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

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Abstract (246/250)

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.

Methods

We searched for randomized controlled trials (RCTs) and observational prospective studies comparing CB and RF ablation with at least 1 year follow-up. After merging individual patient data from 18 datasets, we investigated the sex-specific (procedure failure defined as recurrence of atrial arrhythmia, re-ablation and start of anti-arrhythmic medication), safety (peri-procedural complications) and procedural characteristics of CB versus RF using Kaplan Meier and multi-level 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 (HR for recurrence 0.88, 95% confidence interval (CI) 0.78-0.98, p-value = 0.02) but not in women (HR= 0.98 [0.83-1.16], p-value = 0.82). For women and men, the energy source had no influence on the occurrence of at least one complication. For both sexes, procedural time was significantly shorter with CB (-22.5 min for women and -27.1 min 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.

Trial registration

PROSPERO (CRD42019125515)

Keywords
Women, atrial fibrillation, sex-specific, cryoballoon, radiofrequency, ablation

Introduction

Atrial fibrillation (AF) represents a growing health problem and is currently leading to an increasing burden of morbidity, mortality and hospitalizations 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 women, women live longer and the cumulative lifetime risk of developing AF has been reported to be significantly higher in women than men after 40 years old.[2,3] Furthermore, women with AF show higher mortality rates[4], lower quality of life[3], lower tolerability of anti-arrhythmic drugs[3] and higher stroke incidence than men[5]. Therefore, definitive AF treatment could be particularly beneficial to this patient population.

Cryoballoon (CB) and radiofrequency (RF) are two 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).

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

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

Methods

This systematic review was registered on PROSPERO (CRD42019125515) and was approved by the ethics committee of Basel.

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

In brief, we searched publication databases for the terms “atrial fibrillation”, “pulmonary vein ablation”, “radiofrequency” and “cryo*” on March 28th 2018 and March 15th 2019. We included studies if they met the following pre-specified criteria: 1) Randomized controlled trials (RCT) or prospective observational studies (POS), 2) ≥ 40 patients per group (CB versus RF) for POS, 3) patients undergoing their first ablation, 4) first- or second-generation CB and non-irrigated, non-contact-force irrigated or contact-force guided irrigated RF catheters, 5) investigating an efficacy outcome of time-to-failure (recurrence of atrial arrhythmia, re-ablation and re-start of anti-arrhythmic medication) and a safety outcome (percentage of 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 the supplemental appendix.

For one study, regulations did not allow for sharing of individual patient data (the Fire&Ice (F&I) study). An investigator of the current project (JdFdL) programmed the analysis independently of the F&I study team, which was then studied on the F&I data set at Medtronic Headquarter (Minneapolis) with no modifications. The estimates were provided for a 2-step analysis.

Endpoints

The efficacy endpoint was the recurrence of arrhythmia (AF, atrial flutter or atrial tachycardia), re-ablations or re-start of anti-arrhythmic medications following a 90-day blanking period.

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

The procedural endpoints were the total procedure duration and fluoroscopy time.

Assessment of study quality

Study quality was assessed according to two pre-specified tools : the Cochrane Collaboration risk of bias tool for RCTs[15] and a modified Newcastle-Ottawa Scale (NOS) for non-randomized observational studies (criteria in the 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 (PRISMA) statement. (Supplemental table 1).

Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile ranges (IQR). Mann-Whitney-U test was applied for comparison of continuous variables and Fisher's exact test for comparison of categorical variables. Missing data were imputed and a one-step analysis was conducted on the merged dataset using a multi-level data multiple imputation algorithm (details in the supplement). The same analysis was conducted separately on the 18th dataset (F&I

study) and either the estimates were merged in a two-step analysis (for the models) or the time-to-event results were integrated in the one-step analysis of the 17 other datasets (for the Kaplan-Meier analyses, details in the supplemental).

For the efficacy endpoint, sex-specific Kaplan Meier representing time-to-failure of CB versus RF were constructed. Differences between groups were tested using a log rank test after the proportional hazards (PH) assumption was checked using scaled Schoenfeld residuals. Time-to-event analyses were started after the 90th day post-ablation as all studies planned for a 90-day blanking period.

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

To investigate heterogeneity between individual studies for all endpoints, a two-stage analysis of individual studies was conducted using simplified models and pooled using a Restricted maximum Likelihood (REML) random-effects model.

Heterogeneity was determined using I^2 as measure (significant heterogeneity: I^2 statistic of >50%) and was investigated for three pre-specified variables (publication year, mean age, 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” (R Foundation for Statistical Computing, Vienna, Austria, see supplemental).

Results

Selected studies

A total of 1081 studies were identified and 30 authors of suitable studies were contacted (Figure 1, Supp. table 2). Nine authors did not wish to participate, 1 did not respond and 4 publications were linked to 2 datasets, leaving 18 datasets (5 RCTs, 13 POSs) available for analysis (Supp. table 3-4), 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. Due to 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 included studies varied from 8.8 to 51.6 months and monitoring used either Holter ECGs or Loop recorders (Supp. table 5). Some studies presented a median a follow-up shorter than 12 months given lost-to-follow-up before this time point.

Baseline Patient Characteristics

Baseline patient characteristics 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 an ablation with RF, which was more often used in patients with long-standing AF and 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=0.265). Of the 4615 men, 515 (30.7%) in the CB group and 1075 (36.3%) in the RF group experienced a failure (p=<0.001) (Supp. table 6).

While men undergoing an ablation with CB experienced less recurrences at 2 and 3 years follow-up, this was not the case for women (Figure 2). In the overall population, the advantage of an ablation using CB was present starting after two years of follow-up. The cox PH 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 (HR 0.88, 95%CI [0.78-0.98], p-value = 0.02) but not in women (HR 0.98, 95%CI [0.83-1.16], p-value = 0.3).

Given the large impact of the 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 (Supp. Figure 1)

Safety analysis

Women presented with a higher rate of periprocedural complications, which was driven by access-related complications, phrenic nerve palsy 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 two energy sources for the occurrence of at least one complication in women or men. Also when 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 (Supp figure 2)

Procedural endpoints analysis

While a much shorter total procedure time was observed when CB was used (-22min with CB in women and -27min with CB in men, $p<0.001$), no differences were observed for the fluoroscopy time (Supp. table 7, Supp. Figure 3).

Heterogeneity analyses

While efficacy and procedural estimates by energy source were heterogenous between studies, safety results were more homogenous (Supplemental figure 4A, 5A, 6A and 7A). More importantly, the sex-specific estimates of all observed outcomes also presented with little heterogenicity (Supplemental figure 4B, 5B, 6B and 7B). Mean age of the enrolled patients, year of publication and study design (RCT versus OP) were investigated as sources of heterogeneity but none of these parameters significantly contributed to the heterogeneity between studies for any of the endpoints (Supplemental table 8)

Study quality and publication bias

The quality of the included dataset was summarized in Supplemental table 9 and 10 and Supplemental Figure 8. A Funnel plot of the efficacy outcome by energy source appeared symmetrical (Supplemental Figure 9) and an Egger test did not find any publication bias (p-value of Egger test =0.88).

Discussion

Despite the recognition of the growing importance of sex-based differences in medicine,[16] gathering sufficient data on women is challenging, as they are frequently under-represented[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 versus RF ablation in men and women undergoing a first ablation. We report three main findings. **First**, we found gender-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) as well as in a comprehensive model corrected for a substantial number of comorbidities. **Second**, for both women and men, no differences in the overall complication rate was present 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 starting at 2-year follow-up and this superiority was already observed at 1-year follow-up in males. Interestingly, women did not benefit more from an ablation with CB compared to RF at any time point of the follow-up. This difference in efficacy between females and males was previously observed in a study investigating CB ablations 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 either by "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 males more than females, 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 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 recurrence in female patients could interact with CB more 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 factors (more atrial fibrosis or inflammation[5,26]) are important sex-specific differences in pathophysiological mechanisms of atrial fibrillation 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 following an ablation (such as LA dilation, AF duration, a history of hypertension, etc.[27–29]) were integrated in 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 notice that women experienced twice as many phrenic nerve palsies than men when using CB, a potentially chronic and disabling complication.

Several limitations of this individual-patient 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 which 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 to RF in males but not females). Second, men and women presented with different comorbidity profiles between the CB and RF groups. While we conducted large-scale multivariable models correcting for these variables, we cannot exclude residual confounding resulting from these comorbidities or from other important sex-specific covariate (e.g. hormone replacement therapy in older women) which were not recorded in the studies. However, the different comorbidities in women reflect general clinical practice and therefore bolster the generalizability of our results.

In conclusion, this individual patient data meta-analysis suggests that cryoballoon 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 causal sex-specific mechanisms (e.g. extra-PV triggers, tissue repair/recovery mechanisms post-ablation) could improve success rates of AF ablation in women.

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Eur pacing, arrhythmias, Card Electrophysiol J Work groups Card pacing, arrhythmias, Card Cell Electrophysiol Eur Soc Cardiol Published Online First: October 2018. doi:10.1093/europace/euy239
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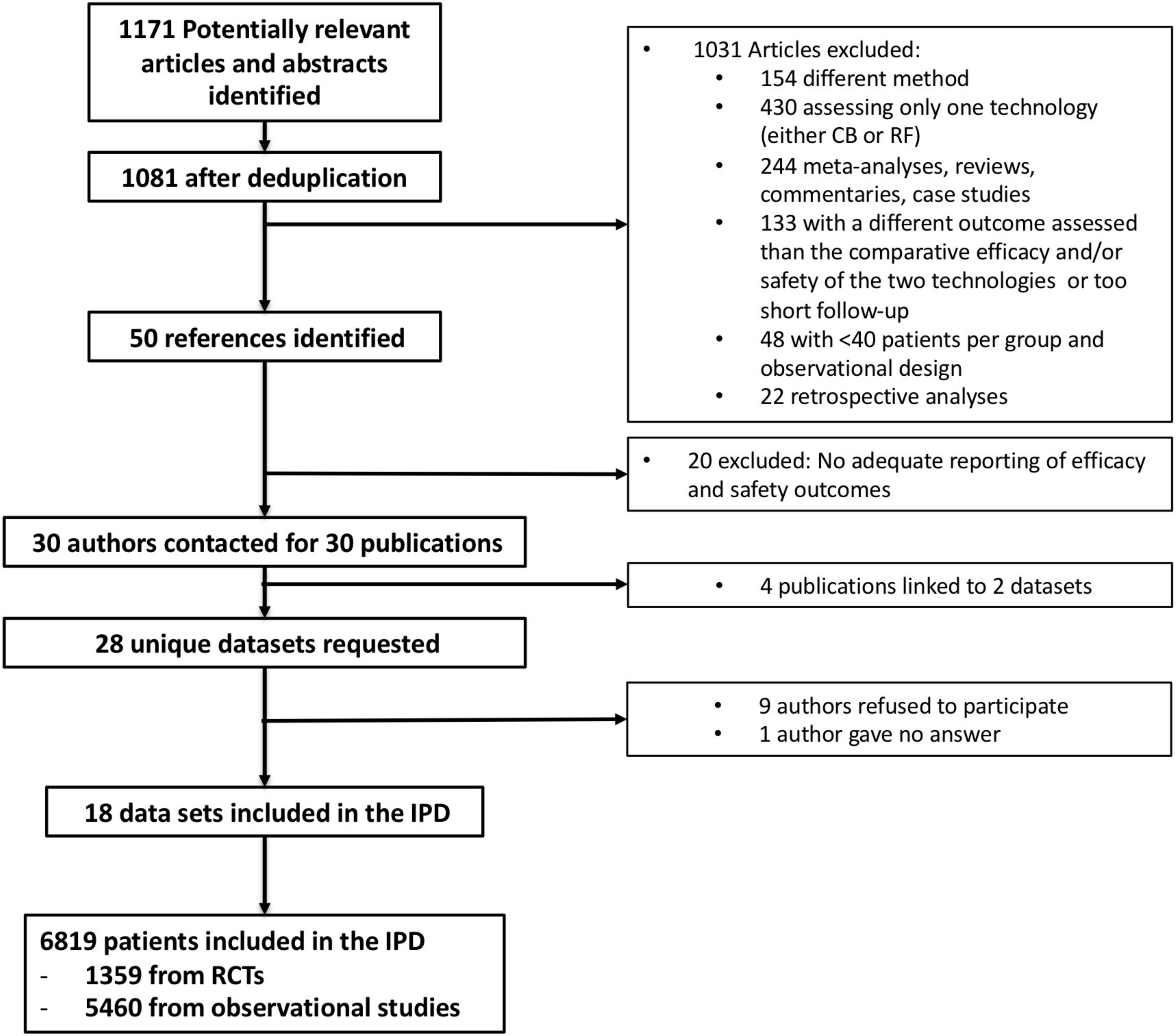
Figure legends

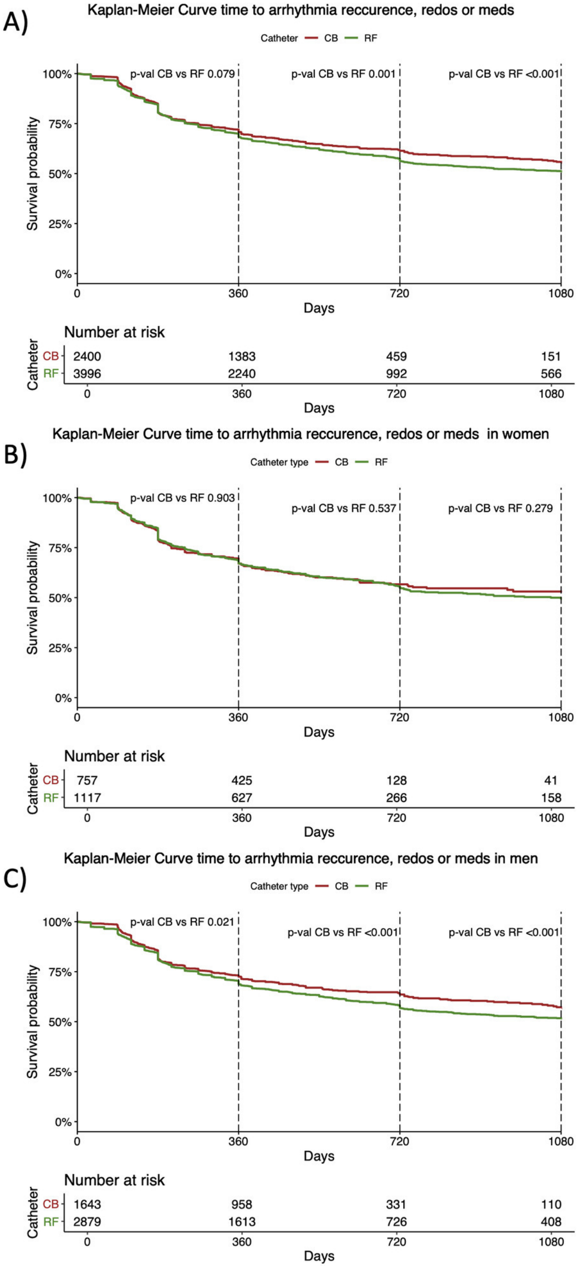
Figure 1 – Studies selection chartflow

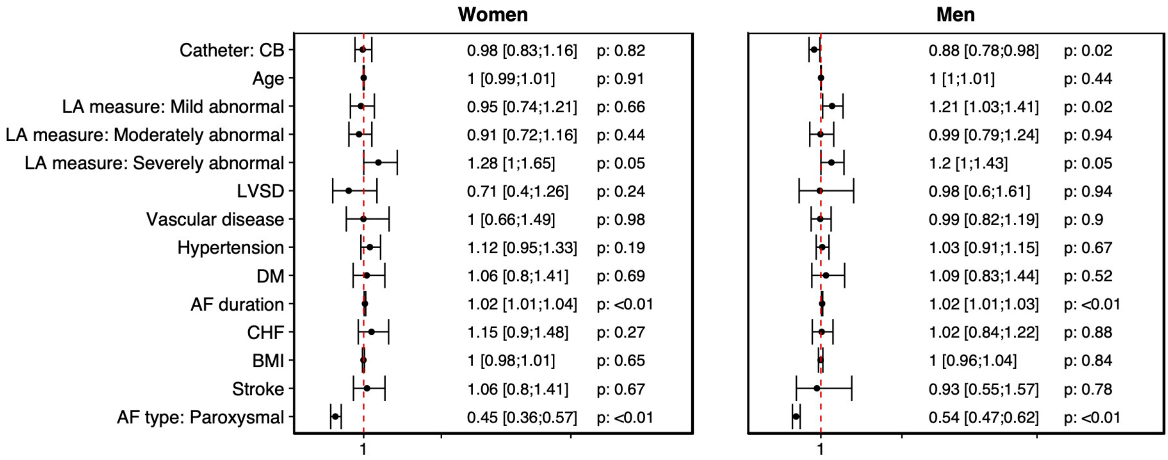
Figure 2 – Kaplan Meier representing the event-free survival for recurrence of arrhythmia, re-ablations or re-start of anti-arrhythmic medication in all datasets for A) the overall cohort, B) women and C) men separately. CB = Cryoballoon, RF = Radiofrequency catheters.

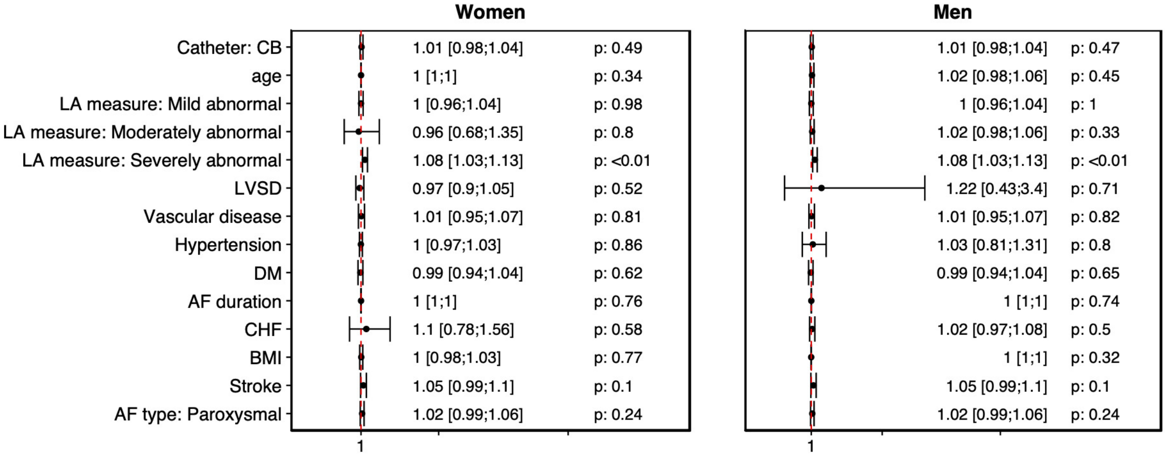
Figure 3 – Pooled estimates of the mixed-effect cox proportional hazard models by energy source for arrhythmia recurrence, re-ablation and re-start of medications up to three years follow-up in all datasets by the patient's sex. CB = Cryoballoon, LVSD= left ventricular systolic dysfunction, DM = diabetes Mellitus, AF = atrial fibrillation, CHF= Congestive heart failure, BMI= Body mass index.

Figure 4 – Pooled estimates of the mixed-effect logistic model for periprocedural complications in all datasets by the patient's sex. CB = Cryoballoon, LVSD= left ventricular systolic dysfunction, DM = diabetes Mellitus, AF = atrial fibrillation, CHF= Congestive heart failure, BMI= Body mass index.


1171 Potentially relevant articles and abstracts identified
1081 after deduplication
1031 Articles excluded:
154 different method
430 assessing only one technology (either CB or RF)
244 meta-analyses, reviews, commentaries, case studies
133 with a different outcome assessed than the comparative efficacy and/or safety of the two technologies or too short follow-up
48 with <40 patients per group and observational design
22 retrospective analyses
50 references identified
20 excluded: No adequate reporting of efficacy and safety outcomes
30 authors contacted for 30 publications
4 publications linked to 2 datasets
28 unique datasets requested
9 authors refused to participate
1 author gave no answer
18 data sets included in the IPD
6819 patients included in the IPD
- 1359 from RCTs
- 5460 from observational studies


A)
Kaplan-Meier Curve time to arrhythmia reccurence, redos or meds
Catheter CB RF
p-val CB vs RF 0.079
p-val CB vs RF 0.001
p-val CB vs RF <0.001
Survival probability
100%
75%
50%
25%
0%
0
360
720
1080
Days
Number at risk
Catheter
CB 2400 1383 459 151
RF 3996 2240 992 566
0
360
720
1080
Days
B)
Kaplan-Meier Curve time to arrhythmia reccurence, redos or meds in women
Catheter type CB RF
p-val CB vs RF 0.903
p-val CB vs RF 0.537
p-val CB vs RF 0.279
Survival probability
100%
75%
50%
25%
0%
0
360
720
1080
Days
Number at risk
Catheter
CB 757 425 128 41
RF 1117 627 266 158
0
360
720
1080
Days
C)
Kaplan-Meier Curve time to arrhythmia reccurence, redos or meds in men
Catheter type CB RF
p-val CB vs RF 0.021
p-val CB vs RF <0.001
p-val CB vs RF <0.001
Survival probability
100%
75%
50%
25%
0%
0
360
720
1080
Days
Number at risk
Catheter
CB 1643 958 331 110
RF 2879 1613 726 408
0
360
720
1080
Days


Women
Men
Catheter: CB
Age
LA measure: Mild abnormal
LA measure: Moderately abnormal
LA measure: Severely abnormal
LVSD
Vascular disease
Hypertension
DM
AF duration
CHF
BMI
Stroke
AF type: Paroxysmal
0.98 [0.83;1.16] p: 0.82
1 [0.99;1.01] p: 0.91
0.95 [0.74;1.21] p: 0.66
0.91 [0.72;1.16] p: 0.44
1.28 [1;1.65] p: 0.05
0.71 [0.4;1.26] p: 0.24
1 [0.66;1.49] p: 0.98
1.12 [0.95;1.33] p: 0.19
1.06 [0.8;1.41] p: 0.69
1.02 [1.01;1.04] p: <0.01
1.15 [0.9;1.48] p: 0.27
1 [0.98;1.01] p: 0.65
1.06 [0.8;1.41] p: 0.67
0.45 [0.36;0.57] p: <0.01
0.88 [0.78;0.98] p: 0.02
1 [1;1.01] p: 0.44
1.21 [1.03;1.41] p: 0.02
0.99 [0.79;1.24] p: 0.94
1.2 [1;1.43] p: 0.05
0.98 [0.6;1.61] p: 0.94
0.99 [0.82;1.19] p: 0.9
1.03 [0.91;1.15] p: 0.67
1.09 [0.83;1.44] p: 0.52
1.02 [1.01;1.03] p: <0.01
1.02 [0.84;1.22] p: 0.88
1 [0.96;1.04] p: 0.84
0.93 [0.55;1.57] p: 0.78
0.54 [0.47;0.62] p: <0.01
1
1



Women
Men
Catheter: CB
age
LA measure: Mild abnormal
LA measure: Moderately abnormal
LA measure: Severely abnormal
LVSD
Vascular disease
Hypertension
DM
AF duration
CHF
BMI
Stroke
AF type: Paroxysmal
1.01 [0.98;1.04] p: 0.49
1 [1;1] p: 0.34
1 [0.96;1.04] p: 0.98
0.96 [0.68;1.35] p: 0.8
1.08 [1.03;1.13] p: <0.01
0.97 [0.9;1.05] p: 0.52
1.01 [0.95;1.07] p: 0.81
1 [0.97;1.03] p: 0.86
0.99 [0.94;1.04] p: 0.62
1 [1;1] p: 0.76
1.1 [0.78;1.56] p: 0.58
1 [0.98;1.03] p: 0.77
1.05 [0.99;1.1] p: 0.1
1.02 [0.99;1.06] p: 0.24
1.01 [0.98;1.04] p: 0.47
1.02 [0.98;1.06] p: 0.45
1 [0.96;1.04] p: 1
1.02 [0.98;1.06] p: 0.33
1.08 [1.03;1.13] p: <0.01
1.22 [0.43;3.4] p: 0.71
1.01 [0.95;1.07] p: 0.82
1.03 [0.81;1.31] p: 0.8
0.99 [0.94;1.04] p: 0.65
1 [1;1] p: 0.74
1.02 [0.97;1.08] p: 0.5
1 [1;1] p: 0.32
1.05 [0.99;1.1] p: 0.1
1.02 [0.99;1.06] p: 0.24
1
1

Table 1 – Patient characteristics

	Women			Men		
	CB	RF	p-value	CB	RF	p-value
Number of patients	787	1192		1714	3126	
Age in years - mean (±sd)	63.35± 9.76	64.01± 9.69	0.13	58.73± 10.34	59.91± 10.08	<0.001
Patients characteristics						
AF type - n (%)			<0.001			<0.001
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)	
longstanding persistent	1 (0.1)	50 (4.2)		4 (0.2)	198 (6.3)	
other[1]	2 (0.3)	37 (3.1)		1 (0.1)	128 (4.1)	
Duration of AF (years) – mean (±sd)	4.62± 4.92	4.61± 4.86	0.96	4.67± 5.14	4.75± 4.99	0.60
BMI (kg/m^2) – mean (sd)	27.11± 5.57	26.12± 5.38	<0.001	27.33± 4.36	26.71± 4.18	<0.001
Hypertension – n (%)	387 (51.8)	548 (53.1)	0.623	708 (43.9)	1252 (48.1)	0.009
DM – n (%)	69 (9.2)	88 (8.4)	0.655	155 (9.5)	274 (10.5)	0.321
CHF – n (%)	86 (12.3)	122 (12.5)	0.932	131 (8.5)	283 (11.5)	0.003
Stroke/TIA – n (%)	52 (7.6)	87 (9.1)	0.320	73 (5.0)	176 (7.4)	0.003
Vascular disease – n (%)	33 (5.9)	53 (6.0)	1.000	121 (10.2)	266 (12.1)	0.100
Measure of LA – n (%)			0.032			<0.001
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 (%) - mean (±sd)	61.99± 6.42	61.85± 7.35	0.65	60.53± 7.36	59.55± 8.29	<0.001

[1] left atrial tachycardia or flutter

LVSD – n (%)	12 (1.6)	39 (3.4)	0.029	62 (3.8)	168 (5.5)	0.011
Catheter data						
Catheter details– n (%)			<0.001			<0.001
Cryoballoon 1st generation	342 (46.8)	0 (0.0)		760 (47.1)	0 (0.0)	
Cryoballoon 2nd generation	389 (53.2)	0 (0.0)		852 (52.9)	0 (0.0)	
RF contact force	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)	

Table 1 – patients characteristics. AF = Atrial Fibrillation, BMI=Body mass index, CB=Cryoballoon, CHF = Congestive Heart Failure, DM = Diabetes Mellitus, LA=Left atrium, LVEF = Left ventricular ejection fraction, LVSD =Left Ventricular Systolic Dysfunction, RF= radiofrequency.

Table 2 - Occurrence of complications

Complications	Women			Men		
	CB	RF	p-value	CB	RF	p-value
Number of patients	787	1192		1714	3126	
At least one complication – n (%)	68 (8.6)	95 (8.0)	0.617	109 (6.4)	158 (5.1)	0.065
Groin complication – n (%)	21 (2.6)	42 (3.5)	0.353	32 (1.8)	51 (1.6)	0.626
Oesophageal fistula – n (%)	0 (0)	1 (0.1)	1.000	0 (0)	2 (0.1)	0.784
Pericardial effusion – n (%)	1 (0.1)	15 (1.3)	0.019	7 (0.4)	37 (1.2)	0.016
Phrenic nerve palsy – n (%)	29 (3.7)	6 (0.5)	<0.001	40 (2.3)	8 (0.3)	<0.001
PV stenosis – n (%)	0 (0)	0 (0)	-	3 (0.2)	2 (0.1)	0.455
Stroke/TIA – n (%)	1 (0.1)	4 (0.3)	0.655	7 (0.4)	14 (0.4)	1.000
Tamponade – n (%)	6 (0.8)	9 (0.8)	1.000	5 (0.3)	8 (0.3)	1.000

Table 2 – Occurrence of complications by sex and catheter type