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Sex-specific association of cardiovascular drug doses with adverse outcomes in atrial fibrillation

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ABSTRACT

Objectives Sex differences occur in atrial fibrillation (AF), including age at first manifestation, pathophysiology, treatment allocation, complication rates and quality of life. However, optimal doses of cardiovascular pharmacotherapy used in women with AF with or without heart failure (HF) are unclear. We investigated sex-specific associations of beta-blocker and renin–angiotensin system (RAS) inhibitor doses with cardiovascular outcomes in patients with AF or AF with concomitant HF.

Methods We used data from the prospective Basel Atrial Fibrillation and Swiss Atrial Fibrillation cohorts on patients with AF. The outcome was major adverse cardiovascular events (MACEs), including death, myocardial infarction, stroke, systemic embolisation and HF-related hospitalisation. Predictors of interest were spline (primary analysis) or quartiles (secondary analysis) of beta-blocker or RAS inhibitor dose in per cent of the maximum dose (reference), in interaction with sex. Cox models were adjusted for demographics, comorbidities and comedication.

Results Among 3961 patients (28% women), MACEs occurred in 1113 (28%) patients over a 5-year median follow-up. Distributions of RAS inhibitor and beta-blocker doses were similar in women and men. Cox models revealed no association between beta-blocker dose or RAS inhibitor dose and MACE. In a subgroup of patients with AF and HF, the lowest hazard of MACE was observed in women prescribed 100% of the RAS inhibitor dose. However, there was no association between RAS dose quartiles and MACE.

Conclusions In this study of patients with AF, doses of beta-blockers and RAS inhibitors did not differ by sex and were not associated with MACE overall.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sex-specific analyses of beta-blocker and renin–angiotensin system (RAS) inhibitor doses in patients with heart failure with reduced ejection fraction have revealed a lower hazard of death or heart failure-related hospitalisation in women receiving low doses compared with maximum doses.

⇒ The pathophysiology and pharmacotherapy of atrial fibrillation show sex differences, but the potential sex-specific associations of different drug doses with cardiovascular outcomes are unknown in this population.

WHAT THIS STUDY ADDS

⇒ This study identifies no associations between beta-blocker doses and major adverse cardiovascular events in patients with atrial fibrillation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of the present study reassure that the recommended maximum doses of beta-blockers and RAS inhibitors appeared safe among patients of both sexes with atrial fibrillation.

INTRODUCTION

Atrial fibrillation (AF) is currently the most prevalent arrhythmia, and its incidence is increasing while survival of patients with AF has not improved in recent years.[1] Among patients with AF, up to 77% suffer from concomitant heart failure (HF) which is a predominant cause of death.[2] In patients with HF with reduced ejection fraction (HFrEF), positive effects on clinical outcomes are established for several drug classes including beta-blockers and renin–angiotensin system (RAS) inhibitors. However, the evidence for the benefit of beta-blockers in patients with AF only is limited to ventricular rate control and for prevention of symptomatic AF.[3–5] RAS inhibitors may prevent incident and recurrent episodes of AF in some populations, for example, AF recurrence in Asian but not in European or American populations.[6 7]

Sex differences are increasingly recognised in AF. The age-adjusted prevalence of AF is lower in females compared with the male sex, but the female sex is associated with a lower quality of life and a higher hazard of complications of AF such as stroke and cardiovascular death.[8 9] In addition, sex differences

exist in treatment allocation in patients with AF, with a higher proportion of men receiving electric cardioversion, radiofrequency ablation or pharmacotherapy compared with women.[10] Cardiovascular pharmacokinetics also differ between the sexes, with beta-blockers causing higher peak concentrations in women,[11] and ACE inhibitors carrying a larger distribution volume and residency time in women.[12] Further, the risk of adverse effects of ACE inhibitors is higher in women compared with men.[13] However, the potential impact of these sex differences in pharmacokinetics on cardiovascular outcomes is unclear.

Recent data show that optimal doses of beta-blocker and RAS inhibitors may differ between women and men. In two European and Asian populations with HFrEF, women receiving submaximal doses of RAS inhibitors or beta-blockers showed a lower hazard of mortality or cardiovascular hospitalisations compared with women receiving maximal doses.[14] Similarly, in Dutch outpatient clinics, an RAS inhibitor dose <50% was associated with lower mortality in women but not in men with HFrEF.[15] However, the sex-specific optimal doses of beta-blockers in patients with AF and doses of RAS inhibitors in patients with both HF and AF are unclear. In addition, despite a lack of a clear benefit of RAS inhibitors in patients with AF only, around half of all patients with AF receive RAS inhibitors,[16 17] with a potential for dose-dependent and sex-specific benefits or harms.

Our goal was thus to assess sex-specific associations between beta-blocker or RAS inhibitor dose and major adverse cardiovascular events (MACE) in (1) patients with AF and (2) in patients with AF and HF.

METHODS

Study design and population

The current study is a post hoc analysis of patients with AF from two prospective cohorts that were developed to determine cardiovascular and neurological outcomes in patients with AF: the Swiss Atrial Fibrillation (Swiss-AF) Cohort Study and Basel Atrial Fibrillation (BEAT-AF) Cohort Study.[18 19] Swiss-AF and BEAT-AF are prospective multicentre cohort studies across 14 and 7 Swiss centres, respectively.[19] Both studies enrolled adult patients from inpatient and outpatient clinics, BEAT-AF between January 2010 and April 2014 and Swiss-AF between March 2014 and August 2017.[18 19] Inclusion criteria included at least one documented episode of AF on an ECG and written informed consent. The Swiss-AF cohort excluded patients with secondary forms of AF (eg, onset after surgery) and with any acute illness within the last 4 weeks.[19] The BEAT-AF cohort had no major exclusion criteria.[18] For the present analysis, we excluded participants with >100% of the maximum allowed daily dose of beta-blockers (n=5) or RAS inhibitors (n=22) from the respective analyses.

Outcomes

The primary outcome was time until the first event of a composite of MACE defined as all-cause death, myocardial infarction, coronary revascularisation, stroke and hospitalisation due to HF.[20] Secondary outcomes were the first event of individual components of the primary outcomes. All outcomes, except coronary revascularisation, were predefined in the protocol of the cohort studies,[18 19] ascertained by annual visits and adjudicated by a blinded committee of clinical experts. Similarly, a pre-existing HF diagnosis at baseline was established using a clinical definition of HF-related symptoms including breathlessness, ankle swelling or fatigue or signs including jugular venous pressure elevation, basal crackles or apex beat displacement resulting from a structural or functional heart abnormality.

Exposures

The doses of beta-blockers, ACE inhibitors and angiotensin receptor blockers, as well as sex, were the main variables of interest.

Drugs and their respective doses were identified from digital study records of medication lists at baseline visits using a systematic automated text search for all compounds under the categories of beta-blockers, ACE inhibitors and angiotensin receptor blockers (online supplemental table 1). Relative daily beta-blocker drug doses were calculated as per cent of maximum doses according to the 2020 European Society of Cardiology (ESC) guidelines for AF.[4] RAS inhibitor doses were calculated as per cent of maximum doses in ESC guidelines for HF.[3] Wherever the two guidelines articles did not include an individual beta-blocker or RAS inhibitor compound, equivalence doses were determined using a web-based calculator.[21] Further, demographic information, comorbidities and medication data were collected by investigators during study visits using electronic questionnaires and included in the present analysis. Body surface area (BSA) was calculated using the formula of Du Bois.[22]

Statistical analysis

Based on previous data, we calculated that 509 events would be needed to obtain 80% power (alpha 0.05) to detect a relative hazard for mortality or HF-related hospitalisation of 0.78 in women treated with submaximal doses of RAS inhibitors and 900 events to detect a relative hazard of 0.84 in women treated with submaximal doses of beta-blockers compared with women treated with the maximal doses, respectively.[14 23] Continuous variables are reported as median (IQR) and categorical variables as frequency (percentage). We analysed the overall population and the subset of the patients with a history of HF at baseline according to a prespecified analysis plan. As a first analysis strategy, beta-blocker or RAS inhibitor drug doses in per cent were used as a continuous variable.[14 24] As a secondary analysis strategy, beta-blocker and RAS inhibitor doses were categorised into five groups containing those with 0% (those without the drug) and

the quartiles of the subset prescribed between 1% and 100%. The hazard of primary and secondary outcomes was calculated using Cox proportional hazards models. For the primary analysis strategy, the restricted cubic spline of drug dose was used as non-linear predictor in Cox models. For the secondary analysis strategy, drug dose categories were included in Cox models. The top quartile or 100% of drug dose (the maximum beta-blocker or RAS inhibitor dose) in men was set as a reference, respectively. Additional variables of interest included in the models were sex and the interaction between drug dose and sex. Models with and without the interaction term were compared using likelihood ratio tests, with $p<0.05$ considered as significant. Models were adjusted for covariates identified from the literature as potential confounders,[14 25] including age, BSA, current smoking status, regular physical activity, history of diabetes, chronic kidney disease, history of coronary artery disease, heart rate, hypertension, history of stroke and/or transient ischaemic attack, oral anticoagulation, antiplatelet therapy, antiarrhythmics, chronic obstructive pulmonary disease (COPD) or asthma, pre-existing HF and the dose percentage of the other drug class (RAS inhibitors for the beta-blocker models and vice versa) at baseline. Patients with lost to follow-up were censored at the last completed visit or recorded event. For secondary outcomes not including all-cause mortality, patients were censored by lost to follow-up and additionally at death. Missing data among model covariates underwent multiple imputations. Prespecified sensitivity analyses were the adjustment for left ventricular ejection fraction (LVEF) in the subset with available echocardiography data, once as a continuous and once as a categorical variable (cut-offs: <40%, 40%–49%, 50% and above); the normalisation of drug dose through division by body mass index (BMI), BSA or body weight or the use of BMI instead of BSA in the models because of their discordance at extreme values[26]; excluding those not prescribed a drug (beta-blockers or RAS inhibitors) in the respective models; and inclusion of AF-specific parameters (device, cardioversion, AF type, AF duration) as potential confounders in the models. As post hoc sensitivity analyses, the analysis was stratified for the different treatment indications, and inverse probability weighting was used to balance patient characteristics. All analyses were performed with RStudio V.2023.06.1.

RESULTS

Demographic and clinical characteristics

Among 3961 participants of the Swiss-AF and BEAT-AF cohorts, 28% were women, the median age was 72 (IQR: 66–78) years, and the most frequent type of AF was paroxysmal (49%). Women were of similar age to men, median BSA was 1.76 m^2 (IQR: 1.65–1.88) in women vs 2.01 m^2 (IQR: 1.89–2.13) in men. Common comorbidities included arterial hypertension (69%), coronary artery disease (27%), diabetes mellitus (16%) and chronic kidney disease (19%). The prevalence of coronary artery disease was 15% in women and 31% in men. Median LVEF was 60% (IQR: 55%–65%) in women vs 55% (IQR: 47%–60%) in men at baseline in the subset with available echocardiography data. Full demographic and clinical characteristics of the overall population are shown in table 1 . Characteristics of the 25% of men and 21% of women with a history of HF at baseline are shown in online supplemental table 2. MACE occurred in 815 (29%) men and 308 (28%) women over a median follow-up of 4.7 (IQR: 3.0–6.0) years. Secondary outcomes included 632 deaths, stroke in 189, myocardial infarction in 137, hospitalisation due to HF in 584 and systemic embolism in 16 participants.

Sex-specific distribution of beta-blocker dose

For beta-blockers, the median dose prescribed was 12.5% (IQR: 1.3%–25%) of the maximum dose according to the 2020 ESC guidelines for AF.[4] 61 (1.5%) participants were prescribed a 100% beta-blocker dose, 540 (13.7%) a 50% dose, 906 (22.9%) 25% dose, 1470 (37.0%) other doses and 984 (24.9%) no beta-blocker. A sex-specific analysis of beta-blocker doses showed a congruent distribution across sexes in the whole population (figure 1A), whereas patients with a history of HF showed a partial overlap between sexes (figure 1B).

Primary sex-specific analysis strategy of beta-blocker dose in association with MACE

As the primary strategy, we used beta-blocker drug dose in percent as a continuous variable in Cox regression models. Here, the hazard of MACE was comparable over the entire dose range of beta-blockers and for both sexes in the full population (figure 1C) and the subgroup with a history of HF (figure 1D). The multivariable Cox models with adjustment for clinical and demographic confounders showed a comparable hazard of MACE over the entire dose range of beta-blocker dose in the whole study population (figure 1E) and in the subgroup with a history of HF (figure 1F). For all these models, the interaction terms (beta-blocker dose and sex) were not significant.

Sex-specific distribution of RAS inhibitor dose

For RAS inhibitors, the overall median dose was 12.5% (IQR: 0%–50%) in the study population. Among the patients, 238 (6.0%) were prescribed a 100% RAS inhibitor dose, 590 (15.0%) a 50% dose, 502 (12.7%) a 25% dose, 984 (24.5%) other doses and 1647 (41.8%) no RAS inhibitors. The sex-specific distribution of RAS inhibitor doses in the whole study population and the subset with pre-existing HF is shown in figure 2A–B.

Primary sex-specific analysis strategy of RAS inhibitor dose in association with MACE

In the model adjusted for RAS inhibitor dose, sex and the interaction RAS inhibitor dose and sex, the hazard of MACE was lower in the RAS inhibitor dose range below 25% of drug dose in the overall study population and

Table 1 Baseline characteristics

	Overall	Men	Women	P value
	n=3961	n=2844	n=1117	
Age (years)	72 (66, 78)	72 (66, 78)	74 (68, 80)	<0.001
BMI (kg/m^2)	26.8 (24.2, 30.0)	26.9 (24.6, 29.9)	26.0 (23.0, 30.4)	<0.001
BSA (m^2)	1.95 (1.81, 2.09)	2.01 (1.89, 2.13)	1.76 (1.65, 1.88)	<0.001
Heart rate (/min)	67 (59, 78)	66 (58, 77)	68 (60, 79)	0.005
Smoking status				<0.001
No	1739 (44%)	1091 (38%)	648 (58%)	
Past	1898 (48%)	1521 (53%)	377 (34%)	
Yes	313 (7.9%)	226 (7.9%)	87 (7.8%)	
Regular physical activity	1907 (48%)	1399 (49%)	508 (45%)	0.042
type of AF				<0.001
Paroxysmal	1939 (49%)	1318 (46%)	621 (56%)	
Permanent	908 (23%)	691 (24%)	217 (19%)	
Persisting	1111 (28%)	832 (29%)	279 (25%)	
CHAD2DS2-VASc score	3 (2, 4)	3 (2, 4)	4 (3, 5)	<0.001
EHRA score				<0.001
I	1407 (36%)	1098 (39%)	309 (28%)	
II	773 (20%)	516 (18%)	257 (23%)	
III	189 (4.8%)	115 (4.0%)	74 (6.6%)	
IV	45 (1.1%)	23 (0.8%)	22 (2.0%)	
History of device				<0.001
None	3263 (82%)	2342 (82%)	921 (82%)	
CRT	40 (1.0%)	30 (1.1%)	10 (0.9%)	
CRT-ICD	71 (1.8%)	62 (2.2%)	9 (0.8%)	
ICD	107 (2.7%)	91 (3.2%)	16 (1.4%)	
Pacemaker	455 (11%)	305 (11%)	150 (13%)	
History of pulmonal vein isolation	836 (21%)	613 (22%)	223 (20%)	0.380
LVEF	57 (50, 61)	55 (47, 60)	60 (55, 65)	<0.001
Arterial hypertension	2736 (69%)	1950 (69%)	786 (70%)	0.279
Diabetes mellitus	635 (16%)	511 (18%)	124 (11%)	<0.001
Coronary heart disease	1059 (27%)	893 (31%)	166 (15%)	<0.001
Kidney disease	741 (19%)	537 (19%)	204 (18%)	0.653
History of stroke/TIA	676 (17%)	484 (17%)	192 (17%)	0.898
Heart failure	942 (24%)	709 (25%)	233 (21%)	0.006
Beta-blocker dose %	12 (2, 25)	12 (0, 25)	12 (3, 25)	0.034
RAS inhibitor dose %	12 (0, 50)	14 (0, 50)	12 (0, 40)	0.203
Class IC antiarrhythmics	205 (5.2%)	134 (4.7%)	71 (6.4%)	0.036
Class III antiarrhythmics	725 (18%)	521 (18%)	204 (18%)	0.967
Antiplatelet therapy	849 (21%)	686 (24%)	163 (15%)	<0.001
Oral anticoagulants	3333 (84%)	2380 (84%)	953 (85%)	0.225

Data are presented as median (IQR) or n (%).
CHAD2DS2-VASc score stands for congestive heart failure, arterial hypertension, age (> 65 = 1 point, > 75 = 2 points), diabetes, previous stroke/transient ischemic attack (2 points).
Missing data were present in BMI (n=5), heart rate (n=14), EHRA score (n=1547) and LVEF (n=2673).
AF, atrial fibrillation; BMI, body mass index; CRT, cardiac resynchronisation therapy; EHRA, European Heart Rhythm Association; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; RAS, renin–angiotensin system; TIA, transitory ischaemic attack.

in the subset with HF (figure 2C). The interaction term yielded no significant effect. However, in the subgroup with a history of HF at baseline, the hazard of MACE showed an interaction with sex (figure 2D): In men, the hazard of MACE remained comparable across the range of RAS inhibitor doses. In women, however, an inverted u-shaped curve was present with a maximum hazard between 25% and 30% of RAS inhibitor dose and around

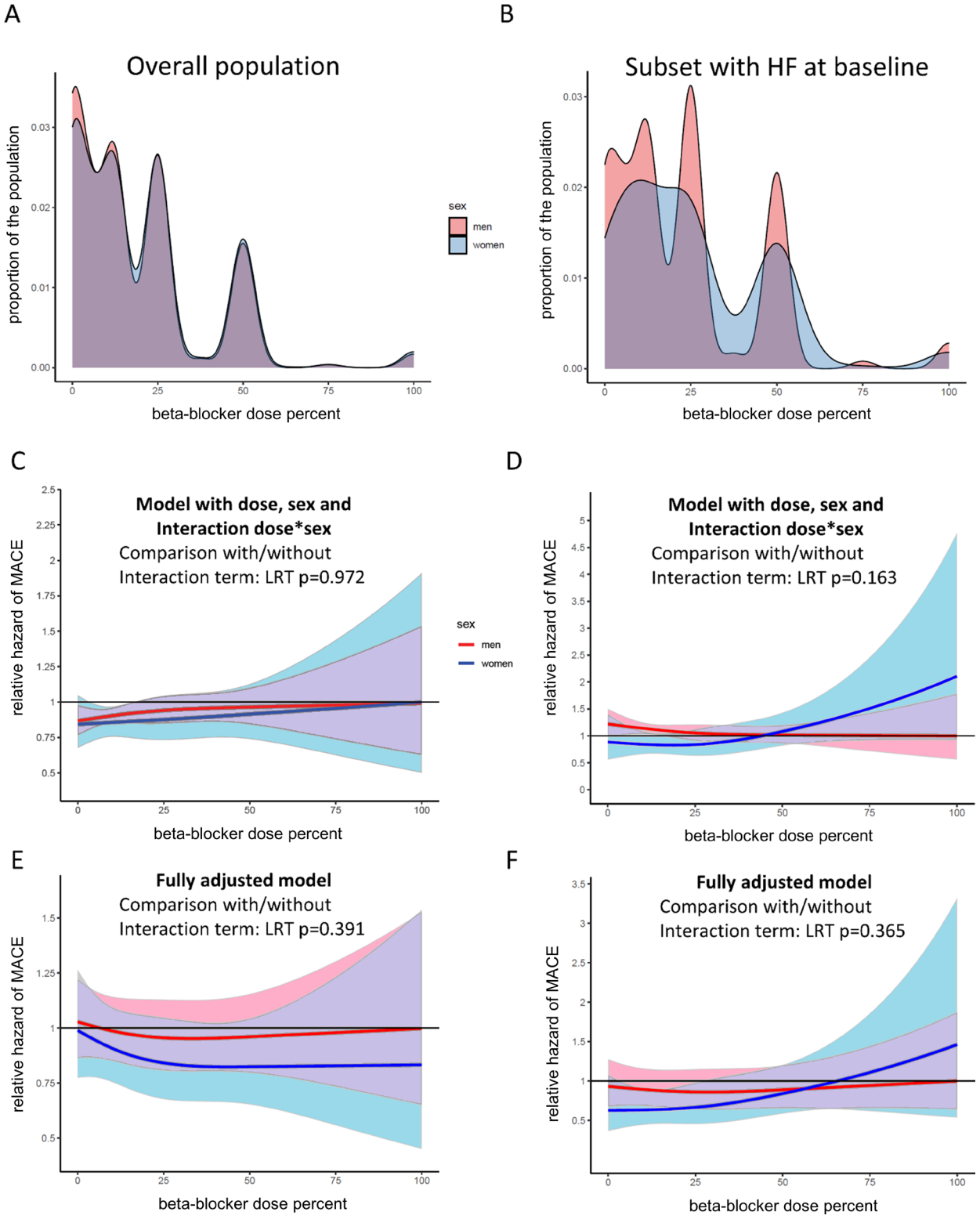

Figure 1 Distribution of beta-blocker dose in relation to recommended daily maximum dose according to sex in the overall population of patients with atrial fibrillation (A) and in the subset with a history of heart failure (HF) (B). Models in C–F show the hazard for major adverse cardiovascular event (MACE) in the overall population (C, E) or the subset with a history of HF (D, F). Models in C and D included sex, betablocker dose and the interaction between sex and betablocker dose for the overall population (C) or the subset with a history of HF (D). Models in E and F were additionally adjusted for age, body surface area, current smoking status, regular physical activity, history of diabetes, chronic kidney disease, history of coronary artery disease, heart rate, history of hypertension, history of stroke and/or transient ischaemic attack, oral anticoagulation, antiplatelet therapy, antiarrhythmics, COPD or asthma, the dose percentage of renin–angiotensin system inhibitors and a history of HF (E only). P values of likelihood ratio tests (LRT) are shown to compare with models without the interaction term. Shaded areas indicate 95% CIs for women (blue), men (red) or overlapping intervals (purple).

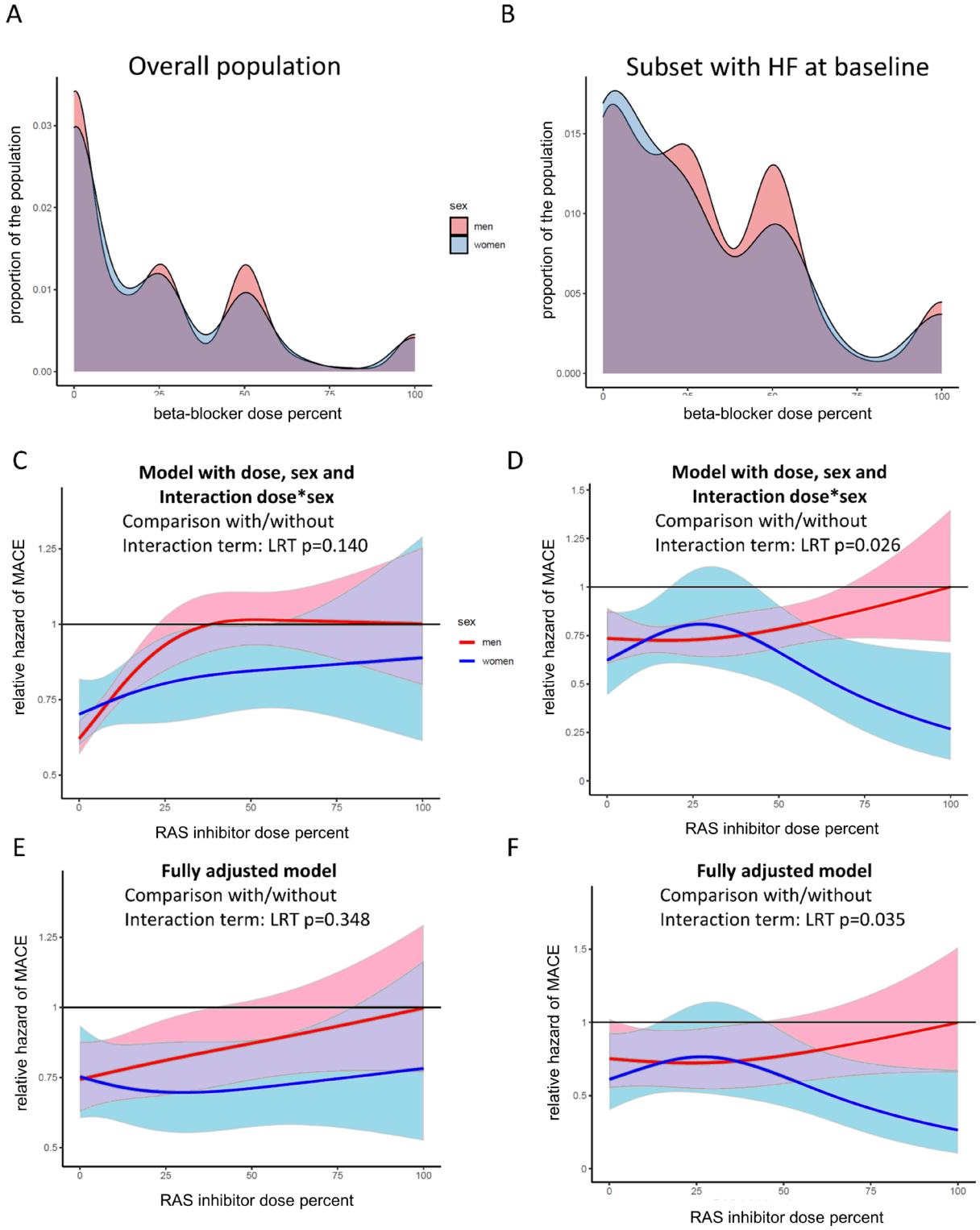

Figure 2 Distribution of renin–angiotensin system (RAS) inhibitor dose in relation to recommended daily maximum dose according to sex in the overall population of patients with atrial fibrillation (A) and in the subset with a history of heart failure (HF) (B). Models in C–F show the hazard for major adverse cardiovascular event (MACE) in the overall population (C, E) or the subset with a history of HF (D, F). Models in C and D included sex, RAS inhibitor dose and the interaction between sex and RAS inhibitor dose for the overall population (C) or the subset with a history of HF (D). Models in E and F were additionally adjusted for age, body surface area, current smoking status, regular physical activity, history of diabetes, chronic kidney disease, history of coronary artery disease, heart rate, history of hypertension, history of stroke and/or transient ischaemic attack, oral anticoagulation, antiplatelet therapy, antiarrhythmics, chronic obstructive pulmonary disease (COPD) or asthma, the dose percentage of beta-blockers and a history of HF (E only). P values of likelihood ratio tests (LRT) are shown to compare with models without the interaction term. Shaded areas indicate 95% CIs for women (blue), men (red) or overlapping intervals (purple).

a threefold decline of relative hazard when approaching 100% RAS inhibitor dose. For this model, the likelihood ratio test showed a p of 0.03 when compared with a model not containing the interaction term of dose with sex, indicating that a relevant interaction was present. Fully adjusted models showed a similar pattern as above: The overall population showed a tendency towards a lower hazard of MACE at lower doses of RAS inhibitors (figure 2E) without a significant interaction between dose and sex. Again, in the subgroup with a history of HF at baseline (figure 2F), an inverted u-shaped curve was present for the hazard of MACE in women according to RAS inhibitor dose, and inclusion of the interaction term significantly affected the model (likelihood ratio test, p=0.04).

Secondary sex-specific analysis strategy of beta-blocker and RAS inhibitor dose in association with MACE

In the prespecified secondary approach, we analysed drug doses of beta-blockers and RAS inhibitors as groups in quartiles together with a fifth category of those not prescribed a drug (online supplemental figure 1). In the multivariable Cox models for the overall population and for the subgroup with a history of HF, all lower beta-blocker dose quartiles and the group prescribed no beta-blockers showed a comparable hazard of MACE in comparison to the top dose quartile, without significant interaction between beta-blocker dose group and sex (table 2). Similar findings were made for the analyses of RAS inhibitor doses in quartiles (table 3).

Secondary outcomes

We analysed all individual components of MACE except systemic embolism as secondary outcomes using categorised beta-blocker doses (online supplemental tables 3–6) or RAS inhibitor doses (online supplemental tables 7–10) and their interaction with sex, respectively. The low number of events precluded an isolated assessment of systemic embolism or an assessment of stroke in association with RAS inhibitor dose in the subgroup with a history of HF. Overall, the secondary analyses resembled those of the composite primary outcome, except for the following: The overall hazard of all-cause mortality was 0.56 (95% CI 0.35 to 0.89, p=0.01) in women compared with men (online supplemental table 3). The third quartile of beta-blocker doses was associated with a higher hazard of stroke compared with the top quartile, with HR 1.89 (95% CI 1.08 to 3.30; p=0.03) (online supplemental table 4). Patients not treated with RAS inhibitors had a lower hazard of myocardial infarction compared with the top dose quartile, with HR 0.50 (95% CI 0.27 to 0.92; p=0.03) (online supplemental table 9). For these analyses, the interaction terms between drug dose and sex yielded no significantly different models.

Sensitivity analyses

We performed several prespecified and post hoc sensitivity analyses as a robustness check of the analysis strategy. All these procedures did not cause substantial changes in the results (data are not shown). The inclusion of LVEF as a variable in Cox models in the subgroup of 1288 patients with available echocardiography did not modify the results. Overall, the reported findings remained robust in sensitivity analyses.

DISCUSSION

In this study, we assessed the associations between beta-blockers or RAS inhibitors and MACE with a focus on the interaction between sex and drug dose. We found no associations between drug dose and MACE in patients with AF, but in patients with pre-existing HF, women treated with RAS inhibitors at submaximal dose showed a higher hazard of MACE compared with those treated with maximal dose.

Our data showing no overall association between beta-blockers and MACE in patients with AF are consistent with the findings of a meta-analysis by Rienstra *et al* reporting that beta-blockers have no effect on mortality or hospitalisations in patients with AF, in contrast to patients with sinus rhythm.[27] Prior work has, however, rarely provided sex-disaggregated data: The landmark study by van Gelder *et al* who reported comparable survival between strict or lenient ventricular rate control in AF included 66% of men but reported no sex-disaggregated outcomes.[28] The meta-analysis on beta-blocker efficacy in patients with AF by Rienstra *et al* reported a meta-regression according to the male:female sex ratio among patients of included studies but found no association between sex ratio and reported beta-blocker efficacy in studies on AF.[27] Next, nearly all dose-specific analyses of beta-blocker doses in association with cardiovascular outcomes were performed among patients with HFrEF: Campodonico *et al* reported that in patients with HFrEF and AF, increasing doses of beta-blockers were associated with improved patient survival.[29] However, the study of Campodonico *et al* included only 16% of women and reported no sex-disaggregated data.[29] The present findings of the Swiss-AF and BEAT-AF population containing both HFrEF and HFpEF are in contrast to some analyses restricted to patients with HFrEF in which women showed fewer deaths or HF-related hospitalisations when prescribed submaximal doses of beta-blockers.[14 15] Nevertheless, the Swiss-AF and BEAT-AF cohorts differ from these populations that had a low prevalence of AF in only 35% of women and 44% of men reported by Santema *et al*,[14] or of any arrhythmia in 21% of women and 25% of men reported by Bots *et al*.[15] Of note, the meta-analysis by Kotecha *et al* showed no evidence for sex as an effect modifier of beta-blocker efficacy in patients HFrEF for several cardiovascular outcomes.[30] Kotecha *et al* further observed no association between sex and beta-blocker discontinuation rates, which speak rather against women with HFrEF being relatively overdosed at standard beta-blocker doses.[30]

Table 2 Composite primary outcome according to beta-blocker dose

Characteristic	N	Event, N	HR	95% CI	P value
Overall population					
BB dose group	3889	1123			
4 (highest)			Reference		
3			1.16	0.92 to 1.46	0.20
2			1.11	0.88 to 1.40	0.36
1 (lowest)			1.18	0.94 to 1.49	0.15
0 (no BB)			1.18	0.95 to 1.48	0.14
Sex	3889	1123			
Men			Reference		
Women			0.83	0.60 to 1.15	0.26
BB dose group×sex	3889	1123			
3×women			1.1	0.72 to 1.67	0.67
2×women			1.15	0.74 to 1.77	0.53
1×women			1.03	0.67 to 1.59	0.89
0×women			1.23	0.81 to 1.86	0.34
Population with a history of heart failure at baseline					
BB dose group	927	376			
4 (highest)			Reference		
3			0.94	0.65 to 1.37	0.74
2			1.18	0.82 to 1.70	0.37
1 (lowest)			1.02	0.70 to 1.49	0.93
0 (no BB)			1.07	0.71 to 1.62	0.75
Sex	927	376			
Men			Reference		
Women			1.1	0.67 to 1.81	0.69
BB dose group×sex	927	376			
3×women			0.63	0.30 to 1.31	0.22
2×women			0.75	0.37 to 1.52	0.43
1×women			0.63	0.31 to 1.30	0.21
0×women			0.64	0.27 to 1.52	0.31

Comparison with a model not containing the interaction term of dose group×sex: Likelihood ratio test p=0.874 (upper panel), p=0.680 (lower panel).
Among all patients, BB dose was 0% in BB dose group 0, in the range of 0.6%–12.5% (minimum–maximum) in BB dose group 1, 12.5%–25% in BB dose group 2, all 25% in BB dose group 03 and 25%–100% in BB dose group 4. Among patients with a history of heart failure at baseline, BB dose was 0% in BB dose group 0, in the range of 1.25%–12.5% in BB dose group 1, 12.5%–25% in BB dose group 2, 25%–50% in BB dose group 03 and 50%–100% in BB dose group 4.
Models were adjusted for age, body surface area, current smoking status, regular physical activity, history of diabetes, chronic kidney disease, history of coronary artery disease, heart rate, history of hypertension, history of stroke and/or transient ischaemic attack, oral anticoagulation, antiplatelet therapy, antiarrhythmics, chronic obstructive pulmonary disease (COPD) or asthma, the dose percentage of renin–angiotensin system inhibitors and a history of heart failure at baseline (upper panel only).
BB, beta-blocker.

Regarding RAS inhibitors, the clinical guidelines by the ESC recommend an uptitration in patients with HFrEF until the maximum tolerated dose is reached, but they make no specific recommendation in patients with HF with preserved LVEF (HFpEF) or AF without HF. In case a causal effect is assumed between the higher dose of RAS inhibitors and a lower hazard of MACE in the primary analysis, the present data would support the use of RAS inhibitors in women with AF and HF. This finding could, however, be due to chance because of the small number of women with 100% dose of RAS inhibitors, especially as the secondary analysis strategy of dose quartiles yielded negative results. The finding could alternatively result from bias from unmeasured confounders such as emotional stress[31] that predisposes women to adverse cardiovascular events.[32–34] In addition, women could have been inadequately underdosed by treating physicians, for example, to prevent side effects. This could for instance lead to undertreated arterial hypertension in women who have arterial hypertension as comorbidity, which is associated with a higher cardiovascular risk.[35] The distribution of doses was, however, similar between the two sexes.

Table 3 Composite primary outcome according to RAS inhibitor dose

Characteristic	N	Event, N	HR	95% CI	P value
Overall population					
RAS inhibitor dose group	3873	1113			
4 (highest)			Reference		
3			0.98	0.78 to 1.23	0.85
2			0.83	0.65 to 1.06	0.13
1 (lowest)			0.91	0.72 to 1.15	0.43
0 (no RAS inhibitor)			0.82	0.66 to 1.01	0.065
Sex	3873	1113			
Men			Reference		
Women			0.87	0.62 to 1.23	0.44
RAS inhibitor dose group×sex	3873	1113			
3×women			0.85	0.52 to 1.38	0.50
2×women			1.08	0.67 to 1.72	0.76
1×women			1.03	0.65 to 1.63	0.89
0×women			1.14	0.77 to 1.68	0.52
Population with a history of heart failure at baseline					
RAS inhibitor dose group	921	371			
4 (highest)			Reference		
3			0.94	0.65 to 1.34	0.72
2			0.92	0.63 to 1.34	0.66
1 (lowest)			0.82	0.56 to 1.20	0.30
0 (no RAS inhibitor)			0.96	0.67 to 1.38	0.83
Sex	921	371			
Men			Reference		
Women			0.69	0.38 to 1.26	0.23
RAS inhibitor dose group×sex	921	371			
3×women			0.9	0.38 to 2.16	0.82
2×women			1.16	0.51 to 2.66	0.72
1×women			1.57	0.71 to 3.46	0.26
0×women			1.12	0.53 to 2.37	0.77

Comparison with a model not containing the interaction term of dose group×sex: Likelihood ratio test p=0.729 (upper panel), p=0.725 (lower panel).
Among all patients, RAS inhibitor dose was 0% in RAS inhibitor dose group 0, in the range of 0.7%–25% (minimum–maximum) in RAS inhibitor dose group 1, 25%–28.6% in RAS inhibitor dose group 2, 28.6%–50% in RAS inhibitor dose group 3 and 50%–100% in RAS inhibitor dose group 4.
Among patients with a history of heart failure at baseline, RAS inhibitor dose was 0% in RAS inhibitor group 0, in the range of 0.7%–17.9% in RAS inhibitor group 1, 18.8%–32.1% in RAS inhibitor group 2, 32.1%–50% in RAS inhibitor group 3 and 50%–100% in RAS inhibitor group 4.
Models were adjusted for age, body surface area, current smoking status, regular physical activity, history of diabetes, chronic kidney disease, history of coronary artery disease, heart rate, history of hypertension, history of stroke and/or transient ischaemic attack, oral anticoagulation, antiplatelet therapy, antiarrhythmics, chronic obstructive pulmonary disease (COPD) or asthma, the dose percentage of beta-blockers and a history of heart failure at baseline (upper panel only).
RAS, renin–angiotensin system.

Strengths of this study include the large and well-characterised cohorts analysed, the long follow-up duration and detailed medical data available, and the pressing nature of the topic that we addressed. This study also has some limitations. First, the observational design did not allow assessing causality. Thus, despite the attempts to balance the population by multivariable adjustments and inverse probability weighting, additional unmeasured confounding may remain such as frailty, intolerance of higher dosing or change of treatment over time for example, because of low blood pressure. Second, few patients with available echocardiography data were included, precluding the adjustment for LVEF in primary models. However, when the subset of patients with available LVEF data was analysed in a sensitivity analysis, no major changes were noted. Next, the clinical decisions in beta-blocker dosing may be influenced by previous device implantation such as pacemakers. Finally, we focused on beta-blockers and RAS inhibitors but did not assess the sex-specific doses of other drug classes that may have influenced the findings. Future studies may take additional drug classes into consideration.

Implications of the present work include that patients with AF of both sexes appeared to show dose-independent cardiovascular outcomes when treatments with beta-blockers or RAS inhibitors were prescribed. Thus, no sex-specific beta-blocker RAS inhibitor dose reconsiderations appear beneficial in patients with AF according to the present data, in contrast to what has been shown for patients with HFrEF.[14] As a research implication, it is important to consider potential differences between different and overlapping populations, such as patients with AF or HF.

CONCLUSION

In conclusion, the present study reveals no overall sex differences in beta-blocker or RAS inhibitor doses nor associations between beta-blocker or RAS inhibitor doses and MACE in two cohorts of patients with AF. This study adds to the emerging knowledge of sex differences in cardiovascular pharmacotherapy and could guide clinical practice.

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