

# Efficacy and safety of cryoballoon ablation versus radiofrequency catheter ablation in atrial fibrillation: an updated meta-analysis

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## Abstract

**Introduction:** Cryoballoon ablation (CBA) and irrigated radiofrequency catheter ablation (RFCA) are the main treatments for drug-refractory symptomatic atrial fibrillation (AF).

**Aim:** To compare the efficacy and safety between CBA and RFCA for the treatment of AF.

**Material and methods:** We searched the Embase and Medline databases for clinical studies published up to December 2016. Studies that satisfied our predefined inclusion criteria were included.

**Results:** After searching through the literature in the two major databases, 20 studies with a total of 9,141 patients were included in our study. The CBA had a significantly shorter procedure time (weighted mean difference (WMD)  $-30.38$  min; 95% CI:  $-46.43$  to  $-14.33$ ,  $p = 0.0002$ ) and non-significantly shorter fluoroscopy time (WMD  $-3.18$  min; 95% CI:  $-6.43$  to  $0.07$ ,  $p = 0.06$ ) compared with RFCA. There was no difference in freedom from AF between CBA and RFCA (CBA 78.55% vs. RFCA 83.13%, OR = 1.15, 95% CI: 0.95–1.39,  $p = 0.14$ ). The CBA was associated with a high risk of procedure-related complications (CBA 9.02% vs. RFCA 6.56%, OR = 1.56, 95% CI: 1.05–2.31,  $p = 0.03$ ), especially phrenic nerve paralysis (PNP, OR = 10.72, 95% CI: 5.59–20.55,  $p < 0.00001$ ). The risk of pericardial effusions/cardiac tamponade was low in the CBA group (CBA 1.05% vs. RFCA 1.86%, OR = 0.62, 95% CI: 0.41–0.93,  $p = 0.02$ ).

**Conclusions:** For AF, CBA was as effective as RFCA. However, CBA had a shorter procedure time and a non-significantly shorter fluoroscopy time, a significantly high risk of PNP and a low incidence of pericardial effusions/cardiac tamponade compared with RFCA.

**Key words:** cryoballoon ablation, radiofrequency catheter ablation, atrial fibrillation, meta-analysis.

## Introduction

Atrial fibrillation (AF) is certainly the most frequent arrhythmia and is associated with an increased risk of stroke, heart failure, and mortality [1]. Today, cryoballoon ablation (CBA) is an acceptable alternative to point-by-point radiofrequency catheter ablation (RFCA) for patients who are suffering from drug-refractory symptomatic AF [2]. However, there is still no universal agreement on which is preferable for treatment of AF. Although large numbers of clinical studies have already demonstrated CBA with a high success rate and low complication rate in the treatment of paroxysmal or persistent AF compared

with RFCA [3, 4], it is still less clear whether CBA is superior to RFCA. Therefore, we intended to update a meta-analysis to compare the efficacy and safety of CBA and RFCA for pulmonary vein isolation (PVI) in patients with AF, and perform analyses in a subgroup to increase the specificity of our findings. All outcomes were assessed in accordance with definitions of the original protocols at the longest follow-up available.

## Aim

This meta-analysis aimed to compare the efficacy and safety between CBA and RFCA for the treatment of AF.

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## Material and methods

Our study was carried out according to the guidelines published by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Supplementary Checklist S1) [5].

### Search strategies

We performed an online search for published studies using the databases of Embase and Medline up to December 2016 and identified all the studies which described the difference between CBA and RFCA in English. Our search strategy started with relevant keywords and medical subject heading terms including the following keywords: atrial fibrillation, AF, cryoballoon, cryoablation, cryoenergy, radiofrequency isolation, radiofrequency ablation, pulmonary vein isolation, PVI. Similar keywords were connected with “or” and dissimilar keywords were connected with “and”. The reference list of all qualified studies was reviewed for identification of further relevant studies.

### Selection criteria

The included studies had to fulfill the following criteria: 1. availability of data regarding procedure time, fluoroscopy time and total procedure-related complications with CBA vs. RFCA; 2. availability of data regarding the freedom from AF with CBA vs. RFCA; 3. the duration of follow-up should be > 6 months after ablation with a 3-month blanking period; 4. the number of patients should be at least 20 in each group.

The major exclusion criteria were as follows: 1. the patients had previous ablation procedures; 2. administration of antiarrhythmic drugs (AADs) during the follow-up after the blanking period; 3. case reports, conference abstracts, review articles, and duplicated data should be excluded; 4. follow-up of studies < 6 months.

### Data extraction and quality assessment

Two authors (Honglan Ma, Dongdong Sun) collected the data independently according to predefined search criteria. The third author (Hui Luan) would resolve the divergences. If available we entered the data into a standard Excel template: author & year, procedure time, fluoroscopy time, ablation time, the patients' number of pericardial effusion/cardiac tamponade events, the patients' number of phrenic nerve paralysis (PNP) events, freedom from AF after the follow-up and so on. Freedom from bias was assessed for each study in accordance with The Cochrane Collaboration method [6].

### Outcome variables

The primary outcomes were freedom from AF after the ablation at the end of follow-up, the total procedure time, fluoroscopy time, ablation time during the ablation

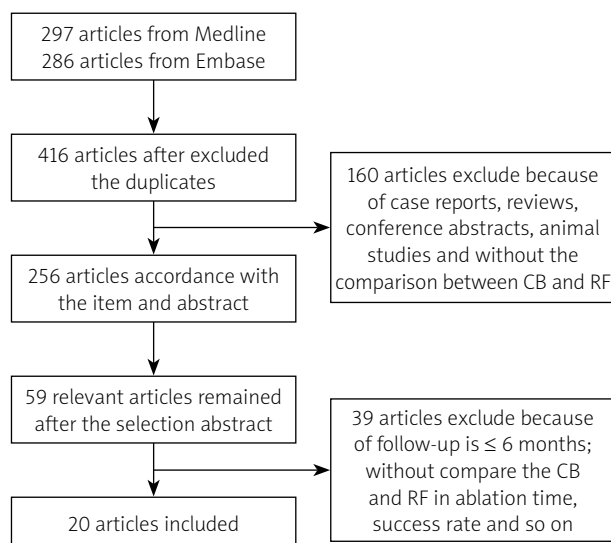
procedures and redo ablation rate during the follow-up. Secondary outcomes were the procedure-related complications, which contained pericardial effusion/cardiac tamponade, stroke, PNP, pulmonary vein stenosis, atrioesophageal fistula or death. Pericardial effusion/cardiac tamponade and PNP were reported as stand-alone complications in CBA and RFCA.

### Statistical analysis

We analyzed outcomes with the help of the Review Manager Version 5.3 software package (RevMan; The Cochrane Collaboration, Copenhagen, Denmark). We compared quantitative outcomes by weighted mean difference (WMD) and its 95% confidence interval (95% CI) between cryoballoon and radiofrequency ablation procedures. We compared the qualitative outcomes by weighted odds ratio (OR) and the corresponding 95% CI, which were counted by the Mantel-Haenszel method. Heterogeneity was assessed by  $\chi^2$  test and quantified using the inconsistency index ( $I^2$ ) statistic, with  $I^2$  values of 25%, 25–50%, or 50% signified as low, moderate, or high heterogeneity [6].  $P$ -values < 0.05 showed statistical significance.

## Results

The process of study selection is summarized in Figure 1. Twenty studies [7–26] with a total of 9141 patients (CBA,  $n = 3659$  vs. RFCA,  $n = 5482$ ) were included in this meta-analysis. The baseline characteristics of included studies were illustrated in Table I. Four [8, 10, 11, 21] studies adopted a 28 mm cryoballoon, and the rest of the studies adopted mixed cryoballoons of 23 mm and 28 mm. All included studies adopted the irrigated radiofrequency. All studies had patients matched for age, gender, atrial fibrillation duration, cardiovascular artery disease, hypertension, diabetes and left atrium diameter



**Figure 1.** Flowchart of study selection procedure

**Table 1.** Baseline characteristics of included studies

Author, year	Ablation type	Number of patients	Number of patient complications	Procedure time [min]	Fluoroscopy time [min]	Ablation time [min]	PNP	Pericardial effusion/tamponade number	Freedom from AF (%)	Follow-up
Malmborg, 2013	CB	50	4	165 ±40	32 ±16	108 ±39	1	0	60	12 ms
	RF	56	1	167 ±40	47 ±17	122 ±33	1	0	54	
Mugnai, 2014	CB	136	NR	112 ±58	31 ±17	NR	11	14	63.20	23 ±13 ms
	RF	260	NR	192 ±49	36 ±14	NR	0	27	57.30	
Kuck, 2016	CB	374	NR	124.4 ±39.0	21.7 ±13.9	NR	10	1	65.40	18 ms
	RF	376	NR	140.9 ±54.9	16.6 ±17.8	NR	0	5	64.10	
Kühne, 2010	CB	25	NR	166 ±32	61 ±25	45 (40–52.5)	1	0	88	12 ±3 ms
	RF	25	NR	197 ±52	46 ±22	47 (44–65)	0	0	92	
Schmidt, 2014	CB	905	NR	160 (130–200)	34 (26–46)	46 (40–57)	18	7	97.50	12 ms
	RF	2870	NR	165 (120–210)	24 (16–37)	33 (21–50)	1	37	97.60	
Castellano, 2014	CB	25	1	215 ±53	45 ±16	90 ±24	0	NR	67	12 ms
	RF	25	1	173 ±63	45 ±16	60 ±27	0	NR	68	
Bittner, 2011	CB	40	NR	171 ±40	26 ±8	33 ±10	0	NR	72	254 ±99 days
	RF	40	NR	224 ±27	35 ±9	65 ±24	0	NR	68	
Wasserlauf, 2015	CB	101	NR	192.9 ±44.0	46.0 ±22.4	NR	1	NR	60.30	0.73 year
	RF	100	NR	283.7 ±78.0	73.0 ±30	NR	0	NR	61.10	
Luik, 2015	CB	156	19	161.0 (132.8–193.2)	24.5 (17.5–31.0)	NR	9	2	73.60	12 ms
	RF	159	8	174.0 (146.5–218.0)	24 (16.9–37.2)	NR	0	3	70.70	
Jourda, 2014	CB	75	2	110.7 ±32.5	21.5 ±8.5	NR	13	NR	62	12 ms
	RF	75	1	134.3 ±48.3	25.3 ±9.9	NR	0	NR	66	
Zsófia oh, 2016	CB	38	NR	73.5 ±16	13.8 ±4.1	NR	2	1	81	12 ms
	RF	58	NR	118.5 ±15	15.8 ±6	NR	0	0	76.50	
Squara, 2015	CB	178	14	109.6 ±40	17.6 ±11	NR	10	0	83.90	18 ms
	RF	198	13	122.5 ±40.7	19.3 ±8.2	NR	0	2	82.20	

**Table 1.** Cont

Author, year	Ablation type	Number of patients	Number of patient complications	Procedure time [min]	Fluoroscopy time [min]	Ablation time [min]	PNP	Pericardial effusion/tamponade number	Freedom from AF (%)	Follow-up
Anyana, 2015	CB	773	67	145 ±49	29 ±13	40 ±14	59	5	76.60	12 ms
	RF	423	10	188 ±42	23 ±14	66 ±26	0	7	60.40	
Straube, 2016	CB	193	17	112 (93.5–130.0)	16.0 (13.0–23.0)	32.0 (28–37.7)	3	1	71	518 days
	RF	180	18	180 (135.0–210.0)	16.0 (11.0–28.0)	37.9 (31.3–53.6)	1	4	60.60	
Gunawardene, 2016	CB	30	6	98.0 ±21.9	15.4 ±3.9	NR	1	0	80	309.7 ±61.8 days
	RF	30	4	114.3 ±18.7	10.0 ±4.3	NR	0	0	90	
Knecht, 2014	CB	51	3	170 ±42	49 ±30	NR	1	1	72	28 ±15 ms
	RF	71	3	171 ±47	41 ±30	NR	0	1		
Khoueiry, 2016	CB	311	40	132.8 ±37	26.1 ±8.7	NR	7	1	83.00	14 ±8 ms
	RF	376	50	114.2 ±33.3	23.8 ±10.7	NR	1	6	85.90	
Siklody, 2012	CB	30	4	177 ±30	38 ±12	46 ±6	2	1	63	12 ms
	RF	30	0	200 ±46	37 ±16	52 ±21	0	0	80	
Kojodjolo, 2016	CB	90	3	108 ±28	27 ±9	NR	2	1	77	14.9 ±7.7 ms
	RF	53	2	208 ±58	62 ±36	NR	0	2	72	15.6 ±7.4 ms
Hunter, 2015	CB	78	4	167 (136–202)	35.7 (26.5–48.2)	40.2 (35–42.2)	5	0	67	12 ms
	RF	77	4	211 (174–250)	28.7 (20.1–41.6)	39.1 (28.7–51.8)	0	2	47	

between CBA and RFCA according to the original design. Also, all studies described a blanking period of 3 months after ablation. No AADs were taken during the follow-up after the blanking period.

**Primary outcomes**

Our included data (20 studies, 9141 patients; CBA, *n* = 3659 vs. RFCA, *n* = 5482) showed similar efficacy in freedom from AF of 78.55% (2874 patients) for CBA compared to 83.13% (4557 patients) for RFCA (OR = 1.15, 95% CI: 0.95–1.39, *p* = 0.14) with high heterogeneity for this risk estimate (*p* = 0.004, *I*<sup>2</sup> = 52%, Figure 2). Four studies [16, 19, 20, 23] had been eliminated temporarily when comparing the procedure time and fluoroscopy time for not using the mean (standard deviation) to describe time. The procedure time (16 studies, 4523 patients) was significantly shorter among patients who underwent CBA than RFCA in our study (WMD –30.38 min; 95% CI: –46.43 to –14.33, *p* = 0.0002, Figure 3 A). There was non-significantly shorter fluoroscopy time with CBA compared with RFCA (WMD –3.18 min; 95% CI: –6.43 to 0.07, *p* = 0.06, Figure 3 B). There was high heterogeneity for this risk estimate in procedure time (*p* < 0.00001, *I*<sup>2</sup> = 98%) and fluoroscopy time (*p* < 0.00001, *I*<sup>2</sup> = 95%). For redo ablation, CBA vs. RFCA was comparable during the follow-up after a blanking period of 3 months (WMD 0.83; 95% CI: 0.57–1.20, *p* = 0.31).

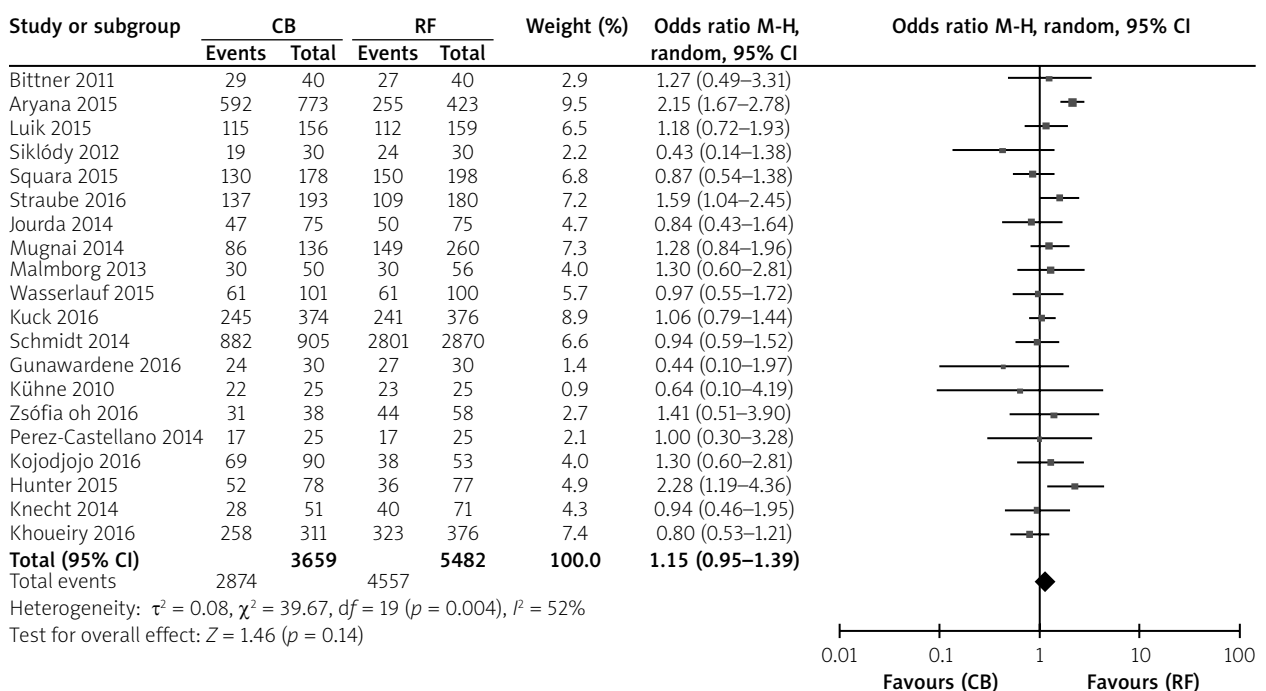
**Secondary outcomes**

In our study, CB ablation was associated with relatively high risk of procedure-related complications (CBA 9.02% vs. RFCA 6.56%, OR = 1.56, 95% CI: 1.05–2.31,

*p* = 0.03) with moderate heterogeneity for this risk estimate (*p* = 0.08, *I*<sup>2</sup> = 39%, Figure 4 A). Pericardial effusion/cardiac tamponade and PNP were reported as stand-alone complications. Fourteen studies with a total of 8504 patients recorded pericardial effusion/cardiac tamponade. There was a significant difference of 1.05% (35 patients) for CBA compared to 1.86% (96 patients) for RFCA (OR = 0.62, 95% CI: 0.41–0.93, *p* = 0.02) with no heterogeneity for this risk estimate (*p* = 0.65, *I*<sup>2</sup> = 0%, Figure 4 B). Almost all PNP occurred in the CBA group during the procedure and follow-up period (CBA 156 patients vs. RFCA 4 patients). Therefore patients seemed more likely to obtain PNP in the CBA group than the RFCA group (OR = 10.72, 95% CI: 5.59–20.55, *p* < 0.00001) after ablation with no heterogeneity for this risk estimate (*p* = 0.53, *I*<sup>2</sup> = 0%, Figure 4 C). However, almost all PNP resolved during the procedure or within 1 year after ablation.

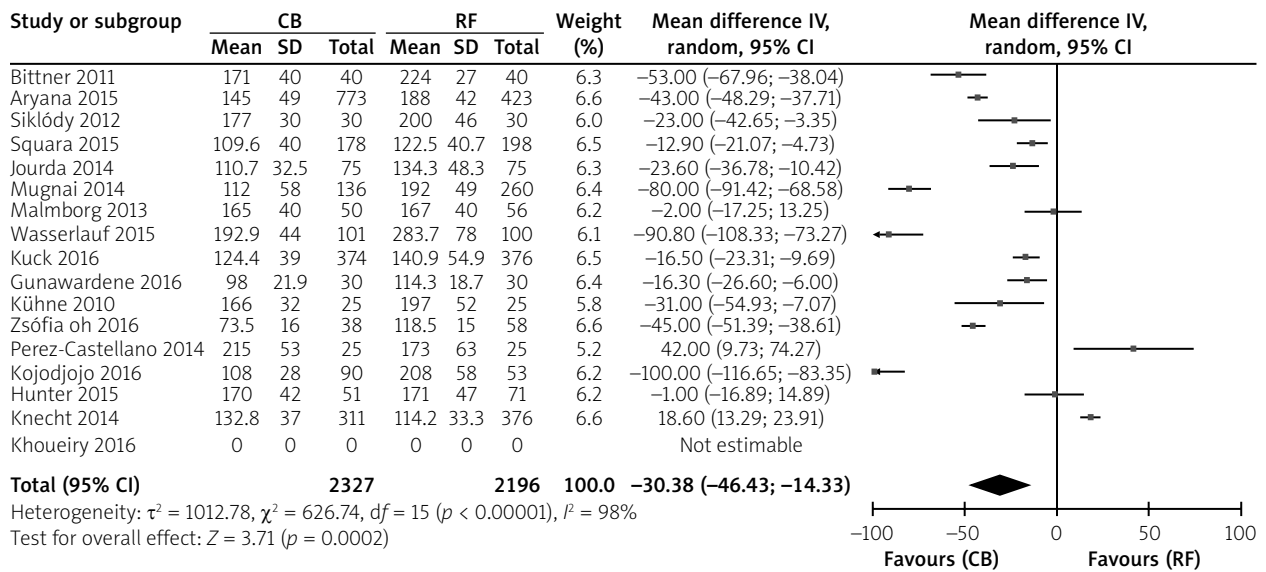
**Discussion**

This meta-analysis compared CBA with RFCA for the treatment of AF. The main findings were as follows: 1. CBA was associated with a significantly shorter procedure time and a non-significantly shorter fluoroscopy time than RFCA; both groups were comparable in the need for redo ablation; 2. CBA had a relatively high risk of procedure-related complications and a low risk of pericardial effusion/cardiac tamponade; 3. There was no significant difference in freedom from AF in a mean follow-up > 12 months between these two groups; 4. CBA had a higher risk of PNP than RFCA, although almost all PNP were resolved during the procedure and follow-up period.

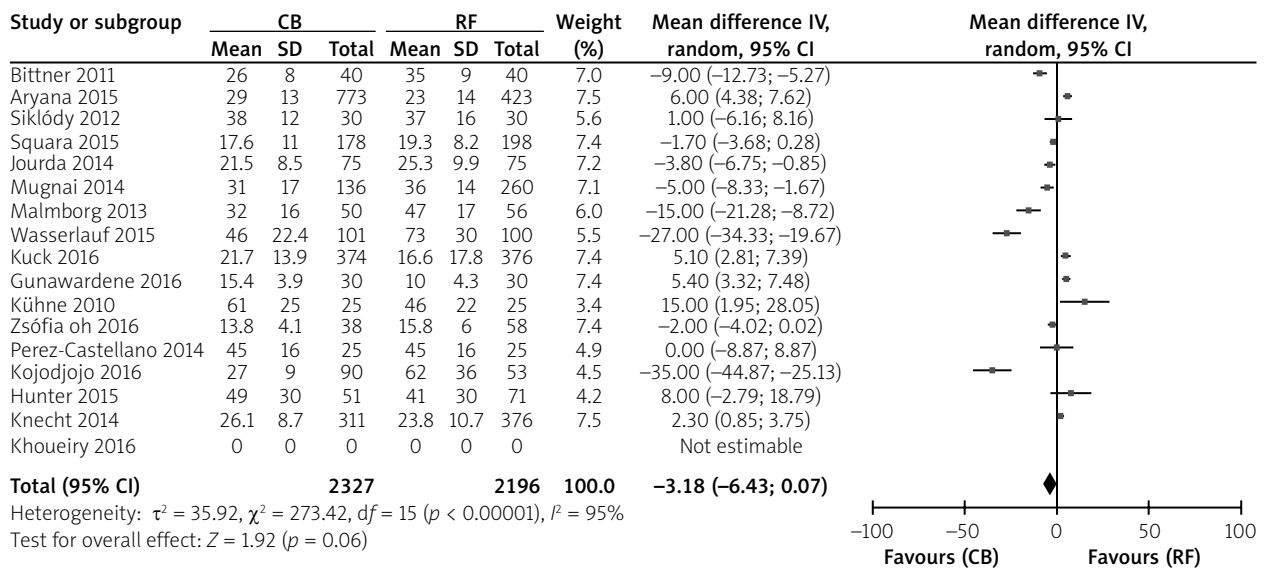


**Figure 2.** Forest plot of freedom from atrial fibrillation

**A. Comparison of procedure time**



**B. Comparison of fluoroscopy time**



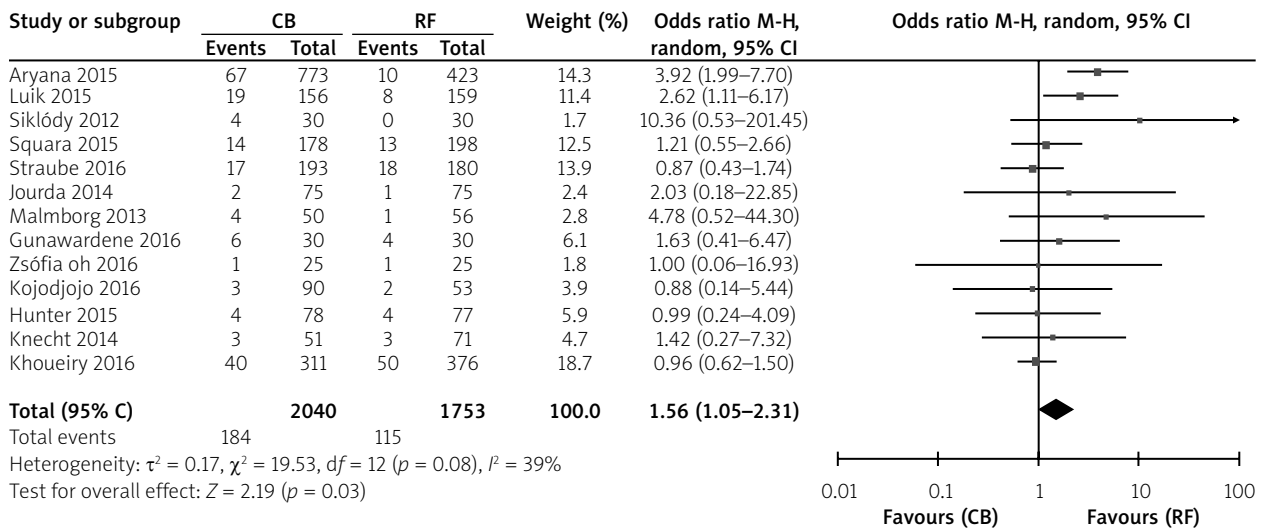
**Figure 3.** Forest plot of procedure and fluoroscopy time

Electrical isolation of the pulmonary veins (PVs) still remains the footstone of atrial fibrillation ablation procedures with the purpose of eliminating the trigger for AF episodes [27]. Radiofrequency and cryoballoon ablations are the two standard ablation systems used for PVI at present. Many experiments and studies have already compared the two standard ablations to determine which is more effective and safer. According to the previous studies [28, 29], the operators could use CBA or RFCA for AF patients because of the similar efficacy and safety, but evidence showed that CBA had a shorter learning curve than RFCA [30]. Hence we expect that CBA may be the main isolation in the future for AF because of the short learning curve. Furthermore, previous studies [31, 32] have reported that the second-generation cryo-

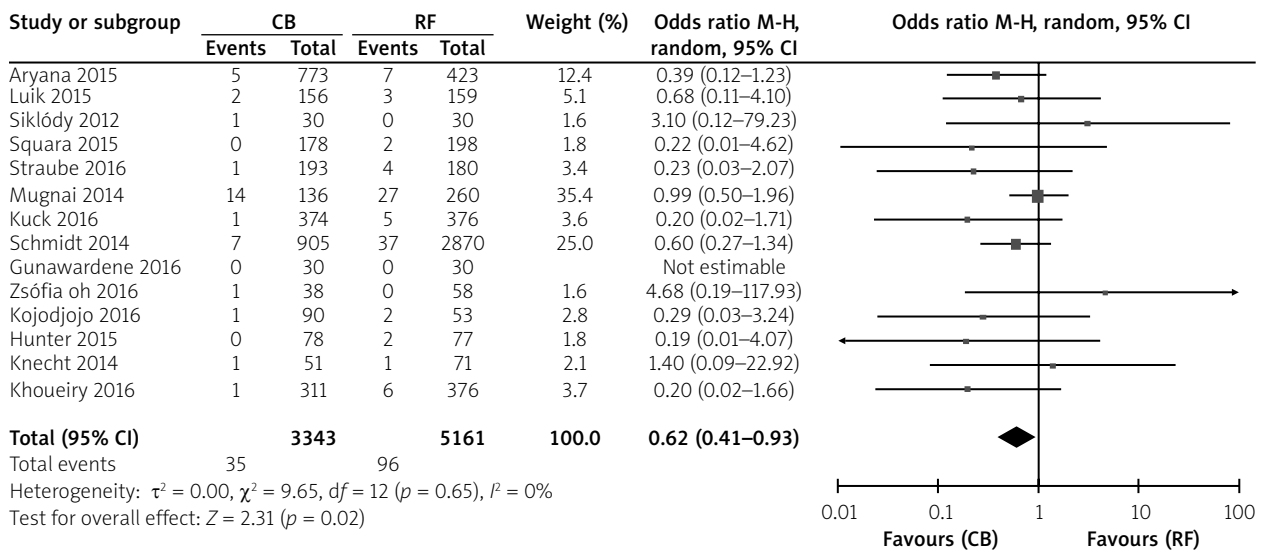
balloon ablation had a higher success rate than the first generation, and contact force ablation would reduce the major complications compared to non-contact force ablation [33]. However, just four [18, 21, 24, 26] of our studies stated that they used the second-generation cryoballoon ablation, and two studies [14, 19] stated that they used the first-generation counterpart.

As in previous studies, there was no significant difference in freedom from AF between CBA and RFCA during the follow-up in our study (CBA 78.55% vs. RFCA 83.13%,  $p = 0.14$ ). Some published studies [9, 18, 34] reported that freedom from AF after ablation ranged from 50% to 80%. However, one study [16] showed a higher success rate of both CBA (97.5%) and RFCA (97.6%) groups compared to other studies. This may relate to it being a multi-

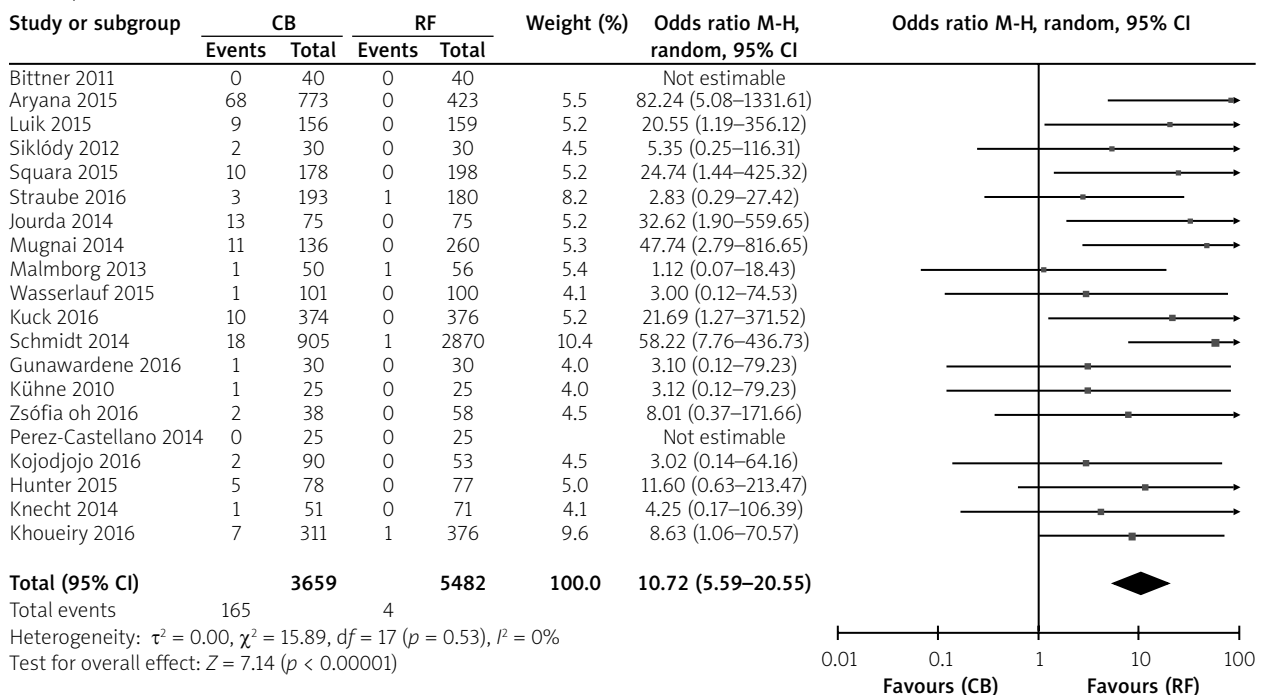
**A. Comparison of total procedure related complications**



**B. Comparison of pericardial effusion/cardiac tamponade**



**C. Comparison of PNP**



**Figure 4.** Forest plot of different procedure-related complications

center prospective registry including a total of 55 German electrophysiological centers with vast experience. Also it was possibly due to methodological limitations including inadequate sample size, patient's selection, and lack of adjustment for confounder bias.

In our meta-analysis, CBA had a shorter procedure time ( $p = 0.0002$ ) and a non-significantly shorter fluoroscopy time ( $p = 0.06$ ) compared with RFCA. The results were in line with most recent studies. As we know, the operators selected either CBA or RFCA on the basis of the patient's pulmonary vein anatomy; in other words, patients with unfavorable anatomy on computed tomography may tend to have RFCA rather than CBA [35]. This may explain why most recent studies reported a shorter procedure time and fluoroscopy time in CBA. Data from the German Ablation Registry showed similar procedure times between CBA and RFCA, but fluoroscopy times were longer in CBA [16]. This difference was likely due to the need for pre-procedural computed tomography imaging, which can further increase the cumulative radiation dose received by the patients. It may also be explained by the different cumulative experience and technical skills at different centers. Additional focal ablation was used (either cryoballoon or RF-based) when PV isolation had not been finished alone in most studies. In our study there was no difference in the need for redo ablation during the follow-up between CBA and RFCA ( $p = 0.31$ ). The increase of operator experience, technical skills and combined ablation might reduce the procedure time, fluoroscopy time and the need for redo ablation whether in CBA or RFCA. We speculate that with the accumulation of operational experience, cryoballoon ablation's advantages over radiofrequency ablation for the treatment of AF will render it more and more viable in clinical practice.

The total procedure-related complication rate was higher in the CBA than the RFCA group (CBA 9.02% vs. RFCA 6.56%,  $p = 0.03$ ), especially the PNP ( $p < 0.00001$ ). As we all know, PNP occurred disproportionately more often in CBA compared with RFCA because of the mechanism of CB ablation as well as the pulmonary vein and phrenic nerve anatomy. The high incidence of PNP in CB ablation accounts for a larger surface area of coolant distribution with CB catheters, which allows a more extended and simultaneous circumferential ablation with the potential reduction of bonus freeze cycle(s) and/or additional touch-up applications [36]. According to known anatomy, the phrenic nerves are relatively close to the pulmonary veins, especially the right phrenic nerve. Sanchez-Quintana *et al.* [37] reported that the right phrenic nerve was in close proximity to the superior caval vein (minimum:  $0.3 \pm 0.5$  mm) and the right superior pulmonary vein (minimum:  $2.1 \pm 0.4$  mm), which may enhance the risk of having PNP during ablation, but almost all PNP resolved during the procedure and follow-up period. Although extensive operator experience

and high technical skills could decrease the incidence of PNP, additional ECG conduction is an easy, effective and helpful additional security measure to prevent PNP from happening in CBA [38].

In previous studies [8, 9, 18, 39], no significant differences were found between CBA and RFCA-related pericardial effusions/cardiac tamponade. In the FIRE and ICE trial [25], there were 5 (1.3%) pericardial effusions with RFCA compared to 1 (0.3%) in CBA ( $p = 0.22$ ). Chierchia *et al.* [40] observed that pericardial effusion occurred in a similar proportion following CBA (11%) and RFCA (16%) for AF, whereas in our meta-analysis, RFCA showed a high risk of pericardial effusions/cardiac tamponade (CBA 1.05% vs. RFCA 1.86%,  $p = 0.02$ ) compared to CBA. However, pericardial effusion/cardiac tamponade was mostly mild and asymptomatic, with benign clinical outcomes not requiring additional hospitalization days.

Despite the strengths of our study including a huge number of patients, and low risk of publication bias, there were still several limitations. Firstly, just several studies were designed in receiver operating characteristic curve, which might increase the selection bias. Secondly, according to the selection criteria, small trials (number of patients  $< 20$ ) and non-English published studies were excluded. Also, we did not attempt to include unpublished data such as those presented at scientific meetings in abstract form. Thirdly, data of procedure and fluoroscopy times were not all recorded as mean (standard deviation). Four studies (4618 patients) were excluded when comparing the procedure and fluoroscopy times. Just 13 studies (3793 patients) recorded the data of the procedure-related complications. Almost all included studies did not record the institutional level of experience (no. ablations/year) with either ablation catheter.

## Conclusions

The results of our meta-analysis showed that CB ablation had a shorter procedure time and non-significantly shorter fluoroscopy time compared with RF ablation. There was no difference in freedom from AF after ablation at the end of follow-up between CBA and RFCA. But the total procedure-related complication rate was higher in CB ablation, especially the PNP. At the same time, our study indicated that RF ablation is associated with a high risk of pericardial effusions/cardiac tamponade.

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## Conflict of interest

The authors declare no conflict of interest.



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