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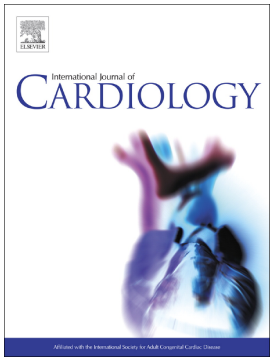

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Sex Differences in Stroke and Major Adverse Clinical Events in Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis of 993,600 Patients

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Dr Irene Marzona and Dr Marco Proietti take responsibility for all aspects of the reliability and freedom of bias of the data presented and their discussed interpretation.

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AUTHORS CONTRIBUTIONS

IM, MP, AN, CR conceived this work; GFR, IR performed the search, screening of search results and bias assessment; AF performed statistical analysis; IM, MP assessed eligibility, extracted data, interpreted results and drafted the manuscript; VR, SB, GYHL, AN, CR critically revised the manuscript for important intellectual content. IM and MP are guarantors of the paper. All authors read and approved the final version of the manuscript.

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DISCLOSURES

MP reports consulting for Boehringer Ingelheim; GYHL reports consultancy for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, Daiichi-Sankyo. All remaining authors have nothing to disclose.

Keywords: atrial fibrillation; women; sex; stroke; outcomes.

ABSTRACT

Background: Atrial fibrillation (AF) is the most commonly diagnosed arrhythmia, which is associated with an increased risk of stroke. Several studies have suggested that female AF patients could have a greater risk for stroke and thromboembolic events (TE).

Methods: A systematic literature review update and meta-analysis was conducted using Pubmed. The search used the terms “atrial fibrillation”, “gender”, “sex”, “female”, “women”, “stroke”, “thromboembolism”. Main aim of the study was to compare and male AF patients for occurrence of stroke and TE. Secondary outcomes were: major bleeding, cardiovascular (CV) death and all-cause death.

Results: Forty-four studies were included in the analysis including 993,603 patients (48.9% women). After pooling the data, there was a higher risk of stroke for women vs. male AF patients (hazard ratio [HR]:1.24; 95% confidence intervals [CI]:1.14-1.36]. Overall, TE risk was not different between female and male patients, despite sensitivity analysis left some uncertainties. No sex differences were found for major bleeding, CV death and all-cause death. A significant relationship between increasing age and the difference in stroke risk between female and male AF patients was found (Delta HR:1.01; 95% CI:1.00-1.03 for each year of age increase).

Conclusions Female patients with AF are at increased risk of stroke compared to men. A significant relationship between increasing age and stroke risk in women compared to men was found, most evident at age >65 years. Female sex may act as a stroke risk modifier, particularly in elderly and very elderly AF subjects, conferring a significant increase in stroke risk.

1. INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, which is associated with a five-fold increase in risk of stroke and thromboembolic events (TE). This increased risk is not homogeneous and depends on the presence of various stroke risk factors[1].

Despite a higher reported prevalence of AF in male subjects[2], several studies have described an increased risk for stroke and cerebrovascular events in women than in men, especially in older patients age ≥75 years old[3]. Indeed, female sex has been included as a risk factor in clinical risk prediction scores for stroke/TE risk stratification[4]. Nevertheless, the increased risk of stroke/TE in women compared to men has a dependency on age and risk factors, such that no excess of stroke risk is evident in female AF patients age <65 or without other risk factors present[1]. Thus, female sex may be a "stroke risk modifier", rather than an actual risk factor per se[5].

Several possible mechanisms have been proposed to explain a sex difference in stroke risk: for example, female sex hormones can favour the occurrence of thrombosis modulating pro-coagulant proteins' levels, platelet and endothelial functions[6]. Moreover, stroke severity, functional outcomes and quality of life are poorer in female than in male patients after occurrence of stroke[7,8]. Significant differences in the medical management of female AF patients, which may partly explain their increased risk of stroke[9]. Also, female AF patients tend to be undertreated and given less appropriate thromboprophylaxis[10].

The aim of this paper is to provide an updated systematic review and meta-analysis of available evidence regarding the differences in stroke and TE between female and male

AF patients. Second, we will investigate sex differences among AF patients in the risk of other major adverse events (major bleeding, cardiovascular (CV) death and all-cause death).

2. METHODS

The present systematic review and meta-analysis was performed according to PRISMA recommendations (http://www.prisma-statement.org/).

2.1 Data Sources and Searches

We planned an update of the systematic review published by Cheng and colleagues[9]. The original paper included all manuscripts published up until 2014. We then performed a comprehensive literature search using PubMed database from 01st January 2015 up to 19th May 2017. According to the original review, the search was performed using the terms “atrial fibrillation”, “gender”, “sex”, “female”, “women”, “stroke”, “thromboembolism”. The full search strategy is reported in the Supplementary Material.

2.2 Studies Selection

According to the original systematic review, studies were included in this systematic review if data about stroke and/or thromboembolic events stratified by sex were reported. Two co-authors (GFR and IR) independently screened the search results. Disagreements were resolved by collegial discussion. All articles retrieved from the search were evaluated according to titles (mostly excluding non-original data papers, commentaries, viewpoints and all entries that clearly did not qualify for inclusion) and abstracts sequentially. Other exclusion criteria were: i) conference abstracts, letters, comments, case reports, editorials; and ii) studies not published in English.

Subsequently, evaluation of full text eligibility was performed independently by two co-authors (IM and MP). Disagreements were resolved by collegial discussion. All full texts, as well as the 30 articles retrieved from the original systematic review, were assessed for meta-analysis eligibility according to the following criteria: i) all studies reporting about at least 1-year of follow-up observation; and ii) all studies providing enough details to obtain number of events, incidence rates or measures of effect according to sex to be included in the meta-analysis process.

2.3 Data Extraction and Quality Assessment

Data were extracted independently by two co-authors (IM and MP). All data on sample size and sex subgroups, number of events, incidence rates or measures of effect were collected. Data about year of study, geographical location and cohort type, age, use of oral anticoagulant (OAC) drugs and follow-up time were also collected. Year of study was categorized as follows: i) 1999-2012; ii) 2013-2015; iii) 2016-2017. Main outcomes considered were stroke and/or TEE. Additionally, data on major bleeding, cardiovascular (CV) death or all-cause death were collected, where available.

All studies were evaluated for the risk of bias by two co-authors (GFR and IR), according to recommendations of the Agency for Healthcare Research and Quality[11], specifically selection, performance, attrition, detection and reporting bias. A publication bias assessment was performed as reported below.

2.4 Data Synthesis and Analysis

For each study, hazard ratios and their standard errors were either extracted or computed on the basis of available information. Choice between fixed and random effects meta-analysis was performed on the basis of the I^2 index, where $I^2 > 25\%$ lead us to conduct

random effects meta-analyses based on linear (mixed-effects) models with inverse-variance weights. A similar approach has been used for the meta-regression. We considered some study specific characteristics as continuous predictors (female prevalence, mean age of the sample, OAC prevalence, maximum follow-up time), while other characteristics were considered as categorical predictors (publication year in three classes [1999-2012, 2013-2015, 2016-2017], type of study [randomized controlled trial (RCT), Insurance Database, Observational Study, Population Cohort] and geographic location [Europe, Middle East/Asia, North America, Multinational]. Further to the meta-regression, we reported subgroup analyses according to the categorical predictors.

Publication bias was assessed by means of funnel plots and regression tests for funnel plot asymmetry. Sensitivity analysis was conducted by removing one study at a time and comparing the resulting meta-analysis with the complete one. All analyses have been performed using R Statistical Package Software version 3.3.3 (R Foundation).

3. RESULTS

After the electronic search, a total of 2157 results were retrieved. After screening procedure, 61 full-texts were assessed for eligibility, with 43 papers excluded [Figure S1]. Further, the 30 articles included in the original systematic review[9] were assessed for eligibility, with 4 records excluded [Figure S1]. A total of 44 papers were finally included in the present systematic review and meta-analysis (Table 1)[12–55].

Overall, seven studies were derived from RCTs, 18 observational studies, 16 population cohort studies and 4 insurance database studies. Prevalence of female sex was largely variable across the studies included with a mean (SD) of 41.9% (8.7%), with the lowest prevalence (20.4%) reported by Boriani et al.[37] and the highest (55.2%) reported by Shanta and colleagues[49] [Figure S2].

3.1 Overview of Included Studies

In the study by Friberg et al., including 100802 patients discharged for AF, stroke occurred more commonly in women than in men[17]. After stratification by $CHADS_2$ score the increased risk of stroke in women was still evident across all strata. In the multivariable analysis the association between ischemic stroke and female sex was still significant (hazard ratio [HR]: 1.18; 95% confidence interval [CI]: 1.12-1.24)[17].

Similar results were observed in another retrospective observational study on 39398 men and 44115 women ≥65 years old discharged from Quebec hospitals with a diagnosis of AF[15]. The higher risk of stroke in women compared to men was particularly evident in very old patients (≥75 years old). The adjusted risk of stroke in women was HR: 1.14 (95% CI: 1.07-1.22); this significant difference was observed irrespective of previous stroke history, with women without a previous stroke still reporting a higher risk compared to men (HR: 1.17; 95% CI: 1.09-1.23)[15]. Conversely, the unadjusted mortality rates were higher in men. Similar results were also seen when patients were stratified according to OAC adherence[15].

In a secondary analysis of the “Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation” (ARISTOTLE) trial, the total number of patients included was 18201, with 35.2% (6416) being women[36]. Women were older than men and reported a higher CHA_2DS_2-VASc score. Risk of stroke was similar in women and men; however, the risk of all cause death (HR: 0.63; 95% CI: 0.55-0.73) or cardiovascular death (HR: 0.62; 95% CI: 0.51-0.75) was lower in women compared to men[36].

In the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry, female AF patients were found to have more symptoms (like palpitations, light-headedness, dizziness, fatigue and chest discomfort) compared to male ones, with an overall worse quality of life (adjusted quality of life 24% lower in women than in men), despite being less likely in persistent and permanent AF[39]. Treatment with antiarrhythmic drugs or oral anticoagulant were no different between men and women. The observed rates of cardiovascular death and all-cause death were similar between sexes, but after adjustment, the risk was significantly lower in women compared to men (HR: 0.56; 95% CI: 0.44-0.72 and HR: 0.57; 95% CI: 0.49-0.67, respectively)[39]. Female AF patients were at higher risk of stroke than men, after adjustment (HR: 1.39; 95% CI: 1.05-1.84)[39].

In the Far East population, the results are less consistent. In the paper by Yang and colleagues, reporting about 2016 Chinese AF patients admitted to emergency room due to AF presence, female sex was a predictive risk factor for stroke (HR: 1.42; 95% CI: 1.00-2.00) but not for major CV events (HR: 1.00; 95% CI: 0.83-1.23)[29]. Kang et al. reported data on 10846 newly diagnosed AF patients from the Korean National Health Insurance Service[44]. Women represented almost half of the sample, were slightly older, more likely to have chronic heart failure or chronic lung disease but history of cerebrovascular diseases or ischemic heart diseases were no different compared to men[29]. While it was found a significant association between each other CHA_2DS_2-VASc score items and stroke occurrence, there was an inverse association between female sex and stroke (HR: 0.75; 95% CI: 0.66-0.86)[29].

3.2 Risk of Bias Evaluation

Risk of bias evaluation is shown in the Supplementary Material (Table S1). Overall, only 1 study was considered to be at high risk of bias, while 4 (9.1%) were considered to be at

medium risk of bias. All the other studies (40 out of 44) were considered at low risk of bias. No publication bias was found for stroke outcome (p=0.39) [Figure S3]. Some small publication bias was identified for the other outcomes, even though none reached statistical significance [Figure S4-S7].

3.3 Meta-Analysis of Included Studies

After extraction, all data were pooled. Data on 993603 AF patients were retrieved from the 44 studies, with 485933 (48.9%) women and 507670 (51.1%) men. Twenty-six studies[12,14–17,19–21,23,24,26,28,29,31–33,35,37,38,40,44,45,47,49,52,55] reported data on stroke occurrence, 22 studies[13,18,19,22,23,25,27,30,31,34,36,37,39,41–43,46,48,50,51,53,54] reported data on TE occurrence, 16 studies[15,36,39,43,46–53] reported data on major bleeding, 7 studies[19,27,35,36,39,45,46] reported data on CV death and, lastly, 13 studies[19,23,25,33,35,36,38,39,43,45,47,50,52] reported data on all-cause death.

Pooling of studies results showed that female AF patients were at higher risk of stroke compared to male AF patients, with a 24% of relative risk increase (HR: 1.24; 95% CI: 1.14-1.36; p<0.001) with a moderate heterogeneity (I^2= 55.96%) [Figure 1]. No difference in TE risk was found in the overall population (HR: 1.08; 95% CI: 0.88-1.32 for female vs. male patients) [Figure 1]. Similarly, no difference was found for the occurrence of major bleeding, CV death and all-cause death [Figure 1]. A random-effects model was used for stroke, TEE, major bleeding and all-cause death [Figure S8-S9-S10-S12], while a fixed-effects model was used for CV death [Figure S11].

3.4 Meta-Regression Analyses

We performed meta-regression analysis (Table 2, Panel A) considering the main study characteristics (patients' age, female sex prevalence, OAC use, follow-up time, year of issue, type of study and geographic location) and reported HRs and 95% CI for subgroups considered (Table 2, Panel B).

3.4.1 a) Continuous Predictors

We found no differences in pooled HRs in relation to female sex prevalence and follow-up time for any outcomes. Conversely, we found a significant increase in HR for stroke occurrence in female vs. male patients with progressively increasing age (Delta HR: 1.01; 95% CI: 1.00-1.03 for each year of increasing age) (Table 2, Panel A).

Looking at the relationship between age and risk of stroke, when comparing female vs. male AF patients, the HR for stroke in female vs. male patients progressively increased with increasing age [Figure 2, Panel A], becoming significant (and progressively higher) for those age ≥65 years old.

Increasing OAC use was associated with a significant reduction in risk for CV death in female vs. male patients (Delta HR: 0.26; 95% CI: 0.10-0.66). There was a significantly higher risk of CV death for female vs. male patients especially with lower use of OAC, while the risk progressively decreased with the increasing use of OAC, becoming non-significant for an OAC prevalence greater than 42% and reversing when almost all patients are treated [Figure 2, Panel B].

3.4.2 b) Categorical Predictors

Meta-regression of categorical predictors found no significant influence of year of study publication on reported stroke risk (Table 2, Panel A), with an increased risk of stroke for female vs. male AF patients in all year subgroups (Table 2, Panel B): 1999-2012 (p=0.001), 2013-2015 (p=0.008), 2016-2017 (p=0.018).

Examining age according to classes, both age 65-75 years old (p=0.002) and age >75 years old (p=0.010) significantly increased stroke risk for women vs. men when compared to age <65 years old (Table 2, Panel A), with the same age categories reporting a relative risk increase of 36% (p<0.001) and 27% (p<0.001), respectively (Table 2, Panel B).

A significant reduction in differential risk for women, compared to men, for major bleeding and CV death was found for the studies more recently published (Table 2, Panel A). For example, for the studies published in the 1999-2012 subgroup, a higher risk in female AF patients was seen for major bleeding (HR: 1.63; 95% CI: 1.03-2.58) and CV death (HR: 2.08; 95% CI: 1.03-4.23), while no difference was found in papers published in 2013-2015 and 2016-2017 (Table 2, Panel B).

While the increased risk of stroke for female patients was non-statistically different across the types of study (Table 2, Panel A), subgroup analysis found that for insurance database and observational studies, the increase in risk did not reach statistical significance (p=0.086 and p=0.148, respectively) (Table 2, Panel B).

Population cohort studies found an increase CV death risk in female vs. male AF patients (Delta HR: 5.08; 95% CI: 1.83-14.11) compared to RCTs. The RCTs subgroups had a lower risk for female vs. male patients (HR: 0.77; 95% CI: 0.60-0.99), while the population

cohort studies subgroup reported a higher risk of CV death for female AF patients (HR: 3.90; 95% CI: 1.45-10.51).

Geographic location affected the risk of stroke, with a significant reduction in women seen for North America (Delta HR: 0.87; 95% CI: 0.79-0.96) and Middle East/Asia (Delta HR: 0.73; 95% CI: 0.63-0.83) (Table 2, Panel A). The risk of stroke for female vs. male AF patients was lower in North America (HR: 1.20; 95% CI: 1.13-1.29) than in Europe (HR: 1.38; 95% CI: 1.28-1.49) while remaining significantly higher in women, studies in Middle East/Asia found no difference in stroke risk between female and male AF patients (p=0.895) (Table 2, Panel B), whilst a lower risk for women compared to men for TE occurrence in Middle East/Asia was found (p=0.001). Conversely, there was an increased risk for TE in female vs. male AF patients for European and Multinational studies (p=0.026 and p=0.002, respectively).

North America and Multinational studies showed a significant reduction in CV death risk for female AF patients (p=0.016 and p=0.004), compared to European studies, that reported an increased CV death risk for female vs. male patients (HR: 2.79; 95% CI: 1.21-6.46).

3.5 Sensitivity Analyses

The increased risk of stroke for female AF patients showed no significant changes when each of the studies included were removed sequentially [Figure S13]. For TE occurrence, removal from the meta-analysis of the studies by Guo et al. (2013)[23] or by Inoue et al. (2014)[27] led to a significantly increased risk for TE in female vs. male AF patients, while in all other cases there was no difference in risk [Figure S14].

4. DISCUSSION

This systematic review and meta-analysis extensively analysed sex differences in stroke and TE risk amongst patients with AF. Collecting almost one million patients and despite the presence of a moderate heterogeneity, we provided evidence about the increased risk of stroke in female AF patients compared to men. There was an age dependency to this relationship, with significant relationship between increasing age and the increased risk for stroke in women compared to men that was most evident at age>65 years.

We did not find any evidence of sex differences in either major bleeding events or all-cause death, whereas possible sex differences in CV death risk may be mediated by OAC therapy, geographic location and type of population examined. As would be expected, we found an inverse relationship between the OAC therapy and risk of CV death in female AF patients. Further, the meta-regression and subgroup analyses showed that population cohort studies demonstrated an increased CV death risk in women, while RCTs suggested a reduced risk of CV death in women. We could hypothesise that in “real-life” cohorts, compared to RCTs that usually enrol more selected patients, the excess of risk in female AF patients could also determine the increased risk for CV death, particularly when not modulated by OAC use, which is usually underprescribed in “real-life” cohorts.

Early observational studies suggested that female sex could be a major risk factor for stroke and TE [24,35,56]. For example, Fang and colleagues found that female AF patients reported a 60% increase in adjusted relative risk for any thromboembolism compared to men, particularly in those aged ≥75 years old[56]. Other large nationwide studies proved that after full adjustments a strong age-dependency of an increased risk of stroke in women remained evident[17]. An analysis derived from the Danish Nationwide registries, reported that female sex did not imply an increased risk of stroke itself, but

rather increased the risk when added to other major risk factors for stroke and TE[57]. These data generated a large debate about the real role of female sex in modulating risk of stroke in AF patients, with some researchers suggesting that female sex was a “risk modifier” rather than a proper “risk factor” per se[58].

In this context, our systematic review and meta-analysis provides some robust evidence on female sex in conferring a higher stroke risk in AF patients. Furthermore, we clearly demonstrated the direct “dose-effect” relationship between age and stroke risk in determining the increased risk in women. Our study does not support the notion that the lower prevalence of women, actually reported in a large number of the studies included could have an influence in confounding the real impact of sex in determining major outcomes[59,60].

Lastly, among Asian patients the higher stroke risk ascribed to women was no longer evident, while an inverse risk (higher risk in men) appeared for occurrence of TE. Thus, race and sex could substantially interact in determining the stroke/TE risk of Asian AF patients[61].

Regarding TE occurrence, our sensitivity analysis suggests that a higher risk for women with AFmay be present. Indeed, alternatively removing from the meta-analysis two studies[23,27] led to a significant increased risk for female patients. Considering that the two studies shared similar characteristics, meta-analytic results after their exclusion could be still externally valid and would imply some evidence of higher TE risk in female AF patients.

Several mechanisms have been described to explain the higher thromboembolic risk in female patients with AF[62]. Sex-gender differences were reported in arterial structure, alterations in blood flow, shear stress and endothelial function[62]. Furthermore, an influence of sex has been described in atrial structure and function, which could affect atrial thrombogenesis mechanisms[63–65]. Also, gender-related alterations in inflammatory and pro-coagulant markers, thrombogenic particles and platelet aggregation may play a role [62]. Indeed, hormone replacement therapy has been reported as a possible factor playing a role in determining thromboembolic risk, but available data have been largely conflicting[3,66].

In the overall analysis, we found no difference between female and male AF patients for CV death. Nevertheless, CV death risk in female patients increased with decreasing OAC use in AF patients. Our meta-analysis reinforces the concept that OAC therapy also plays a pivotal role in the reduction of CV death risk, especially in women. Indeed, there is an inverse association between use of OAC and death risk, with ~35% risk reduction in both CV and all-cause death[67]. In a large Spanish cohort, the cessation of OAC therapy was associated with an increased risk of all-cause death[68]. The adherence of clinicians to guideline recommendations for OAC therapy is associated with a reduction in all-cause death risk[69,70]. These data underline once more the benefits of OAC in AF patients regardless of sex, yet a lower OAC prescription rate is constantly reported amongst female AF patients[71–73].

Interestingly, there was evidence of an increased risk of CV death for female AF patients in population cohort studies, while an increased risk for CV death in male AF patients is present in RCTs. In fact, RCTs disproportionally excluded elderly women with high prevalence of co-morbidities while, in the population cohort studies, female patients were

usually older than male ones at the baseline, reflecting a more complex clinical status and an increased CV risk. Conversely, in the RCTs clinical characteristics were often more similar across the patients included regardless sex.

Our results suggest that better assessment of the overall baseline risk in female patients is needed, especially amongst the elderly. Given other evidence suggesting that female patients are less appropriately prescribed OAC[10], our results underline the need for proper guideline-adherent prescription of OAC independent of sex, with female patients appropriately prescribed according to their baseline risk.

4.1 Limitations and Strength

The main limitation of this meta-analysis is related to the absence of a meta-regression analysis according to baseline thromboembolic risk, as defined by $CHADS_2$ or CHA_2DS_2-VASc scores. Even though thromboembolic risk was generally higher in female than in male AF patients, many of the studies included in the systematic review had no formal risk assessment score used, whereas in those where scores were reported there was wide heterogeneity in application and definition. Notwithstanding, given the large number of patients included in the meta-analysis and the consistency of results reported in the meta-regression analysis we provided fairly robust conclusions about the increased risk of stroke in female AF patients. Moreover, the variability related to type of studies included and geographic location further reinforces the strength of our results, extending the external validity of this meta-analysis.

5. CONCLUSION

Women with AF are at increased risk of stroke compared to men. There was an age dependency to this relationship, with significant relationship between increasing age and

the increased risk for stroke in women compared to men that was most evident at age >65 years. Some evidence may suggest an increased risk for female AF patients also for TE and CV death. Female sex may act as a risk modifier, particularly in elderly AF subjects, conferring a significant increase in risk for stroke and major adverse events.

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Table 1: Baseline Characteristics of Included Studies

Study	Year	Cohort Type	Location	N	Age (Mean)	OAC Use	FU years (Mean)
Hart[12]	1999	RCT	Multinational	M: 1449 W: 563	NA	Overall: 14.4%	2
Inoue[13]	2000	Multicentre Observational Study	United States	M: 507 W: 233	NA	Overall: 9.9%	3.4
Wang[24]	2003	Population Cohort	United States	M: 462 W: 406	NA	Overall: 18.8%	4.3
Friberg[35]	2004	Population Cohort	Denmark	M: 166 W: 110	M: 69.0 W: 67.0	Overall: 2.2% M: 4.9% W: 3.7%	4.7
Rienstra[46]	2005	RCT	Multinational	M: 330 W: 192	M: 67 W: 71	Overall: 100%	2.3
Gomberg-Maitland[51]	2006	RCT	Multinational	M: 5072 W: 2257	M: 69.8 W: 73.4	Overall: 49.4% M: 49.8% W: 48.7%	1.5

Dagres[52]	2007	Multicentre Observational Study	Europe	M: 3084 W: 2249	M: 64 W: 70	Overall: 65%	1
Poli[53]	2009	Single Centre Observational Study	Italy	M: 505 W: 275	M: 74 W: 76 (Median)	Overall: 100%	3.1
Ruigomez[54]	2009	Population Cohort	UK	M: 405 W: 426	NA	NA	3.6
Lin[55]	2011	Population Cohort	Taiwan	M: 4287 W: 3633	NA	Overall: 0%	4.5 (Median)
Van Staa[14]	2011	Population Cohort	UK	M: 40140 W: 39704	NA	Overall: 20.1%	4.0
Avgil Tsadok[15]	2012	Population Cohort	Canada	M: 39398 W: 44115	M: 77.2 W: 80.2 (Median)	Overall: 59.5% M: 58.2% W: 60.6%	2.8
Chao[16]	2012	Insurance Database	Taiwan	M: 509 W: 320	NA	Overall: 0%	4.8
Friberg[17]	2012	Population Cohort	Sweden	M: 50135 W: 50667	M: 74.7 W: 80.9	Overall: 0%	1.2 (Median)

Mikkelsen[18]	2012	Population Cohort	Denmark	M: 42458 W: 44744	M: 71.0 W: 78.2	Overall: 0%	12
Potpara[19]	2012	Single Centre Observational Study	Serbia	M: 547 W: 315	M: 49.6 W: 56.7	Overall: 17.2% M: 21.0% W: 10.5%	10
Sullivan[20]	2012	RCT	United States	M: 2466 W: 1584	M: 68.3 W: 71.3	Overall: 77.8% M: 76.9% W: 79.3%	3.5
Bosch[21]	2013	Multicentre Observational Study	Germany	M: 1721 W: 1021	M: 67.5 W: 71.2	Overall: 93.8% M: 94.1% W: 93.4%	1
Disertori[22]	2013	Multicentre Observational Study	Italy	M: 747 W: 487	NA	Overall: 50.7%	1
Guo[23]	2013	Single Centre Observational Study	China	M: 753 W: 281	M: 78 W: 71 (Median)	Overall: 14.4% M: 13.8% W: 16.0%	1.9 (Median)

Poli[25]	2013	Multicentre Observational Study	Italy	M: 1361 W: 1654	M: 82.6 W: 83.1 (Median)	Overall: 100%	2.5
Aakre[26]	2014	Population Cohort	United States	M: 1400 W: 1320	NA	Overall: 5%	4.37
Inoue[27]	2014	Multicentre Observational Study	Japan	M: 5241 W: 2165	M: 69 W: 73	Overall:86.5% M: 86.5% W: 86.3%	2
Siu[28]	2014	Single Centre Observational Study	Hong Kong	M: 4663 W: 5064	NA	Overall: 19.7%	3.19
Yang[29]	2014	Population Cohort	China	M: 911 W: 1104	NA	Overall: 18.6% M: 16.6% W: 20.3%	1
Avgil Tsadok[30]	2015	Population Cohort	Canada	M: 31324 W: 31786	M: 76.3 W: 80.3	Overall: 74.8% VKA + 25.2% D M: 73.4% VKA + 26.6% D W: 76.2% VKA + 23.8% D	1.3

Bekwelem[31]	2015	RCTs	Multinational	M: 23622 W: 14351	NA	Overall: 24.7% VKA + 31.8% D + 7.4% A M: 25.5% VKA + 32.6% D + 7.0% A W: 23.5% VKA + 30.6% D + 8.0% A	2.4
Chao[32]	2015	Insurance Database	Taiwan	M: 22351 W: 14290	M: 59.1 W: 59.1	Overall: 0%	5.2
Shantsila[33]	2015	Population Cohort	UK	M: 1218 W: 1041	M: 73 W: 79	Overall: 50% M: 52% W: 47%	1
Tomita[34]	2015	Multicentre Observational Study	Japan	M: 703 W: 294	M: 66 W: 71	Overall: 23.4% M: 23.9% W: 22.4%	2
Vinereanu[36]	2015	RCT	Multinational	M: 11785 W: 6416	M: 69 W: 72 (Median)	Overall: 49.9% VKA + 50.1% A M: 50.1% VKA + 49.9% A W: 49.6 VKA + 50.4% A	1.8
Boriani[37]	2016	Multicentre Observational Study	Italy	M: 1909 W: 489	M: 67 W: 68 (Median)	Overall: 23.2% M: 23.2% W: 23.1%	3.6

Kassim[38]	2016	Single Centre Observational Study	United States	M: 2537 W: 1774	M: 66.8 W: 72.5	Overall: 70.6% VKA + 22.7% NOACs M: 71.7% VKA + 24.6% NOACs W: 69.9% VKA + 19.9% NOACs	3.3
Piccini[39]	2016	Multicentre Observational Study	United States	M: 5842 W: 4293	M: 73 W: 77 (Median)	Overall: 71.2% VKA + 4.9% D M: 71.2% VKA + 5.0% D W: 71.2% VKA + 5.0% D	2
Wandell[40]	2016	Population Cohort	Sweden	M: 6269 W: 5248	M: 71.8 W: 76.9	Overall: 48.8% M: 52.7% W: 44.0%	5.4
Xing[41]	2016	Single Centre Observational Study	Japan	M: 294 W: 119	NA	Overall: 0%	1.99
Andersson[42]	2017	Population Cohort	Sweden	M: 26977 W: 21456	M: 69.5 W: 74.1	Overall: 43.9% M: 44.8% W: 42.8%	4
Camm[43]	2017	Multicentre Observational Study	Multinational	M: 15915 W: 12709	M: 67.6 W: 72.4	Overall: 46.3% VKA + 17.9% NOACs M: 46.0% VKA + 17.9% NOACs W: 46.8% VKA + 17.1% NOACs	1

Kang[44]	2017	Population Cohort	Korea	M: 5768 W: 5078	M: 65.9 W: 61.8	Overall: 0%	2.8
O'Neal[45]	2017	RCT	Multinational	M: 641 W: 550	NA	NA	3.4 (Median)
Renoux[47]	2017	Insurance Database	Canada	M: 71135 W: 76487	M: 73.7 W: 77.1	Overall: 43%	2.9
Schnabel[48]	2017	Multicentre Observational Study	Europe	M: 3866 W: 2546	M: 70.1 W: 74.1	Overall: 94% M: 94% W: 94%	1
Shanta[49]	2017	Insurance Database	United States	M: 65734 W: 81137	NA	Overall: 69.2% VKA + 15.0% D + 15.8% R M: 66.0% VKA + 16.3% D + 17.7% R W: 71.9% VKA + 13.8% D + 14.3% R	1.2 (Median)
Shehab[50]	2017	Multicentre Observational Study	Middle East	M: 1063 W: 980	M: 55.1 W: 58.5	Overall: 30.7% M: 25.1% W: 36.8%	1

Legend: A= Apixaban; D= Dabigatran; FU= Follow-Up; M= Men; NA= Not Available; OAC= Oral Anticoagulant; R= Rivaroxaban; RCT= Randomised Controlled Trial; VKA= Vitamin K Antagonist; W= Women.

Table 2: Meta-regression Analysis for Clinical Predictors for Women vs. Men for Outcomes*

	Stroke		TEE		Major Bleeding		CV Death		All-Cause Death	
	Delta HR (95% CI)	p	Delta HR (95% CI)	p	Delta HR (95% CI)	p	Delta HR (95% CI)	p	Delta HR (95% CI)	p
A) DIFFERENCES IN POOLED HR ACCORDING TO CONTINUOUS AND CATEGORICAL PREDICTORS										
Continuous Predictors										
Age (*years*)	**1.01 (1.00-1.03)**	**0.037**	1.01 (0.97-1.04)	0.648	0.99 (0.96-1.03)	0.708	0.98 (0.92-1.04)	0.570	1.01 (0.97-1.05)	0.779
Females (*%*)	1.00 (0.99-1.01)	0.992	1.02 (0.99-1.05)	0.067	0.99 (0.97-1.02)	0.584	0.99 (0.96-1.04)	0.893	1.03 (0.99-1.07)	0.157
OAC use (*%*)	1.03 (0.76-1.39)	0.842	1.67 (0.71-3.95)	0.239	0.78 (0.39-1.58)	0.499	**0.26 (0.10-0.66)**	**0.005**	1.09 (0.39-3.01)	0.875
FU (*years*)	0.96 (0.91-1.01)	0.138	0.99 (0.93-1.06)	0.907	0.99 (0.84-1.16)	0.864	1.12 (0.95-1.31)	0.171	1.06 (0.90-1.24)	0.486
Categorical Predictors										
Age classes										
<65 years *(ref.)*	-	-	-	-	-	-	-	-	-	-
65-75 years	**1.38 (1.13-1.70)**	**0.002**	1.22 (0.59-2.50)	0.588	0.85 (0.29-2.50)	0.773	0.74 (0.15-3.61)	0.705	0.71 (0.30-1.66)	0.428
>75 years	**1.29 (1.06-1.57)**	**0.010**	1.33 (0.56-3.14)	0.522	0.77 (0.26-2.25)	0.630	No studies		1.10 (0.43-2.84)	0.842
Year of Issue										

1999-2012 *(ref.)*	-	-	-	-	-	-	-	-	-	-
2013-2015	0.97 (0.79-1.21)	0.806	0.82 (0.49-1.36)	0.437	**0.57 (0.34-0.95)**	**0.032**	**0.38 (0.18-0.82)**	**0.014**	**2.00 (1.04-3.85)**	**0.038**
2016-2017	0.95 (0.77-1.18)	0.652	1.23 (0.73-2.06)	0.440	0.67 (0.41-1.09)	0.106	**0.41 (0.19-0.87)**	**0.021**	**2.17 (1.19-3.95)**	**0.011**
Type of Study										
RCT *(ref.)*	-	-	-	-	-	-	-	-	-	-
Observational	0.84 (0.60-1.18)	0.305	0.70 (0.46-1.07)	0.097	0.96 (0.63-1.47)	0.132	1.25 (0.83-1.89)	0.290	0.95 (0.49-1.86)	0.882
Population Cohort	0.88 (0.67-1.15)	0.337	0.89 (0.59-1.35)	0.582	0.70 (0.44-1.11)	0.867	**5.08 (1.83-14.11)**	**0.002**	2.01 (0.79-5.12)	0.143
Insurance DB	0.81 (0.60-1.08)	0.153	No studies		0.89 (0.59-1.33)	0.567	No studies		1.16 (0.44-3.08)	0.763
Location										
Europe *(ref.)*	-	-	-	-	-	-	-	-	-	-
North America	**0.87 (0.79-0.96)**	**0.007**	1.04 (0.78-1.38)	0.804	0.87 (0.53-1.40)	0.556	**0.33 (0.13-0.81)**	**0.016**	1.24 (0.61-2.55)	0.552
Middle East/Asia	**0.73 (0.63-0.83)**	**<0.001**	**0.42 (0.27-0.65)**	**<0.001**	0.79 (0.25-2.43)	0.676	0.49 (0.13-1.84)	0.291	0.79 (0.32-1.96)	0.613
Multinational	1.01 (0.84-1.23)	0.890	1.14 (0.89-1.46)	0.297	1.00 (0.58-1.73)	0.990	**0.27 (0.11-0.66)**	**0.004**	1.09 (0.52-2.22)	0.838
B) POOLED HR AND 95% CI ACCORDING TO SUBGROUPS										
Age classes										
<65 years	0.98 (0.83-1.16)	0.844	0.89 (0.45-1.74)	0.730	1.35 (0.47-3.85)	0.579	1.20 (0.25-5.81)	0.821	1.04 (0.47-2.30)	0.920
65-75 years	**1.36 (1.21-1.53)**	**<0.001**	1.08 (0.84-1.39)	0.528	1.15 (0.91-1.46)	0.252	0.88 (0.73-1.07)	0.215	0.74 (0.53-1.03)	0.070
>75 years	**1.27 (1.15-1.40)**	**<0.001**	1.18 (0.69-2.02)	0.552	1.03 (0.83-1.29)	0.769	No studies		1.15 (0.68-1.94)	0.605
Year of Issue										

1999-2012	**1.27 (1.10-1.47)**	**0.001**	1.09 (0.74-1.61)	0.669	**1.63 (1.03-2.58)**	**0.038**	**2.08 (1.03-4.23)**	**0.043**	**0.45 (0.26-0.78)**	**0.004**
2013-2015	**1.24 (1.06-1.45)**	**0.008**	0.89 (0.65-1.23)	0.481	0.94 (0.75-1.16)	0.538	0.79 (0.58,1.08)	0.138	0.90 (0.62-1.31)	0.586
2016-2017	**1.21 (1.03-1.42)**	**0.018**	1.34 (0.95-1.88)	0.096	1.09 (0.92-1.28)	0.330	0.85 (0.65-1.12)	0.254	0.98 (0.76-1.27)	0.876
Type of Study										
RCT	**1.43 (1.12-1.82)**	**0.004**	1.33 (0.97-1.84)	0.081	1.07 (0.85-1.35)	0.542	**0.77 (0.60-0.99)**	**0.041**	0.80 (0.47-1.44)	0.457
Observational	1.19 (0.94-1.52)	0.148	0.94 (0.72-1.22)	0.628	1.17 (0.91-1.50)	0.231	0.96 (0.69-1.33)	0.807	0.76 (0.55-1.06)	0.103
Population Cohort	**1.25 (1.12-1.40)**	**<0.001**	1.19 (0.91-1.54)	0.204	0.85 (0.62-1.16)	0.308	**3.90 (1.45-10.51)**	**0.007**	1.61 (0.78-3.34)	0.201
Insurance DB	1.15 (0.98-1.36)	0.086	No studies		1.07 (0.85-1.35)	0.542	No studies		0.93 (0.43-2.03)	0.855
Location										
Europe	**1.38 (1.28-1.49)**	**<0.001**	**1.19 (1.02-1.38)**	**0.026**	1.20 (0.78-1.84)	0.415	**2.79 (1.21-6.46)**	**0.016**	0.81 (0.50-1.33)	0.412
North America	**1.20 (1.13-1.29)**	**<0.001**	1.23 (0.97-1.56)	0.087	1.04 (0.84-1.28)	0.742	0.91 (0.64-1.30)	0.601	1.01 (0.60-1.70)	0.965
Middle East/Asia	1.10 (0.91-1.12)	0.895	**0.50 (0.33-0.75)**	**0.001**	0.94 (0.33-2.67)	0.909	1.37 (0.49-3.81)	0.546	0.64 (0.30-1.37)	0.256
Multinational	**1.40 (1.17-1.67)**	**<0.001**	**1.35 (1.12-1.65)**	**0.002**	1.20 (0.86-1.68)	0.281	**0.70 (0.60-0.99)**	**0.041**	0.88 (0.52-1.49)	0.626

Legend: *Grey Cells and Bold Text Depict Statistically Significant Association; CI= Confidence Interval; CV= Cardiovascular; DB= Database; FU= Follow-Up; HR= Hazard Ratio; OAC= Oral Anticoagulant; RCT= Randomized Clinical Trial; TEE= Thromboembolic Events.

FIGURES LEGENDS

Figure 1: Pooled Hazard Ratios for Study Outcomes

Legend: CI= Confidence Intervals; CV= Cardiovascular; HR= Hazard Ratio; TEE= Thromboembolic Events.

Figure 2: Meta-regression Analysis According to Continuous Predictors

Legend: Panel A) Risk of Stroke according to Age: Full Black Line refers to HR, while Dashed Black Lines refer to 95% CI. Red Full line refers to Non-significance line; CI= Confidence Interval; HR= Hazard Ratio; **Panel B) Risk of CV Death according to OAC Use:** Full Black Line refers to HR, while Dashed Black Lines refer to 95% CI. Red Full line refers to Non-significance line; CI= Confidence Interval; CV= Cardiovascular; HR= Hazard Ratio; OAC= Oral Anticoagulant.

HIGHLIGHTS

- Sex differences have been in reported in patients with atrial fibrillation (AF)
- Female AF patients have a significantly higher risk for stroke than male ones
- Stroke risk in female AF patients is significantly associated with increasing age
- Data suggest a possibly increased risk for thromboembolic events (TE)
- A higher risk for cardiovascular (CV) death in females is mediated by OAC use
- Data are needed to elucidate the role of female sex in TE and CV death in AF

Outcome	HR	95% CI		I2	p-value
Stroke	1.24	1.14	1.36	55.96	<0.001
TEE	1.08	0.88	1.32	83.39	0.457
Major Bleeding	1.10	0.92	1.3	69.21	0.280
CV Death	0.89	0.73	1.08	0.00	0.243
All-Cause Death	0.86	0.64	1.14	91.98	0.306

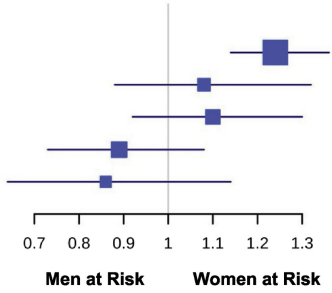

Figure 1

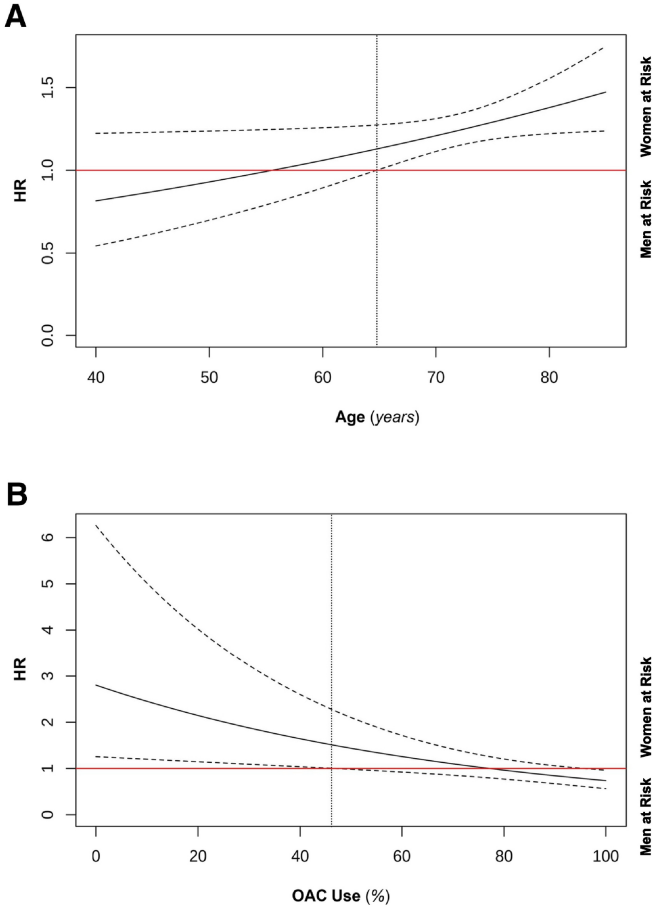
A
HR
0.0
0.5
1.0
1.5
40
50
60
70
80
Age (years)
Women at Risk
Men at Risk
B
HR
0
1
2
3
4
5
6
0
20
40
60
80
100
OAC Use (%)
Women at Risk
Men at Risk

Figure 2