of Cardiology

Atrial fibrillation

The increased risk of stroke/transient ischemic attack in women with a cardiac implantable electronic device is not associated with a higher atrial fibrillation burden

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Aims To evaluate if the increased thromboembolic risk in female patients may be related to a higher burden of atrial fibrillation (AF).

Methods and results Data collected in a prospective observational research of patients implanted with a cardiac implantable electrical device (CIED) were analysed. We included 2398 patients: 489 (20.4%) were female and 1909 (79.6%) were male (oral anticoagulants treatment in 23.2%, independent of gender). During the follow-up (mean 42.8, median 37.7 months), 26 thromboembolic events occurred in 22 patients, with an incidence rate ratio of both stroke and stroke/transient ischemic attack (TIA) significantly higher in females compared with males [2.00, 95% confidence interval (CI) 1.53–2.61, $P < 0.001$ for stroke; 1.77 (95% C1.37–2.31, $P < 0.001$ for stroke/TIA]. An AF burden $\geq$5 min was a common finding (44% of patients), with no difference between men and women. The maximum daily AF burden and the time to evolution in permanent AF did not differ according to gender. The results of multivariate Cox regression showed that female gender, as well as history of CABG, were significant independent predictors of stroke and female gender was also an independent predictor of stroke/TIA.

Conclusions Among patients implanted with a CIED, an AF burden of at least 5 min is a common finding, (44% of patients). Female patients have a risk of stroke and TIAs that is around two-fold that of male patients, but this increased risk cannot be ascribed to a higher burden of AF or to differences in the evolution to permanent AF.

Clinical Trial Registration ClinicalTrials.gov Identifier: NCT01007474

Keywords Atrial fibrillation • Anticoagulation • Implantable defibrillator • Pacemaker • Stroke

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What's new?

- In patients with atrial fibrillation (AF), female gender was found to be a risk factor for stroke, but the reasons for the increased risk are unknown.
- Among patients implanted with a cardiac implantable electrical device, we found that a burden of AF of at least 5 min is common (44% of patients) and that female patients have a risk of stroke and transient ischemic attacks (TIAs) around two-fold that of male patients.
- According to our prospectively collected data, the increased risk of stroke found in female patients cannot be ascribed to a higher burden of AF, or to differences in the evolution to permanent AF.
- Further studies are needed in order to evaluate the reasons and mechanisms for the increased risk of stroke and TIA associated with female gender among patients with AF.

Introduction

In patients with atrial fibrillation (AF), risk stratification for stroke is the cornerstone of clinical decision making.[1] In patients with AF female gender has emerged as a stroke risk factor in many studies and meta-analyses[2] and has been included in the CHA_2DS_2-VASc score, which is the stroke risk stratification scheme recommended in most guidelines.[1,2] However, there is an age dependency to stroke risk in females, and there is no significant increase in the overall risk of stroke in female patients age <65 years with lone AF.[2] The precise reasons why female gender increases the thromboembolic risk are not completely known.[3,4]

The relationship between stroke and AF burden has recently been the object of growing interest, since AF burden provides an overall assessment of the amount of time spent in AF, and has been associated with an increased risk of stroke.[5–9] Even if clinical risk stratification is based on clinical factors, data from patients implanted with a cardiac implantable electrical device (CIED) providing continuous monitoring of the atrial rhythm showed that the maximum daily AF burden is associated with an increased risk of ischaemic stroke or transient ischemic attack (TIA), even after adjustment for oral anticoagulants use and the $CHADS_2$ score.[10,11] This suggests that measuring daily AF burden may have important clinical relevance[8] and supports the search for specific thresholds of AF burden associated with a substantial increase in the risk of ischaemic stroke.[6,7,11] Indeed, AF burden can improve the predictive value of clinical risk scores, such as $CHADS_2$, for stroke and thromboembolism.[7]

In this analysis, based on data collected in a prospective observational research of patient with a CIED we tested the hypothesis that the increased thromboembolic risk in female patients may be related to a higher burden of AF, by comparing the maximum AF daily burden in men and women during long-term follow-up.

Methods

Project design and patient population

Patients participating to the Italian ClinicalService® Project [ClinicalTrials.gov Identifier: NCT01007474],[12] a national medical care project aiming to improve the quality of diagnostic and therapeutic strategies through the use of implantable cardiac devices in clinical practice, were considered for the present analysis. The project consists of a shared environment for prospective collection, management, analysis and reporting of data from patients in whom Medtronic devices have been implanted.

In the Italian ClinicalService® Project, patients are prospectively followed by participating centres according to clinical practice and guidelines through standard in-hospital visits. An independent scientific committee of physicians prospectively identifies key clinical questions on a yearly basis for analysis and publication. A charter assigns the ownership of data to the centres and governs the conduct and relationship of the scientific committee and Medtronic. The project was approved by each site's Medical Ethics Committee or Medical Director and conforms to the principles outlined in the Declaration of Helsinki. Each patient provided informed consent for data collection and analysis.

For the present analysis, patients were included if they had a CIED with an atrial lead, had not permanent atrial tachyarrhythmia/atrial fibrillation (AT/AF), had a clinical follow-up duration of at least 183 days or more, and had device data continuously stored during the observation period.

Research objectives

The main research objective was to evaluate whether the thromboembolic risk in female patients may be related to AF burden or other patients characteristics.

The main endpoint was the incidence of any thromboembolic event, stroke or TIA. Secondary endpoints were incidence of stroke, daily AF burden, estimated as the number of minutes of AF recorded in a day. The sensitivity and specificity of device detection of AF burden in Medtronic devices have been established in previous studies and has been shown to exceed 95% for both measures.[13] In every patient, the maximum daily AF burden experienced during follow-up was analysed, as done previously.[11] In every patient the maximum daily AF burden, as well as the attainment of predefined cut-offs of daily AF burden (5 min, 1 h, 6 h, 12 h, and 23 h) and the percentage of days with daily AF burden beyond predefined cut-offs were assessed. The choice of cut-off points was based on previously reported thresholds (5 min, 6 h, and 23 h),[7,11] thus resulting in multiple cut-off points available for a more complete characterization of the consequences of AF burden. Patients with no AF burden or less than 5 min of AF burden were categorized as not having AF.

During follow-up, patients were considered as having evolved to permanent AF if data from the device showed AF (for at least 23 h) during the last 60 days of the observation period.

Statistical analyses

Baseline patients' characteristics collected in ClinicalService® case report forms have been summarized by gender and compared between groups. Variables on a continuous scale have been described as mean, standard deviation, median and interquartile range, minimum, and maximum, as appropriate, while variables on a categorical scale were presented as counts and percentages. Summary statistics were reported with maximum 2 decimals, as appropriate. Continuous variables were compared using the *t*-test or the non-parametric Mann–Whitney test, as appropriate depending on normality of distributions. Comparisons of categorical variables were performed by means of the Chi-square test or Fisher's exact test for extreme proportions, as appropriate.

The distribution of maximum daily burden of AF per patient and the distribution of the percentage of days with daily AF burden beyond predefined cut-offs per patient were compared between groups by means of the Mann–Whitney test. To analyse the time to first AF, survival analysis was carried out by means of the Kaplan–Meier method. Different curves were compared using the log-rank test. The annual rates of

thromboembolic events were reported [with the 95% Poisson confidence intervals (CI)], and compared between groups using the Negative binomial model to account for over dispersion of the data.

Predictors of thromboembolic events were found between the baseline characteristics and the arrhythmia incidence characterizations during the follow-up (at least one day of daily AF burden beyond pre-defined cut-offs) by means of the Cox regression.

To account for missingness of baseline data and to ensure enough power to our analysis, the strategy of multiple imputation has been chosen. Assuming that observations are missing at random, a fully conditional specification method has been used to impute missing values for all variables listed in *Table 1*. Five multiple imputed datasets have been created and the research of possible predictors has been performed on each of them, combining results using appropriate methods. All the imputed variables have then been tested in univariate Cox regression and those with a univariate *P*-value < 0.15 (together with gender which is associated with the main objective of the analysis) were subsequently put in a multivariate Cox regression to identify independent predictors of event. A complete-case analysis has been performed as sensitivity analysis to confirm results obtained on multiple imputed data.

Analyses were carried out using SAS [version 9.3] and a $P < 0.05$ was considered as statistically significant.

Results

We included 2398 patients, of whom 489 (20.4%) were female and 1909 (79.6%) were male. In *Table 1*, demographics and baseline characteristics are presented, overall and by gender. As expected, ischemic heart disease, previous myocardial infarction (MI) and previous revascularization procedures were more common in male patients. The distribution in categories of $CHADS_2$ score did not show significant differences between male and female patients. The distribution of CHA_2DS_2-VASc score differed between female and male patients, as expected since female gender is a component of this score. The type of implanted device was a biventricular implantable cardioverter defibrillator (ICD) for cardiac resynchronization therapy (CRT) in 75% of cases, with dual chamber ICDs more represented in male than female patients, and dual-chamber pacemakers accounting for $< 10\%$ of cases. The proportion of patients treated with oral anticoagulants (vitamin K antagonists) was 23%, independent of gender. A history of atrial tachyarrhythmias was present in approximately the same proportion.

Stroke and stroke/transient ischemic attack events during follow-up

Patients were followed for a mean follow-up of 43 ± 28 months (42 ± 25 for female and 43 ± 28 for male patients, $P = 0.874$). Median follow-up interquartile range (IQR) was overall 38 (21–59) months, being 39 (22–60) for females and 38 (21–59) for males, respectively.

At the end of the observation period, the proportion of patients treated with an oral anticoagulant (OAC) did not significantly differ between women (99/489 = 20.2%) and men (447/1909 = 23.4%, $P = 0.136$). During the follow-up period, 26 thromboembolic events occurred in 22 patients. As shown in *Table 2*, the incidence rate ratio of both stroke and stroke/TIA demonstrates that the risk was significantly higher in females compared with males.

The results of multivariate Cox regression, that considered imputed data to account for missing baseline data, showed that female gender, as well as history of coronary artery by-pass graft (CABG), were significant independent predictors of stroke (*Table 3*), also after correction for oral anticoagulant agent use. In particular female patients were associated to higher risk of stroke [hazard ratio (HR) = 3.43, 95% CI = 1.05–11.18, $P = 0.041$, compared with male patients] and higher risk of stroke or TIA (HR = 2.65, 95% CI = 1.03–6.80, $P = 0.043$, compared with male patients). A second multivariate model, also including age as a separate variable, confirmed that female patients were associated to a higher risk of stroke or TIA (HR = 2.59, 95% CI = 1.01–6.67, $P = 0.049$, compared with male patients), as shown in Supplementary material online (*Table w1* of the supplementary web-only appendix).

Sensitivity analysis

A complete-case analysis was performed to confirm results obtained on multiple imputed data by applying multivariate Cox regression analysis on collected data, without data imputation. Results are reported in the supplementary appendix (Supplementary material on line, *Table w2*) and confirm the analyses based on imputed data; in particular female patients were associated to higher risk of stroke (HR = 6.53, 95% CI = 1.74–24.55, $P = 0.005$, compared with male patients) and higher risk of stroke or TIA (HR = 5.48, 95% CI = 1.83–16.44, $P = 0.002$, compared with male patients).

Atrial fibrillation burden during follow-up

The proportions of male and female patients achieving different thresholds of maximum daily burden during follow-up are shown in *Table 4*. Overall a daily AF burden of at least 5 min was a common finding, occurring in 44% of patients.

The time to a maximum daily AF burden ≥ 5 min, ≥ 1, ≥ 6, and ≥ 12 h, respectively, is shown, according to gender, in Kaplan–Meier curves of *Figure 1* and indicates that male patients are associated with a higher incidence and an earlier occurrence of daily AF burden durations longer than 6, 12, and 23 h. The time ***to a daily maximum*** AF burden ≥ 23 h, ≥ 7 days, ≥ 30 days and to permanent AF, respectively, is shown, according to gender, in Kaplan–Meier curves shown in *Figure 2*, and shows that attainment of AF burden durations as long as days or weeks, as well as the time to evolution in permanent AF did not differ according to gender.

Data on maximum daily AF burden (in hours) and on the percentage of days with an AF burden higher than specific thresholds (Supplementary material online, *Tables w3* and *w4* of the supplementary web-only appendix) further confirm that the presence and duration of AF found during follow-up in female patients was not higher compared to male patients.

Data on maximum daily AF burden (in hours), on the percentage of patients with an AF burden higher than specific thresholds and on the percentage of days with an AF burden higher than specific thresholds (Supplementary material online, *Table w5* of the supplementary web-only appendix) show that both the incidence of AF longer than specified AF durations and the burden of AF were significantly higher in patients with age ≥ 75 years as compared with younger patients.

Maximum AF burden did not show a significant association with stroke or stroke/TIA at univariate analysis, as shown in Supplementary material online (*Tables w6* and *w7* of the supplementary web-only appendix).

Table 1 Characteristics of the research population at enrolment, according to gender

Variable	Total (*n*=2398)	Women (*n*=489)	Men (*n*=1909)	*P*-value
Age at device implant Median (IQR) (year)	67.0 (60–74)	68.0 (60– 74)	67.0 (60– 74)	0.169
Hypertension *N* (%)	1136 (55.8%)	232 (54.2%)	904 (56.2%)	0.456
Diabetes *N* (%)	483 (23.3%)	91 (20.8%)	392 (24.0%)	0.156
Ischemic heart disease *N* (%)	1164 (49.1%)	126 (26.0%)	1038 (55.0%)	<0.001
Previous MI *N* (%)	991 (41.8%)	102 (21.0%)	889 (47.1%)	<0.001
Previous PTCA *N* (%)	528 (22.0%)	64 (13.1%)	464 (24.3%)	<0.001
Previous CABG *N* (%)	476 (20.6%)	30 (6.3%)	446 (24.3%)	<0.001
Valvular heart disease *N* (%)	387 (16.1%)	83 (17.0%)	304 (15.9%)	0.574
Valvular surgery *N* (%)	202 (8.4%)	38 (7.8%)	164 (8.6%)	0.560
Chronic kidney disease *N* (%)	181 (9.3%)	27 (6.5%)	154 (10.0%)	0.032
COPD *N* (%)	224 (11.5%)	32 (7.7%)	192 (12.5%)	0.006
History of HF *N* (%)	1885 (80.3%)	386 (80.1%)	1499 (80.4%)	0.869
Of ischemic aetiology *N* (%)	814 (34.7%)	88 (18.3%)	726 (38.9%)	<0.001
NYHA class				0.127
I *N* (%)	158 (7.0%)	38 (8.0%)	120 (6.7%)	
II *N* (%)	951 (42.1%)	179 (37.8%)	772 (43.2%)	
III *N* (%)	1111 (49.2%)	246 (51.9%)	865 (48.5%)	
IV *N* (%)	39 (1.7%)	11 (2.3%)	28 (1.6%)	
Previous hospitalizations *N* (%)	790 (42.1%)	164 (41.6%)	626 (42.2%)	0.834
HF hospitalizations *N* (%)	489 (26.1%)	102 (25.9%)	387 (26.1%)	0.934
History of stroke *N* (%)	62 (2.9%)	6 (1.3%)	56 (3.3%)	0.025
History of TIA *N* (%)	44 (2.1%)	12 (2.7%)	32 (1.9%)	0.308
History of Stroke/TIA *N* (%)	101 (4.7%)	18 (4.0%)	83 (4.9%)	0.411
$CHADS_2$ score				0.756
0 *N* (%)	108 (5.8%)	25 (6.3%)	83 (5.7%)	
1 *N* (%)	536 (28.9%)	121 (30.7%)	415 (28.4%)	
2 *N* (%)	671 (36.2%)	138 (35.0%)	533 (36.5%)	
≥ 3 *N* (%)	538 (29.0%)	110 (27.9%)	428 (29.3%)	
CHA_2DS_2-VASc score				<0.001
0 *N* (%)	38 (1.8%)	0 (0.%)	38 (2.3%)	
1 *N* (%)	175 (8.4%)	14 (3.1%)	161 (9.8%)	
2 *N* (%)	346 (16.6%)	70 (15.5%)	276 (16.9%)	
≥ 3 *N* (%)	1527 (73.2%)	367 (81.4%)	1160 (70.9%)	
History of ventricular arrhythmias *N* (%)	881 (37.6%)	119 (25.0%)	762 (40.8%)	<0.001
History of syncope *N* (%)	266 (13.4%)	44 (10.9%)	222 (14.0%)	0.107
History of atrial tachyarrhythmias *N* (%)	544 (22.7%)	109 (22.3%)	435 (22.8%)	0.815
Previous atrial cardioversion *N* (%)	130 (7.4%)	24 (6.6%)	106 (7.6%)	0.522
ECG findings/diagnosis				
LBBB *N* (%)	1306 (57.0%)	289 (61.0%)	1017 (55.9%)	0.047
Third degree AV block *N* (%)	161 (7.2%)	38 (8.2%)	123 (6.9%)	0.335
Sinus node disease *N* (%)	169 (7.4%)	37 (7.8%)	132 (7.2%)	0.655
Echo findings:				
LVEF Median (IQR)	28.0 (24–33)	29.0 (25– 32)	28.0 (24–33)	0.451
LVEF < =0.35 *N* (%)	1645 (87.9%)	338 (88.3%)	1307 (87.8%)	0.824
Type of implanted device				<0.001
DDD/DDDR pacemaker *N* (%)	80 (3.3%)	32 (6.5%)	48 (2.5%)	
Dual-chamber ICD *N* (%)	505 (21.1%)	73 (14.9%)	432 (22.6%)	
CRT-P *N* (%)	37 (1.5%)	10 (2.0%)	27 (1.4%)	
CRT-D *N* (%)	1776 (74.1%)	374 (76.5%)	1402 (73.4%)	
ICD/CRT-D implant for primary prevention *N* (%)	1828 (82.1%)	381 (89.0%)	1447 (80.5%)	<0.001
Pharmacological treatment				
ACE-inhibitor/ARB2 *N* (%)	1759 (81.1%)	347 (80.1%)	1412 (81.3%)	0.569

Continued

Table 1 *Continued*

Variable	Total (n=2398)	Women (n=489)	Men (n=1909)	P-value
Beta-blocker *N* (%)	1697 (78.2%)	352 (81.3%)	1345 (77.5%)	0.085
Diuretic *N* (%)	1819 (83.9%)	372 (85.9%)	1447 (83.4%)	0.195
Amiodarone *N* (%)	524 (24.2%)	77 (17.8%)	447 (25.7%)	<0.001
Anti-platelet *N* (%)	1047 (48.3%)	178 (41.1%)	869 (50.1%)	<0.001
OAC *N* (%)	503 (23.2%)	100 (23.1%)	403 (23.2%)	0.958
OAC/anti-platelet *N* (%)	1457 (67.2%)	264 (61.0%)	1193 (68.7%)	0.002

For each patient, characteristic percentages are estimated on patients with collected data for that characteristic.
IQR, interquartile range; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HF, heart failure; NYHA, New York Heart Association; TIA, transient ischemic attack; ECG, electrocardiogram; LBBB, left bundle branch block; AV, atrio ventricular; LVEF, left ventricle ejection fraction; DDD, dual chamber pacing; DDDR, dual chamber pacing with rate response; CRT-P, cardiac resynchronization pacemaker; CRT-D, cardiac resynchronization defibrillator; ACE, angiotensin-converting-enzyme; ARB2, angiotensin II receptor blockers; OAC, oral anticoagulant.

Table 2 Stroke and TIA events during follow-up according to gender

Variable	Women	Men
Stroke	5/489 (1.02%)	10/1909 (0.52%)
Stroke/TIA	8/489 (1.64%)	14/1909 (0.73%)
Exposure time (years)	1714	6844
Rate of stroke per 100 pt/year (95% CI)	0.29 (0.12–0.70)	0.15 (0.08–0.27)
Rate of stroke/TIA per 100 pt/year (95% CI)	0.47 (0.23–0.93)	0.26 (0.17–0.42)
Incidence rate ratio female/male for stroke (95% CI)	2.00 (1.53–2.61) P<0.001	
Incidence rate ratio female/male for stroke/TIA (95% CI)	1.77 (1.37–2.31) P<0.001	

CABG, coronary artery bypass graft; CI, confidence interval; TIA, transient ischemic attack.

Discussion

Our research conducted in patients implanted with a CIED allowing continuous monitoring of atrial rhythm, demonstrated that females have an increased risk of stroke and TIAs during follow-up, but this increased risk cannot be ascribed to a higher burden of AF. Moreover, an AF burden of at least 5 min is a common finding in patients implanted with a CIEDS, in whom the amount of time spent in AF can be precisely quantified by means of continuous monitoring of atrial rhythm.

Since AF is frequently asymptomatic[14,15] and differences in the ratio of asymptomatic to symptomatic AF episodes have been reported in relation to gender,[15,16] use of device-measured AF burden appears an appropriate method to investigate the relationship between AF disease burden and the risk of stroke/TIA events. The ASSERT study found that device detected AF lasting at least 6 min in duration was associated with a 2.5 fold increase in the risk of ischemic stroke or systemic embolism over a follow-up of 2.5 years.[6] Other studies have evaluated the relationship between device-detected AF burden and the risk of stroke and thromboembolism,[5,10] but the relationship between AF burden and gender has not been reported.

Female gender is a risk factor for stroke in AF patients not taking oral anticoagulants, although there is an age-dependency to this risk.[16] Even if oral anticoagulants are highly effective in reducing the risk of stroke, some residual risk persists and female gender is among the factors predictive of the risk of stroke even despite warfarin treatment.[17] In the meta-analysis by Wagstaff *et al.*[3] based on 5 randomized-controlled trials and 12 prospective observational studies, women with AF were at increased risk of stroke, particularly women aged ≥75 years, and the relative increase in risk of stroke appeared similar regardless of oral anticoagulation.

The reasons predisposing to an increased risk of stroke in female patients are still object of debate and a series of factors have been considered as contributing to the risk of thromboembolism (co-morbidities, hormonal effects, endothelial dysfunction, and prothrombotic factors).[3] Many factors are involved in the process of thrombogenesis in AF and can be studied through assessment of a series of biomarkers.[19,20] In a previous study that assessed both burden and biomarkers of thrombogenesis, but did not report on stroke events, gender was not significantly associated with blood markers for the hypercoagulable state and blood markers were not correlated to an increasing amount of AF burden.[20]

Although assessment of the risk of stroke is based on clinical risk factors, previous studies found that integration of clinical data with AF presence/duration/burden may improve risk stratification, thus providing additional tools on clinical decision making on prescription of anticoagulants.[7,11,21] The impact of anticoagulation therapy on stroke and thromboembolism, in relation to device detected AF burden, in combination with clinical risk stratification will be prospectively addressed by controlled trials.[21] Anyway the determinants of stroke are complex and it is noteworthy that CHA_2DS_2-VASC and $CHADS_2$ scores predict risk of stroke or death in elderly patients with implanted pacemakers even regardless of AF history.[21]

Table 3 Predictors of stroke and stroke or TIA at univariate and multivariate Cox regression analysis

	Cox Regression—Stroke						Cox Regression—Stroke or TIA					
	Univariate model			Multivariate model			Univariate model			Multivariate model		
Variable	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Women	1.94	0.66–5.66	0.228	3.43	1.05–11.18	0.041	2.28	0.96–5.45	0.063	2.65	1.03–6.80	0.043
Age ≥75 years	1.93	0.66–5.65	0.233				2.25	0.94–5.37	0.069			
Stroke/TIA history	3.38	0.76–15.04	0.110	3.59	0.81–16.03	0.094	2.22	0.52–9.51	0.285			
$CHADS_2 \geq 3$	1.77	0.58–5.45	0.317				1.90	0.78–4.65	0.158			
$CHA_2DS_2VASc \geq 3$	2.83	0.62–13.00	0.183				2.93	0.85–10.13	0.091	2.20	0.61–7.90	0.229
Chronic kidney disease	0.77	0.10–5.84	0.798				0.87	0.12–6.32	0.889			
COPD	3.30	1.00–10.91	0.052	3.32	0.98–11.29	0.056	2.18	0.71–6.64	0.173			
History of ventricular tachyrrhythmias	0.57	0.18–1.79	0.335				0.58	0.23–1.49	0.258			
History of AT/AF	1.31	0.42–4.11	0.647				1.36	0.53–3.47	0.526			
NYHA 3-4	0.91	0.33–2.51	0.855				1.30	0.55–3.06	0.550			
Ischemic heart disease	3.03	0.96–9.50	0.058				1.89	0.79–4.51	0.151			
Dilated cardiomyopathy	1.47	0.33–6.52	0.612				1.45	0.43–4.90	0.550			
CABG	3.38	1.23–9.32	0.019	4.34	1.44–13.13	0.009	1.36	0.53–3.48	0.081	2.47	0.96–6.36	0.062
PTCA	1.32	0.42–4.14	0.637				2.17	0.91–5.18	0.519			
Amiodarone	1.15	0.36–3.60	0.815				0.91	0.33–2.46	0.846			
Other AAD	1.09	0.35–3.43	0.880				0.86	0.32–2.35	0.774			
Digioxin	2.87	0.98–8.40	0.055				2.14	0.83–5.46	0.114			
Anti-platelet	1.04	0.37–2.92	0.941				0.83	0.35–1.99	0.680			
OAC	2.21	0.77–6.40	0.143				1.92	0.78–4.72	0.158			
OAC/anti-platelet	2.21	0.62–7.84	0.221				1.50	0.58–3.84	0.401			
At least 1 day with AF daily burden ≥ 5 minutes	0.82	0.29–2.31	0.707				1.79	0.76–4.19	0.180			
At least 1 day with AF daily burden ≥ 1 hour	1.21	0.43–3.40	0.717				1.53	0.66–3.54	0.322			
At least 1 day with AF daily burden ≥ 6 hours	1.38	0.47–4.03	0.559				1.59	0.67–3.80	0.294			
At least 1 day with AF daily burden ≥ 12 hours	1.31	0.42–4.11	0.646				1.36	0.53–3.48	0.522			
At least 1 day with AF daily burden ≥ 23 hours	1.17	0.33–4.15	0.807				1.40	0.51–3.79	0.513			
At least 7 consecutive days with AF daily burden ≥ 23 hours	1.07	0.24–4.75	0.929				0.70	0.16–3.01	0.633			
At least 30 consecutive days with AF daily burden ≥ 23 hours	0.63	0.08–4.77	0.652				0.42	0.06–3.13	0.398			
At least 60 consecutive days with AF daily burden ≥ 23 h	0.77	0.10–5.85	0.799				0.51	0.07–3.82	0.515			
Maximum Daily Burden	1.01	0.96–1.07	0.593				1.02	0.98–1.06	0.358			

PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; AT, atrial tachycardia or atrial flutter; AF, atrial fibrillation; HF, heart failure; NYHA, New York Heart Association; TIA, transient ischemic attack; AAD, antiarrhythmic drug; OAC, oral anticoagulation.

Table 4 Proportion of patients with at least 1 day during follow-up with daily AF burden beyond specified thresholds of AF burden duration

Variable	Overall (*n*=2398)	Women (*n*=489)	Men (*n*=1909)	*P*-value
At least 1 day with AF daily burden ≥ 5 min	43.7% (1049)	40.7% (199)	44.5% (850)	0.128
At least 1 day with AF daily burden ≥ 1 h	35.3% (846)	31.5% (154)	36.2% (692)	0.050
At least 1 day with AF daily burden ≥ 6 h	27.1% (649)	22.5% (110)	28.2% (539)	0.011
At least 1 day with AF daily burden ≥ 12 h	22.5% (540)	18.6% (91)	23.5% (449)	0.020
At least 1 day with AF daily burden ≥ 23 h	18.2% (436)	14.1% (69)	19.2% (367)	0.009
At least 7 consecutive days with AF daily burden ≥ 23 h	13.3% (319)	11.2% (55)	13.8% (264)	0.134
At least 30 consecutive days with AF daily burden ≥ 23 h	10.7% (257)	8.8% (43)	11.2% (214)	0.123
Chronic permanent AF	5.5% (132)	4.3% (21)	5.8% (111)	0.189

AF, atrial fibrillation.

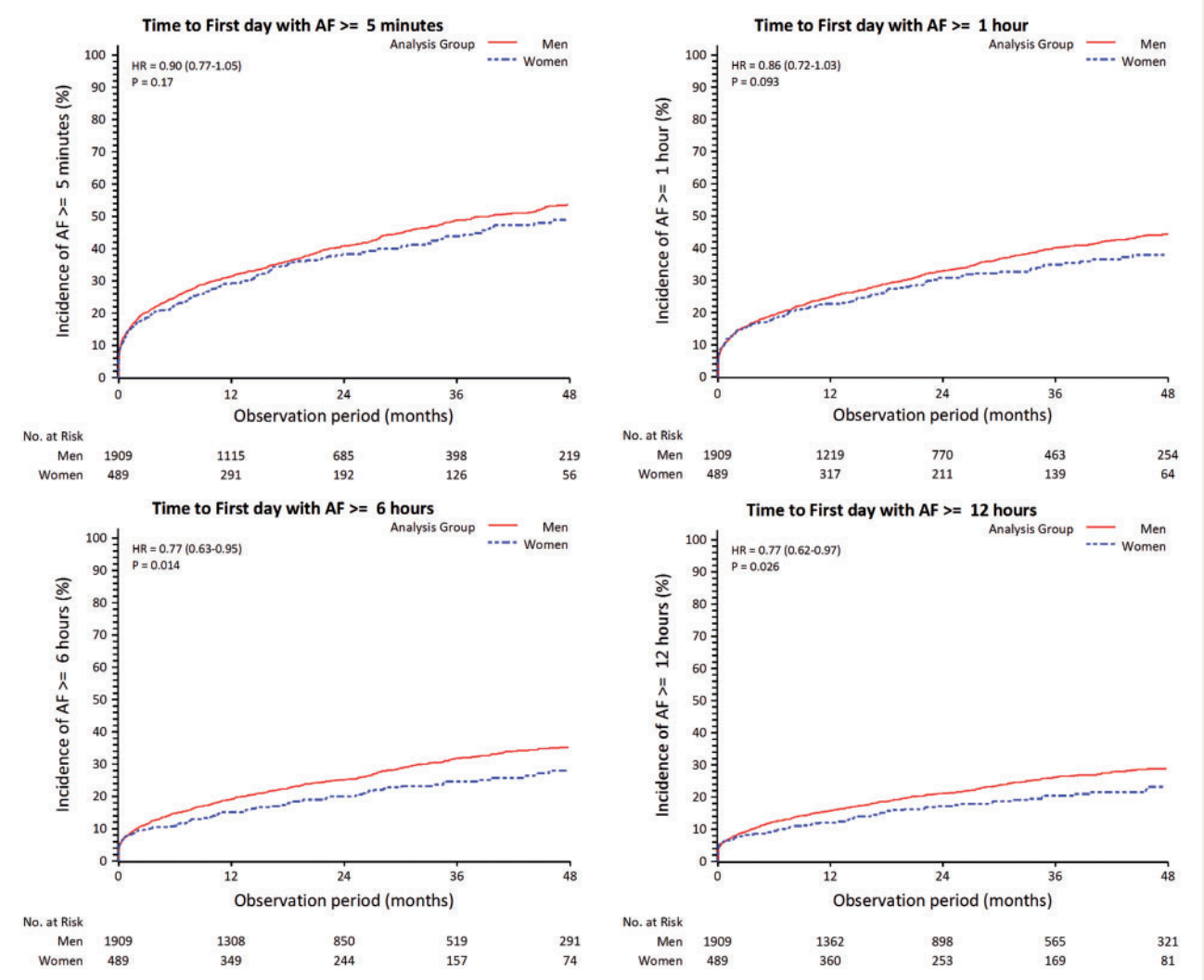

Figure 1 Time to first day with a maximum daily AF burden ≥ 5 min, ≥ 1, ≥ 6, and ≥ 12 h, according to gender.

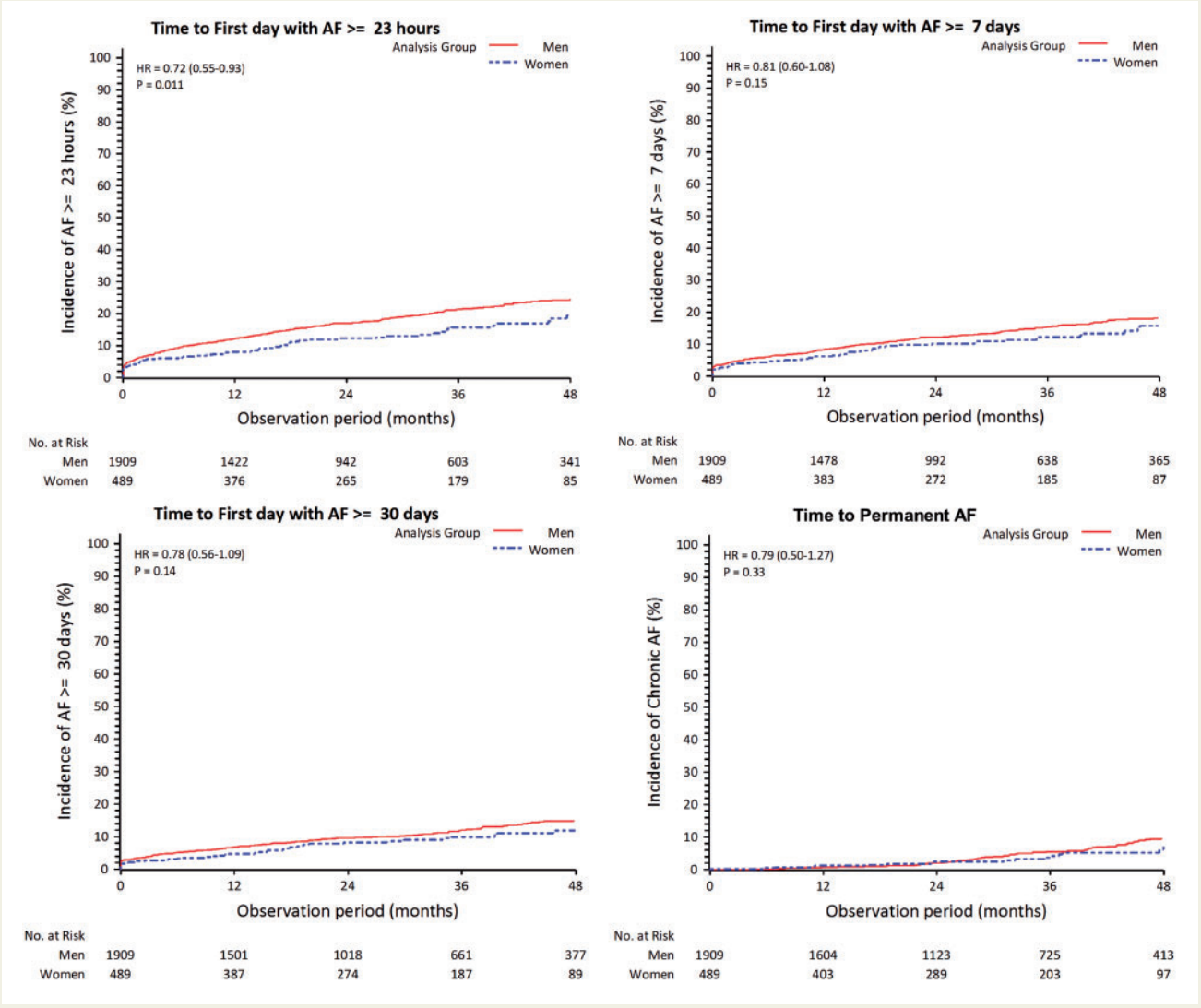

Figure 2 Time to attainment of an AF burden duration $\geq$ 23 h, $\geq$ 7 days, $\geq$ 30 days and to permanent AF according to gender.

In our research, an AF burden of at least 5 min was found in 44% of patients during follow-up and this stresses that device-detected AF is a common finding in CIED patients, even independently on previous history of AF. In literature, both prevalence and incidence of device detected atrial tachyarrhythmias are variable, depending on underlying heart disease, indication to device implant, time of observation, and previous history of clinically overt AF. In the ASSERT study, subclinical atrial tachyarrhythmias with at least 6 min duration were detected within 3 months in around 10% of patients implanted with a CIED[6] and in a 2.5-year follow-up additional subclinical atrial tachyarrhythmias occurred in around 25% of patients, with around 16% patients developing a symptomatic AF.[6]

As mentioned, several studies have found a significant association between device-detected AF burden and the risk of stroke and thromboembolism.[5–6,11] According to us, the observation that female CIED patients had a higher stroke risk compared with male subjects, but not a higher AF burden, did not necessarily contradict the positive relationship between AF burden and stroke frequently reported in the literature. Indeed we know that stroke risk cannot only and simply be associated to AF burden but rather to many clinical aspects, such as patient status and comorbidities, left atrium electrical and structural remodelling, and also other unknown factors.

The present research reflects real life and is related to patients implanted with a CIED and with history of heart failure in the large majority of cases. In view of the characteristics of this analysis, some limitations are evident, conditioning potential residual confounding. The absolute event rate of ischemic stroke was low, probably reflecting a general trend towards lower rates of strokes and TIAs as compared to those predicted by $CHADS_2$ scores. The risk of ischemic stroke can be reduced by the use of anticoagulants, but we accounted for use of anticoagulants in our multivariable model. The diagnosis of TIA and stroke was that of daily clinical practice, in line with the observational nature of this research.

Conclusions

In a population of patients implanted with a CIED, an AF burden of at least 5 min is a common finding, occurring in 44% of patients. Females with a CIED have a risk of stroke and TIAs during follow-up that is around two-fold that of males, but this increased risk cannot be ascribed to a higher burden of AF or to differences in the evolution to permanent AF. Further studies are needed in order to evaluate the reasons for the increased risk of stroke and TIA associated with female gender in subjects with AF.

Supplementary material

Supplementary material is available at *Europace* online.

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