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Impact of gender on event rates at 1 year in patients with newly diagnosed non-valvular atrial fibrillation: contemporary perspective from the GARFIELD-AF registry

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ABSTRACT

Objectives: Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) explored the impact of gender, risk factors and anticoagulant (AC) treatment on 1-year outcomes in patients with non-valvular atrial fibrillation (NVAF).

Design: GARFIELD-AF is a prospective non-interventional registry.

Setting: Investigator sites (n=1048) are representative of the care settings/locations in each of the 35 countries.

Participants: Patients ≥18yrs with newly diagnosed (≤6 weeks' duration) NVAF and ≥1 investigator-determined stroke risk factors.

Main outcome measures: Event rates per 100 person-years were estimated from the Poisson model and HRs and 95% CIs calculated.

Results: Of 28 624 patients (women 44.4%; men 55.6%) enrolled, there were more elderly (≥75 years) women (46.9%) than men (30.4%). All-cause mortality rates per 100 person-years (95% CI) for women and men were 4.48 (4.12 to 4.87) and 4.04 (3.74 to 4.38), respectively, stroke/systemic embolism (SE) (1.62 (1.41 to 1.87) and 1.17 (1.01 to 1.36)) and major bleeding (0.93 (0.78 to 1.13) and 0.79 (0.66 to 0.95)). After adjustment for baseline risk factors in treated and untreated patients, HRs (95% CI) for women (relative to men) for stroke/SE rates were 1.3-fold higher in women (HR 1.30 (1.04 to 1.63)), and similar for major bleeding (1.13 (0.85 to 1.50)) and all-cause mortality (1.05 (0.92 to 1.19)). Antithrombotic treatment patterns in men and women were almost identical. 63.8% women and 62.9% men received AC± antiplatelets. Relative to no AC treatment, the reduction in stroke/SE rates with AC treatment was greater (p=0.01) in men (HR 0.45 (0.33 to 0.61)) than women 0.77 (0.57 to 1.03). All-cause mortality reduction with AC treatment was similar (women: 0.65 (0.54 to 0.77); men: 0.57 (0.48 to 0.68)). The risk of major bleeding when treated with AC versus no AC was 2.33 (1.41 to 3.84) in men and 1.86 (1.16 to 2.99) in women (p value=0.53).

Conclusions: Women have a higher risk of stroke/SE and the reduction in stroke/SE events rates with AC treatment is less in women than in men.

Trial registration number: NCT01090362.

Strengths and limitations of this study

- Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) is the largest prospective, ongoing, observational, multicentre, prospective study of patients aged ≥18 years with newly diagnosed NVAF and ≥1 investigator-determined stroke risk factor(s).
- The GARFIELD-AF registry reflects 'real-world' care settings for unselected patients with non-valvular AF globally.
- The interpretation of the differences in stroke/systemic embolism events between men and women is hampered by the lack of data on dosing and persistence with AC treatment.

INTRODUCTION

Every year, ~15 million people around the world experience a stroke, and 5 million die from their disease.[1] Ischaemic stroke accounts for the majority of these events,[2] and patients with atrial fibrillation (AF) are up to five times more likely to experience a stroke than patients without AF.[3 4]

Gender differences in the prevalence and prognosis of patients with AF are widely reported (mainly based on epidemiological studies from Europe and North America).[5–7]

These studies show that the age-adjusted prevalence of AF is higher in men than women (596 per 100 000 in men and 373 per 100 000 in women),[5] but with greater longevity, women make up the greater proportion (60%) of those with AF who are over the age of 75 years.[5 8 9] The prognosis for women with AF markedly differs from men.[10] Female gender independently increases the risk of stroke,[11–16] and women with AF have a higher mortality rate, even after adjustment for baseline comorbid conditions and treatment with anticoagulants (ACs).[17 18] For this reason, female gender is a recognised risk factor for stroke in the CHA$_2$DS$_2$-VASc stroke risk stratification scheme[19] as used in international guidelines for stroke prevention in AF.[20–23] The reason for these disparities in prognosis between men and women are not fully understood.

In this paper, we analysed the impact of gender and gender-associated differences in risk factors and AC treatment on 1-year outcomes in patients with newly diagnosed non-valvular atrial fibrillation (NVAF) based on data from the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF).[24]

Previously, we have shown that the use of AC in NVAF does not differ between men and women enrolled in GARFIELD-AF, although many patients received suboptimal thromboprophylaxis, with underuse in moderate-to-high risk patients and overuse in low-risk patients.[25]

MATERIALS AND METHODS
Study design and patients
GARFIELD-AF is an ongoing observational, multicentre, prospective study[24] of patients aged ≥18 years with newly diagnosed (≤6 weeks' duration) NVAF and ≥1 investigator-determined stroke risk factor(s). Risk factors are determined by the investigators (a complete list of investigators is given in the online supplementary appendix) and are not prespecified in the protocol, nor are they limited to the components of existing risk stratification schemes. Patients with a transient reversible cause of AF and those for whom follow-up to 2 years is not envisaged or not possible are excluded from the study. Sites were identified globally and on a national level from hospital, community and anticoagulation clinic settings to ensure proportional representation of AF treating care settings in all countries (as previously described[24]).

Study ethics
The central ethics committees and regulatory authorities that provided approval are listed in the online supplementary appendix. The registry is being conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements and the International Conference on Harmonisation–Good Pharmacoepidemiological and Clinical Practice guidelines. All patients provided written informed consent.

Data collection
Data collected at enrolment included patient and clinical characteristics, medical history, care setting at diagnosis, type of AF, symptoms and antithrombotic treatment (vitamin K antagonists (VKAs), factor Xa inhibitors and direct thrombin inhibitors). These data were used to calculate the CHA$_2$DS$_2$-VASc score (Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled)-Vascular disease, Age 65–74 and Sex category (Female)), CHADS$_2$ and HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Elderly (>65 years), Drugs/alcohol concomitantly); data on labile International Normalized Ratio (INR) was not collected and so was not included in the HAS-BLED. Major bleeding was defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria.

The electronic case report form (eCRF) was designed by Dendrite Clinical Systems (Henley-on-Thames, UK). Oversight of operations and data management are being managed by the sponsor and coordinating centre (Thrombosis Research Institute, London,[7] UK), with support from Quintiles (Durham, NC, USA), The University of Birmingham Department of Primary Care Clinical Sciences (Birmingham, UK), Thrombosis Research Group—Brigham and Women's Hospital (Boston, MA, USA) and AIXIAL (Paris, France). Submitted data are examined for completeness and accuracy by the coordinating centre (Thrombosis Research Institute, London, UK). All quality control measures are undertaken under the guidance of an independent audit committee. Key protocol-driven elements of the audit include: frequent electronic data monitoring; remote site monitoring by clinical research associates including source document verification of 20% of all cases as per the Monitoring Plan. Outcome events were reported by investigators, after review of patient notes and clinical records, and audited using a combination of remote electronic monitoring and more conventional onsite monitoring. Stroke/ systemic embolism (SE), major bleeding and all-cause mortality rates (per 100 persons-years) occurring during the first year of follow-up are calculated using the number of events and the population at risk at the beginning of the follow-up period. Only the first occurrence of each event was taken into account.

Statistical analysis
Continuous variables are presented as mean ±SD, and categorical variables are presented as frequency and percentage. Patients with missing values were not removed from the study (available case analysis). Occurrences of major clinical outcomes are described using the person-time event rate (per 100 person-years) and 95% CI. We estimated person-year rates using a Poisson model, with

the number of events as the dependent variable and the log of time as an offset, that is, a covariate with a known coefficient of 1.

HRs and 95% CIs were calculated using a proportional hazards Cox regression model after multiple imputations by the Multiple Imputation by Chained Equations (MICE) algorithm assuming that data are missing at random. HRs were adjusted for: age group, race, smoking, diabetes mellitus, hypertension, previous stroke/systemic embolism, history of bleeding, cardiac failure, vascular disease, moderate-to-severe renal disease, AC treatment and type of AF. The proportional hazards assumption was assessed visually using a plot of the survivor function over time by gender. As the model used to estimate the HRs includes interaction between gender and risk factors, we carried out multiple imputations separately for men and women to allow the associations between risk factors and the clinical outcomes to differ according to gender. The model for multiple imputation included baseline characteristics (age, race, type of AF, history of bleeding, diabetes, hypertension, previous stroke, congestive heart failure, vascular disease, AC treatment and hypercholesterolaemia) and clinical endpoints (indicators of death, stroke/SE, major bleeding). We imputed five complete data sets and compared the distribution of the completed and observed data for baseline characteristics to check for any anomalies. Three models were fitted for each clinical outcome: (1) a model estimating the main effect of gender and risk factors. This model does not include interactions between gender and risk factors. The effect of risk factors on clinical outcome is assumed to be the same for men and women; (2) a model with interactions between gender and each risk factor. Using this model, the effect of each risk factor on clinical outcomes separately for men and women were estimated and (3) a model with significant interactions between gender and risk factors. This model includes only significant interactions tested in model 2. Model 1 is presented in online supplementary figure S1 and as online supplementary data, model 2 is presented in main text of the manuscript, whereas model 3 is presented as online supplementary data. All data analyses were performed at the Thrombosis Research Institute using SAS V.9.4 (SAS Institute, Cary, NC, USA) and Stata Statistical Software: Release 14 (StataCorp, College Station, TX, USA).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advice on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community. However, we are now including the Anti-Clot Treatment Scale (ACT) as part of the patient assessment in cohort 5 in order to provide a measure of patient-reported outcomes.

RESULTS
Baseline characteristics

A total of 28 624 patients (women 12 709 (44.4%) and men 15 915 (55.6%)) with newly diagnosed NVAF were enrolled into the GARFIELD-AF registry at 1048 sites in 35 countries between March, 2010 and October, 2014. The data were extracted from the study database on 3rd August, 2015. Baseline characteristics are presented by gender in table 1. The mean (SD) age of women and men were 72.4±10.4 years and 67.6±11.7 years, respectively; a greater proportion of women than men (46.9% vs 30.4%) were 75 years or older.

Lifestyle risk factors measured at baseline showed that more men than women were current or ex-smokers (women 15.9%; men 50.1%) or heavy drinkers (women 0.4%; men 4.2%), with a greater proportion of women being abstinent (men 39.2%; women 73.0%).

A slightly higher proportion of women compared with men were diagnosed with paroxysmal AF (women 29.1%; men 25.1%). Women were slightly more likely to have a history of hypertension or raised blood pressure $\geq 140/90$ mm Hg (women 84.8%; men 79.5%) (table 1). Vascular disease and history of prior coronary artery bypass graft and heart failure (left ventricular ejection fraction <40%) at the time of diagnosis of NVAF were more common in men.

At baseline, mean HAS-BLED scores were 1.5±0.9 and 1.4±0.9, mean (±SD) $CHADS_2$ scores were 2.0±1.1 and 1.8 ±1.1 and mean CHA_2DS_2-VASc scores were 4.0±1.4 and 2.6 ±1.5 for women and men, respectively. Overall, 97.0% of women and 76.5% of men had a CHA_2DS_2-VASc score ≥ 2.

Treatment patterns

The pattern of antithrombotic treatment in men and women was almost identical (figure 1). At the time of diagnosis, 63.8% women and 62.9% men received AC with or without antiplatelet (AP) therapy; most patients (women 46.8%; men 46.0%) were prescribed VKAs— with or without AP treatment, and the remainder (women 17.1%; men 16.9%) received non-VKA oral AC (NOACs). Approximately one-quarter of patients (women 23.9%; men 24.9%) received AP treatment only. The proportion of women and men who received neither AC treatment nor AP treatment was 12.3% and 12.2%, respectively. Of patients with a low risk of stroke, 39.7% of women (CHA_2DS_2-VASc score=1) and 43.3% of men (CHA_2DS_2-VASc score=0) received AC treatment. Of patients with a high risk of stroke (CHA_2DS_2-VASc score ≥ 2), 35.2% of women and 33.3% of men did not receive AC treatment. A minority of women (n=16) used hormone replacement therapy (HRT) (at least two prescriptions at any point prior to a diagnosis of AF) and were similarly distributed in the group of anticoagulated (n=7) and non-anticoagulated patients (n=9).

Clinical outcomes over 1 year

Figure 2 displays unadjusted event rates per 100 person-years and the adjusted HRs for women (with reference

Table 1 Baseline characteristics of women and men with newly diagnosed atrial fibrillation: the GARFIELD-AF registry

Variable*	Men (n=15 915)	Women (n=12 709)
Age, mean (SD), years	67.6±11.7	72.4±10.4
Age group (years), n (%)		
<65 years	5847 (36.7)	2670 (21.0)
65–74 years	5235 (32.9)	4082 (32.1)
≥75 years	4832 (30.4)	5957 (46.9)
Race, n %†		
Caucasian/Hispanic/Latino	10 994 (69.1)	9240 (72.7)
Asian	4228 (26.6)	2928 (23.0)
Body mass index, mean (SD), kg/m^2	27.7±5.1	27.9±6.2
LVEF category, n (%)		
<40%	1226 (13.1)	4378 (6.2)
≥40%	8098 (86.9)	6609 (93.8)
Type of AF diagnosed, n (%)		
Permanent	2052 (12.9)	15 834 (12.5)
Persistent	2585 (16.2)	1782 (14.0)
Paroxysmal	3988 (25.1)	3692 (29.1)
New (unclassified)	7289 (45.8)	5651 (44.5)
Medical history, n (%)		
Congestive heart failure, NYHA Class, n (%)		
I	632 (21.2)	416 (17.0)
II	1408 (47.3)	1241 (50.7)
III	792 (26.6)	682 (27.8)
IV	146 (4.9)	111 (4.5)
Carotid occlusive disease, n (%)	505 (3.2)	361 (2.9)
PE or DVT, n (%)	362 (2.3)	403 (3.2)
Systemic embolism	100 (0.6)	94 (0.7)
Coronary artery bypass graft, n (%)	689 (4.4)	164 (1.3)
Moderate to severe CKD, n (%)	1458 (9.2)	1511 (11.9)
Stroke/TIA, n (%)	1839 (11.6)	1583 (12.5)
Stroke, n (%)	1243 (7.8)	1013 (8.0)
History of bleeding, n (%)	469 (3.0)	311 (2.5)
Blood pressure, mm Hg		
Systolic blood pressure, mm Hg, mean (SD)	132.8 (±19.3)	135.0 (±20.7)
Diastolic blood pressure, mm Hg, mean (SD)	80.1 (±12.8)	79.8 (±13.0)
Blood pressure ≥140/90 mm Hg, n (%)	4037 (27.2)	3741 (31.5)
History of hypertension, n (%)	11 945 (75.2)	10 212 (80.5)
History of hypertension or raised blood pressure ≥140/90 mm Hg, n (%)	12 634 (79.5)	10 773 (84.8)
Hypercholesterolaemia, n (%)	6232 (39.9)	5276 (42.3)
Diabetes mellitus, n (%)	3479 (21.9)	2728 (21.5)
Vascular disease‡, n (%)	2820 (17.7)	1508 (11.9)
CHA2DS2-VASc score		
Mean (SD)	2.6 (1.5)	4.0 (1.4)
0, n (%)	676 (4.4)	_
1, n (%)	2966 (19.1)	370 (3.0)
≥2, n (%)	11 857 (76.5)	12 082 (97.0)
Mean HAS-BLED score (SD)	1.4 (0.9)	1.5 (0.9)
Heavy alcohol consumption, n (%)	565 (4.2)	40 (0.4)
Current/previous smoker, n (%)	7210 (50.1%)	1850 (15.9%)

*Missing patients from analyses: Number of patients (men, women) with missing values: age (0,0), race (429 346), body mass index (3231, 2858), blood pressure (1051, 830), LVEF (6591, women), type of AF diagnosed (1, 1), congestive heart failure, NYHA class (228, 189), carotid occlusive disease (117, 87), PE or DVT (46, 47), systemic embolism (48, 43), coronary artery bypass graft (350, 208), moderate to severe CKD (2, 1), stroke (33, 30), history of bleeding (37, 38), hypertension (22, 23), hypercholesterolaemia (300, 248), diabetes mellitus (1, 1) vascular disease (1, 1), CHA2DS2-VASc score (416, 257), HAS-BLED score (5230, 3947), alcohol consumption (2516, 1893) smoking habits (1529, 1052).
†346 women and 427 men were unwilling to declare their race or their race was not recorded.
‡Peripheral artery disease or coronary artery disease with a history of acute coronary syndromes.
AF, atrial fibrillation; CKD, chronic kidney disease; CHA$_2$DS$_2$-VASc score, Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled)-Vascular disease, Age 65–74 and Gender category (Female); DVT, deep venous thrombosis; HAS-BLED, Hypertension (uncontrolled, >160 mm Hg systolic), Abnormal renal/liver function, Stroke, Bleeding history or predisposition (anaemia), Elderly (>65) and Drugs/alcohol concomitantly (antiplatelet agents, non-steroidal anti-inflammatory drug); LVEF, left ventricular erection fraction; NYHA, New York Heart Association; PE, Pulmonary embolism; TIA, Transient ischaemic attack.
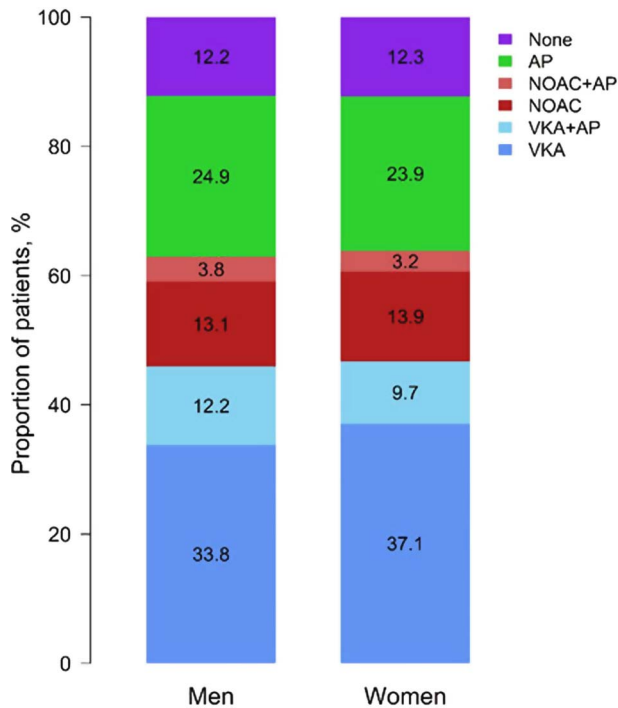
Figure 1 Antithrombotic treatment at diagnosis. AP, antiplatelet; NOAC, non-vitamin K antagonist oral anticoagulants; VKA, vitamin K antagonists.

to men). Unadjusted event rates per 100 person-years (95% CI) in women and men, respectively, were: stroke/SE (1.62 (1.41 to 1.87) and 1.17 (1.01 to 1.36)), major bleeding (0.93 (0.78 to 1.13) and 0.79 (0.66 to 0.95)) and all-cause mortality (4.48 (4.12 to 4.87) and 4.04 (3.74 to 4.38)). When HRs (95% CI) were adjusted for baseline risk factors (as defined in figure 2), stroke/SE were 1.3-fold higher for women compared with men (HR 1.30 (1.04 to 1.63)), whereas the HR for major bleeding was 1.13 (0.85 to 1.50) and for all-cause mortality, the HR was 1.05 (0.92 to 1.19).

Multivariate Cox regression analysis of HRs adjusted for risk factors by gender

Adjusted HRs estimated using model 1 describe the effect of gender on clinical outcomes (figure 2 and online supplementary tables S1–S3). Model 2 with HRs adjusted for risk factors by gender for all clinical outcomes is presented in figure 3 and in table 2. Additional information from the statistical models 1 and 3 and missing values are presented in the appendix (see online supplementary tables S1–S4, respectively). Our results are robust when removing non-significant interactions (model 3), but for descriptive purposes, we present the results from model 2, which includes 24 852
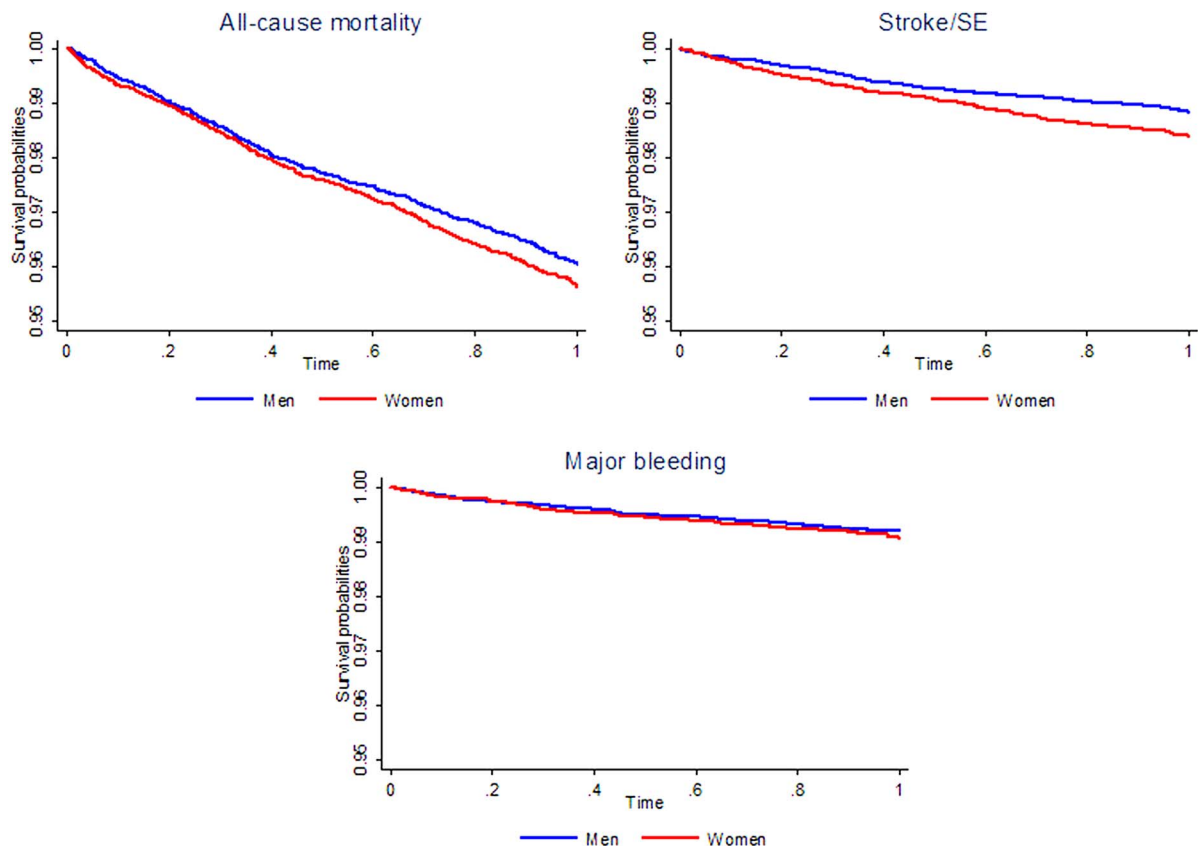
Figure 2 Kaplan-Meir curves for men and women for all-cause mortality, stroke/SE and major bleeding during the first year of follow-up. SE, systemic embolism.

Figure 3 Forest plot of HRs for 1-year clinical outcomes according to risk factors in men and women (Square to men and Circle to women). AC, anticoagulation; AF, atrial fibrillation; SE, systemic embolism; TIA, transient ischaemic attack. Adjustment factors for HRs: age group, race, smoking, diabetes mellitus, hypertension, previous stroke/TIA/systemic embolism, history of bleeding, congestive heart failure (CHF), vascular disease, moderate-to-severe renal disease, anticoagulant treatment and type of atrial fibrillation. Hypertension was defined as a documented history of hypertension or blood pressure >140/90 mm Hg. Results of Model 2.
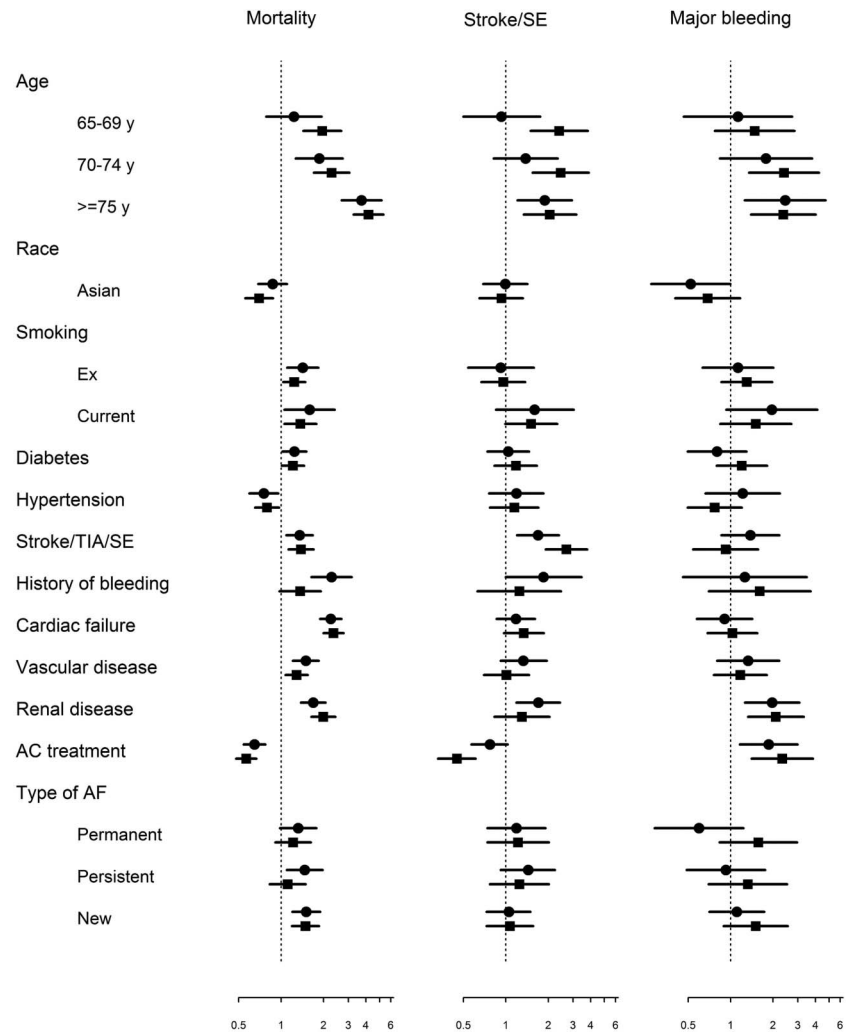
complete cases and 3772 patients with at least one imputed value (table 2).

The analyses show that the risk of all clinical endpoints increases with advancing age in men and women. Men from the age of 65 years have an elevated risk of all endpoints compared with younger men with AF (<65 years). In contrast, the stroke risk is elevated in women only from the age of 70 onwards compared with women with AF (<65 years).

Patients with NVAF from Asia have a lower risk of all-cause mortality and major bleeding (but not stroke) compared with patients of other ethnicities (Caucasian, Hispanic or Latino); the risk of events is similar across ethnicities of the same gender (figure 3 and table 2).

Current smoking is a risk factor for all events and cessation of smoking was associated with reduced risk of events (relative to current smokers) in both genders. Diabetes mellitus carried a similar risk for all-cause mortality in men and women with NVAF. Hypertension (predominantly characterised by a history of hypertension) was associated with a reduction in the risk of 1-year all-cause mortality in men and women and was an equally important risk factor for stroke in men and women. Hypertension was also associated with an increased risk

of major bleeding in women, but not men, but this gender difference was not statistically significant (women: HR 1.22 (95% CI 0.66 to 2.24); men: HR 0.77 (95% CI 0.50 to 1.20); p=0.23; table 2). An equally important risk factor for all-cause mortality in women and men with AF was congestive heart failure (HR >2). A history of bleeding was associated with a higher risk of all events, but with a significantly elevated risk of all-cause mortality in women compared with men (women: HR 2.28 (95% CI 1.64 to 3.17), men HR 1.37 (95% CI 0.98 to 1.91) p=0.03; table 2).

Severe renal disease was associated in an elevated risk of all events in both genders. The risk of stroke in patients with vascular disease appeared to be elevated in women but not men (women: HR 1.33 (0.92 to 1.95); men: HR 1.01 (0.70 to 1.46); although the difference was not statistically significant p=0.30) (figure 3 and table 2).

In women and men, prior stroke/transient ischaemic attack/SE was a risk factor for a subsequent stroke event and this risk was significantly lower in women than in men (women: 1.69 (1.20 to 2.38); men: 2.69 (1.92 to 3.77); p=0.06).

Compared with no AC treatment, AC treatment lowered the risk of stroke/SE to a greater extent in men

Table 2 Adjusted HRs (95% CIs) according to risk factors by gender and p values for the interaction between gender and risk factors

Risk factor	All-cause mortality		Stroke/SE		Major bleeding	
	Women	Men	Women	Men	Women	Men
Age	p=0.71		p=0.17		p=0.64	
65–69 years (ref: <65)	1.23 (0.78 to 2.67)	1.96 (1.44 to 2.67)	0.93 (0.50 to 1.75)	2.39 (1.50 to 3.81)	1.13 (0.47 to 2.73)	1.48 (0.77 to 2.84)
70–74 years (ref: <65)	1.86 (1.27 to 2.74)	2.28 (1.71 to 3.05)	1.38 (0.82 to 2.33)	2.45 (1.55 to 3.87)	1.78 (0.84 to 3.78)	2.39 (1.35 to 4.24)
≥75 years (ref: <65)	3.72 (2.69 to 5.15)	4.17 (3.27 to 5.32)	1.89 (1.21 to 2.94)	2.05 (1.34 to 3.16)	2.44 (1.26 to 4.72)	2.37 (1.40 to 4.01)
Race	p=0.33		p=0.89		p=0.51	
Asian (ref: Caucasian/Hispano/Latino)	0.87 (0.69 to 1.10)	0.70 (0.56 to 0.88)	0.99 (0.60 to 1.42)	0.93 (0.65 to 1.32)	0.52 (0.27 to 0.99)	0.69 (0.41 to 1.17)
Smoking	p=0.61		p=0.98		p=0.76	
Ex-smoker (ref: no)	1.42 (1.11 to 1.84)	1.24 (1.04 to 1.48)	0.92 (0.54 to 1.58)	0.96 (0.67 to 1.37)	1.13 (0.63 to 2.01)	1.30 (0.86 to 1.97)
Current smoker (ref: no)	1.59 (1.06 to 2.40)	1.37 (1.06 to 1.78)	1.60 (0.85 to 3.03)	1.51 (0.99 to 2.31)	1.96 (0.93 to 4.12)	1.55 (0.84 to 2.70)
Diabetes mellitus	p=0.86		p=0.63		p=0.21	
Yes (ref: no)	1.24 (1.02 to 1.51)	1.21 (1.01 to 1.46)	1.04 (0.74 to 1.46)	1.18 (0.83 to 1.66)	0.80 (0.50 to 1.30)	1.20 (0.80 to 1.81)
Hypertension	p=0.73		p=0.90		p=0.23	
Yes (ref: no)	0.75 (0.60 to 0.95)	0.79 (0.65 to 0.97)	1.19 (0.76 to 1.85)	1.15 (0.77 to 1.70)	1.22 (0.66 to 2.24)	0.77 (0.50 to 1.20)
Stroke/TIA/SE	p=0.88		p=0.06		p=0.27	
Yes (ref: no)	1.35 (1.09 to 1.68)	1.38 (1.13 to 1.70)	1.69 (1.20 to 2.38)	2.69 (1.92 to 3.77)	1.38 (0.86 to 2.22)	0.92 (0.54 to 1.57)
History of bleeding	p=0.03		p=0.40		p=0.72	
Yes (ref: no)	2.28 (1.64 to 3.17)	1.37 (0.98 to 1.91)	1.85 (1.00 to 3.44)	1.25 (0.63 to 2.46)	1.26 (0.46 to 3.47)	1.61 (0.70 to 3.69)
Congestive heart failure	p=0.72		p=0.57		p=0.68	
Yes (ref: no)	2.25 (1.89 to 2.68)	2.35 (2.00 to 2.77)	1.18 (0.86 to 1.61)	1.34 (0.97 to 1.86)	0.91 (0.58 to 1.42)	1.03 (0.69 to 1.55)
Vascular disease	p=0.29		p=0.30		p=0.70	
Yes (ref: no)	1.50 (1.21 to 1.85)	1.29 (1.08 to 1.55)	1.33 (0.92 to 1.95)	1.01 (0.70 to 1.46)	1.33 (0.80 to 2.21)	1.17 (0.76 to 1.80)
Severe renal disease	p=0.25		p=0.36		p=0.85	
grade III-IV-V (ref: I, II, no, unknown)	1.69 (1.38 to 2.07)	1.99 (1.64 to 2.42)	1.70 (1.19 to 2.42)	1.30 (0.83 to 2.04)	1.97 (1.27 to 3.07)	2.10 (1.33 to 3.30)
AC treatment	p=0.28		p=0.01		p=0.53	
Yes (ref: no)	0.65 (0.54 to 0.77)	0.57 (0.48 to 0.67)	0.77 (0.57 to 1.03)	0.45 (0.33 to 0.61)	1.86 (1.16 to 2.99)	2.33 (1.41 to 3.84)
Type of AF	p=0.49		p=0.96		p=0.27	
Permanent AF (ref: no)	1.32 (0.98 to 1.78)	1.22 (0.91 to 1.62)	1.19 (0.74 to 1.91)	1.22 (0.74 to 2.02)	0.60 (0.29 to 1.23)	1.57 (0.84 to 2.96)
Persistent AF (ref: no)	1.47 (1.10 to 1.97)	1.11 (0.83 to 1.49)	1.44 (0.92 to 2.23)	1.25 (0.77 to 2.02)	0.93 (0.49 to 1.76)	1.33 (0.70 to 2.51)
New AF (ref: no)	1.51 (1.20 to 1.89)	1.49 (1.20 to 1.86)	1.05 (0.73 to 1.49)	1.07 (0.73 to 1.56)	1.11 (0.71 to 1.73)	1.51 (0.89 to 2.54)

AC, anticoagulants; AF, atrial fibrillation; ref, reference; SE, systemic embolism; TIA, transient ischaemic disease. Results of Model 2.

than women (women: HR 0.77 (95% CI 0.57 to 1.03); men: HR 0.45 (95% CI 0.33 to 0.61)), and this interaction was significant (p=0.01). The reduction in all-cause mortality with AC treatment was similar in both genders (women: HR 0.65 (95% CI 0.54 to 0.77); men: HR 0.57 (95% CI 0.48 to 0.68)). Men, however, had a higher risk of major bleeding when treated with ACs (HR 2.33 (95% CI 1.41 to 3.84)) compared with women (HR 1.86 (95% CI 1.16 to 2.99)); although this interaction was not significant.

DISCUSSION

The GARFIELD-AF study found that women had a higher risk of stroke/SE than men even after adjustment of risk factors (congestive heart failure, age, hypertension, diabetes mellitus, prior stroke/SE, vascular disease and history of bleeding). The event rates from GARFIELD-AF correspond to the results from two recent meta-analyses of pooled data from the literature which determined that the unadjusted risk of stroke in women, relative to men, was 1.47 (95% CI 1.18 to 1.83)[26] and the adjusted risk was 1.31 (1.18 to 1.46).[27]

The impact of gender on all-cause mortality in patients with AF is inconsistently reported in the literature.[26] The results from the GARFIELD-AF study of >28 000 patients found that the unadjusted rate of all-cause mortality per 100 person-years was only slightly elevated in women (4.48) compared with men (4.04). After adjustment for baseline risk factors, all-cause mortality in women, relative to men, was similar.

Our analysis highlights differences in patient characteristics between men and women presenting with NVAF. One of the most notable differences is age. At the time of enrolment in the GARFIELD-AF registry, the mean age of patients with newly diagnosed NVAF was lower for men than women (68 vs 72 years). This result is comparable with age distribution between women and men which has been reported in other studies of patients with AF such as the Monitoring and Observing the Value of Exercise (MOVE) study (67 vs 71 years),[28] RAte Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) (67 vs 71 years)[29] and the Euro Heart Survey (ESC) (64 vs 70 years).[30]

Of note, there was a greater proportion of women than men who were 75 years or older at the time of diagnosis of NVAF which is in accordance with other studies.[8 31] There was also a trend toward a greater prevalence of comorbid vascular disease in men (than women) and comorbid hypertension in women. Otherwise, the prevalence of other risk factors for stroke (diabetes, prior stroke/SE) is similar in men and women. The Framingham study found that gender differences in blood pressure gradually narrow with age. Eventually, women develop higher blood pressure than men (beyond age 60 years) with the accelerated onset of arterial stiffening beyond menopause (especially in women with a history of hypertension).[32]

As reflected in the mean CHA$_2$DS$_2$-VASc scores (4.0±1.4 and 2.6±1.5 for women and men) beyond the impact of gender, there are only small differences in the risk factors for stroke in men and women with newly diagnosed NVAF. This difference can be explained by the greater age of female patients.[33] In GARFIELD-AF, we found that only prior stroke and AC treatment were significantly associated with gender-related differences in stroke event rates after adjustment for baseline risk factors.

It is recognised that the risk of thromboembolism increases with advancing age in patients above 65 years.[34] Similar to the Danish registry, which calculated stroke rates according to sex and age, we found that the risk of stroke tended to be elevated in women only from the age of 70 years and in men from 65 years onwards compared with patients of the same gender with AF (<65 years). However, the Loire Valley AF study reported that in relatively young patients with AF (<65 years), the risk of stroke/thromboembolism can be independently increased by the presence of heart failure, prior stroke or vascular disease.[31] In GARFIELD-AF, even though men were younger than women at the time of AF diagnosis (mean age for men: 67.6 years), they were more likely to present with vascular disease, be current/past smokers (and/or heavy drinkers) and as likely to have had a history of heart failure (New York Heart Association (NYHA) class III–IV) or prior stroke/transient ischaemic attack as older women. We found that there was an unexpectedly higher risk of recurrent stroke in men than in women in the year following the diagnosis of AF.

The effects of AC treatment on stroke prevention were significantly greater in men than in women but were also associated with greater risk of bleeding. We found that the pattern of AC treatment did not differ markedly in men and women or among the minority of women (n=19) who had received HRT. Nevertheless, subtle differences in prescribing patterns by gender are evident. For example, AC treatment in combination with AP therapy was more frequently prescribed for men than women, which may have contributed to the increased risk of bleeding with AC treatment in men. Other published studies have shown that gender and age also influence dose. For example, women require less warfarin to maintain a therapeutic INR than men at an equivalent age and dosing reduces proportionally with increasing age.[35] The greater risk of bleeding in men may be explained by more aggressive AC dosing in men (relative to women). Conversely, the lower impact of AC treatment on stroke rates in women may be due to poorer anticoagulation control as determined by Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM).[36] In this study, women were more likely to be outside the time in therapeutic range (TTR) and have subtherapeutic INRs. However, the GARFIELD-AF showed that the mean (SD) TTR is similar in men, 55.6 (27.1) and women, 55.2 (26.9).

An important consideration in women is the impact of age on prescribing practice and adherence to

medication, since a higher proportion of women than men were elderly (75 years or older). There is also evidence (from a recent meta-analysis of randomised controlled studies reporting annualised event rates) that women with AF have a significantly greater residual risk of stroke/SE (compared with men) when treated using warfarin. The AFFIRM study, for example, showed that women who had a comparably high TTR (>66%) still had significantly more ischaemic strokes.[36] However, this gender difference is not observed in randomised controlled trials (RCTs) with NOACs.[15] The same meta-analysis of RCTs also found that NOAC agents are associated with significantly more major bleeding in men than women. The reason for these gender differences in controlled clinical trials is not completely understood.[15]

CONCLUSIONS

Across the models, we found that only prior stroke and AC treatment were significantly associated with gender-related differences in stroke event rates after adjustment for baseline risk factors. The increased benefit of AC treatment on stroke prevention in men, relative to women, is not fully understood, but suggests that women may be less well anticoagulated.

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