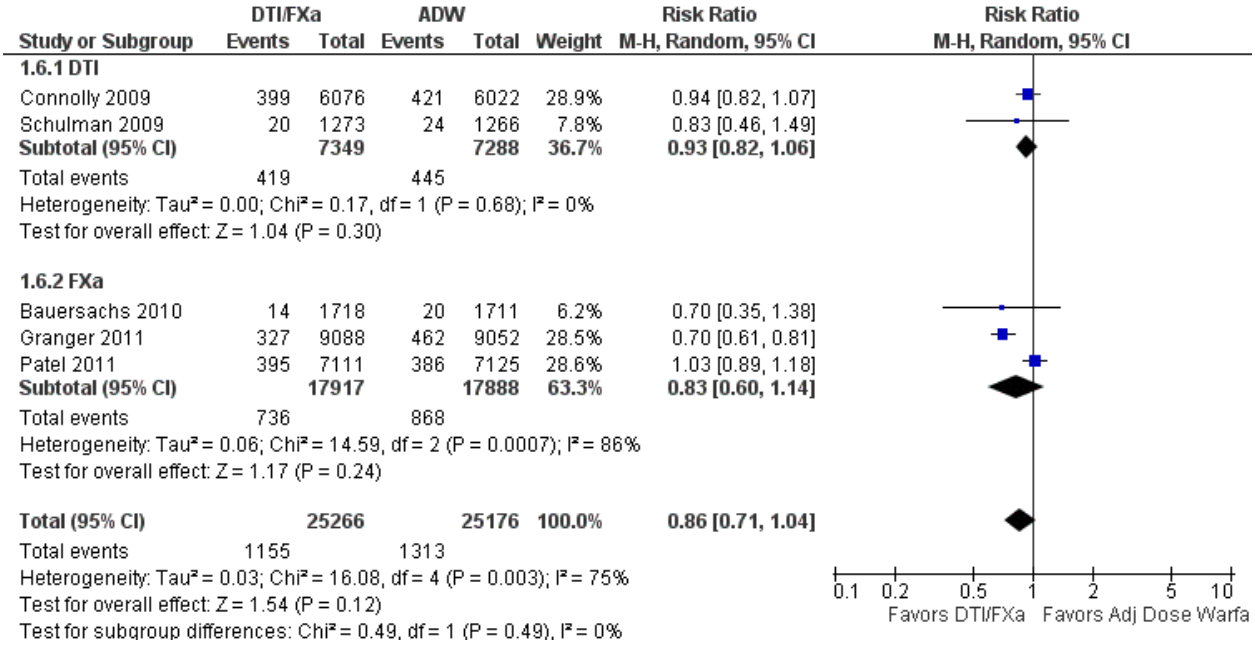


Figure 18. Adverse effects: Fatal bleeding without ximelagatran

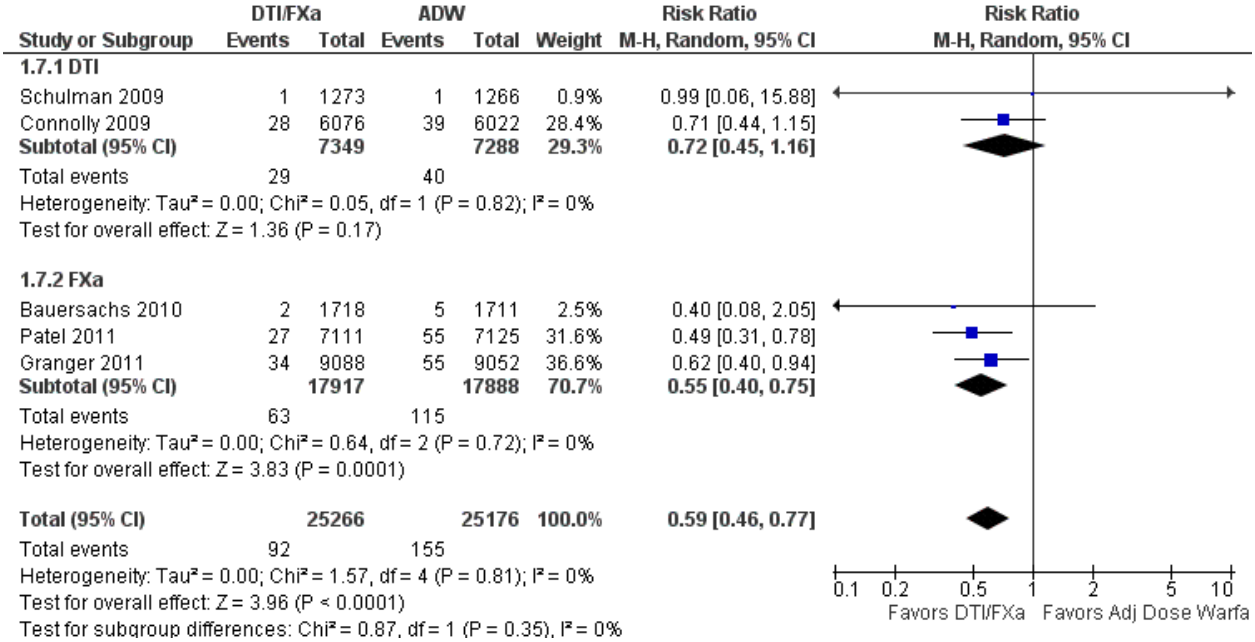


Figure 19. Adverse effects: Gastrointestinal bleeding without ximelagatran

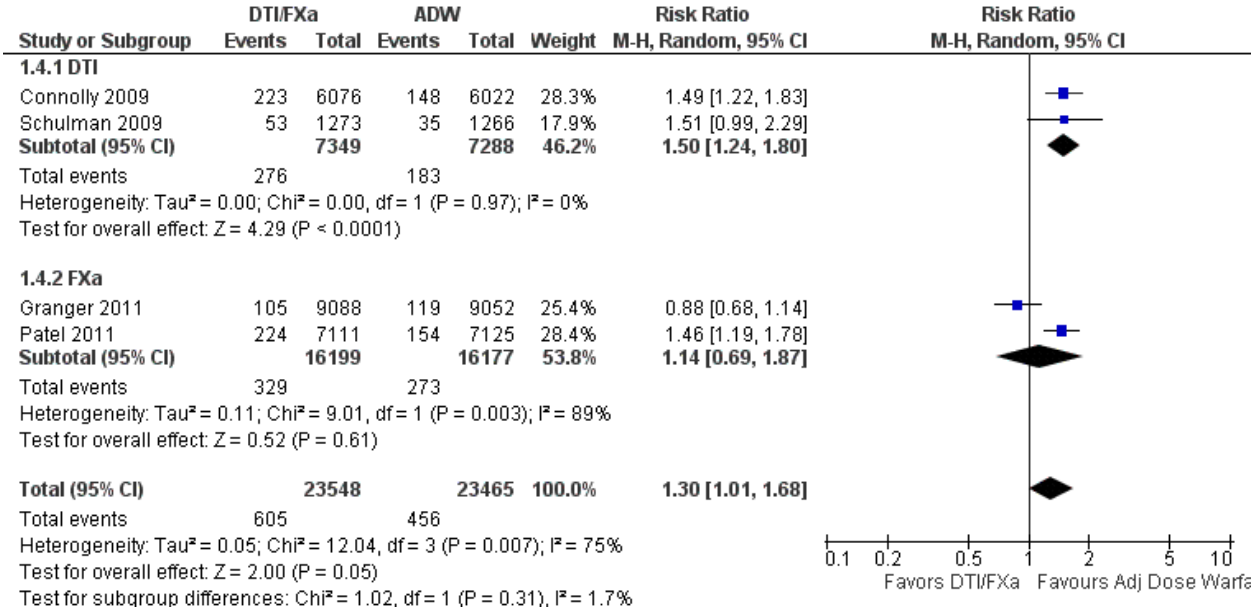


Figure 20. Adverse effects: Myocardial infarction without ximelagatran

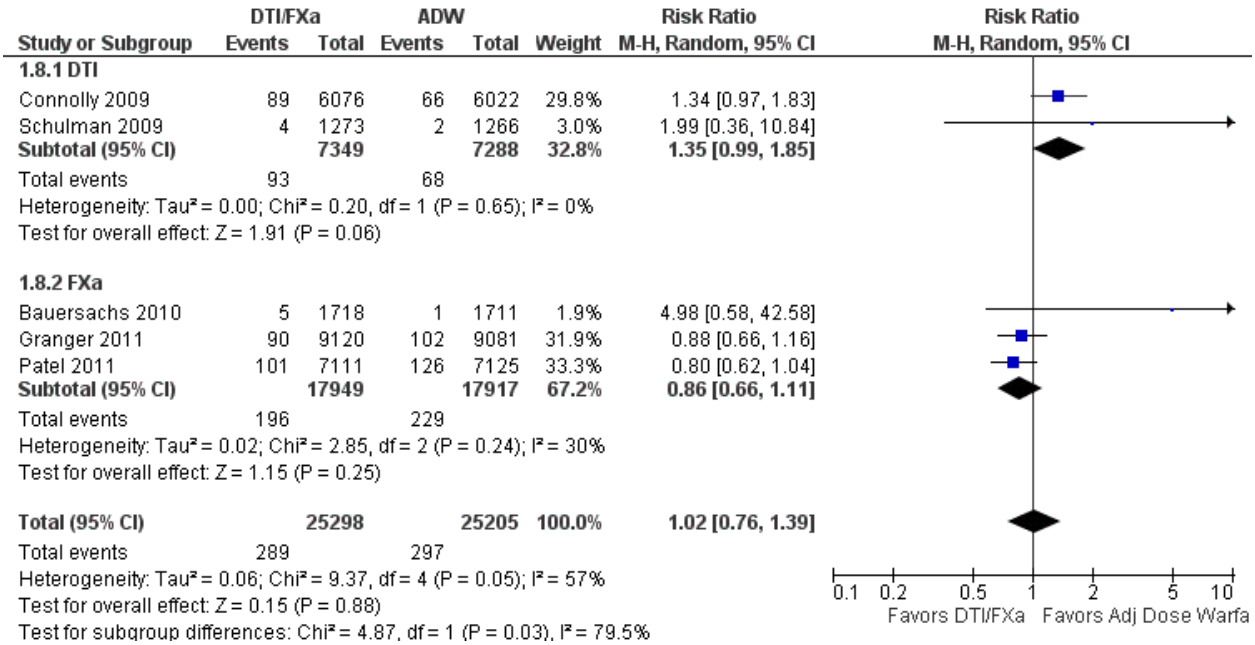
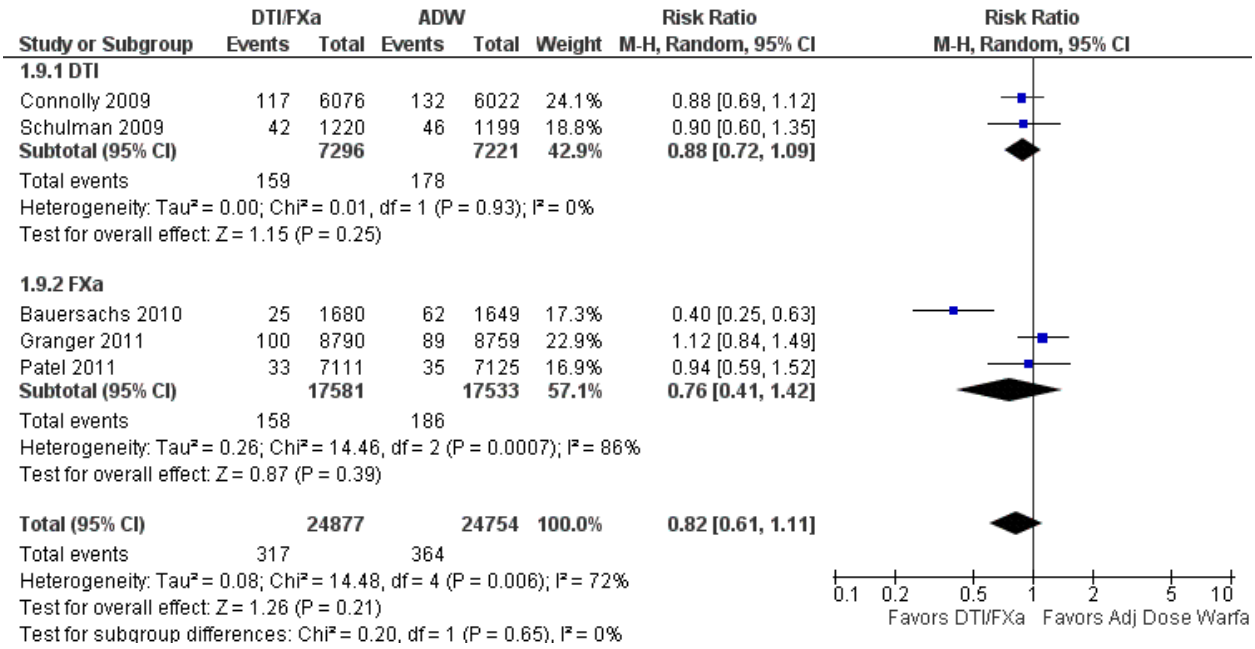


Figure 21. Adverse effects: Liver dysfunction without ximelagatran



RESULTS FROM OBSERVATIONAL STUDIES

We reviewed 377 observational studies on adverse effects of newer oral anticoagulants and excluded 349 on the basis of our inclusion/exclusion criteria. We performed a full-text review on the remaining 28 studies and included 10 of these for data abstraction. Three of the 10 were subgroup analyses from included RCTs and have been discussed previously under KQ 1. Seven of the 10 were case studies, and one was a systematic review. These are discussed below by major outcome.

Bleeding

Three case reports described bleeding associated with dabigatran treatment; one of these was in the context of concurrent use of a thrombolytic medication.

Splenic hemorrhage

A 78-year-old woman presented to the emergency department with acute-onset abdominal pain and vomiting. She had a past medical history of stroke secondary to AF and had been switched 1 week earlier from warfarin to dabigatran 100 mg orally twice daily for thromboprophylaxis. She denied any history of trauma. A computed tomography (CT) scan revealed extravasation from the posterior aspect of the spleen and hemoperitoneum.[81]

Cerebral hemorrhage after concurrent thrombolytic treatment

A 62-year-old diabetic male was started on dabigatran 110 mg twice daily following cardioversion for nonvalvular AF. Following the third dose of dabigatran, he developed aphasia and right hemiplegia. A CT scan revealed a perfusion deficit in the left middle cerebral artery area and no evidence of intracranial hemorrhage. All of his coagulation test values were within normal limits apart from a borderline high prothrombin time. He was started on thrombolytic

therapy and 12 hours later became comatose. A brain CT scan showed a lobar hemorrhage with mass effect. The patient died 2 days later.[77]

Gastrointestinal bleeding and epistaxis

Legrand et al. reported two cases of bleeding in elderly patients on dabigatran treatment.[79] The first case was an 84-year-old woman who had been on dabigatran 75 mg twice daily for AF for a period of 4 months prior to presentation. She presented with rectal bleeding associated with a fecaloma. Her CrCl was 32 mL/min and her body weight was 40 kg. She developed a massive rectal hemorrhage after digital evacuation of the fecaloma and died of hemorrhagic shock despite resuscitation and transfusion of blood and fresh frozen plasma. The trough plasma concentration of dabigatran was very high (5600 ng/mL; expected range, 31-225 ng/mL). The second case was an 89-year-old woman (weight 45 kg), who was given dabigatran 110 mg twice daily for prevention of stroke in AF. At presentation for a scheduled procedure 5 months after starting on dabigatran, she reported recurrent episodes of epistaxis of 1 week duration. Preoperative laboratory evaluation revealed anemia, prolonged baseline coagulation studies, and elevated dabigatran plasma concentration (2670 ng/mL). Her CrCl was low at 29 mL/min. Her procedure was cancelled and dabigatran was discontinued with a favorable outcome.

Thrombosis

Two case reports described ischemic stroke in patients taking dabigatran and successful treatment with thrombolytic medication.

Ischemic stroke

One study reported a 48-year-old woman with an acute onset of left-sided hemiplegia and hemihypesthesia, who was found to have an ischemic stroke in the area of the right middle cerebral artery.[78] The patient had a history of AF and was randomized to dabigatran on the RELY-ABLE study (NCT00808067). She was started on thrombolytic therapy with recombinant tissue plasminogen activator almost 7 hours after her last dose of dabigatran. All coagulation tests were within normal limits, apart from fibrinogen, which was borderline high. The patient improved and suffered no complications.

Another study reported a 76-year-old woman with a history of diabetes and hypertension, who presented with acute right-sided hemiplegia and aphasia.[80] The patient was on dabigatran 220 mg once daily as thromboprophylaxis following knee replacement therapy. She was started on thrombolytic therapy 15 hours following her last dose of dabigatran. Treatment was completed successfully with no bleeding complications.

Myocardial Infarction

We identified a single systematic review that addressed adverse effects for newer oral anticoagulants. This review of seven mostly short-term trials evaluated dabigatran for heterogeneous indications and found a higher risk of myocardial infarction or acute coronary syndrome (OR 1.33; 95% CI, 1.03 to 1.71) compared with warfarin, enoxaparin, or placebo.[70]

We did not identify any primary reports of observational studies evaluating MI.

Mechanical Valve Thrombosis

Clinical experience is currently limited as to the efficacy and safety of the newer oral anticoagulants for thromboprophylaxis in patients with prosthetic valves. As noted in KQ 3, no trials have published outcomes for this indication. We identified a single case report of anticoagulation failure with dabigatran. A 62-year-old man with a bileaflet mechanical aortic valve (St. Jude Medical) and a history of AF was switched, upon his request, from warfarin to dabigatran 150 mg twice daily for thromboprophylaxis.[82] Eleven months later, he presented with facial droop and hemiparesis, which resolved over 24 hours. An MRI study of the patient's brain showed multiple cerebral ischemic infarcts, and later a transesophageal echocardiogram showed a thrombus on the posterior disc of the prosthetic aortic valve. Dabigatran was stopped, and the patient was started on phenindione with 100 mg aspirin. A followup transesophageal echocardiogram showed disappearance of the thrombus.

SUMMARY OF FDA BULLETINS

QuarterWatch is a nonprofit Federally certified Institute for Safe Medication Practice, which monitors adverse events reported to the FDA through MedWatch. On October 6, 2011, a report by QuarterWatch stated that, within months of its release, dabigatran generated more reports (307) than 98.7 percent of other drugs monitored. Reported adverse events were equally divided between hemorrhagic and thrombotic events. Only 36 percent of reports listed that dabigatran was used for its approved indications. Another 46 percent reported that the drug was used to prevent blood clots or stroke in general terms. Furthermore, other reports clearly stated the drug was used for off-label indications such as thromboprophylaxis after orthopedic surgery.[103]

On January 12, 2012, QuarterWatch released a report of serious adverse events linked to dabigatran. During the first quarter of 2011, 932 serious adverse events were linked to dabigatran, including 120 deaths, 25 permanent disabilities, and 543 hospitalizations. Of the 932 cases, 505 involved hemorrhage—more than any other monitored drug, including warfarin. The adverse events occurred in elderly patients with a median age of 80 years, compared with 56 years in all other monitored drugs. The report raised questions about using a fixed dose for all patient populations. Older age and impaired renal function lead to a longer half-life and higher drug levels. Currently, dosage adjustment is recommended for only patients with severe renal impairment. However, mild and moderate renal impairment can increase dabigatran levels by 50 percent and 300 percent, respectively. The report recommends that the FDA and the manufacturer reevaluate the dose of dabigatran for elderly patients and those with moderate renal impairment.[104]

The FDA Advisory Committee Briefing Document on adverse events associated with rivaroxaban reported that, in the ROCKET-AF study, the posttreatment discontinuation events were higher in patients on rivaroxaban (12.63 per 100 patient years) compared with patients on adjusted-dose warfarin (8.36 per 100) (HR 1.51; 95% CI, 1.02 to 2.23). This higher event rate may be due to fewer patients transitioning from rivaroxaban to warfarin having a therapeutic INR during the period of 3 to 30 days after treatment. This finding points to the need for particular care when transitioning patients from short-acting newer oral anticoagulants to warfarin.

SUMMARY AND DISCUSSION

We identified eight good-quality RCTs comparing newer oral anticoagulants to conventional anticoagulant therapy with warfarin, either alone or in combination with low molecular weight heparin. Of these eight studies, five compared newer oral anticoagulants to warfarin for prevention of stroke in nonvalvular AF. Three studies compared newer oral anticoagulants with a combination of parenteral anticoagulation and warfarin for management of VTE. Overall, newer oral anticoagulants were no worse and were—for some clinical outcomes—superior to adjusted-dose warfarin. However, in the absence of head-to-head comparisons between the newer anticoagulants, our analysis may have failed to detect important differences between drug classes or between individual drugs. Comparative effects on HRQOL and patient experience were not reported. The observational literature on adverse effects is sparse, consisting only of case-reports describing bleeding and thrombotic events. The FDA has issued alerts that it is evaluating reports of serious bleeding with dabigatran, mostly in older adults or those with impaired renal function. Our main findings and the strength of evidence (SOE) for each major outcome are summarized by key question in the next section.

SUMMARY OF EVIDENCE BY KEY QUESTION

Key Question 1—Chronic Atrial Fibrillation

Table 10 summarizes the findings and SOE for each major outcome. In brief, newer oral anticoagulants were associated with a lower rate of all-cause mortality compared with warfarin (high SOE). Newer oral anticoagulants were also associated with fewer hemorrhagic strokes (moderate SOE). For these outcomes, we estimated the absolute risk difference to be 8 fewer deaths and 4 fewer hemorrhagic strokes for every 1000 patients treated with the newer oral anticoagulants compared with adjusted-dose warfarin over approximately 2 years of treatment. However, VTE-related mortality and ischemic stroke were not significantly lower with newer oral anticoagulants.

For dabigatran, the comparative effects on vascular outcomes were dependent, in part, on the quality of adjusted-dose warfarin treatment. While anticoagulation control in the VHA appears to be at least as good as that found in clinical trials, the ROCKET-AF study had a mean TTR that was worse than typical standards. In the RE-LY study, the advantages of dabigatran were greater at sites with poor INR control than at those with good INR control for all vascular events, nonhemorrhagic events, and mortality. Warfarin and dabigatran showed comparable outcomes in centers with good mean TTR.[99]

Return to Contents

Table 10. Summary of the strength of evidence for KQ 1—chronic AF

Number of Studies (Subjects)	Domains Pertaining to SOE				SOE
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)[a]
All-cause mortality					**High SOE**
3 (44,442)	RCT/Good	Consistent	Direct	Precise	RR = 0.88 (0.82 to 0.95) RD = 8 (3 to 11) fewer deaths/1000
VTE-related mortality					**Moderate SOE**
2 (30,299)	RCT/Good	Some inconsistency	Direct	Some imprecision	RR = 0.77 (0.57 to 1.02)
Ischemic stroke					**Moderate SOE**
3 (44,442)	RCT/Good	Consistent	Direct	Some imprecision	RR = 0.89 (0.78 to 1.02)
Hemorrhagic stroke					**Moderate SOE**
3 (44,442)	RCT/Good	Some inconsistency	Direct	Some imprecision	RR = 0.45 (0.31 to 0.68) RD = 4 (2 to 5) fewer hemorrhagic strokes/1000
Discontinuation due to adverse effects					**Low SOE**
3 (44,502)	RCT/Good	Important inconsistency	Direct	Important imprecision	RR = 1.26 (0.86 to 1.84)
Major bleeding					**Low SOE**
3 (44,474)	RCT/Good	Important inconsistency	Direct	Some imprecision	RR = 0.88 (0.70 to 1.09)

Abbreviations: CI = confidence interval; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; SOE = strength of evidence

[a]The risk difference and 95% CI are based on the assumed risk for the control group (using the median control group risk across studies) and the relative intervention effects (and 95% CI).

Key Question 2—Venous Thromboembolism

Table 11 summarizes the findings and SOE for each major outcome. In comparison with the chronic AF studies, there are fewer studies and patients enrolled and shorter duration of followup for this population. The summary risk ratio favored newer oral anticoagulants for all-cause mortality, VTE-related mortality, recurrent VTE, and major bleeding, but in each instance the CI included no effect. Overall, these results support the conclusion that newer anticoagulants are no worse than adjusted-dose warfarin for major clinical outcomes.

Table 11. Summary of the strength of evidence for KQ 2—venous thromboembolism

Number of Studies (Subjects)	Domains Pertaining to SOE				SOE
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
All-cause mortality					**Moderate SOE**
2 (5988)	RCT/Good	Consistent	Direct	Some imprecision	RR = 0.84 (0.59 to 1.18)
VTE-related mortality					**Low SOE**
2 (5988)	RCT/Good	Consistent	Direct	Important imprecision	RR = 0.56 (0.19 to 1.69)
Recurrent DVT/PE					**Moderate SOE**
2 (5988)	RCT/Good	Some inconsistency	Direct	Some imprecision	RR = 0.86 (0.55 to 1.33)
Discontinuation due to adverse effects					**Moderate SOE**
2 (5988)	RCT/Good	Consistent	Direct	Some imprecision	RR = 1.19 (0.93 to 1.51)
Major bleeding					**Moderate SOE**
2 (5988)	RCT/Good	Consistent	Direct	Some imprecision	RR = 0.77 (0.49 to 1.20)

Abbreviations: CI = confidence interval; NA = not applicable; NR = not reported; RCT = randomized controlled trial; RR = risk ratio; SOE = strength of evidence

Key Question 3—Mechanical Heart Valves

We did not identify any published studies that compared newer oral anticoagulants to adjusted-dose warfarin in patients with mechanical heart valves. Current evidence is insufficient to estimate the relative effects of newer anticoagulants compared with warfarin for patients with mechanical heart valves.

Key Question 4—Adverse Effects

The adverse effects of newer oral anticoagulants compared with adjusted-dose warfarin were generally consistent across treatment indications. After excluding the ximelagatran studies, the summary risk ratio for discontinuation due to adverse effects was higher for newer anticoagulants, but this result was not statistically significant. The effects on bleeding rates are complex. *Fatal bleeding* was significantly lower for newer oral anticoagulants, an effect that was consistent across drug classes. *Major bleeding* was lower for newer oral anticoagulants, but this effect was not statistically significant and varied significantly across studies. In contrast, *gastrointestinal bleeding* was increased with newer oral anticoagulants. Gastrointestinal bleeding was significantly increased in patients treated with dabigatran and rivaroxaban compared with warfarin.[99] The efflux of dabigatran by p-glycoprotein transporters into the gastrointestinal tract may be a mechanism for this finding.[105] Both the clinical trial subgroup analyses and the FDA reports suggest that bleeding risk may be increased in older adults and in those with impaired renal function. Further, the differential bleeding risk may be related to the quality of warfarin anticoagulation.

Another potential adverse effect is myocardial infarction. We found no increased risk when combining results from all studies. However, for dabigatran alone, we found an elevated risk (RR = 1.35) that approached statistical significance. A separate meta-analysis, primarily of short-term trials, found a statistically significant increase in myocardial infarction or acute coronary syndrome (OR 1.33; 95% CI, 1.03 to 1.71).[70] Liver dysfunction was substantially higher for ximelagatran, a drug withdrawn from the market due to this adverse effect. Elevated rates of liver dysfunction have not been seen with the other newer oral anticoagulants. The SOE was low for several outcomes because CIs included clinically important differences and there was unexplained variability in treatment effects.

Return to Contents

Table 12. Summary of findings for KQ 4—adverse effects

Outcome	Strength of Evidence	Summary
Drug discontinuation due to adverse effects	Low	Across all indications, discontinuation due to adverse effects was higher with newer oral anticoagulants (RR 1.23; 95% CI, 0.94 to 1.61), but the 95-percent CI was large and included no effect. In subgroup analysis, rates of discontinuation were higher for dabigatran compared with FXa inhibitors. A clinically important increase in drug discontinuation compared with warfarin cannot be excluded.
Major bleeding	Low	Across all indications, the risk of major bleeding was lower with newer oral anticoagulants (RR 0.86; 95% CI, 0.71 to 1.04), but the 95-percent CI was large and included no effect. A clinically important decrease in major bleeding compared with warfarin cannot be excluded. In December 2011, the FDA issued a notice that it was evaluating reports of serious bleeding with dabigatran.
Fatal bleeding	Moderate	Across all indications, the risk of fatal bleeding was lower with newer oral anticoagulants (RR 0.59; 95% CI, 0.46 to 0.77). Risk difference was 1 fewer death per 1000 patients.
Gastrointestinal bleeding	Moderate	Across all indications, the risk of gastrointestinal bleeding was increased with newer oral anticoagulants (RR 1.30; 95% CI, 1.17 to 1.49). Risk difference was 1 additional gastrointestinal bleed per 1000 patients.
Myocardial infarction	Low	Across all indications, the risk of myocardial infarction was not different with newer oral anticoagulants (RR 1.02; 95% CI, 0.76 to 1.39). In a subgroup analysis, the risk was increased with dabigatran (RR 1.35; CI, 0.99 to 1.85) compared with FXa inhibitors (RR 0.86; CI, 0.66 to 1.11); p = 0.03 for between-group comparison.
Liver dysfunction	Moderate	Across all indications, the risk of liver dysfunction was not different with newer oral anticoagulants (RR 0.82; 95% CI, 0.61 to 1.11).

CLINICAL AND POLICY IMPLICATIONS

Clinicians have used adjusted-dose warfarin to prevent systemic emboli related to chronic AF, recurrent VTE, or mechanical heart valves for decades. The benefits and limitations of warfarin are well known. Adjusted-dose warfarin reduces the risk of stroke by 62 percent in patients with chronic AF, the most common indication for anticoagulation in veterans, compared with a 19-percent reduction with aspirin.[74] The primary limitations of warfarin are the variability in anticoagulant effect together with drugñdrug and drugñfood interactions that require frequent laboratory monitoring. A recent VA multicenter trial showed that home warfarin monitoring compared with high-quality conventional monitoring did not affect stroke rate, major bleeding episodes, or mortality rates but did lead to small improvements in patient satisfaction and quality of life.[23]

Our review shows that the newer oral anticoagulants are a viable option for long-term anticoagulation. DTIs and FXa inhibitors have the advantage of more predictable anticoagulation, fewer drug–drug interactions, and equivalent or better mortality and vascular outcomes compared with warfarin. The data are most robust for chronic AF, with fewer studies evaluating use to prevent recurrent VTE and no studies in patients with mechanical heart valves.

The absolute benefits for clinical outcomes are small. For chronic AF, the number needed to treat compared with warfarin over a 2-year period is 132 to prevent 1 death, 260 to prevent 1

hemorrhagic stroke, and 758 to prevent 1 fatal bleeding episode. Because no studies reported effects on patient experience and HRQOL, effects on these important outcomes are unknown. A recent systematic review[74] found that, for most patients, warfarin therapy does not have important negative impacts on quality of life.

Safety and Use of Newer Oral Anticoagulants in VA

For clinicians and policymakers, important questions remain. These include questions about which patients are most likely to benefit and which, if any, of the new drugs are most effective. Patients with higher bleeding risks and markedly impaired renal function were excluded from these studies. Clinicians should also consider the quality of INR monitoring available to their patients. In a prespecified subgroup analysis, Wallentin et al.[99] found that the advantage of dabigatran over warfarin in terms of major bleeding rates was evident only at sites with poor-quality anticoagulation (TTR <57.1%), while rates of major bleeding were not significantly different at sites with higher quality anticoagulation. Hence, better INR controlled to similar bleeding rates between both groups. In the VHA, time in treatment exceeds this threshold, but newer oral anticoagulants could have important advantages for individual patients who have difficulty maintaining a therapeutic INR. However, since newer oral anticoagulants are dosed twice daily, compared with once daily dosing of warfarin, better outcomes would not be expected if poor medication adherence were the cause of the subtherapeutic INR. A pragmatic concern related to adherence is the FDA notification that dabigatran may lose potency if placed in pill boxes and that it should be dispensed and stored only in the original bottle or blister package.[106]

Although newer oral anticoagulants are associated with a lower risk of fatal bleeding compared with warfarin, this advantage may be tempered by the increased risk of gastrointestinal bleeding with dabigatran.[70,84,91,99] The FDA is currently evaluating reports of high rates of serious bleeding. The reports of bleeding appear to be concentrated in older adults and those with impaired renal function. Another worrisome finding is elevated rates of myocardial infarction with dabigatran, although the strength of evidence for this finding is low. The higher myocardial infarction rate could be related to the drug specifically, to differences in the patient sample studied, or to the protective effect of warfarin on myocardial infarction.[69] Alternatively, increased risk of myocardial infarction maybe due to a rebound thrombin effect after the discontinuation of dabigatran, a DTI.[105] VA should carefully consider the potential benefits and harms, along with patients at higher risk for adverse effects when establishing eligibility criteria for newer oral anticoagulants.

Clinicians may wonder whether the benefits of newer oral anticoagulants observed in chronic AF will extend to those patients with mechanical heart valves. While this is possible, we caution against extrapolating these data since the INR target for patients with mechanical valves is higher and the dosing may differ. A Phase II trial is currently underway comparing three different doses of dabigatran.

Guidelines

The 2011 American College of Cardiology Guideline update for the management of AF was published before the studies evaluating rivaroxaban and apixaban were published. It recommends dabigatran as a useful alternative to warfarin in patients with chronic nonvalvular AF who do not have severe renal failure or advanced liver disease.[9,107] This guideline also noted that

patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran. The more recent American College of Chest Physicians guidelines recommend dabigatran 150 mg for prevention of stroke in AF over the use of adjusted-dose vitamin K antagonists.[25] Both the nonprofit QuarterWatch and other groups have raised concern or made recommendations for dosing adjusted to age or renal function. The European Society of Cardiology recommends dabigatran at a dose of 150 mg be used in patients with a low risk of bleeding, while the lower dose of 110 mg is reserved for those with a high risk of bleeding.[108] In Canada, dabigatran is approved for the prevention of stroke in AF, and dabigatran 110 mg twice daily is recommended for elderly patients 80 years of age or older or those at a high risk of bleeding.[109] In the United States, the FDA has only approved the 150 mg dose and recommends a dose of 75 mg twice daily for patients with CrCl of 15 to 30 mL/min.[110]

Cost and Cost-Effectiveness

An important disadvantage of the newer oral anticoagulants is their higher drug acquisition costs. The cost-effectiveness of dabigatran compared with warfarin for stroke prophylaxis has been evaluated in three recent publications.[93,94,111] Each of these analyses found dabigatran to be cost-effective. However, the studies varied in the factors affecting cost-effectiveness, including drug costs used in the analyses, assumptions about the adequacy of warfarin anticoagulation, and the baseline risk of bleeding or stroke. Depending on the study, cost-effectiveness increased with lower drug costs for the newer oral agents, worse INR control, and higher baseline risk of bleeding or stroke. However, none of these analyses considered the possible expansion in the pool of patients who might be offered and choose chronic anticoagulation with newer agents. An analysis of Medicare beneficiaries showed that only two-thirds of patients with chronic AF who were ideal candidates for anticoagulation were discharged on warfarin. Although an expansion in the indicated use of anticoagulation would be beneficial clinically, it would increase health care costs since these drugs have been shown to be cost-effective, not cost-saving. In an era where health systems and individuals are considering costs ever more carefully, a budget impact analysis would be useful to VA policymakers. Policymakers will have to consider how best to meet the needs of patients while considering health care value. A study by Rose et al. has made the business case for quality improvement programs to improve adjusted-dose warfarin treatment as another viable alternative.[100]

STRENGTHS AND LIMITATIONS

Our study has a number of strengths, including a protocol-driven review, a comprehensive search, careful quality assessment, and rigorous quantitative synthesis methods. Our study, and the literature, also has limitations. An important limitation is the lack of head-to-head comparisons of the newer oral anticoagulants and an inability to examine the comparative effectiveness across classes (DTIs versus FXa inhibitors) or within class. As the literature grows, subgroup analyses or a network meta-analysis that includes studies comparing warfarin with placebo or aspirin might better address this question—but this comparison was beyond the scope or our review. Based on currently available data, important differences in efficacy or frequency of adverse effects could be present but undetected. A limitation of the literature is the relatively short-term experience with these drugs. It is possible that additional adverse effects may emerge with more widespread and longer duration use.

RECOMMENDATIONS FOR FUTURE RESEARCH

We used the framework recommended by Robinson et al.[112] to identify gaps in evidence and classify why these gaps exist (Table 13).

Table 13. Evidence gaps and future research

Evidence Gap	Reason	Type of Studies to Consider
Absence of data for patients with mechanical heart valves	Insufficient information	Multicenter RCTs
Uncertain effects on patient experience and health-related quality of life	Insufficient information	Multicenter RCTs and/or qualitative studies
Uncertain relative benefits across and within newer oral anticoagulant drug classes	Insufficient information	Multicenter RCTs comparing newer anticoagulants with each other and network meta-analyses
Uncertain effects on health system costs	Insufficient information	Budget impact analysis
Effects on thrombosis and systemic embolism when newer anticoagulants are stopped prior to invasive procedures	Insufficient information	Pharmacokinetic studies; observational studies
Management of patients on newer anticoagulants with bleeding complications	Insufficient information	RCTs; observational studies
Adverse effects with long-term use and in usual clinical practice	Insufficient information	Observational studies

Abbreviation: RCT = randomized controlled trial

Return to Contents

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Return to Contents

APPENDIX A. SEARCH STRATEGIES

Table A-1. Search strategy for RCTs (PubMed, February 2012)

Step	Category	Terms	Result
1	Newer anticoagulants	dabigatran OR desirudin OR ximelagatran OR edoxaban OR rivaroxaban OR apixaban OR betrixaban OR YM150 OR razaxaban OR "factor Xa inhibitors" OR "factor Xa inhibitor" OR "fxa inhibitors" OR "fxa inhibitor" OR "direct thrombin inhibitor" OR "direct thrombin inhibitors" OR DTIs OR "novel anticoagulants" OR "new anticoagulants" OR "novel anticoagulant" OR "new anticoagulant" OR "newer anticoagulants" OR "newer anticoagulant" **AND**	3289
2	Disorders of interest	"Venous Thrombosis"[Mesh:noexp] OR "Venous Thromboembolism"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Atrial Fibrillation"[Mesh] OR "Heart Valve Prosthesis"[Mesh] OR "Aortic Valve"[Mesh] OR "Mitral Valve"[Mesh] OR deep vein thrombosis OR AF OR dvt OR PE OR pulmonary embolism OR mechanical heart valve OR mechanical heart valves OR "mechanical valve" OR "mechanical valves" OR "mechanical mitral" OR "mechanical aortic" OR thromboembolism AND	217463
3	Study designs	randomized controlled trial[Publication Type] OR random*	711597
4	Combine results and apply limits	#1 AND #2 AND #3 English, Publication Date from 2001 to 2011	320

Table A-2. Search strategy for observational studies (February 2012)

Step	Category	Terms	Results
1	Newer anticoagulants	Dabigatran[tiab] OR desirudin[tiab] OR edoxaban[tiab] OR rivaroxaban[tiab] OR apixaban[tiab] OR betrixaban[tiab] OR YM150[tiab] OR razaxaban[tiab] OR "dabigatran etexilate"[Supplementary Concept] OR "desirudin"[Supplementary Concept] OR "edoxaban"[Supplementary Concept] OR "rivaroxaban"[Supplementary Concept] OR "apixaban"[Supplementary Concept] OR "betrixaban"[Supplementary Concept] OR "razaxaban hydrochloride"[Supplementary Concept] OR "factor Xa, Glu-Gly-Arg-"[Supplementary Concept] OR "KFA1411"[Supplementary Concept] **AND**	1112
2	Disorders of interest	"Venous Thrombosis"[Mesh:noexp] OR "Venous Thromboembolism"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Atrial Fibrillation"[Mesh] OR "Heart Valve Prosthesis"[Mesh] OR "Aortic Valve"[Mesh] OR "Mitral Valve"[Mesh] OR "deep vein thrombosis"[tiab] OR "atrial fibrillation"[tiab] OR dvt[tiab] OR "pulmonary embolism"[tiab] OR "mechanical heart valve"[tiab] OR "mechanical heart valves"[tiab] OR "mechanical valve"[tiab] OR "mechanical valves"[tiab] OR "mechanical aortic"[tiab] OR thromboembolism[tiab] **AND**	145374
3	Study designs	("evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention studies"[MeSH Terms] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH Terms] OR "case-control"[tiab] OR "cohort studies"[MeSH Terms] OR cohort[tiab] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tiab] OR "follow up"[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab] OR "Case Reports"[Publication Type] OR "case report"[tiab] OR "case series"[tiab] OR observational[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	4927238

Step	Category	Terms	Results
3	Combine results and apply limits	#1 AND #2 AND #3 Publication Date from 2001 to 2012	278
4	Additional study designs	"Case Reports"[Publication Type] OR "Case-Control Studies"[Mesh]) OR "Cohort Studies"[Mesh] OR "case report"[tiab] OR cohort[tiab] OR case-control[tiab] OR "case series"[tiab]	2841521
5	Combine results and apply limits	#1 AND #2 AND #4 Publication Date from 2001 to 2012	47

Table A-3. Search strategy for systematic reviews (PubMed, February 2012)

Step	Category	Terms	Results
1	New oral anticoagulants	Dabigatran[tiab] OR desirudin[tiab] OR edoxaban[tiab] OR rivaroxaban[tiab] OR apixaban[tiab] OR betrixaban[tiab] OR YM150[tiab] OR razaxaban[tiab] OR "dabigatran etexilate"[Supplementary Concept] OR "desirudin"[Supplementary Concept] OR "edoxaban"[Supplementary Concept] OR "rivaroxaban"[Supplementary Concept] OR "apixaban"[Supplementary Concept] OR "betrixaban"[Supplementary Concept] OR "razaxaban hydrochloride"[Supplementary Concept] OR "factor Xa, Glu-Gly-Arg-"[Supplementary Concept] OR "KFA1411"[Supplementary Concept]	1121
2	Disorders of interest	"Venous Thrombosis"[Mesh:noexp] OR "Venous Thromboembolism"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Atrial Fibrillation"[Mesh] OR "Heart Valve Prosthesis"[Mesh] OR "Aortic Valve"[Mesh] OR "Mitral Valve"[Mesh] OR "deep vein thrombosis"[tiab] OR "atrial fibrillation"[tiab] OR dvt[tiab] OR "pulmonary embolism"[tiab] OR "mechanical heart valve"[tiab] OR "mechanical heart valves"[tiab] OR "mechanical valve"[tiab] OR "mechanical valves"[tiab] OR "mechanical aortic"[tiab] OR thromboembolism[tiab]	145502
3	Study designs	Systematic[sb]	170174
3	Combine results and apply limits	Search #1 AND #2 AND #3 Publication Date from 2001 to 2012	64

Return to Contents

APPENDIX B. STUDY SELECTION FORM

Criteria for Inclusion and Exclusion of RCTs

Inclusion criteria:

- An RCT or a secondary data analysis from an RCT comparing a newer anticoagulant to an eligible comparator (warfarin and LMWH are the two comparators we are accepting for the various key questions)
- Sample population with history of chronic nonvalvular AF, deep venous thromboembolism, or mechanical valve replacement. Atrial fibrillation may be assessed by any accepted threshold on any valid diagnostic tool (e.g., electrocardiogram and/or echocardiogram).
- Sample population ≥18 years of age
- Outpatient setting (community clinic, medical clinic or office, or transitioning from inpatient for acute treatment to long-term outpatient management)
- Random allocation to the intervention groups
- Reports at least one of the included outcomes:
    - **KQs 1–3:** The main outcome is a thromboembolic event. Thromboembolic events must be documented radiologically and produce clinical symptoms. Asymptomatic thromboembolism (e.g., detected on surveillance imaging) will not be included.
    - **KQs 1–3**: Other outcomes are mortality, health-related quality of life, and patient treatment experience—the latter two measured by a validated instrument.
    - **KQ 4:** Adverse effects will be specific to the interventions examined and will include bleeding complications, myocardial infarction, and gastrointestinal adverse effects.
- Study duration of at least 6 months (KQ 2 acute treatment) or at least 12 months (KQ 1, KQ 2 chronic treatment, KQ 3, KQ 4)
- Peer-reviewed publication

Exclusion criteria:

- Non-English language publication
- Cross-sectional studies
- Pregnant population
- Studies with sample size <50
- Studies with <6 months postrandomization outcomes

Return to Contents

Eligibility Criteria for Observational Studies

- **Patients**: chronic atrial fibrillation or VTE treated with an oral DTI or FXa inhibitor
- **Comparator**: none or adjusted-dose warfarin
- **Outcomes**: adverse events
- **Timing**: ≥ 3months use
- **Setting**: any outpatient
- **Study designs**:
    - Comparative: secondary analyses from RCTs (including patient level meta-analysis), cohort studies (prospective or retrospective-including analyses of claims databases), case control, cross-sectional.
    - Noncomparative: case-reports, case-series.

Return to Contents

APPENDIX C. EXCLUDED STUDIES

All citations listed in Tables C-1 and C-2 were reviewed in their full-text version and excluded for the reason indicated. An alphabetical reference list follows each table.

Table C-1. Excluded RCTs with reasons

Reference	Not full publication, peer-reviewed, or primary data	Not study population of interest	New drug or comparator not of interest	No relevant outcomes reported at ≥6 months
Adams 2005	X			
Ageno 2005	X			
Agnelli 2009		X		
Amadeus Investigators 2008			X	
Anonymous 2004	X			
Anonymous 2009	X			
Berry 2005	X			
Botticelli Investigators 2008				X
Buller 2007			X	
Buller 2007			X	
Buller 2007			X	
Camm 2009	X			
Chung 2011				X
Cohen 2006		X		
Connolly 2011			X	
Connolly 2010	X			
Dahl 2010	X			
Deitcher 2006			X	
EAFT Study Group 1993			X	
Eriksson 2005			X	
Eriksson 2003				X
Fiessinger 1996			X	
Halperin 2005	X			
Halperin 2005	X			
Hankey 2004	X			
Hankey 2009	X			
Hankey 2011	X			
Harenberg 2002	X			
Hart 1999			X	
Heidbuchel 2010	X			
Hull 2006			X	
Kaul 2005	X			
Kubitza 2006	X			
Kwok 2004	X			
Lee 2003			X	
Lip 2009				X
Lopez-Beret 2001			X	
Meyer 2002			X	
Olsson 2010				X
Paikin 2011	X			
Party 2010			X	
Persist Investigators 2004				X
Petersen 2003				X
Prandoni 2010	X			
Prins 2009			X	
Rother 2010	X			

Reference	Not full publication, peer-reviewed, or primary data	Not study population of interest	New drug or comparator not of interest	No relevant outcomes reported at ≥6 months
Salam 2004	X			
Schulman 2005			X	
Segal 2001			X	
SPIAF Investigators 1996			X	
SPIAF Investigators 1991			X	
Taylor 2001			X	
Wahlander 2006			X	
Wallentin 2010	X			
Weitz 2010				X
Weitz 2010				X

Abbreviations: EAFT = European Atrial Fibrillation Trial; SPIAF = Stroke Prevention in Atrial Fibrillation

LIST OF EXCLUDED RCTs

Adams HP. Prevention of embolism among patients with atrial fibrillation. *Curr Neurol Neurosci Rep*. 2005;5(1):9-12.

Ageno W, Turpie AG. Clinical trials of deep vein thrombosis prophylaxis in medical patients. *Clin Cornerstone*. 2005;7(4):16-22.

Agnelli G, Eriksson BI, Cohen AT, et al. Safety assessment of new antithrombotic agents: lessons from the EXTEND study on ximelagatran. *Thromb Res*. 2009;123(3):488-97.

Amadeus Investigators. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. *The Lancet*. 2008;371(9609):315-321.

Anonymous. Results of THRIVE treatent study show that ximelagatran is safe and effective against throbosis. *J Support Oncol*. 2004;2(1):56.

Anonymous. Dabigatran: safer, more effective and easier to use than warfarin. *Cardiovasc J Afr*. 2009;20(5):311-2.

Berry C, Norrie J, McMurray JJ. Ximelagatran compared with warfarin for the prevention of systemic embolism and stroke. An imputed placebo analysis. *Cardiovasc Drugs Ther*. 2005;19(2):149-51.

Botticelli Investigators. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. *Journal of thrombosis and haemostasis : JTH*; 2008:1313-8.

Buller HR, Cohen AT, Davidson B, et al. Idraparinux versus standard therapy for venous thromboembolic disease. *New England Journal of Medicine*. 2007;357(11):1094-1104.

Buller HR, Cohen AT, Davidson B, et al. Extended prophylaxis of venous thromboembolism with idraparinux. *New England Journal of Medicine*. 2007;357(11):1105-1112.

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Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ*. 2006;332(7537):325-327.

Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-17.

Connolly SJ, Ezekowitz MD, Yusuf S, et al. Newly identified events in the RE-LY trial. *N Engl J Med*. 2010;363(19):1875-6.

Dahl OE, Huisman MV. Dabigatran etexilate: advances in anticoagulation therapy. *Expert Rev Cardiovasc Ther*. 2010;8(6):771-4.

Deitcher SR, Kessler CM, Merli G, et al. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. *Clin Appl Thromb Hemost*. 2006;12(4):389-96.

EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*. 1993;342(8882):1255-62.

Eriksson H, Lundstrom T, Wahlander K, et al. Prognostic factors for recurrence of venous thromboembolism (VTE) or bleeding during long-term secondary prevention of VTE with ximelagatran. *Thromb Haemost*. 2005;94(3):522-7.

Eriksson H, Wahlander K, Gustafsson D, et al. A randomized, controlled, dose-guiding study of the oral direct thrombin inhibitor ximelagatran compared with standard therapy for the treatment of acute deep vein thrombosis: THRIVE I. *J Thromb Haemost*. 2003;1(1):41-7.

Fiessinger JN, Lopez-Fernandez M, Gatterer E, et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. *Thromb Haemost*. 1996;76(2):195-9.

Halperin JL. Anticoagulation for atrial fibrillation in the elderly. *Am J Geriatr Cardiol*. 2005;14(2):81-6.

Halperin JL. Ximelagatran: oral direct thrombin inhibition as anticoagulant therapy in atrial fibrillation. *J Am Coll Cardiol*. 2005;45(1):1-9.

Hankey GJ. At last, a RE-LYable alternative to warfarin for atrial fibrillation. *Int J Stroke*. 2009;4(6):454-5.

Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. *Circulation*. 2011;123(13):1436-50.

Hankey GJ, Klijn CJ, Eikelboom JW. Ximelagatran or warfarin for stroke prevention in patients with atrial fibrillation? *Stroke*. 2004;35(2):389-91.

Harenberg J, Ingrid J, Tivadar F. Treatment of venous thromboembolism with the oral thrombin inhibitor, ximelagatran. *Isr Med Assoc J*. 2002;4(11):1003-5.

Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med*. 1999;131(7):492-501.

Heidbuchel H, Verhamme P. Dabigatran for stroke prevention in atrial fibrillation: from RE-LY to daily clinical practice. *Acta Cardiol*. 2010;65(5):491-7.

Hull RD, Pineo GF, Brant RF, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med*. 2006;119(12):1062-72.

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Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003;349(2):146-53.

Lip GY, Rasmussen LH, Olsson SB, et al. Oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a randomized dose-guiding, safety, and tolerability study of four doses of AZD0837 vs. vitamin K antagonists. *Eur Heart J*. 2009;30(23):2897-907.

Lopez-Beret P, Orgaz A, Fontcuberta J, et al. Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. *J Vasc Surg*. 2001;33(1):77-90.

Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med*. 2002;162(15):1729-35.

Olsson SB, Rasmussen LH, Tveit A, et al. Safety and tolerability of an immediate-release formulation of theoral direct thrombin inhibitor AZD0837 in the prevention of stroke and systemic embolism in patients with atrial fibrillation. *Thromb Haemost*. 2010;103(3):604-12.

Paikin JS, Haroun MJ, Eikelboom JW. Dabigatran for stroke prevention in atrial fibrillation: the RE-LY trial. *Expert Rev Cardiovasc Ther*. 2011;9(3):279-86.

Paty I, Trellu M, Destors JM, et al. Reversibility of the anti-FXa activity of idrabiotaparinux (biotinylated idraparinux) by intravenous avidin infusion. *J Thromb Haemost*. 2010;8(4):722-9.

Persist Investigators. A novel long-acting synthetic factor Xa inhibitor (SanOrg34006) to replace warfarin for secondary prevention in deep vein thrombosis. A Phase II evaluation. *J Thromb Haemost*. 2004;2(1):47-53.

Petersen P, Grind M, Adler J. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. *J Am Coll Cardiol*. 2003;41(9):1445-51.

Prandoni P, Taher A. Insights from the dabigatran versus warfarin trial in patients with venous thromboembolism (the RE-COVER trial). *Expert Opin Pharmacother*. 2010;11(6):1035-7.

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Rother J, Crijns H. Prevention of stroke in patients with atrial fibrillation: the role of new antiarrhythmic and antithrombotic drugs. *Cerebrovasc Dis*. 2010;30(3):314-22.

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Wahlander K, Eriksson H, Lundstrom T, et al. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. *British Journal of Haematology*; 2006:68-77.

Wallentin L, Ezekowitz MD, Eikelboom J, et al. Efficacy and safety of dabigatran compared to warfarin at different levels of INR control for stroke prevention in 18,113 patients with atrial fibrillation in the RE-LY trial. *Circulation*. 2010;120(21):2158.

Weitz JI, Cao C, Eriksson BI, et al. A dose-finding study with TAK-442, an oral factor Xa inhibitor, in patients undergoing elective total knee replacement surgery. *Thromb Haemost*. 2010;104(6):1150-7.

Weitz JI, Connolly SJ, Patel I, et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thromb Haemost*. 2010;104(3):633-41.

Table C-2. Excluded observational studies

Reference	Background only	Not full publication	Not study population of interest	No relevant outcomes (adverse effects) reported at >2 weeks from drug initiation	Not good quality
Aalbers 2010	X				
Anonymous 2011		X			
Baruch 2011			X		
Beyer-Westendorf 2011	X				
Bovio 2011	X				
Camm 2009		X			
Coleman 2012					X
Cotton 2011	X				
Eerenberg 2011	X				
Gerotziafas 2005				X	
Jacobs 2012	X				
Kaeberich 2011			X		
Lip 2010					
Loke 2011	X				
McKellar 2011			X		
Poultside 2012			X		
Roskell 2010					X
Tzeis 2011	X				
Watanabe 2012		X			

LIST OF EXCLUDED OBSERVATIONAL STUDIES

Aalbers J. Rivaroxaban equals warfarin treatment in atrial fibrillation patients at high risk of stroke. *Cardiovasc J Afr*. 2010;21(6):342-3.

Anonymous. New insights and results from the RE-LY trial. *Cardiovasc J Afr*. 2011;22(5):284-6.

Baruch L, Sherman O. Potential inaccuracy of point-of-care INR in dabigatran-treated patients. *Ann Pharmacother*. 2011;45(7-8):e40.

Beyer-Westendorf J, Buller H. External and internal validity of open label or double-blind trials in oral anticoagulation: better, worse or just different? *J Thromb Haemost*. 2011;9(11):2153-8.

Bovio JA, Smith SM, Gums JG. Dabigatran etexilate: a novel oral thrombin inhibitor for thromboembolic disease. *Ann Pharmacother*. 2011;45(5):603-14.

Camm. Dabigatran: safer, more effective and easier to use than warfarin. *Cardiovasc J Afr*. 2009;20(5):311-2.

Coleman CI, Sobieraj DM, Winkler S, et al. Effect of pharmacological therapies for stroke prevention on major gastrointestinal bleeding in patients with atrial fibrillation. *Int J Clin Pract*. 2012;66(1):53-63.

Cotton BA, McCarthy JJ, Holcomb JB. Acutely injured patients on dabigatran. *N Engl J Med*. 2011;365(21):2039-40.

Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. 2011;124(14):1573-9.

Gerotziafas GT, Samama MM. Heterogeneity of synthetic factor Xa inhibitors. *Curr Pharm Des*. 2005;11(30):3855-76.

Jacobs JM, Stessman J. Dabigatran: Do We Have Sufficient Data?: Comment on "Dabigatran Association With Higher Risk of Acute Coronary Events". *Arch Intern Med*. 2012.

Kaeberich A, Reindl I, Raaz U, et al. Comparison of unfractionated heparin, low-molecular-weight heparin, low-dose and high-dose rivaroxaban in preventing thrombus formation on mechanical heart valves: results of an in vitro study. *J Thromb Thrombolysis*. 2011;32(4):417-25.

Lip GY, Lane DA. Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients? *Am J Med*. 2010;123(9):785-9.

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.

McKellar SH, Abel S, Camp CL, et al. Effectiveness of dabigatran etexilate for thromboprophylaxis of mechanical heart valves. *J Thorac Cardiovasc Surg*. 2011;141(6):1410-6.

Poultsides LA, Gonzalez Della Valle A, Memtsoudis SG, et al. Meta-analysis of cause of death following total joint replacement using different thromboprophylaxis regimens. *J Bone Joint Surg Br*. 2012;94(1):113-21.

Roskell NS, Lip GY, Noack H, et al. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate. *Thromb Haemost*. 2010;104(6):1106-15.

Tzeis S, Andrikopoulos G. Novel Anticoagulants for Atrial Fibrillation: A Critical Appraisal. *Angiology*. 2011.

Watanabe M, Siddiqui FM, Qureshi AI. Incidence and management of ischemic stroke and intracerebral hemorrhage in patients on dabigatran etexilate treatment. *Neurocrit Care*. 2012;16(1):203-9.

Return to Contents

APPENDIX D. SAMPLE DATA EXTRACTION FORMS

Elements abstracted from RCTs

Study abstracted (Author, year, ID#)

Companion Study Ref IDs (Author, Year)

Form 1

Study Sites

☐ Single Center ☐ Multicenter ☐ Not reported/unclear

Geographical Location

Single Center: ☐

Enter City and State (if U.S.); Country (If outside the U.S.).

☐

Multicenter: ☐

Enter number of sites. Enter NR, if not reported.

Select all applicable geographical locations.

☐ U.S. ☐ Canada ☐ UK ☐ Europe ☐ S. America ☐ C. America ☐ Asia

☐ Africa ☐ Australia/NZ. ☐ Middle East ☐ Not reported/Unclear ☐ Other ☐

Funding Source

Check all that apply:

☐ Government ☐ Private Foundation ☐ Industry ☐ Not Reported ☐ Other ☐

Return to Contents

Study Design

☐ 1. Patient Level RCT

☐ 2. Other

Comparator Setting (check all that apply):

☐ Specialized anticoagulation clinic

☐ Other

☐ Not Reported/unclear

Enrollment Approach
Check all that apply:

☐ Consecutive patients

☐ Convenience sample

☐ Other

☐ Not Reported/unclear

Study Inclusion and Exclusion Criteria

1) Age range (years)

2) Diagnosis

☐ DVT/PE

Symptomatic?

☐ Yes ☐ No

Objectively confirmed?

☐ Yes ☐ No

☐ Afib

EKG?

☐ Yes ☐ No

3) Intended duration of Anticoagulation therapy? (check one choice)

Choose an item.

Check all exclusion criteria used in the study (check all that apply)

☐ Asymptomatic

☐ Yes ☐ No

☐ Alcohol or Drug Abuse

☐ Upper age limit Age

☐ Medical instability Type

☐ Anemia (give cut-off)

☐ Antiplatelet treatment

☐ ASA (give dosage)

☐ Clopidogrel

☐ NSAIDS

☐ Dipyridamole/ASA

☐ Clinically significant liver disease

☐ transaminase study threshold

☐ High risk of bleeding

Define:

☐ Clinically significant kidney disease

☐ eGFR (ml/min) study threshold

☐ Platelet count (threshold)

Study Enrollment/Study Completion

Note: Patients who are eligible, but refuse participation should be counted in the "eligible" number.

Assessed for eligibility (N):

Eligible (N):

Randomized (N):

Completed follow-up (N):

Comments:

ANTICOAGULATION TREATMENT

Acute Treatment ☐ Yes ☐ No

☐ Heparin (unfractionated)

☐ LMWH

"Duration of acute treatment" # days

Newer Anticoagulant Drug and Standard dosing

a) Drug Name: **Choose an item.**

b) Dose mg

c) Frequency **Choose an item.**

d) Were there dose modifications for sub-populations ☐ Yes ☐ No

Newer Anticoagulant intended duration of treatment.

Choose an item.

If others:

Comparator Anticoagulant Drug and Dosing

a) Comparator Drug Name Choose an item.

b) If a=adjusted dose Warfarin, then INR range low
high

If a= any other answer, then Dose mg

c) Frequency **Choose an item.**

Comparator Anticoagulant intended duration of treatment.

Choose an item.

Visit frequency monitoring

On average at least monthly?

☐ Yes ☐ No

Return to Contents

Form 2

Baseline Characteristics

Dichotomous variables

		Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparator 2** Choose an item. **N=**
GENDER	**Female** ☐ Not reported	N= %=	N= %=	N= %=
	Male ☐ Not reported	N= %=	N= %=	N= %=
RACE	**White** ☐ Not reported	N= %=	N= %=	N= %=
	Blacks ☐ Not reported	N= %=	N= %=	N= %=

RACE	**Latino/Hispanic** ☐ Not reported	N= %=	N= %=	N= %=
	Asian ☐ Not reported	N= %=	N= %=	N= %=
RACE	**Other *** ☐ Not reported **(includes Native American, Pacific Islander, etc.)**	N= %=	N= %=	N= %=
Antiplatelet drug use	**ASA (>80 mg daily)** ☐ Not reported	N= %=	N= %=	N= %=
	Clopidogrel ☐ Not reported	N= %=	N= %=	N= %=

Antiplatelet drug use	**NSAIDS** ☐ Not reported	N= %=	N= %=	N= %=
	Aggrenox ☐ Not reported	N= %=	N= %=	N= %=
	Dipyridamole ☐ Not reported	N= %=	N= %=	N= %=
History of heart disease	**History of Ischemic heart disease** **Define:** ischemic OR angina OR acute coronary syndrome (ACS) ☐ Not reported	N= %=	N= %=	N= %=

Impaired Renal Function	**Define:** Moderate **Define:** Severe ☐ Not reported	N= %= N= %=	N= %= N= %=	N= %= N= %=

Comments:

Continuous variables

	Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparator 2** Choose an item. **N=**
Age (years) ☐ Not reported	Choose an item. Choose an item.	Choose an item. Choose an item.	Choose an item. Choose an item.
eGFR/ Creatinine Clearance (mL/min) ☐ Not reported	Choose an item. Choose an item.	Choose an item. Choose an item.	Choose an item. Choose an item.
Obesity? Choose an item. ☐ Not reported	Choose an item. Choose an item.	Choose an item. Choose an item.	Choose an item. Choose an item.

Time from index event ☐ Not reported	Choose an item. Choose an item.	Choose an item. Choose an item.	Choose an item. Choose an item.

Comments:

Do these key questions apply to this article, yes/no?

KQ 1:
For patients with chronic nonvalvular AF, what is the comparative effectiveness of long-term anticoagulation using newer anticoagulants versus warfarin on stroke incidence, mortality, health-related quality of life (HRQOL), and patient treatment experience?

☐ Yes ☐ No

KQ 2:
For patients with venous thromboembolism, are there differential effects of newer anticoagulants versus warfarin or low molecular weight heparins (LMWHs) on recurrent thromboembolism, mortality, HRQOL, and patient treatment experience?

☐ Yes ☐ No

KQ3 does not appear because no studies of mechanical heart valves.

KQ 4:
When used for long-term anticoagulation treatment, what is the nature and frequency of adverse effects for newer anticoagulants versus warfarin?

☐ Yes ☐ No

Considering all baseline characteristics, are there significant baseline imbalances between the groups?

☐ Yes ☐ No

Comments:

Return to Contents

Form 3a: Atrial Fibrillation

Risk factor screen type

☐ CHADS 2 ☐ CHADS 2 VASC ☐ No CHADS ☐

Comparative Analysis Choose an item.	**Primary AC Intervention** Choose an item. **N=** ☐	**Comparator 1** Choose an item. **N=** ☐	**Comparator 2** Choose an item. **N=** ☐	**Comparative analysis** ☐ **New vs Comp** ☐ **Comp vs New**
CHADS total score ☐ Not reported	Mean ☐ SD ☐	Mean ☐ SD ☐	Mean ☐ SD ☐	Choose an item. ☐ Choose an item. ☐
CHADS score=1 ☐ Not reported	N ☐ % ☐	N ☐ % ☐	N ☐ % ☐	Choose an item. ☐ Choose an item. ☐
CHADS score=2 ☐ Not reported	N ☐ % ☐	N ☐ % ☐	N ☐ % ☐	Choose an item. ☐ Choose an item. ☐
CHADS score=3 ☐ Not reported	N ☐ % ☐	N ☐ % ☐	N ☐ % ☐	Choose an item. ☐ Choose an item. ☐
CHADS score >=4 ☐ Not reported	N ☐ % ☐	N ☐ % ☐	N ☐ % ☐	Choose an item. ☐ Choose an item. ☐

Prior TE ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Cancer ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Known Thrombophilic condition ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Pregnancy, post-partum or OBGYN complications ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Recent surgery/trauma ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Immobilization ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Estrogen therapy ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.

Others condition ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.

If No CHADS, please record the following:

Age >75 years ☐ Not reported	Mean SD	Mean SD	Mean SD	Choose an item. Choose an item.
Diabetes Mellitus ☐ Not reported	Mean SD	Mean SD	Mean SD	Choose an item. Choose an item.
HF ☐ Not reported	Mean SD	Mean SD	Mean SD	Choose an item. Choose an item.
HTN ☐ Not reported	Mean SD	Mean SD	Mean SD	Choose an item. Choose an item.

Comments:

Form 3b: VTE

If DVT/PE, risk factors-Indication for anticoagulation

	Total	**Primary AC Intervention** Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparative analysis** ☐ **New vs Comp** ☐ **Comp vs New**
DVT ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
PE ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
DVT/PE ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Prior TE ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Cancer ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.

Known Thrombophilic condition ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Pregnancy, post-partum or OBGYN complications ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Recent surgery/trauma ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Immobilization ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Estrogen therapy ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Others condition ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.

Form 4a: Outcome Measures Reported

☐ Yes ☐ No ☐ Unclear

Central Adjudication

Timing of the outcome data reported in the table below [Repeat this table as needed]

☐ 24 months ☐ 12 months ☐ 6 months ☐ Other

	Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparator 2** Choose an item. **N=**
Adherence: newer AC, defined as 1) % above cut-off **OR** 2) Average, % of medication taken **OR** ☐ Not reported	% N %	% N %	% N %
Adherence: If comparator= Warfarin, % time in therapeutic range: Below range: Above range: ☐ Not reported			

	Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparative analysis** ☐ new vs comp ☐ comp vs new
Death all cause ☐ Not reported	N % Choose an item.	N % Choose an item.	Choose an item. Choose an item.
Death TE ☐ Not reported	N % Choose an item.	N % Choose an item.	Choose an item. Choose an item.
Stroke Ischemic ☐ Not reported	N % Choose an item.	N % Choose an item.	Choose an item. Choose an item.
Peripheral arterial embolism ☐ Not reported	N % Choose an item.	N % Choose an item.	Choose an item. Choose an item.
Stroke Hemorrhage ☐ Not reported	N % Choose an item.	N % Choose an item.	Choose an item. Choose an item.

Combined Stroke ☐ Not reported	N %	N %	Choose an item. Choose an item.
Quality of life ☐ Not reported	N %	N %	Choose an item. Choose an item.

Comment:

Form 4b: Outcome Measures Reported

Central Adjudication ❍ Yes ❍ No ❍ Unclear

Timing of the outcome data reported in the table below [Repeat this table as needed]

❍ 24 months ❍ 12 months ❍ 6 months Other

	Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparator 2** Choose an item. **N=**
Adherence: newer AC, defined as 1) % above cut-off **OR** 2) Average, % of medication taken **OR** ☐ Not reported	% N %	% N %	% N %

Adherence: If comparator= Warfarin, % time in therapeutic range:

% Below range:

% Above range:

☐ Not reported

Return to Contents

	Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparator 2** Choose an item. **N=**
Death all cause ☐ Not reported	N %	N %	N %
Death TE ☐ Not reported	N %	N %	N %
Stroke Ischemic ☐ Not reported	N %	N %	N %
Peripheral arterial embolism ☐ Not reported	N %	N %	N %
Stroke Hemorrhage ☐ Not reported	N %	N %	N %
Combined Stroke ☐ Not reported	N %	N %	N %

Quality of life ☐ Not reported	N %	N %	N %

Return to Contents

Form 5

Adverse Event Outcomes

Timing of the outcome data reported in the table below [Repeat this table as needed]

☐ 24 months ☐ 12 months ☐ 6 months ☐ Other

	Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparative analysis** ☐ new vs comp ☐ comp vs new
Any adverse events ☐ Not reported	N %	N %	Choose an item. Choose an item.
Serious adverse events ☐ Not reported	N %	N %	Choose an item. Choose an item.
Adverse event-drug discontinuation ☐ Not reported	N %	N %	Choose an item. Choose an item.

Return to Contents

Major bleeding-total ☐ Not reported	N %	N %	Choose an item. Choose an item.
Major bleeding-fatal ☐ Not reported	N %	N %	Choose an item. Choose an item.
Major bleeding-require transfusion ☐ Not reported	N %	N %	Choose an item. Choose an item.
Myocardial infarction ☐ Not reported	N %	N %	Choose an item. Choose an item.
LFT >3X ULN Choose an item. ☐ Not reported	N %	N %	Choose an item. Choose an item.
Intracranial bleeding ☐ Not reported	N %	N %	Choose an item. Choose an item.

Elements Abstracted From Observational Studies

- Study design
- Setting/study sites
- Geographic location
- Patient demographics
  - Age
  - Race/ethnicity
  - Gender
  - Diagnosis
  - Important medical history (e.g., CHADS score, EGR)
  - Comorbidities
- Types of adverse effects reported
- Suspected agent
- Degree of certainty that agent was causative
- Duration of illness
- Was patient hospitalized?
- Was episode fatal?
- Did episode resolve?
- Other necessary description of episode

Return to Contents

APPENDIX E. PEER REVIEW COMMENTS

Reviewer	Comment	Response
Question 1: Are the objectives, scope, and methods for this review clearly described?		
1	Yes, and no comments from reviewer 1.	Thank you.
2	Yes, and no comments from reviewer 2.	Thank you.
3	Yes, and comment was "Methods, scope, and objectives are sufficiently described."	Thank you.
4	Yes, and comment was "Very clear, comprehensive report of the current literature."	Thank you.
Question 2: Is there any indication of bias in our synthesis of the evidence?		
1	No, and no comments from reviewer 1.	Thank you.
2	No, and no comments from reviewer 2.	Thank you.
3	Search methods identified all relevant studies (published and unpublished), the identified studies are of good quality, and author's analysis of the data does not appear to be influenced by any obvious source of bias. However, the analysis is potentially misleading by combining together the findings from clinical trials for all new anticoagulants - thus obfuscating any differences (in efficacy or safety) that might exist between these new agents (for example – figure 14 suggests there are significant differences in medication discontinuation rates)... or diminishing the effect a medication or class of medication may have had on outcomes relative to warfarin. At the very least, the reader should be alerted to this potential flaw in the analytical methods (e.g. the analysis, as constructed, assumes that "new anticoagulants" are substantially similar and were treated as a single class of medications).	We conducted additional analyses and presented results by drug class. However, these analyses consist of indirect comparisons (across studies that may differ in other ways, such as differences in the patient population or quality of adjusted-dose warfarin) and should be considered hypothesis generating. We added statements in the Discussion section and both the global Summary and Strengths and Limitations sections.
4	While the report is a comprehensive review of the current literature with sound results, the text is currently written in a biased manner favoring the newer anticoagulants without equally balancing the disadvantages and unknowns. Recommend revising to be more balanced in describing the findings and including disadvantages and unknowns. Examples provided below: Exec Summary, p. 1: potential benefits of newer anticoagulants are over-stated, and clinical limitations are not included (i.e., dabigatran is associated with higher GI bleeding than warfarin; downside is that there is not a readily available means of quantifying anticoag effect of newer agents in cases of emergency such as bleeding or emergent procedure/surgery needed). There is also more recent concern raised by FDA as well as other agencies outside of US about serious bleeding events with dabigatran, particularly in the elderly and renally impaired.	We have performed a secondary search of the observational literature and the FDA Web site looking specifically for reports of adverse events. These data are included under KQ 4 and in the Executive Summary.

Reviewer	Comment	Response
4	Page 5, page 36: "In the trial of dabigatran for chronic AF, myocardial infarction was increased, but the enrolled sample had higher CHADS2 scores than other trials." First, this statement is incorrect; mean CHADS2 score for RE-LY ~2.1; mean CHADS2 score ROCKET ~3.5. Second, the "but…" phrase does not explain the increase in MI. CHADS2 score is an assessment of stroke risk in patients with AF.	Thank you for pointing out this factual error that was an artifact of editing. The ROCKET study did have a higher mean CHADS score, and this factual error has been corrected. While it is true that the CHADS2 score is an assessment of stroke risk in patients with AF, many of the risk factors used in this assessment (e.g., HTN, DM, history of vascular disease) are risk factors for myocardial infarction too. We have clarified this point in the discussion.
4	Intro and Page 10: It is misleading to state that the newer agents are free from monitoring. It is more accurate, fair and balanced to state that there is not a need for "routine anticoagulant monitoring". All patients on anticoagulants should be monitored for s/sx bleeding, stroke, AEs, medication adherence. In addition, certain newer anticoagulants require monitoring of renal function (i.e., dabigatran, rivaroxaban).	Agreed. We have modified this statement to state: "These drugs characteristically have a predictable anticoagulant effect, eliminating the need for routine monitoring. However, patients on newer anticoagulants should still be monitored for any adverse events, including bleeding. Bleeding risk is increased with concurrent use of antiplatelet medications, older age, and renal impairment since most of these drugs are eliminated through the kidneys. (Harder 2011)"
4	GI bleeding and GI related adverse events were not included in KQ4; these events were reported more often with dabigatran.	We have now addressed GI bleeding and GI-related events in KQ 4.
4	Page 39, summary of KQ1: only the favorable outcomes of the newer anticoagulants are discussed. It may be stated that there was no significant difference found in VTE related mortality and ischemic stroke.	Agreed. The following statement was added to the paragraph: "However, VTE-related mortality and ischemic stroke were not significantly lower with newer oral anticoagulants."

Reviewer	Comment	Response
4	Page 39, summary of KQ1: bleeding outcomes and INR control – "The difference in bleeding related outcomes are dependent in part upon the quality of adjusted-dose warfarin treatment; these studies reported rates of time in therapeutic range that were similar to those observed in the VHA." Statement is misleading and an oversimplification as is. First, it would be more accurate to state that it is the MEAN or AVERAGE TTR from the clinical trials. Second, VHA national data show that ~70% of INRs are between 1.8 and 3.3. The method used to calculate TTR in the clinical trials differed and therefore limits the ability to directly compare numbers. The take home message to me is that outcomes with dabigatran vs. warfarin were similar when INR control was good. Further, outcomes with dabigatran were better when INR control was poor. INR control in the rivaroxaban study was poorer than typical standard. Suggest revision of the statement to include these limitations. Also suggest adding that anticoagulation control in VHA appears to be at least as good as the mean TTR in clinical trials.	The discussion of bleeding rates has been revised to: "While anticoagulation control in the VHA appears to be at least as good as that found in clinical trials, the ROCKET-AF study had a mean TTR that was worse than typical standards. In the RE-LY study, the advantages of dabigatran were greater at sites with poor INR control than at those with good INR control for all vascular events, nonhemorrhagic events, and mortality. Warfarin and dabigatran showed comparable outcomes in centers with good mean TTR."
4	Page 39, summary of KQ1: "Except for discontinuations due to adverse effects, other outcomes also favored newer anticoagulants but were not statistically significant." The MI outcome did not favor newer anticoagulants and should be stated here.	The statement was revised to: "Except for discontinuations due to adverse effects, other outcomes also favored newer anticoagulants; however, they were not statistically significant."
4	Page 40, summary of KQ2: Agree with conclusion; however similarly as for KQ1, only the positive effects of newer anticoagulants is included. It should also be stated that rate of DC due to AEs was higher with newer anticoagulants, though not statistically significant.	We have added this text: "When the study examining ximelagatran was included, results were similar except that drug discontinuation due to adverse effects was significantly higher than rates with adjusted-dose warfarin."
4	Page 41, summary of KQ4: same incorrect statement about the dabigatran, higher CHADS2 – see comment above.	ROCKET-AF had a higher mean CHADS2, and the text has been corrected to reflect this.
4	Page 41, summary of KQ4: "Fatal bleeding was significantly lower for newer anticoagulants in the chronic AF studies, and the point estimate favored these drugs for fatal bleeding in patients with VTE and major bleeding in both groups." For the VTE AEs, these were not statistically significant. Statement currently is unbalanced, showing bias in reporting to the newer anticoagulants.	We agree and have changed the statement to: "The newer oral anticoagulants were associated with a consistent decrease in mortality (0.88; 95% CI, 0.82 to 0.95), without significant variability across studies or differences between drug classes. Similarly, rates of fatal bleeding were consistently lower with newer oral anticoagulants (Table 9). There was a non–statistically significant reduction in major bleeding, but this effect varied importantly across studies—variability that was not explained by drug class."

Reviewer	Comment	Response
4	Page 42, "It is possible that the newer agents may improve patient experience and HRQOL." Statement is biased; a more balanced statement is that it is unknown whether new agents may improve patient experience and HRQOL.	This statement has been rephrased to: "Because no studies reported effects on patient experience and HRQOL, effects on these important outcomes are unknown."
4	Page 42, it states that patients with high bleeding risk were excluded from clinical trials, yet in the next paragraph it goes on to recommend these newer agents in patients at higher than average risk of bleeding. I don't agree with this statement and it is not supported by evidence.	Agreed. We have changed the wording to: "In the RE-LY study, the advantages of dabigatran were greater at sites with poor INR control than at those with good INR control for all vascular events, nonhemorrhagic events, and mortality. Warfarin and dabigatran showed comparable outcomes in centers with good mean TTR."
4	Page 42, including only part of the recommendation from ACCP/AHA on dabigatran is biased. The update also states that: because of BID dosing and greater risk of nonhemorrhagic AEs with dabigatran, patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran.	The discussion has been updated to include the point that patients already taking warfarin and who have excellent INR control may have little to gain by switching.
4	Page 42 – Clinical and Policy Implications: It is not balanced in that this section currently omits discussion of the unknowns or disadvantages of newer anticoagulants. 1) unknown outcomes in the setting of lower adherence – Adherence in clinical trials was very high and likely to be lower in real-world setting. Given the short half-life of the newer agents and the fact that patients discontinue them more frequently, the clinical implications of lower adherence rates are unknown (but potentially important, increased stroke risk).; 2) Higher GI bleeds, GI adverse effects with dabigatran; 3) higher bleeding rates with the newer anticoagulants vs. warfarin in the elderly –this is important and extremely applicable to the VA population; 4) higher MI with dabigatran	We have added the following text: "In a prespecified subgroup analysis, Wallentin et al.99 found that the advantage of dabigatran over warfarin in terms of major bleeding rates was evident only at sites with poor-quality anticoagulation (TTR <57.1%), while rates of major bleeding were not significantly different at sites with higher quality anticoagulation. Hence, better INR control led to similar bleeding rates between both groups. In the VHA, time in treatment exceeds this threshold, but newer oral anticoagulants could have important advantages for individual patients who have difficulty maintaining a therapeutic INR. However, since newer oral anticoagulants are dosed twice daily, compared with once daily dosing of warfarin, better outcomes would not be expected if poor medication adherence were the cause of the subtherapeutic INR." *(continued)*

Reviewer	Comment	Response
4 continued		Also: "Although newer oral anticoagulants are associated with a lower risk of fatal bleeding compared with warfarin, this advantage may be tempered by the increased risk of gastrointestinal bleeding with dabigatran.70,84,91,99 The FDA is currently evaluating reports of high rates of serious bleeding. The reports of bleeding appear to be concentrated in older adults and those with impaired renal function. Another worrisome finding is elevated rates of myocardial infarction with dabigatran, although the strength of evidence for this finding is low." And: "VA should carefully consider the potential benefits and harms, along with patients at higher risk for adverse effects when establishing eligibility criteria for newer oral anticoagulants."
4	Page 42, "In a prespecified subgroup analysis, Wallentin et al.22 found that major bleeding rates with dabigatran were lower than warfarin at sites where time in therapeutic range was low (<57.1%); rates were not significantly different at sites with higher quality anticoagulation." This statement is somewhat misleading by not also including that major GI bleeding was significantly HIGHER with dabigatran vs. warfarin when INR control was good. Also, for the primary endpoint of stroke or systemic embolism, outcomes were similar with dabigatran and warfarin when INR control was good. In other words, dabigatran was not superior to warfarin when INR control was good.	Agreed. We have rephrased the statement to: "In a prespecified subgroup analysis, Wallentin et al.99 found that the advantage of dabigatran over warfarin in terms of major bleeding rates was evident only at sites with poor-quality anticoagulation (TTR <57.1%), while rates of major bleeding were not significantly different at sites with higher quality anticoagulation. Hence, better INR control led to similar bleeding rates between both groups. In the VHA, time in treatment exceeds this threshold, but newer oral anticoagulants could have important advantages for individual patients who have difficulty maintaining a therapeutic INR. However, since newer oral anticoagulants are dosed twice daily, compared with once daily dosing of warfarin, better outcomes would not be expected if poor medication adherence were the cause of the subtherapeutic INR."

Reviewer	Comment	Response
Question 3: Are there any published or unpublished studies that we may have overlooked?		
1	No, and no comments from reviewer 1.	Thank you.
2	• Hohnloser S, Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY trial. Circulation 2012; DOI: 10.1161/?CIRCULATIONAHA.111.055970. Available at: http://circ.ahajournals.org. • Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med 2012; DOI: 10.1001/archinternmed.2011.1666. Available at: http://archinte.ama-assn.org/ • Jacobs JM, Stessman J. Dabigatran: Do we have sufficient data? Arch Intern Med 2012; DOI: 10.1001/archinternmed.2011.1721. Available at: http://archinte.ama-assn.org/	The cited articles were published after our draft report was submitted. However, in response to peer review, we conducted a secondary search for observational studies and recent meta-analyses that address adverse effects of the newer anticoagulants. The updated data on myocardial ischemic events (Hohnloser et al.) are included in a newly conducted sensitivity analysis. The meta-analysis by Uchino et al. is cited in the Discussion section. The article by Jacobs et al was reviewed but is an editorial and not eligible for inclusion.
3	No – none that I am aware.	Thank you.
4	No, and no comments from reviewer 4.	Thank you.
Question 4: Please write additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.		
1	Make it clear early on that the review covers warfarin and newer oral anticoagulants.	This has been clarified throughout the document.
1	Define 'patient treatment experience.'	Patient experience is a more inclusive set of outcomes than patient satisfaction. It has been defined as: The sum of all interactions, shaped by an organization's culture that influence patient perceptions across a continuum of care.
1	KQ4: Where there differences in bleeding when stratifying data based on age or indication (e.g., age ≥ 80 vs. < 80)?	From Eikelboom et al. 2011: 18113 patients in RE-LY study randomized to 110 mg, 150 mg dabigatran BID, or warfarin for a median followup of 2 years: • Risk of major bleeding with 150 mg dabigatran was lower than warfarin in those <75 years of age (2.12% vs. 3.04%; P<0.001) and a trend toward higher risk of major bleeding in those ≥75 (4.37%; P=0.07; P for 5.10 % vs. interaction <0.001). • In patients with AF, both doses of dabigatran are associated with lower risk of major bleeding in patients <75 years of age. In those ≥75, intracranial bleeding risk is lower, but extracranial bleeding risk is the same or higher in both doses of dabigatran.

Reviewer	Comment	Response
1	KQ2: No data are presented on LMWHs. Remove this from KQ or reword to indicate heparins overlapped with warfarin. Also, how many VTEs were DVTs versus PEs? Are results applicable to DVTs and PEs?	Agreed. It may be confusing although it is common practice to overlap warfarin with LMWH or other parenteral anticoagulants. We have changed the wording of KQ 2 to: "For patients with venous thromboembolism, are there differential effects of newer oral anticoagulants versus warfarin on recurrent thromboembolism, mortality, HRQOL, and patient treatment experience?"
1	Future research: CEAs could help address uncertain effects on health care systems in addition to BIAs. CEAs involving dabigatran noted, but none involving other agents.	In the literature search performed for the Budget Impact Analysis we plan to conduct, we did not find any CEAs on new oral anticoagulants other than Dabigatran.
1	Page 10: Warfarin has significant interactions with herbal supplements in addition to drugs and foods.	Agreed. This interaction has been noted in the report.
1	Page 10: Physicians are still concerned about inability to reverse effects of newer anticoagulants in patients at higher risk of bleeding even though half-lives are shorter (e.g., patient who is 76 years old and h/o GI bleed).	Agreed. We have added the statement: "However, there are valid concerns about the lack of specific antidotes for newer oral anticoagulants that would prevent the timely reversal of their anticoagulant effect in a bleeding patient. This is especially worrisome in elderly patients and those with renal disease, where drug clearance may be longer and the anticoagulant effects prolonged."
1	Contraindications (page 13): What is the data source?	We have changed the heading to "Precautions."
1	Objective (page 15): Clarify that data on primary VTE prevention s/p surgery are not presented.	We have added a statement that a later report will summarize the data on newer anticoagulants used for primary VTE prevention.
1	Figure 1: eliminate or clarify inclusion of LMWHs	We have adjusted Figure 1 as suggested.
1	Search strategy: standard of care was usually warfarin, rather than VKAs	Warfarin is one of the vitamin K antagonists.

Reviewer	Comment	Response
1	Clinical implications: The risk of major bleeding is unclear with newer agents in patients at higher risk for a major bleed (e.g., older elderly, h/o major bleed, renal insufficiency, h/o stroke).	We have refined the discussion to state: "Gastrointestinal bleeding was significantly increased in patients treated with dabigatran and rivaroxaban compared with warfarin.(Wallentin 2010) The efflux of dabigatran by p-glycoprotein transporters into the gastrointestinal tract may be a mechanism for this finding. (Bovio 2011) The European Society of Cardiology recommends dabigatran at a dose of 150 mg be used in patients with a low risk of bleeding, while the lower dose of 110 mg is reserved for those with a high risk of bleeding.(Camm 2010) In Canada, dabigatran is approved for the prevention of stroke in AF, and dabigatran 110 mg twice daily is recommended for elderly patients 80 years of age or older or those at a high risk of bleeding.(Cairns 2011) In the United States, the FDA has only approved the 150 mg dose and recommends a dose of 75 mg twice daily for patients with CrCl of 15 to 30 mL/min. (Beasley 2011)"
2	Page 9 – Therapeutic Options for Anticoagulation, Paragraph 1, Line 6 – additional LMWH advantage includes decreased risk of HIT. Line 8 – additional LMWH disadvantage is that it is not completely reversible by protamine.	We have added the following statement: "Unfractionated heparin requires hospital admission and continuous monitoring and carries the risk of heparin-induced thrombocytopenia. The advantages of low molecular weight heparin include longer half-life, better bioavailability, a predictable dose-response that minimizes the need for laboratory monitoring, and a decreased risk of heparin-induced thrombocytopenia.(Key 2010) The disadvantages of low molecular weight heparin include the need for subcutaneous administration once or twice daily, which patients find painful and inconvenient. Further, protamine sulfate only partially reverses heparin's anticoagulant effect. (Crowther 2002)"

Reviewer	Comment	Response
2	Page 10 – Line 1 – Point of care INR testing is simple and relatively inexpensive. Paragraph 1, Line 4 and 5 – bridging also with LMWH, generally performed in an outpatient setting, which is more convenient for the patient and less costly to the health plan (compared to admission). Paragraph 2, Line 10 – Although a shorter t1/2 is beneficial compared to warfarin, a lack of antidote for DTI and Xa inhibitors is problematic in acute hemorrhage or emergent surgery, whereas the effect of warfarin may be reversed rapidly with PCC. Paragraph 4 – Line 4 – May consider additional information regarding post-marketing bleeding in Pradaxa and 12/7/2011 FDA Safety Announcement.	This FDA Safety Announcement and several others have been addressed under KQ 4.
2	Page 11 – Paragraph 1, Line 2 – Consider noting that dabigatran is susceptible to Pgp drug:drug interactions.	Thank you. This observation has been added both to the text and the appropriate table.
2	Page 12 – Column 6, Row 8 – Typo Should read Ecarin clotting time. Row 10 – PPIs not included in package insert.	The reference has been changed to a more recent one that does include PPIs.
2	Page 13 – Column 1 – May be worthwhile adding additional row listing precautions.	"Contraindications" has been changed to "Precautions."
2	Page 36 – Paragraph 2, Line 7/8 – Do the authors have a citation for the two statements that adverse events are related to # medical conditions and # medications and that duration of treatment may increase absolute rates of adverse events?	Oldgren 2011 has been added to the text in the "Meta-analyses for KQ 1" section, 2nd paragraph, 4th sentence.
2	Page 36 – Paragraph 3, Line 10 – Is this true? I thought Rocket-AF had higher average CHADS2 score?	Agreed. This text has been corrected.
2	Page 41 – Paragraph 1, Line 6 – See previous comment regarding CHADS2 score and Rocket-AF vs. RE-LY.	We have corrected this text.
2	Page 42 – Paragraph 1, Line 5 – Should also add aspirin + clopidogrel. Paragraph 2, Line 3 – For now fewer drug interactions are noted, but new information may emerge. Paragraph 3, Line 11 – The shorter t1/2 life of new anticoagulants may be problematic in patients with non-compliant behavior (ie – increase in death rates after discontinuation of treatment in Rocket-AF).	The ACTIVE-W trial of ASA plus clopidogrel was stopped early due to inferiority compared with warfarin. Other studies are ongoing. We decided not to add this detail as it may distract the reader from the main point that warfarin is superior to antiplatelet agents.
3	I am troubled by the fact that all of the new anticoagulants are considered as a group – rather than as individual agents (or, at the very least, two distinct classes of medications). Each of these new agents have unique pharmacological and pharmacokinetic properties. While the efficacy of these agents in clinical trials appears to have been similar (for both a-fib and VTE treatment indications), the adverse event and side effect profiles clearly were not (dabigatran had a relatively higher incidence of GI side effects … rivaroxaban was associated with relatively higher rate of GI bleeding … and apixaban was not associate with either of these adverse events). Thus I believe combining, analyzing, and summarizing the results of the clinical trials of these distinct classes of medications (DTIs and direct Xa inhibitors) is not appropriate.	Thank you for this comment. Our analysis assumes a class effect. Although each drug has unique pharmacological and pharmacokinetic properties, they are all developed as anticoagulants. However, we have revised our analytic approach to analyze by drug class when there were sufficient studies for meaningful analyses. Further, we have revised the results and discussion to emphasize when the results were variable across drugs or drug class and to point out that our analyses is limited because we cannot reliably detect differences between individual drugs.

Reviewer	Comment	Response
3	Not sure why the ROCKET-AF study (Patel 2011 – reference 74) is consistently listed as Patel 2010 in the tables and figures; was this a typographical error?	The report has been revised to ensure that studies are consistently listed by author/year in the tables and figures.
4	Page 9: minor correction to be complete: Though not very commonly used, UFH may be given SC for acute VTE treatment as well as IV: "unfractionated heparin administered intravenously"	The statement has been revised to state that UFH is typically given intravenously.
4	Page 10: consider adding: warfarin's interaction with certain disease states in addition to drugs, foods. (e.g., CHF, thyroid, acute infection)	Thank you for the suggestion, but we decided to omit this detail as we believe the current text makes it abundantly clear that interindividual and intraindividual variability in warfarin response, along with food and drug interactions, is a disadvantage.
4	Page 10-11: consider adding: dabigatran's advantage over warfarin in the lack of drug-food interaction. Also, while dabigatran doesn't interact with drugs via CYP enzyme system, there are fewer but significant interactions through P-gp transporter system.	Agreed. We have added the following statement: "Dabigatran acts as a substrate for the p-glycoprotein transporter system, which makes it more prone to drug-drug interactions." It is also present in the table.
4	Page 12, Table 1: ECT time is best measure of anticoagulant effect of dabigatran, although this test is not widely available outside of a research setting at this time.	Agreed. This has been added to the report.
4	Page 13, Table 1, Contraindications: Warfarin and severe renal impairment – I could not find evidence of this to be true. Reviewed the Harder reference provided where it directs you to UK product information. The link provided in the reference in the Harder article lists renal impairment as a precaution, not contraindication. Also per US PI, severe renal impairment is NOT a contraindication. These patients likely have higher risk of bleeding and need lower doses of warfarin but it is not a contraindication to use	Agreed. We have changed the heading to "Precautions."
Optional Dissemination and Implementation Questions		
Question 5: Are there any clinical performance measures, programs, quality improvement measures, patient care services, or conferences that will be directly affected by this report? If so, please provide detail.		
1	No comment from reviewer 1.	NA
2	No comment from reviewer 2.	NA
3	No comment from reviewer 3.	NA
4	The implications of this report are unclear at this time.	Acknowledged
Question 6: Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.		
1	No comment from reviewer 1.	NA
2	While it may be outside of the scope and stated objective of the review, it would be helpful to include a more comprehensive discussion of the major clinical trials including criticism and clinical applicability	We feel that it is outside the scope of this review to discuss the major trials separately.

Reviewer	Comment	Response
3	No comment from reviewer 3.	NA
4	The report should be revised to read more balanced; it is biased toward the newer agents without describing the potential disadvantages and unknowns.	Agreed. We have revised the report to be more balanced, and we highlight the potential disadvantages of the newer oral anticoagulants. For example, we state: "Wallentin et al. found that the advantage of dabigatran over warfarin in terms of major bleeding rates was only evident at sites with poor-quality anticoagulation (time in therapeutic range <57.1%), while rates of major bleeding were not significantly different at sites with higher quality anticoagulation. Hence, better INR control led to similar bleeding rates between both groups. In the VHA, time in treatment exceeds this threshold, but newer anticoagulants could have important advantages for individual patients who have difficulty maintaining a therapeutic INR. However, since newer anticoagulants are dosed twice daily, compared with once daily dosing warfarin, better outcomes would not be expected if poor medication adherence were the cause of the subtherapeutic INR. A pragmatic concern related to adherence is the FDA notification that dabigatran may lose potency if placed in pill boxes and that it should only be dispensed and stored in the original bottle or blister package. Although newer anticoagulants are associated with a lower risk of fatal bleeding compared to warfarin, this advantage may be tempered by the increased risk of gastrointestinal bleeding with dabigatran. The FDA is currently, evaluating reports of high rates of serious bleeding. The reports of bleeding appear to be concentrated in older adults and those with impaired renal function. Another worrisome finding is elevated rates of myocardial infarction with dabigatran, although the strength of evidence for this finding is low." And we have added a word of caution: "VA should carefully consider the potential benefits and harms, along with patients at higher risk for adverse effects when establishing eligibility criteria for newer anticoagulants."

Reviewer	Comment	Response
Question 7: Please provide us with contact details of any additional individuals/stakeholders who should be made aware of this report.		
1	No comment from reviewer 1.	NA
2	No comment from reviewer 2.	NA
3	No comment from reviewer 3.	NA
4	No comment from reviewer 4.	NA

Return to Contents

APPENDIX F. ONGOING CLINICAL TRIALS

Table F-1. Ongoing RCTs of atrial fibrillation interventions (KQ 1)

Study title	VA/DoD population?	Intervention	Comparator	Sponsor and ClinicalTrials.gov ID	Funding Start/Stop	Status
Long-Term Safety in Atrial Fibrillation Patients	No	AZD0837	Vitamin K antagonists (warfarin)	AstraZeneca NCT00645853	Oct 2007–May 2009	Completed
RELY-ABLE Long Term Multi-center Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed RE-LY Trial	No	Dabigatran dose 1 high dose twice daily	Dabigatran dose 2 low dose twice daily	Boehringer Ingelheim Pharmaceuticals NCT00808067	Nov 2008–Apr 2013	Ongoing, not recruiting
The IMPACT of BIOTRONIK Home Monitoring Guided Anticoagulation on Stroke Risk in Patients With Implanted ICD and CRT-D Devices	No	Dabigatran etexilate, warfarin	Dabigatran etexilate, warfarin	Biotronik NCT00559988	Feb 2008–Feb 2015	Recruiting
Direct Factor Xa Inhibitor YM150 for Prevention of Stroke in Subjects With Non-Valvular Atrial Fibrillation	No	YM150	Warfarin	Astellas Pharma Inc. NCT00448214	Mar 2007–Oct 2008	Completed

Return to Contents

Table F-2. Ongoing RCTs of venous thromboembolism interventions (KQ 2)

Study title	VA/DoD population?	Intervention	Comparator	Sponsor and ClinicalTrials.gov ID	Funding Start/Stop	Status
Phase III Study Testing Efficacy & Safety of Oral Dabigatran Etexilate vs Warfarin for 6 m Treatment for Acute Symp VTE	No	Dabigatran etexilate	Warfarin	Boehringer Ingelheim Pharmaceuticals NCT00680186	Apr 2008–May 2011	Completed, recent
Secondary Prevention of Venous Thrombo Embolism (VTE)	No	Dabigatran	Warfarin	Boehringer Ingelheim Pharmaceuticals NCT00329238	May 2006–Oct 2010	Completed, abstract presented, but no publication to date
Oral Direct Factor Xa Inhibitor Rivaroxaban In Patients With Acute Symptomatic Pulmonary Embolism With Or Without Symptomatic Deep-Vein Thrombosis: Einstein-PE Evaluation	No	Xarelto (rivaroxaban, BAY59-7939)	Enoxaparin followed by vitamin K antagonist	Bayer NCT00439777	Mar 2007–Oct 2011	Completed, recent
Comparative Investigation of Low Molecular Weight (LMW) Heparin/Edoxaban Tosylate (DU176b) vs. LMW Heparin/ Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots.	No	LMW Heparin/ Edoxaban	LMW Heparin/ Warfarin	Daiichi Sankyo Inc. NCT00986154	Oct 2009–Sep 2012	Recruiting Methods paper published

Return to Contents

Table F-3. Ongoing RCTs of mechanical heart valve interventions (KQ 3)

Study title	VA/DoD population?	Intervention	Comparator	Sponsor and ClinicalTrials.gov ID	Funding Start/Stop	Status
Dabigatran Etexilate in Patients With Mechanical Heart Valves	No	Dabigatran etexilate	Warfarin	Boehringer Ingelheim Pharmaceuticals NCT01452347	Oct 2011–Aug 2012	Recruiting
A Safety and Efficacy Trial Evaluating the Use of Apixaban in the Treatment of Symptomatic Deep Vein Thrombosis and Pulmonary Embolism	No	Placebo for enoxaparin Placebo for warfarin Apixaban	Active comparator: Enoxaparin Warfarin Placebo for apixaban	Bristol-Myers Squibb NCT00643201	July 2008–Mar 2013	Recruiting
A Phase 3, Randomized, Double-Blind, Double-Dummy, Parallel Group, Multi-Center, Multi-National Study for Evaluation of Efficacy and Safety of DU-176b Versus Warfarin In Subjects With Atrial Fibrillation - Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation (ENGAGE - AF TIMI - 48)	No	DU-176b plus warfarin placebo tablets	Warfarin tablets plus DU-176b	Daiichi Sankyo Inc. NCT00781391	Nov 2008–Feb 2012	Ongoing; methods paper published
Long-term, Open-label Follow-up Treatment of Patients With A-fib Who Have Been Previously Treated with BIBR 1048	No	Dabigatran	None- open label, nonrandomized Phase II study	Boehringer Ingelheim Pharmaceutical NCT00157248	Dec 2003–Jan 2009	Terminated; has results

Return to Contents

APPENDIX G. CRITERIA USED IN QUALITY ASSESSMENT

General Instructions:
For each risk of bias item, rate as "Yes," "No," or "Unclear." After considering each of the quality items, give the study an overall quality rating of good, fair, or poor.

Detailed Quality Items:
If an item is rated as "No," describe why in the comments column.

Randomization and allocation concealment:

a. **Randomization adequate?* Was the allocation sequence adequately generated?

❏ No ❏ Yes ❏ Not reported/Unclear

b. **Allocation concealment?* Was allocation adequately concealed?

❏ No ❏ Yes ❏ Not reported/Unclear

Outcomes:

a. **Outcome assessors blinded (hard outcomes)?* Were *Outcome assessors* blind to treatment assignment for "hard outcomes" such as mortality?

❏ No ❏ Yes ❏ Not reported/Unclear

b. **Outcome assessors blinded (soft outcomes)?* Were *Outcome assessors* blind to treatment assignment for "soft outcomes" such as symptoms?

❏ No ❏ Yes ❏ Not reported/Unclear

c. *Lack of measurement bias?* Were the measures used reliable and valid? If so, choose "Yes," indicating no important measurement bias.

❏ No ❏ Yes ❏ Not reported/Unclear

Data analysis:

a. **All outcomes reported?* Are reports of the study free of suggestion of selective outcome reporting (systematic differences between planned and reported findings)?

❏ No ❏ Yes ❏ Not reported/Unclear

b. **Incomplete outcome data adequately addressed?*

❍ Yes (no systematic differences between groups in withdrawals from study and no high overall loss to follow-up; all eligible, randomized patients are included in analysis (ITT) ❍ No

❍ Not reported/Unclear

c. *Adequate power for main effects?*

❑ No ❑ Yes ❑ Not reported/Unclear

Results:

a. *Other selection bias?* Were systematic differences observed in baseline characteristics and prognostic factors across the groups compared?

❑ No ☑ Yes ❑ Not reported/Unclear

b. **Comparable groups maintained?* (Includes crossovers, adherence, and contamination). Consider issues of crossover (e.g., from one intervention to another), adherence (major differences in adherence to the interventions being compared), contamination (e.g., some members of control group get intervention), or other systematic differences in care that was provided.

❑ No ❑ Yes ❑ Not reported/Unclear

Conflict of interest:

a. *Was there the absence of potential important conflict of interest?* The focus here is financial conflict of interest. If no financial conflict of interest (e.g., if funded by government or foundation and authors do not have financial relationships with drug/device manufacturer), then answer "Yes."

❑ No ❑ Yes ❑ Not reported/Unclear

* Items contained in Cochrane Risk of Bias Tool

Overall study rating:

Choose an item.

Please assign each study an overall quality rating of "Good," "Fair," or "Poor" based on the following definitions:

A "Good" study has the least bias, and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.

A "Fair" study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.

A "Poor" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Comments:

❍ Form status:

❍ Fully complete - ready for export

Not ready for export - should be discussed further/ changes reconciled with the abstractor

Table G-1 lists the rating for each risk of bias item as well as the overall rating for each of the included studies.

Return to Contents

Table G-1. Quality assessment of the included studies

Quality Item	Albers et al., 2005	Bauersachs et al., 2010	Connolly et al., 2009	Fiessinger et al., 2005	Granger et al., 2011	Olsson et al., 2003	Patel et al., 2011	Schulman et al., 2009
Randomization adequate?	Yes	Yes	Yes	Yes	NR/unclear	Yes	Yes	Yes
Allocation concealment?	Yes	Yes	Yes	Yes	No	Yes	NR/unclear	Yes
Outcome assessors blinded? (hard outcomes)	Yes	Yes	NR/unclear	Yes	Yes	Yes	Yes	Yes
Outcome assessor blinded? (soft outcomes)	Yes	Yes	NR/unclear	Yes	Yes	Yes	Yes	Yes
Lack of measurement bias?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
All outcomes reported?	Yes	Yes	Yes	NR/unclear	Yes	Yes	Yes	Yes
Incomplete outcome data adequately addressed?	Yes	NR/unclear	Yes	Yes	Yes	Yes	No	Yes
Adequate power for main effects?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Other selection bias?	No	No	No	Yes	No	No	No	No
Comparable groups maintained?	Yes	Yes	Yes	NR/unclear	Yes	Yes	Yes	Yes
Absence of potential important conflict of interest?	No	No	No	No	No	No	No	No
Overall rating	Good	Good	Good	Good	Good	Good	Good	Good

Abbreviation: NR = not reported

Return to Contents

APPENDIX H. GLOSSARY

Abstract screening

The stage in a systematic review during which titles and abstracts of articles identified in the literature search are screened for inclusion or exclusion based on established criteria. Articles that pass the abstract screening stage are promoted to the full-text review stage.

ClinicalTrials.gov

A registry and results database of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov provides information about a trial's purpose, location, and participant characteristics among other details.

Cochrane Database of Systematic Reviews

A bibliographic database of peer-reviewed systematic reviews and protocols prepared by the Cochrane Review Groups in The Cochrane Collaboration.

Companion article

A publication from a trial that is not the article containing the main results of that trial. It may be a methods paper, a report of subgroup analyses, a report of combined analyses, or other auxiliary topic that adds information to the interpretation of the main publication.

Confidence interval (CI)

The range in which a particular result (such as a laboratory test) is likely to occur for everyone who has a disease. "Likely" usually means 95 percent of the time. Clinical research studies are conducted on only a certain number of people with a disease rather than all the people who have the disease. The study's results are true for the people who were in the study but not necessarily for everyone who has the disease. The CI is a statistical estimate of how much the study findings would vary if other different people participated in the study. A CI is defined by two numbers, one lower than the result found in the study and the other higher than the study's result. The size of the CI is the difference between these two numbers.

Cytochrome P-450 (CYP) enzyme system

A family of liver enzymes that serve two major functions: (1) biosynthesis of steroids, fatty acids, and bile acids and (2) metabolism of endogenous and a wide variety of exogenous substrates, such as toxins and drugs. They are classified into CYP gene family and subfamilies; for example, CYP1, CYP2 and CYP3 are responsible for most drug metabolism.

Data abstraction

The stage of a systematic review that involves a pair of trained researchers extracting reported findings specific to the research questions from the full-text articles that met the established inclusion criteria. These data form the basis of the evidence synthesis.

Deep vein thrombosis (DVT)

A blood clot that develops in the deep veins of the legs.

Direct thrombin inhibitors (DTIs)
A new class of anticoagulants that bind directly to thrombin and block its interaction with its substrates.

DistillerSR
An online application designed specifically for the screening and data extraction phases of a systematic review.

Efflux transporter p-glycoprotein
Transporters that pump out unwanted toxic substances through specific efflux pumps. P-glycoprotein is the most common efflux transporter that allows drug molecules to pass through membranes.

Embase
The Excerpta Medica database (EMBASE) produced by Elsevier, a major biomedical and pharmaceutical database indexing over 3500 international journals in the following fields: drug research, pharmacology, pharmaceutics, toxicology, clinical and experimental human medicine, health policy and management, public health, occupational health, environmental health, drug dependence and abuse, psychiatry, forensic medicine, and biomedical engineering or instrumentation. There is selective coverage for nursing, dentistry, veterinary medicine, psychology, and alternative medicine.

Exclusion criteria
The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions.

Factor Xa (FXa) inhibitor
A new class of anticoagulants that bind directly to factor Xa and block its interaction with other substrates.

Full-text review
The stage of a systematic review in which a pair of trained researches evaluates the full-text of study articles for potential inclusion in the review.

GRADE
Grading of Recommendations Assessment, Development, and Evaluation (GRADE), a system of assessing the quality of medical evidence and evaluating the strength of recommendations based on the evidence.

Inclusion criteria
The criteria, or standards, set out before the systematic review. Inclusion criteria are used to determine whether an individual study can be included in a systematic review. Inclusion criteria may include population, study design, sex, age, type of disease being treated, previous treatments, and other medical conditions.

Mitral stenosis
A heart valve disorder that involves the mitral valve, which separates the upper and lower chambers on the left side of the heart. Stenosis refers to a condition in which the valve does not open fully, restricting blood flow.

Nonvalvular atrial fibrillation (AF)
An abnormal cardiac rhythm that occurs at the absence of mitral stenosis. AF is characterized by rapid uncoordinated firing of electrical impulses in the upper chambers of the heart (atria), which prevents the blood from being effectively pumped into lower chamber of the heart (ventricles).

Optimal information size
The number of patients that need to be included in a pooled analysis (meta-analysis) to provide sufficient power to detect the smallest clinically important difference in treatment effect.

PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses, an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.

Publication bias
The tendency of researchers to publish experimental findings that have a positive result, while not publishing the findings when the results are negative or inconclusive. The effect of publication bias is that published studies may be misleading. When information that differs from that of the published study is not known, people are able to draw conclusions using only information from the published studies.

PubMed®
A database of citations for biomedical literature from MEDLINE®, life science journals, and online books in the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and preclinical sciences.

Pulmonary embolism (PE)
Blocking of the pulmonary artery (lungs) or one of its branches by a clot.

Randomized controlled trial
A prospective, analytical, experimental study using primary data generated in the clinical environment. Individuals similar at the beginning of the trial are randomly allocated to two or more treatment groups and the outcomes the groups are compared after sufficient followup time. Properly executed, the RCT is the strongest evidence of the clinical efficacy of preventive and therapeutic procedures in the clinical setting.

RevMan
Review Manager, a software program used for preparing and maintaining Cochrane systematic reviews.

Risk
A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability,

but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Statistical significance

A mathematical technique to measure whether the results of a study are likely to be true. Statistical significance is calculated as the probability that an effect observed in a research study is occurring because of chance. Statistical significance is usually expressed as a P-value. The smaller the P-value, the less likely it is that the results are due to chance (and more likely that the results are true). Researchers generally believe the results are probably true if the statistical significance is a P-value less than 0.05 ($p<.05$).

Strength of evidence (SOE)

A measure of how confident reviewers are about decisions that may be made based on a body of evidence. SOE is evaluated using one of four grades: (1) *High* confidence that the evidence reflects the true effect; further research is very unlikely to change reviewer confidence in the estimate of effect; (2) *moderate* confidence that the evidence reflects the true effect; further research may change the confidence in the estimate of effect and may change the estimate; (3) *low* confidence that the evidence reflects the true effect; further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; and (4) *insufficient*; the evidence either is unavailable or does not permit a conclusion.

Systematic review

A summary of the clinical literature. A systematic review is a critical assessment and evaluation of all research studies that address a particular clinical issue. The researchers use an organized method of locating, assembling, and evaluating a body of literature on a particular topic using a set of specific criteria. A systematic review typically includes a description of the findings of the collection of research studies. The systematic review may also include a quantitative pooling of data, called a meta-analysis.

Venous thromboembolism (DVT/PE)

Obstruction of a vein or veins (embolism) by a blood clot (thrombus) in the blood stream.

Vitamin K antagonist (warfarin)

An anticoagulant that acts by inhibiting the synthesis of vitamin K-dependent coagulation factors; i.e., I, VII, IX and X.

Return to Contents