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ORIGINAL ARTICLE
Atrial fibrillation

Differences in the risk of stroke, bleeding events, and mortality between female and male patients with atrial fibrillation during warfarin therapy

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Aims Females with atrial fibrillation (AF) have been suggested to carry a higher risk for thromboembolic events than males. We compared the residual risk of stroke, bleeding events, and cardiovascular and all-cause mortality among female and male AF patients taking warfarin.

Methods and results Data from several nationwide registries and laboratory databases were linked with the civil registration number of the patients. A total of 54 568 patients with data on the quality of warfarin treatment (time in therapeutic range) 60 days prior to the events were included (TTR60). Gender differences in the endpoints were reported for the whole population, pre-specified age groups, and different TTR60 groups. During the 3.2 ± 1.6 years follow-up, there were no differences in the adjusted risk of stroke [hazard ratio (HR) 0.97, 95% confidence interval (CI) 0.91–1.03, $P = 0.304$] between the genders. Cardiovascular mortality (HR 0.82, 95% CI 0.78–0.88, $P < 0.001$) and all-cause mortality (HR 0.79, 95% CI 0.75–0.83, $P < 0.001$) were lower in women when compared with men. There were no differences in the risk of stroke, cardiovascular mortality, and all-cause mortality between the genders in the TTR60 categories except for those with TTR60 <50%. Bleeding events were less frequent in females (HR 0.52, 95% CI 0.49–0.56, $P < 0.001$).

Conclusion There were no differences in the risk of stroke between female and male AF patients taking warfarin. Cardiovascular mortality, all-cause mortality, and risk of bleeding events were lower in females. Hence, female gender was not a risk marker for adverse outcomes in AF patients with proper warfarin therapy.

Keywords Atrial fibrillation • Sex difference • Anticoagulation therapy • Stroke • Bleeding • Mortality

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults.[1] It has been estimated that in 2030 there will be 14–17 million patients with AF in Europe.[2] Atrial fibrillation is a leading cause of stroke and peripheral embolism. However, the risk of stroke is not homogenous, and it varies according to the age of the patients and in the presence of other risk factors such as congestive heart failure, hypertension, diabetes, and vascular diseases.[3,4] In addition, female gender has been included as a risk factor in the CHA_2DS_2-VASc score which is recommended for stroke risk prediction in the European Society of Cardiology (ESC) guidelines for management of AF.[5]

The impact of female gender on the risk of stroke among patients with AF is controversial. In a recent meta-analysis, AF was associated with a stronger risk of stroke and death in women when compared with men.[6] The results of some studies indicate that women may carry an increased risk of stroke and peripheral embolism,[3,4,7–10]

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whereas others have found an association between the risk of stroke and the gender only in the age group of 75 years and above.[11,12] In contrast, a prospective Danish register study failed to show any increase in the risk of stroke in female AF patients without anticoagulation after adjustment for lifestyle, antithrombotic therapy, and relevant comorbidities.[13] According to Nielsen *et al.*,[14] female gender has altered impact on the outcome in AF patient with different CHA_2DS_2-VASc score, and hence gender may modify the risk of stroke.

It is well established that oral anticoagulation therapy (OAC) reduces the risk of stroke and mortality in patients with AF. In warfarin treated patients, the better the laboratory-assessed quality of warfarin therapy (time in therapeutic range, TTR), the better the outcome.[15] However, only limited data are available on the influence of the quality of warfarin therapy on the outcome in the two genders.[16–18] The FinWAF study was designed to evaluate the risks of stroke, bleeding events, cardiovascular, and all-cause mortality in relation to the quality of warfarin therapy. Here, we assessed if gender has any significant effect on the outcome of patients with AF using warfarin.

Methods

Study design and data sources

The aim of this pre-specified substudy of the FinWAF trial (EU PAS Register Number EUPAS4700) was to assess if the residual risk of clinical endpoints among anticoagulated AF patients was gender specific. Data from seven Finnish nationwide population registries and six laboratory databases were linked together by using the unique personal civil registration number.[15] The permits for data collection and linkage were received from the Social Insurance Institute, the National Institute for Health and Welfare, Population Register Centre, and Statistics Finland. International Statistical Classification of Diseases (10th revision, ICD-10) was used to code and classify the underlying diagnosis and causes of hospitalization and death.

The study was performed in accordance with Declaration of Helsinki and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance code of conduct. The ethical committee of the Hospital District of Helsinki and Uusimaa and the five university laboratories providing the INR data accepted the protocol.

Study population and follow-up

All patients included in the study fulfilled three criteria: (i) AF diagnosis (ICD-10 code I48) between 1 January 2005 and 31 December 2009, (ii) at least one warfarin purchase, and (iii) at least one INR measurement between 1 January 2007 and 31 December 2009. After implementing the inclusion and exclusion criteria (age under 18 years, permanent residence outside Finland during the follow-up period) 54 568 patients were eligible for the study.

The follow-up period began at the date of first warfarin purchase after 1 January 2007, and continued until the first outcome event or death occurred, or until the end of study period (31 December 2011).

Background variables

Information on age, gender, comorbidities, and medications were collected from the national registries. The stroke risk score was calculated for each patient without assigning a point for female gender as a CHA_2DS_2-VA score: congestive heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes mellitus (1 point), stroke or transient ischaemic attack (TIA) or systemic thromboembolism (2 points), vascular disease (1 point), and age 65–74 years (1 point).

INR measurements and time in therapeutic range

The results of the INR measurements were collected from the databases of six accredited regional central laboratories, which cover about two-thirds of the Finnish population. Time in therapeutic range was calculated and updated daily via linear interpolation using the Rosendaal method[19] as the percentage of days that the INR values were between 2.0 and 3.0 within the previous 60 days (TTR60). The method has been described in detail and validated previously.[15] In addition, a summary TTR capturing the entire follow-up period as a single TTR value (sTTR) was calculated for both genders to sum up the overall quality of warfarin therapy.

Endpoints

The endpoints of the study were: (i) any ischaemic stroke or TIA, (ii) bleeding event leading to hospitalization, (iii) death due to cardiovascular cause, and (iv) death due to any cause. Sex differences in these endpoints were investigated in the whole population, and according to the TTR60 levels of <40%, 40–50%, 50–60%, 60–70%, 70–80%, and >80%, and to the age groups of <65, 65–74, and ≥75 years.

Statistical analyses

Continuous variables are expressed as mean ± standard deviation and compared with independent variables *t*-test or Mann–Whitney *U*-test when appropriate. Categorical variables are expressed as numbers and percentages and compared by Fisher's exact test. All tests were two-sided, and a *P*-value of <0.05 was considered statistically significant.

Stratified incidence rates of the outcome events for both genders were estimated in each pre-specified age group and time-dependent TTR category (TTR60). The 95% confidence intervals (CIs) for these rates were derived by applying the Poisson assumption. Hazard ratios (HRs) for the study endpoints in women when compared with men were estimated using the Cox proportional hazards model, adjusted for age, congestive heart failure, hypertension, diabetes, previous stroke or TIA, renal impairment (serum creatinine >90 μmol/L in women and >100 μmol/L in men), vascular disease, and any previous hospitalization.

Results

Baseline characteristics

The study population consisted of 28 722 male and 25 846 (47%) female AF patients using warfarin. The mean age was higher in women

Table 1 Baseline characteristics of study population

	All, *n* (%)	Women, *n* (%)	Men, *n* (%)	*P*-value
Patients	54 568	25 846 (47.0)	28 722 (53.0)	
Age (years), mean ± SD	73.1 ± 10.8	76.8 ± 9.5	69.8 ± 10.9	<0.001
<65	11 573 (21.2)	2813 (10.9)	8760 (30.5)	<0.001
65–74	15 333 (28.1)	6053 (23.4)	9280 (32.3)	<0.001
≥75	27 662 (50.7)	16 980 (65.7)	10 682 (37.2)	<0.001
Congestive heart failure	9727 (17.8)	5141 (19.9)	4586 (16.0)	<0.001
Cardiomyopathy	1505 (2.8)	342 (1.3)	1163 (4.1)	<0.001
Hypertension	13 166 (24.1)	7184 (27.8)	5982 (20.8)	<0.001
Pulmonary embolism	815 (1.5)	445 (1.7)	370 (1.3)	<0.001
Stroke or TIA	6669 (12.2)	3466 (13.4)	3203 (11.2)	<0.001
Thyrotoxicosis	426 (0.8)	296 (1.2)	130 (0.5)	<0.001
Vascular disease	13 708 (25.1)	6255 (24.2)	7453 (26.0)	<0.001
Coronary artery disease	12 480 (22.9)	5694 (22.0)	6786 (23.6)	<0.001
Peripheral arterial disease	2237 (4.1)	946 (3.7)	1291 (4.5)	<0.001
Venous thromboembolism	1637 (3.0)	959 (3.7)	678 (2.4)	<0.001
Bleeding	2549 (4.7)	958 (3.7)	1591 (5.5)	<0.001
Myocardial infarction	2410 (4.4)	1111 (4.3)	1299 (4.5)	0.211
Intracranial haemorrhage	320 (0.6)	129 (0.5)	191 (0.7)	0.013
Anaemia	11 887 (21.8)	4871 (18.9)	7016 (24.4)	<0.001
Renal impairment	10 823 (19.8)	4941 (19.1)	5882 (20.5)	<0.001
Diabetes	5301 (9.7)	2358 (9.1)	2943 (10.3)	<0.001
Cancer	10 408 (19.1)	5182 (20.1)	5226 (18.2)	<0.001
CHA_2DS_2-VA score (without a point for female gender)	2.3 ± 1.5	2.6 ± 1.5	2.0 ± 1.5	<0.001
0	6732 (12.3)	1648 (6.4)	5084 (17.7)	<0.001
1	9951 (18.2)	3573 (13.8)	6378 (22.2)	<0.001
2	16 253 (29.8)	8464 (32.8)	7789 (27.1)	<0.001
3–4	16 721 (30.6)	9238 (35.7)	7483 (26.1)	<0.001
5–8	4911 (9.0)	2923 (11.3)	1988 (6.9)	<0.001

than in men (76.8 ± 9.5 vs. 69.8 ± 10.9, $P < 0.001$). Hypertension, congestive heart failure, and prior stroke or TIA were more common among women. In contrast, vascular disease, diabetes, and prior bleeding events were more common in men. The mean CHA_2DS_2-VA score was higher in women than in men (2.63 ± 1.48 vs. 2.02 ± 1.52, $P < 0.001$). Detailed information about baseline characteristics in the whole study population and in the two genders is shown in *Table 1*.

INR measurements and time in therapeutic range during the follow-up

The mean and median follow-up period was 3.2 ± 1.6 years and 3.4 years (2.0–4.7), respectively. The mean annual number of INR measurements was 18.5 ± 14.5 (median 16.6) in the whole study population. The number of annual INR measurements was higher for females compared with male patients (19.3 ± 14.5 vs. 17.9 ± 14.5, $P < 0.001$).

During the follow-up time the mean and median sTTR for the whole study population was 61.1 ± 25% and 67.0% (49.7–78.7), respectively. The mean sTTR was significantly higher among women than men (62.5 ± 23.6% vs. 59.8 ± 26.4%, $P < 0.001$).

Gender differences in the study endpoints

The crude unadjusted incidence rate per 1000 patient years for stroke or TIA, and cardiovascular and all-cause mortality were higher among female than male patients. In contrast, the unadjusted incidence rate of bleeding events was lower in women than in men (Supplementary material online, *File S1*).

However, among the unadjusted pre-specified age groups of <65, 65–74, and ≥75 years, there were no gender-specific differences in rate of stroke or TIAs, but the incidence of bleeding events and cardiovascular, and all-cause mortality were lower in women irrespective of age. (*Figure 1* and *Table 2*).

The risk of stroke or TIA and cardiovascular mortality were higher in women than in men among patients with TTR60 ≤50%. In the other TTR60 groups, there was no difference in the incidence of these endpoints. In TTR60 group <40% all-cause mortality was higher in women but in the other TTR60 groups the risk did not differ between the genders. The risk of bleeding events was significantly lower among women in all TTR60 groups (*Table 3*). The patient outcome improved in both genders linearly along TTR60 (*Figure 2* and *Table 3*).

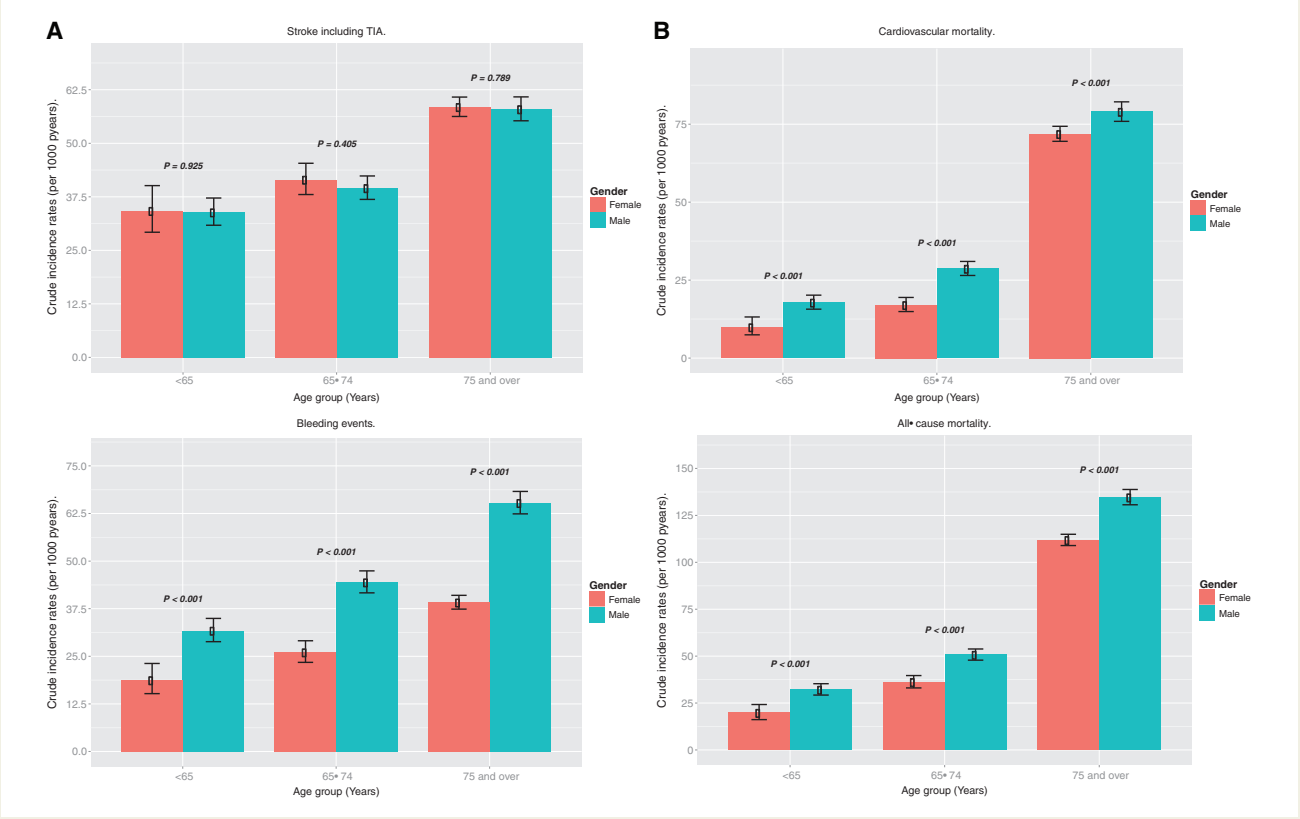

Figure 1 Crude incidence rates per 1000 patient years of (*A*) stroke or transient ischaemic attack and bleeding events and (*B*) cardiovascular and all-cause mortalities with 95% confidence intervals in age groups of <65, 65–74, and ≥75 years for both genders.

Table 2 Incidence rates per 1000 patient years for the study outcomes by age group for both genders

Outcomes	Age group (years)	Incidence rate: female	Incidence rate: male	*P*-value
Stroke or TIA	<65	34.22 (29.21–40.1)	33.89 (30.86–37.22)	0.9025
	65–74	41.51 (38.02–45.32)	39.54 (36.89–42.37)	0.405
	75 and over	58.48 (56.26–60.78)	57.97 (55.24–60.83)	0.789
Bleeding events	<65	18.74 (15.19–23.13)	31.75 (28.84–34.95)	<0.001
	65–74	26.08 (23.40–29.08)	44.45 (41.66–47.43)	<0.001
	75 and over	39.15 (37.38–41.01)	65.28 (62.40–68.30)	<0.001
Cardiovascular mortality	<65	9.90 (7.44–13.18)	17.80 (15.69–20.19)	<0.001
	65–74	17.02 (14.91–19.43)	28.66 (26.50–31.00)	<0.001
	75 and over	71.86 (69.49–74.31)	78.99 (75.92–82.18)	<0.001
All-cause mortality	<65	19.81 (16.18–24.24)	32.15 (29.27–35.30)	<0.001
	65–74	36.21 (33.07–39.65)	50.75 (47.84–53.83)	<0.001
	75 and over	111.90 (108.93–114.95)	134.64 (130.62–138.78)	<0.001

After adjusting for the baseline characteristics there were no difference in the risk of stroke or TIA between the genders (HR 0.97, 95% CI 0.91–1.03, $P = 0.304$). The adjusted risk for bleeding events (HR 0.52, 95% CI 0.49–0.56, $P < 0.001$), cardiovascular mortality (HR 0.82, 95% CI 0.78–0.88, $P < 0.001$), and all-cause mortality (HR 0.79, 95% CI 0.75–0.83, $P < 0.001$) were lower in women than in men (*Table 4*).

Discussion

This nationwide cohort study revealed no difference in the adjusted risk of stroke between female and male AF patients who were anticoagulated with warfarin. The risk of bleeding events, cardiovascular, and all-cause mortality were lower in women than in men regardless of age. Moreover, there were no gender-specific differences in the

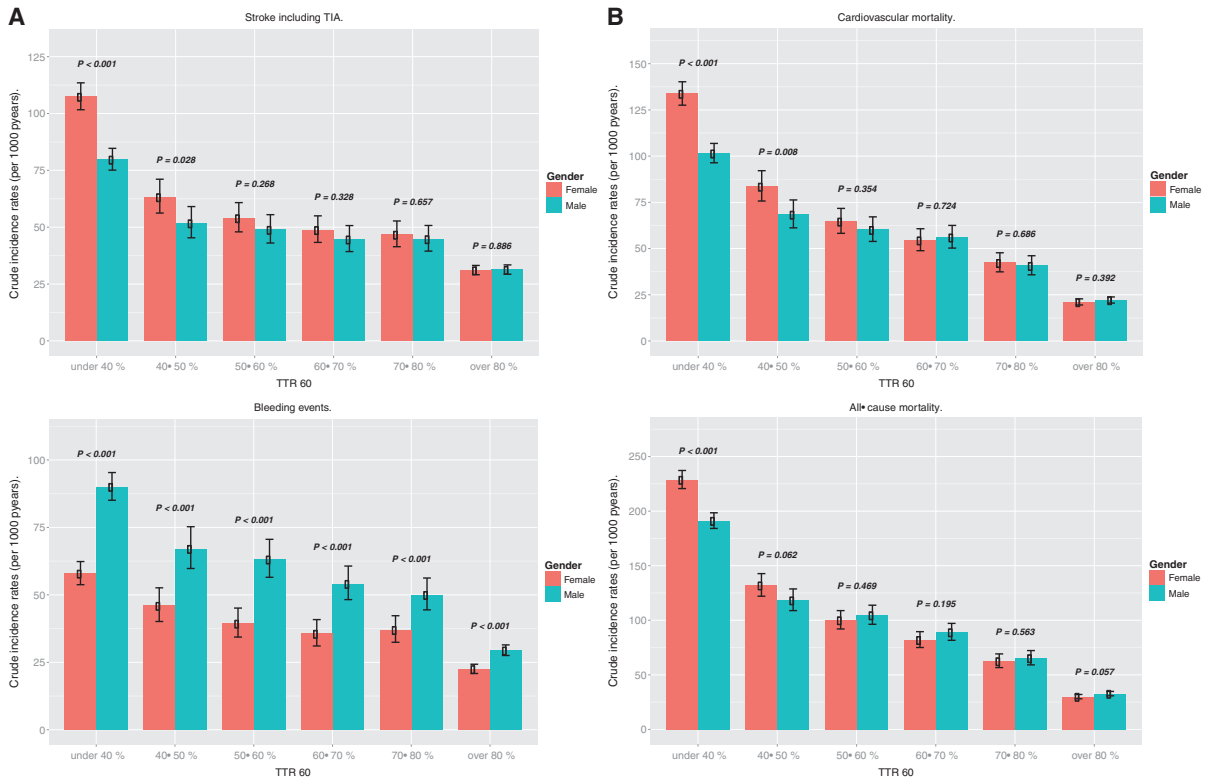

Figure 2 Incidence rates per 1000 patient years of (*A*) stroke or transient ischaemic attack and bleeding events and (*B*) cardiovascular and all-cause mortalities with 95% confidence intervals in time in therapeutic range groups of <40, 40–50, 50–60, 60–70, 70–80, and ≥80% for both genders.

risk of stroke and adverse outcome in the patients with TTR60 over 50%, and the risk of bleeding events was lower in women than in men in all TTR60 groups. Hence, female gender was not a risk factor for adverse outcome in patients with AF treated properly with warfarin.

Association between gender and the risk of stroke or transient ischaemic attack and mortality

In our study, the unadjusted risk of stroke or TIA, and cardiovascular and all-cause mortality were elevated in women. The same observation has been made in previously.[11,20] In the SPORTIF trials,[17] and in the meta-analysis of Pancholy *et al.*,[16] the residual risk of stroke and peripheral embolism was higher in women compared with men with comparable quality of warfarin therapy. However, in these studies female patients were significantly older and had more risk factors for stroke than men. Therefore, when evaluating the impact of gender on the risk of stroke and cardiovascular outcome in AF patients it is important to adjust the data for age and other baseline characteristics and assess the quality of OAC.

Despite significantly higher CHA_2DS_2-VA score for stroke in women, we found no difference in the adjusted risk of stroke between female and male AF patients. Moreover, cardiovascular and all-cause mortality were lower in women. In keeping with our findings, Senoo *et al.*[18] have shown that after adjustment for baseline characteristics there were no difference in the rate of stroke and cardiovascular death between anticoagulated female and male patients. Our results are also in line with the results of a recently published register study in which the stroke risk and mortality were similar in female and male patients after matching on age and time-dependent adjustment for underlying diseases and confounding factors.[21]

In patients with AF the risk for stroke and adverse cardiac outcome increases with age. The impact of the gender on the age-related risk of stroke is controversial. In the meta-analysis of Wagstaff *et al.*[12] the risk of stroke was elevated in women compared to men, particularly in age group of over 75 years. In contrast, Renoux *et al.*[21] found no sex difference in stroke risk in any age group including those over 75 years of age after proper multivariate adjustment. In our study, the residual risk for stroke or TIA increased with age in anticoagulated AF patients, but there were no significant differences between the genders in any age group.

Association between gender and risk of bleeding events

Consistent with prior data,[18,21] we showed that female patients had lower risk for bleeding events compared with males both before and after adjusting for baseline characteristics in all pre-specified age and TTR60 groups. Reasons for this are unclear. The summary TTR over the whole study period was slightly better in females (62%) than in males (60%). Although statistically significant, it is unlikely that this

Table 3 Incidence rates per 1000 patient years for the study outcomes by gender and TTR60 with *P*-values

Outcomes	TTR60 (%)	Incidence rate: female	Incidence rate: male	*P*-value
Stroke or TIA	<40	107.4 (101.65–113.48)	79.75 (75.09–84.69)	<0.001
	40–50	63.23 (56.22–71.12)	51.75 (45.36–59.05)	0.028
	50–60	54 (47.96–60.8)	48.88 (43.03–55.51)	0.268
	60–70	48.79 (43.31–54.98)	44.64 (39.29–50.71)	0.328
	70–80	46.74 (41.43–52.73)	44.77 (39.48–50.77)	0.657
	>80	31.07 (29.08–33.21)	31.29 (29.31–33.41)	0.886
Bleeding events	<40	57.9 (53.78–62.34)	90.05 (85.07–95.32)	<0.001
	40–50	45.95 (40.14–52.6)	67.06 (59.77–75.24)	<0.001
	50–60	39.36 (34.35–45.1)	63.14 (56.5–70.56)	<0.001
	60–70	35.59 (31.03–40.81)	54.09 (48.22–60.67)	<0.001
	70–80	37.01 (32.41–42.26)	49.98 (44.43–56.22)	<0.001
	>80	22.49 (20.83–24.28)	29.42 (27.52–31.45)	<0.001
Cardiovascular mortality	<40	133.75 (127.57–140.24)	101.49 (96.4–106.85)	<0.001
	40–50	83.51 (75.7–92.13)	68.36 (61.22–76.32)	0.008
	50–60	64.65 (58.25–71.75)	60.13 (53.85–67.14)	0.354
	60–70	54.45 (48.85–60.69)	56.05 (50.24–62.53)	0.724
	70–80	42.25 (37.4–47.73)	40.65 (35.81–46.15)	0.686
	>80	21.08 (19.49–22.78)	22.11 (20.5–23.84)	0.392
All-cause mortality	<40	228.76 (220.62–237.19)	191.15 (184.11–198.45)	<0.001
	40–50	131.98 (122.06–142.71)	118.32 (108.81–128.67)	0.062
	50–60	100.08 (92.04–108.82)	104.65 (96.26–113.78)	0.469
	60–70	82.01 (75.07–89.59)	89.05 (81.64–97.12)	0.195
	70–80	62.56 (56.59–69.16)	65.32 (59.1–72.19)	0.563
	>80	29.95 (28.05–31.97)	32.69 (30.72–34.77)	0.057

Table 4 Hazard ratios with 95% confidence intervals for study endpoints in women and compared with men

Endpoint	HR	CI	*P*-value
Stroke or TIA	0.97	0.91–1.03	0.304
Bleeding events	0.52	0.49–0.56	<0.001
Cardiovascular mortality	0.82	0.78–0.88	<0.001
All-cause mortality	0.79	0.75–0.83	<0.001

The Cox proportional hazards model was adjusted for age, congestive heart failure, hypertension, diabetes, previous stroke or TIA, renal impairment (serum creatinine >90 μmol/L in females and >100 μmol/L in males), vascular disease, and any previous hospitalization.

difference alone would explain why the bleeding risk was lower in females. It is possible, that surgical interventions and other incidents such as cancer requiring interruption of warfarin therapy may have been involved. However, the sensitivity analyses investigating the effects of any previous hospitalizations found no impact on the overall results.

Impact of gender on warfarin control

In many previous studies, INR control during warfarin therapy has been worse in women compared with men.[18,22,23] In the study by Senoo *et al.*,[18] TTR (unlike female gender) emerged as an independent predictor for combined adverse outcome of cardiovascular death, stroke, and peripheral embolism. In the current study, the summary TTR was better in female patients.

A major strength of our study is that the quality of warfarin therapy was estimated using continuously calculated TTR60. TTR60 describes the quality of warfarin therapy over the 60 days before the index event. Hence, it is likely to depict temporal associations between the quality of warfarin therapy and clinical outcomes more precisely than a summary TTR over the entire follow-up period. Poor TTR60 was associated with increased risk of stroke and impaired cardiovascular outcome in both genders. When dividing the patients into groups according to their TTR60 level, no gender-dependent differences were detected in the risks of stroke, and cardiovascular and all-cause mortality in patients with TTR60 over 50%.

Clinical implications

In the light of our data, female gender is not associated with adverse outcomes in anticoagulated AF patients after adjustment for baseline characteristics. That is, there were no differences in the risk of stroke between the genders, and cardiovascular and all-cause mortality and risk of serious bleeding events were lower in females. Hence, in clinical practice female gender should not be considered as a marker of adverse outcome in warfarin anticoagulated patients.

A good TTR60 was associated with reduced risk of stroke and improved cardiovascular outcome in both genders regardless of age. Bleeding risk was lower in females in all age and TTR60 groups indicating that also elderly female patients should be offered OAC therapy. On the other hand, in females with extremely poor warfarin control (i.e. TTR60 <40%) the risk of adverse events was elevated compared to men indicating that poor warfarin control is devastating in females.

Limitations

Although all the registries used in the FinWAF trial have been validated,[24–27] it is possible that some secondary diagnoses may have been underused in hospital discharge documents and death certificates leading to a lower overall CHA_2DS_2-VA score. Moreover, no data on lifestyle variables, such as smoking, alcohol consumption, physical activity, or obesity were available.

No information on the use of over-the-counter drugs such as aspirin and non-steroid anti-inflammatory drugs is included in the national drug prescription register. The main indication to combine aspirin to warfarin therapy would be prior myocardial infarction (MI). However, there were no sex difference in prior MIs or MIs during study period in any TTR60 group. Additionally, as our data were adjusted for prior stroke or TIA and vascular disease, which are the other common indications for aspirin, it is unlikely that our findings were related to a difference in the use of aspirin between the genders.

Clopidogrel was used more by male patients prior a follow-up period (male 4.6%, female 3.5%, $P < 0.001$) and during a follow-up period (male 4.7%, female 3.1%, $P < 0.001$). However, the results were adjusted for prior stroke and vascular disease. Additionally, in the sensitivity analysis where time periods of clopidogrel use were excluded, there were no changes in the results in any endpoint according to age or TTR60 groups.

During the study period the use of direct oral anticoagulants (DOACs) in Finland was rare. Hence, it was not possible to assess the relationship between the gender and clinical outcome in patients using DOACs. Finally, because all patients were anticoagulated, we cannot evaluate if the female gender had significant impact on the baseline risk for stroke in non-anticoagulated patients. It is possible—although unlikely in the light of recent data by other investigators[5]—which the baseline risk of stroke in non-anticoagulated patients was higher in females but the difference was eliminated by proper oral OAC therapy.

Conclusions

After taking into account age and other risk factors female AF patients anticoagulated with warfarin did not carry increased risk for stroke or death compared with men. TTR60 was a strong predictor for the outcome in both genders. Another important finding in our study was that risk for bleeding complications was lower among women in all age groups.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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Corrigendum

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The authors wish to inform readers that Juan Tamargo's affiliation was incomplete in the original version – 'CIBERCV' was omitted in error. This has now been corrected online.

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The authors wish to inform readers that there were errors in the statement of the conclusion in this paper, including the omission of a reference. This has now been corrected online. The authors apologise for the error.