Efficacy and Safety of Edoxaban in Nonvalvular Atrial Fibrillation: A Meta-analysis of Randomized Controlled Trials

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Goals: Edoxaban is a potential alternative to warfarin for preventing thromboembolism in atrial fibrillation. However, the efficacy and safety, and the optimal regimen of edoxaban are still controversial. This study compared the efficacy and safety of edoxaban and warfarin in nonvalvular atrial fibrillation, and the effects of different edoxaban dosages. *Methods:* A systematic search for randomized controlled trials comparing edoxaban with warfarin in nonvalvular atrial fibrillation was conducted using PubMed, EMBASE, and the Cochrane Library databases. The main measures and outcomes included efficacy end points (thromboembolic events and all-cause mortality) and safety end points (all bleeding events, major bleeding events, clinically relevant nonmajor bleeding, and minor bleeding). *Results:* Four studies including 23,001 patients were included in the meta-analysis. Edoxaban was noninferior to warfarin for preventing stroke and systemic embolism (risk ratio [RR] = 1.00; 95% confidence interval [CI], .88-1.13; $Z = .01$; $P = .99$). In safety analyses, edoxaban was superior to warfarin in terms of major bleeding, clinically relevant nonmajor bleeding, and minor bleeding (all $P < .00001$). In terms of optimal dosing, 30 mg/day edoxaban had a significantly lower risk of all bleeding (RR = .79; 95% CI, .75-.83; $Z = 9.07$; $P < .00001$) than 60 mg/day, but was inferior at preventing stroke and systemic embolism (RR = 1.31; 95% CI, 1.13-1.51; $Z = 3.56$; $P = .0004$). *Conclusions:* Edoxaban was noninferior to warfarin in terms of efficacy and superior to warfarin in terms of safety. The benefits of edoxaban were related to the dose; efficacy was better at 60 mg/day, but there was lower risk of bleeding at 30 mg/day. **Key Words:** Edoxaban—warfarin—nonvalvular atrial fibrillation—stroke—systemic embolism—bleeding.

Introduction

Atrial fibrillation (AF) is a major health issue in modern society, with a fivefold increased risk of stroke, a threefold increased incidence of congestive heart failure, and a twofold risk of mortality.[1,2] Globally, more than one half of patients with AF qualify for treatment with an oral anticoagulant (OAC). Selecting an OAC involves a careful balance between reducing the risks of a stroke and side effects from bleeding.[3-9] Bleeding concerns should not deter healthcare providers from carefully evaluating and re-evaluating patients with AF for their thrombotic risk, and should not be used to exclude patients from OAC therapy.[10-14]

Warfarin, the most prescribed OAC, acts by lowering the serum levels of vitamin K-dependent procoagulant proteins. It is highly effective in preventing AF-related strokes and systemic embolism, and reduces the risks of AF-related strokes by 64% compared to placebo and 37% compared with antiplatelet therapy. However, the clinical management of warfarin remains problematic because

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Received May 1, 2015; revision received July 27, 2015; accepted July 30, 2015.
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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.07.026

it has a narrow therapeutic index; it has a high risk of causing bleeding; it needs continuous monitoring; and it has potential genetic and age-related variations in dose–response.[15-18] These challenges have led to suboptimal warfarin use in clinical practice and have encouraged the search for more convenient and safe OACs.

Novel oral anticoagulants (NOACs) have been emerging as alternatives to warfarin for thromboembolic prophylaxis in AF because they have predictable anticoagulant effects; they do not need monitoring; they have fewer food and drug interactions; and they have better efficacy/safety ratios. To date, three NOACs have been approved to prevent stroke and systemic embolism in NVAF by the Food and Drug Administration and the European Medicines Agency: dabigatran etexilate, a direct inhibitor, and rivaroxaban and apixaban, factor Xa inhibitors[11,19] Edoxaban is another newly discovered inhibitor of factor Xa. It has been tested for the prevention and treatment of venous thromboembolism and prevention of stroke in AF.[20-24] However, the efficacy and safety of edoxaban, compared with warfarin, for preventing thromboembolism in NVAF remain controversial. Even the dosing of edoxaban has not been agreed upon.[25,26] Here we evaluate the overall efficacy and safety of edoxaban using a Bayesian meta-analysis to assess whether edoxaban could be an alternative to warfarin, and to determine its optimal regimen in the treatment of NVAF.

Methods

Search Strategy and Study Selection

To identify the relevant studies, PubMed, EMBASE, the Cochrane Library, and Web of Science were systematically searched using the following three key terms: "edoxaban," "warfarin," and "atrial fibrillation." Only human studies were considered relevant. The published language was restricted to English, and only studies which completed and published before May 2014 were included. The criteria for selecting studies were as follows: (1) prospective randomized controlled trials (RCTs) comparing edoxaban and warfarin in patients with NVAF; (2) RCTs with primary end points that included an efficacy index (thromboembolic events, stroke/transient ischemic attack [TIA] events, death events, etc.) and safety index (bleeding events); and (3) RCTs with a follow-up duration of 12 or more weeks. The exclusion criteria were as follows: (1) nonrandomized or noncontrolled clinical trials; (2) review articles, (3) animal studies, (4) duplicate reports, and (5) ongoing or unpublished studies.

Data Extraction and Quality Assessment

The data extracted from each study included baseline subject characteristics (e.g., number of patients, mean age, weight, body mass index, risk factors, use of aspirin); efficacy indexes (e.g., stroke/TIA events, systemic embolism, cardiovascular or all-cause mortality, etc.); and safety parameters (all bleeding, major bleeding, clinically relevant nonmajor [CRNM] bleeding, and minor bleeding). Two reviewers worked independently and used a predesigned chart to extract data from each study. A third reviewer was used to make a decision if there was disagreement between the two primary reviewers. Five main parameters were used in the quality assessment: randomization method, blinding, allocation concealment, the method of addressing incomplete outcome data, and intention-to-treat analysis. All quality parameters were scored as A (adequate), B (unknown—it was unclear whether the parameter was reported in the published data), or C (inadequate). The definitions of bleeding events were similar in all the included RCTs. Major bleeding was defined as life-threatening bleeding associated with a critical area or organ (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome); clinically overt bleeding accompanied by a drop in hemoglobin of 2 g/dL or more, or a blood transfusion of 800 mL or more. CRNM bleeding was defined as bleeding not meeting the criteria for major bleeding but resulting in the need for medical intervention; spontaneous skin hematomas ($\geq$25 cm^2); or spontaneous ear–nose–throat bleeding or gingival bleeding lasting for 5 minutes or more. Minor bleeding was defined as any bleeding that did not meet the criteria for major bleeding or CRNM bleeding.[21,27]

Statistical Analysis

The pooled effects of all studies were presented as risk ratios (RRs) with 95% confidence intervals (CIs), and sensitivity analyses were performed when significant heterogeneity was observed. We used the standard chi-square test to assess the heterogeneity between studies. The heterogeneity between studies was considered significant with an I^2 of more than 50% and a P value less than .10. The fixed effect model was used to assess the pooled study effects when the heterogeneity between studies was not significant; otherwise the randomized effect model was used, and sensitivity analyses were required. Publication bias was assessed first using funnel plots, and any significantly asymmetrical funnel plots were confirmed using Egger's and Begg's tests. Data analysis was performed using Review Manager 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark) and STATA 12.0 (StataCorp LP, College Station, TX). In the subgroup analysis, only 30 and 60 mg/day doses of edoxaban were assessed because they were used in all four RCTs. However, both 45 mg/day (Yamashita et al.[20]) and 120 mg/day (Weitz et al.[22]) edoxaban doses were used in one trial respectively, so these two dose levels were not used as subgroups.