

# Mixed Treatment Comparison Meta-Analysis of Aspirin, Warfarin, and New Anticoagulants for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation

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## ABSTRACT

**Background:** Warfarin and aspirin are used to prevent stroke in patients with atrial fibrillation (AF). There are inherent challenges with both treatments, including variable and inconsistent benefit and increased bleeding risks. The availability of new anticoagulants offers some alternatives.

**Objective:** A mixed treatment comparison meta-analysis to evaluate direct and indirect treatment data including aspirin, warfarin apixaban, dabigatran, edoxaban, and rivaroxaban for the prevention of primary or secondary stroke in patients with AF.

**Methods:** A comprehensive, systematic literature search was conducted to identify randomized trials comparing aspirin, warfarin, apixaban, dabigatran, edoxaban, and rivaroxaban in patients with AF requiring treatment for stroke prevention. Open-label and blinded designs were included if they evaluated any stroke or any bleeding event. Data on stroke and bleeding events were abstracted, verified, evaluated, scored, and entered into Aggregate Data Drug Information System version 1.16 to generate a mixed treatment comparison meta-analysis. Direct and indirect comparisons were evaluated, and we looked for inconsistency in closed loop structures. Data are reported as rate ratios with 95% credible intervals. In addition, we reviewed variance statistics and explored variance with node-splitting models.

**Results:** Our literature search yielded 30 articles, 21 of which were included. All treatments except aspirin reduced the risk of any stroke compared with placebo. Warfarin (0.43 [0.33–0.57]), apixaban (0.37 [0.27–0.54]), dabigatran (0.34 [0.21–0.57]), rivaroxaban (0.36 [0.22–0.60]), and aspirin with clopidogrel (0.73 [0.53–0.99]) were more protective than aspirin alone. Warfarin and the new anticoagulants were

similar in the reduction of stroke, vascular death, and mortality. There was no difference in major bleeding between any treatment group. There were more nonmajor bleeding events when comparing warfarin and apixaban (1.83 [1.05–4.03]); no other differences between warfarin and the other new anticoagulants were found.

**Conclusions:** This mixed treatment comparison meta-analysis found similarity between warfarin and the new anticoagulants with the exception of one comparison, in which warfarin was associated with more non-major bleeding than apixaban. Thus, the new anticoagulants are therapeutically comparable when warfarin is inappropriate. (*Clin Ther.* 2013;35:967–984) © 2013 Elsevier HS Journals, Inc. All rights reserved.

**Key words:** aspirin, mixed treatment comparison, network meta-analysis, novel anticoagulants, stroke prevention, warfarin.

## INTRODUCTION

The true global prevalence of atrial fibrillation (AF) is difficult to determine and varies according to geographic locations. In the United States, Canada, and most of Europe, the prevalence of AF is estimated at 1%.<sup>1,2</sup> This represents ~11 million persons with AF in countries with a Western economy. Outside of the United States, Canada, and Europe, AF prevalence varies widely by age, and there is a higher prevalence in older white populations.<sup>3,4</sup> Global prevalence of AF varies substantially by country and region, with much

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lower rates in African and South Asian populations.<sup>5-9</sup> Improvements in health care quality have contributed to human longevity and overall survival despite the burden of some chronic diseases, suggesting there may be an increase in AF prevalence over the next decade.

Stroke continues to be the most burdensome consequence of AF, and patients with valvular disease and AF have a 3- to 7-fold increase in thromboembolic risk; these patients thus require anticoagulation. In patients with nonvalvular AF, the absolute risk of stroke varies 20-fold, although the mean annualized rate is 4.5%, with an estimated 500,000 strokes annually attributable to nonvalvular AF worldwide.<sup>10</sup>

Globally, more than one half of patients with AF qualify for treatment with an oral anticoagulant; thus, selection of drug therapy must involve a careful evaluation between reducing the risks of stroke and anticipated bleeding.<sup>7,11-15</sup> Despite the risk of stroke, anticoagulation remains underused, especially in older persons with AF, because of the risk of bleeding associated with such therapy. However, bleeding concerns should not deter health care providers from carefully evaluating and reevaluating patients with nonvalvular AF with respect to thrombotic risk.<sup>16-22</sup>

Aspirin, an antiplatelet agent, is indicated for patients who have the lowest thrombotic risk and is appropriate when warfarin is impractical or unavailable. Dual antiplatelet therapy with aspirin and clopidogrel is appropriate in selected high-risk patients when warfarin therapy is not feasible.<sup>17,23</sup> Decisions about antiplatelet or anticoagulant therapy have become more complex since the introduction of newer anticoagulants, some of which have been evaluated in large clinical trials with direct evidence of benefit, though these trials have been controversial. Although newer anticoagulants have been endorsed by practice guidelines, they are used infrequently due to unavailability, familiarity with warfarin, or inexperience with these newer agents.<sup>17</sup>

A full series of direct randomized trials between newer anticoagulants is currently unrealistic and impractical. Indirect evaluation by using mixed treatment comparison (MTC) meta-analysis allows for assessment of newer agents individually and compared with warfarin, aspirin, and combinations of aspirin with clopidogrel. Although direct comparisons are

preferable, indirect analysis provides some insight when placed in the appropriate context. An MTC meta-analysis comparing antiplatelet and anticoagulant therapy in patients with nonvalvular AF has been conducted previously but was published before the newer anticoagulants became available.<sup>24</sup> Our evaluation compares available antiplatelet agents, warfarin, and new anticoagulants introduced since the previous review.

## METHODS

This review focused on antiplatelet or anticoagulant use in patients with nonvalvular AF. We evaluated the risk of any stroke or embolism, all-stroke, ischemic stroke, systemic embolism, vascular death, all-cause mortality, major and nonmajor bleeding, and intracranial hemorrhage (Table I).

MEDLINE, EMBASE, and the Cochrane Collaboration were reviewed for randomized controlled trials using antiplatelet or anticoagulant therapy for primary or secondary stroke prevention in patients with nonvalvular AF from January 1, 1991, through August 31, 2012. Search terms included *atrial fibrillation, stroke, aspirin, warfarin, clopidogrel, apixaban, dabigatran, rivaroxaban, and edoxaban*. We included randomized, double-blind, controlled trials published in English. In addition, we included open-label trials using warfarin adjusted to achieve an international normalized ratio (INR) of 2 to 3 to maintain therapeutic efficacy and safety. Finally, key articles were cross-referenced for additional data (Table II). Five reviewers analyzed studies to evaluate methods and patient characteristics and to ascertain randomization, blinding, and allocation concealment. Reviewers then assigned quality scores, and any identified discrepancies were resolved with additional review and discussion.<sup>25</sup>

## Statistical Analysis

MTC meta-analysis was used to create direct and indirect treatment effect comparisons and to establish a Bayesian evidence network.<sup>26-28</sup> These comparisons were built by using Markov chain Monte Carlo analysis within the freely available Aggregate Data Drug Information System (ADDIS) version 1.16.<sup>29</sup> Trials using antiplatelet agents and anticoagulants in patients with nonvalvular AF were selected, and an evidence network was constructed showing the direct

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