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Sex-specific comparative outcomes between oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis

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ABSTRACT

Aims Women with atrial fibrillation (AF) are under-represented in randomised controlled trials (RCTs) of direct oral anticoagulants (DOACs). This systematic review and meta-analysis of RCTs and observational studies examined sex-specific outcomes of DOACs in AF.

Methods PubMed, Embase, Web of Science and Cochrane Library were searched from January 2008 to November 2022. Sex-specific comparative outcomes of stroke/systemic embolism (SE), major bleeding, intracranial haemorrhage (ICH) and gastrointestinal bleeding (GIB) between oral anticoagulants were pooled using random effects models. P values for interaction were calculated to examine differences in results between sexes. RCTs and observational studies were meta-analysed separately.

Results 5 RCTs and 33 observational studies were included, totalling 1 085 931 women and 1 387 123 men. Meta-analyses showed that for both sexes, DOAC versus warfarin was generally associated with lower risk of stroke/SE, major bleeding and ICH; in DOAC–DOAC comparisons, rivaroxaban versus dabigatran had higher GIB risk. The only sex-specific difference observed was that when compared with warfarin, women had higher GIB risk with rivaroxaban (women: pooled risk ratio (pRR)=1.34, 95% CI=1.18 to 1.51; men: pRR=0.97, 95% CI=0.85 to 1.10; p value for interaction (p for interaction)<0.001) and possibly dabigatran (women: pRR=1.25, 95% CI=0.92 to 1.70; men: pRR=0.83, 95% CI=0.72 to 0.97; p-for-interaction=0.02). The sex difference in GIB remained for rivaroxaban when a Bonferroni-corrected significance level was used (α=0.003). No sex-specific GIB data for apixaban and edoxaban was available for the meta-analysis.

Conclusions For both sexes, DOACs generally demonstrated favourable effectiveness and safety over warfarin. However, observational data suggested that women may have higher GIB risk with rivaroxaban and possibly dabigatran than warfarin. Further studies are warranted to verify our findings and elucidate sex-specific GIB risk with apixaban and edoxaban, of which the data is currently lacking.

PROSPERO registration number CRD42022325027.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Randomised controlled trials (RCTs) in patients with atrial fibrillation have demonstrated direct oral anticoagulants (DOACs) to be at least as effective as warfarin in reducing stroke with lower overall bleeding risk. However, the RCTs under-represented women and were not designed to investigate sex-specific outcomes, obscuring potential sex-specific differences in the effects of DOACs.

WHAT THIS STUDY ADDS

⇒ This systematic review and meta-analysis of RCTs and observational studies found both sexes to generally demonstrate favourable safety and effectiveness with DOACs compared with warfarin, but observational data indicates that gastrointestinal bleeding (GIB) risk may be raised in women with rivaroxaban and dabigatran compared with warfarin.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Data from observational studies suggests that GIB risk may differ with the types of DOAC in women. Further research studies are warranted to verify our findings and elucidate sex-specific GIB risk with apixaban and edoxaban, of which the data is currently lacking.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide.[1] Women with AF have higher risks of stroke than men.[2] Sex is therefore considered a risk modifier for stroke in AF, informing the decision to include women in the CHA2DS2-VASc Score.[3 4] Higher stroke risk in women could reflect differing pathophysiological mechanisms for stroke[5] and sex-specific interactions with the pharmacodynamics and pharmacokinetics of cardiovascular drugs, particularly warfarin.[6] However, whether there are sex differences in the effects of direct oral

anticoagulants (DOACs), which are currently recommended for use over warfarin,[7 8] is unclear.[6]

In randomised controlled trials (RCTs), DOACs are at least as effective as warfarin in reducing stroke with lower overall bleeding risk.[9–12] However, as the RCTs were not designed to have adequate power to investigate sex-specific outcomes, important sex-based interactions with DOACs could have been undetected. Women have been under-represented in RCTs assessing DOACs, and the generalisability of RCT findings to real-world practice is limited by the strict eligibility criteria.[13] Although recent observational studies have contributed data on sex-specific DOAC effectiveness and safety, a comprehensive assessment of the sex-specific outcomes of DOACs from the available evidence is lacking.

This systematic review and meta-analysis aimed to summarise the published evidence from RCTs and observational studies to compare the sex-specific effectiveness and safety between DOACs and warfarin. We also examined if the outcomes vary between anticoagulant users from different geographical regions.

METHODS

This study was conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[14] The protocol was registered in PROSPERO, the international prospective register of systematic reviews, (CRD42022325027).

To clarify, the terminology 'sex' is used and not 'gender'. When mentioning sex, we are referring to the biology of living things, that is, biological features, such as chromosomal genotypes and reproductive organs that distinguish men and women at birth.

Data sources and search strategy

A systematic literature search was conducted through PubMed, Embase, Web of Science and Cochrane Library for studies published from 1 January 2008, the year when the first DOAC (dabigatran) was marketed, to 23 November 2022. Full search strategies are available in online supplemental tables S1–S4.

Study selection

Three investigators (PM, ED and JDC) independently screened the titles and abstracts of all identified records and screened the full texts of the potentially relevant articles to assess their eligibility. The reference lists of the included studies, prior systematic reviews and introduction and discussion sections of retrieved studies were also reviewed to identify additional relevant studies. Disagreements were resolved by discussion or consultation with a fourth investigator (WL).

Eligibility criteria

Studies were included if they: (1) were RCTs or longitudinal observational studies; (2) were conducted in patients with AF who received oral anticoagulant treatment; and (3) compared stroke or systemic embolism (SE), or bleeding outcomes between any DOAC (dabigatran, rivaroxaban, apixaban and edoxaban) and warfarin or other vitamin K antagonists (VKAs) in men and women. The primary outcome was stroke/SE. The secondary outcomes were bleeding which included major bleeding, intracranial haemorrhage (ICH), gastrointestinal bleeding (GIB) and any bleeding. Studies which did not explicitly define their bleeding outcomes as major bleeding, ICH or GIB and included other bleeding events or a composite of bleeding outcomes were classified as any bleeding. Outcome definitions as reported by each included study can be found in online supplemental table S5.

Studies were excluded if they were: (1) reviews or systematic reviews, cross-sectional studies, case reports, conference abstracts, editorials or commentaries, (2) animal or in vitro studies, (3) not published in English or (4) did not report sex-specific outcomes.

Data extraction

Three investigators (PM, ZW and JDC) extracted the data independently using prespecified forms. We gathered data on (1) study characteristics; (2) patient characteristics; (3) specific intervention/exposure group (DOAC type and dosage) and control groups; and (4) outcomes of interest and follow-up. Studies with incomplete data were clarified by contacting the corresponding author where possible. When authors did not respond, we used information reported to calculate the required data or excluded the study from the meta-analyses.

Quality assessment

Three investigators (PM, ZW and JDC) independently appraised the quality of the included studies using the revised Cochrane Risk of Bias Tool for Randomised Trials (RoB V.2.0)[15] and the Newcastle-Ottawa Scale for observational studies (see online supplemental appendix 1 for full details).[16]

Statistical analyses

In the primary meta-analyses, we pooled the results of studies that reported outcomes for all DOAC users as a group. Prespecified subgroup analyses were performed on individual DOACs and geographical regions of the study populations where data permitted (Asia, Europe, North America). Subgroup analyses were only possible with observational data as the number of RCTs was too small. Post hoc analyses for DOAC head-to-head comparisons were performed.

RCTs and observational data were analysed separately. Valvular heart disease was analysed separately from patients without valvular disease. For observational studies, we extracted results which had the greatest adjustment for potential confounding factors. The results from all included studies were expressed as hazard ratios (HRs) or risk ratios (RRs). HRs were considered comparable to RRs.[17] The DerSimonian and Laird random effects model was used to estimate sex-specific pooled RRs (pRR) with 95% confidence intervals (CI) as the common effect

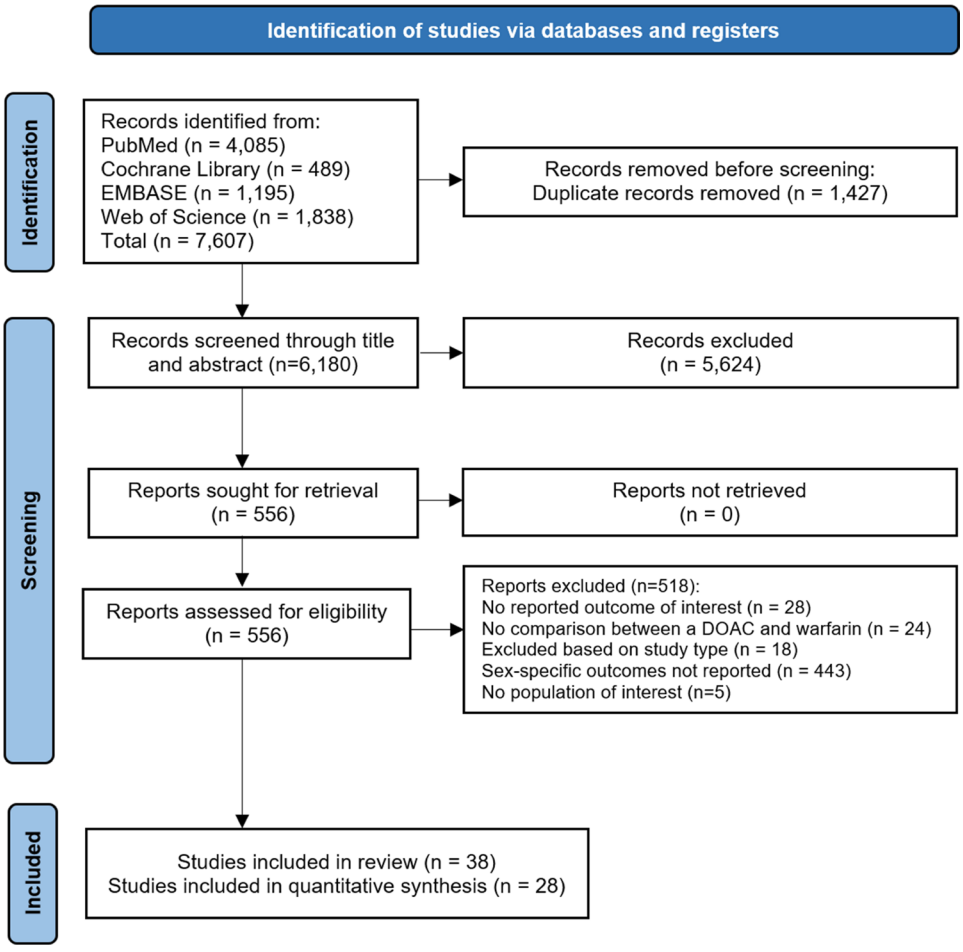


Figure 1 Study selection flowchart. DOAC, direct oral anticoagulant.

estimate. Heterogeneity between studies was investigated using I^2 with low (I^2<25%), moderate (I^2=25%–75%) and high (I^2>75%) thresholds. A p value for interaction (p-for-interaction) was calculated to assess differences in pRR between sexes and geographical regions. A p-for-interaction<0.1 indicated a statistically significant subgroup difference.[18] Post hoc, we applied Bonferroni corrected significance levels of 0.003 and 0.001 for the sex-specific oral anticoagulant and geographical region comparisons, respectively (online supplemental appendix 2). Studies ineligible for meta-analysis due to incomplete data or overlapping study populations were narratively reviewed (online supplemental appendix 3).

Analyses were conducted using R V.4.2.2. Risk of bias plot of RoB V.2.0 was created by robvis.[19]

RESULTS

Study selection and baseline characteristics

6180 unique records were identified, of which 38 studies met the inclusion criteria and were included in the systematic review and 28 were included in the meta-analyses (figure 1). 5 RCTs and 33 observational studies were included in the systematic review (online supplemental table S6). The RCTs were all multicentre and international studies. Four RCTs were large (n≥14 263) and conducted in patients with AF. One smaller-sized RCT (n=1426) was conducted in patients with AF after a successful transcatheter aortic valve replacement. Collectively, the RCTs had 45 713 men and 27 396 women.

All observational studies were cohort study designs using data from national administrative/clinical databases, medical institutions or stroke centres. 16 observational studies were conducted in North America, 11 in Asia and 6 in Europe. Most observational studies were conducted in an unselected AF population. Selected AF populations included patients with type 2 diabetes mellitus, chronic kidney disease, bioprosthetic heart valves, liver disease, patients aged≥80 years and patients with body mass index>30 kg/m^2.

Four RCTs were eligible for meta-analysis for stroke/SE (44 965 men and 26 718 women) and three for bleeding outcomes (33 451 men and 20 119 women). 19 observational studies including 8 02 483 men and 6 56 375 women and 24 observational studies including 1 076 058 men and 7 54 115 women were eligible for meta-analyses on stroke/SE and bleeding outcomes, respectively. Warfarin was considered the comparator group in the meta-analysis as only a minority of patients from two observational studies may have included VKAs other than warfarin.[20 21]

Quality assessment

Three of the five RCTs were judged as low risk of bias and two were rated as some concerns (online supplemental table S7 and online supplemental figure S1). For observational studies, 31 out of 33 received a good quality rating and two studies received a fair quality rating (online supplemental table S8 and online supplemental appendix 1).

Sex-specific outcomes for DOACs versus warfarin

Stroke/SE

Meta-analysis of four RCTs showed both sexes had a lower risk of stroke/SE using DOACs versus warfarin, with no evidence of sex-specific interaction (women: pRR=0.79, 95% CI=0.66 to 0.94, I^2=36%; men: pRR=0.84, 95% CI=0.75 to 0.93, I^2=0%; p-for-interaction=0.60). Results were similar for observational studies (women: pRR=0.75, 95% CI=0.58 to 0.97, I^2=85%; men: pRR=0.81, 95% CI=0.67 to 0.98, I^2=76%; p-for-interaction=0.64) (figure 2).

Major bleeding, GIB and ICH

Meta-analysis of three RCTs suggest DOACs have lower risk of major or non-major clinically relevant bleeding versus warfarin in women but not in men (women: pRR=0.75, 95% CI=0.59 to 0.94, I^2=77%; men: pRR=0.91, 95% CI=0.71 to 1.16, I^2=90%). There was no statistical difference between the sex-specific estimates (p-for-interaction=0.27). In the meta-analysis of observational studies, both sexes had lower risks of major bleeding with DOACs than warfarin (women: pRR=0.87, 95% CI=0.77 to 0.97, I^2=65%; men: pRR=0.79, 95% CI=0.68 to 0.91, I^2=81%; p-for-interaction=0.33) (figure 3).

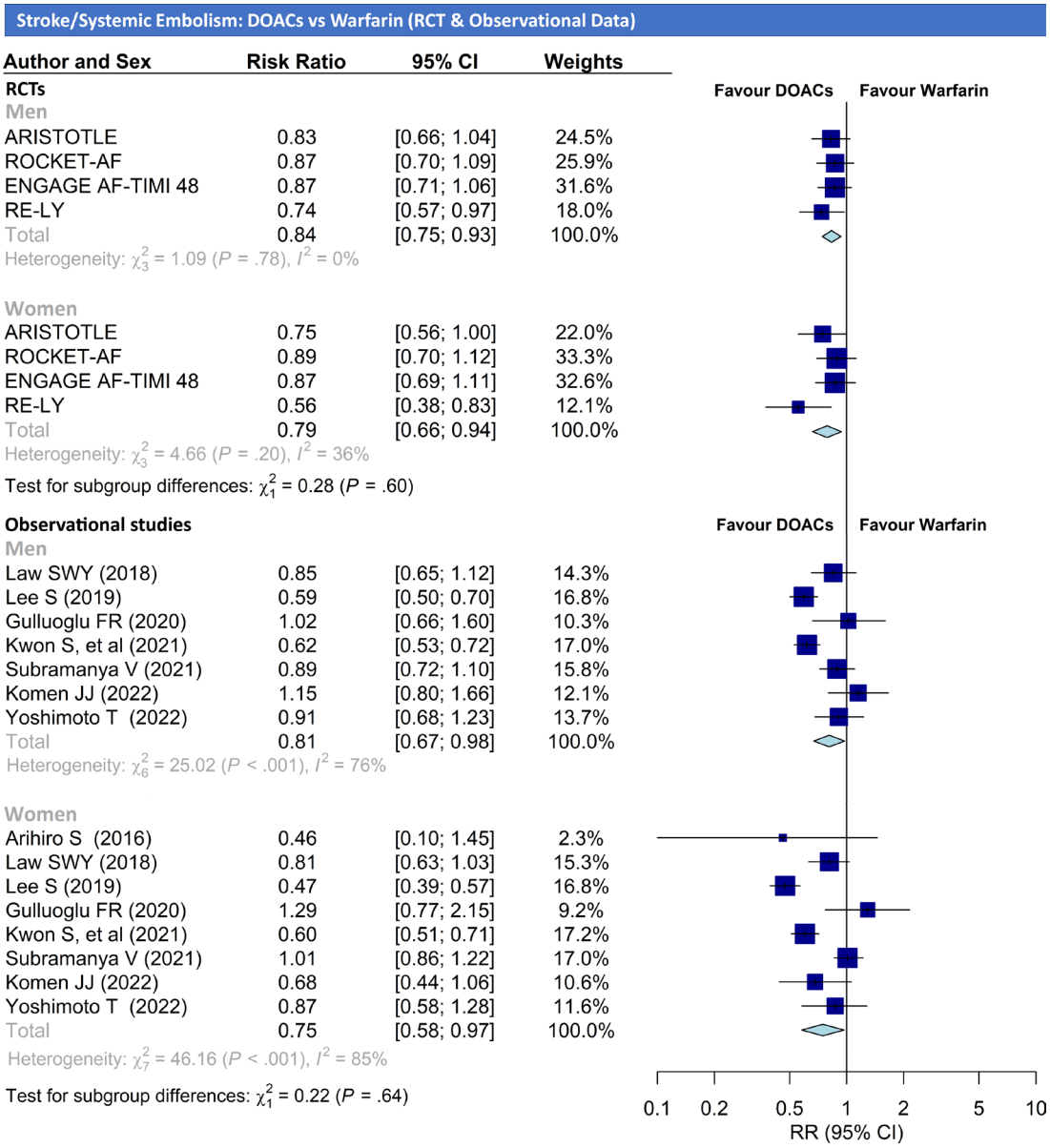
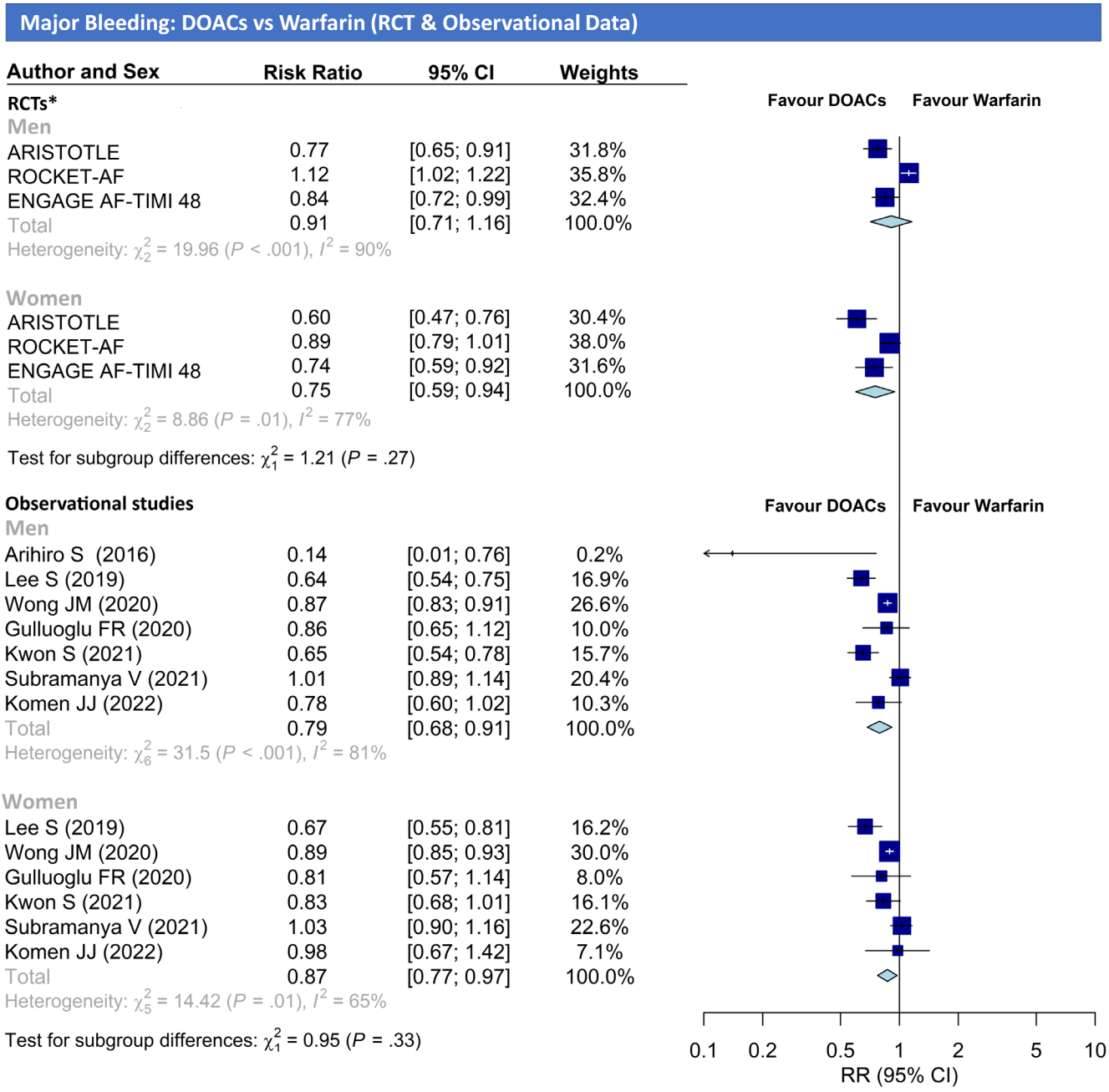


Figure 2 Forest plot of meta-analysis for stroke/systemic embolism with direct oral anticoagulants (DOACs) versus warfarin by sex. RCT, randomised controlled trial; RR, risk ratio.



*Outcomes for ARISTOTLE and ENGAGE AF-TIMI 48 are major bleeding. ROCKET-AF include major and nonmajor clinically relevant bleeding.

Figure 3 Forest plot of meta-analysis for major bleeding with direct oral anticoagulants (DOACs) versus warfarin. Randomised controlled trial (RCT) data compares major or non-major clinically relevant bleeding of DOACs versus warfarin by sex. Observational data compares major bleeding of DOACs versus warfarin by sex. RR, risk ratio; Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, ARISTOTLE; Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48, ENGAGE AF-TIMI 48; Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation, ROCKET-AF.

For GIB and ICH, sex-specific data were available only from observational studies. DOAC versus warfarin was associated with a lower risk of GIB in men but not women, with no evidence of sex-specific interaction (women: pRR=0.98, 95% CI=0.85 to 1.13, I^2=50%; men: pRR=0.86, 95% CI=0.75 to 0.99, I^2=56%; p-for-interaction=0.22) (figure 4). For ICH, a lower risk with DOACs was found in both sexes (women: pRR=0.56, 95% CI=0.42 to 0.74, I^2=63%; men: pRR=0.54, 95% CI=0.44 to 0.68, I^2=52%; p-for-interaction=0.86) (online supplemental figure S2).

Valvular heart disease

Two observational studies provided sex-specific data on the outcomes of DOACs as a group (dabigatran, rivaroxaban or apixaban) versus warfarin in patients with AF and bioprosthetic heart valves. Meta-analyses showed that

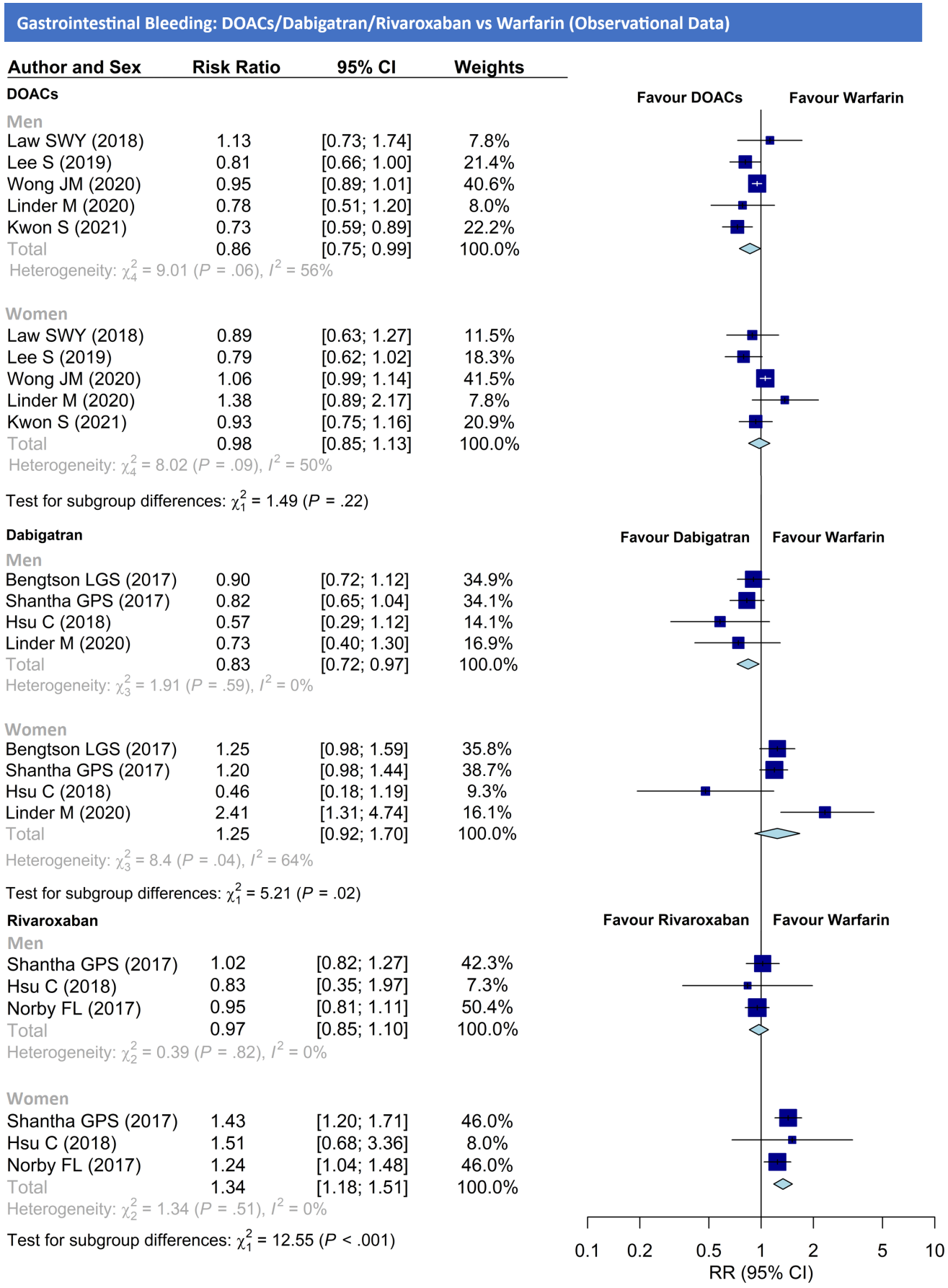


Figure 4 Forest plot of meta-analysis for observational studies comparing gastrointestinal bleeding of direct oral anticoagulants (DOACs), dabigatran and rivaroxaban versus warfarin by sex. RR, risk ratio.

in both sexes, there was no difference between DOACs and warfarin for stroke/SE (women: pRR=1.01, 95% CI=0.56 to 1.82, I^2=30%; men: pRR=1.38, 95% CI=0.88 to 2.15, I^2=0%; p-for-interaction=0.42) and major bleeding (women: pRR=0.66, 95% CI=0.37 to 1.18, I^2=0%; men: pRR=1.13, 95% CI=0.55 to 2.31, I^2=35%; p-for-interaction=0.25) (online supplemental figure S3).

One RCT assessed edoxaban against VKAs in patients with AF after a successful transcatheter aortic-valve replacement but did not report numeric estimates. Forest plots showed both sexes with higher incidence of major bleeding with edoxaban versus VKAs. No interaction tests were conducted but overlapping CIs suggest substantial sex difference is unlikely. Sex-specific data on stroke/SE, ICH or GIB were not reported.

Subgroup analyses

Individual DOACs

Stroke/SE

Meta-analysis showed dabigatran associated with lower risk of stroke/SE versus warfarin in both sexes, while rivaroxaban and apixaban had lower or similar risk. There was no indication of sex-specific interaction in each comparison (online supplemental figure S4). Only one study reported data for edoxaban finding no precise differences in stroke/SE versus warfarin in both sexes (online supplemental table S9).

Bleeding

Sex differences in the relative GIB risk versus warfarin were identified for dabigatran and rivaroxaban. Rivaroxaban versus warfarin was associated with a higher risk of GIB in women, but not men (women: pRR=1.34, 95% CI=1.18 to 1.51, I^2=0%; men: pRR=0.97, 95% CI=0.85 to 1.1, I^2=0%; p-for-interaction<0.001). For dabigatran, the point estimate for women suggests potentially higher risk of GIB versus warfarin but with 95% CI overlapping the null, whereas men had lower risk (women: pRR=1.25, 95% CI=0.92 to 1.70, I^2=64%; men: pRR=0.83, 95% CI=0.72 to 0.97, I^2=0%; p-for-interaction=0.02) (figure 4). Statistical evidence for GIB risk differences between sex remained only for rivaroxaban after Bonferroni correction (α=0.003). GIB data for apixaban was not available.

For major bleeding, ICH and any bleeding, there was no indication of sex-specific interactions in each DOAC comparison (online supplemental figures S2, S5 and S6). Meta-analysis for major bleeding showed both sexes using dabigatran or apixaban with lower associated risk versus warfarin. For rivaroxaban, major bleeding risk was comparable to warfarin in both sexes. For ICH, meta-analysis for dabigatran and rivaroxaban showed lower associated risk of ICH versus warfarin in both sexes. For any bleeding, both sexes with dabigatran and rivaroxaban were associated with lower or similar risk versus warfarin. ICH and any bleeding data for apixaban was unavailable.

Data for edoxaban was provided by one study. Both sexes with edoxaban had lower associated risk of major bleeding versus warfarin. For GIB and ICH, point estimates for both sexes suggested lower risk versus warfarin, but estimates were imprecise (online supplemental table S9).

Analysis by geographical regions

With each DOAC, Asians had lower stroke/SE and major bleeding risk versus warfarin and exhibited lower RRs for stroke/SE compared with other regions (online supplemental figure S7 and online supplemental table S10). For major bleeding, rivaroxaban versus warfarin was associated with lower risk among Asians, but similar or raised risk in other regions, whereas DOACs as a group among men were associated with greater reductions in major bleeding for Asians. Apixaban and dabigatran had lower or comparable major bleeding risk versus warfarin in all regions and sexes. GIB risk in men was lower or similar across regions with each DOAC versus warfarin comparison. Among women, GIB risk was lower or similar in Asians using DOACs, but comparable or raised in Europeans and North Americans. For ICH, DOACs as a group and dabigatran were associated with a lower risk versus warfarin for both sexes except for Europe which showed no precise difference in ICH risk. Some statistically significant differences in stroke/SE and major bleeding between regions remained after Bonferroni correction (α=0.001), but not for GIB and ICH.

Head-to-head DOAC comparisons

Meta-analysis of three observational studies found similar risk of stroke/SE between rivaroxaban and dabigatran. Two of these studies provided data for GIB and ICH. Meta-analysis showed both sexes with increased risk of GIB with rivaroxaban versus dabigatran, and for ICH, point estimates suggest increased risk with rivaroxaban in both sexes, although estimates were imprecise (online supplemental figure S8). Meta-analysis for major bleeding was not possible due to overlapping populations, but individual estimates from two studies showed both sexes with rivaroxaban associated with a higher risk (online supplemental table S11). Apixaban was compared with rivaroxaban and dabigatran in one study, reporting lower risk of stroke/SE and major bleeding with apixaban than dabigatran and rivaroxaban in both sexes (online supplemental table S11).

Narrative review

The excluded data and narrative summaries were generally consistent with meta-analyses for stroke/SE and major bleeding, with no noticeable differences between sexes across DOACs. One study reported data showing lower GIB with DOACs versus warfarin in both sexes among Asians, consistent with the geographical analysis (online supplemental table S9). One study that was narratively reviewed reported raised GIB in women with dabigatran versus warfarin consistent with our results (online supplemental table S12).

DISCUSSION

Key findings

This systematic review and meta-analysis compared the sex-specific effectiveness and safety of DOACs to warfarin.

Our study identified sex-specific interactions for GIB, with observational data suggesting women may have potentially higher risk of GIB with rivaroxaban and dabigatran compared with warfarin, which were not observed in men. The sex-specific interaction for GIB with rivaroxaban was observed even after Bonferroni correction. No other sex-specific interaction was found, with DOACs generally being associated with lower risk of stroke/SE, major bleeding and ICH compared with warfarin in both sexes. To our knowledge, this is the first and most comprehensive systematic review and meta-analysis to investigate the effectiveness and safety of DOACs in AF by sex, with the inclusion of representative real-world data outside RCT settings.

Comparison to other studies

A previous systematic review and meta-analysis reported sex-specific estimates of GIB risk with DOACs, using observational and RCT data published until October 2018.[22] The study found women to have raised GIB risk with DOACs as a group versus warfarin but not men.[22] However, the study neither evaluated sex-specific GIB risk by individual DOACs nor primarily intended to investigate sex-specific outcomes, and no sex-specific interaction tests were reported. Using updated data up to November 2022, our study identified that the raised relative GIB risk against warfarin in women may apply to rivaroxaban and possibly dabigatran. It is unclear why women may experience raised GIB. The pharmacokinetics of drugs frequently differ between sexes due to differences in body size, fat content, gastrointestinal physiology and renal functions. This can influence the processing, absorption and excretion of drugs, potentially altering drug safety and explaining the raised GIB in women.[23] Supporting this, women patients treated with DOACs have been observed to have higher rates of GIB compared with men,[24] although this is based on limited research and more studies are required to investigate differences in GIB risk between the sexes.

A meta-analysis[25] of four landmark RCTs in patients with AF found reduced risk of stroke/SE and major bleeding with DOACs and no evidence of sex-specific interaction. Our results for DOACs, which contribute further by including observational studies, are consistent with those reported results. Additionally, our subgroup meta-analysis using real-world data for dabigatran, apixaban and rivaroxaban demonstrated lower stroke/SE risk versus warfarin in both sexes, generally aligning with the landmark RCTs.[9 11 12] For edoxaban, the one available observational study[26] showed consistency with the landmark RCT,[27] reporting similar stroke/SE risk versus warfarin in both sexes. For ICH, RCTs have established reduced risk of ICH with DOACs versus warfarin,[9 11 12 27] but to our knowledge, there are no published sex-specific assessments. Our findings are consistent with a reduced risk of ICH for both sexes. This is important given the uncertainty of managing patients with AF and ICH.[28]

In our geographical analysis, reduced stroke/SE risk with DOACs versus warfarin was consistently observed in Asians. Furthermore, our findings suggest Asians with DOACs may experience improved risk reductions in bleeding compared with other regions. These results agree with a post hoc meta-analysis of RCTs[29] showing DOACs versus VKAs to reduce stroke/SE and major bleeding more in Asians relative to non-Asians. Asians are known to have enhanced pharmacokinetic and pharmacodynamic profiles with antithrombotic agents and greater natural tendency of bleeding compared with Caucasians.[30] Thus, Asians often have lower target international normalised ratio levels with warfarin which could increase thromboembolism risk, and therefore may experience greater reduction of stroke/SE with DOACs.[30–32] Additionally, Asians are prone to excessive bleeding with warfarin possibly due to their lower body weight and genetic susceptibility to overanticoagulation with warfarin.[30 33] Asians could therefore benefit more from DOACs regarding major bleeding risk.[34]

A systematic review and meta-analysis[35] comparing rivaroxaban and dabigatran showed similar stroke/SE risk, but increased GIB with rivaroxaban. Our post hoc meta-analysis of observational data agrees with these findings, and further demonstrates this for both men and women seperately. Given the post hoc nature of the analyses and that these are based on solely observational data, we emphasise that these results should be interpreted carefully.

Implications for clinical practice

For both sexes, our results demonstrate DOACs generally exhibiting improved effectiveness and safety versus warfarin in terms of reducing stroke and major bleeding risk. This reaffirms the use of DOACs in both sexes with AF, concurring with the current guidelines recommending DOACs over warfarin.[7 8] However, with observational data, our study identified sex-specific differences for GIB. Specifically, GIB risk may be raised with rivaroxaban and possibly dabigatran in women but not men, and other recent evidence is indicative of higher risk of GIB with DOACs than warfarin in women.[22 24] Further research should verify the sex-specific difference in GIB as this result was generated using pooled data from a small number of observational studies subject to potential confounding bias. In addition, GIB data for apixaban and edoxaban was not available and is urgently needed to better understand if sex-specific differences in GIB exist and whether there are preferable DOAC choices in women.[36] Thus, we call for future studies to report sex-specific data when examining outcomes of DOACs to elucidate these research gaps. Furthermore, other approaches to reduce GIB can be considered in patients with higher risk, such as the use of gastroprotective agents.[37]

Strengths and limitations

To our knowledge, this is the first and most comprehensive systematic review and meta-analysis comparing sex-specific effectiveness and safety of the DOACs versus warfarin using both RCTs and more representative real-world data. We conducted analyses on individual DOACs, across geographical settings and post hoc head-to-head DOAC comparisons. We summarised all the best available evidence on several important outcomes directly relevant to clinical practice, enabling useful interpretations which improve therapeutic decision-making and inform avenues for future research.

This study has limitations. There was limited literature assessing sex-specific outcomes and most studies were not designed for sex-specific analyses, reducing statistical power. Furthermore, subgroup analyses of individual DOACs contained a small number of studies. Statistical assessment of publication bias was not conducted due to limited studies in each meta-analysis (n<10). There was substantial heterogeneity between studies, likely representing the variation of individual DOACs in the pooled DOAC groups and differences in DOAC dosages, outcome definitions, study populations and durations of follow-up. Furthermore, observational data are limited by residual confounding, although adequate methods to account for confounding were adopted by included studies, and meta-analyses of RCTs were mostly consistent with observational data. Finally, the generalisability of these findings to younger patients is not possible, as the mean age of patients in most studies was >65 years.

Directions for future research

Studies are required to verify our findings on sex-specific GIB risk discrepancies. Our subgroup analysis contained a small number of observational studies, and the mechanistic reasons for sex-specific differences in GIB risk need exploration. Additionally, sex-specific GIB data for apixaban and edoxaban is needed. Furthermore, future research is needed to investigate effective approaches to reduce GIB risk, such as the use of gastroprotective agents, in women and high-risk patients with AF using DOACs.[37] Age-specific interactions with DOACs also need investigation as age may modify the risk of GIB in women.[38]

CONCLUSION

Among patients with AF, both sexes demonstrated generally favourable effectiveness and safety with DOACs compared with warfarin, supporting the preference of DOACs over warfarin in both sexes. However, meta-analysis of observational data suggests that GIB risk may be raised in women with AF using rivaroxaban and possibly dabigatran when compared with warfarin. Further studies are required to verify this finding and elucidate sex-specific GIB risk with apixaban and edoxaban, of which data is currently lacking.

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REFERENCES

1 Benjamin EJ, Muntner P, Alonso A, *et al*. Heart disease and stroke statistics—2019 update: a report from the American heart association. *Circulation* 2019;139:e56–528.
2 Wang TJ, Massaro JM, Levy D, *et al*. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community the Framingham heart study. *JAMA* 2003;290:1049–56.
3 Nielsen PB, Overvad TF. Female sex as a risk modifier for stroke risk in atrial fibrillation: using Cha2Ds2-Vasc versus Cha2Ds2-VA for stroke risk stratification in atrial fibrillation: a note of caution. *Thromb Haemost* 2020;120:894–8.
4 Nielsen PB, Skjøth F, Overvad TF, *et al*. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a Cha2Ds2-VA score rather than Cha2Ds2-Vasc? *Circulation* 2018;137:832–40.
5 Schnabel RB, Benjamin EJ. Sex and stroke risk in atrial fibrillation – more work to be done. *JACC Clin Electrophysiol* 2018;4:615–7.
6 Rosano GMC, Lewis B, Agewall S, *et al*. Gender differences in the effect of cardiovascular drugs: a position document of the working group on pharmacology and drug therapy of the ESC. *Eur Heart J* 2015;36:2677–80.
7 January CT, Wann LS, Calkins H, *et al*. AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol* 2019;74:104–32.
8 Hindricks G, Potpara T, Dagres N, *et al*. ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for cardio-thoracic surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European society of cardiology (ESC) developed with the special contribution of the European heart rhythm association (EHRA) of the ESC. *Eur Heart J* 2020;42:373–498.
9 Connolly SJ, Ezekowitz MD, Yusuf S, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51.
10 Giugliano RP, Ruff CT, Braunwald E, *et al*. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–104.
11 Granger CB, Alexander JH, McMurray JJV, *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92.
12 Patel MR, Mahaffey KW, Garg J, *et al*. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–91.
13 Hägg L, Johansson C, Jansson J-H, *et al*. External validity of the ARISTOTLE trial in real-life atrial fibrillation patients. *Cardiovasc Ther* 2014;32:214–8.
14 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:71.
15 Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366.
16 Wells GA, Shea B, O'Connell D, *et al*. *The newcastle-ottawa scale (nos) for assessing the quality of nonrandomised studies in meta-analyses*.
17 Stare J, Maucort-Boulch D. Odds ratio, hazard ratio and relative risk. *Adv Meth Stat* 2016;13:59–67.
18 Richardson M, Garner P, Donegan S. Interpretation of subgroup analyses in systematic reviews: a tutorial. *Clin Epidemiol Glob Health* 2019;7:192–8.
19 McGuinness LA, Higgins JPT. Risk-of-bias visualization (robvis): an R package and shiny web App for visualizing risk-of-bias assessments. *Res Synth Methods* 2021;12:55–61.
20 Komen JJ, Pottegård A, Mantel-Teeuwisse AK, *et al*. Oral anticoagulants in patients with atrial fibrillation at low stroke risk: a multicentre observational study. *Eur Heart J* 2022;43:3528–38.
21 Balsam P, Lodziński P, Gawałko M, *et al*. Antithrombotic management and long-term outcomes of patients with atrial fibrillation. *J Clin Med* 2021;10.
22 Gu Z-C, Wei A-H, Zhang C, *et al*. Risk of major gastrointestinal bleeding with new vs conventional oral anticoagulants: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2020;18:792–9.
23 Madla CM, Gavins FKH, Merchant HA, *et al*. Let's talk about sex: differences in drug therapy in males and females. *Adv Drug Deliv Rev* 2021;175:113804.
24 Ferroni E, Denas G, Gennaro N, *et al*. Gender related differences in gastrointestinal bleeding with oral anticoagulation in atrial fibrillation. *J Cardiovasc Pharmacol Ther* 2022;27.
25 Ruff CT, Giugliano RP, Braunwald E, *et al*. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955–62.
26 Lee S-R, Choi E-K, Han K-D, *et al*. Edoxaban in Asian patients with atrial fibrillation: effectiveness and safety. *J Am Coll Cardiol* 2018;72:838–53.
27 Zelniker TA, Ardissino M, Andreotti F, *et al*. Comparison of the efficacy and safety outcomes of edoxaban in 8040 women versus 13 065 men with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. *Circulation* 2021;143:673–84.
28 Ivany E, Lotto RR, Lip GYH, *et al*. Managing uncertainty: physicians' decision making for stroke prevention for patients with atrial fibrillation and intracerebral hemorrhage. *Thromb Haemost* 2022;122:1603–11.
29 Wang K-L, Lip GYH, Lin S-J, *et al*. Non–vitamin K antagonist oral anticoagulants for stroke prevention in Asian patients with nonvalvular atrial fibrillation: meta-analysis. *Stroke* 2015;46:2555–61.
30 Kim HK, Tantry US, Smith SC, *et al*. The East Asian paradox: an updated position statement on the challenges to the current Antithrombotic strategy in patients with cardiovascular disease. *Thromb Haemost* 2021;121:422–32.
31 Chao T-F, Guo Y. Should we adopt a standard International normalized ratio range of 2.0 to 3.0 for Asian patients with atrial fibrillation. *Thromb Haemost* 2020;120:366–8.
32 Pandey AK, Xu K, Zhang L, *et al*. Lower versus standard INR targets in atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. *Thromb Haemost* 2020;120:484–94.
33 Mega JL, Walker JR, Ruff CT, *et al*. Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet* 2015;385:2280–7.
34 Gorog DA, Gue YX, Chao T-F, *et al*. Assessment and mitigation of bleeding risk in atrial fibrillation and venous thromboembolism: executive summary of a European and Asia-Pacific expert consensus paper. *Thromb Haemost* 2022;122:1625–52.
35 Bai Y, Deng H, Shantsila A, *et al*. Rivaroxaban versus dabigatran or warfarin in real-world studies of stroke prevention in atrial fibrillation. *Stroke* 2017;48:970–6.
36 Lau WCY, Torre CO, Man KKC, *et al*. Comparative effectiveness and safety between apixaban, dabigatran, edoxaban, and rivaroxaban among patients with atrial fibrillation: a multinational population-based cohort study. *Ann Intern Med* 2022;175:1515–24.
37 Steffel J, Verhamme P, Potpara TS, *et al*. The 2018 European heart rhythm association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;39:1330–93.
38 Graham DJ, Reichman ME, Wernecke M, *et al*. Cardiovascular, bleeding, and mortality risks in elderly medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation* 2015;131:157–64.