



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

April 2012

Prepared for:

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

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PREFACE

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

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

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

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

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

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

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

EXECUTIVE SUMMARY

BACKGROUND

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

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

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

This review was commissioned by the Evidence-based Synthesis Program of the Department of Veterans Affairs (VA) to evaluate newer anticoagulants compared with warfarin. The topic was nominated after a topic refinement process that included a preliminary review of published peer-reviewed literature, consultation with internal partners and investigators, and consultation with key stakeholders. We further developed and refined the following key questions (KQs) based on the review of published peer-reviewed literature in consultation with VA and non-VA experts:

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

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

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

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

METHODS

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

DATA SYNTHESIS

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

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

RATING THE BODY OF EVIDENCE

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

PEER REVIEW

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

RESULTS

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

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

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

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

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

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

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

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

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

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

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

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

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

Number of Studies (Subjects)	Domains Pertaining to SOE			SOE
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision
All-cause mortality				
2 (5988)	RCT/Good	Consistent	Direct	Some imprecision
Moderate SOE				
VTE-related mortality				
2 (5988)	RCT/Good	Consistent	Direct	Important imprecision
Low SOE				
Recurrent DVT/PE				
2 (5988)	RCT/Good	Some inconsistency	Direct	Some imprecision
Moderate SOE				
Discontinuation due to adverse effects				
2 (5988)	RCT/Good	Consistent	Direct	Some imprecision
Moderate SOE				
Major bleeding				
2 (5988)	RCT/Good	Consistent	Direct	Some imprecision
Moderate SOE				

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

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

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

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

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

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

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

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

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

RECOMMENDATIONS FOR FUTURE RESEARCH

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

Table ES-4. Evidence gaps and future research

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

Abbreviation: RCT = randomized controlled trial

CONCLUSION

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

ABBREVIATIONS TABLE

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