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Recurrence of Atrial Fibrillation After Cryoballoon Ablation in Women Is Less Pulmonary Vein Mediated as Compared to Men: Lessons From Repeat Ablation Procedures

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ABSTRACT

Background: Data on sex-related outcomes of pulmonary vein isolation (PVI) of cryoballoon ablation (CBA) in atrial fibrillation (AF) are sparse.

Aim: To compare sex-differences in PV reconnection, strategy and outcome of repeat ablations after CBA.

Methods: Repeat procedures were performed using radiofrequency ablation guided by 3D mapping. PV reconnection characteristics were compared in 229 patients (77 (33.6%) females). In durable PVI patients, we compared left atrial voltage maps, ablation strategy and 1-year outcome. Clinical success was defined as freedom of documented AF or atrial tachycardia (AT) > 30 s.

Results: Female patients had a lower overall number of PV reconnections (0.8 ± 0.9 vs 1.2 ± 1.0, $p < 0.001$) driven by less reconnected left PVs: 13/77 (16.9%) vs 51/152 (33,6%), $p = 0.008$ and 7/77 (9.1%) vs 39/152 (25.7%), $p = 0.003$ for LSPV and LIPV, respectively. Durable PVI was more frequent in women (34/77 (44.1%) vs 37/152 (24.4%), $p = 0.001$). Female sex was the only independent predictor for durable PVI (HR = 2.003; 95% CI 1.090–3.682; $p = 0.025$). In durable PVI patients, substrate ablation was more frequently performed in women (21/35 (60%) vs 13/35 (37.1%), $p = 0.044$), mainly targeting the higher prevalent atrial low-voltage zones (21/35 (60.0%) vs 12/36 (33.3%), $p = 0.017$). At 1 year, recurrence of AF/AT did not differ between sexes: 6/35 (17.1%) versus 8/35 (22.9%), $p = 0.591$.

Conclusions: The higher persistence of durable PVI in women points to a sex difference in AF recurrence driver after CBA. In durable PVI patients, a higher prevalence of low-voltage regions results in more substrate ablation in women. Despite sex differences in ablation strategy, 1-year outcome was similar.

1 | Introduction

Past studies show a higher risk of atrial fibrillation (AF) recurrence after catheter ablation in women (AF) [1–6]. Different explanations have been suggested including reporting bias due to higher symptom burden and more advanced AF due to later referral in women [7, 8]. However, more recently, Andrade et al. reported no sex-related differences in arrhythmia recurrence or improvement of quality of life after ablation for paroxysmal AF in the CIRCA-dose trial [9]. These findings might be a result of a change in practice over time, in which female patients are ablated earlier as compared to previous cohorts [9]. Of interest, most of these studies encompass catheter ablation using radiofrequency (RF) energy. Data on sex differences in cryoballoon ablation (CBA) remain sparse [4, 5]. In the present study we aim to determine whether sex differences are present by studying a large cohort of patients undergoing a first repeat ablation after CB pulmonary vein isolation (PVI). More specific, we ought to compare (1) PV reconnections characteristics between men and women in in a large group of repeat ablation studies and (2) 3D left atrial (LA) voltage map findings, ablation strategy and 1-year outcome in the subgroup of patients with durable PVI at repeat ablation.

2 | Methods

2.1 | Study Design

In this observational, retrospective single-center study, we analyzed 229 consecutive AF patients (derived from the Middelheim-PVI registry 2 composed of 1000 consecutive patients) who underwent a first repeat ablation between March 2017 and July 2022 after CBA at the Middelheim Heart Center in Antwerp. Atrial arrhythmia recurrence was detected by ambulatory electrocardiogram, Holter monitor, or implantable loop recorder. The study was approved by the local ethics committee.

2.2 | Index CB Ablation Procedure

Since more than a decade, first PVI procedures are performed with cryotherapy in our center. Our routine PVI protocol using CB has been previously described in detail [10]. In brief, after single transseptal puncture, a 15-Fr steerable sheath (FlexCath Advance™, Medtronic Inc. Minneapolis, USA) was advanced into the LA cavity and an inner-lumen mapping catheter (Achieve™, Medtronic Inc. Minneapolis, USA) was advanced and positioned in each PV ostium. A second-generation 28-mm CB (Artic Front Advance™, Medtronic Inc. Minneapolis, USA) was advanced, inflated and positioned at the PV ostium. Contrast injection was performed and cryoablation was started when vessel occlusion was deemed optimal. Effort was made to record PV activity before cryoablation, allowing real-time monitoring of PV entrance block. All relevant procedural data were systematically collected.

2.3 | Repeat RF Ablation Procedure

All repeat ablations were performed using RF energy. After double transseptal puncture, a 3D electro-anatomical map of the LA was acquired. A 3-dimensional (3D) reconstruction of the LA was made guided by a 3D non-fluoroscopic navigation system (CARTO™, Biosense-Webster, Johnson & Johnson, USA) and a dedicated mapping catheter (Pentarray™, Biosense Webster. California, USA). RF ablation was performed with an open-irrigated-tip catheter with contact-force monitoring (Thermocool Smarttouch™, Biosense Webster. California, USA) in power-controlled mode with a power limit of 35 W and maximum temperature of 48°C. The power was reduced at the posterior wall to 30 W and further adopted in case of esophageal temperature rise during ablation.

PV reconnection (PVR) was evaluated per individual PV—left superior PV, left inferior PV, right superior PV, and right inferior PV—irrespective of a common ostium anatomy. When ostial PVI was observed, this was considered as PVR and more antral PVI was performed. In case of PV reconnection, re-isolation was performed. If PVI proved to be durable at baseline, further ablation strategy was performed on a case-by-case basis at the discretion of the operator. Ablation strategy was categorized as targeted or empirical ablation. In targeted ablation an induced non-PV trigger or atrial arrhythmia was targeted. In empirical ablation common non-PV triggers or substrate (mainly low voltage zones (LVZ)) were targeted. When both targeted and empirical targets were ablated, the ablation strategy was considered targeted. LWZ were graded based on location (anterior, posterior, septal, roof of left atrium, or right atrium). When LVZ extended to more than two zones, the LVZ was graded as diffuse.

2.4 | Follow-up

All patients underwent follow-up consultations and electrocardiogram at scheduled (6–12 months) and unscheduled (if symptoms) visits. In case of symptoms, the related arrhythmia was documented by electrocardiogram, Holter monitoring (1- to 7-day), or event recording. Clinical success at 1-year follow-up was defined as freedom of documented AF/AT > 30 s, without AADs, and after a 2-month blanking period.

3 | Statistical Analysis

The Shapiro-Wilk test was used to examine if a continuous variable was normally distributed. Continuous variables with normal distribution were expressed as mean ± standard deviation. Continuous variables without normal distribution were expressed as median (interquartile range (IQR)). Categorical variables were expressed as percentages. The 2-sided Student *t*-test for independent samples was used to compare continuous variables when values were homoscedastic, and its non-parametric equivalent (Mann-Whitney U test) was used when variables were heteroscedastic. The Chi-square or Fisher exact test was used to compare categorical variables. Kaplan-Meier survival analysis was performed to analyze the cumulative event rates (recurrence of AF/AFl/AT) and the log-rank test was used to detect significant differences between groups. To assess the contribution of baseline patient characteristics to recurrence of arrhythmias multivariable Cox proportional hazard regression analysis was used. Only variables which were statistically significant in univariable analysis were used for the multivariable analysis. A p value of < 0.05 was considered statistically significant. IBM SPSS Statistics (version 22; SPSS Inc., Chicago, Illinois) was used for all statistical analyses.

4 | Results

4.1 | Analysis of all Repeat Ablation Procedures ($N = 229$)

4.1.1 | Comparison of Baseline Variables and Procedural Characteristics of the Index CBA

Of the 229 recurrent AF patients undergoing a repeat ablation after CBA, 77 patients (34%) were female. Sex-differences in baseline variables and procedural characteristics of the index CBA are outlined in Tables 1 and 2.

Compared to men, female patients were older (66.4 ± 9.0 vs 63.1 ± 10.0 years, $p = 0.017$), had higher CHA_2DS_2-VASc scores (2.7 ± 1.3 vs 1.7 ± 1.7, $p < 0.001$) and smaller LA diameters (42.2 ± 7.1 vs 45.6 ± 6.4, $p < 0.001$). AF type differed at baseline with more prevalent paroxysmal AF in women (59.7% vs 43.4%, $p = 0.020$). Time to AF/AT recurrence after index CBA (9.4 ± 8.3 months in women vs. 10.9 ± 10.1 in men, $p = 0.080$) nor the time between index and repeat ablation (16.9 ± 13.2 months in women vs 14.2 ± 16.0 in men, $p = 0.217$) differed between sexes. There were no differences in incidence of left common pulmonary veins (12/77 (15.6%) in women vs. 20/152 in men (13.2%), $p = 0.617$) or right middle pulmonary veins (7/77 (9.1%) in vs. 12/152 (8.0%), $p = 0.757$).

No major differences in baseline recording of PV signals and freezing characteristics were seen between women and men besides a higher temperature at isolation of the RIPV (−28.5 ± 9.4 vs −37.2 ± 10.0°C, $p < 0.001$) and higher minimum temperature of the RIPV (−48.1 ± 5.3 vs −49.4 ± 6.1°C, $p = 0.035$).

All veins could be successfully isolated with the CB at index PVI.

4.1.2 | Comparison of PV Reconnection Characteristics ($N = 229$)

PV reconnection characteristics at repeat ablation study are summarized in Table 3.

Durable isolation of all PVs was seen in 71 out of the 229 patients, (31.0%), significantly more in women (34/77 (44.1%)) then men (37/152 (24.4%)) ($p < 0.001$). Also, the overall number of reconnected PVs was lower in women (0.8 ± 0.9 vs 1.2 ± 1.0 in men, $p < 0.001$) driven by less reconnected left PVs: 13/77 (16.9%) vs 51/152 (33,6%), $p = 0.008$ and 7/77 (9.1%) vs 39/152 (25.7%), $p = 0.003$ for LSPV and LIPV, respectively.

Uni- and multivariable adjusted predictors of durable PVI of all veins are outlined in Table 4. Female sex was the only independent predictor of finding durable PVI of all veins at repeat ablation (HR = 2.003; 95% CI 1.090–3.682; $p = 0.025$).

TABLE 1 | Baseline variables of patients undergoing a repeat ablation procedure.

	Total ($N = 229$)	Female patients ($N = 77$)	Male patients ($N = 152$)	p value
Age (years, mean ± SD)	64.2 ± 9.8	66.4 ± 9.0	63.1 ± 10.0	**0.017**
BMI (kg/m^2, mean ± SD)	28.0 ± 4.9	28.1 ± 6.0	27.9 ± 4.2	0.746
AHT (N, %)	122 (53.3%)	47 (61.0%)	75 (49.3%)	0.094
DM (N, %)	27 (11.8%)	10 (13.0%)	17 (11.2%)	0.689
Previous CVA/TIA(N, %)	23 (10.0%)	6 (7.8%)	17 (11.2%)	0.420
CHA_2DS_2-VASC score (mean ± SD)	2.1 ± 1.5	2.7 ± 1.3	1.7 ± 1.7	**< 0.001**
OSAS (N, %)	23 (10.0%)	3 (3.9%)	20 (13.2%)	0.280
Structural heart disease (N, %)	74 (32.3%)	20 (26.0%)	54 (35.5%)	0.186
LA diameter (mm, mean ± SD)	44.4 ± 6.8	42.2 ± 7.1	45.6 ± 6.4	**< 0.001**
LCPV	32 (14.0%)	12 (15.6%)	20 (13.2%)	0.617
RMPV	19 (8.3%)	7 (9.1%)	12 (8.0%)	0.757
Diagnosis-to-ablation time (months, mean ± SD)	39.1 ± 51.6	35.6 ± 50.9	41.0 ± 52.0	0.277
Type of AF (N, %)				
Paroxysmal AF	112 (48.9%)	46 (59.7%)	66 (43.4%)	**0.020**
Persistent AF < 1 year	107 (46.7%)	27 (35.1%)	80 (52.7%)	**0.012**
Persistent AF > 1 year	10 (4.4%)	4 (5.2%)	6 (3.9%)	0.944
No of prior AAD (mean ± SD)	1.5 ± 0.8	1.6 ± 0.8	1.4 ± 0.8	0.218
Tachycardia-induced cardiomyopathy (N, %)	26 (11.4%)	10 (13.0%)	16 (10.5%)	0.579

Note: Data are presented as the mean value ± SD or number (%) of patients.
Abbreviations: AAD, antiarrhythmic drugs; AF, atrial fibrillation; BMI, body mass index; CVA, cerebrovascular accident; DM, diabetes mellitus; LA, left atrium; LCPV, left common pulmonary vein; OSAS, obstructive sleep apnea syndrome; RMVP, right middle pulmonary vein; TIA, transient ischemic attack.

TABLE 2 | Freezing characteristics and PV recording for each PV at index CBA.

	Total ($N = 229$)	Female patients ($N = 77$)	Male patients ($N = 152$)	p value
LSPV				
Number of freezes (N, ±SD)	1.3 ± 0.6	1.2 ± 0.5	1.4 ± 0.6	0.319
Total freeze duration (sec)	193.9 ± 26.4	191.8 ± 24.1	195.2 ± 27.9	0.971
Time at −40°C (sec)	50.7 ± 16.9	51.2 ± 15.1	50.2 ± 18.0	0.369
Temperature at 60 s	−43.4 ± 4.7	−42.8 ± 4.0	−43.8 ± 5.1	0.103
Time to isolation (sec)	47.9 ± 24.2	44.8 ± 20.0	49.9 ± 26.5	0.294
Temperature at isolation	−37.1 ± 8.2	−35.3 ± 8.1	−38.4 ± 8.1	0.082
Minimal temperature	−51.4 ± 5.8	−50.7 ± 5.4	−51.8 ± 6.0	0.110
Thawing time (sec)	57.7 ± 21.5	55.5 ± 18.8	59.1 ± 23.0	0.352
PVP recording during freeze (N, %)	101 (44.1%)	38 (49.4%)	63 (41.4%)	0.897
LIPV				
Number of freezes (N, ±SD)	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	0.533
Total freeze duration (sec)	257.0 ± 100.8	254.1 ± 87.0	159.0 ± 109.1	0.775
Time at −40°c	60.7 ± 27.2	62.0 ± 28.1	59.9 ± 26.7	0.828
Temperature at 60 s	−41.5 ± 5.0	−40.6 ± 3.9	−42.1 ± 5.6	0.212
Time to isolation (sec)	41.6 ± 26.3	40.9 ± 26.4	42.0 ± 26.6	0.997
Temperature at isolation	−32.8 ± 9.6	−31.4 ± 9.4	−33.5 ± 9.8	0.445
Minimal temperature	−46.8 ± 6.1	−45.6 ± 4.6	−47.6 ± 6.8	0.211
Thawing time (sec)	45.2 ± 16.4	44.5 ± 17.1	45.6 ± 16.0	0.855
PVP recording during freeze (N, %)	71 (31.0%)	23 (29.9%)	48 (31.6%)	0.139
RSPV				
Number of freezes (N, ±SD)	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	0.300
Total freeze duration (sec)	187.0 ± 32.2	182.4 ± 27.8	190.0 ± 34.3	0.180
Time at −40°c (sec)	48.9 ± 19.4	49.7 ± 18.8	48.5 ± 19.8	0.385
Temperature at 60 s	−43.6 ± 4.0	−43.5 ± 3.5	−43.7 ± 4.3	0.871
Time to isolation (sec)	35.5 ± 20.5	37.6 ± 22.1	34.4 ± 19.6	0.619
Temperature at isolation	−33.1 ± 13.6	−34.9 ± 19.4	−32.2 ± 9.2	0.429
Minimal temperature	−50.5 ± 5.2	−50.0 ± 4.6	−50.8 ± 5.5	0.757
Thawing time (sec)	54.0 ± 18.3	52.4 ± 16.1	54.9 ± 19.5	0.616
PVP recording during freeze (N, %)	89 (38.7%)	32 (41.6%)	57 (37.5%)	0.937
RIPV				
Number of freezes (N, ±SD)	1.2 ± 0.5	1.1 ± 0.4	1.2 ± 0.5	0.459
Total freeze duration (sec)	228.7 ± 89.2	216.1 ± 72.8	236.5 ± 97.5	0.733
Time at −40°c (s)	−58.4 ± 29.5	−60.7 ± 29.3	−57.0 ± 29.6	0.164
Temperature at 60 s	41.7 ± 4.4	41.3 ± 3.9	41.9 ± 4.7	0.079
Time to isolation (sec)	39.5 ± 28.8	30.9 ± 15.7	45.0 ± 33.8	0.077
Temperature at isolation	−33.9 ± 10.6	−28.5 ± 9.4	−37.2 ± 10.0	**< 0.001**
Minimal temperature	−48.9 ± 5.8	−48.1 ± 5.3	−49.4 ± 6.1	**0.035**
Thawing time (sec)	47.4 ± 19.7	44.0 ± 14.8	49.5 ± 22.0	0.071
PVP recording during freeze (N, %)	85 (37.1%)	31 (40.2%)	54 (35.5%)	0.819

Note: Data are presented as the mean value ± SD or number (%) of patients.
Abbreviations: LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein; PVP, pulmonary vein potential; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

TABLE 3 | PV reconnection patterns at repeat ablation procedure.

	Total ($N = 229$)	Females ($N = 77$)	Males ($N = 152$)	p value
≥ 1 reconnected PV (*N*, %)	158 (69.0%)	43 (55.8%)	115 (75.6%)	**< 0.001**
Durable PVI (*N*, %)	71 (31.0%)	34 (44.1%)	37 (24.4%)	
N of reconnected PVs (mean ± SD)	1.1 ± 1.0	0.8 ± 0.9	1.2 ± 1.0	**< 0.001**
4 (*N*, %)	7 (3.1%)	0 (0%)	7 (4.6%)	**0.010**
3 (*N*, %)	14 (6.1%)	4 (5.2%)	10 (6.6%)	
2 (*N*, %)	40 (17.5%)	9 (11.7%)	31 (20.4%)	
1 (*N*, %)	97 (42.4%)	30 (39.0%)	67 (44.1%)	
0 (*N*, %)	71 (31.0%)	34 (44.1%)	37 (24.4%)	
Reconnected PV				
LSPV (*N*, %)	64 (27.9%)	13 (16.9%)	51 (33.6%)	**0.008**
LIPV (*N*, %)	46 (20.1%)	7 (9.1%)	39 (25.7%)	**0.003**
RSPV (*N*, %)	55 (24.0%)	16 (20.8%)	39 (25.7%)	0.414
RIPV (*N*, %)	88 (38.4%)	23 (29.9%)	65 (42.8%)	0.058

Note: Data are presented as the mean value ± SD or number (%) of patients.
Abbreviations: LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein potential; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

TABLE 4 | Univariable and multivariable-adjusted predictors of finding durable PVI of all veins at repeat procedure.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.048	1.015–1.082	**0.004**	0.610	0.998–1.076	0.061
Female sex	2.458	1.372–4.401	**0.002**	2.003	1.090–3.682	**0.025**
Persistent AF	0.836	0.476–1.469	0.534			
AHT	1.821	1.025–3.235	**0.041**	1.469	0.784–2.753	0.230
DM	1.360	0.589–3.140	0.472			
BMI	0.980	0.924–1.039	0.502			
Structural heart disease	1.389	0.759–2.541	0.286			
LA diameter	0.998	0.957–1.040	0.914			
Diagnosis-to-ablation time	1.001	0.995–1.006	0.745			
180 s freezing time strategy	0.818	0.413–1.623	0.566			
LCPV	1.723	0.792–3.750	0.170			
Time to AF recurrence	1.010	0.979–1.043	0.522			
eGFR	0.986	0.969–1.003	0.096			

Abbreviations: AF, atrial fibrillation; AHT, arterial hypertension; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; eGFR, Glomerular Filtration Rate; HR, hazard rate; LA, left atrium; LCPV, left common pulmonary vein.

4.2 | Subanalysis of Patients With Durable PVI at Repeat Procedure ($N = 71$)

4.2.1 | Comparison Between Female and Male Patients With Durable PVI at Repeat Ablation ($N = 71$)

Findings at repeat ablation in the subgroup of patients with durable PVI are depicted in Table 5. Baseline LA 3D voltage mapping showed a higher prevalence of low-voltage zones in women: 22/35 (62.9%) vs 12/36 (33.3%) in men, $p = 0.017$). This difference was driven by significantly more diffuse LVZ (17/35 (48.6%) vs 7/36 (19.4%), $p = 0.014$).

Non-PV triggers were encountered in 21/71 (29.6%) patients. There were no differences in the overall prevalence nor in the type of non-PV triggers between sexes.

Also for inducible arrhythmias, no difference between sexes was seen. Supraventricular re-entry tachycardias (AVNRT, AVRT or macro-reentry atrial tachycardia) were induced and ablated in 24/71 (33.8%) of patients. CTI-dependent macro-reentry flutter was the most prevalent treated arrhythmia in this group. The number of patients with AVNRT was low (2/71 (2.8%)).

From the 71 patients with durable PVI, 70 (98.6%) underwent further ablation during this procedure. The single patient where no further ablation was performed was a 70-year-old male patient without any low-voltage zones at LA voltage map in which multiple non-sustained atrial tachycardias could be induced under high dose of isoprenaline. In the absence of a clear ablation target, ablation was renounced and opted for medical therapy. The ablation strategy characteristics in patients who underwent ablation at repeat procedure are summarized in Table 6.

There were significantly more female patients who underwent an empirical substrate ablation strategy (21/35 (60.0%) vs 13/35 (37.1%), $p = 0.044$). This difference was driven by a higher prevalence of LVZ in female patients at baseline LA voltage map (Figure 1): 20/22 (90.1%) of female patients with LVZ underwent empiric substrate ablation as opposed to 8/12 (66.7%) male patients with LVZ.

However, despite these sex differences in ablation strategy in durable PVI patients, 1-year clinical outcome did not differ (Figure 2).

5 | Discussion

The main findings of our study are:

1. PV reconnection patterns differ between females and males with more durable PVI and a lower number of reconnected PVs in women.
2. Female sex was the only predictor of finding durable PVI during repeat ablation after CB ablation for AF.
3. Ablation strategy differed between sexes in patients with durable PVI with more empirical

TABLE 5 | Findings at repeat ablation in patients with durable pulmonary vein isolation.

	Total ($N = 71$)	Females ($N = 35$)	Males ($N = 36$)	p value
Low-voltage zones	33 (46.5%)	22 (62.9%)	12 (33.3%)	**0.017**
Anterior	5 (7.0%)	3 (8.6%)	2 (5.6%)	0.669
Posterior	2 (2.8%)	1 (2.9%)	1 (2.8%)	1.000
Septum	0 (0%)	0 (0%)	0 (0%)	/
Roof	1 (1.4%)	0 (0%)	1 (2.8%)	1.000
Right atrium	2 (2.8%)	1 (2.9%)	1 (2.8%)	1.000
Diffuse	23 (32.4%)	17 (48.6%)	7 (19.4%)	**0.014**
Non-PV triggers	21 (29.6%)	12 (35.3%)	9 (24.3%)	0.210
Antrum	5 (7.0%)	4 (11.8%)	1 (2.7%)	0.199
CS	3 (4.2%)	3 (8.8%)	0 (0%)	0.115
LAA	2 (2.8%)	1 (2.9%)	1 (2.7%)	1.000
SVC	8 (11.3%)	4 (11.8%)	4 (10.8%)	1.000
PB	6 (8.5%)	2 (5.9%)	4 (10.8%)	0.674
CT	0 (0%)	0 (0%)	0 (0%)	/
Septum	4 (5.6%)	2 (5.9%)	2 (5.4%)	1.000
Inducible arrhythmia	24 (33.8%)	10 (29.4%)	14 (37.8%)	0.543
Re-entry tachycardia	2 (2.8%)	1 (2.9%)	1 (2.7%)	1.000
AVNRT	0 (0%)	0 (0%)	0 (0%)	/
AVRT	16 (22.5%)	6 (17.6%)	10 (27.0%)	0.284
Atrial flutter	5 (7.0%)	2 (5.9%)	3 (8.1%)	1.000
CTI-dependent	3 (4.2%)	2 (5.9%)	1 (2.7%)	0.614
Mitral annular flutter	1 (1.4%)	1 (2.9%)	0 (0%)	0.493
Roof-dependent flutter	2 (2.8%)	0 (0%)	2 (5.4%)	0.493
Septal flutter				
Anterior flutter				

Abbreviations: AVNRT, atrioventricular node re-entry tachycardia; AVRT, atrioventricular re-entry tachycardia; CS, coronary sinus; CT, crista terminalis; CTI, cavo-tricuspid isthmus; LAA, left atrial appendage; PB, posterior box; PV, pulmonary vein; SVC, superior vena cava.

TABLE 6 | Ablation strategy at repeat ablation procedure in patients with durable pulmonary vein isolation.

	Total ($N = 70$)	Females ($N = 35$)	Males ($N = 35$)	p value
Targeted non-pulmonary vein trigger ablation	22 (31.4%)	12 (34.3%)	10 (28.6%)	0.553
Targeted provoked arrhythmia ablation	23 (32.9%)	10 (28.6%)	13 (37.1%)	0.497
Empiric trigger ablation	5 (7.1%)	2 (5.7%)	3 (8.6%)	0.514
Empiric substrate ablation	34 (48.6%)	21 (60.0%)	13 (37.1%)	**0.044**

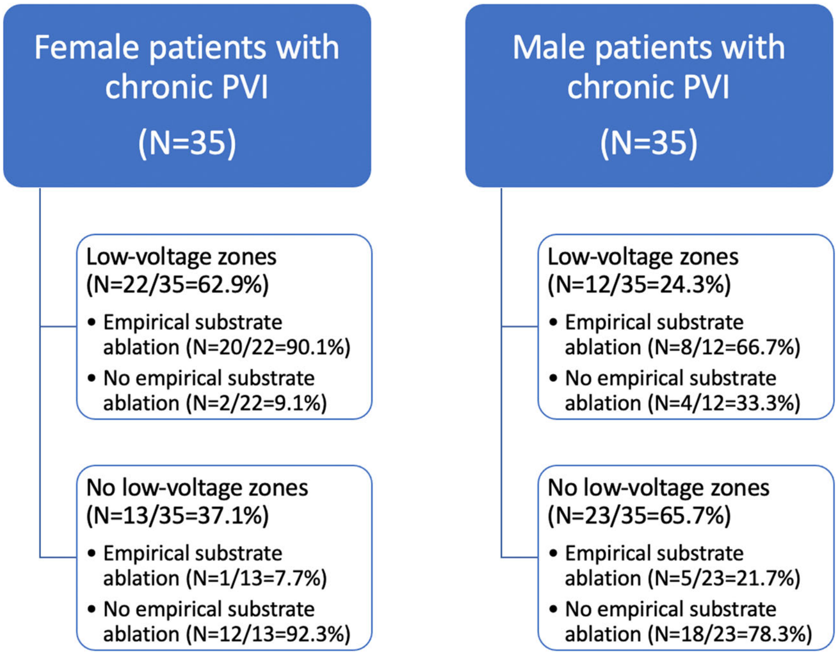

FIGURE 1 | Ablation strategy of repeat ablation procedure in patients with durable PVI in relation to the presence of low-voltage zones.

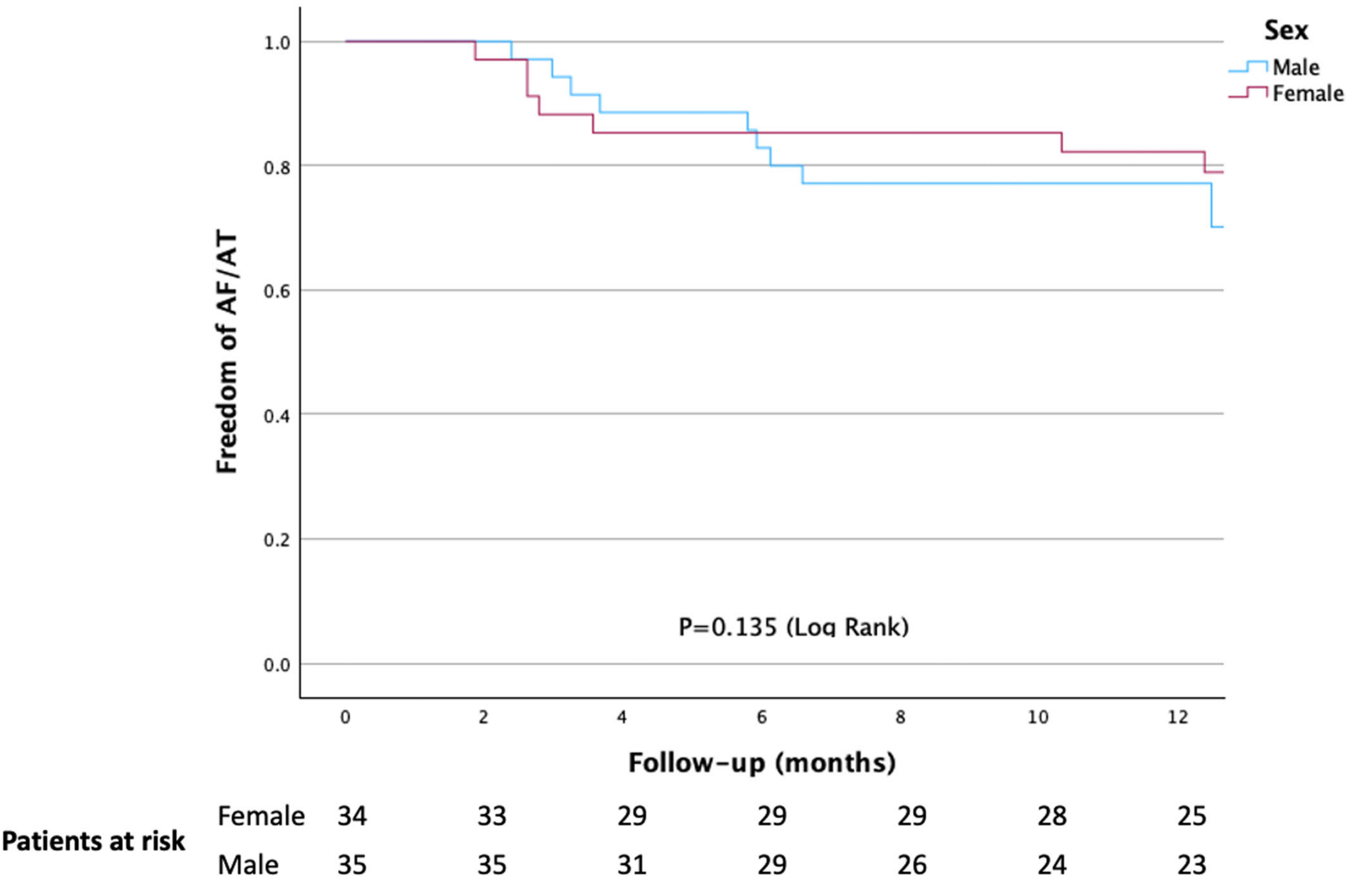

FIGURE 2 | Kaplan-Meier analysis of atrial arrhythmia free survival following first repeat RF ablation after index CB ablation in female and male patients.

substrate ablation in women due to a higher presence of atrial low-voltage areas. Despite this difference in ablation approach, 1-yeat outcome was similar between male and female patients with durable PVI.

5.1 | Female Sex is Predictor of Finding Durable PVI During Repeat Ablation After CBA

In a meta-analysis published in 2019, Cheng et al. showed that recurrence rate after catheter ablation for atrial fibrillation was higher in women as compared to men at 2.4-year follow-up (61.2% vs. 68.6%; OR 0.75, 95% CI: 0.69–0.81; $p < 0.0001$). However, detailed information regarding used energy form for ablation was not available and therefore these results cannot be extrapolated to patients undergoing CBA [11]. Studies analyzing sex-differences in patients undergoing CBA are sparse. Ricciardi et al. demonstrated that male sex was protective for recurrence after CB ablation (HR 0.77; 95% CI 0.60–0.98; $p = 0.0033$) in a multi-center observational analysis of 2125 patients [4]. Recently, Hermida et al. reported female sex as the only predictor of recurrence after CB ablation for paroxysmal AF (HR 1.87; 95% CI 1.28–2.73; $p = 0.001$). There was however no sex-difference in outcome after CB ablation for persistent AF [5].

Recurrence after catheter ablation for AF is assumed to be primarily mediated by pulmonary vein reconnection [12]. Several studies reporting on repeat procedures after index RF PVI, describe a lower PV reconnection rate in female patients [6, 13, 14]. Only one previous study described sex differences in PV status after CB ablation: Hermida et al. reported no sex-difference in PV status at repeat ablation after index CB ablation in 30 female and 39 male patients (PVR in 80% vs 74% respectively, $p = 0.77$) [5].

However, our study in a bigger cohort of patients, showed significant differences between sexes in PV status at the time of repeat ablation: at patient-level, female patients had more frequent durable isolation of all PVs (34/77 (44.1%) vs 37/152 (24.4%), $p = 0.001$) and at PV level, female patients had a lower number of PV reconnections (0.8 ± 0.9 vs 1.2 ± 1.0, $p < 0.001$). The differences were driven by less reconnections of the left-sides veins in female patients.

In the study of Hermida at al. differences in PV diameters as measured by use of computed tomography scan before index CBA were reported. All PV diameters were on average 1 mm wider in male patients. In this study the smaller 23 mm-cryoballoon was used in 15% of female patients as opposed to 4% of male patients [5]. In contrast, in our study only the bigger 28 mm-cryoballoon was used in both female and male patients, possibly explaining the difference in PV status between females and males in both studies.

Furthermore, we demonstrated for the first time that female sex is a predictor of finding all PVs durably isolated at repeat ablation procedure after index CB PVI (HR = 2.003; 95% CI 1.090–3.682; $p = 0.025$). This contrasts to the findings of a study of de Pooter et al. in which no clinical or procedural differences were found between patients who presented with durable PVI or PVR at repeat ablation after index RF ablation [15]. Unfortunately, our study did not identify any other predictors of finding durable PVI at repeat ablation, limiting the possibility to plan the procedure.

5.2 | More Low-Voltage Zones in Female Patients With Durable PVI at Repeat Ablation

Atrial fibrosis is a major determinant in the development and progression of AF [16]. Were in most patients the triggers of AF originate in the PVs, atrial fibrosis serves as the substrate for the arrhythmia to persist [17]. Different histopathological studies showed a correlation between AF and the degree of atrial fibrosis, both in postmortem and surgical histological specimens [18–20]. The presence of late-gadolinium contrast enhancement on magnetic resonance imaging or LVZ in high-density electro anatomical mapping at the level of the LA, is considered as a surrogate marker for atrial fibrosis [17, 21]. Both modalities have been used in multiple observational studies who reported a correlation between the presence of left atrial fibrosis and higher recurrence rate of atrial arrhythmia after PVI [17, 22–24].

Akoum et al. reported the association of female sex and a higher burden of atrial fibrosis in AF patients. Of interest, female patients with a prior history of stroke had a higher atrial fibrosis burden compared with both women and men without stroke history, possibly explaining the association of female sex and stroke in AF [25].

Wong et al. reported that female patients who underwent index RF ablation for symptomatic refractory AF had more advanced atrial remodeling than male patients, based on differences in high-density LA electroanatomical maps (lower voltage, slower conduction velocity and greater complex fractionated potentials). This was associated with a higher risk of single and multiprocedural atrial arrhythmia recurrence [26].

In a recent multi-center prospective study, Van Leuven et al. analyzed sex-related differences in the extent and location of spontaneous LVZ as found by high-density mapping during index RF ablation. They found larger LVZ in females, uniformly spread in all LA regions. Interestingly, they reported a different prognostic role of LVZ between sexes: The presence of any LVZ was associated with recurrence of atrial arrhythmia in the total population and in male patients, but not in female patients. In female patients, only a higher burden of LVZ (> 15%) was associated with a higher atrial arrhythmia recurrence rate [27].

In our study we report for the first time differences between sexes in the prevalence of LVZ in patients presenting with durable PVI at repeat ablation. In this population LVZ were more prevalent in female patients (21/35 or 60.0% vs. 12/36 or 33.3%, $p = 0.017$). There were no differences in locations of LVZ between sexes, except for a higher prevalence of diffuse LVZ in female patients (16/35 or 45.7% vs. 7/36 or 19.4%, $p = 0.014$).

Our findings of higher LVZ prevalence in patients presenting with durable PVI at repeat ablation and better PVI durability at repeat procedure in female patients, suggests a less PV-mediated and more substrate-mediated AF course in female patients. Interestingly, this was also suggested in a prospective multi-center study by Bergonti et al. In this study, a novel method to measure atrial fibrillation cycle length (based on the average of 10 consecutive signals (FARS10)) was shown to predict clinical outcome after catheter ablation in paroxysmal atrial fibrillation. Patients with long pulmonary vein cycle lengths had a higher recurrence rate and slow pulmonary vein activity might be a marker of advanced atrial substrate and non-PV triggers. Notably, the authors reported slower pulmonary vein AF cycle lengths in women as compared to men [28]. A higher prevalence of HFpEF and higher rates of inflammation have been considered as possible reasons of a more advanced atrial substrate in female AF patients [6, 29, 30]. This might be of interest in clinical practice, since LVZ-guided ablation has been proposed as a potential ablation strategy in AF patients, mainly when persistent AF is present [31–34].

5.3 | Sex Differences in Ablation Strategy but Same Clinical Outcome in Patients With Durable PVI at Repeat Ablation

The assessment of PVI durability is the first step in every repeat ablation procedure for atrial fibrillation. When PVR is found, the ablation strategy is straightforward by reisolating reconnected veins [35]. In the repeat study of the landmark Fire & Ice trial comparing RF and CBA ablation, durable PVI was reported in only 19%. The total number of reconnected veins was lower in patients originally treated with the cryoballoon (1.4 ± 1.1 vs. 2.1 ± 1.4; $p = 0.010$). The likelihood of finding durable PVI is however increasing as a result of improvements in ablation material and techniques. De Pooter et al. reported durable PVI in 62% patients who were originally treated using the "CLOSE"-protocol, a contact force-guided RF ablation protocol [15]. Our group recently reported durable PVI in 70% patients in a small cohort of 20 patients who underwent repeat ablation after index ablation using CBA with additional electro-anatomical mapping [36].

Patients who present with durable PVI at repeat ablation have a worse clinical outcome compared to patients presenting with PV reconnection [15]. In patients with durable PVI at repeat ablation, the best ablation strategy remains uncertain, because data in this population is sparse (only 2 small single-center studies). Baldinger et al. showed in a small cohort ($N = 26$) that the clinical outcome after repeat procedure in these patients was worse if they presented with AF recurrence (20% freedom of atrial arrhythmia) as compared to AT recurrence (67% freedom of atrial arrhythmia) after index procedure after a follow-up of 17 ± 11 months [37]. Sadek et al. described a bigger cohort ($N = 52$) of patients who presented with durable PVI at repeat ablation for atrial arrhythmia recurrence. Of this cohort, 27 patients underwent repeat ablation for AF recurrence and 25 for AT recurrence with arrhythmia control (defined as no arrhythmia recurrence or < 2 recurrences over follow-up of at least 1 year) in 59% and 64% respectively, after a follow-up of $19 + 6$ months [38].

To the best of our knowledge, we describe the biggest cohort of patients presenting with durable PVI at repeat ablation ($N = 71$). In contrast of both previous studies, all these patients underwent CBA as index ablation procedure. We showed, for the first time, that female patients presenting with durable PVI at repeat ablation after index CBA were more likely to undergo empirical substrate ablation driven by a higher prevalence of LVZ in this population. However, despite different ablation strategies, the 1-year outcome of female and male patients with durable PVI at repeat ablation was the same.

6 | Limitations

Our study has some limitations. First, the study is retrospective and single-center with its inherent limitations, which may restrict our ability to draw substantial conclusions. Second, only a subgroup of patients had cardiac implantable electronic devices and therefore, the frequency of (asymptomatic) atrial arrhythmia recurrence might have been underestimated. Third, the assessment of LVZ was on a descriptive base without strict criteria as mentioned in previous studies [21]. Therefore no burden of LVZ could be calculated. Fourth, since understanding and mapping technology evolved over the study period, no uniform electrophysiological study was performed. Also, a consensus on protocol of non-PV trigger identification is currently lacking. Therefore, it is possible that not all patients with non-PV triggers could be identified. The absence of a standard comprehensive electrophysiological study might explain why we did not find a significant difference in prevalence of non-PV triggers between sexes in contrast to previous studies [39]. Finally, it has to be stressed that the importance of lifestyle factors in AF pathophysiology has emerged in recent years [40, 41]. Clinical outcome after repeat ablation might be further improved by managing this risk factors in a structural way. Sex differences in AF risk factors and their impact on ablation outcome might be useful topics for further research.

7 | Conclusions

Durable PVI at repeat ablation occurs more frequently in female patients. The higher prevalence of low-voltage regions in women and more empirical substrate ablation strategy are suggestive of a less PV-mediated and more substrate-based AF in women. However, in spite of this differences, clinical outcome 1-year after repeat ablation was the same in both sexes.

Ethics Statement

The study was approved by the local ethical committee.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.All data will be made available upon reasonable request.

References

1. G. B. Forleo, C. Tondo, L. De Luca, et al., "Gender-Related Differences in Catheter Ablation of Atrial Fibrillation," *EP Europace* 9, no. 8 (2007): 613–620.

2. M. Takigawa, T. Kuwahara, A. Takahashi, et al., "Differences in Catheter Ablation of Paroxysmal Atrial Fibrillation Between Males and Females," *International Journal of Cardiology* 168, no. 3 (2013): 1984–1991.

3. K. H. Kuck, J. Brugada, A. Fürnkranz, et al., "Impact of Female Sex on Clinical Outcomes in the Fire and Ice Trial of Catheter Ablation for Atrial Fibrillation," *Circulation: Arrhythmia and Electrophysiology* 11, no. 5 (2018): e006204.

4. D. Ricciardi, G. Arena, R. Verlato, et al., "Sex Effect on Efficacy of Pulmonary Vein Cryoablation in Patients With Atrial Fibrillation: Data From the Multicenter Real-World 1STOP Project," *Journal of Interventional Cardiac Electrophysiology* 56, no. 1 (2019): 9–18.

5. A. Hermida, J. Burtin, M. Kubala, et al., “Sex Differences in the Outcomes of Cryoablation for Atrial Fibrillation,” *Frontiers in Cardiovascular Medicine* 9 (2022): 893553.

6. H. Sugumar, S. Nanayakkara, D. Chieng, et al., “Arrhythmia Recurrence Is More Common in Females Undergoing Multiple Catheter Ablation Procedures for Persistent Atrial Fibrillation: Time to Close the Gender Gap,” *Heart Rhythm: The Official Journal of the Heart Rhythm Society* 17, no. 5 Pt A (2020): 692–698.

7. M. Grecu, C. Blomström-Lundqvist, J. Kautzner, et al., investigators E-EEAFAL-TR., “In-Hospital and 12-month Follow-Up Outcome From the ESC-EORP EHRA Atrial Fibrillation Ablation Long-Term Registry: Sex Differences,” *EP Europace* 22, no. 1 (2020): 66–73.

8. N. Patel, A. Deshmukh, B. Thakkar, et al., “Gender, Race, and Health Insurance Status in Patients Undergoing Catheter Ablation for Atrial Fibrillation,” *American Journal of Cardiology* 117, no. 7 (2016): 1117–1126.

9. R. J. R. Yao, L. Macle, M. W. Deyell, et al., Investigators C-DS., “Impact of Female Sex on Clinical Presentation and Ablation Outcomes in the CIRCA-DOSE Study,” *JACC: Clinical Electrophysiology* 6, no. 8 (2020): 945–954.

10. E. Ströker, Y. De Greef, B. Schwagten, et al., “Over-The-Needle Trans-Septal Access Using the Cryoballoon Delivery Sheath and Dilator in Atrial Fibrillation Ablation,” *Pacing and Clinical Electrophysiology* 42, no. 7 (2019): 868–873.

11. X. Cheng, Q. Hu, L. Gao, J. Liu, S. Qin, and D. Zhang, “Sex-Related Differences in Catheter Ablation of Atrial Fibrillation: A Systematic Review and Meta-Analysis,” *EP Europace* 21, no. 10 (2019): 1509–1518.

12. P. B. Nery, D. Belliveau, G. M. Nair, et al., “Relationship Between Pulmonary Vein Reconnection and Atrial Fibrillation Recurrence,” *JACC: Clinical Electrophysiology* 2, no. 4 (2016): 474–483.

13. T. H. Kim, J. Park, J. S. Uhm, B. Joung, M. H. Lee, and H. N. Pak, “Pulmonary Vein Reconnection Predicts Good Clinical Outcome After Second Catheter Ablation for Atrial Fibrillation,” *Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology: Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 19, no. 6 (2017): 961–967.

14. Y. J. Park, J. W. Park, H. T. Yu, et al., “Sex Difference in Atrial Fibrillation Recurrence After Catheter Ablation and Antiarrhythmic Drugs,” *Heart (British Cardiac Society)* 109, no. 7 (2023): 519–526.

15. J. De Pooter, T. Strisciuglio, M. El Haddad, et al., “Pulmonary Vein Reconnection no Longer Occurs in the Majority of Patients After a Single Pulmonary Vein Isolation Procedure,” *JACC: Clinical Electrophysiology* 5, no. 3 (2019): 295–305.

16. M. Allessie, “Electrical, Contractile and Structural Remodeling During Atrial Fibrillation,” *Cardiovascular Research* 54, no. 2 (2002): 230–246.

17. N. F. Marrouche, D. Wilber, G. Hindricks, et al., “Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation: The DECAAF Study,” *Journal of the American Medical Association* 311, no. 5 (2014): 498–506.

18. J. G. Smith, C. Newton-Cheh, P. Almgren, et al., “Assessment of Conventional Cardiovascular Risk Factors and Multiple Biomarkers for the Prediction of Incident Heart Failure and Atrial Fibrillation,” *Journal of the American College of Cardiology* 56, no. 21 (2010): 1712–1719.

19. P. G. Platonov, L. B. Mitrofanova, V. Orshanskaya, and S. Y. Ho, “Structural Abnormalities in Atrial Walls Are Associated With Presence and Persistency of Atrial Fibrillation but not With Age,” *Journal of the American College of Cardiology* 58, no. 21 (2011): 2225–2232.

20. S. Kainuma, T. Masai, M. Yoshitatsu, et al., “Advanced Left-Atrial Fibrosis Is Associated With Unsuccessful Maze Operation for Valvular Atrial Fibrillation,” *European Journal of Cardio-Thoracic Surgery* 40, no. 1 (2011): 61–69.

21. M. Bergonti, F. R. Spera, T. G. Ferrero, et al., “Characterization of Atrial Substrate to Predict the Success of Pulmonary Vein Isolation: The Prospective, Multicenter MASH-AF II (Multipolar Atrial Substrate High Density Mapping in Atrial Fibrillation) Study,” *Journal of the American Heart Association* 12, no. 1 (2023): e027795.

22. A. Verma, O. M. Wazni, N. F. Marrouche, et al., “Pre-Existent Left Atrial Scarring in Patients Undergoing Pulmonary Vein Antrum Isolation,” *Journal of the American College of Cardiology* 45, no. 2 (2005): 285–292.

23. M. Masuda, M. Fujita, O. Iida, et al., “Left Atrial Low-Voltage Areas Predict Atrial Fibrillation Recurrence After Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation,” *International Journal of Cardiology* 257 (2018): 97–101.

24. K. Vlachos, M. Efremidis, K. P. Letsas, et al., “Low-Voltage Areas Detected by High-Density Electroanatomical Mapping Predict Recurrence After Ablation for Paroxysmal Atrial Fibrillation,” *Journal of Cardiovascular Electrophysiology* 28, no. 12 (2017): 1393–1402.

25. N. Akoum, C. Mahnkopf, E. G. Kholmovski, J. Brachmann, and N. F. Marrouche, “Age and Sex Differences in Atrial Fibrosis Among Patients With Atrial Fibrillation,” *EP Europace* 20, no. 7 (2018): 1086–1092.

26. G. R. Wong, C. J. Nalliah, G. Lee, et al., “Sex-Related Differences in Atrial Remodeling in Patients With Atrial Fibrillation: Relationship to Ablation Outcomes,” *Circulation: Arrhythmia and Electrophysiology* 15, no. 1 (2022): e009925.

27. O. Van Leuven, M. Bergonti, F. R. Spera, et al., “Gender-Related Differences in Atrial Substrate in Patients With Atrial Fibrillation,” *The American Journal of Cardiology* 203 (2023): 451–458.

28. M. Bergonti, C. Ascione, P. Compagnucci, et al., “Atrial Fibrillation Cycle-Length (AF-CL) Inside the Pulmonary Veins Predicts Paroxysmal AF Ablation Success- The Induce-AF Study,” *Journal of Interventional Cardiac Electrophysiology* 67, no. 4 (2024): 751–758.

29. A. L. Beale, P. Meyer, T. H. Marwick, C. S. P. Lam, and D. M. Kaye, “Sex Differences in Cardiovascular Pathophysiology: Why Women Are Overrepresented in Heart Failure With Preserved Ejection Fraction,” *Circulation* 138, no. 2 (2018): 198–205.

30. Y. N. V. Reddy, M. Obokata, B. J. Gersh, and B. A. Borlaug, “High Prevalence of Occult Heart Failure With Preserved Ejection Fraction Among Patients With Atrial Fibrillation and Dyspnea,” *Circulation* 137, no. 5 (2018): 534–535.

31. Y. Huo, T. Gaspar, R. Schönbauer, et al., “Low-Voltage Myocardium-Guided Ablation Trial of Persistent Atrial Fibrillation,” *NEJM Evidence* 1, no. 11 (2022): EVIDoa2200141.

32. M. Bergonti, F. R. Spera, T. G. Ferrero, et al., “Anterior Mitral Line in Patients With Persistent Atrial Fibrillation and Anterior Scar: A Multicenter Matched Comparison-The Miline Study,” *Heart Rhythm: The Official Journal of the Heart Rhythm Society* 20, no. 5 (2023): 658–665.

33. J. Junarta, M. U. Siddiqui, J. M. Riley, S. J. Dikdan, A. Patel, and D. R. Frisch, “Low-Voltage Area Substrate Modification for Atrial Fibrillation Ablation: A Systematic Review and Meta-Analysis of Clinical Trials,” *EP Europace* 24, no. 10 (2022): 1585–1598.

34. A. M. Al-Kaisey, R. Parameswaran, S. A. Joseph, P. M. Kistler, J. B. Morton, and J. M. Kalman, “Extensive Right Atrial Free Wall Low-Voltage Zone as the Substrate for Atrial Fibrillation: Successful Ablation by Scar Homogenization,” *EP Europace* 23, no. 1 (2021): 59–64.

35. H. Calkins, G. Hindricks, R. Cappato, et al., “2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation,” *Heart Rhythm: The Official Journal of the Heart Rhythm Society* 14, no. 10 (2017): e275–e444.

36. M. Tijskens, J. P. Abugattas, H. Thoen, et al., “Adding Electroanatomical Mapping to Cryoballoon Pulmonary Vein Isolation Improves

1-Year Clinical Outcome and Durability of Pulmonary Vein Isolation: A Propensity Score-Matched Analysis," *Journal of Cardiovascular Development and Disease* 11, no. 2 (2024): 57.

37. S. H. Baldinger, J. S. Chinitz, S. Kapur, et al., "Recurrence of Atrial Arrhythmias Despite Persistent Pulmonary Vein Isolation After Catheter Ablation for Atrial Fibrillation," *JACC: Clinical Electrophysiology* 2, no. 6 (2016): 723–731.

38. M. M. Sadek, S. Maeda, W. Chik, et al., "Recurrent Atrial Arrhythmias in the Setting of Chronic Pulmonary Vein Isolation," *Heart Rhythm: The Official Journal of the Heart Rhythm Society* 13, no. 11 (2016): 2174–2180.

39. P. Santangeli, E. S. Zado, M. D. Hutchinson, et al., "Prevalence and Distribution of Focal Triggers in Persistent and Long-Standing Persistent Atrial Fibrillation," *Heart Rhythm: The Official Journal of the Heart Rhythm Society* 13, no. 2 (2016): 374–382.

40. R. K. Pathak, M. E. Middeldorp, D. H. Lau, et al., "Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation," *Journal of the American College of Cardiology* 64, no. 21 (2014): 2222–2231.

41. A. D. Elliott, C. V. Verdicchio, R. Mahajan, et al., "An Exercise and Physical Activity Program in Patients With Atrial Fibrillation," *JACC: Clinical Electrophysiology* 9, no. 4 (2023): 455–465.

Appendix

See Table A1.

TABLE A1 | Clinical characteristics of patients with durable PVI at repeat procedure ($N = 71$).

	Total ($N = 71$)	**Females ($N = 35$)**	**Males ($N = 36$)**	***p* value**
Patient characteristics				
Age	62.2 ± 12.3	64.8 ± 9.2	61.1 ± 13.4	0.379
BMI	28.0 ± 4.9	28.1 ± 5.9	27.9 ± 4.2	0.243
Arterial hypertension	45 (63.4%)	21 (61.2%)	24 (64.9%)	0.786
Diabetes	10 (14.1%)	5 (14.7%)	5 (13.5%)	0.885
Previous stroke/TIA	9 (12.7%)	2 (5.9%)	7 (18.9%)	0.099
CHADS-VASc score	2.1 ± 1.5	2.8 ± 1.3	1.7 ± 1.5	**< 0.001**
0	8 (11.3%)	0 (0%)	8 (21.6%)	**0.03**
1	9 (12.7%)	6 (17.6%)	3 (8.1%)	
2	17 (23.9%)	9 (26.5%)	8 (21.6%)	
≥ 3	37 (52.1%)	19 (55.9%)	18 (48.6%)	
Obstructive sleep apnea	5 (7.0%)	1 (2.9%)	4 (10.8%)	0.195
Structural heart disease	26 (36,7%)	9 (26.5%)	17 (45.9%)	0.089
LA diameter (mm)	44.4 ± 6.8	42.3 ± 7.1	45.5 ± 6.4	0.083
Characteristics of AF before PVI				
Diagnosis-to-ablation time (months)	39.1 ± 51.6	33.8 ± 48.5	42.0 ± 53.1	0.143
Paroxysmal AF	37 (52.1%)	19 (55.9%)	18 (48.6%)	0.542
Persistent AF < 1 year	31 (43.7%)	13 (38.2%)	18 (48.6%)	0.377
Persistent AF > 1 year	3 (4.2%)	2 (5.9%)	1 (2.7%)	0.506
Number of AAD before PVI	1.5 ± 0.8	1.6 ± 0.7	1.4 ± 0.8	0.683
Tachycardia-induced cardiomyopathy	10 (14.1%)	4 (11.7%)	6 (16.2%)	0.558
Follow-up after PVI				
Time to AF recurrence (months)	9.7 ± 9.2	11.2 ± 10.5	8.9 ± 8.3	0.348
Time to repeat procedure (months)	15.6 ± 15.6	17.4 ± 13.6	14.7 ± 16.5	0.816