Gender differences in stroke risk of atrial fibrillation patients on oral anticoagulant treatment

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Summary

The efficacy of adjusted-dose oral anticoagulant treatment (OAT) in the prevention of stroke in atrial fibrillation (AF) is well documented. Available data show that AF patients are widely heterogeneous in terms of ischaemic stroke risk. The role of female gender as a predictor of stroke risk is inconsistent, in particular it is unclear if warfarin treatment is able to prevent stroke equally in both sexes. We performed a prospective study on 780 AF patients on OAT, followed by an Anticoagulation Clinic, to evaluate if female gender is a risk factor for stroke among patients on OAT and if the quality of anticoagulation is different between genders. No difference was found in relation to the quality of anticoagulation between genders (p=0.5). During follow-up 33 patients had major bleedings (rate 1.37x100 pt/yrs) but no difference was found between genders in bleeding risk. Forty patients had ischaemic events [rate 1.66x100 pt/yrs; males rate 1.2 x100 pt/yrs; females rate 2.43x100 pt/yrs; p=0.042; relative risk (RR) of females vs. males 2.0 (95% confidence interval [CI] 1.3–3.1); p= 0.004]. The higher rate of ischaemic events in females with respect to males was confirmed at Cox regression analysis after correction for age (p=0.009). In addition, strokes occurring in females were more disabling, and RR for severe and fatal stroke, defined according to Modified Rankin scale, of females vs. males was 3.1 (95% CI 1.3–6.5; p=0.001). In conclusion, our data show a higher risk of stroke in anticoagulated AF females with respect to males, despite a similar quality of anticoagulation.

Keywords

Atrial fibrillation, stroke, warfarin, female gender, quality of anticoagulation

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Introduction

Atrial fibrillation (AF) is associated with an increased risk of stroke and the efficacy of adjusted-dose warfarin treatment in the prevention of thrombotic complications of AF is well documented by trials published during the past 20 years (1). However, available data show that AF patients are widely heterogeneous in terms of ischaemic stroke risk, which ranges from 1–2% to 12–18%/year (2). Because the net benefit of antithrombotic therapy depends on the underlying risk of stroke, an accurate analysis of risk factors associated with stroke is needed to define the appropriate antithrombotic strategy for the individual patient. Several clinical characteristics have been investigated: age, hypertension, diabetes, heart failure, cardiac disease, history of previous stroke or transient ischamic attack (TIA) and gender. Published results are in agreement in indicating age, hypertension and history of previous stroke/TIA as good predictors of stroke risk whereas data about gender and other clinical characteristics of patients are contradictory (3). The Stroke Prevention in Atrial Fibrillation (SPAF) reported that women are at higher risk for ischaemic stroke (4). Similar results were found in other studies (5–6). However, several other authors did not confirm this finding (7–11). A recent systematic review confirmed that this issue needs to be better clarified (6). Analysing non-anticoagulated AF patients, the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study found that women are at higher risk for stroke when off warfarin (12). However, when anticoagulation is started, warfarin appears to be as effective in women as in men. On the other hand, no study found a significant independent association between gender and bleeding complications (13).

Aim of our study was to evaluate in a cohort of AF patients prospectively followed up by an Anticoagulation Clinic if female

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gender is a risk factor for stroke. In addition, since information about the quality of oral anticoagulant treatment (OAT) among females is scanty, we further investigated if the quality of anticoagulation is different between genders and if this aspect could influence the risk of stroke.

Methods

Patients

From June 1998 to December 2007, we prospectively investigated 780 AF patients referred for the control of OAT to the Anticoagulation Clinic of the Azienda Ospedaliero-Universitaria Careggi, University of Florence. Methodology used for the enrolment and follow-up has been previously described (14). Briefly, OAT indication was established according to American College of Chest Physicians (ACCP) (15) and Italian Federation of Anticoagulation Clinics (FCSA) guidelines (16).

All patients were treated with warfarin and international normalised ratio (INR) was maintained at the intended therapeutic range of 2–3. We calculated patient/years (pt/yrs) by our patients database. PARMA System 5.7 (17) was used and date of starting OAT and dates of all visits were recorded. Time of observation was calculated on consecutive periods of observation. When a patient left the Centre for more than two months this interval was excluded from the analysis and adverse events eventually occurred during this period were not included in the analysis. For the calculation of time in range, the Rosendaal method was used (18).

Patients' demographic and clinical data were collected. The presence of traditional cardiovascular risk factors and other characteristics associated with ischaemic complications in AF was assessed on the basis of patients' interview, echocardiography and hospital records.

Follow-up visits were scheduled every 2–4 weeks for INR monitoring. Hospital admissions, concomitant therapies, intercurrent illnesses, bleeding and thrombotic events during follow-up were recorded. Patients who missed check-ups for more than two months were contacted (personally or through their family or general practitioner) and the reason for interrupting treatment monitoring was recorded. In the case of death, further information about its cause was requested. When this information was lacking, national register of causes of death and autopsy results (if available) were consulted.

Outcomes

Data were censored after the occurrence of TIA or stroke, major bleeding, after the cessation of OAT or when the patient stopped being monitored by our Anticoagulation Clinic. Stroke was defined as a syndrome characterised by rapidly developing clinical symptoms and/or signs of focal and at times global loss of brain function, lasting > 24 hours, not explained by other causes and in the absence of primary haemorrhage. Ischaemic stroke was defined as a stroke with either a normal brain computed tomography (CT) or evidence of a recent infarction in the clinically relevant area of the brain on a CT or magnetic resonance imaging (MRI) within three weeks of the event, while previous TIA was diagnosed when neurological defects lasted <24 hours. The Modified Rankin Disability Scale was used to measure functional outcome 90 days after stroke (19). The diagnosis of TIA was accepted only if the event led to hospital admission and neuroradiologic imaging and neurologic evaluation were performed. Bleeding was classified as major when fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal; when surgery or transfusion of more than two blood units were required or when haemoglobin was reduced of 2 g/dl or more. All cases of bleeding not classified as major were considered minor; clinically unrelevant bleedings were not recorded (20). When an ischaemic or bleeding event occurred, the INR related to the event was recorded. INR was defined as temporally related to the adverse event when it was obtained at the time of the event or during the preceding eight days. No patient was on hormonal replacement therapy. Finally, we applied to our patients $CHADS_2$ score for stroke risk stratification (21). The use of aspirin in association to OAT was limited to patients with a recent episode of acute coronary syndrome or when they had recurrent ischaemic episodes. Patients were instructed to avoid aspirin use and were routinely asked for it; aspirin use was recorded on electronic files.

Table 1: Clinical characteristics of patients and oral anticoagulant treatment (OAT) quality. Bleeding and thrombotic events during OAT.

	Males	Females	P-value
Number (%)	505 (64.7)	275 (35.3)	
Follow-up (pt/yrs)	1544	862	
Median age (years)	74 (37–94)	76 (43–92)	<0.001
Chronic AF (%)	415 (82.2)	218 (80.4)	0.6
Time spent in range (%)	70	71	0.4
Time spent below range (%)	15	14	0.5
Time spent above range (%)	14	15	0.6
Mean warfarin dosage (mg)	25.2 ±12.2	22.7±10.6	0.02
Major bleeding before starting OAT (%)	18 (3.6)	7 (2.5)	0.6
Major bleeds (rate x 100 pt/yrs)	22 (1.4)	11 (1.3)	1.0
Fatal bleeds (rate x 100 pt/yrs)	7 (0.5)	1 (0.1)	0.04
Stroke/TIA (rate x 100 pt/yrs)	19 (1.2)	21 (2.4)	0.04

Pt/yrs, patient/years; AF, atrial fibrillation; OAT, oral anticoagulant treatment; TIA, transient ischaemic attack.

Statistical analysis

Incidence rates for ischaemic and bleeding events were calculated as the number of events per 100 pt/yrs of observation (22). For this calculation observation started at the beginning of follow-up and ended when patients experienced an adverse event or were censored. The SPSS statistical software package (Statistical Package for Social Sciences, Chicago, IL, USA; software for Windows, version 11.5) was used for data processing. Data are expressed as median and range due to their skewed distribution. Preliminary statistics were performed using Wilcoxon test. Statistical analysis

Table 2: Baseline risk factors for stroke/TIA and $CHADS_2$ stratification of patients.

Patients	Males	Females	P-value
Left ventricular dysfunction (%)	125 (32.0)	40 (19.6)	0.02
Hypertension (%)	311 (62.1)	180 (66.2)	0.86
Diabetes (%)	98 (19.7)	58 (21.3)	0.84
Previous stroke/TIA (%)	139 (27.5)	89 (32.6)	0.34
Peripheral artery disease (%)	83 (16.6)	27 (9.8)	0.01
Dyslipidemia (%)	114 (24.6)	72 (28.5)	0.3
Smoking habitus (%)	102 (21.7)	28 (10.9)	<0.001
Coronary artery disease (%)	131 (26.1)	33 (12.1)	< 0.001
$CHADS_2$=0	47 (9.3)	10 (3.6)	0.8
$CHADS_2$=1	107 (21.3)	61 (22.3)	0.9
$CHADS_2$=2	154 (30.5)	78 (28.5)	0.6
$CHADS_2$=3	105 (20.9)	67 (24.3)	0.8
$CHADS_2$=4	65 (12.9)	43 (15.7)	0.6
$CHADS_2$=5	18 (3.6)	16 (5.8)	0.1
$CHADS_2$=6	9 (1.8)	-	-

TIA, transient ischaemic attack.

Table 3: Univariate analysis of risk factors for ischaemic events for patients on oral anticoagulant treatment (OAT).

	OR	95% CI	P-value
Previous stroke/TIA	7.1	3.51–14.05	<0.001
Hypertension	2.3	1.05–5.08	0.03
Female gender	2.1	1.12–4.01	0.02
Age	1.0	0.98–1.07	0.3
Diabetes	1.4	0.65–2.84	0.4
Left ventricular dysfunction	1.0	0.43–2.29	0.1
Coronary artery disease	0.5	0.20–1.39	0.2

CI, confidence interval; OR, odds ratio; TIA, transient ischaemic attack.

Table 4: Multivariate analysis of risk factors for ischaemic events for patients on oral anticoagulant treatment (OAT) adjusted for age.

	OR	95% CI	P-value
Previous stroke/TIA	7.7	3.61–16.31	<0.001
Hypertension	3.9	1.75–8.55	0.001
Female gender	2.9	1.46–5.63	0.002

CI, confidence interval; OR, odds ratio; TIA, transient ischaemic attack.

was performed using Fisher's exact test (categorical data) and a p-value <0.05 was chosen for statistical significance. Univariate analysis was conducted to evaluate the independent risk factors for cerebral ischaemic events and a p-value <0.05 was chosen for statistical significance. Multivariate regression model was constructed using age and variables showing a p-value <0.05 at univariate analysis. The independent effect of gender on the risk of ischaemic events on OAT was investigated by performing the incidence rate ratio (23) and a Cox regression analysis.

Results

Patients characteristics and OAT quality

We performed a prospective study on 780 AF patients (505 males, 275 females) for a total follow-up period of 2,406 pt/yrs. The characteristics of patients are listed in Table 1. Females were significantly older than men (p<0.001). Patients spent 14%, 71% and 15% of time below, within and above the intended therapeutic range, respectively; no difference was found in relation to the quality of anticoagulation between genders (Table 1). Mean warfarin dosage was significantly higher in men respect to women (p=0.02). During follow-up, 65 patients died (overall mortality rate 2.7 per 100 pt/yrs, 95% CI 0.5–5.1) including 52 men (mortality rate of 3.4, 95% CI 0.7–5.6 and 1.5, 95% CI0.2–2.4 per 100 pt/yrs for men and women, respectively). Twenty-five patients (3.2%) had had an episode of major bleeding before starting OAT (Table 1).

Bleeding events during OAT

Thirty-three patients had major bleeding (rate 1.37 per 100 pt/yrs, 95% CI 0.1–2.1) (Table 1): 18 cerebral, 13 gastrointestinal, 1 muscular haematoma, 1 haematuria. The INR value related to bleeding events was >4 in 4/33 patients (12%), 1/11 females (9%) and 3/22 males (14%) (p=1.0). Nine haemorrhages, eight cerebral, were fatal: seven in males, two in females (RR 2.2 – 95% CI 1.0–4.3; p=0.04). Twenty-nine patients (3.7%) were also on treatment with aspirin 100 mg daily, 6/275 females (2.2%) and 23/505 (4.5%) (p=0.1). The rate of bleeding events between patients on and off aspirin treatment was similar (1.1 per 100 pt/yrs vs 1.4 per 100 pt/yrs, p=1.0).

Cerebral ischaemic events during OAT

Forty patients had ischaemic events (rate 1.66 per 100 pt/yrs) including 19 males (rate 1.2– 95% CI 0.7–2.4 per 100 pt/yrs) and 21 females (rate 2.43– 95% CI 1.4–3.6 per 100 pt/yrs). The RR of females respect to males was 2.0 (95% CI 1.3–3.1); p< 0.01) (Table 1). Twenty-three were strokes (1 fatal), 13 were TIAs, four were peripheral emboli. No difference in the rate of tromboembolic events was found in relation to the type of AF, chronic or paroxysmal (rate 1.5 per 100 pt/yrs vs 2.0 per 100 pt/yrs; p=0.3). The higher rate of thrombotic events in females respect to males was confirmed at Cox regression analysis after correction for age (hazard ratio [HR] 2.3; 95% CI 1.2–4.4; p<0.01). In addition strokes occurring in females were more disabling. By using Modified Rankin scale for severe and fatal (Rankin ≥3) stroke, 8/13 women and 4/10 men had severe stroke (RR of females vs. males was 3.1; 95% CI 1.3–6.5; p<0.01). The INR value related to thromboembolic events was <2 in 20/40 patients (50%), 12/21 females (57%) and 8/19 males (42%) (p=0.3). Classic risk factors for stroke and distribution of patients in relation to $CHADS_2$ score are reported in Table 2. When echocardiographic data were evaluated, the number of patients with enlargement of atria was

similar in the two genders (68% females, 69% males; p=0.9) and in relation to the occurrence of stroke (p=0.1). Univariate analysis showed that history of previous ischaemic event, hypertension and female gender are significantly associated with the occurrence of cerebral ischaemic events during OAT (Table 3).

A multivariate analysis adjusted for age, gender, previous ischaemic event, hypertension, confirmed that previous ischaemic event, hypertension and female gender are independent risk factors for the occurrence of embolic events during OAT (Table 4).

Discussion

Our cohort of AF patients shows a prevalence of women of 35.3%, consistent to other studies. Indeed, the majority of studies published to date have concluded that AF is more prevalent in men than in women (3), with a rate of females ranging from 28% (4) to 42% (12).

In our patients on chronic warfarin treatment, women had higher risk of ischaemic stroke than men. Among women higher rates of thromboembolic events were not related to age or to the presence of classic stroke risk factors. It is known that patients treated with warfarin suffer from less severe stroke than patients off warfarin (24). However, in our cohort women on warfarin experienced more severe and disabling strokes than men, suggesting that OAT provide a lower protection than in men. It should be noted that the quality of anticoagulation was similar in the two genders, ruling out that the occurrence of thromboembolic events was due to a poor quality of the therapy. The ATRIA Study (12), analysing AF patients not on OAT, reported a higher rate of stroke among females, suggesting that women carry an intrinsic higher risk of stroke. Similarly, a higher rate of stroke among women was found in the cohort of Framingham study (5) and among women on aspirin or aspirin plus fixed, low-dose warfarin treatment in data-set of SPAFI-III studies (4). In our population, that included only patients on OAT, we confirmed that stroke risk in females remains higher than in men even when reduced by warfarin treatment. Pengo et al. (25), analysing a similar cohort of AF patients on OAT, did not find higher rate of stroke among females. However, the total follow-up period of this study was shorter than our and only one ischaemic stroke was recorded. Conversely, the analysis of SPORTIF (26) trials found a higher stroke risk among women on OAT, but the statistical power of the study referring specifically data involving women was limited. The higher rate of stroke among females in our cohort could not be related to the presence of another possible favouring factor such as estrogen replacement therapy, because this practice is rarely used in elderly women in our country and none of our patients was on this treatment.

In our population, as expected, the presence of coronary artery disease was significantly higher among men with respect to women. Similarly, also left ventricular dysfunction, probably as a consequence of coronary arteriopathy, and peripheral arteriopathy were more frequent in men. Coronary and peripheral artery disease are both part of atherotrombotic vascular disease, that is associated with high stroke risk. Nevertheless, according to the probable cardioembolic origin of ischaemic events recorded, stroke is more frequent among women that are less affected by atherothrombosis. The difference in the rate of thromboembolism between women and men seems not related to the contemporary aspirin therapy. Actually, the use of antiplatelet therapy in our cohort was limited to a small number of patients and not significantly different among genders. Other authors (5) hypothesised that the different atrial structure in women could influence the different thromboembolic risk. However, in our group the number of patients with enlargement of atria at transthoracic echocardiography was similar between genders.

Our data confirmed that the history of previous stroke/TIA is an independent risk factor for stroke, with an OR 7.7 (27). Hypertension was also confirmed as a risk factor for stroke with an increase of risk of about two folds. In our study the presence of diabetes mellitus was not a significantly independent risk factor for stroke, in agreement with other studies (8, 9, 11, 28).

We confirmed that bleeding risk in AF patients is similar between genders (12–13) and we observed a low rate of bleeding events, in agreement with previous observations obtained in patients followed by devoted agencies (24, 25, 28, 29). The Anticoagulation Clinics usually provide better OAT quality control and a lower warfarin related bleeding rate (29–30). There is wide evidence that elevated INR levels are related with bleeding risk (20, 31–33). Instead, the relation between INR<2 and increased stroke risk has been reported (34), but when the analysis was extended to the quality of OAT over time, this relation seemed less clear (24, 35).

Limitations of the study

A limitation of the study is that it was conducted in a single centre were patients are intensively followed for OAT manage-

What is known about this topic?

– The efficacy of adjusted-dose oral anticoagulant treatment (OAT) in the prevention of stroke in atrial fibrillation (AF) is well documented and an accurate stratification of patients' risk is needed to choose the appropriate antithrombotic strategy.
– Published results are in agreement in indicating age, hypertension and history of previous stroke/TIA as good predictors of stroke risk; whereas the evidence about gender and other clinical characteristics of patients is less convincing. Actually, the analysis of published data on female gender as a risk factor for stroke in AF patients gave contradictory results.

What does this paper add?

– In this paper we evaluate in a cohort of AF patients (prospectively followed by an anticoagulation clinic) if female gender is a risk factor for stroke and if the quality of anticoagulation is different between genders.
– In the literature, there is no information about the quality of OAT among females and if this aspect could influence the risk of stroke. Our data show a higher stroke risk in females with respect to males, despite a similar quality of anticoagulation. Bleeding risk of women on OAT was not different from men, and women were less likely than men to develop cerebral bleeding.

ment reaching a good quality of OAT. Therefore, the number of cerebral ischaemic events recorded is limited.

Conclusions

In conclusion, our data indicate a higher risk of stroke in females with respect to males, despite a similar quality of anticoagulation. This finding was independent of age and of the presence of other risk factors for stroke, supporting the use of anticoagulant therapy in females. Overall, we found no difference in bleeding risk by gender. Our data suggest that men may be at higher risk for cerebral bleeding. However, the number of events was too small for definitive conclusion and this finding warrants further investigation.

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