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Atrial fibrillation in women: treatment

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Abstract

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Competing interest statement

E.M.H. has served on Advisory Boards for Armetheton, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Janssen, Medtronic, Pfizer, and Portola. P.T.E. is a principal investigator on a grant from Bayer HealthCare to the Broad Institute. The other authors declare no competing interests.

Review criteria

PubMed was searched for full-text manuscripts in English language. For the search terms for each topic, see Supplementary information S6 (table). Additional studies were included after reviewing the references of relevant manuscripts. Only RCTs were included for treatment efficacy. Observational studies of all types were included for utilization and prescription patterns. Men-only studies or studies with a very small proportion of women were excluded unless they were included in a combined analysis.

SUPPLEMENTARY INFORMATION

See online article: S1 (table) | S2 (table) | S3 (table) | S4 (table) | S5 (table) | S6 (table)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

Sex-specific differences in the epidemiology, pathophysiology, presentation, prognosis, and treatment of atrial fibrillation (AF) are increasingly recognized. Women with AF generally experience worse symptoms, poorer quality of life, and have higher risk of stroke and death than men with AF. Effective treatment of the arrhythmia in women is critical to reduce the rate of adverse events. We review the current evidence on sex-specific differences in the utilization and outcomes of treatments for AF, including rate-control and rhythm-control strategies, and stroke-prevention therapy. In addition, we provide a critical evaluation of potential disparities and biases in health-care use that may be associated with differences in the outcomes between women and men. We underscore current knowledge gaps that need to be addressed in future studies to improve the management of AF in women. In particular, we suggest several strategies to produce quality evidence from randomized, clinical trials for women with AF.

Sex-specific differences in the epidemiology, pathophysiology, presentation, and prognosis of atrial fibrillation (AF) have been well-described in this journal¹. Despite a lower prevalence of AF in women than in men worldwide², women generally experience worse symptoms and quality of life, and a higher risk of stroke and death compared with men^{1,3}.

Thromboembolic stroke owing to AF accounts for approximately one-fifth of ischaemic strokes⁴, and one-quarter of all strokes in adults aged >80 years⁵. AF-related stroke is associated with severe outcomes, including 30-day mortality of 24–33%^{4,6,7}. Female sex is a well-recognized independent risk factor for AF-related stroke. Among patients who have experienced a stroke, AF is more common in women than in men^{8,9}. Women are older at the time of stroke^{10–12} and have a higher incidence of stroke when aged >75 years¹⁰. Moreover, compared with men, women are significantly more likely to be living alone or widowed before a stroke¹², and suffer from greater neurological deficits after a stroke¹³. Therefore, improving stroke prevention in women with AF is critical to reducing the public-health burden of AF.

In this Review, we describe sex-specific differences in the two major components of AF management: rate or rhythm control and stroke prevention (FIG. 1). We describe differences in treatment utilization in AF between women and men, and evaluate potential sex-specific disparities or biases in health-care use. In addition, we assess sex-specific differences in enrolment, treatment efficacy, and treatment complications reported in randomized, controlled trials (RCTs) of AF. Finally, we identify potential barriers to effective treatment of AF in women that need to be addressed in the future.

Evaluating sex-specific differences

Differences, disparities, and biases in health care

Sex-specific differences in health-care utilization in cardiovascular treatments are well-documented^{14–16}. However, a systematic approach to examining sex-specific differences in AF treatment has been lacking. In our critical evaluation of studies that report sex-specific differences in the treatment of AF, we apply a three-tiered framework on differences, disparities, and biases proposed by Rathore and Krumholz¹⁷ (FIG. 2). For a sex-specific difference to be considered a disparity, the difference must be associated with worse clinical

outcomes and cannot simply be a reflection of patient-related factors. For instance, it might be inappropriate to invoke a health-care disparity if women with AF do not receive a treatment because of differential eligibility, contraindications to treatment, patient preferences, or confounding owing to demographic and medical characteristics. However, overly stringent enrolment criteria in clinical trials might enhance trials' internal validity, but inadvertently reduce the studies' generalizability¹⁸. Establishing a health-care disparity implies that there are systemic factors associated with differences in treatment causing worse outcomes in one group compared with another. When sex-specific disparities are not caused by systemic health-care factors, they can indicate inherent unconscious biases in individual providers or the health-care system leading to lower quality of care. Whereas sex-related unconscious bias and stereotyping have been well-documented in health care^{16,19,20} and academic science^{21–23}, whether such biases occur in AF care has been inadequately studied. In subsequent discussions, we delineate challenges in establishing disparities or biases in sex-specific differences related to AF treatment.

Randomized clinical trials

We present sex-specific differences in treatment efficacy and safety using results derived from subgroup and *post-hoc* analyses of RCTs. Although subgroup and *post-hoc* analyses are often the main source for sex-specific data, they have a higher likelihood of producing false-positive results compared with prespecified analyses. In addition, many RCTs were not powered to study sex-specific differences in primary or secondary outcomes, which might contribute to false-negative findings. Our ability to derive sex-specific results is further limited by underrepresentation of women in cardiovascular disease prevention trials²⁴. Only 25–30% of the participants in the major trials of warfarin were women (FIG. 3). The proportion of women participants has increased in trials of the non-vitamin K antagonist oral anticoagulants (NOACs) to approximately 40%, to reflect more accurately the relative prevalence of AF in women compared with men. Despite the described limitations, our aim is to emphasize the importance of sex-specific differences in treatment outcomes in RCTs in order to provide evidence-based management for all patients and to highlight potential differences in response to treatment between women and men for further investigation.

Rate and rhythm control

There have been limited studies to investigate sex-specific outcomes and complications with rate-control and rhythm-control strategies. We focus our discussion on the most clinically salient topics relevant to sex-specific differences, and provide critical evaluation of RCTs (details of individual trials are listed in TABLE 1) and large observational studies available to date. For a comprehensive list of the observational studies, see Supplementary information S1 (table).

The AHA/ACC/HRS²⁵ and the ESC²⁶ guidelines recommend both pharmacological control of ventricular rate and pharmacological and electrical cardioversion as first-line therapy for all types of AF (class I). Several RCTs to evaluate rate versus rhythm control have demonstrated no significant differences in clinical outcomes between the two treatment

strategies^{27–30}. However, US guidelines suggest that earlier restoration of sinus rhythm can slow progression of AF and reduce morbidity²⁵.

Utilization

Data from the Euro Heart Survey³¹ showed that, in an unadjusted analysis of patients with typical symptoms, there was no sex-specific difference in the use of rate versus rhythm control, whereas in patients with atypical or no symptoms, women were more likely to receive rate over rhythm control compared with men. In comparison, the Euro Observational Programme Pilot survey on AF³² reported that, in an unadjusted analysis among patients with typical symptoms, women were more likely to receive rate over rhythm control than men, and there was no sex-specific difference in treatment for asymptomatic patients. The survey also reported that men were more likely to have asymptomatic AF than women³³. Neither of the studies adjusted for important prognostic factors including age, duration of AF, and structural remodelling such as left atrial enlargement. Multivariable-adjusted analyses from the Center for Medicare and Medicaid have shown that, among the beneficiaries of Medicare who were aged ≥66 years at the time of AF diagnosis, women were slightly more likely than men to receive both rate (HR 1.16, 95% CI 1.15–1.17) and rhythm (HR 1.04, 95% CI 1.03–1.05) control³⁴. However, given the lack of adjustment for duration and burden of AF, symptoms, and left atrial enlargement, it remains unclear whether there is a true sex-specific disparity in utilization of rate versus rhythm control in clinical practice. Sex and age effects on the pharmacology of available agents to treat AF, as well as patient preferences might influence the choice between rate-control and rhythm-control therapy; however, these topics have not currently been addressed adequately in the literature.

Outcomes

Sex-specific differences in outcomes of rate versus rhythm control were investigated in subgroup analyses of the AFFIRM and RACE trials. In the AFFIRM trial³⁵, the risk of death did not differ by sex between rate-control and rhythm-control strategies. In comparison, the RACE trial²⁸ reported that women treated with rhythm control had a higher incidence of the primary end point (composite of cardiovascular mortality, heart failure, thromboembolic complications, adverse effects of antiarrhythmic drugs, and pacemaker implantation) compared with women treated with rate control (32.0% vs 10.5%; absolute difference 21.5%, 90% CI 12.1–30.8%). In men, the incidence of the primary end point did not differ significantly between the two treatment groups (17.2% vs 21.1%; absolute difference –3.9%, 90% CI –11.1% to 3.2%). Interpretation and clinical translation of the sex-specific analysis of the RACE trial are challenging because of the small sample size and the use of a composite end point consisting of a wide range of outcomes without reporting the individual event rates.

Cardioversion

In patients with no contraindications, the AHA/ACC/HRS and ESC guidelines recommend amiodarone, dofetilide, flecainide, intravenous ibutilide, and propafenone, for pharmacological cardioversion^{25,26}. There have been no consistent reports of sex-specific differences in the type of antiarrhythmic used in observational studies^{31,32}. Likewise, no sex-

specific differences in likelihood of sinus rhythm have been shown with the use of antiarrhythmics³⁶. Some studies have reported that rhythm-control medications increased the risk of torsades de pointes^{37,38} and sick sinus syndrome in women compared with men³⁹.

A few unadjusted analyses from observational studies have reported that electrical cardioversion is less common in women than in men^{31,32,40}. Without a critical evaluation of confounders associated with use of electrical cardioversion and in the absence of established superiority of cardioversion to rate control, we cannot establish disparities in the use of cardioversion in the treatment of AF. Electrical cardioversion is generally associated with similar success rates in women and men^{41,40,42}, although one study suggested after multivariable adjustments that the risk of AF recurrence was higher in women than in men⁴³.

Catheter ablation

Catheter ablation is currently recommended as a treatment for patients with symptomatic AF that is uncontrolled by antiarrhythmic drugs or for patients who cannot tolerate pharmacologic treatments (class I for paroxysmal AF, class IIa for persistent AF, class IIb for >12 months of persistent AF)^{25,44}. Selection of appropriate patients is a complex process that requires careful consideration of clinical factors including symptoms, presence of heart disease, obesity, sleep apnoea, left atrial size, duration of persistent AF, and patient preferences⁴⁴. A few large administrative registries have reported that, after multivariable adjustments, women are less likely to undergo catheter ablation than men^{34,45}, and that women are underrepresented in catheter ablation meta-analyses^{46–49}. A review on the association between sex and outcomes of catheter ablation for AF has also reported that women are referred less often and later than men⁵⁰. However, the differences in utilization of catheter ablation between women and men might be secondary to sex-specific differences in clinical factors, and not primarily associated with female sex *per se*. Moreover, sex-specific differences in ablation utilization might represent less willingness by women to undergo invasive cardiovascular procedures compared with men, similar to earlier studies on the use of coronary angiography for myocardial infarction^{51–54}.

In observational settings, the risk of long-term recurrence of AF after catheter ablation seems to be similar between women and men after adjusting for age, left atrial size, and proportion of paroxysmal AF⁴⁸. One meta-analysis reported higher recurrence rates among women; however, the researchers acknowledged a higher mean age in the women than in the men⁴⁷.

Important procedural complications of catheter ablation include vascular injury, pericardial effusion or tamponade, pulmonary vein stenosis, oesophageal injury, stroke, and systemic thromboembolism⁴⁶. Several studies have attempted to address potential sex-specific differences in the rates of complications after catheter ablation, but have produced inconsistent results; some studies showed no significant difference^{55–57}, whereas others reported female sex to be a predictor of higher complication rates^{58–63}. In one of the larger studies, Medicare beneficiaries displayed no sex-specific differences in 30-day stroke or mortality outcomes, but women were more likely to develop pericardial effusions after the procedure⁶². Interpretation of the results is limited owing to low event rates, compounded by the relative lack of representation of women and the use of composite end points. In

addition, the biological underpinnings of the reported sex-specific differences remain largely unknown.

Stroke prevention

Untreated AF is associated with a threefold to fivefold increased risk of stroke⁵. AF-related stroke is often severe; 24–33% of individuals with stroke in the setting of AF die within 30 days, and an additional 35% lose their ability to live independently^{6,7,64}. Oral anticoagulation therapy with warfarin reduces the risk of stroke by 64% compared with placebo, and by 39% compared with aspirin⁶⁵. NOACs are as effective as warfarin and have improved safety profiles. The AHA/ACC/HRS²⁵ and ESC²⁶ guidelines currently recommend anticoagulation in individuals with a CHA₂DS₂-VASc score of 2 or 1, respectively. A percutaneous left atrial appendage closure device (WATCHMAN; Boston Scientific, USA) was approved by the FDA in 2015 as an additional strategy for stroke prevention in AF⁶⁶.

Oral anticoagulant prescription

Investigators from GARFIELD-AF registry have reported that the overall rate of anticoagulant use (vitamin K antagonists, factor Xa inhibitors, direct thrombin inhibitors, unfractionated or low-molecular-weight heparin) did not differ between women (60.8%) and men (60.9%)⁶⁷. There were no sex-specific differences in the rates of anticoagulant use among those with a CHADS₂ score = 2; both undertreatment and overtreatment were common regardless of sex. By contrast, among the patients with a CHA₂DS₂-VASc score = 2 enrolled in the PINNACLE registry, women were more likely than men to receive aspirin instead of oral anticoagulants (OACs) after multivariable adjustments (relative prescription rate of aspirin instead of OAC for men 0.91, 95% CI 0.90–0.92, $P < 0.001$)⁶⁸.

A few observational studies have investigated utilization of NOACs in clinical practice. In the GARFIELD-AF registry, 11.8% of men and 11.7% of women received factor Xa inhibitors or direct thrombin inhibitors⁶⁷. Data from Get With The Guidelines – Stroke showed no difference in the discharge prescription of dabigatran or rivaroxaban versus warfarin between women and men hospitalized for AF-related stroke or transient ischaemic attack during 2010–2012⁶⁹. On the contrary, among the 18,611 OAC-naïve patients with AF in a Danish registry, men were less likely than women to be started on apixaban, dabigatran, or rivaroxaban, versus warfarin during 2011–2013 (multivariable-adjusted male sex OR 0.88, 95% CI 0.83–0.94, $P < 0.001$)⁷⁰. Reasons for the variation by sex are unclear, but might represent residual confounding owing to sex-specific differences in baseline comorbidities (see Supplementary information S2 (table)).

A population-based cohort study from Quebec, Canada reported that women were more likely than men to be prescribed the lower dose of dabigatran (110 mg), even after adjustment for age and baseline comorbidities associated with CHA₂DS₂-VASc and HAS-BLED scores (multivariable-adjusted OR 1.35, 95% CI 1.24–1.48)⁷¹. Both younger (age <75 years) and older (age ≥75 years) women were also more likely than men to receive the lower dose (22.8% vs 18.5%, and 83.5% vs 76.0%; $P < 0.05$ for both age groups). The finding remains to be replicated, and it is unclear whether these results indicate a disparity in

the way clinicians assess the risk of stroke or bleeding in women compared with men. The finding that women are more likely than men to receive the lower dose of dabigatran, when the higher dose (150 mg) has been demonstrated to be superior to warfarin in prevention of stroke and systemic embolism⁷², warrants further investigation.

Warfarin

The AHA guidelines currently recommend warfarin with well-controlled International Normalized Ratio (INR) as a class I indication for stroke prevention in nonvalvular AF⁷³. Owing to decades of experience with the drug and its cost-efficiency particularly in low-income and middle-income countries, anticoagulation with warfarin remains the most widely used stroke prevention therapy in AF worldwide. The main sex-specific findings on the efficacy and bleeding complications of warfarin are discussed below. For detailed results, see Supplementary information S3 and S4 (tables).

Efficacy compared with placebo—Sex-specific differences in the efficacy of warfarin compared with placebo in the prevention of stroke or systemic embolism was investigated in a meta-analysis of five RCTs (AFASAK, CAFA, BAATAF, SPAF, and SPINAF studies; TABLE 1). Warfarin was found to reduce the risk of stroke by 84% (95% CI 55–95%, $P < 0.001$) in women and 60% (95% CI 3–68%, $P = 0.04$) in men⁷⁴. No formal test for interaction between sex and efficacy was performed, and the confidence intervals overlapped. In addition, the meta-analysis incorporated a male-only study (SPINAF) and combined results from trials with different target INRs, further limiting our ability to draw sex-specific conclusions.

Residual risk of stroke or systemic embolism—A few studies have reported that women treated with warfarin have a higher residual risk of stroke or systemic embolism than men. In a meta-analysis of the warfarin-treatment groups of the ARISTOTLE, BAFTA, RE-LY, ROCKET AF, and SPORTIF III and V trials, women had a significantly higher residual risk of stroke and systemic thromboembolism than men (OR 1.28, 95% CI 1.11–1.47, $P = 0.001$)⁷⁵. Also, in a *post-hoc* analysis of the AFFIRM trial, among individuals receiving warfarin, women had an increased residual risk of ischaemic stroke compared with men even after adjusting for percentage time in therapeutic range (TTR; multivariable-adjusted HR 1.54, 95% CI 1.10–2.16, $P = 0.01$)⁷⁶.

Risk of bleeding—Potential sex-specific differences in the risk of major bleeding among warfarin users were investigated in *post-hoc* analyses of the SPORTIF III and V trials. In a combined analysis of the participants randomly assigned to warfarin treatment, no significant difference was found in the risk of major bleeding between women and men⁷⁷. In the meta-analysis of the ARISTOTLE, BAFTA, RE-LY, ROCKET AF, and SPORTIF III and V trials, the risk of major bleeding was similar in women and men among the participants receiving warfarin⁷⁵. Of note, sex is not included as a risk factor in the prospectively designed bleeding risk scores HEMORR₂HAGES⁷⁸, HAS-BLED⁷⁹, ATRIA⁸⁰, and the newer risk score ORBIT⁸¹ that are currently used in clinical practice.

Quality of anticoagulation control—Optimal use of warfarin in clinical practice is challenging owing to its narrow therapeutic index and variability in dose response between individuals. Monitoring is performed by measuring the INR; the therapeutic range for stroke prevention in AF is defined as INR of 2.0–3.0. An INR <2.0 is less effective for prevention of ischaemic stroke^{82,83}, and an INR >3.5–4.0 increases the risk of bleeding^{84,85}. TTR is closely associated with the risk of stroke, bleeding, and mortality^{86,87}, and has been used as a marker for quality of anticoagulation therapy. Various factors including age, female sex, lower income, black ethnicity, chronic diseases, cognitive impairment, polypharmacy, INR target range, setting of anticoagulation care, and patient adherence have been associated with lower TTR^{88–90}. The SAME-TT₂R₂ score, a risk-assessment tool includes female sex as one of the predictors of low TTR⁹¹.

The higher residual stroke risk in warfarin-treated women compared with men has been suggested to be partly owing to reduced TTR in women. Among the warfarin users in the AFFIRM trial⁷⁶, women were more likely than men to have an INR <2 ($29 \pm 0.7\%$ vs $26 \pm 0.5\%$; $P = 0.0002$). Women were also reported to spend a higher percentage of time outside the therapeutic range ($40 \pm 0.7\%$ vs $37 \pm 0.5\%$; $P = 0.0001$) compared with men. Similarly, in the RE-LY trial⁹³, male sex was associated with increased TTR in multivariable analysis (1.37% increase in mean TTR, 95% CI 0.30–2.45, $P = 0.01$).

Data from observational studies have been inconsistent; some studies report lower TTR in women^{94–96}, whereas others report no sex-specific differences in TTR^{11,97–101}. In addition, sex has not been consistently associated with INR stability in longitudinal studies^{102,103}.

NOACs

To date, four NOACs have been approved by the FDA and European Medicines Agency for stroke prevention in nonvalvular AF — the direct thrombin inhibitor dabigatran, and the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban. With the exception of edoxaban, which was approved in 2015, NOACs have been recommended by both the Canadian Cardiovascular Society¹⁰⁴ and the ESC²⁶ as the preferred agents over warfarin for stroke prevention in nonvalvular AF. The AHA recommend warfarin and NOACs on an equal footing²⁵. All the NOACs have consistently demonstrated noninferiority with regard to efficacy and improved safety, including a reduced risk of intracranial haemorrhage, compared with warfarin in clinical trials^{72,105–107}. Various challenges with the use warfarin have further encouraged the use of NOACs in clinical practice^{70,108–110}. Major sex-specific data from the NOAC trials are discussed below, and see Supplementary information S5 (table).

Efficacy compared with warfarin—A meta-analysis of the ARISTOTLE (apixaban 5 mg twice daily), ENGAGE AF-TIMI 48 (edoxaban 60mg once daily), RE-LY (dabigatran 150 mg twice daily), and ROCKET AF (rivaroxaban 20 mg once daily) trials showed no sex-specific differences in the efficacy of stroke prevention between NOACs and warfarin (relative risk for NOACs versus warfarin in women 0.78, 95% CI 0.65–0.94, and in men 0.84, 95% CI 0.75–0.94, $P = 0.52$ for interaction)¹¹¹. Sex-specific subgroup analyses of the

individual RCTs for each drug reported similar findings^{72,105,106,112}, as did *post-hoc* analyses of the ARISTOTLE¹¹³ and AVERROES¹¹⁴ trials.

Residual risk of stroke or systemic embolism—A meta-analysis of the participants randomly assigned to receive a NOAC in the AVERROES, ARISTOTLE, RE-LY (150 mg), and ROCKET AF trials reported similar rates of all stroke or systemic embolism in women and men (OR 1.15, 95% CI 0.97–1.35, $P=0.11$)⁷⁵. A *post-hoc* analysis of the AVERROES trial¹¹⁴ showed that, in the apixaban group, women had higher risk of ischaemic stroke than men, but no significant difference was found after multivariable adjustments. In addition, in combined analysis of the apixaban and warfarin groups of the ARISTOTLE trial¹¹³, no significant difference was found in the rate of stroke or systemic embolism between women and men after multivariable adjustments.

Relative risk of bleeding compared with warfarin—A meta-analysis of the ARISTOTLE, ENGAGE AF-TIMI 48 (60 mg), and ROCKET AF trials reported no significant sex-specific difference in the relative risk of major bleeding when comparing factor Xa inhibitors to warfarin (relative risk for factor Xa inhibitors versus warfarin in women 0.75, 95% CI 0.58–0.97, and in men 0.90, 95% CI 0.72–1.12, $P=0.29$ for interaction)¹¹¹. Likewise, subgroup analyses in the individual trials demonstrated that, compared with warfarin, apixaban¹⁰⁵ and both doses of edoxaban¹⁰⁷ reduced the risk of major bleeding similarly for both women and men. The only trial that reported an interaction by sex for risk of bleeding was the ROCKET AF study¹⁰⁶, in which rivaroxaban increased the risk of major and nonmajor clinically relevant bleeding compared with warfarin in men (HR 1.12, 95% CI 1.02–1.22), but not in women (HR 0.89, 95% CI 0.79–1.01, $P=0.004$ for interaction).

Female sex and risk of bleeding—Several studies have investigated female sex as a prognostic factor for bleeding among users of OACs. A meta-analysis of the ARISTOTLE, AVERROES, RE-LY (150 mg), and ROCKET AF trials reported that women treated with NOACs had lower rates of major bleeding compared with men (OR 0.84, 95% CI 0.75–0.96, $P=0.007$)⁷⁵. Women receiving rivaroxaban or warfarin in the ROCKET AF trial¹¹⁵ had a reduced risk of major bleeding compared with men after multivariable adjustment (HR 0.82, 95% CI 0.70–0.95, $P=0.009$). Similarly, in patients treated with apixaban or warfarin in the ARISTOTLE trial¹¹⁶, female sex was associated with a lower risk of major bleeding (HR 0.74, 95% CI 0.63–0.87, $P=0.002$). Another *post-hoc* analysis of the ARISTOTLE trial¹¹³ suggested a trend for lower risk of major bleeding in women compared with men (HR 0.86, 95% CI 0.74–1.01), although the result was not significant.

Left atrial appendage closure

Since its approval by the FDA in 2015, percutaneous left atrial appendage closure (using the Watchman device) has been available as a stroke-prevention strategy. The ESC currently recommends percutaneous left atrial appendage closure only for individuals with a high risk of stroke and contraindication to anticoagulation therapy (class IIb)²⁶, whereas the AHA does not give a class recommendation for percutaneous left atrial appendage closure as a stroke-prevention strategy²⁵. The PROTECT AF trial¹¹⁷ showed that the Watchman device

was noninferior to warfarin for the prevention of stroke, systemic embolism, and death (rate ratio [RR] 0.62, 95% CI 0.35–1.25), but the rate of adverse events was higher (RR 1.69, 95% CI 1.01–3.19). Sex-specific subgroup analysis for efficacy showed inconsistent results (women RR 1.47, 95% CI 0.52–4.11; men RR 0.32, 95% CI 0.13–0.77), most likely owing to a lack of power with inclusion of only 210 women (30% of the total study population).

Pharmacological mechanisms

As noted in a 2015 statement from the ESC¹¹⁸, there are important sex-specific differences in the pharmacodynamics and pharmacokinetics of cardiovascular drugs. Important distinctions exist in absorption, body composition, distribution, and excretion of drugs between women and men. In addition, differences in endogenous and exogenous sex hormones might have an important role. Although sex-specific differences in the pharmacology of AF treatment drugs is likely, how they contribute to sex-related variation in the efficacy and safety of AF medications is uncertain.

In the RACE study³⁹, no significant sex-specific difference in heart-rate response to treatment was noted. However, in the study of pharmacokinetics, women had higher plasma concentrations of β -blockers^{119–122} and possibly also of verapamil^{123–125} than men. The differences in concentrations seemed to be related to differences in activity of drug-metabolism pathways and gastrointestinal absorption. Women also seemed to have increased cardiac norepinephrine activation compared with men¹²⁶, which might partially explain why there was a similar heart-rate response despite higher concentrations of atrioventricular nodal-blocking agents³⁹.

Women treated with warfarin spend more time outside the therapeutic range compared with men, but the underlying mechanisms are unknown. The pharmacokinetics and pharmacodynamics of warfarin are complex, and might vary by sex. In a large, prospective cohort study of 4,616 patients from >100 anticoagulation clinics across the USA, women required 4.5 mg (95% CI 3.8–5.3 mg, $P<0.001$) less in total weekly warfarin dose than men at any given age, and women aged ≥ 80 years required the lowest total weekly dose¹²⁷. Lower mean body mass or hepatic fat content in women¹²⁷ and sex-specific differences in warfarin metabolism by cytochrome P450 owing to differences in sex hormones might partially account for the enhanced dose response to warfarin in women^{128,129}. Whether sex-specific differences in pharmacokinetics are translated to sex-related differences in INR stability needs further investigation.

Future directions

Potential future directions and research strategies for evaluating sex-specific differences in the treatment of AF are outlined in TABLE 2. Strategies to produce high-quality evidence for women require reporting sex-specific results in RCTs²⁴. Although the best-quality sex-specific data would come from RCTs adequately powered to test independent effects in women and men, the design of such trials will be resource intensive. Nevertheless, increasing female participation in RCTs to reflect the current prevalence of disease will improve the generalizability of the trials. Identification of potential barriers to female

participation in AF stroke prevention trials might facilitate their participation in future studies. Women with AF might be less eligible for these trials owing to their older age and lower renal function; nevertheless, there might be misperceptions in the assessment of bleeding risk in women versus men, which might affect screening of women for inclusion in the trials. Moreover, social or medical factors might further discourage participation by women²⁴. A multicentre RCT that was designed to investigate sex-specific differences in participation in cardiovascular disease prevention trials reported that women showed less willingness to participate, after adjusting for cardiovascular comorbidities, and greater perception of harm from participating in trials compared with men¹³⁰.

Pragmatic randomized trials, which maintain internal validity of experimental trials, but include less-stringent inclusion and exclusion criteria, might improve the generalizability of experimental trials. Enrolling women and patients underrepresented in standard clinical trials will help to determine effectiveness and safety of treatments for AF in real-world clinical practice¹³¹.

Investigations into the ethnic disparities in care patients with AF have revealed unconscious racial biases and a lack of knowledge of racial disparities in the risk of stroke in AF¹³². Factors influencing variation in utilization and outcomes in AF treatments by sex, including patient preferences and comorbidities versus disparities and unconscious biases require further investigation. Continued investigation into sex-specific differences in utilization, effectiveness, and complications of different treatment modalities will help to identify and address potential barriers to effective treatment in women.

Conclusions

The evidence for sex-specific differences in the utilization and outcomes of treatments for AF is accumulating. Understanding the underlying biological and sociocultural mechanisms for the sex-specific differences and identifying potential barriers to effective treatment in AF will help to reduce the public-health burden of AF. Ensuring adequate enrollment of women in clinical trials of AF and *a priori* specified secondary analyses of efficacy and complications of therapies by sex are essential to develop an adequate evidence-base to manage women with AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

Evaluation of sex-specific differences, disparity, and bias in health-care utilization requires presence of adverse outcomes and investigation into treatment eligibility, contraindications to treatment, patient preferences, and confounding owing to patient characteristics

Women are less likely to undergo rhythm-control treatment than men; among individuals undergoing rhythm-control treatment, women are less likely to receive electrical cardioversion and catheter ablation than men

No significant differences exist in the use of oral anticoagulants between women and men; however, among individuals receiving dabigatran, women are more likely to receive the lower dose than men

Warfarin and non-vitamin K antagonist oral anticoagulants (NOACs) have similar efficacy in women and men; however, among individuals receiving warfarin, women might have higher residual risk of stroke or systemic embolism

Warfarin and NOACs have similar bleeding risks in women and men

Future studies need to examine patient, provider, and health-system factors to address whether disparities or bias contribute to sex-specific differences in utilization and outcomes of treatments for atrial fibrillation

Figure 1. Overview of treatment of atrial fibrillation in women compared with in men

A summary of the major findings for each aspect covered in this Review. NOAC, non-vitamin K antagonist oral anticoagulant.

Figure 2. Three-tiered framework for sex-specific analysis of observational studies
 A tiered pyramid depicting the concepts of difference, disparity, and bias. Red arrows indicate steps that might need intervention.

Figure 3. Participation of women in anticoagulation trials for stroke prevention in atrial fibrillation

A pie chart showing proportion of women (blue) represented in anticoagulation trials compared with men (orange). The numbers indicate the year of publication of the study. The sizes of the individual pie charts correspond to the relative overall size of the trial.

Table 1

Trials for treatment of atrial fibrillation

Trial (year)	Patient sample	Number of patients Ethnicity Proportion women	Study design	Follow-up	Treatment	Primary outcomes
Rate/rhythm control						
RACE (2002) ²⁸	Patients with recurrent persistent AF or atrial flutter who had one or two electrical cardioversions in the past 2 years	522 NS 36.6%	Randomized, multicentre	Mean 2.3 years	Rate control (target heart rate <100 bpm at rest) vs rhythm control	Composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, need for pacemaker implantation, or severe adverse effects of antiarrhythmics drugs
AFFIRM (2002) ³⁵	Patients with AF who require long-term therapy and who were aged 65 years or had risk factors for stroke or death	4,060 11.4% ethnic minority 39.3%	Randomized, multicentre	Median 3.5 years	Rate control (target heart rate <80 bpm at rest and <110 bpm with activity) vs rhythm control	Mortality
Warfarin						
AFASAK (1989) ¹³³	Patients with ECG-proven chronic nonrheumatic AF	1,007 NS 46.4%	Randomized, two-centre in Denmark, open-label for warfarin, double-blind for aspirin and placebo	NS	Warfarin vs aspirin 75 mg vs placebo	Thromboembolic complication (stroke, TIA, embolic complications to the viscera and extremities)
BAATAF (1990) ¹³⁴	Patients with ECG-proven nonrheumatic AF	420 NS 28.0%	Randomized, multicentre, unblinded	Mean 2.2 years	Warfarin (low-dose) with target INR 1.5–2.7 vs control (placebo or aspirin)	Efficacy: ischaemic stroke. Safety: intracerebral haemorrhages
CAFA (1991) ¹³⁵	Patients with ECG-proven chronic AF or paroxysmal AF at least three times during the past 3 months	378 NS 25.4%	Randomized, multicentre, double-blind	Mean 15.2 months	Warfarin (target INR 2.0–3.0) vs placebo	Efficacy: ischaemic stroke or systemic embolism. Safety: intracranial or fatal haemorrhage
SPAF (1991) ¹³⁶	Patients with ECG-proven nonvalvular AF in 12 months before randomization	1,330 84% white 29.1%	Randomized, multicentre, open-label for warfarin, double-blind for aspirin and placebo	Mean 1.3 years	Warfarin, aspirin 325 mg, placebo	Ischaemic stroke or systemic embolism

Trial (year)	Patient sample	Number of patients Ethnicity Proportion women	Study design	Follow-up	Treatment	Primary outcomes
SPINAF (1992) ¹³⁷	Patients with ECG-proven (two ECGs 4 weeks apart) nonrheumatic AF	525 Only male veterans included	Randomized, multicentre, double-blind	Mean 1.7–1.8 years	Warfarin (low-intensity, target INR 1.2–1.5) vs placebo	Ischaemic stroke
BAFTA (2007) ¹³⁸	Aged 75 years with ECG-proved AF or atrial flutter within the past 2 years	973 NS 45%	Randomized, multicentre in UK, open-label, blind assessment of end points	NS	Warfarin (target INR 2.0–3.0) vs aspirin 75 mg	Fatal and nonfatal stroke (ischaemic or haemorrhagic), intracranial haemorrhage, arterial embolism
Non-vitamin K antagonist oral anticoagulants						
SPORTIF III and V (2006) ⁷⁷	Patients with ECG-proven nonvalvular AF (within 2 weeks before randomization) at increased risk of stroke [*]	7,329 92.2% white 30.8%	Randomized, multicentre, open-label use of ximelagatran in SPORTIF III, double-blind in SPORTIF V	SPORTIF III 4,941 patient-years SPORTIF V 6,405 patient-years	Ximelagatran 36 mg twice daily vs warfarin	Stroke or systemic embolism
RE-LY (2009) ⁷²	Patient with NVAf at increased risk of stroke [*]	18,113 NS 36.4%	Randomized, multicentre, single-blind, open-label use of warfarin	Median 2.0 years	Dabigatran 150 mg or 110 mg twice daily vs warfarin	Efficacy: stroke or systemic embolism
ROCKET AF (2011) ¹⁰⁶	Patients with nonvalvular AF at increased risk of stroke [*]	14,264 NS 39.7%	Randomized, multicentre, double-blind, double-dummy	Median 707 days	Rivaroxaban 20 mg once daily vs warfarin	Efficacy: stroke (ischaemic or haemorrhagic) or systemic embolism. Safety: major [†] and nonmajor clinically relevant bleeding
ARISTOTLE (2011) ¹⁰⁵	Patients with nonvalvular AF at increased risk of stroke [*]	18,201 NS 35.2%	Randomized, multicentre, double-blind, double-dummy	Planned for 2 years of follow-up	Apixaban 5 mg twice daily vs warfarin	Efficacy: stroke or systemic embolism. Safety: major bleeding [‡]
AVERROES (2011) ¹¹²	Aged 50 years with nonvalvular AF at increased risk of stroke [*] and currently not receiving vitamin K antagonist	5,599 NS 41.5%	Randomized, multicentre, double-blind, double-dummy	Mean 1.1 years	Apixaban 5 mg twice daily vs aspirin 81–324 mg daily	Efficacy: stroke (ischaemic or haemorrhagic) or systemic embolism. Safety: major bleeding [‡]
ENGAGE AF-TIMI 48 (2013) ¹⁰⁷	ECG-proven AF within 12 months before randomization with CHADS ₂ 2	21,105 NS 38.1%	Randomized, multicentre, double-blind, double-dummy	Total 56,346 patient-years	High (60 mg) or low (30 mg) dose edoxaban once daily vs warfarin	Efficacy: stroke (ischaemic or haemorrhagic) or systemic embolism.

Trial (year)	Patient sample	Number of patients Ethnicity Proportion women	Study design	Follow-up	Treatment	Primary outcomes
Left atrial appendage closure						
PROTECT AF (2013) ¹¹⁷	Patients with AF and CHADS ₂ 1	707 91.5% white 29.7%	Randomized, multicentre	Mean 18 months	Left atrial appendage closure vs warfarin	Efficacy: ischaemic stroke, cardiovascular or unexplained death, haemorrhagic stroke, systemic embolism. Safety: excessive bleeding or procedure related complications

* Has at least one of the following risk factors: history of stroke or TIA, left ventricular ejection fraction <40%, NYHA class II or higher HF symptoms, age 75 years, age 65–74 years plus diabetes mellitus, hypertension, or coronary artery disease. †Fatal bleeding, critical bleeding (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), bleeding that results in drop of haemoglobin concentration >2g/dl, or bleeding that requires >2 units of blood transfusion. AF, atrial fibrillation; ECG, electrocardiogram; INR, international normalized ratio; NS, not specified; TIA, transient ischaemic attack.

Table 2

Future research and directions

Knowledge gap	Future study
<i>Rate and rhythm control</i>	
Sex-specific differences in rhythm-control strategy	Identify mechanisms explaining sex-specific differences in outcomes associated with rhythm-control strategy including possible differences in complications after catheter ablation
Sex-specific differences in resource utilization	Determine patient, clinician, and system factors behind lower utilization of procedures among women, despite similar outcomes in women and men
Risk–benefit evaluation	Identify sex-specific predictors of outcomes including genetics and biomarkers
<i>Stroke prevention</i>	
Undertreatment in women	Identify barriers to guideline-recommended oral anticoagulation Identify reasons why women are more likely than men to receive aspirin than oral anticoagulation Identify reasons why women are more likely than men to receive lower dose of dabigatran
Sex-specific differences in stroke and bleeding risks	Achieve better understanding of stroke and bleeding risk under contemporary medication schemes
<i>Effects of cardiovascular drugs</i>	
Sex-specific differences in pharmacokinetics and pharmacodynamics	Identify mechanisms explaining sex-specific differences in pharmacokinetics of β -blockers Investigate mechanisms for increased risk of complications from antiarrhythmic drugs in women Identify mechanisms explaining sex-specific differences in pharmacokinetics and pharmacodynamics of warfarin
<i>Lack of sex-specific evidence in trials</i>	
Sex-specific differences in trial participation	Identify potential barriers to participation of women including exclusions and screening bias
Reporting of sex-specific results in trials	Collect sex-specific information Prespecify analyses of sex-specific results, and formally test for effect modification by sex
<i>Differences versus disparities versus bias</i>	
When sex-specific differences in AF treatment, utilization, or outcomes are demonstrated, examine underlying factors	Examine patient, clinician, and system factors including eligibility, contraindications, patient preferences, confounding, and role of stereotypes and unconscious biases