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Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism? A sex-based meta-analysis

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ABSTRACT

Introduction: Bleeding complications occur more frequently in women than men in clinical trials of warfarin and thrombolytics. It is unknown whether these sex-related differences exist for new oral anticoagulants, including dabigatran, rivaroxaban, and apixaban. To determine whether women suffer more bleeding complications with these agents, we conducted a systematic review and meta-analysis of randomized controlled trials on new oral anticoagulants for venous thromboembolism (VTE).

Materials and Methods: Medline, Embase, and the Cochrane-controlled trial register on the Cochrane library were searched to identify studies that evaluated novel oral anticoagulants versus any comparator, and reported outcomes, including major bleeding and recurrent VTE, stratified by sex. No language restrictions were applied. Studies were evaluated according to a priori inclusion criteria and critically appraised using established internal validity criteria. Pooled relative risk was estimated using a random effects model.

Results: Eight studies were eligible, comprising 9417 patients. There was no difference in the primary efficacy outcome of recurrent VTE between men and women [Relative Risk (RR) 1.02, 95% confidence interval (CI) 0.74-1.39]. However, men had less major bleeding with novel oral anticoagulants compared to women [RR 0.79, 95% CI 0.66-0.97, p = 0.03]. All-cause mortality was not reported by sex in any of the studies.

Conclusion: Women suffer more bleeding complications than men when receiving novel oral anticoagulants for VTE. Future clinical trials should report outcomes stratified by sex, and further studies are needed to investigate the clinical impact of this sex-related safety difference.

Introduction

Oral anticoagulants are effective for acute treatment and prevention of venous thromboembolism (VTE), but are limited by bleeding complications [1]. The annual frequency of any warfarin-induced bleeding is 15% to 20% per year [2]. Major bleed frequency is between 0.32% and 2.1% per year with warfarin [3], and life-threatening or fatal bleed frequency ranges between 0-0.25% [3].

Many factors, including female sex, are linked to an increased risk of bleeding for patients using anticoagulants [4]. Female sex is an independent predictor of bleeding in several cardiovascular and VTE observational studies that used warfarin or thrombolytics [5–7]. In acute coronary syndrome, females sex is associated with a 43% higher risk for major bleeding (odds ratio, OR 1.43; 95% CI 1.23- 1.66) [6].

Recently, several new oral anticoagulants (NOACs), including dabigatran [8–10], ximelagatran [11–14], rivaroxaban [15–19], and apixaban [20–22] have been compared to warfarin for stroke prevention in atrial fibrillation (AF) and for acute treatment of VTE. They were also compared to placebo in the extended treatment of VTE for secondary prevention. While these agents are non-inferior to warfarin for thrombotic outcomes [23], they also carry a risk of major and fatal bleeding. It is unknown whether there are sex- related differences either for efficacy outcomes or bleeding outcomes. To determine whether sex is a risk factor for bleeding or recurrent VTE with the NOACs, we conducted a systematic review and meta-analysis of randomized trials of NOACs for acute and extended VTE treatment.

Materials and Methods

We performed a systematic review of randomized controlled trials (RCTs) that included adult patients (≥18 years old) treated with NOACs for acute or extended VTE treatment. Patients treated for other indications, including atrial fibrillation, were excluded in order to minimize study heterogeneity when comparing safety and efficacy endpoints. The review was reported according to the PRISMA statement [24,25]. *A priori* the protocol was registered at PROSPERO (CRD42013003680).

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Literature Search

Databases searched included Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE from inception through January 2013. A search strategy aimed to identify all published and unpublished literature, in any language, related to our topic was employed. The detailed medical subject heading terms and/or keywords used are listed in the appendix. We also screened major Hematology international conferences (American Society of Hematology, European Hematology Association) for abstracts from their annual meetings from 2008-2012. We searched registries of health technology assessments and clinical trials, and contacted authors, experts and manufacturers of the new oral anticoagulants (Astra Zeneca, Bayer, Janssen Pharmaceutica, Pfizer, Bristol-Myers Squibb, and Boehringer Ingelheim) for additional studies and unpublished data. The search was supplemented by a manual search of the reference list of retrieved studies.

Study Selection

To be eligible, studies had to meet the following criteria: 1) was a randomized controlled trial comparing the use of a NOAC (dabigatran, rivaroxaban, apixaban and ximelagatran) to warfarin/low molecular weight heparin (LMWH) for the initial treatment of an acute DVT or PE, or comparing the use of a NOAC to placebo for the extended treatment of DVT or PE; 2) the diagnosis of VTE was objectively established with the use of compression ultrasonography or venography of leg veins or ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries; 3) the study reported primary efficacy outcomes (recurrent VTE); and 4) the study reported primary safety outcomes (major and clinically relevant bleeding with predefined and accepted criteria). Exclusion criteria included: 1) use of NOAC in prophylactic doses; 2) use of NOAC for indications other than acute VTE treatment and extended duration VTE treatment; and 3) failure to report sex stratified efficacy and safety outcomes (excluded after attempts made to contact author and drug manufacturers to release unpublished data). Though the direct thrombin inhibitor ximelagatran was withdrawn from the market in 2006 because of hepatotoxicity, VTE efficacy and bleeding safety were reported and we elected to include these data for completeness.

Two reviewers (GA, HA) screened each citation. Studies considered relevant by one or both reviewers were retrieved, and the full text was independently assessed by two reviewers for inclusion. Disagreements were resolved by discussion. A bibliographic web-based tool (www.wizfolio.com) was used to download all references and ensure the absence of references duplication.

Data Extraction

Two reviewers independently abstracted the data describing baseline characteristics (including age, sex, comorbidities, previous VTE, use of antiplatelet therapy), treatment interventions and outcomes. Discrepancies were solved by discussion. We contacted authors of the respective publications to obtain missing information. Results of intention-to-treat analyses were collected if reported. In the included trials, primary efficacy outcome was defined as: any recurrent VTE (PE, DVT or both) occurring at a new site or any extension of the initial clot while on treatment, diagnosed objectively using any accepted validated diagnostic tool. The primary safety outcome was major and clinically relevant non-major bleeding, which was defined homogenously across all trials. Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding causing a fall in hemoglobin level of 20 g/L. Clinically relevant non-major bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but that was associated with the need for medical intervention, hospitalization or drug discontinuation. The secondary outcome was all-cause mortality.

Quality Assessment

We used three quality assessment tools. For studies included in the quantitative data synthesis and meta-analysis, we used Newcastle-Ottawa Scale in each arm and considered each arm as a separate observational study [26]. The McMaster Quality Assessment Scale of Harms (McHarm) [27] was used to evaluate the reporting of adverse events. In qualitative review studies, the Cochrane Collaboration's tool for assessing risk of bias in randomized trials was used [28]. Two reviewers independently assessed each study's risk of bias and disagreements were resolved by discussion.

Data Synthesis and Analysis

The Cochrane Collaboration recommended program, Review Manager V 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011), was used to analyze data. Overall estimated effect size and variation were expressed as relative risk (RR) with a 95% confidence interval (CI). The DerSimonian-Laird random effects model assumption was used to adjust for within and between study heterogeneity [29]. The Cochrane's chi-square (Q) test was calculated; a value <0.10 indicated significant heterogeneity. The corresponding I^2 statistic was calculated to quantify heterogeneity [30]. Forest plots were used to illustrate the individual studies, their final pooled effect size, and each individual study's weight (which is based on the inverse of variance plus heterogeneity). To assess whether analysis of studies with outcomes stratified by gender would reveal data representative of all trials that did not report outcomes stratified by gender, we performed a sensitivity analysis.

Results

Study Selection and Characteristics

Thirteen trials published in eleven papers [9,10,12–14,16–19,21,22] were identified by our search strategy (Fig. 1). After examining all manuscripts completely, eight studies were found to be suitable for the quantitative data synthesis and meta-analysis of the primary efficacy outcomes, while the other five were used for the qualitative review. Only five of the eight studies reported sex-stratified bleeding and were meta-analyzed for the safety outcome. Analysis was performed on pooled data reported from the NOACs arms of the original RCTs. Characteristics of the eight studies that were eligible for the meta-analysis are included in Table 1. Three studies used rivaroxaban, one study used ximelagatran, one study used apixaban and three studies used dabigatran. In three studies, patients were enrolled for acute venous thromboembolism treatment [9,16,17] while in the remaining five [10,12,16,21,31], patients were previously treated for 6–12 months then enrolled for prevention of recurrent VTE. The EINSTEIN investigator study [16] reported acute DVT cohorts and the extended VTE cohorts and was considered two separate studies. The median age of the participants was 57.5 years, and the female proportion ranged between 34.7% and 53% (median 43.7%). Patients were treated for acute VTE (PE, DVT or both) in one trial, for acute DVT only in 6 trials, for PE only in 1 trial, for extended VTE treatment in 5 trials.

Quality Assessment and Risk of Bias

Most of the studies scored between 6–7 stars in New-Castle Ottawa scale [26] indicating moderate quality and moderate risk of bias (Table 1). The EINSTEIN studies had high quality scores (8 stars). Mortality rate was assessed by record linkage in all studies. There was a $<5\%$ loss of follow up in all studies. McMaster Quality Assessment Scale of Harm (McHarm) [27] was also used to assess the quality of reporting adverse events; overall, the quality of included studies was high, scoring between 12–14 points. Harm was predefined in all studies.