Journal of Interventional Cardiac Electrophysiology (2019) 56:9–18
https://doi.org/10.1007/s10840-019-00601-3

Sex effect on efficacy of pulmonary vein cryoablation in patients with atrial fibrillation: data from the multicenter real-world 1STOP project

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Received: 13 February 2019 / Accepted: 22 July 2019 / Published online: 26 August 2019

Abstract

Purpose Pulmonary vein isolation (PVI) using cryoablation (PVI-C) is a widespread therapy for treating symptomatic, recurrent atrial fibrillation (AF). The impacts of sex on efficacy and safety of PVI-C in a real-world clinical practice is lacking. In a multicenter prospective project, we evaluated whether clinical characteristics, procedure parameters, procedural complications, long-term AF recurrence rates, and/or AF-related symptoms differed according to sex in patients treated with PVI-C.

Methods Data from the study population were collected in the framework of the 1STOP ClinicalService® project, involving 47 Italian cardiology centers. Multivariable statistical analyses were conducted to determine if any baseline clinical characteristics impacted the efficacy of PVI-C.

Results From April 2012, 2125 patients (27% female, 59 ± 11 years, 73% paroxysmal AF, and mean left atrial diameter = 42 ± 8 mm) underwent PVI-C. According to baseline characteristics, women were more likely to be older, with higher clinical risk scores (e.g., CHA_2DS_2-VASc), and a higher number of tested antiarrhythmic drugs before the index PVI-C procedure. Male and female cohorts showed comparable procedure time (mean = 107.7 ± 46.8 min) and a similar incidence of periprocedural complications (4.5% overall), even after adjustment for baseline characteristics ($P = 0.880$). The multivariable analyses demonstrated that the strongest predictor of AF recurrences was sex (0.74; 95% CI 0.58–0.93; $P = 0.011$). After propensity score adjustment, the hazard ratio from a multivariable model, which included age and AF type (persistent) as covariates, was 0.76 (0.60–0.97) ($P = 0.025$).

Conclusions According to the 1STOP project, in a real-world setting, PVI-C was relatively safe regardless of the patient's sex; however, when considering efficacy of the procedure, female patients had a lower long-term efficacy in comparison to males.

Clinical trial registration NCT01007474

Keywords Atrial fibrillation · Catheter ablation · Cryoablation · Cryoballoon

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1 Introduction

Several clinical trials have demonstrated that pulmonary vein isolation (PVI) by cryoablation (PVI-C) is a reliable, targeted therapy to treat patients with drug refractory symptomatic atrial fibrillation (AF), both persistent and paroxysmal forms [1–7]. Also, sex differences in the AF epidemiology, clinical management, therapeutic treatment, and efficacy have been described [8–13]. Particularly, female sex was independently associated with atrial arrhythmia recurrence in a cohort of 750 patients treated by PVI method for paroxysmal AF in the FIRE AND ICE Trial [13].

Since 2012, 47 cardiology centers have been prospectively collecting clinical data from patients whom underwent PVI-C according to typical clinical practice. Clinical information, procedures, and outcomes were stored in a large cardiovascular data repository [6, 14]. The aim of this research was to assess sex differences during PVI-C with regard to overall procedural safety, acute procedural characteristics, and long-term efficacy in a large multicenter series of patients.

2 Methods

Since September 2012, all patients who underwent PVI-C using the second-generation cryoballoon (Arctic Front Advance Cardiac CryoAblation Catheter System; Medtronic Inc., Minneapolis, MN, USA) and who were followed at any of the 47 Italian cardiology centers since their participation in the 1STOP project were included in the analysis. The 1STOP project is a part of a larger Italian medical care research study, The Italian ClinicalService Project (NCT01007474) which is a clinical data repository for an integrated network consortium of Italian cardiac hospitals with the shared goal of evaluating and improving the usage of Medtronic medical therapies in clinical practice through the mutual collection, examination, and analysis of pooled data. In this project, an independent scientific committee of physicians prospectively identifies key clinical questions on a yearly basis for analysis and dissemination. A charter assigns the ownership of data to the centers and governs the conduct and relationship of the scientific committee and Medtronic. Medtronic did not have any role in identifying research objectives, interpreting results, or drafting the manuscript [6, 14].

At each center, the project was approved by the institutional review board and local ethics committees and conforms to the principles outlined in the Declaration of Helsinki. Each patient included in the 1STOP project provided informed consent for data collection and analysis. Data collection was performed prospectively, while data analyses regarding the specific objectives presented in this manuscript were performed retrospectively on endpoints that were prespecified before access to any clinical or device data were obtained.

Baseline visit recordings included the collection of demographic data, clinical patient history, AF history, AF-related symptoms, 12-lead ECG, and cardiovascular medications. No standardized protocol for PVI-C was shared with the participating centers; however, standardized procedural data were collected, including procedural times, number of freeze applications, nadir temperatures, devices used, number of treated pulmonary veins (PVs), adverse events, and periprocedural complications. Follow-up visits were scheduled at 3-month intervals during the first year and every 6 months thereafter. Although the follow-up visits were conducted according to the "standard-of-care" clinical practice(s) at each center, uniform collection methods were used to gather data (including the collection of AF-related symptoms, 12-lead ECG, 24-h Holter, and 7-day Holter). In 190 (8.9%) patients, an implantable loop recorder was used to monitor the AF recurrence during follow-up. Out of these 190 patients, 45 were implanted in the 3 months before the ablation procedure. Also, the presence of any new adverse event(s) was recorded during each follow-up visit. Pseudonymized data were entered into an electronic database by trained and qualified personnel at each center.

The following AF-related symptoms collected at baseline and follow-up included palpitations, weakness, fatigue, dizziness, and shortness of breath, and patients were also scored via the EHRA classification. AF recurrence was defined as an ECG documented episode of AF or atrial tachycardia lasting at least 30 s. Since antiarrhythmic drug (AAD) management following PVI-C was performed according to each center's clinical practice rather than a standardized protocol, we analyzed long-term AF recurrence(s) regardless of the usage of AADs. Using a landmark 90-day blanking period, recurrences of any atrial arrhythmia within the first 3 months after the index PVI-C procedure were not considered as failures.

2.1 Statistical analysis

Descriptive statistics were used to summarize patient characteristics. Continuous variables were reported using mean and standard deviation, minimum and maximum value, and median with the interquartile range. Categorical variables were given as counts and percentages. Comparisons between groups were performed using the Wilcoxon signed-rank test for continuous variables, while comparisons of categorical variables were performed by means of the chi-square test or Fisher's exact test for extreme proportions, as appropriate. Statistical tests were based on a two-sided significance level of $P < 0.05$.

Clinical outcomes evaluated during the follow-up consisted of AF recurrences and repeat ablations, both considered as single outcomes. Moreover, we assessed "time-to-first" event by means of Kaplan-Meier estimate. The Breslow method was used, and the groups were compared by means of the Wilcoxon signed-rank test. AF recurrences within the first 90 days following an index procedure were not counted as failure event(s). Furthermore, to specifically evaluate longer term efficacy, a second landmark analysis for AF recurrence after 6 months was employed as a secondary endpoint to evaluate survival probabilities during the 6- to 36-month follow-up period.

The annual rates of complications were reported with 95% Poisson confidence intervals. The Poisson regression model was used to calculate the incidence rate ratio (IRR), with the d-scale option. An IRR < 1 showed a lower incidence of event in the male group, while an IRR > 1 showed a higher incidence of event in the male group. A logistic multivariable model was utilized to adjust procedural complications' occurrence. Covariates included in the model selection process were those resulted significant in univariate cox analysis. Stepwise model selection entry criterion = 0.05 was used in this model. Since the number of AF recurrences per patient during follow-up was not available, only the survival analysis was performed for this endpoint. To find predictors for AF recurrences, a Cox regression model was utilized for both univariate and multivariable analyses, and the model fit statistics were reported. Parameters that resulted with a $P < 0.10$ in univariate evaluation were analyzed also in a multivariable model, with a backward selection. Under multivariable analysis, a baseline characteristic remained significant if $P < 0.05$ was achieved. To account for differences in baseline characteristics between men and women, propensity score (PS) methods were utilized to estimate an adjusted HR for efficacy between men and women. The PS method was used to adjust the group's HR in multivariable Cox analysis; the Cox multivariable model included propensity score (as a continuous variable), age, and AF type as covariates in the model. The SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA), was used to perform statistical analyses.

3 Results

During this 1STOP analysis, 2125 patients who underwent an index PVI-C were collected and followed; 584 patients (27%) were female and 1541 (73%) were male. Baseline characteristics are described in Table 1. Compared to males, female patients were more likely to be older (62.4 ± 9.9 vs. 58.8 ± 10.6; $P < 0.001$), to have higher clinical risk scores (e.g., CHA_2DS_2-VASc, valve disease, and number of tested AADs), and to have higher EHRA scores. Males were more likely to have ischemic cardiomyopathy, persistent AF, and larger left atrial dimensions. Importantly, between male and female cohorts, no differences were observed in the duration of time from first AF diagnosis until the time of index PVI-C, which was approximately an average of 4 years ($P = 0.885$).

3.1 Clinical outcomes: procedural data and complications

Procedure data and periprocedural complications are shown in Tables 2 and 3, respectively. The mean procedure duration was 108 min, including a mean procedure time of 109 min in the male cohort and 105 min in the female group ($P = 0.062$). Mean cryoablation time was 23.5 min (24.0 min in males and 22.5 min in females; $P = 0.031$). Overall, 7946/8186 (97.1%) of PVs were isolated with the cryoballoon alone. In 60 veins, focal radiofrequency touch-up lesions were applied to achieve acute PVI, with no differences between the two groups ($P = 0.744$). Ultimately, 8006/8186 (97.8%) PVs were acutely isolated. In the overall population, 95 (4.5%) patients experienced a periprocedural complication with no difference between the two groups ($P = 0.497$). The rate of periprocedural complications remained not different between groups when the comparison was adjusted for all differences in baseline characteristics ($P = 0.880$; Table 3). The incidence of complications was primarily driven by transient diaphragmatic nerve paralysis (41 patients, 29 (1.9%) males and 12 (2.1%) females; $P = 0.796$). Additionally, slight differences occurred in pericardial effusions, six patients including one (0.1%) in male group and five (0.9%) in female group ($P = 0.002$). Cardiac tamponade (with no surgical correction) occurred in another six patients with two (0.1%) in the male group and four (0.7%) in the female cohort ($P = 0.052$).

3.2 Clinical outcomes: long-term efficacy and predictors of AF recurrence

The mean follow-up of the population was 16.8 ± 13.9 months (minimum follow-up duration was 1 month; maximum follow-up duration was 73 months) with no difference in follow-up duration between genders. During follow-up, 535 (25.2%) patients had at least one AF recurrence episode, including 378 (24.5%) in the male group and 157 events (26.9%) in female cohort. The annual rate of AF recurrence (per 100 patients) was 20.5 (95% CI 17.5–24.1) for females and 18.1 (95% CI 16.4–20.1) for males. Figure 1a depicts the Kaplan-Meier survival curve for AF recurrence. Additionally, a landmark analysis for later-term AF recurrences manifesting at 6 months and beyond was performed. In this analysis, the unadjusted cumulative AF recurrence was significantly higher in the female cohort

Table 1 Baseline characteristics of the population of patients according to sex with statistical tests for significant differences between males and females. Number in parenthesis given as a division formula when full cohort number was not used

Baseline characteristics	Total ($N = 2125$)	Male ($N = 1541$)	Female ($N = 584$)	P value
Age (years)	59.8 ± 10.6	58.8 ± 10.6	62.4 ± 9.9	< 0.001
Body mass index	27.1 ± 4.1	27.1 ± 3.6	27.1 ± 5.2	0.037
Weight (kg)	81.7 ± 14.3	85.1 ± 12.7	72.8 ± 14.5	< 0.001
Height (cm)	173.5 ± 9.1	177.1 ± 7.2	164.0 ± 6.5	< 0.001
AF-related symptoms	91.9% (1953)	91.5% (1410)	93.0% (543)	0.264
EHRA score	1.9 ± 0.7	1.8 ± 0.7	1.9 ± 0.7	0.010
Type of atrial fibrillation				
Paroxysmal	72.5% (1541)	70.8% (1091)	77.1% (450)	0.016
Persistent	24.6% (523)	26.2% (403)	20.5% (120)	
Long-standing	2.9% (61)	3.0% (47)	2.4% (14)	
Time from AF diagnosis to ablation (months)	52.1 ± 77.7	51.8 ± 65.0	52.8 ± 104.3	0.885
Number of failed AADs ≥ 2	46.7% (992)	44.1% (679)	53.6% (313)	< 0.001
History of stroke/TIA	4.7% (100)	4.3% (66)	5.8% (34)	0.148
Cardiac insufficiency	4.4% (93)	4.8% (74)	3.3% (19)	0.138
Hypertension	50.0% (1062)	49.6% (764)	50.7% (298)	0.647
Any valve disease	5.9% (125)	5.1% (78/1520)	8.2% (47)	0.007
Any other CV disease	3.8% (81)	4.1% (63)	3.1% (18)	0.312
CHA_2DS_2-VASc score				
0	22.0% (467)	30.7% (467)	0.0% (0/528)	< 0.001
1	30.8% (654)	33.1% (510)	24.8% (144)	
2	25.3% (538)	23.2% (355)	30.7% (183)	
3	14.3% (304)	9.6% (148)	26.3% (156)	
4	5.3% (113)	2.3% (35)	13.1% (78)	
≥ 5	2.2% (47)	1.1% (17)	5.1% (30)	
CHA_2DS_2-VASc (female hard coding)*				
0	29.0% (616)	30.7% (473)	24.8% (143)	< 0.001
1	23.9% (506)	33.1% (506)	0.0% (0)	
2	25.3% (538)	23.2% (358)	30.7% (181)	
3	14.3% (305)	9.6% (148)	26.2% (153)	
4	5.3% (113)	2.3% (38)	13.1% (77)	
≥ 5	2.2% (47)	1.1% (18)	5.1% (29)	
$CHADS_2$ score				
0	43.1% (916)	43.2% (666)	42.8% (250)	0.148
1	41.3 (877)	42.4% (653)	38.5% (224)	
2	11.3% (240)	10.3% (159)	13.9% (81)	
3	3.4% (71)	3.3% (50)	3.5% (21)	
≥ 4	1.0% (21)	0.9% (13)	1.3% (8)	
Diabetes	5.4% (115)	5.6% (86)	4.8% (29)	0.449
Chronic renal insufficiency	2.5% (53)	2.5% (38)	2.4% (15)	0.839
Ischemic cardiomyopathy	6.1% (129)	7.5% (115)	2.3% (14)	< 0.001
Hypertensive cardiomyopathy	17.4% (369)	17.9% (275)	16.1% (94)	0.337
Primitive cardiomyopathy	3.7% (78)	3.9% (60)	3.1% (18)	0.399
Left atrial measurement				
Diameter (mm)	42.1 ± 8.3	42.6 ± 5.9	40.8 ± 12.2	< 0.001
Indexed diameter (mm/m^2)	23.1 ± 5.2	22.5 ± 3.4	24.6 ± 7.9	< 0.001
Area (cm^2)	22.1 ± 6.2	22.7 ± 6.6	20.8 ± 4.9	< 0.001
Indexed area (cm^2/m^2)	12.1 ± 3.4	12.0 ± 3.6	12.5 ± 3.0	< 0.001
Volume (cm^3)	68.0 ± 26.3	71.1 ± 25.9	60.5 ± 26.0	< 0.001
Indexed volume (cm^3/m^2)	37.2 ± 14.3	37.2 ± 13.3	37.3 ± 16.7	0.647

Data are presented as mean ± standard deviation or percentage with count number in parenthesis

*Female hard coding ChadsVasc score has been calculated as the standard ChadsVasc score, with the following exception: when a female patient had no other risk factors, the total score has been considered = 0

Table 2 Procedure characteristics of the male sex cohort, female sex cohort, and total population

Procedural characteristics	Total (*N* = 2125)	Male (*N* = 1541)	Female (*N* = 584)	*P* value
Procedure duration (min)	107.7 ± 46.8	108.7 ± 47.2	105.3 ± 45.9	0.062
Fluoroscopy duration (min)	29.5 ± 29.2	29.9 ± 33.0	28.4 ± 5.5	0.308
Acute success rate*	97.8% (8006/8186)	97.7% (5804/5939)	98.0% (2202/2247)	0.457
Cryoballoon 23 mm	2.5% (53)	1.8% (28)	4.3% (25)	0.002
Cryoballoon 28 mm	98.1% (2072)	98.7% (1513)	96.6% (559)	0.002
Left superior pulmonary vein				
Number of ablations	1.5 ± 5.4	1.6 ± 6.4	1.4 ± 0.8	0.470
Time-to-isolation (s)	59.6 ± 53.1	60.8 ± 56.9	56.8 ± 42.8	0.503
Left inferior pulmonary vein				
Number of ablations	1.3 ± 1.3	1.3 ± 1.5	1.3 ± 0.6	0.025
Time-to-isolation (s)	61.6 ± 56.9	63.7 ± 60.0	55.8 ± 46.8	0.247
Right superior pulmonary vein				
Number of ablations	1.2 ± 1.6	1.2 ± 1.9	1.3 ± 0.5	0.531
Time-to-isolation (s)	59.5 ± 61.2	61.0 ± 64.8	55.8 ± 51.4	0.979
Right inferior pulmonary vein				
Number of ablations	1.2 ± 1.5	1.2 ± 1.7	1.2 ± 0.5	0.011
Time-to-isolation (s)	70.4 ± 73.7	73.6 ± 76.3	61.9 ± 65.7	0.046
Followed with implantable loop recorder	8.9% (190)	9.2% (142)	8.2% (48)	0.473

Data are presented as mean ± standard deviation or percentage with count number in parenthesis

*Acute success rate = total isolated pulmonary veins/total targeted pulmonary veins with the cryoballoon alone

compared to the male group (Fig. 1b). The 2-year survival probability was 65.2% (95% CI 58.5–71.1) in the female group as compared with 71.0% (95% CI 67.2–74.5) in the male group ($P = 0.002$).

During the follow-up visits, 620 (29.2%) patients reported at least one symptom related to AF: 425 (27.6%) male patients and 195 (33.4%) female patients, $P = 0.009$. Figure 2 presents the freedom from ECG documented AF combined with freedom from AF-related symptoms reported by patients without ECG documentation from time of ablation (without the 3-month blanking period). At 12-month follow-up, the EHRA score for the male group was 1.1 ± 0.4 and was 1.2 ± 0.4 ($P = 0.370$) for the female group. During the follow-up, 132 (6.2%) patients had 141 repeat ablations. Of the repeat ablation procedures, 36 (6.1%) female

Table 3 Periprocedural complications in the male sex cohort, female sex cohort, and total population

Complications	Total (*N* = 2125)	Male (*N* = 1541)	Female (*N* = 584)	*P* value
Patients with at least one complication	4.5% (95)	4.3% (66)	5.0% (29)	0.497*
Diaphragmatic paralysis (total events)	2.0% (42)	1.9% (29)	2.2% (13)	0.603
Permanent	0.0% (1)	0.0% (0)	0.2% (1)	0.275
Transient	1.9% (41)	1.9% (29)	2.1% (12)	0.796
Pericardial effusion	0.3% (6)	0.1% (1)	0.9% (5)	0.002
Arteriovenous fistula	0.2% (5)	0.3% (4)	0.2% (1)	1.000
Cardiac tamponade	0.3% (6)	0.1% (2)	0.7% (4)	0.052
Pneumothorax or hemothorax	0.0% (0)	0.0% (0)	0.0% (0)	1.000
Femoral pseudo-aneurism	0.1% (3)	0.1% (2)	0.2% (1)	1.000
Stroke	0.0% (0)	0.0% (0)	0.0% (0)	1.000
Transient ischemic attack	0.0% (1)	0.1% (1)	0.0% (0)	1.000
Pulmonary vein stenosis	0.0% (0)	0.0% (0)	0.0% (0)	1.000
Hematoma	0.4% (9)	0.5% (8)	0.2% (1)	0.270
Other complication(s)	1.3% (28)	1.5% (23)	0.9% (5)	0.251

Data are presented as mean ± standard deviation or percentage with count number in parenthesis

*The *P* value adjusted for all baseline differences was $P = 0.880$

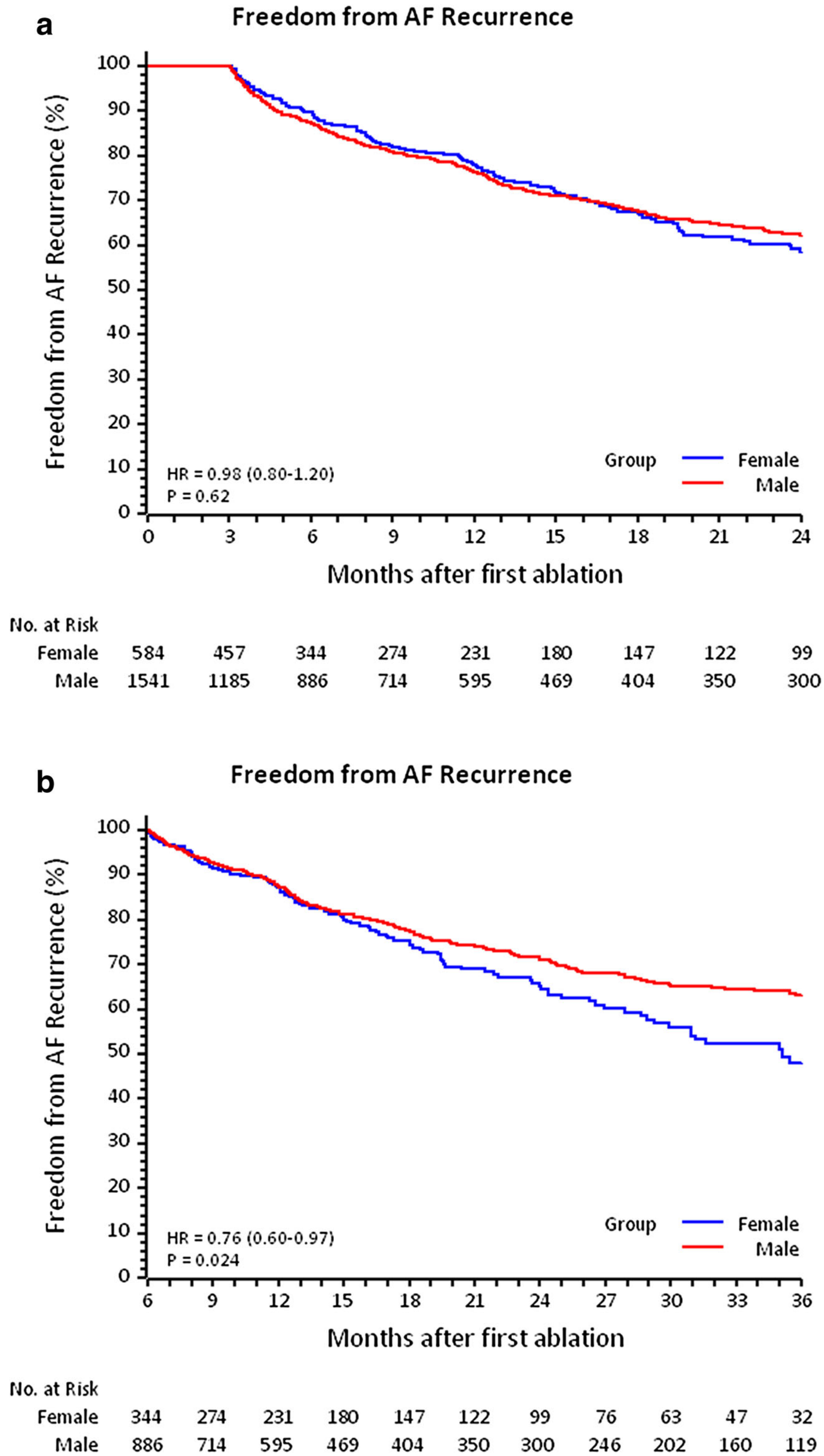

Fig. 1 Freedom from atrial fibrillation (AF) recurrence. **a** The analysis of "time-to-first" event of AF recurrence was described by means of the Kaplan-Meier curves (Breslow's method) and compared between the groups by means of the Wilcoxon test. **b** Depicts the landmark analysis for AF recurrences at 6 months via the Kaplan-Meier curves and survival probabilities during the period of 6–36 months

patients underwent 36 re-do procedures and 96 (6.2%) male patients underwent 105 re-do procedures. Of note, eight repeat procedures were performed 36 months after the index procedure. Most patients who were indicated for a repeat ablation suffered from recurrence of atrial fibrillation, while 5 (3.7%) patients recurred with atrial flutter (4 (4.1%) male patients, 1(2.7%) female patients, $P = 0.729$). No difference in the annual rate of repeat ablation was found between the two groups (IRR = 1.06 (95% CI 0.85–1.31); $P = 0.604$).

Variables associated with an increased AF recurrence rate on univariate analysis were further evaluated in a

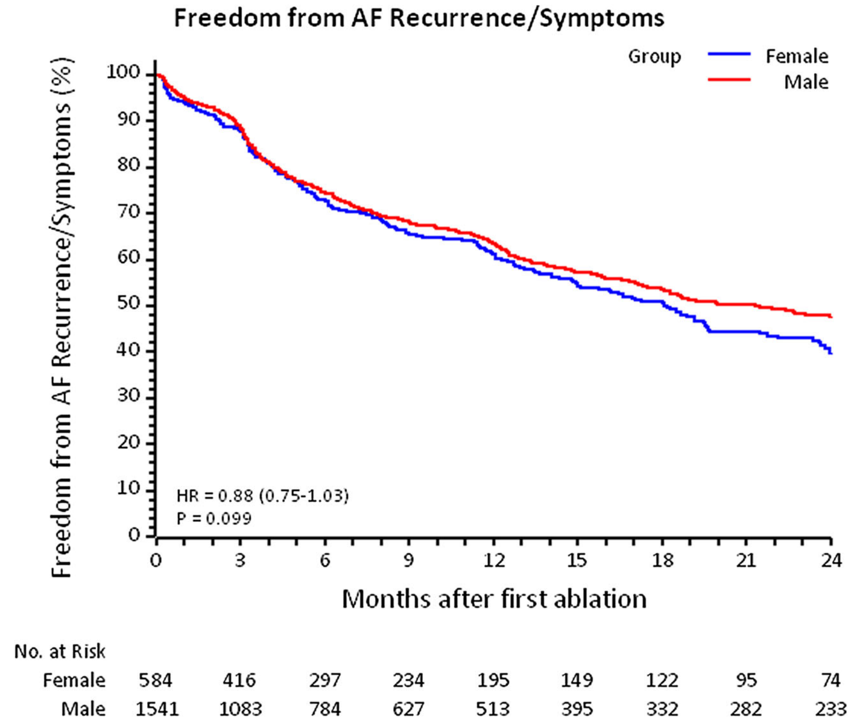

Fig. 2 The analysis of "time-to-first" event was described by means of the Kaplan-Meier curves and compared between the groups by means of freedom from atrial fibrillation (AF) recurrence or AF symptoms without ECG documentation

multivariable analysis, including sex, age at procedure, type of AF, and left atrial diameter (Table 4). Female sex, AF type, and age were confirmed as independent predictors of AF recurrence upon multivariable model analysis. After propensity score adjustment, the hazard ratio (HR) from the multivariable model, which included age and AF type (persistent) as covariates, was 0.76 (0.60–0.97) ($P = 0.025$).

Table 4 Multivariable analysis of long-term efficacy outcomes against baseline patient characteristics with significant univariate association

Baseline characteristics	Univariate		Multivariate	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Sex	0.76 (0.60–0.97)	0.025*	0.77 (0.60–0.98)	0.033
Age (as a continuous variable)	1.01 (1.00–1.03)	0.021*	1.01 (1.00–1.02)	0.043
Age above median (61 years)	1.19 (0.95–1.48)	0.123		
Body mass index > 26	0.86 (0.67–1.11)	0.249		
Number of failed AADs ≥ 2	0.97 (0.77–1.23)	0.806		
Type of atrial fibrillation—paroxysmal	0.65 (0.54–0.78)	0.01*	0.45	< 0.001
Type of atrial fibrillation—persistent	1.55 (1.29–1.86)	0.01*	1.55 (1.21–1.98)	< 0.001
Cardiac insufficiency	0.89 (0.46–1.73)	0.731		
Valve disease	0.97 (0.55–1.73)	0.929		
Hypertension	1.16 (0.97–1.37)	0.101		
CHA_2DS_2-VASc > 2	1.09 (0.84–1.43)	0.509		
Ischemic cardiomyopathy	0.80 (0.48–1.35)	0.407		
Left atrial volume (cm^3) > 64	1.26 (0.85–1.86)	0.256		
Left atrial area (cm^2) > 21	1.27 (0.92–1.75)	0.149		
Left atrial diameter (mm) > 41	1.46 (1.10–1.95)	0.010*	1.37 (0.99–1.88)	0.055
Indexed left atrial volume (cm^3/m^2) (continuous)	1.01 (1.00–1.03)	0.049		
Indexed left atrial area (cm^2/m^2) (continuous)	1.05 (1.00–1.10)	0.037		
Indexed left atrial diameter (mm/m^2) (continuous)	1.05 (1.01–1.10)	0.010		

*Significant univariable characteristic tested further with multivariable analysis

4 Discussion

4.1 Primary findings

The study aimed to assess the potential effect of sex on clinical procedural characteristics, AF treatment, PVI-C efficacy, and safety in a group of patients with drug refractory symptomatic AF. Specifically, the primary results of this research were the following: (1) in a large real-world cohort of patients who underwent PVI-C, less than 30% were female; (2) on average, female patients were older with higher thromboembolic risk scores; (3) PVI-C was safe in both male and female patients; and (4) female sex significantly increased the risk of AF recurrence by 23%.

4.2 Patient population and procedural data

Age and sex are the two most powerful predictors of AF incidence [15, 16]. Male sex is associated with a 1.5-fold risk of AF, even after adjusting for age and predisposing baseline conditions [15, 16]. Nevertheless, the current guidelines on AF management and treatment do not differentiate the therapeutic approach based on sex [1, 2]. Consequently, PVI is considered a cornerstone of catheter ablation to treat recurrent symptomatic AF regardless of the patient's sex [1, 2].

In our analysis, women who underwent PVI-C tended to be older and had higher prevalence of risk factors (e.g., higher CHA_2DS_2-VASc score and/or more AAD usage), which was in line with previously published study results [5–11]. In the 1STOP population, female patients presented more often in paroxysmal AF disease compared to men and had less ischemic cardiomyopathy. Body mass index, weight, and height were also significantly different between the two populations. Despite having a different clinical risk profile, the overall incidence of periprocedural complications was the same between males and females, and neither venous access injury nor transient phrenic nerve palsy was differently associated with the male or female cohorts. However, in our cohort, pericardial effusion and cardiac tamponades were more frequent in the female cohort. A smaller mean left atrial dimension and thinner atrial wall may be an explanation for this clinical observation as previously investigated [17–20]. Elayi et al. reported an analysis of 85,977 patients (of which 32% were women) who underwent catheter ablation for AF and found that overall complications were more frequent in the female cohort compared to men (12.4% vs. 9.0%; $P < 0.001$) [20]. They also found that predefined major complications were also more prevalent in women compared to men (4.7% vs. 2.7%; $P < 0.001$) [20]. Additionally, in our study, procedural data (e.g., acute success rate, procedure time, and fluoroscopy duration) were comparable between male and female cohorts which ensured that differences in safety and/or efficacy were not procedure related, and moreover, the procedural data confirmed the relative simplicity and reproducibility of the PVI-C procedure [20, 21]. Procedural data reflected the standard clinical practice of the involved centers. Center learning curves, operators' attitudes, the center procedure volume, and technical evolution of devices may have contributed to the observed procedure and fluoroscopic durations [22].

4.3 Clinical outcomes

Our results are in line with and confirm the findings that were reported in the FIRE AND ICE Trial when examining the predictors of AF recurrence after an index PVI catheter ablation procedure [13]. Specifically, the trial revealed that female sex was associated with a 37% increased risk of atrial arrhythmia recurrence, and furthermore, differences in baseline characteristics could not themselves explain the disparity in outcomes beyond the primary sex distinction [13]. Previous studies have demonstrated that (regardless of baseline health conditions) sex influenced the clinical outcomes after AF catheter ablation [23–27]. Some study findings have ascribed this sex-based differential clinical outcome to differences in the electrophysiological characteristic of the left atrium and PV which might increase the risk for arrhythmogenesis in men [23, 24]. Yet, others have postulated the differential response is due (in part) to differences in baseline atrial fibrosis and the continuing mechanisms of fibrotic disease [25, 26].

In our study, the cumulative AF recurrence rate, as estimated by the Kaplan-Meier survival calculation, demonstrated a comparable response to PVI-C in the first 6-month period after index catheter ablation across both sex cohorts. However, after 6 months post-ablation, the two Kaplan-Meier curves depicting combined freedom from documented AF recurrence and AF-reported symptoms without documentation begin to diverge in the favor of men and this differential was maintained throughout 36 months of follow-up. A very similar time point-dependent divergence between male and female cohorts was observed in the FIRE AND ICE Trial data which examined both outcomes of PVI-C and PVI by radiofrequency energy as one cohort [13]. Summarizing the similar sex-dependent outcomes, it might be plausible that women have a propensity for developing non-pulmonary vein arrhythmia trigger(s) and/or have a less durable PVI after catheter ablation. Additionally, it is plausible that sex-related hormones play a role in AF initiation, lesion healing after catheter ablation, continuation of arrhythmia triggers, and/or structural remodeling events that promote AF recurrence/continuation. In line with the results reported in literature [28–30], we observed that improvements in AF-related symptoms were seen in both males and females following ablation.

Finally, even with the sex-specific difference in efficacy, it is interesting that the frequency of repeat ablations between genders was similar (or favors men) when examined in this clinical study [26]. In a recent study, Kaiser et al. reported on an analysis of 21,091 patients who underwent a catheter ablation for AF. Although women were significantly more likely to be rehospitalized with AF (within 1 year after the index ablation procedure), the female cohort was less likely to undergo further cardioversions or repeated ablations [26]. These findings suggest that further clinical study is necessary to fully understand the sex-specific response to AF catheter ablation to better assess whether sex-based differences and/or disparities in the management of AF before ablation and during follow-up could impact the efficacy of ablation for the treatment of AF.

5 Limitations

This analysis is a single-arm multicenter project without the usage of a control group. Although this registry reports the real-world clinical practice across a large user group, the lack of a standardized prospective protocol potentially biases the patient selection, treatment, and management. Also, although the authors have outlined each study before data analyses, there is no prospective hypothesis that is tested throughout the 1STOP registry collection of data or series of manuscripts [6, 14]. Consequently, these observational findings must be further evaluated with large, controlled studies.

6 Conclusions

Our analysis shows that in a real-world cohort of patients who underwent PVI-C, only a minority were female. Female patients tended to be older and have higher thromboembolic risk scores than males. PVI-C was relatively safe for both females and males; however, female sex significantly increased the risk of AF recurrence. These results should not discourage women from catheter ablation for the treatment of AF, but instead, the findings should encourage women to proactively seek treatment for AF earlier in the manifestation of the disease.

Funding This research was performed within the framework of the Italian ClinicalService®, a project funded by Medtronic Italia, an affiliate of Medtronic Inc. No other funding sources were involved in the research.

Compliance with ethical standards

At each center, the project was approved by the institutional review board and/or local ethics committees and conforms to the principles outlined in the Declaration of Helsinki. Each patient included in the 1STOP project provided informed consent for data collection and analysis.

Conflict of interest Danilo Ricciardi received consultancy fees from Boston Scientific and Medtronic. Claudio Tondo and Roberto Verlato received modest consultancy and speaker's fees from Medtronic. Giulio Molon received modest consultancy fees from Medtronic and Boston Scientific, and speaker's fees from Medtronic, Boston Scientific, St. Jude, and Boehringer Ingelheim. The other authors declare that they have no competing interests.

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