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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

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- 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.

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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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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]

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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

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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.

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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?

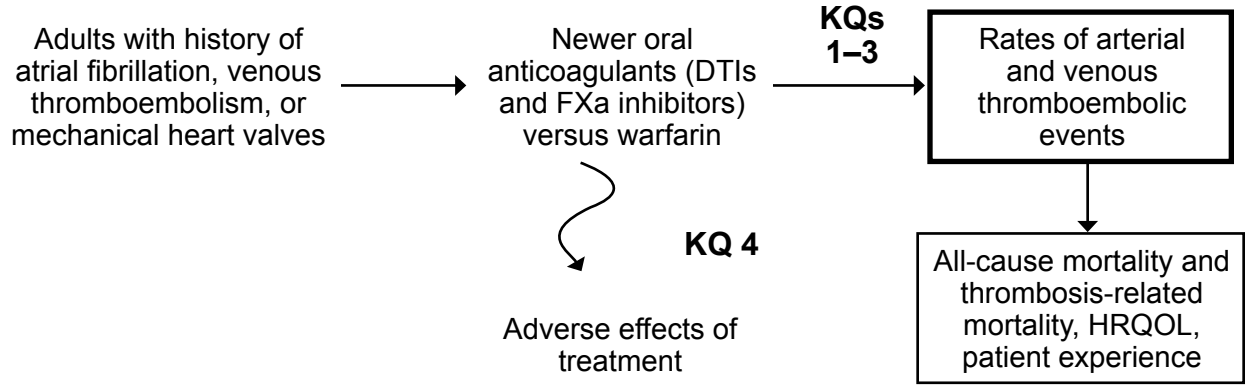
Key Question 3. For patients with mechanical heart valves, what is the comparative effectiveness of newer oral anticoagulants versus warfarin on the incidence of thromboembolic complications, mortality, HRQOL, and patient treatment experience?

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.

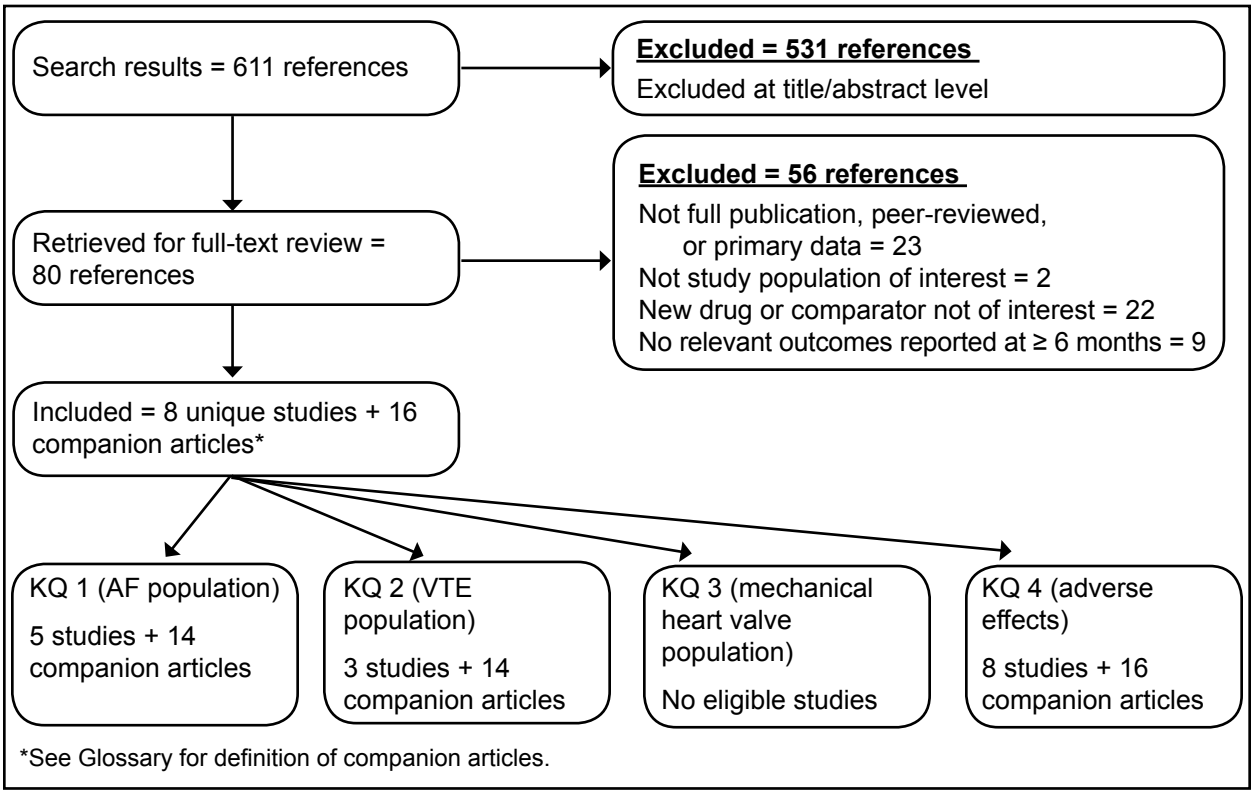
Our search of the observational literature including systematic reviews via PubMed (Figure 3) identified 369 unique citations. An additional 8 citations were identified from personal communications of experts and bibliographies of included studies for a total of 377 unique citations. After applying inclusion 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.

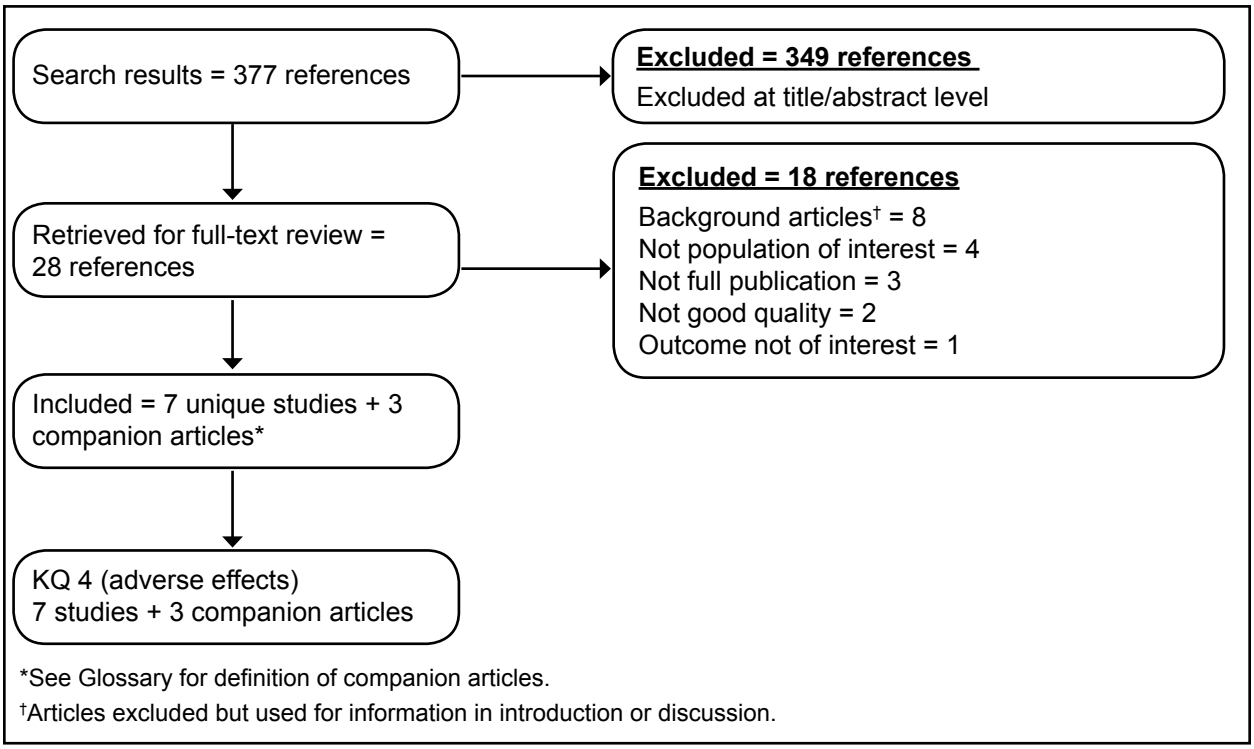
Finally, we searched www.clinicaltrials.gov, which revealed nine unpublished studies that met our eligibility criteria (Appendix F). Of these, four are ongoing trials and two have completed data collection within the last 6 months. The other three trials (NCT00645853, NCT00448214, NCT00329238) were scheduled 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.

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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

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Forest Plots for Studies Without Ximelagatran (Atrial Fibrillation)

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

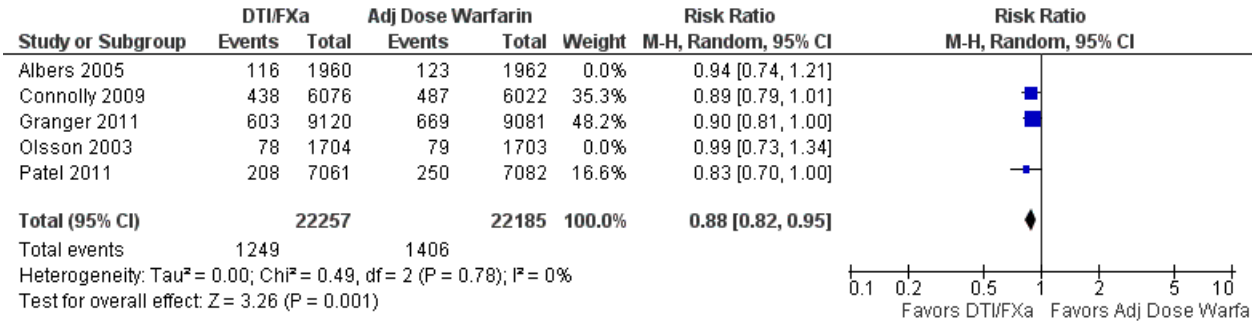


Figure 5. AF: Ischemic stroke without ximelagatran[a]

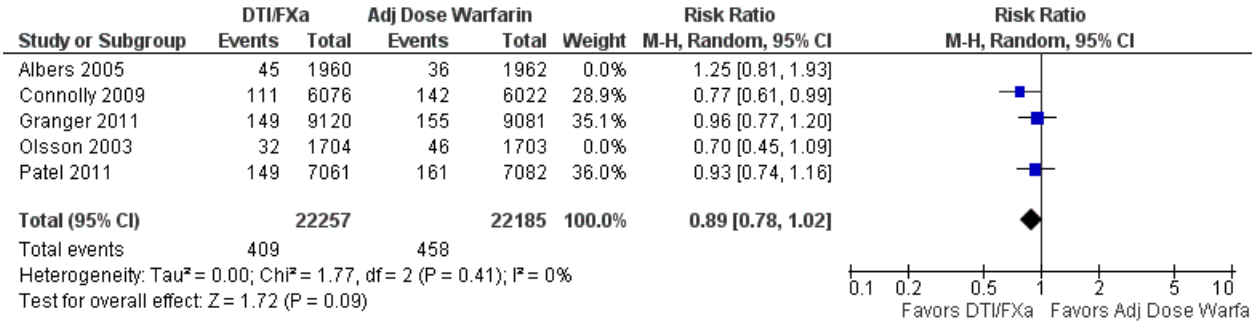
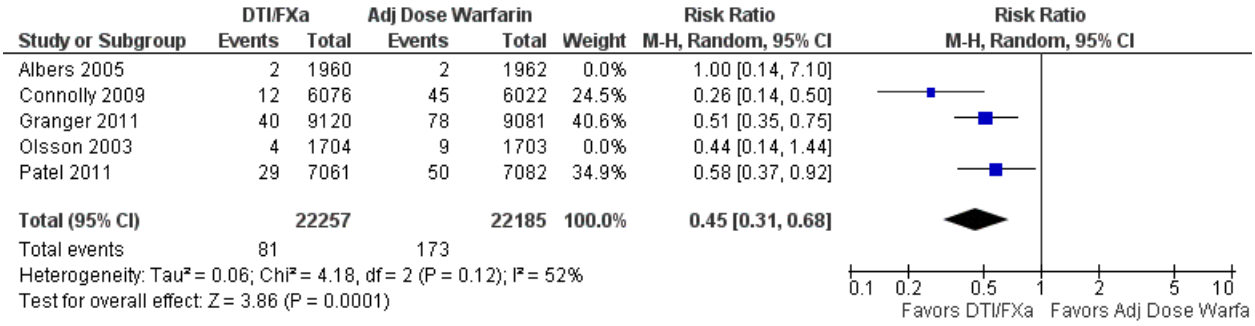


Figure 6. AF: Hemorrhagic stroke without ximelagatran[a]



[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

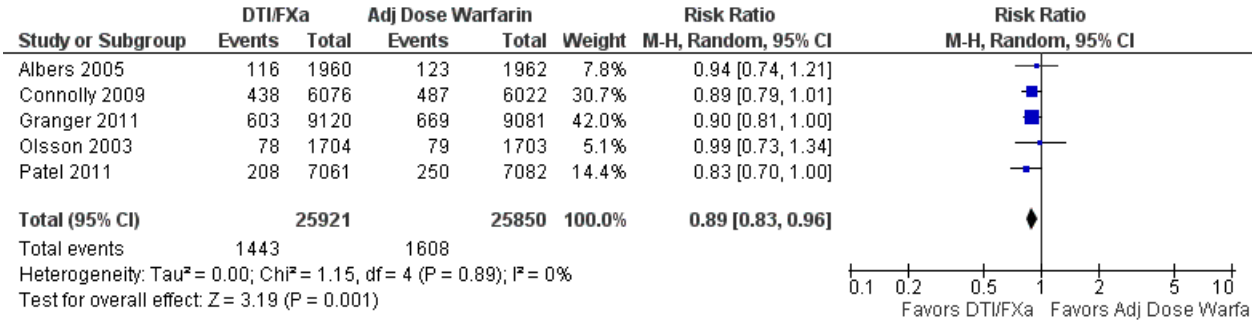


Figure 8. AF: Ischemic stroke with ximelagatran

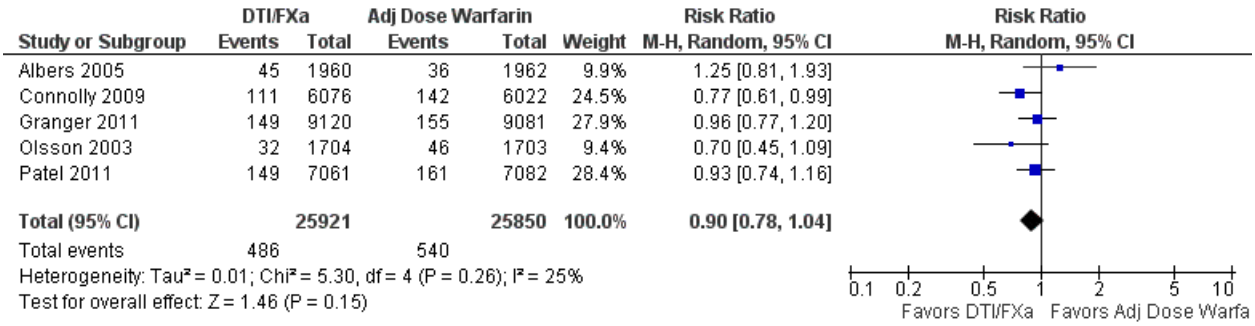
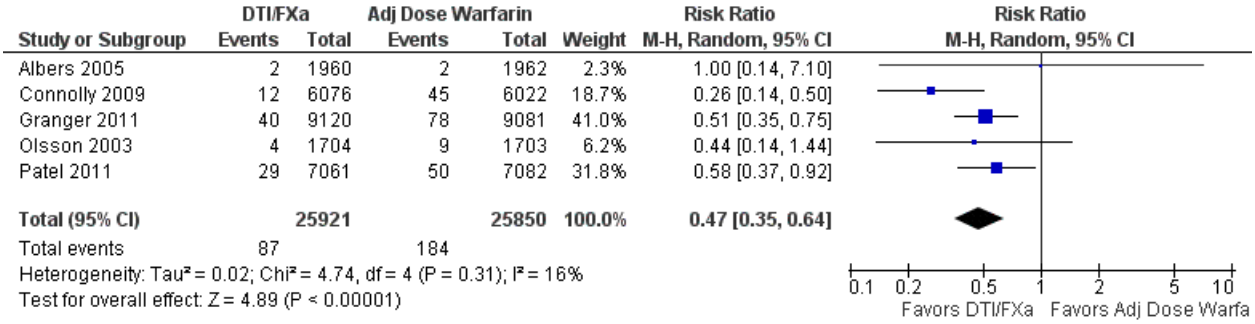


Figure 9. AF: Hemorrhagic stroke with ximelagatran



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]

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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

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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]

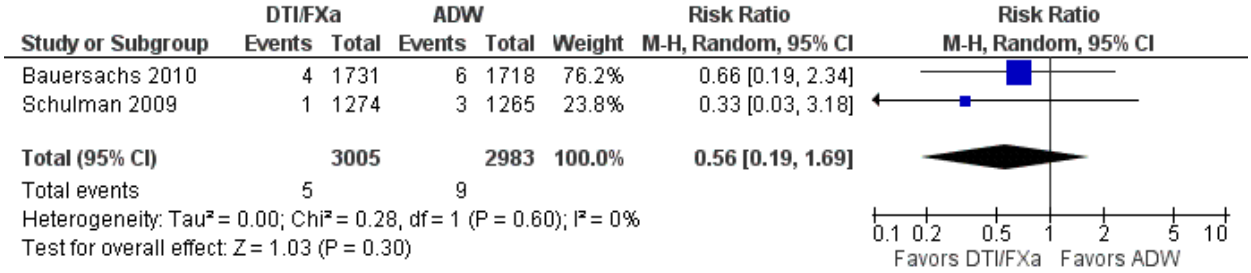
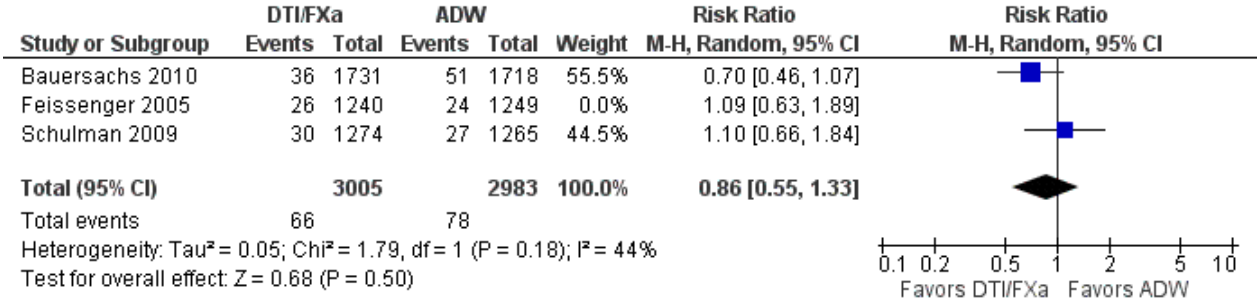


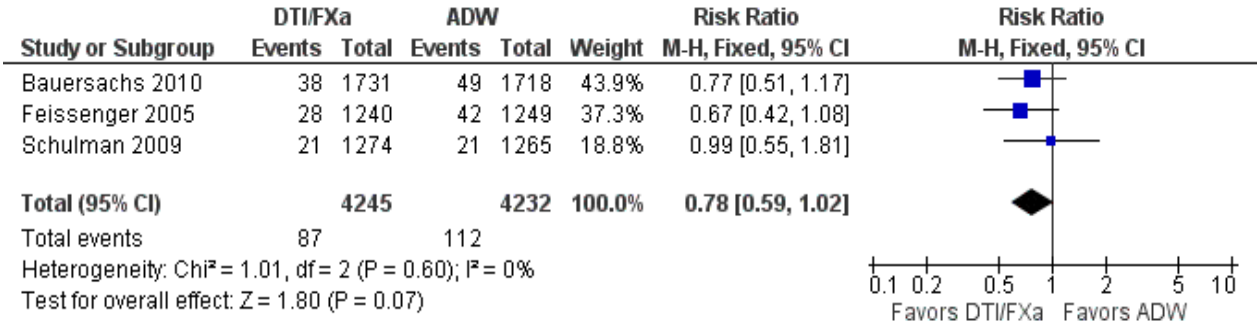
Figure 12. VTE: Recurrent DVT/PE without ximelagatran[a]



[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)

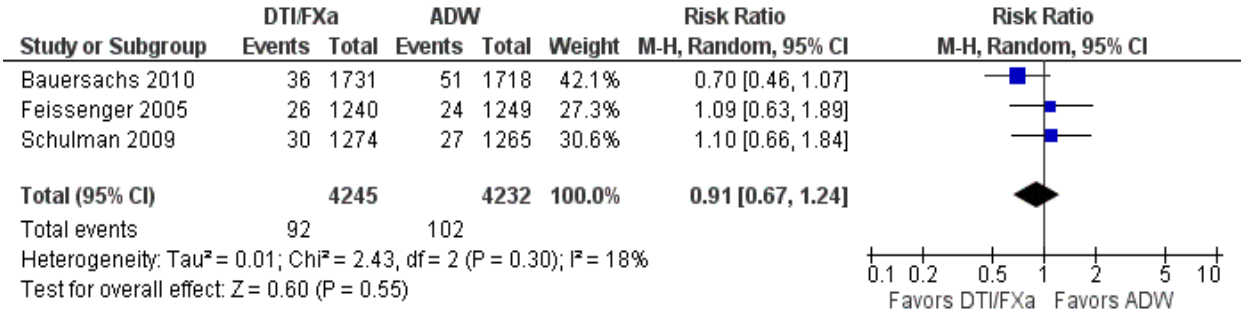
Figure 13. VTE: All-cause mortality with ximelagatran



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

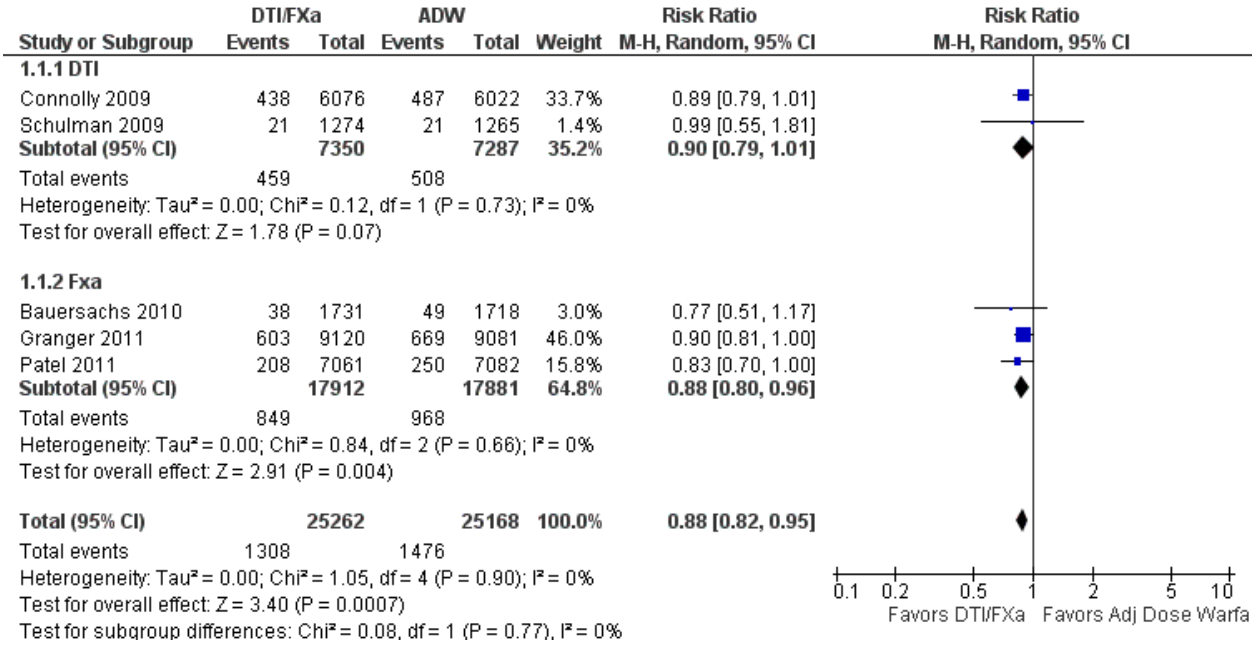


Figure 16. Adverse effects: Discontinued due to adverse effects without ximelagatran

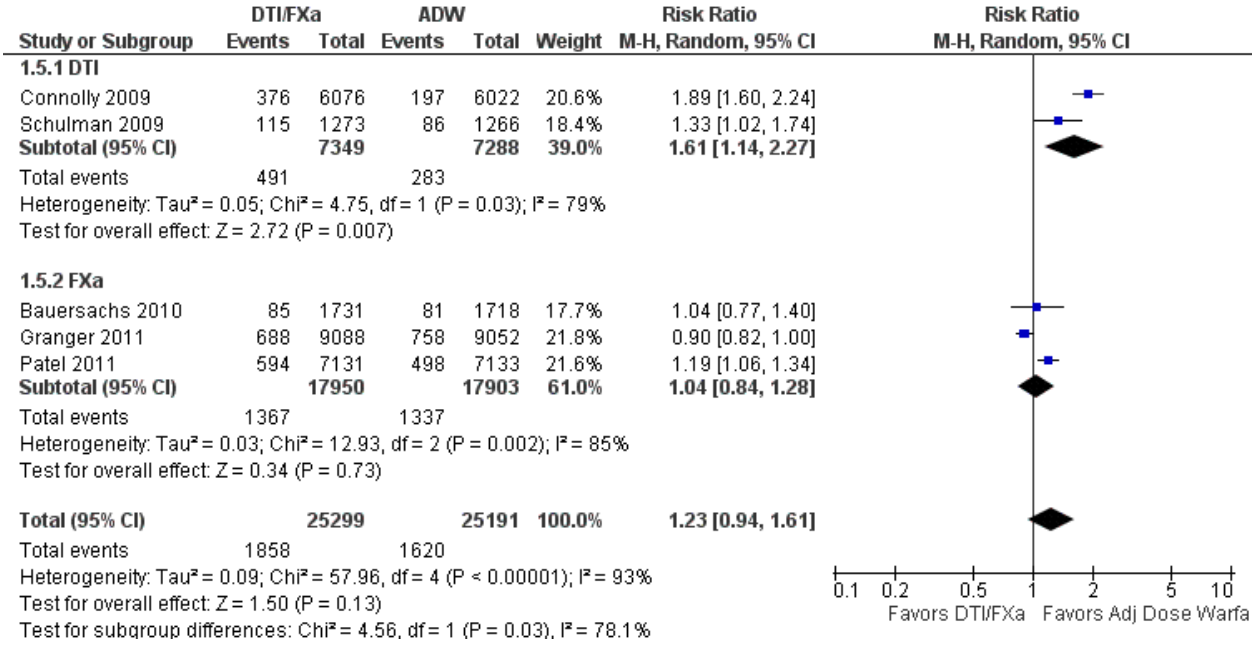


Figure 17. Adverse effects: Major bleeding without ximelagatran

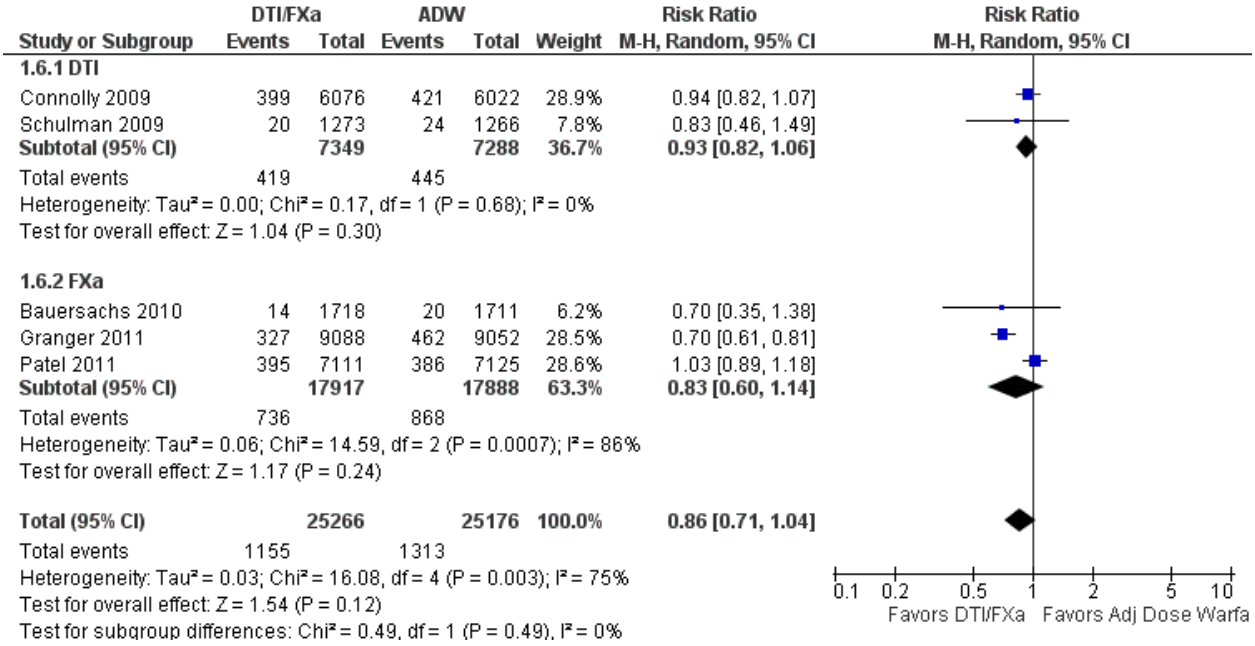


Figure 18. Adverse effects: Fatal bleeding without ximelagatran

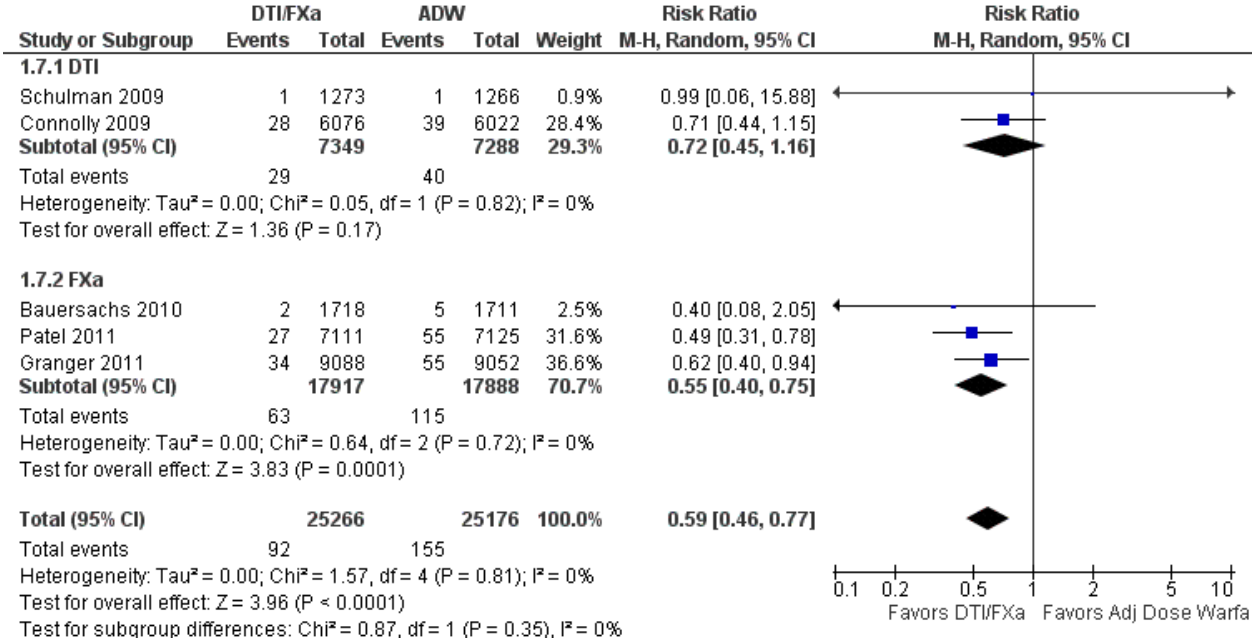


Figure 19. Adverse effects: Gastrointestinal bleeding without ximelagatran

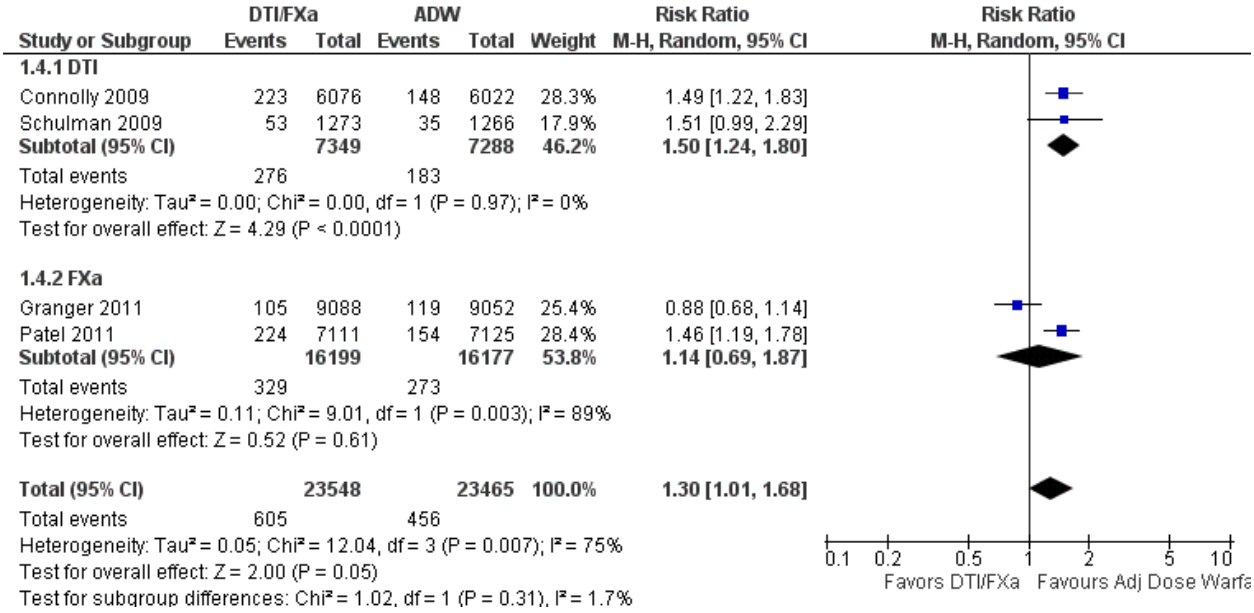


Figure 20. Adverse effects: Myocardial infarction without ximelagatran

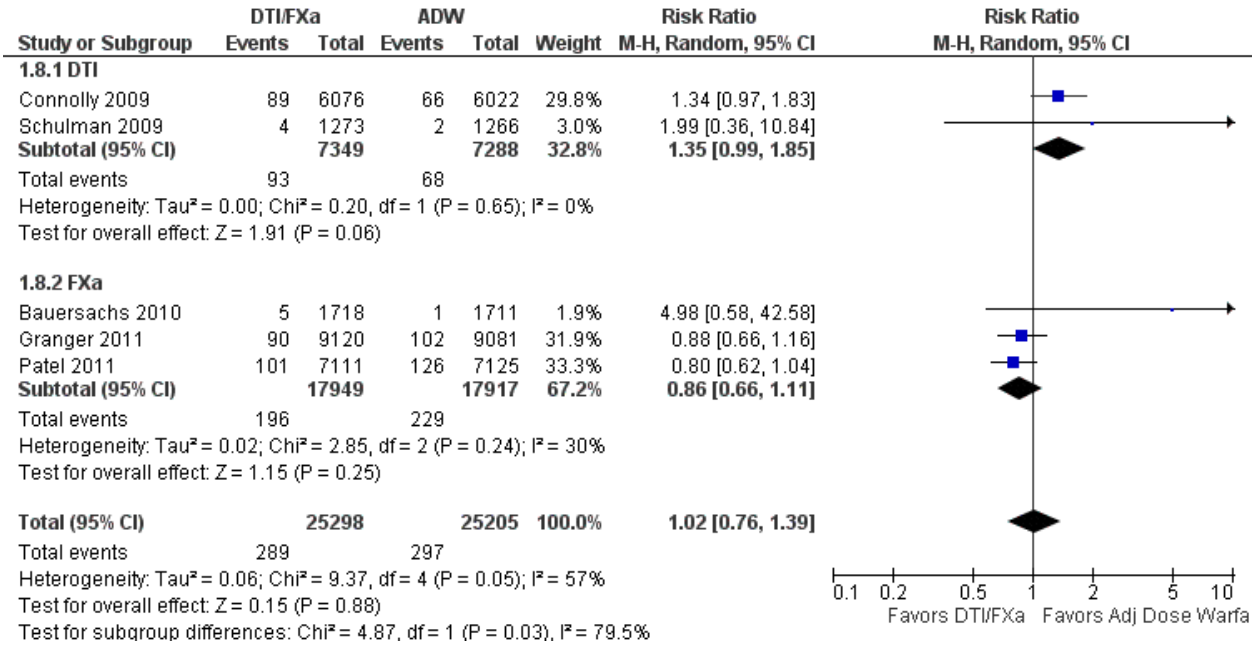
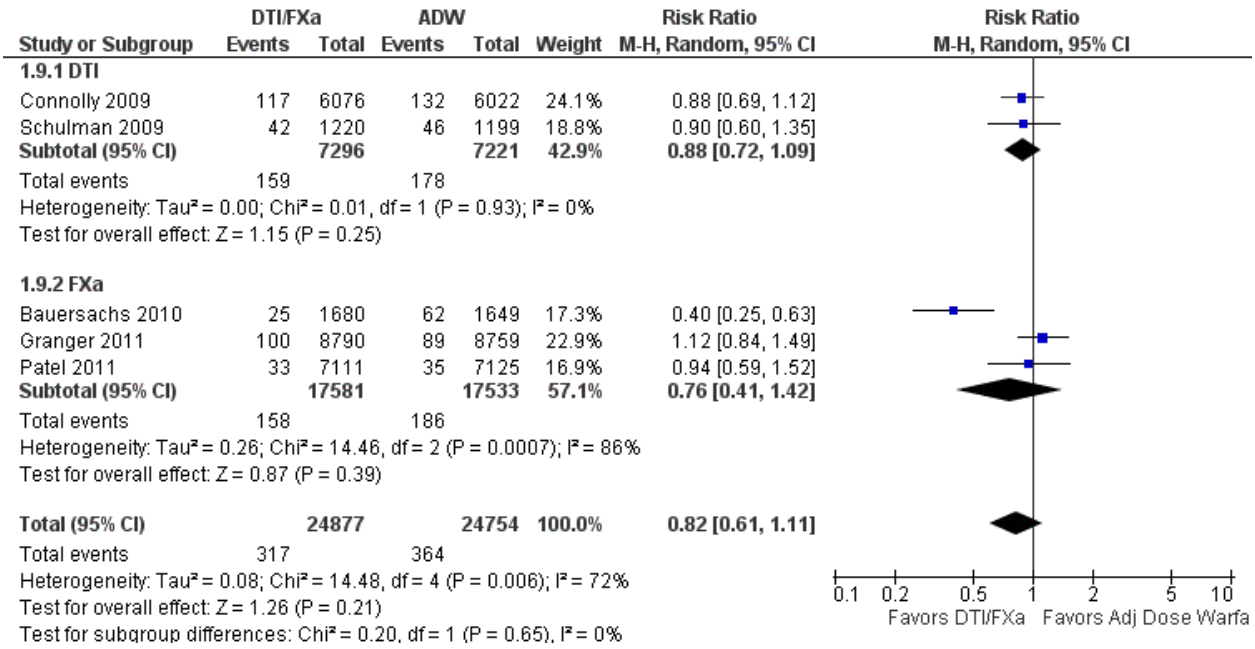


Figure 21. Adverse effects: Liver dysfunction without ximelagatran



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]

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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.

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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

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