Sex-specific efficacy and safety of cryoballoon versus radiofrequency ablation for atrial fibrillation: An individual patient data meta-analysis

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BACKGROUND Atrial fibrillation (AF) is a growing health burden, and pulmonary vein isolation (PVI) using cryoballoon (CB) or radiofrequency (RF) represents an attractive therapeutic option. Sex-specific differences in the epidemiology, pathophysiology, and clinical presentation of AF and PVI are recognized.

OBJECTIVE We aimed at comparing the efficacy, safety, and procedural characteristics of CB and RF in women and men undergoing a first PVI procedure.

METHODS We searched for randomized controlled trials and prospective observational studies comparing CB and RF ablation with at least 1 year of follow-up. After merging individual patient data from 18 data sets, we investigated the sex-specific (*procedure failure* defined as recurrence of atrial arrhythmia, reablation, and reinitiation of antiarrhythmic medication), safety (periprocedural complications), and procedural characteristics of CB vs RF using Kaplan-Meier and multilevel models.

RESULTS From the 18 studies, 4840 men and 1979 women were analyzed. An analysis stratified by sex correcting for several covariates showed a better efficacy of CB in men (hazard ratio for recurrence 0.88; 95% confidence interval 0.78–0.98, $P = .02$) but not in women (hazard ratio 0.98; 95% confidence interval 0.83–1.16; $P = .82$). For women and men, the energy source had no influence on the occurrence of at least 1 complication. For both sexes, the procedure time was significantly shorter with CB (−22.5 minutes for women and −27.1 minutes for men).

CONCLUSION CB is associated with less long-term failures in men. A better understanding of AF-causal sex-specific mechanisms and refinements in CB technologies could lead to higher success rates in women.

KEYWORDS Ablation; Atrial fibrillation; Cryoballoon; Radiofrequency; Sex-specific; Women

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Introduction

Atrial fibrillation (AF) represents a growing health problem and is currently leading to an increasing burden of morbidity, mortality, and hospitalization worldwide.[1]

Sex-specific differences in the epidemiology, pathophysiology, and clinical presentation of AF are recognized.[2] While the prevalence of AF is higher in men than in women, women live longer and the cumulative lifetime risk of developing AF has been reported to be significantly higher in women than in men after 40 years of age.[2,3] Furthermore, women with AF show a higher mortality rate,[4] lower quality of life,[3] lower tolerability of antiarrhythmic drugs,[3] and higher stroke incidence than do men.[5] Therefore, definitive AF treatment could be particularly beneficial to this patient population.

Cryoballoon (CB) and radiofrequency (RF) are 2 commonly used energy sources for AF ablation and have been shown to be equally safe and effective in the limited number of available randomized controlled trials (RCTs),[6–10] which randomized a total of 1359 patients (521 women, 838 men).

After catheter ablation for AF, female sex has been associated with an increased risk of arrhythmia recurrence, with a different complication profile and cardiovascular rehospitalization.[11–13] However, little is known about the comparative efficacy and safety of both ablation technologies in male vs female patients.

To investigate this important sex-specific question, we conducted an individual patient data meta-analysis of RCTs and large prospective observational studies (POSs) comparing RF and CB ablation for AF in men and women.

Methods

This systematic review was registered in PROSPERO (ID: CRD42019125515) and was approved by the Ethics Committee of Basel.

Search, study selection, call for data, individual patient data collection, and data set merging

In brief, we searched publication databases for the terms *atrial fibrillation*, *pulmonary vein ablation*, *radiofrequency*, and *cryo** on March 28, 2018, and March 15, 2019. We included studies if they met the following prespecified criteria: (1) RCTs or POSs; (2) ≥40 patients per group (CB vs RF) for POSs; (3) patients undergoing their first ablation procedure; (4) first- or second-generation CB and nonirrigated, non–contact force irrigated, or contact force–guided irrigated RF catheters; (5) investigating an efficacy outcome of time to failure (recurrence of atrial arrhythmia, reablation, and reinitiation of antiarrhythmic medication) and a safety outcome (percentage of the recorded complications); and (6) following patients for at least 12 months. As recommended by the literature for systematic reviews of rapidly evolving technologies, we did not focus exclusively on RCTs but also included observational studies.[14] Details are available in Online Supplemental Appendix.

For 1 study, regulations did not allow sharing of individual patient data—the FIRE AND ICE (F&I) study. An investigator of the present project (J.d.F.d.L.) programmed the analysis independently of the F&I study team, which was then studied on the F&I data set at Medtronic headquarters (Minneapolis, MN) with no modifications. The estimates were provided for a 2-step analysis.

End points

The efficacy end point was the recurrence of arrhythmia (AF, atrial flutter, or atrial tachycardia), reablation, or reinitiation of antiarrhythmic medication after a 90-day blanking period.

The safety end point was the composite of all recorded periprocedural complications (death; cerebrovascular events; serious treatment-related adverse events, including acute myocardial infarction, stroke, pericardial effusion, tamponade, phrenic nerve palsy, pulmonary vein stenosis, and esophageal injury; and groin complications).

The procedural end points were the total procedure time and fluoroscopy time.

Assessment of study quality

Study quality was assessed according to 2 prespecified tools: the Cochrane Collaboration's risk of bias tool for RCTs[15] and a modified Newcastle-Ottawa Scale for nonrandomized observational studies (criteria in the Online Supplement).

Statistical analysis

The analysis was performed according to the recommendations of the Cochrane Collaboration, and the reporting was in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (Online Supplemental Table 1).

Continuous variables are presented as mean ± SD or median with interquartile range. The Mann-Whitney *U* test was applied for the comparison of continuous variables and the Fisher exact test for comparison of categorical variables.

Missing data were imputed, and a 1-step analysis was conducted on the merged data set using a multilevel data multiple imputation algorithm (details in the Online Supplement). The same analysis was conducted separately on the 18th data set (F&I study), and either the estimates were merged in a 2-step analysis (for the models) or the time-to-event results were integrated into the 1-step analysis of the 17 other data sets (for details on Kaplan-Meier analyses, see the Online Supplement).

For the efficacy end point, sex-specific Kaplan-Meier curves representing time to failure of CB vs RF were constructed. Differences between groups were tested using a log-rank test after the proportional hazards assumption was checked using scaled Schoenfeld residuals. Time-to-event analyses were initiated after 90 days postablation as all studies planned for a 90-day blanking period.

To account for clustering of studies and the influence of important comorbidities, sex-specific multilevel model taking into account the type of catheter intervention (RF vs CB) and covariates previously highlighted as decisive for the recurrence of AF after ablation[11] were derived.

To investigate heterogeneity between individual studies for all end points, a 2-stage analysis of individual studies was conducted using simplified models and pooled using a restricted maximum likelihood random effects model.

Heterogeneity was determined using I^2 as a measure (significant heterogeneity: I^2 statistic of >50%) and was investigated for 3 prespecified variables—publication year, mean age, and study type—using meta-regressions. Evidence for publication bias was assessed graphically using funnel plots and the Egger test.

All statistical analyses were performed using the statistical software "R" Version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria; see the Online Supplement).

Results

Selected studies

A total of 1081 studies were identified, and 30 authors of suitable studies were contacted (Figure 1 and Online Supplemental Table 2). Nine authors did not wish to participate, 1 did not respond, and 4 publications were linked to 2 data sets, leaving 18 data sets (5 RCTs, 13 POSs) available for the analysis (Online Supplemental Tables 3 and 4), accounting for a total of 6819 patients (4840 men, 1979 women). As some patients were lost to follow-up during the 90-day blanking period, 6507 patients were available for the efficacy analysis. Because of missing data, 5725 and 6308 patients were available for the analysis of fluoroscopy time and total procedure time, respectively.

The mean duration of follow-up in the included studies varied from 8.8 to 51.6 months and monitoring used was either Holter electrocardiograms or loop recorders (Online Supplemental Table 5). Some studies presented a median follow-up of <12 months, given lost to follow-up before this time point.

Baseline patient characteristics

Baseline patient characteristics stratified by sex and energy source are presented in Table 1.

Overall, women were older and presented more often with a severely dilated left atrium (LA). For both men and women, a larger proportion of patients underwent ablation with RF, which was more often used in patients with long-standing AF and a dilated LA.

Efficacy analysis

Of the 1892 women, 277 (35.8%) in the CB group and 439 (38.4%) in the RF group experienced a failure ($P = .265$). Of the 4615 men, 515 (30.7%) in the CB group and 1075 (36.3%) in the RF group experienced a failure ($P \leq .001$) (Online Supplemental Table 6).

While men undergoing ablation with CB experienced less recurrences at 2 and 3 years of follow-up, this was not the case for women (Figure 2). In the overall population, the advantage of ablation using CB was present beginning after 2 years of follow-up. The Cox proportional hazards models correcting for a large number of clinically relevant covariates are presented in Figure 3.

The combined hazard ratio of the energy source showed a better efficacy of CB in men (hazard ratio 0.88; 95% confidence interval 0.78–0.98; $P = .02$) but not in women (hazard ratio 0.98; 95% confidence interval 0.83–1.16; $P = .3$).

Given the large impact of AF type in this model and the importance of the differentiation between paroxysmal and persistent AF, the same efficacy analysis was conducted in patients with paroxysmal AF only, which provided similar results (Online Supplemental Figure 1).

Safety analysis

Women presented with a higher rate of periprocedural complications, which was driven by access-related complications,

Table 1 Patient characteristics

	Women			Men		
Characteristic	CB	RF	*P*	CB	RF	*P*
No. of patients	787	1192		1714	3126	
Age (y)	63.35 ± 9.76	64.01 ± 9.69	.13	58.73 ± 10.34	59.91 ± 10.08	<.001
Patient characteristics						
AF type			<.001			<.001
Paroxysmal	747 (95.0)	883 (74.2)		1545 (90.4)	1998 (64.0)	
Persistent	36 (4.6)	220 (18.5)		160 (9.4)	797 (25.5)	
Long-standing persistent	1 (0.1)	50 (4.2)		4 (0.2)	198 (6.3)	
Other*	2 (0.3)	37 (3.1)		1 (0.1)	128 (4.1)	
Duration of AF (y)	4.62 ± 4.92	4.61 ± 4.86	.96	4.67 ± 5.14	4.75 ± 4.99	.60
BMI (kg/m^2)	27.11 ± 5.57	26.12 ± 5.38	<.001	27.33 ± 4.36	26.71 ± 4.18	<.001
Hypertension	387 (51.8)	548 (53.1)	.623	708 (43.9)	1252 (48.1)	.009
DM	69 (9.2)	88 (8.4)	.655	155 (9.5)	274 (10.5)	.321
CHF	86 (12.3)	122 (12.5)	.932	131 (8.5)	283 (11.5)	.003
Stroke/TIA	52 (7.6)	87 (9.1)	.320	73 (5.0)	176 (7.4)	.003
Vascular disease	33 (5.9)	53 (6.0)	1.000	121 (10.2)	266 (12.1)	.100
LA measure			.032			<.001
Normal	229 (35.9)	388 (37.0)		618 (45.1)	1057 (38.4)	
Mildly abnormal	138 (21.6)	185 (17.7)		287 (21.0)	446 (16.2)	
Moderately abnormal	148 (23.2)	220 (21.0)		278 (20.3)	678 (24.6)	
Severely abnormal	123 (19.3)	255 (24.3)		186 (13.6)	572 (20.8)	
LVEF (%)	61.99 ± 6.42	61.85 ± 7.35	.65	60.53 ± 7.36	59.55 ± 8.29	<.001
LVSD	12 (1.6)	39 (3.4)	.029	62 (3.8)	168 (5.5)	.011
Catheter data						
Catheter details			<.001			<.001
First-generation CB	342 (46.8)	0 (0.0)		760 (47.1)	0 (0.0)	
Second-generation CB	389 (53.2)	0 (0.0)		852 (52.9)	0 (0.0)	
Contact force-guided irrigated RF catheter	0 (0.0)	371 (31.1)		0 (0.0)	1005 (32.1)	
RF irrigated no contact force	0 (0.0)	696 (58.4)		0 (0.0)	1746 (55.9)	
RF not irrigated	0 (0.0)	125 (10.5)		0 (0.0)	375 (12.0)	

Values are presented as mean ± SD or as n (%).

AF = atrial fibrillation; BMI = body mass index; CB = cryoballoon; CHF = congestive heart failure; DM = diabetes mellitus; LA = left atrial; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; RF = radiofrequency; TIA = transient ischemic attack.

*LA tachycardia or flutter.

phrenic nerve palsies, and tamponades (Table 2). For both sexes, RF was associated with more pericardial effusions and CB with more phrenic nerve palsies. However, there was no significant difference between the 2 energy sources for the occurrence of at least 1 complication in women or men. Also when the models were corrected for several comorbidities, the use of CB or RF was associated with a similar number of complications in both sexes (Figure 4).

Again, a subgroup analysis was conducted in patients with paroxysmal AF only, showing similar results (Online Supplemental Figure 2).

Procedural end point analysis

While a much shorter total procedure time was observed when CB was used (−22 minutes with CB in women and −27 minutes with CB in men; $P < .001$), no differences were observed in fluoroscopy time (Online Supplemental Table 7 and Online Supplemental Figure 3).

Heterogeneity analyses

While efficacy and procedural estimates by energy source were heterogeneous between studies, safety results were more homogeneous (Online Supplemental Figures 4A, 5A, 6A, and 7A). More importantly, the sex-specific estimates of all observed outcomes also presented with less heterogeneity (Online Supplemental Figures 4B, 5B, 6B, and 7B). Mean age of the enrolled patients, year of publication, and study design (RCT vs OP) were investigated as sources of heterogeneity, but none of these parameters significantly contributed to the heterogeneity between studies for any of the end points (Online Supplemental Table 8).

Study quality and publication bias

The quality of the included data set was summarized in Online Supplemental Tables 9 and 10 and Online Supplemental Figure 8. A funnel plot for the efficacy outcome by energy source appeared symmetrical (Online Supplemental Figure 9), and an Egger test did not find any publication bias (Egger test, $P = .88$).

Discussion

Despite the recognition of the growing importance of sex-based differences in medicine,[16] gathering sufficient data

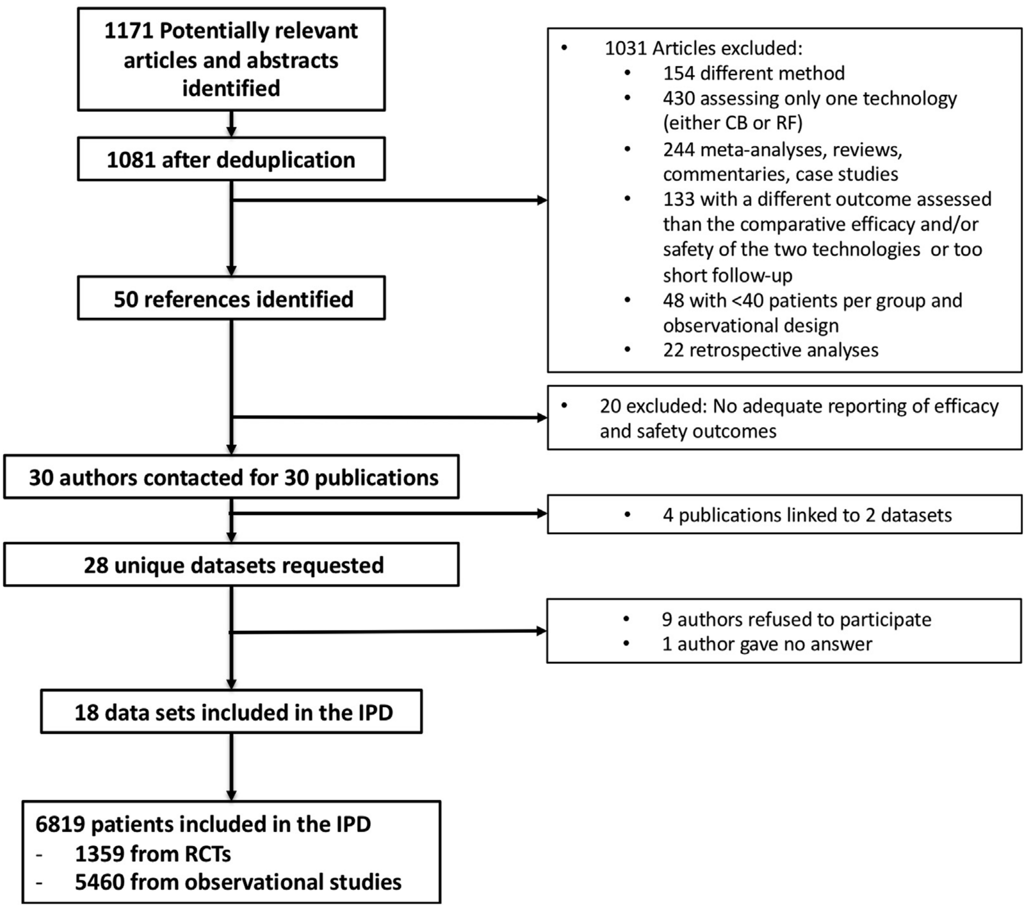

Figure 1 Study selection flowchart. CB = cryoballoon; IPD = individual patient data; RCT = randomized controlled trial; RF = radiofrequency.

on women is challenging, as they are frequently underrepresented,[17,18] particularly in invasive trials.[19,20] Moreover, as shown in our previous research, the lack of sufficient published sex-specific subgroup analyses hinders any classical meta-analytic conclusion.[21] We therefore conducted this large individual patient data meta-analysis to investigate the efficacy, safety, and procedural outcomes of CB vs RF ablation in men and women undergoing a first ablation procedure. We report 3 main findings. First, we found sex-specific differences in efficacy between CB and RF, with a lower long-term AF recurrence rate with CB in men but not in women. This difference was found both in unadjusted analyses (represented in the Kaplan-Meier curves) and in a comprehensive model corrected for a substantial number of comorbidities. Second, for both women and men, no difference in the overall complication rate was found when CB or RF was used. CB was associated with more phrenic palsies and RF with more pericardial effusions for both sexes. Third, CB ablation was found to be more efficient as it was associated with a much shorter overall procedure time.

In the overall population, CB performed better than RF beginning at 2 years of follow-up and this superiority was already observed at 1 year of follow-up in men. Interestingly, women did not benefit more from ablation with CB compared with RF at any time point of follow-up. This difference in efficacy between female and male patients was previously observed in a study investigating CB ablation procedures only, with lower long-term success in female patients.[22] The better long-term performance of CB raise further questions regarding the cellular damages and their durability induced by either "freezing" or "burning" the cells. For instance, late or peripheral apoptotic mechanisms as well as deep lesions have been associated with CB[23,24] and could possibly be responsible for delayed efficacy. Several hypotheses could contribute to the absence of superiority of CB in women as compared with men. First, CB technologies might have been primarily developed for the larger "male cardiac anatomy" and tested in male patients more than in female patients, therefore limiting the generalizability of the technology to women. While a 23-mm CB is available for smaller-sized pulmonary veins,[25] such as supposedly the ones of women's hearts, women more often presented with a severely dilated LA in our analysis, suggesting that larger or other devices may be required in these patients for adequate pulmonary vein occlusion and energy transmission. Second, similar factors as the ones proposed for higher arrhythmia

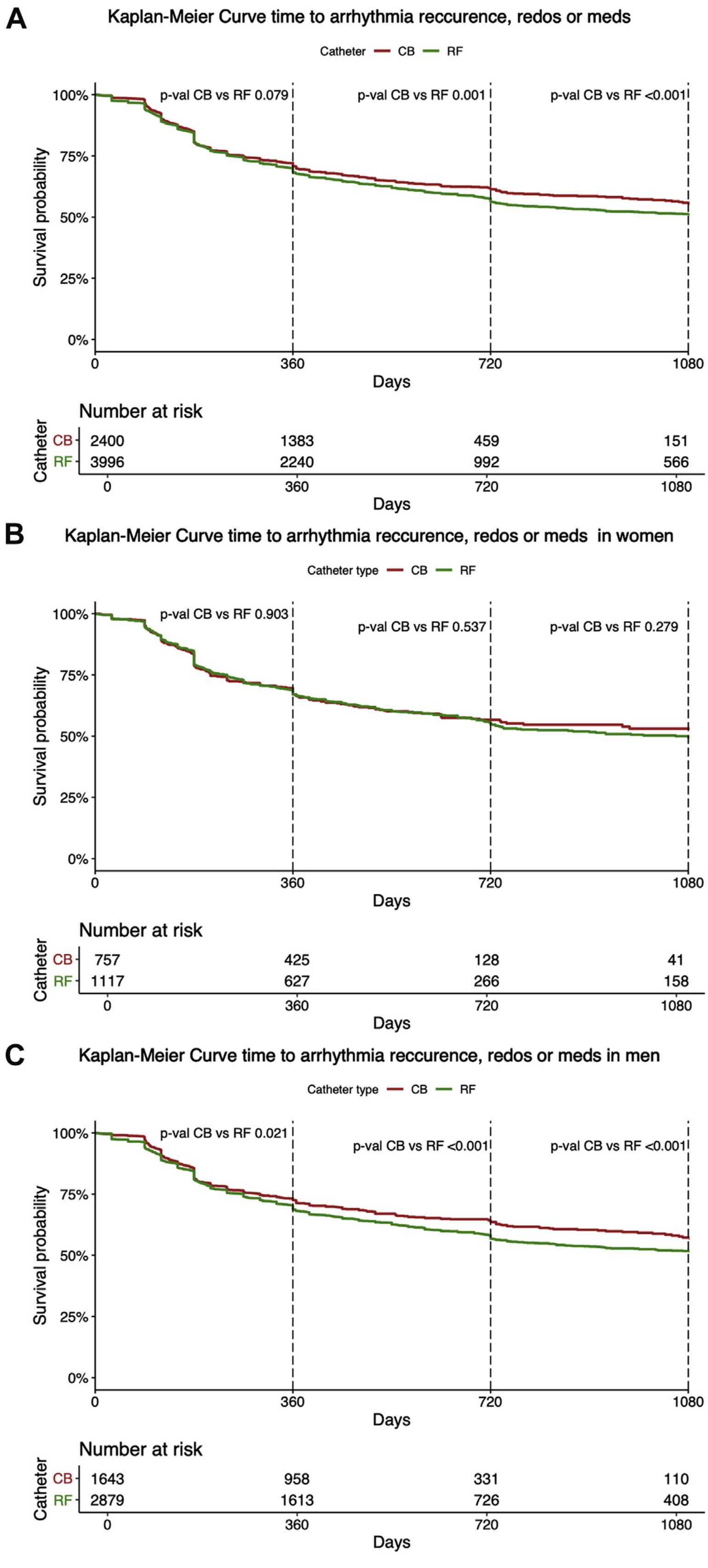

Figure 2 Kaplan-Meier curves representing the event-free survival for recurrence of arrhythmia, reablation, or reinitiation of antiarrhythmic medication in all data sets for (**A**) the overall cohort and (**B**) women and (**C**) men separately. CB = cryoballoon; RF = radiofrequency.

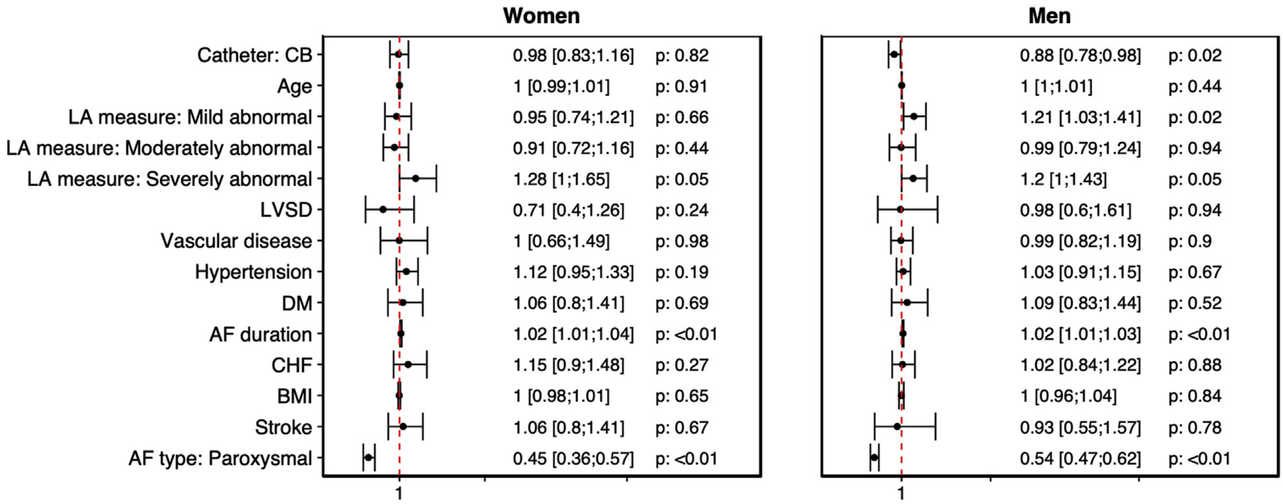

Figure 3 Pooled estimates were calculated using the mixed effect Cox proportional hazards models by energy source for arrhythmia recurrence, reablation, and reinitiation of medication up to 3 years of follow-up in all data sets by the patient's sex. AF = atrial fibrillation; BMI = body mass index; CB = cryoballoon; CHF = congestive heart failure; DM = diabetes mellitus; LA = left atrial; LVSD = left ventricular systolic dysfunction.

recurrence in female patients could interact more with CB than with RF. For instance, electrical (such as more non–pulmonary vein foci[3,5]), endocrine (such as hormone replacement therapy in older women or during menopause[2]), and structural (more atrial fibrosis or inflammation[5,26]) factors are important sex-specific differences in pathophysiological mechanisms of AF, which may also interact with the type of ablation energy selected.

As other cofactors known to play an important role in the recurrence of AF after ablation (such as LA dilation, AF duration, and a history of hypertension[27–29]) were integrated into our predictive model, they are less likely to contribute to the decreased efficacy of CB in women.

In several previous studies, female sex has been associated with an increased rate of complications.[3,30,31] While we confirmed these observations and found that women presented with a higher rate of complications (driven by groin complications, tamponades, and phrenic nerve palsies), we could not observe any higher risk associated with CB or RF in multivariable models. It is however important to note that women experienced twice as many phrenic nerve palsies than did men when using CB, a potentially chronic and disabling complication.

Study limitations

Several limitations of this individual patient data meta-analysis are to consider. First, some large observational studies[32,33] did not participate. However, all the available RCTs agreed to participate and the studies that could not be integrated showed trends corroborating our observations (high recurrence rates in women across all catheters used[12] and a similar tendency toward a better efficacy of CB compared with RF in male patients but not female patients). Second, men and women presented with different comorbidity profiles between the CB and RF groups. While we developed large-scale multivariable models correcting for these variables, we cannot exclude residual confounding resulting from these comorbidities or from other important sex-specific covariate (eg, hormone replacement therapy in older women), which were not recorded in the studies. However, different comorbidities in women reflect general clinical

Table 2 Occurrence of complications

	Women			Men		
Complication	CB	RF	*P*	CB	RF	*P*
No. of patients	787	1192		1714	3126	
At least 1 complication	68 (8.6)	95 (8.0)	.617	109 (6.4)	158 (5.1)	.065
Groin complication	21 (2.6)	42 (3.5)	.353	32 (1.8)	51 (1.6)	.626
Esophageal fistula	0 (0)	1 (0.1)	1.000	0 (0)	2 (0.1)	.784
Pericardial effusion	1 (0.1)	15 (1.3)	.019	7 (0.4)	37 (1.2)	.016
Phrenic nerve palsy	29 (3.7)	6 (0.5)	<.001	40 (2.3)	8 (0.3)	<.001
PV stenosis	0 (0)	0 (0)	–	3 (0.2)	2 (0.1)	.455
Stroke/TIA	1 (0.1)	4 (0.3)	.655	7 (0.4)	14 (0.4)	1.000
Tamponade	6 (0.8)	9 (0.8)	1.000	5 (0.3)	8 (0.3)	1.000

Values are presented as n (%).

CB = cryoballoon; PV = pulmonary vein; RF = radiofrequency; TIA = transient ischemic attack.

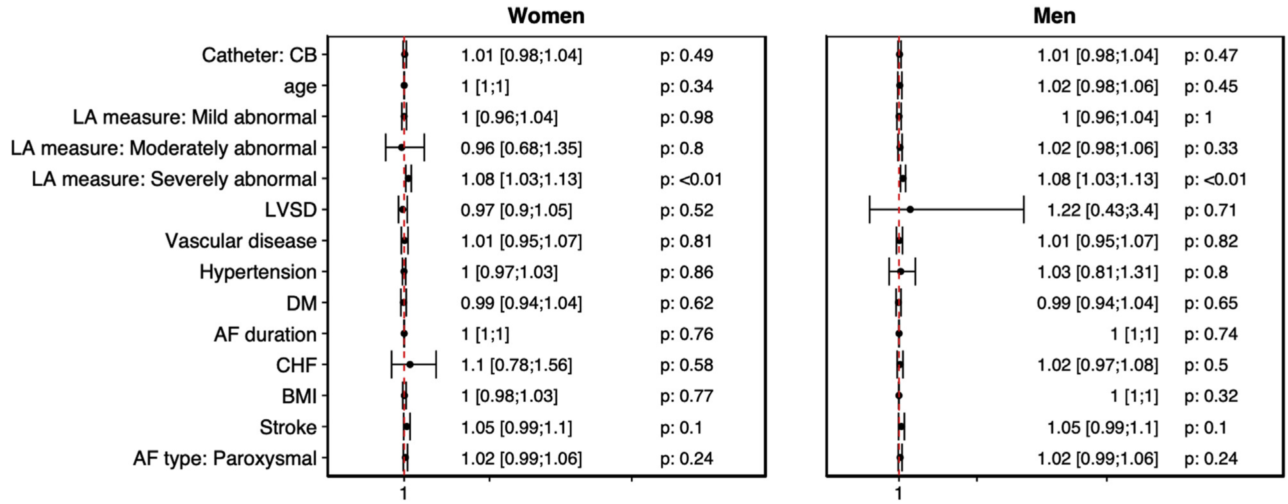

Figure 4 Pooled estimates calculated using the mixed effect logistic model for periprocedural complications in all data sets by the patient's sex. AF = atrial fibrillation; BMI = body mass index; CB = cryoballoon; CHF = congestive heart failure; DM = diabetes mellitus; LA = left atrial; LVSD = left ventricular systolic dysfunction.

practice and therefore bolster the generalizability of our results.

Conclusion

This individual patient data meta-analysis suggests that CB ablation is associated with less long-term failures in men but not in women. Further research is needed to determine whether refinements in ablation technologies, adaptation of devices or mapping software specifically for female patients, or a better understanding of AF-causal sex-specific mechanisms (eg, extrapulmonary vein triggers and tissue repair/recovery mechanisms postablation) could improve success rates of AF ablation in women.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2020.04.020.

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