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Gender Differences in Efficacy and Safety of Direct Oral Anticoagulants in Atrial Fibrillation: Systematic Review and Network Meta-analysis

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Abstract

Background: Studies indicate that women with atrial fibrillation (AF) are less likely to receive anticoagulants despite their higher risk of stroke compared with men. **Objective**: To evaluate whether the efficacy and safety of direct oral anticoagulants (DOACs) differ in women with AF as compared with men. Our secondary aim was to examine gender differences regarding the safety and efficacy of specific DOACs. **Data Sources:** MEDLINE, EMBASE, Cochrane, and ClinicalTrials.gov were searched through March 2017. **Study Selection and Data Extraction:** Randomized clinical trials that reported on major bleeding and stroke with DOACs in women and men with AF were included. Meta-analysis and network meta-analysis was performed. **Data Synthesis:** Five trials met the inclusion criteria. Among 66 389 patients, 37.8% were women. Women treated with DOACs were at higher risk of stroke and systemic embolism compared with men (RR = 1.19; 95% CI = 1.04-1.35; I^2 = 10%) but there was a significantly lower risk of major bleeding in women compared with men (RR = 0.86; 95% CI = 0.78-0.94; I^2 = 0%). Network meta-analyses suggested differences between various DOACs in men and women. **Limitations:** Patient-level data enabling control for differences in baseline risk and head-to-head comparisons between DOACs were not available. **Relevance to Patient Care and Clinical Practice:** Undertreatment with DOACs among women cannot be justified. **Conclusion:** Women treated with DOACs had a lower rate of major bleeding and higher rate of stroke and systemic emboli compared with men. Further investigation of DOACs, including differences between the DOACs in specific populations is warranted.

Keywords

direct oral anticoagulants, atrial fibrillation, bleeding, stroke, gender, women

Introduction

There is concern that women may respond differently compared with men to cardiovascular medication because of pharmacokinetic, pharmacodynamic, and clinical differences.[1] For instance, warfarin dosage is known to be associated with gender, and women required fewer milligrams per week than men.[1] Indeed, studies have documented sex differences in the incidence of adverse effects for several cardiovascular medications, with women with atrial fibrillation (AF) having higher risk for adverse events than men (1.5- to 1.7-fold).[2] Women are also at higher risk of stroke than men. However, though the risks and benefits of direct oral anticoagulants (DOACs) may differ with gender, data on gender differences with DOACs is limited.[1]

Despite the higher risk of stroke in women with AF compared with men, studies indicate that women with AF are less likely to be prescribed warfarin or DOACs for the prevention of stroke.[3-5] A meta-analysis of observational studies reported that women were significantly less likely to receive warfarin compared with men.[6] Another study in the ambulatory setting also reported lower warfarin use among women compared with men.[7] One of the potential

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explanations for lower warfarin use among women is the perception of a higher risk of bleeding complications in women,[7] thus leading to decreased prescription of warfarin and higher rates of ischemic stroke in women with AF.[7]

In recent years, DOACs—namely, dabigatran, rivaroxaban, apixaban, and edoxaban—have been used for the prevention of stroke in patients with AF, in many circumstances replacing the vitamin K antagonists (VKAs).[8-10] Although some studies reported that women may react differently to anticoagulants compared with men,[7,11] phase III studies of DOACs in patients with nonvalvular AF were underpowered to confirm both efficacy and safety among women. This has been discussed in the guidelines of the American Heart Association and the American Stroke Association.[12]

Our primary aim was to assess whether the efficacy and safety of DOACs as a class are different in women with AF as compared with men with AF. Our secondary aim was to examine gender differences in the safety and efficacy of specific DOACs.

Methods

Study Identification

We searched the MEDLINE, EMBASE, and Cochrane databases through November 2015 to identify all published randomized clinical trials involving the comparison of DOACs with VKAs for nonvalvular AF without language or date restrictions. The search was updated until March 2017. We manually reviewed and evaluated clinicaltrials.gov, online resources, conference abstracts, and published systematic reviews. Relevant studies were identified by using the following search terms: *controlled clinical trial, CT, phase III trials, apixaban, rivaroxaban, dabigatran, edoxaban, NOAC*, and *new oral anticoagulant* (see the online appendix). The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework guidelines.[13] Because this study was a review and meta-analysis, no internal review board was required.

Study Selection, Data Extraction, and Outcomes

Two authors independently reviewed eligible studies to assess for potential inclusion. Disagreements were resolved by consensus. The primary efficacy end point of this analysis was defined as stroke or systemic embolism. The primary safety end point of this analysis was defined as major bleeding, which was defined as clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), decrease in hemoglobin concentration of more than 2 g/dL, transfusion of >2 units of whole blood or packed red blood cells, or permanent disability.[14]

Extraction of relevant data was performed by 1 reviewer and confirmed by a second; data for efficacy outcomes by gender in the ROCKET-AF and ENGAGE-AF studies and for safety outcomes in the ROCKET-AF, ENGAGE-AF, and RE-LY studies, were also extracted from the US Food and Drug Administration's (FDA's) open access data website (Drugs@FDA). Study quality was assessed by 2 reviewers using The Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[15] Disagreements were resolved by consensus.

Studies were included if they satisfied the following criteria: randomized clinical trials (RCTs) of adults comparing DOACs with standard antithrombotic therapy for the treatment of nonvalvular AF. DOACs included dabigatran etexilate, rivaroxaban, apixaban, and edoxaban. Standard antithrombotic therapy included VKAs (warfarin or acenocoumarol, phenprocoumon, fluindione), heparin derivatives and heparin-like anticoagulants (dalteparin, enoxaparin, nadroparin, tinzaparin, danaparoid, fondaparinux), and acetylsalicylic acid or other platelet aggregation inhibitors. We included all RCTs that reported data on gender irrespective of patients' characteristics. We excluded trials of DOACs for other indications (ie, treatment or prevention of VTE in surgical and nonsurgical patients, treatment of acute coronary syndrome, following valve replacement), pharmacokinetic studies in healthy adults, reviews, case reports, nonrandomized trials, and observational studies.

We also excluded from the analysis data of edoxaban when dosed at 30 mg, with 15 mg given in the setting of decreased creatinine clearance from the ENGAGE AF study,[16] because this dosage was not approved for standard use by the FDA and European Medicines Agency (EMA). We thus included only edoxaban studies that assessed dosages of 60 or 30 mg given in the setting of decreased creatinine clearance.

Because the AVERROES study enrolled only patients for whom warfarin was unsuitable, its population may have differed substantially from studies with warfarin as comparator. We therefore performed a sensitivity analysis omitting the AVERROES study.

Statistical Analysis

We calculated Mantel-Haenszel random-effect pooled risk ratios and the corresponding 95% CIs, so as to determine the risk ratios for major bleeding and to assess the efficacy for DOACs versus warfarin in the prevention of stroke and systemic embolism, using RevMan version 5.3 (Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). Network meta-analysis was performed using the software R, version 3.0.3 (R Core Team, 2014).[17] The package "netmeta" was used to conduct the quantitative analyses within the R environment.[18] The protocol for this study was registered at the PROSPERO registry of systematic reviews (registry number: CRD42014013730).

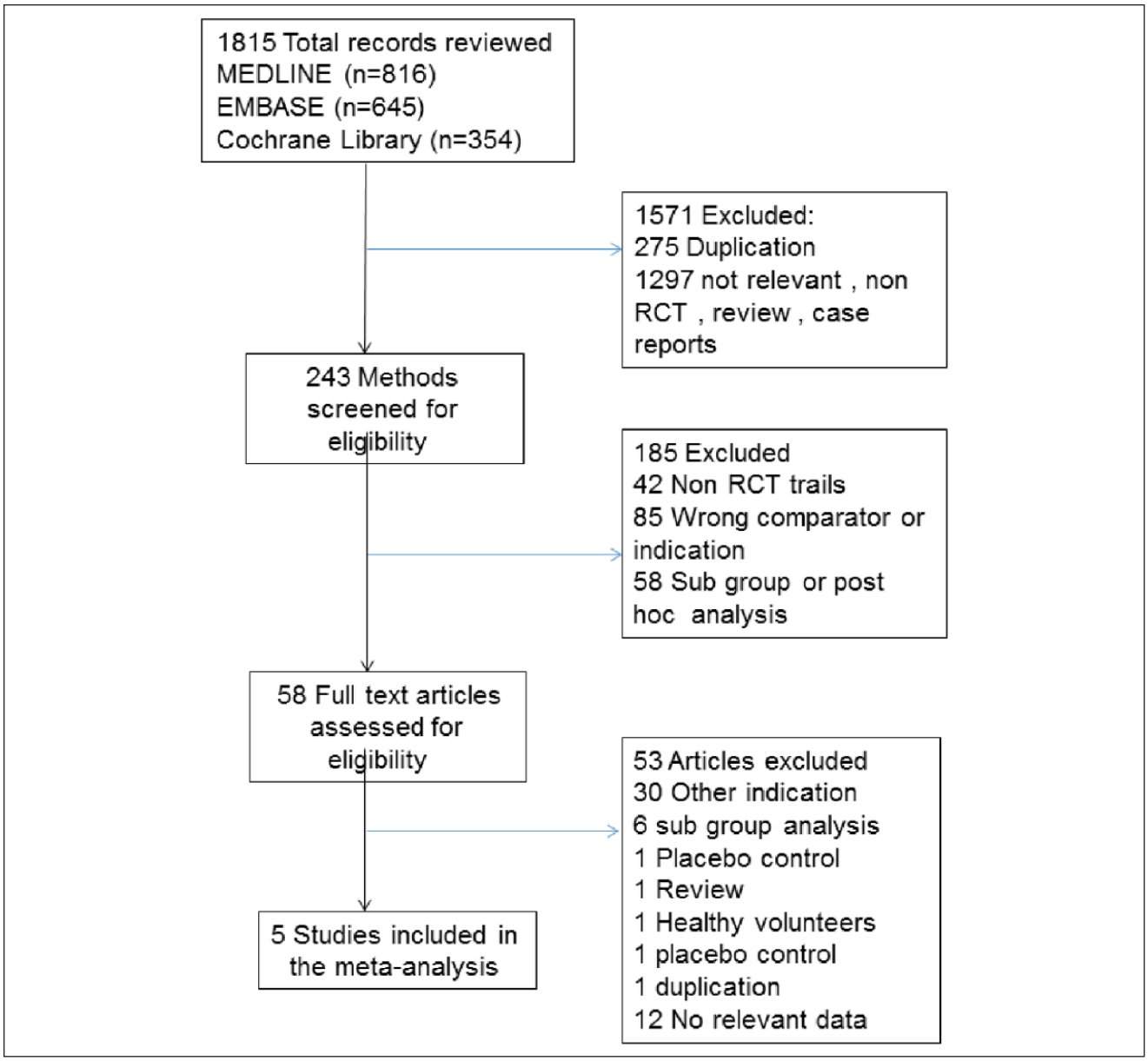

Figure 1. Flow chart showing the systematic literature search and study selection process.
Abbreviation: RCT, randomized controlled trial.

Results

Literature Search

A systematic search was conducted between October 2013 and March 2017. Of items searched, 1815 citations met the initial search criteria, and 5 articles met the inclusion criteria in the final analyses for efficacy and safety (Figure 1).[16,19-22]

The studies in this analysis included 66 389 patients, of whom 37.8% were women. Quality assessment is summarized in Appendix Table S1; the overall risk of bias among the included studies was low. Trials were all funded by pharmaceutical industry sources. The follow-up period ranged from 1.1 to 2.8 years. The major characteristics of the included trials are presented in Table 1.

Quantitative Outcome

Efficacy and Safety of DOACs in Women Compared With Men

Efficacy. The efficacy of DOACs in women versus men was assessed using a total of 1034 events in 38 111 patients, of whom 37.3% were women. The overall relative risk of stroke and systemic embolism in patients on DOACs was higher in women compared with men (RR = 1.19, 95% CI = 1.04-1.35, I^2 = 10%; Figure 2A).

Table 1. Main Characteristics of the Randomized Trials Included in the Meta-analysis.

Study	n	Study Population	Intervention	Control	Mean Age (years) DOAC/ Comparator	Male Sex (%) DOAC/ Comparator	Follow-up (years)
RE-LY,[21] 2009	18 113	AF	Dabigatran 150 mg BID or 110 mg BID[a]	Warfarin	71.4/71.6	63.8/63.3	2
ROCKET AF,[20] 2011	14 264	AF	Rivaroxaban 20 mg daily[b]	Warfarin	73/73	60.3/60.3	1.6
ARISTOTLE,[19] 2011	18 201	AF	Apixaban 5 mg BID[c]	Warfarin	70/70	64.5/65	1.8
AVERROES,[22] 2011	5599	AF	Apixaban 5 mg BID[c]	Aspirin	70/70	59/58	1.1
ENGAGE AF,[16] 2013	21 105	AF	Edoxaban 30 or 60 mg OD[d]	Warfarin	72/72	61.7/62.5	2.8

Abbreviations: AF, atrial fibrillation; BID, twice daily; DOAC, direct oral anticoagulants; OD, once daily.
[a]Patients were randomly assigned to receive either 110-mg or 150-mg doses of dabigatran.
[b]A 15-mg rivaroxaban dose was used in patients with a creatinine clearance of 30 to 49 mL/min.
[c]Apixaban doses of 2.5 mg were used in patients with 2 or more of the following criteria: age of at least 80 years, body weight of no more than 60 kg, or a serum creatinine level of 1.5 mg/dL (133 µmol/L) or more.
[d]Patients were randomly assigned to receive 60- or 30-mg doses of edoxaban. For patients in either group, the dose was halved if any of the following characteristics were present at the time of randomization or during the study: estimated creatinine clearance of 30 to 50 mL/min, a body weight of 60 kg or less, or the concomitant use of verapamil or quinidine.

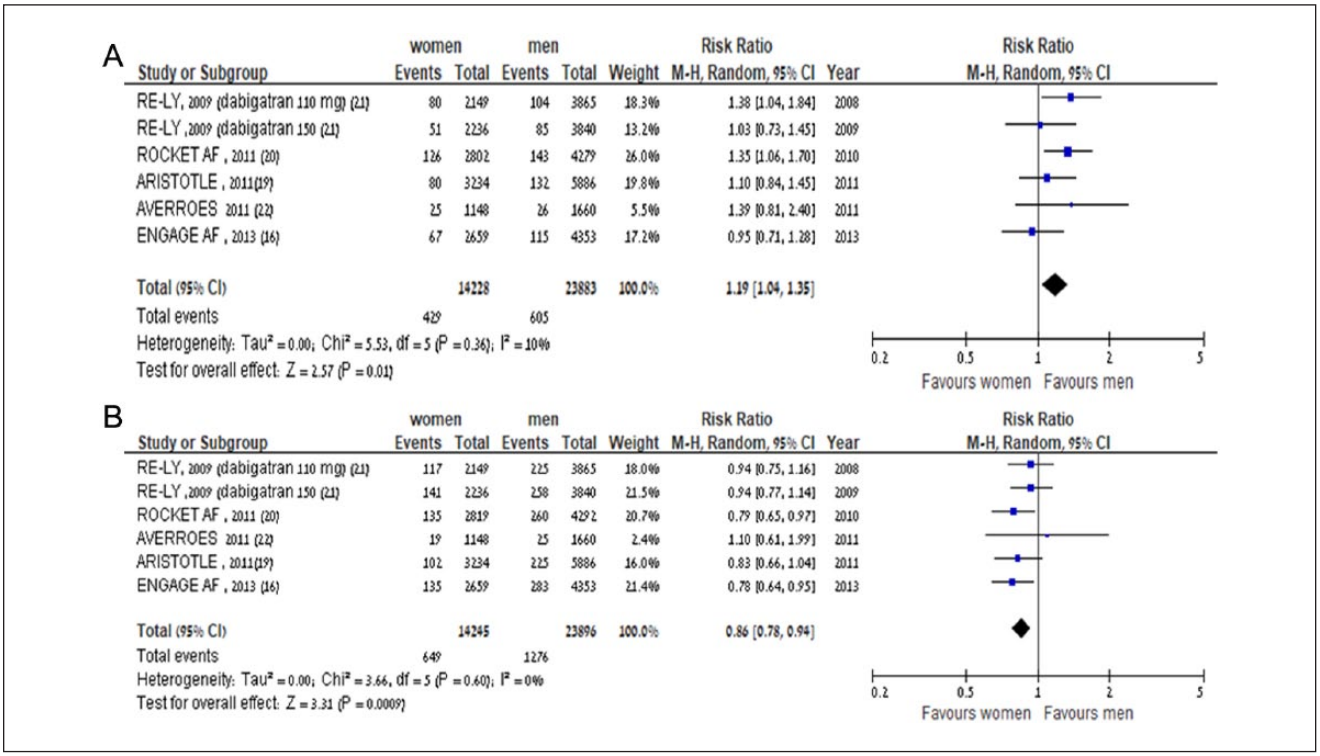

Figure 2. Efficacy and safety in women versus men during treatment with direct oral anticoagulants: A. Risk for stroke and systemic embolism in women versus men. B. Risk for major bleeding in women versus men.

Safety. The relative risk of major bleeding in women versus men during treatment with DOACs was assessed in the setting of a total of 1925 major bleeding events in 38 141 patients, of whom 37.3% were women. DOACs were associated with a significantly lower risk of major bleeding in women compared with men (RR = 0.86, 95% CI = 0.78-0.94, I^2 = 0%; Figure 2B).

Sensitivity analysis. One trial (AVERROES) used aspirin as comparator and enrolled only patients for whom warfarin was unsuitable. To assess whether inclusion of this trial altered results, we performed a sensitivity analysis excluding the AVERROES study. Efficacy and safety outcomes were equivalent between the analysis with and without the AVERROES study (Figure S1).

Table 2. Major Bleeding, Difference Between the Specific Medications in Women and Men.

	Women			Men		
	OR	Lower 95% Confidence Limit	Upper 95% Confidence Limit	OR	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Apixaban vs dabigatran 110 mg	0.73	0.51	1.04	0.95	0.73	1.22
Apixaban vs dabigatran 150 mg	0.62[a]	0.44	0.88	0.81	0.63	1.04
Apixaban vs edoxaban	0.84	0.60	1.18	0.90	0.71	1.15
Apixaban vs rivaroxaban	0.57[a]	0.40	0.81	0.73[a]	0.57	0.95
Dabigatran 110 mg vs dabigatran 150 mg	0.86	0.66	1.10	0.86	0.71	1.03
Dabigatran 110 mg vs edoxaban	1.16	0.82	1.62	0.96	0.75	1.22
Dabigatran 110 mg vs rivaroxaban	0.79	0.56	1.12	0.78	0.60	1.00
Dabigatran 150 mg vs edoxaban	1.35	0.97	1.88	1.11	0.88	1.42
Dabigatran 150 mg vs rivaroxaban	0.92	0.97	1.30	0.90	0.70	1.16
Edoxaban vs rivaroxaban	0.68[a]	0.49	0.95	0.81	0.64	1.03

Abbreviation: mg, milligram; OR, odds ratio.
[a]The ORs and 95%CIs do not include 1.0.

Differences in efficacy and safety of specific DOACs. The very low heterogeneity (I^2 = 12% in women and 0% in men) in findings related to the efficacy of the DOACs indicates that there are no major differences between the different drugs. In the setting of the high heterogeneity in the safety profile of DOACS compared with warfarin (I^2 = 67% in women and 43% in men), we assessed the possibility that specific DOACs may differ from each other in terms of the risk of major bleeding, using Network meta-analysis with frequentist methods. The network plot for major bleeding outcomes are shown in Figure S2. In women, there was a lower rate of major bleeding in patients taking apixaban compared with dabigatran 150 mg (odds ratio [OR] = 0.62; 95% CI = 0.44-0.88) and rivaroxaban (OR = 0.57; 95% CI = 0.40-0.81). Less major bleeding was also observed with edoxaban compared with rivaroxaban (OR = 0.68; 95% CI = 0.49-0.95). In men, there was a lower rate of major bleeding in patients treated with apixaban compared with rivaroxaban (OR = 0.73, 95% CI = 0.57-0.95; Table 2). Visual inspection of the funnel plots revealed no indication of publication bias (Appendix Figure S3).

Discussion

In this meta-analysis, we report that in women, treatment with DOACs is associated with a lower rate of major bleeding, but a higher rate of stroke and systemic emboli, when compared with men The lower risk of major bleeding in women compared with men was unique to DOACs and was not observed in the warfarin arm (RR = 0.93, 95% CI = 0.84-1.04, I^2 = 25%; Appendix Figure S4A).

We performed indirect comparisons using network meta-analysis that indicated, for the first time, that there were significant differences among the specific DOACs between women and men: in women, apixaban and edoxaban were associated with a significantly lower risk of major bleeding as compared with other DOACs, whereas in men, apixaban was associated with a significantly lower risk of major bleeding compared with rivaroxaban.

Our findings of a lower risk of DOAC-associated major bleeding in women as compared with men are supported by previous studies. Reduced risk of bleeding in women as compared with men has been previously reported with apixaban and rivaroxaban in a subanalysis of the ROCKET and ARISTOTLE studies[23,24] and in a previous meta-analysis on gender differences in bleeding risk.[25] This finding has several possible explanations. First, the lower risk for major bleeding in women as compared with men may be related to dosage adjustment based on body weight, which is recommended for apixaban and edoxaban.[16,19,22] Indeed, in our network meta-analysis, the lower risk of bleeding in women was observed with apixaban and edoxaban, as compared with other DOACS. The role of low body weight as a risk factor for bleeding has been demonstrated with other anticoagulants that require dose adjustment according to body weight. In a study of enoxaparin-related bleeding in hospitalized patients, low body weight (<55 kg) was found to be a risk factor for bleeding, observed in women treated with enoxaparin.[11] Second, the lower rate of major bleeding may be related to differences between men and women in regard to receiving antiplatelets, with the proportion of male patients being higher. In the RE-LY study (dabigatran) and the ENGAGE study (edoxaban), patients who received concomitant antiplatelets were more frequently male.[26,27] In the ARISTOTLE study (apixaban) and the ROCKET AF study (rivaroxaban), more male participants underwent percutaneous coronary intervention and required antiplatelet therapy.[28,29] Several studies have shown that the combination of antiplatelet and oral anticoagulation therapy increases the risk of bleeding.[26,27,29-31]

Only few previous reports have addressed gender differences in the response to DOACs,[23-25,32] and our meta-analysis is the first to report that DOACs have a decreased efficacy in women as compared with men. Previous meta-analyses that have addressed this issue did not find gender differences in the efficacy of DOACs.[32,33] In a subanalysis of the ARISTOTLE study, similar efficacy was reported for apixaban in women and men.[24] There were no gender differences reported in a prior meta-analysis[25] as well.

The result indicating an increased rate of stroke with DOACs in women compared with men can also be explained in a number of ways. It is possible that women respond differently to DOACs because women differ from men in several pharmacokinetic, pharmacodynamic, and clinical characterstics.[1] Another possibility is that women were more likely to receive reduced doses of some DOACs because of lower body weight. There is some controversy as to whether some DOACs with dose adjustments are as effective as the full dose.[34,35] However it is also possible this is the result of differences in baseline risk of stroke, because in the subanalysis of the ARISTOTLE and AVERROES studies, women were on average older,[24,36] and the percentage of women with CHADS2 score >3 was higher. Because we had no access to patient-level data, we could not compute baseline risk-adjusted estimates. In addition, because most of the studies did not report the prevalence of stroke risk factors (such as age or CHADS2 score) by sex, we could not perform a metaregression evaluating whether these group-level factors modified the observed difference in stroke rate between men and women. The reduced efficacy in women compared with men is also seen in the warfarin arm in these studies (RR = 1.23, 95% CI = 1.08-1.39, I^2 = 0%; Appendix Figure S4B) and supports the argument that this effect is not related to the kind of treatment but to a higher risk of stroke in women.[3,4]

A second explanation for the difference between our work and previous meta-analyses is the much larger numbers of patients on DOACs included in our meta-analysis compared with previous studies (38 141 as compared with 26 260[25] treated with DOACs), increasing the power of our study to detect differences in efficacy. Furthermore, the quality of our data may have been enhanced because we utilized data extracted from the FDA reports on drugs@FDA, in addition to data from the published reports that were used in previous meta-analyses. Moreover, we included all 4 DOACs in our meta-analysis, whereas other meta-analyses did not include edoxaban.[25]

Our study has several limitations, largely shared by all meta-analyses. First, 12 studies met the inclusion criteria, but outcome data were available only in 5 of those studies. However, the studies that were not included in our analyses were of small size and included only 4301 patients, whereas our analysis included 66 389 patients. It is, therefore, unlikely that outcome data from these studies would significantly change our conclusions. A second limitation is that our analysis refers to the DOACs as a class and does not differentiate between the different DOACs, although these agents do differ in terms of mechanisms of action and pharmacokinetics. This includes differences in sensitivity to renal dysfunction,[37] low body mass, advanced age, and differing drug interactions[9] that may possibly lead to differential gender effects. We used network meta-Analysis to assess the probability that specific DOACs may differ from each other in their efficacy and safety. However, it should be noted that no head-to-head comparisons between DOACs were performed in RCTs, such that the network meta-analysis was informed by indirect comparisons only, and results should be viewed as exploratory. Third, our analysis aggregated post hoc analyses of DOACs in women and men, whereas the trials were not specifically designed to assess the treatment effect of DOACs according to gender. Fourth, the data on dabigatran safety according to gender were based on the original results of the RE-LY study, although the outcomes of this study were subsequently revised twice.[38] Although, reportedly, these revisions did not change the primary efficacy and safety analyses of this study, it is unclear whether they could possibly have affected certain analyses. Fifth, difference in age or CHADS2 could contribute to our finding of gender differences in risk of stroke with DOACs; however, we cannot asses the effect of these baseline risk factors because patient-level and group-level data for these variables were not available. Sixth, the differences among the specific DOACs in terms of bleeding risk may be related to variability in patient characteristics between the studies. Differences in CHADS2 scores have been reported. To date, unfortunately, we cannot investigate this hypothesis because bleeding risk scores are not available for rivaroxaban and edoxaban.

Relevance to Patient Care and Clinical Practice

In this meta-analysis, DOACs are associated with a significantly lower risk of major bleeding in women, as opposed to men. Indirect comparison between specific DOACs regarding their safety and efficacy suggest the importance of dose adjustment to body weight in women. As some studies indicate, women with AF are less likely to be prescribed anticoagulation despite their higher risk of stroke compared with men. These findings suggest that undertreatment with DOACs among women cannot be justified.

Conclusion

Treatment with DOACs in women is associated with a lower rate of major bleeding and higher rate of stroke and systemic emboli when compared with men. This suggests that undertreatment of women for fear of bleeding cannot

be justified. Further investigation of DOACS, including a more thorough investigation of the safety and efficacy of the dose reductions of the various DOACS in specific populations, is warranted.

Authors' Note

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Declaration of Conflicting Interests

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Supplemental Material

The supplementary material for this article is available online.

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