

University of Groningen

Assessment of sex-related differences and outcome in patients who underwent cryoballoon pulmonary vein isolation for atrial fibrillation

Ekrami, Neda Khalilian; Magni, Federico T; Dayalani, Vijay; van Gelder, Isabelle C; Groenveld, Hessel F; Tieleman, Robert G; Wiesfeld, Ans Cp; Tan, Eng S; Rienstra, Michiel; Blaauw, Yuri

Published in:
BMJ Open

DOI:
[10.1136/bmjopen-2022-063359](https://doi.org/10.1136/bmjopen-2022-063359)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Ekrami, N. K., Magni, F. T., Dayalani, V., van Gelder, I. C., Groenveld, H. F., Tieleman, R. G., Wiesfeld, A. C., Tan, E. S., Rienstra, M., Blaauw, Y., & Mulder, B. A. (2022). Assessment of sex-related differences and outcome in patients who underwent cryoballoon pulmonary vein isolation for atrial fibrillation: an observational cohort study. *BMJ Open*, 12(11), Article e063359. <https://doi.org/10.1136/bmjopen-2022-063359>

Copyright



Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

BMJ Open Assessment of sex-related differences and outcome in patients who underwent cryoballoon pulmonary vein isolation for atrial fibrillation: an observational cohort study

Neda Khalilian Ekrami, Federico T Magni, Vijay Dayalani, Isabelle C van Gelder, Hessel F Groenveld, Robert G Tieleman, Ans CP Wiesfeld, Eng S Tan, Michiel Rienstra, Yuri Blaauw , Bart A Mulder 

To cite: Ekrami NK, Magni FT, Dayalani V, *et al.* Assessment of sex-related differences and outcome in patients who underwent cryoballoon pulmonary vein isolation for atrial fibrillation: an observational cohort study. *BMJ Open* 2022;**12**:e063359. doi:10.1136/bmjopen-2022-063359

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-063359>).

Received 29 March 2022
Accepted 06 October 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands

Correspondence to
Dr Bart A Mulder;
b.a.mulder@umcg.nl

ABSTRACT

Objectives Pulmonary vein isolation (PVI) is widely accepted as an effective and safe treatment for symptomatic atrial fibrillation (AF). However, data on sex-related differences and associations with clinical outcome and safety of PVI with cryoballoon ablation are limited. We sought to compare sex-related efficacy and safety of cryoballoon ablation and identify sex-related associations with clinical outcomes.

Methods and results We included 650 consecutive patients with AF undergoing PVI with cryoballoon ablation at our institution between 2013 and 2017. The efficacy outcome was the first documented recurrence (>30 s) of AF, atrial flutter or atrial tachycardia (AF/AT) or repeat ablation during follow-up, after a 90-day blanking period. The safety outcome was the incidence of periprocedural complications. Mean age of the population was 58±10, and 210 (32.3%) patients were women. Women were older, had a higher body mass index, had more renal dysfunction and less coronary artery disease as compared with men. The rate of AF/AT recurrence was similar between women and men at 12-month follow-up (27.6% vs 24.8%, $p=0.445$). The incidence of periprocedural complications was higher in women (12.9% vs 4.6%; $p<0.001$), specifically groin haematomas and phrenic nerve palsy. On multivariate analysis, left atrial volume index (adjusted OR 1.05, 95% CI 1.00 to 1.10; $p=0.032$) was associated with the incidence of procedural complications in women. For men, no relation with complications could be found.

Conclusion The efficacy of cryoballoon ablation was similar between women and men; however, women had a higher risk of procedural complications.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained tachycardia with an estimated prevalence in 2017 of 37.5 million adults worldwide.¹ Approximately, one in four adults develop AF in their lifetime, resulting in an increased global burden of hospitalisations and mortality.^{1 2} Significant sex-related

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The paper describes a contemporary homogenous well-characterised cohort of patients with atrial fibrillation (AF).
- ⇒ In total, 650 consecutive patients underwent pulmonary vein isolation with cryoballoon, in a similar way, in a single centre.
- ⇒ There was no implantable recording to identify AF/AT recurrences, which is a limitation of this study.
- ⇒ We recognise that due to the retrospective nature of the study, not all potential variables were available and, therefore, there may be residual confounding.

differences in clinical presentation and treatment of AF have been recognised. Women are often older and present with more symptoms at time of diagnosis, report a lower quality of life and have a higher mortality rate.^{3–5}

In the last two decades, pulmonary vein isolation (PVI) with cryoballoon ablation is often performed for non-pharmacological rhythm control therapy for AF.^{1 6 7} Recent studies that examined sex-related outcomes after PVI have indicated that women have a higher risk of atrial arrhythmia recurrence after catheter ablation and more frequently experienced periprocedural complications, specifically cardiac perforation/tamponade and groin complications.^{4 5 8} Although the patient sample sizes in these studies were robust, the analyses included patients undergoing heterogeneous index ablation strategies such as cryoballoon ablation or radiofrequency ablation.^{4 8 9} There is a paucity of data on the difference in procedural safety and efficacy between men and women exclusively undergoing PVI with cryoballoon ablation.^{5 8} This present study, therefore, sought

to examine sex-related differences and evaluate efficacy and safety of PVI with cryoballoon ablation in a large homogenous contemporary cohort of patients with AF.

METHODS

Study population

All patients with symptomatic AF who underwent PVI using the second-generation cryoballoon from January 2013 to December 2017 at the University Medical Center Groningen, The Netherlands, were included in this observational cohort study. Each patient provided informed consent for the ablation procedure. Baseline visit recordings included demographic data, patient AF history and symptoms, relevant medical history, physical examination, 12-lead ECG, echocardiography, antiarrhythmic drug (AAD) use and use of other cardiovascular medication. Data collection and analysis were performed retrospectively on the prespecified efficacy and safety outcomes.

Catheter ablation procedure

Cryoballoon ablation was performed under conscious or deep sedation. Femoral venous access was not guided by ultrasound. Access to the left atrium was achieved with a single transeptal puncture with an SL-0 sheath (St. Jude Medical, Minneapolis, Minnesota) using intracardiac echocardiography. The SL-0 sheath was then replaced by a steerable sheath (FlexCath Advance, Medtronic), after which left atrial and pulmonary vein (PV) anatomy were visualised by angiography. In order to record PV signals prior to ablation, an innerlumen mapping catheter (Achieve catheter, Medtronic) was placed through the steerable sheath proximal to each PV ostium. The ablation was performed using the second-generation 28 mm cryoballoon (Arctic Front Advance Cardiac CryoAblation Catheter System; Medtronic, Minneapolis, Minnesota). Until 2017, at least two cryothermal applications (lasting 240 s) were delivered to isolate each vein. In 2017, the approach proposed by Aryana *et al* was adopted.¹⁰ The endpoint of the procedure was electrical isolation of PV signals. This was evaluated using the circular Achieve mapping catheter to verify entrance block of all isolated veins. Pacing within the PV's was performed to assess exit block if there was doubt of entrance block. Diaphragmatic stimulation was performed during ablation of the right side veins to avoid phrenic nerve injury.

Postablation management and follow-up

All patients were followed up for at least 12 months after the procedure. Follow-up visits were scheduled at 3, 6 and 12 months at the outpatient clinic, after which follow-up was discontinued on the condition that the patient had not experienced a recurrence of AF, atrial flutter or atrial tachycardia (AF/AT). Patients were monitored with a 12-lead (ECG and 24-hour Holter prior to each follow-up visit. Additionally, the presence of any adverse events, including AF/AT recurrence, documented during

a visit to the general practitioner, hospital admission or emergency room was noted during each follow-up visit. Patients were screened for procedural complications before discharge as well as at the follow-up outpatient clinic visits. Additionally, patients were advised to contact their treating physician if they experienced any complications related to the cryoablation between discharge and the 3-month follow-up. Phrenic nerve palsy was examined through diaphragmatic tone on an X-ray before discharge in patients who experienced phrenic nerve palsy. Complications were defined as described in the 2017 hours/EHRA/ECAS Expert Consensus Statement on catheter and surgical ablation of AF.¹¹

Outcomes

The primary efficacy outcome of this study was the first documented recurrence of AF/AT lasting more than 30 s or repeat ablation during a follow-up of 12 months, after a blanking period of 90 days. The safety outcome was the incidence of periprocedural complications, including but not limited to vascular access complications, phrenic nerve palsy at discharge, cardiac tamponade and thromboembolism. Vascular access complications included groin haematomas, pseudoaneurysms and arteriovenous fistulas. Thromboembolic complications included cerebrovascular accidents, transient ischaemic attacks, pulmonary embolisms and deep vein thrombosis.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

Statistical analysis

A two-sided $p < 0.05$ was considered statistically significant. Descriptive statistics were used to summarise patient characteristics. Continuous data were presented as a mean with SD or a median with IQR and categorical data were presented as counts with percentages. Differences in baseline characteristics and periprocedural complications between sexes were assessed by means of a t test or Mann-Whitney-Wilcoxon tests for continuous variables and a χ^2 test for categorical variables. Cumulative incidence of AF/AT recurrence was estimated using the Kaplan-Meier method and compared with the log-rank test by sex and by AF type. Furthermore, univariate and multivariate Cox proportional hazards regression analyses were performed to assess the association between baseline patient characteristics and the risk of AF/AT recurrence occurring in a patient. HRs and 95% CIs were reported. The covariates included in the multivariable regression model were chosen based on their clinical relevance, significance in the univariate analyses with a p value of < 0.10 and availability of at least 80% of data. These chosen covariates were included in the multivariate model via backward selection.

To assess the association between women and periprocedural complications and identify associations with

Table 1 Baseline characteristics of the population of patients at index visit according to sex

Baseline characteristics	Total (N=650)	Women (N=210)	Men (N=440)	P value
Age (years)	58±10	61±10	59±10	0.017
BMI (kg/m ²)	28±4	29±5	27±4	<0.001
Type of AF:				
Paroxysmal	509 (78%)	170 (81%)	339 (77%)	0.214
Persistent	140 (22%)	39 (19%)	101 (23%)	
Duration AF (years)	3.8 [1.8–7.2]	3.7 [1.8–6.5]	3.8 [1.8–7.5]	0.403
Duration follow-up since cryoballoon ablation (months)	12 (11–21)	13 (11–22)	12(11–20)	0.581
Medical history:				
Diabetes mellitus	59 (9%)	27 (13%)	32 (7%)	0.020
Hypertension	241 (37%)	93 (44%)	148 (34%)	0.009
Heart failure	38 (6%)	11 (5%)	27 (6%)	0.648
COPD	27 (4%)	11 (5%)	16 (4%)	0.339
Coronary artery disease	69 (11%)	14 (7%)	55 (13%)	0.024
Peripheral vascular disease	19 (3%)	7 (3%)	12 (3%)	0.668
Stroke/CVA	44 (7%)	16 (8%)	28 (6%)	0.551
Chronic kidney disease (eGFR <60 mL/min/1.73 m ²)	53 (8%)	28 (14%)	25 (6%)	0.001
Anti-arrhythmic drug use	433 (67%)	153 (73%)	280 (64%)	0.020
AAD use: class I	245 (38%)	89 (42%)	156 (36%)	0.088
AAD use: class III	229 (35%)	75 (36%)	154 (35%)	0.859
Number of failed AADs≥2	52 (8%)	16 (8%)	36 (8%)	0.805
CHA ₂ DS ₂ -VASc Score	1±1	2±1	1±1	<0.001
Echocardiography				
Moderate/severe MV insufficiency	24 (4%)	9 (5%)	15 (4%)	0.533
LA volume index (mL/m ²)	34±10	33±10	34±10	0.483
LVEF (%)	55 (55–55)	55 (55–55)	55 (55–55)	0.964
LA diameter (mm)	40±6	38±7	41±5	0.007
LA volume (cm ³)	69±19	64±19	71±18	0.016

Data are presented as mean±SD or median (IQR) or number (%). Statistical tests conducted: t-tests for normally distributed continuous variables, Mann-U Whitney tests for non-normally distributed continuous variables and χ^2 tests for categorical variables. AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LA, left atrial; LVEF, left ventricular ejection fraction; MV, mitral valve.

complications in women, a multivariate logistic regression model was constructed. This model included covariates based on their clinical relevance, significance on univariate analysis ($p<0.10$) with the occurrence of at least one periprocedural complication and availability of data ($\geq 80\%$). ORs and 95% CIs were reported. During multivariable analysis, a baseline characteristic remained significant if $p<0.05$ was achieved. All statistical analyses were performed using SPSS software (SPSS, Chicago, Illinois).

RESULTS

Baseline patient characteristics

A total of 650 patients with symptomatic drug-refractory AF were included in the study, 32.3% were women (table 1). Women were older (61±10 years vs 59±10 years;

$p=0.017$), had a higher body mass index (BMI) (29±5 kg/m² vs 27±4 kg/m²; $p<0.001$) and a smaller left atrium (38±7 mm vs 41±5 mm; $p=0.007$) than men. Women had a higher prevalence of diabetes mellitus (13% vs 7%; $p=0.02$), hypertension (44% vs 34%; $p=0.009$) and chronic kidney disease (14% vs 6%; $p=0.001$). Coronary artery disease was less common in women (7% vs 13%; $p=0.024$). No differences were observed in the duration of time from first AF diagnosis until time of first cryoballoon ablation (median 3.8 years, IQR 1.8–7.2 years). Prior to PVI, women were more often treated with AADs (73% vs 64%; $p=0.02$).

Efficacy of ablation and predictors of AF recurrence

Median follow-up was 12 months (IQR 11–21), maximum follow-up duration was 69 months. During a follow-up period of 12 months, 167 (25.7%) patients had at least

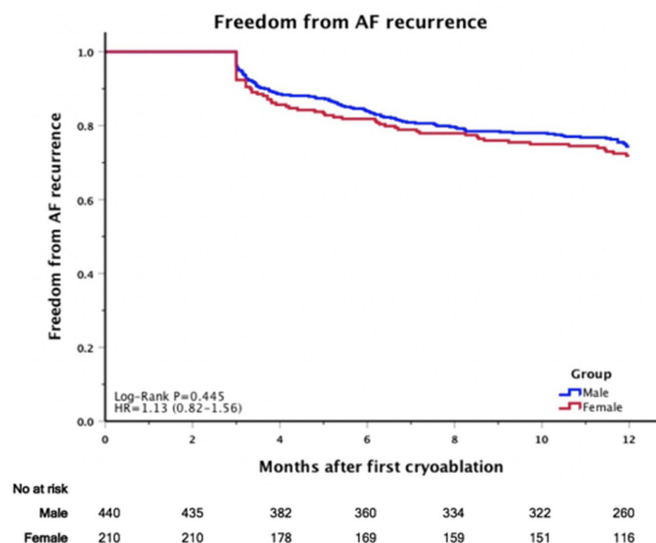


Figure 1 Success at 12 months of follow-up between women and men after cryoballoon ablation. AF, atrial fibrillation.

one AF/AT recurrence episode. After a follow-up of 12 months, the rate of AF/AT recurrences was similar between women and men (27.6% vs 24.8%, log-rank $p=0.445$, **figure 1**). Freedom from AF/AT recurrence at 12-month follow-up remained similar between women and men regardless of AF type; patients with paroxysmal AF (26.3% vs 21.8%, log-rank $p=0.298$, **figure 2A**), patients with persistent AF (33.3% vs 34.7%, log-rank $p=0.829$, **figure 2B**). In the total population, sex itself was not associated with AF recurrence (data not shown). Variables significantly associated with an increased AF/AT recurrence in multivariate analysis were type of AF, number of failed AADs, chronic kidney disease and left ventricular ejection fraction (LVEF) (data not shown).

Separate sex analysis showed for women an association between AF recurrence with diabetes mellitus and heart failure. For men, an association with type of AF was found (**table 2**). During follow-up, 125/650 (19.2%) patients with an AF/AT recurrence underwent repeat PVI; there

was no difference between 43/210 (20.4%) women and 82/440 (18.6%) men.

Periprocedural complications

Periprocedural complications are shown in **table 3**.

In total, 47 (7.2%) patients experienced a periprocedural complication. Women had significantly higher complication rates than men (12.9% vs 4.8%; $p<0.001$). In particular, women experienced higher rates of phrenic nerve palsy (4.8% vs 1.6%; $p=0.018$) and vascular access complications, specifically groin haematomas (2.4% vs 0.2%; $p=0.011$) than men (**figure 3**). In the multivariable logistic regression analysis (**table 4**), LAVI was significantly associated with the occurrence of any periprocedural complication (adjusted OR 1.05, 95% CI 1.00 to 1.10; $p=0.032$). In men, no associations were found with the occurrence of periprocedural complication (data not shown).

DISCUSSION

In this retrospective cohort study, women were younger, had more often diabetes and hypertension as compared with men. AF/AT recurrences at 12 months after initial PVI were similar for women and men, regardless of AF type. However, women experienced more procedure-related complications, particularly phrenic nerve palsy and groin haematomas.

Sex-based differences in risk factors

In our study, women were on average older, had a higher BMI and a smaller left atrium than men. Women had a higher prevalence of diabetes mellitus, hypertension and chronic kidney disease, and prior to PVI, women were more often treated with AADs. This is in line with findings from previous studies that also showed that women catheter ablation of AF are on average older with increased comorbidities compared with men.^{3-5 12} As compared with the study by Ricciardi *et al*, ours show different results on multiple occasions. First, the population under investigation.¹² Our female group was on average older, had a

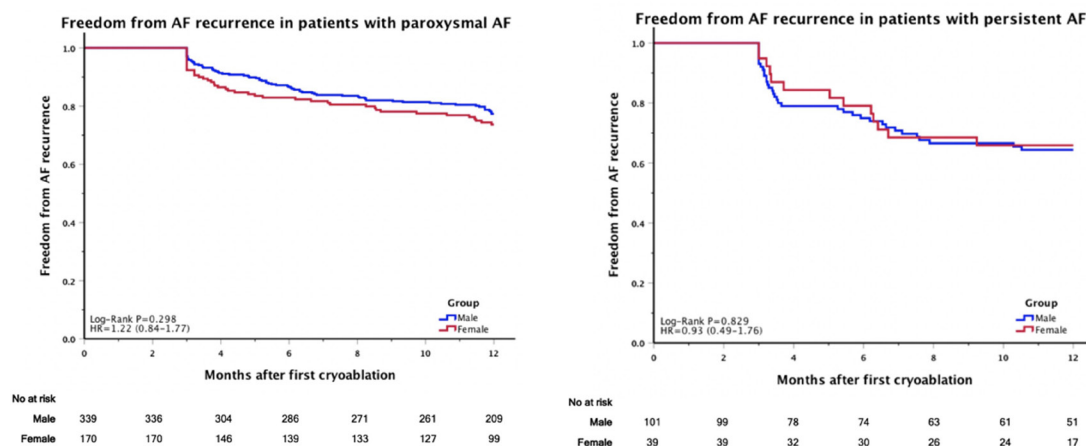


Figure 2 Freedom from AF recurrence between women and men with (A) paroxysmal AF and (B) persistent AF at 12 month follow-up after cryoballoon ablation. AF, atrial fibrillation.

Table 2 Univariate and multivariate Cox proportional hazard analysis of AF recurrence during a follow-up of 12 months after cryoablation according to sex

Cohort	Baseline characteristics	Univariate		Multivariate	
		Hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
Women (N=210)	Age	0.99 (0.96 to 1.02)	0.545*	0.98 (0.95 to 1.01)	0.193
	Diabetes mellitus	2.84 (1.40 to 5.78)	0.004†	3.13 (1.50 to 6.55)	0.002
	Heart failure	2.73 (1.07 to 6.95)	0.035†	2.84 (1.10 to 7.33)	0.031
Men (N=440)	Age	1.00 (0.98 to 1.02)	0.847*	1.00 (0.98 to 1.02)	0.999
	Type of AF (persistent)	1.71 (1.10 to 2.67)	0.018†	1.71 (1.10 to 2.68)	0.018
	Chronic kidney disease (eGFR <60 mL/min/1.73 m ²)	2.21 (1.11 to 4.40)	0.024†		
	LVEF	0.96 (0.93 to 0.99)	0.008†		

*Demographic variables tested further with multivariable analysis.
 †Significant univariable baseline characteristic ($\alpha \leq 0.10$) tested further with multivariable analysis.
 AF, atrial fibrillation; eGFR, Estimated Glomerular Filtration Rate ; LVEF, left ventricular ejection fraction.

higher BMI and a smaller left atrium than men. Women had a higher prevalence of diabetes mellitus, hypertension and chronic kidney disease, and prior to PVI, women were more often treated with AADs. This highlights a slightly more ‘diseased’ female group. Second, in our study, variables significantly associated with an increased AF/AT recurrence in multivariate analysis were type of AF, number of failed AADs, chronic kidney disease and LVEF. In the study by Ricciardi *et al*, female sex, AF type and age were confirmed as independent predictors of AF recurrence on multivariable model analysis. Finally, Ricciardi *et al* observed no difference in rate of periprocedural complications between the two groups and no association with known risk factors.¹² In the ORBIT-AF trial, women were shown to be less likely to undergo an electrical cardioversion (26.7% vs 32.4%, $p < 0.001$) and to be referred for AF ablation (4.9% vs 5.9%, $p = 0.04$).¹³ In our study, no differences were observed in the duration of time from first AF diagnosis until time of first cryoballoon

ablation (median 3.8 years, IQR 1.8–7.2 years), suggesting no delay in ablation treatment. With regards to AAD use, as shown in a post hoc analysis of the RACE I trial, a trial conducted in the Netherlands, the higher prevalence of failed AADs among women was partly explained by the higher incidence of AAD-related adverse effects.¹⁴

Sex-based differences in efficacy and indicators of recurrences after cryoballoon ablation

A study suggested a significantly lower rate of freedom from AF/AT recurrence in women.⁸ A post hoc analysis of FIRE and ICE reported that women with paroxysmal AF had a 37% increased risk of atrial arrhythmia recurrence, which could not be fully attributed to the difference in baseline characteristics.⁸ Cheng *et al* noted that the rate of freedom from AF/AT recurrences was 25% lower in women than in men at 2.4-year follow-up. These analyses examined outcomes of both PVI by cryoballoon ablation and radiofrequency energy ablation in patients with AF as

Table 3 Periprocedural complications of the population of patients at index visit according to sex

Periprocedural complications	Total (n=650)	Women (n=210)	Men (n=440)	P value
At least one complication	49 (7.5%)	27 (12.9%)	20 (4.8%)	<0.001
Thromboembolism	5 (0.8%)	2 (1.0%)	3 (0.7%)	0.712
Stroke	4 (0.6%)	2 (1.0%)	2 (0.5%)	0.448
TIA	1 (0.2%)	0 (0.0%)	1 (0.2%)	0.489
Vascular access complications	24 (3.7%)	13 (6.2%)	10 (2.3%)	0.011
Haematoma	6 (0.9%)	5 (2.4%)	1 (0.2%)	0.007
Pseudoaneurysm	12 (1.8%)	7 (3.3%)	5 (1.1%)	0.052
AV fistula	6 (0.9%)	2 (1.0%)	4 (0.9%)	0.957
Phrenic nerve palsy	19 (2.9%)	10 (4.8%)	7 (1.6%)	0.018
Cardiac tamponade	3 (0.5%)	2 (1.0%)	1 (0.2%)	0.202

Data are presented as number (%). χ^2 tests conducted to check for differences between the two sexes.
 AV, arteriovenous; CVA, cerebrovascular accident; TIA, transient ischaemic attack.

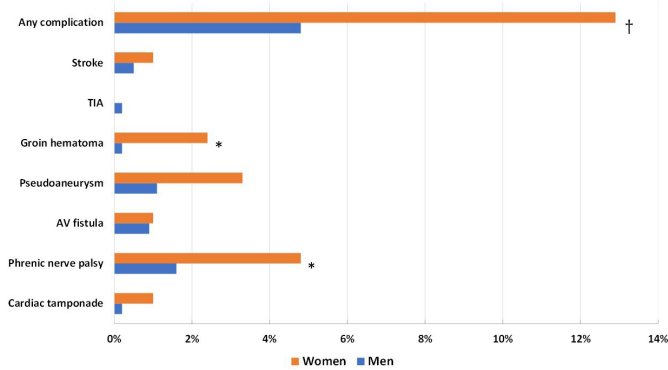


Figure 3 Rates of occurrence are calculated as percentage of those with periprocedural complications within each sex. AV, arteriovenous; CVA, cerebrovascular accident; TIA, transient ischaemic attack. * $p < 0.05$, † $p < 0.001$.

one cohort. This could explain the discrepancy between their study and ours, which exclusively looked at cryoballoon ablation in patients with AF. There is a sparseness of literature that focuses on sex-related differences in outcomes of patients with AF exclusively undergoing PVI with a cryoballoon. A recent study found a comparable response between men and women at 24 months

after cryoballoon ablation (HR 0.98, 95% CI 0.80 to 1.20; $p = 0.62$). However, long-term follow-up (up to 36 months) showed a significantly higher unadjusted cumulative AF recurrence for women.¹² Important to realise is that at 36 months less than 10% of patients included were still at risk for failure, implying a less robust conclusion that can be drawn. The sample size used in the long-term analysis may, therefore, have been underpowered and may have exaggerated the results to some extent.¹² Furthermore, as compared with our study, we are a single-centre experience with a fixed protocol for PVI. In the present study, freedom from AF/AT recurrence was similar in women and men (72.4% vs 75.2%) at 12-month follow-up, regardless of AF type. Our results are in line with other studies which report a similar success rate in both women and men within the range of 65–89% at 12 months.^{15–17} Moreover, sex was not found to be significantly associated with AF/AT recurrence, consistent with findings from other studies on cryoballoon ablation in symptomatic patients with AF.^{18,19} Furthermore, in our multivariate analysis, we revealed that patients suffering from persistent AF had an increased risk of AF/AT recurrence after initial cryoballoon ablation. A finding consistent with other studies that

Table 4 Univariate and multivariate logistic regression analysis of periprocedural complications associated with cryoablation in women

Baseline characteristics	Univariate		Multivariate	
	Unadjusted odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
Age	1.02 (0.98 to 1.06)	0.397*	1.00 (0.96 to 1.04)	0.954
BMI	0.96 (0.89 to 1.04)	0.325		
Duration of AF	1.04 (0.95 to 1.14)	0.391		
Type of AF:				
Paroxysmal	0.64 (0.25 to 1.64)	0.358		
Persistent	1.55 (0.61 to 3.96)	0.358		
Number of failed AADs ≥ 2	2.36 (0.70 to 7.92)	0.164		
Diabetes mellitus	0.79 (0.22 to 2.82)	0.716		
Hypertension	1.82 (0.81 to 4.03)	0.145		
Heart failure	0.64 (0.08 to 5.18)	0.673		
COPD	1.48 (0.30 to 7.23)	0.629		
Coronary artery disease	1.09 (0.23 to 5.15)	0.914		
Peripheral vascular disease	0.00 (0.00 to 0.00)	0.999		
Stroke/CVA	0.92 (0.20 to 4.30)	0.919		
Renal dysfunction (eGFR < 60 mL/min/1.73 m ²)	0.51 (0.19 to 1.40)	0.191		
CHA ₂ DS ₂ VASc Score	1.07 (0.82 to 1.40)	0.629		
LA diameter (index)	1.06 (0.94 to 1.19)	0.337		
LAVI	1.05 (1.01 to 1.09)	0.030†	1.05 (1.00 to 1.10)	0.032
LEVF	1.01 (0.92 to 1.10)	0.891		

*Demographic variables tested further with multivariable analysis.

†Significant univariable baseline characteristic ($\alpha \leq 0.10$) tested further with multivariable analysis.

AAD, antiarrhythmic drug; AF, atrial fibrillation; BMI, body mass index; CVA, cerebrovascular accident; eGFR, Estimated Glomerular Filtration Rate; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction.

determined significant associations between persistent AF and a long history of AF with AF/AT recurrence after cryoballoon ablation.^{20 21}

Sex-based differences in safety and predictors of periprocedural complications in women

Women undergoing PVI with cryoballoon were found to have a higher risk of complications, mainly driven by phrenic nerve palsy and groin haematomas. These findings are consistent with those from other studies in which women experienced higher rates of vascular access complications, mainly groin haematomas and femoral pseudoaneurysms.^{4 8 9} This increased risk could potentially be attributed to the fact that women included in this study had significantly higher BMI. We found an increased risk of phrenic nerve palsy during cryoballoon ablation in women. Underlying mechanisms that play a role in the observed sex difference in the occurrence of phrenic nerve palsy are unknown.²² In our study, LAVI was found to be associated with periprocedural complications in women. An enlarged left atria could result in increased risk given that cryoballoon ablation in these atria occurs distally and deeper within the PVs resulting in lesions closer to the course of the phrenic nerve. Other explanations could be that the angle between the PV and the left atrial wall in some patients might increase the risk for phrenic nerve palsy. Furthermore, a relation between the incidence of phrenic nerve injury, female sex and lower BMI has been reported before.^{23 24}

LIMITATIONS

First, although this study reports outcomes in a large contemporary homogenous cohort of AF patients, this is a single centre, non-randomised, retrospective cohort study and as such is subject to all limitations inherent to the study design. However, there was no selection bias as all consecutive patients undergoing PVI with cryoballoon between 2013 and 2017 at our institution were included in the analyses. Lastly, although the majority of patients with recurrence of AF/AT presented with sustained forms of atrial arrhythmia, AF/AT recurrence rates may have been underestimated. As AF/AT recurrences were documented by ECG and Holter monitoring, some asymptomatic non-sustained AF/AT episodes may have been missed. At the time of this study, we did not routinely use ultrasound guided vascular access and the figure of eight stitch was only introduced in recent years. This may have affected the rate of complications registered in our population. However, as shown in the ULTRA-FAST trial, investigating the efficacy and safety of ultrasound-guided venipuncture of femoral veins in patients undergoing catheter ablation for AF, rates of major vascular complications were not reduced using ultrasound to guide femoral access.²⁵

CONCLUSION

Women undergoing their first PVI with cryoballoon ablation had similar rates of success as men. However, women experienced higher rates of vascular access complications and phrenic nerve palsy.

Twitter Bart A Mulder @BA_Mulder

Contributors NKE, FM, VD, YB and BAM designed the study. NKE, FM, VD and BAM drafted the manuscript. VD and BAM performed all statistical analyses. NKE, FM, VD, ICvG, YB, HFG, RGT, ACPW, YEST, MR and BAM provided substantial contributions to data interpretation and critical revisions, and NKE, FM, VD, ICvG, YB, HFG, RGT, ACPW, YEST, MR and BAM approved the final manuscript. NKE, FM, VD, YB and BAM are responsible for the overall content as guarantor and thereby accept full responsibility for the finished work and the conduct of the study, including access to the data.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author upon a reasonable request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Yuri Blaauw <http://orcid.org/0000-0003-2366-3686>

Bart A Mulder <http://orcid.org/0000-0002-4411-3918>

REFERENCES

- Hindricks G, Potpara T, Dagres N. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for Cardio-Thoracic surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of cardiology (ESC) developed with the special contribution of the European heart rhythm association (EHRA) of the ESC. *Eur Heart J* 2020;42.
- Chugh SS, Havmoeller R, Narayanan K, *et al.* Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation* 2014;129:837–47.
- Kloosterman M, Crijns HJGM, Mulder BA, *et al.* Sex-Related differences in risk factors, outcome, and quality of life in patients with permanent atrial fibrillation: results from the race II study. *Europace* 2020;22:1619–27.
- Kloosterman M, Chua W, Fabritz L, *et al.* Sex differences in catheter ablation of atrial fibrillation: results from AXAFA-AFNET 5. *Europace* 2020;22:1026–35.
- Linde C, Bongiorni MG, Birgersdotter-Green U, *et al.* Sex differences in cardiac arrhythmia: a consensus document of the European heart rhythm association, endorsed by the heart rhythm Society and Asia Pacific heart rhythm Society. *Europace* 2018;20:1565–1565ao.
- Kuck K-H, Brugada J, Fürnkranz A, *et al.* Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med* 2016;374:2235–45.
- Mulder BA, Luermans JGLM, Hindricks G, *et al.* Innovations and paradigm shifts in atrial fibrillation ablation. *Europace* 2021;23:ii23–7.
- Kuck K-H, Brugada J, Fürnkranz A, *et al.* Impact of female sex on clinical outcomes in the fire and ice trial of catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2018;11:e006204.
- Cheung JW, Cheng EP, Wu X, *et al.* Sex-based differences in outcomes, 30-day readmissions, and costs following catheter



- ablation of atrial fibrillation: the United States nationwide readmissions database 2010-14. *Eur Heart J* 2019;40:3035-43.
- 10 Aryana A, Kenigsberg DN, Kowalski M, *et al.* Verification of a novel atrial fibrillation cryoablation dosing algorithm guided by time-to-pulmonary vein isolation: results from the Cryo-DOSING study (Cryoballoon-ablation dosing based on the assessment of Time-to-Effect and pulmonary vein isolation guidance). *Heart Rhythm* 2017;14:1319-25.
 - 11 Calkins H, Hindricks G, Cappato R, *et al.* 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. *Europace* 2018;20:157-208.
 - 12 Ricciardi D, Arena G, Verlato R, *et al.* Sex effect on efficacy of pulmonary vein cryoablation in patients with atrial fibrillation: data from the multicenter real-world 1STOP project. *J Interv Card Electrophysiol* 2019;56:9-18.
 - 13 Piccini JP, Simon DN, Steinberg BA, *et al.* Differences in clinical and functional outcomes of atrial fibrillation in women and men: two-year results from the ORBIT-AF registry. *JAMA Cardiol* 2016;1:282-91.
 - 14 Rienstra M, Van Veldhuisen DJ, Hagens VE, *et al.* Gender-Related differences in rhythm control treatment in persistent atrial fibrillation: data of the rate control versus electrical cardioversion (race) study. *J Am Coll Cardiol* 2005;46:1298-306.
 - 15 Forleo GB, Tondo C, De Luca L, *et al.* Gender-Related differences in catheter ablation of atrial fibrillation. *Europace* 2007;9:613-20.
 - 16 Takigawa M, Kuwahara T, Takahashi A, *et al.* Differences in catheter ablation of paroxysmal atrial fibrillation between males and females. *Int J Cardiol* 2013;168:1984-91.
 - 17 Grecu M, Blomström-Lundqvist C, Kautzner J, *et al.* In-Hospital and 12-month follow-up outcome from the ESC-EORP EHRA atrial fibrillation ablation long-term registry: sex differences. *Europace* 2020;22:66-73.
 - 18 Neumann T, Wójcik M, Berkowitsch A, *et al.* Cryoballoon ablation of paroxysmal atrial fibrillation: 5-year outcome after single procedure and predictors of success. *Europace* 2013;15:1143-9.
 - 19 Akkaya E, Berkowitsch A, Zaltsberg S, *et al.* Second-Generation cryoballoon ablation as a first-line treatment of symptomatic atrial fibrillation: two-year outcome and predictors of recurrence after a single procedure. *Int J Cardiol* 2018;259:76-81.
 - 20 Irfan G, de Asmundis C, Mugnai G, *et al.* One-Year follow-up after second-generation cryoballoon ablation for atrial fibrillation in a large cohort of patients: a single-centre experience. *Europace* 2016;18:987-93.
 - 21 Chew DS, Black-Maier E, Loring Z, *et al.* Diagnosis-to-Ablation time and recurrence of atrial fibrillation following catheter ablation: a systematic review and meta-analysis of observational studies. *Circ Arrhythm Electrophysiol* 2020;13:e008128.
 - 22 Packer DL, Kowal RC, Wheelan KR, *et al.* Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic front (stop AF) pivotal trial. *J Am Coll Cardiol* 2013;61:1713-23.
 - 23 Ströker E, de Asmundis C, Saitoh Y, *et al.* Anatomic predictors of phrenic nerve injury in the setting of pulmonary vein isolation using the 28-mm second-generation cryoballoon. *Heart Rhythm* 2016;13:342-51.
 - 24 Pott A, Wirth H, Teumer Y, *et al.* Predicting phrenic nerve palsy in patients undergoing atrial fibrillation ablation with the Cryoballoon- Does sex matter? *Front Cardiovasc Med* 2021;8:746820.
 - 25 Yamagata K, Wichterle D, Roubíček T, *et al.* Ultrasound-Guided versus conventional femoral venipuncture for catheter ablation of atrial fibrillation: a multicentre randomized efficacy and safety trial (ultra-fast trial). *Europace* 2018;20:1107-14.