



# Second-generation cryoballoon vs. contact-force sensing radiofrequency catheter ablation in atrial fibrillation: a meta-analysis of randomized controlled trials

Yang Wang<sup>1</sup> · Wei Wang<sup>2,3</sup> · Jianming Yao<sup>4</sup> · Lianghua Chen<sup>2</sup> · Shaolei Yi<sup>2,3</sup>

Received: 22 May 2020 / Accepted: 29 September 2020  
© Springer Science+Business Media, LLC, part of Springer Nature 2020

## Abstract

**Objectives** It is imperative to understand the influence of second-generation cryoballoon (CB-2) and contact-force sensing radiofrequency ablation (CF-RF) on clinical outcomes in atrial fibrillation (AF). This updated meta-analysis of randomized controlled trials (RCTs) examined the efficacy and safety of CB-2 vs. CF-RF in patients with AF.

**Methods** RCTs on the use of CB-2 vs. CF-RF in patients with AF were included. The primary outcome was the recurrence of AF, and the key secondary outcomes included serious complications, acute pulmonary vein isolation (PVI), procedure duration, and fluoroscopy time.

**Results** A total of 261 articles were identified, and five studies with a total of 845 participants were included in the study. A total of 93% of participants had paroxysmal AF, 7% of participants had persistent AF, and none of participants had permanent AF. There were 499 participants in the CB-2 arm and 346 in the CF-RF arm. AF recurrence was comparable in the CB-2 group (30.3%) and the CF-RF group (29.2%) (OR = 0.93; 95%CI = 0.56–1.54;  $P = 0.79$ ;  $I^2 = 48\%$ ). There were no statistical differences in acute PVI ( $P = 0.92$ ;  $I^2 = 0\%$ ) and serious complications ( $P = 0.87$ ;  $I^2 = 47\%$ ) between the two groups. The procedure duration was shorter in the CB-2 group than in the CF-RF group (MD = -13.39; 95%CI = -15.58, -7.19;  $P < 0.0001$ ;  $I^2 = 59\%$ ).

**Conclusion** Our study demonstrated that CB-2 and CF-RF had comparable recurrences of AF and similar incidences of serious complications in AF patients during the ablation process.

**Keywords** Atrial fibrillation · Catheter ablation · Second-generation cryoballoon · Contact-force sensing radiofrequency

---

Wei Wang is the co-first author

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s10840-020-00893-w>) contains supplementary material, which is available to authorized users.

---

✉ Shaolei Yi  
leisci@163.com

Wei Wang  
wangfuniuren@163.com

- <sup>1</sup> Department of Radiation Oncology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, China
- <sup>2</sup> Department of Cardiology, Shandong Provincial Hospital affiliated to Shandong First Medical University, Jinan, China
- <sup>3</sup> Department of Cardiology, Shandong Provincial Hospital affiliated to Shandong University, 324 Jingwulu, Jinan 250010, Shandong Province, China
- <sup>4</sup> Department of Cardiology, Jinan Municipal Hospital of Traditional Chinese Medicine, Jinan, China

## 1 Introduction

Catheter ablation has been proven to be an effective therapeutic method for restoring and maintaining sinus rhythm in patients with atrial fibrillation (AF) [1, 2]. Pulmonary vein isolation (PVI) is the cornerstone of catheter-based treatment for AF [3], and cryoballoon ablation (CB) and point-by-point radiofrequency (RF) ablation are currently the most widely used catheter ablation technologies for PVI.

In RF ablation, PVI is accomplished in a point-by-point manner, guided by 3D electroanatomic mapping techniques. The technique is considered technically challenging, especially for less experienced operators [4]. In cryoballoon ablation, PVI is performed in a “single shot” manner, which seems to be more accessible; however, the effects of cryoballoon ablation have been reported to be affected by pulmonary vein morphology [5]. To overcome these disadvantages, further improved

**Table 1** Characteristics of the included studies

		Study				
		2018 Buist et al.	2018 Gunawardene et al.	2018 Watanabe et al.	2019 Giannopoulos et al.	2019 Andrade et al.
Population		Paroxysmal or early persistent AF	Paroxysmal AF	Paroxysmal AF	Paroxysmal AF	Paroxysmal or persistent AF
Randomized method		CB-2;CF-RF 1:1	CB-2;CF-RF 1:1	CB-2;CF-RF 1:1	CB-2;CF-RF 2:1	CB-2(4 min);CB-2(2 min);CF-RF 1:1:1
CB-2 group	Type of cryoballoon	28 mm CB-2	28 mm CB-2	28 mm CB-2	28 mm CB-2	23 mm/28 mm CB-2
	Ablation protocol	240	240	180	240--180	240 s for CB-2(4 min);120 s for CB-2(2 min)
CF-RF group	Ablation protocol	20–30	17–30	17	NA	20 (10–40)
	Power (W)	≤30–40 W for 20–30 s	≤30 W for 30–60 s	30 W	NA	NA
	Temperature	≤45 °C	≤45 °C	NA	NA	NA
	CF (g)	NA	10	10–15	NA	NA
	FIT	>400 g	NA	NA	400	400
Primary outcome		The pulmonary vein reconnection; arrhythmia-free survival	Early recurrences of atrial fibrillation after PVJ	PV stenosis right after and 3 months after the ablation procedure	The change in LA ejection fraction (LAEF) at 1 month	The time to first recurrence of atrial tachyarrhythmia: the repeat ablation procedure
Follow-up duration (month)		12	12	12	6	12

AF atrial fibrillation, CF contact force, CF-RF contact force sensing radiofrequency ablation, CB-2 second-generation cryoballoon ablation, PV pulmonary vein, PVJ pulmonary vein isolation, FIT grams force-time integral

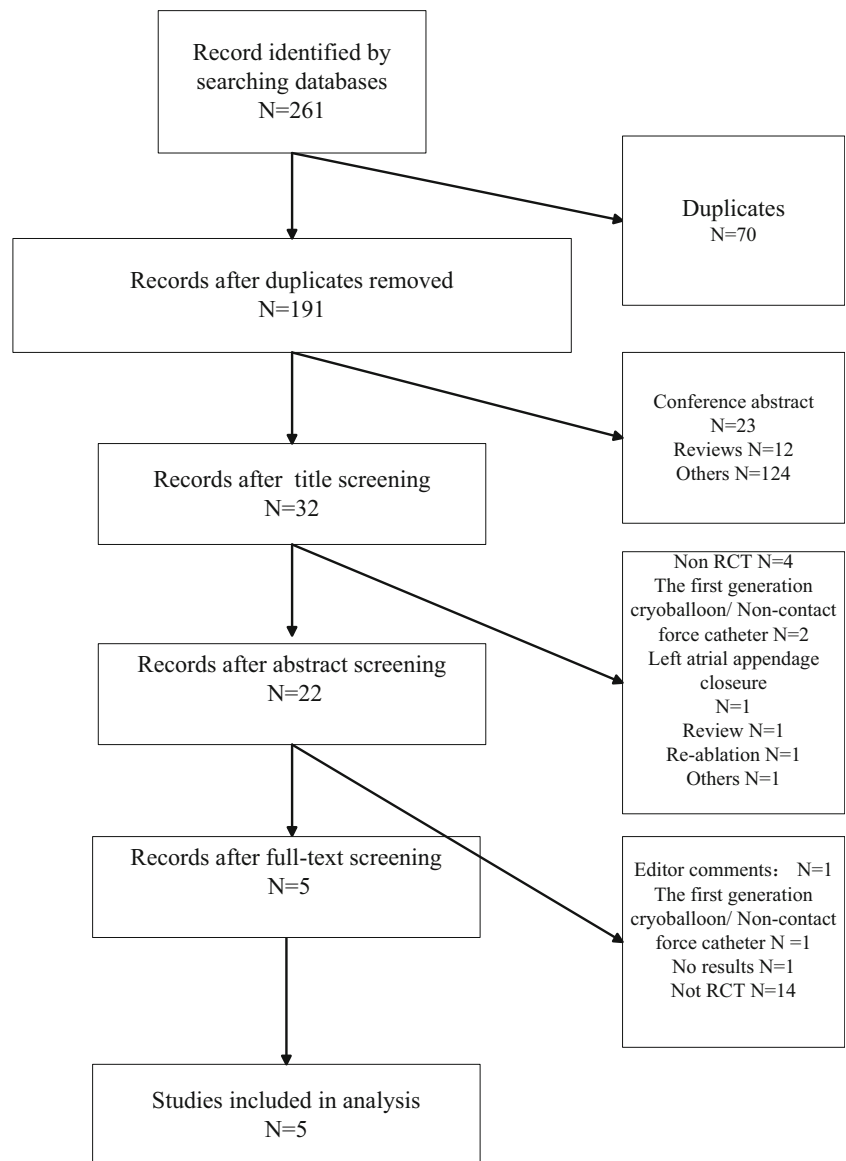
products were provided. In RF, the advanced-generation product is called a contact-force sensing radiofrequency catheter (CF-RF), and in cryoballoon ablation, the advanced generation product is called a second-generation cryoballoon catheter (CB-2). It is believed that both advanced-generation products have revolutionized the field of AF ablation [6, 7].

Many studies have been conducted to compare RF and CB, and it has been reported that these two ablation strategies have comparable efficacy and safety in the treatment of AF [8–10]. Most of these previous studies used first-generation CB and non-contact force-sensing RF catheters or only used advanced-generation catheters in a small proportion of patients with AF; thus, these studies were not sufficiently powered to detect differences between CB-2 and CF-RF [11]. Therefore, the current priority is to examine the influence

of advanced generation catheters on the comprehensive clinical outcomes.

Although several controlled trials of CB-2 and CF-RF have been reported [12–14], these results were contradictory. Buist et al. reported that increased arrhythmia-free survival and a more durable PVI were observed when using CB-2 compared with CF-RF [12]. Giannopoulos et al. reported that the arrhythmia recurrence rate was not significantly different between the CB-2 (23.8%) and CF-RF groups (26.3%) ( $P = 0.762$ ) [13]. Furthermore, a 2017 meta-analysis of CB-2 and CF-RF has been reported [7]; however, only 2 retrospective cohort studies and 4 controlled clinical trials were included and no randomized controlled trials (RCTs) were included. Given these limitations, we performed an updated meta-analysis of RCTs to examine the efficacy and safety of CB-2 vs. CF-RF in patients with AF.

**Fig. 1** Flow chart of the studies search. RCT randomized controlled trials



## 2 Methods

### 2.1 Search strategy and study selection

Four databases, including PubMed, the Cochrane Central Registered Control System, EMBASE, and ClinicalKey, were used to retrieve articles until December 30, 2019. The following words were applied for searching as MeSH or keywords: “atrial fibrillation” AND “second-generation cryoballoon catheter” AND “contact-force radiofrequency ablation catheter” AND “randomized controlled trial.” The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were performed.

### 2.2 Eligibility criteria

The included studies met the following criteria: published in English, first ablation for AF, and original data regarding CB-2 vs. CF-RF in the patient with AF; and RCT study that met the following criteria were excluded: conference abstracts, reviews, follow-up duration less than 3 months, less than 10 patients in each arm, not containing major interest outcomes, patients receiving both CB-2 and CF-RF ablation during the index procedure, and original data regarding ablation vs. atrioventricular node ablation or surgical ablation. If duplicate reports were published, only the most complete one was included.

### 2.3 Data extraction and critical appraisal

Data were extracted from the incorporated articles that passed the initial quality assessment. The information included study design, number of patients in each study arm, baseline characteristics, procedural details of CB-2 and CF-RF, and follow-up duration, and the interest outcome measures were extracted from each study. The Cochrane risk of bias tool for RCTs was used to perform the quality assessment of the included studies [15].

### 2.4 Outcomes

The primary outcome of this study was the recurrence of AF. Key secondary outcomes included serious complications, the acute success of pulmonary vein isolation during ablation procedure (acute PVI), procedure duration, and fluoroscopy time. If an adverse event had the potential to result in permanent injury or death, required blood transfusion, required hospitalization for more than 24 h, or required intervention for treatment, it was considered a serious complication.

### 2.5 Statistical analysis

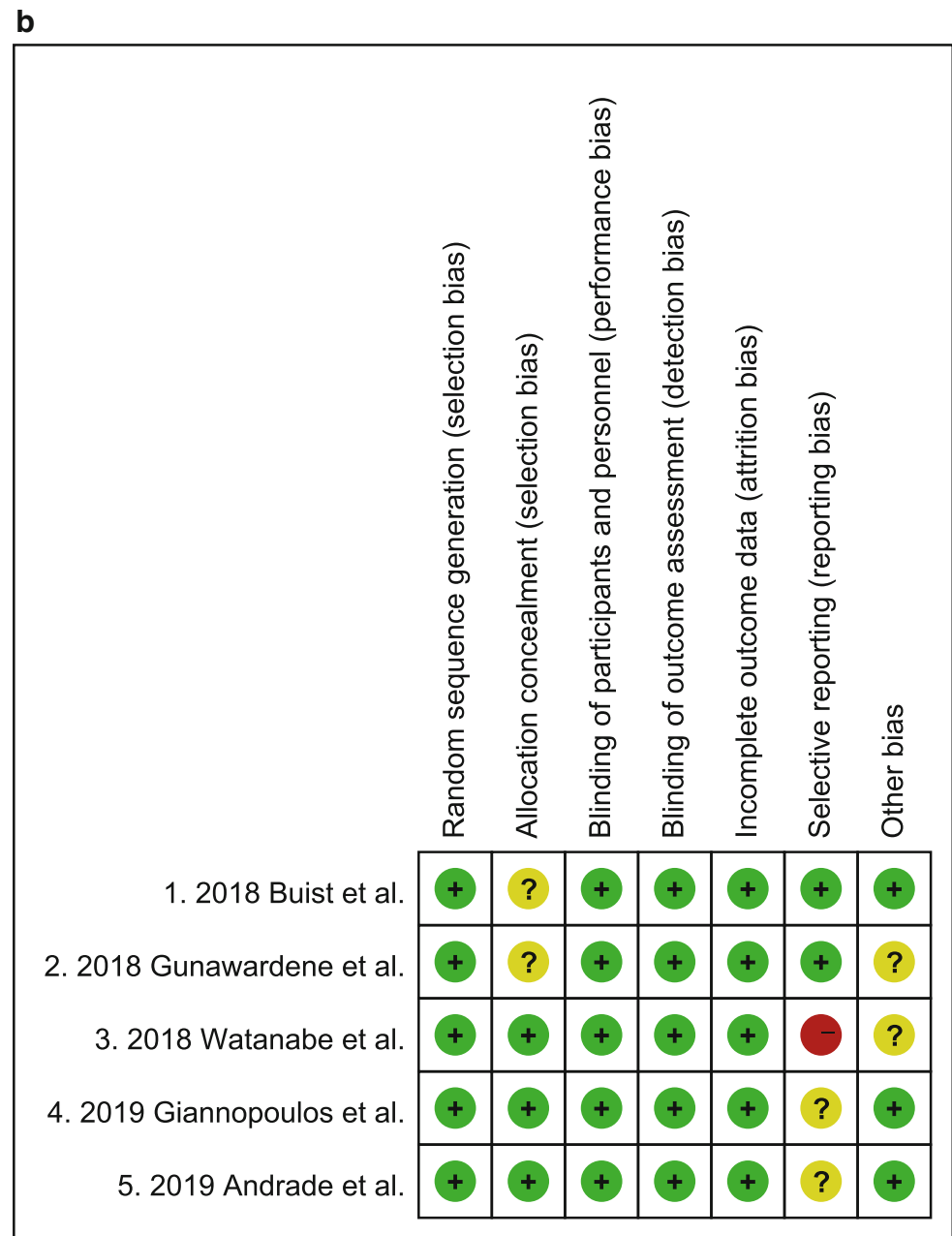
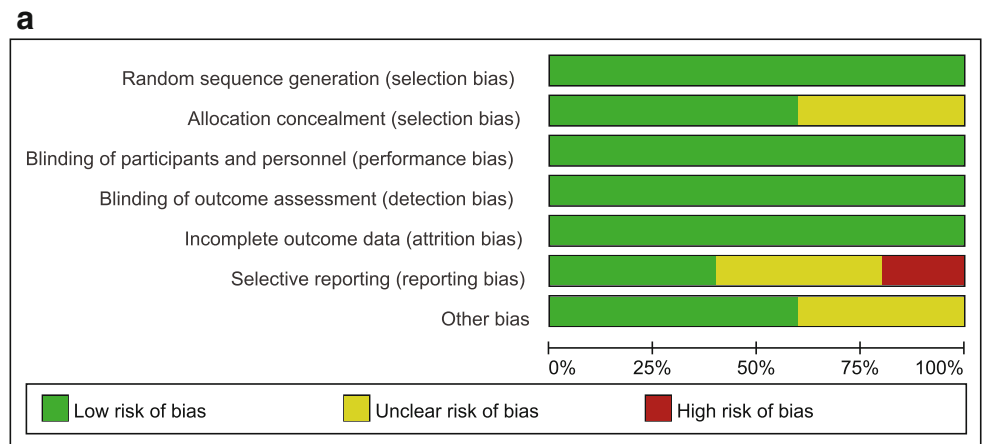
Continuous variables were expressed as weighted mean differences and 95% confidence intervals (CIs), and the  $I^2$

**Table 2** Characteristics of the involved patients

Studies	Group	Patient numbers	Age (years mean ± SD)	Male n (%)	LVEF %	LAD (mm mean ± SD)	BMI (kg/m <sup>2</sup> mean ± SD)	Persistent AF n (%)	Paroxysmal atrial fibrillation n (%)	Hypertension n (%)	Diabetes n (%)	Heart failure n (%)	CHA <sub>2</sub> DS <sub>2</sub> -VASc
2018 Buist et al.	CB-2	133	59.7 ± 9.9	92 (69.2%)	NA	NA	27.8 ± 4.4	16 (12.0%)	117 (88.0%)	57 (43.2%)	14 (10.6%)	NA	1.37 ± 1.32
	CF-RF	136	58.2 ± 10.8	99 (72.8%)	NA	NA	27.1 ± 3.9	24 (17.6%)	112 (82.4%)	52 (38.5%)	9 (16.7%)	NA	1.25 ± 1.26
2018 Gunawardene et al.	CB-2	30	62.0 ± 9.5	18 (60%)	59.8 ± 4.5	NA	27.7 ± 3.2	0	30 (100%)	16 (53%)	NA	NA	1.73 ± 2.03
	CF-RF	30	57.4 ± 10.5	24 (80)	59.2 ± 5.0	NA	28.4 ± 3.6	0	30 (100%)	17 (56%)	NA	NA	1.35 ± 1.85
2018 Watanabe et al.	CB-2	25	62 ± 12	17 (68)	63 ± 5	39 ± 6	23.6 ± 3.5	0	25 (100%)	16 (64%)	3 (12%)	2 (8%)	NA
	CF-RF	25	68 ± 9	19 (76)	58 ± 8	42 ± 5	24.2 ± 3.3	0	25 (100%)	14 (56%)	5 (20%)	2 (8%)	NA
2019 Giannopoulos et al.	CB-2	80	61 ± 8.89	NA	28.4 ± 18.5	40 ± 5.18	28.2 ± 4.3	0	80 (100%)	41 (51.3%)	9 (11.3%)	2 (2.5%)	1 ± 1.33
	CF-RF	40	59.1 ± 9.6	NA	29.8 ± 7.85	41.07 ± 4.29	29.7 ± 7.7	0	40 (100%)	18 (45.0)	6 (15.0%)	2 (5%)	1 ± 0.74
2019 Andrade et al.	CB-2	231	58.9 ± 10.31	152 (65.8%)	59.3 ± 5.81	37.95 ± 8.95	NA	9 (3.9%)	222 (96.1)	80 (34.6%)	NA	4 (1.73%)	1 ± 0.65
	CF-RF	115	58.6 ± 9.2	79 (68.7%)	59.1 ± 6.6	37.4 ± 8.5	NA	10 (8.7%)	105 (91.3%)	40 (34.8%)	NA	2 (1.7%)	1 ± 0.67

AF atrial fibrillation, CF contact force, CF-RF contact force sensing radiofrequency ablation, CB-2 second-generation cryoballoon ablation

Fig. 2 Risk of bias graph



**Table 3** The sensitivity analysis of recurrence of AF

Removed study	OR (95%CI)	P value	Model	I <sup>2</sup> (P value)
1. 2018 Buist et al.	1.21(0.83,1.77)	P = 0.32	Random	0% (P = 0.66)
2. 2018 Gunawardene et al.	0.86(0.51,1.44)	P = 0.56	Random	53% (P = 0.10)
3. 2018 Watanabe et al.	0.93(0.52,1.68)	P = 0.82	Random	61% (P = 0.05)
4. 2019 Giannopoulos et al.	0.98(0.51,1.88)	P = 0.95	Random	61% (P = 0.05)
5. 2019 Andrade et al.	0.76(0.44,1.30)	P = 0.31	Random	23% (P = 0.27)

AF atrial fibrillation

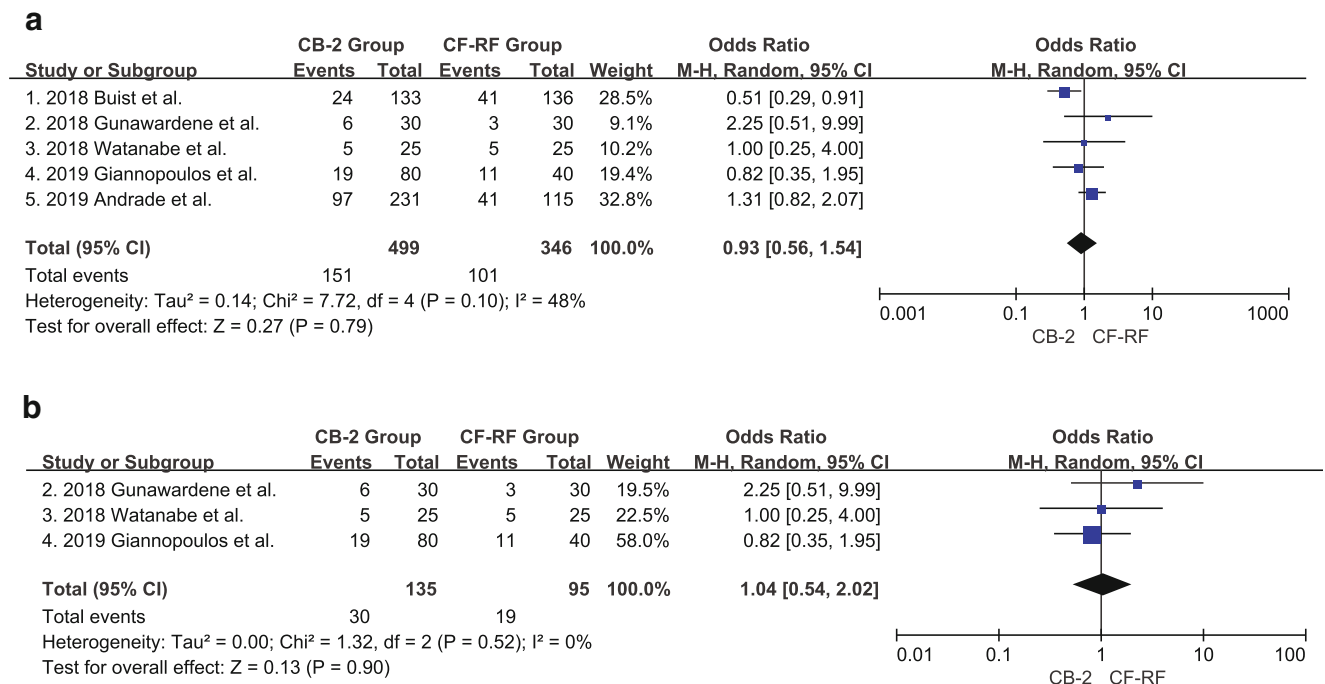
statistic was used to assess heterogeneity. A sensitivity analysis was conducted in which one study was removed at a time to test the stability of the results. Methods would be used to convert that to mean and standard deviation, if values were presented as median and inter-quartile range in included studies, as described previously [16]. Review Manager Version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) was used to perform the analysis. A P value of <0.05 was considered statistically significant.

### 3 Results

#### 3.1 Eligible study selection

Five studies were involved in our study. A total of 261 articles were retrieved by database searching, as shown in Fig. 1. There were 70 duplicates. The high number of duplicates may be due to different databases containing articles from

the same journal source. After the titles and abstracts were screened, 22 articles remained, and after full-text screening, five remained finally. All five involved studies were RCTs, two of which enrolled paroxysmal and persistent AF patients [12, 17], and the remaining three studies only enrolled patients with paroxysmal AF [13, 18, 19]. One study randomly assigned patients with paroxysmal AF in a 1:2 allocation scheme [13]. One study randomly assigned to patients to three groups as follows: contact-force guided RF ablation group, 4-min cryoballoon ablation group, and 2-min cryoballoon ablation group [17], from which data in the 4-min cryoballoon ablation group and 2-min cryoballoon were combined during the extraction of data. With the exception of one study [17], in which 23-mm and 28-mm second-generation cryoballoons were used accordingly, the other four studies used only the 28-mm second-generation cryoballoon catheter during cryoablation process [12, 13, 18, 19]. In the CB-2 arm, the freezing time was 240 s in most of the included studies [12, 13, 18, 19], and in two of the involved studies, PVI was



**Fig. 3** Primary outcomes. **a** Analysis of all 5 involved studies; **b** the subgroup analysis of 3 studies only containing participants with paroxysmal AF. AF atrial fibrillation, CF-RF contact force sensing radiofrequency ablation, CB-2 second-generation cryoballoon ablation

evaluated through a waiting process [12, 17]. In one study, additional ablation was done by using a touch-up freeze cryocatheter if PVI was not achieved by the first-cycle cryoballoon treatment [19]. The follow-up duration was 12 months in four studies and 6 months in one study (Table 1).

Table 2 shows the baseline characteristics of the involved patients. Of all the included studies, a total of 845 participants were included in the research, with 499 participants in the CB-2 arm and 346 in the CF-RF arm. The mean age of all participants was  $59.45 \pm 10.13$  years, and the percentage of males was 69.0%. A total of 93% of participants included had paroxysmal AF, 7% of participants included had persistent AF, and none of participants included had permanent AF. The Cochrane risk of bias tool was used to evaluate the studies, and the result is shown in Fig. 2.

### 3.2 Primary outcome

All five studies and 845 participants were available for the analysis of the primary outcome. The incidence of recurrence of AF was comparable in the CB-2 group (30.3%) and the CF-RF group (29.2%) (OR = 0.93; 95%CI = 0.56–1.54;  $P = 0.79$ ;  $I^2 = 48\%$ ) (Fig. 3a). A subgroup analysis was conducted based on whether participants in the study had persistent AF, and the result was consistent with previous analysis of primary outcome (Fig. 3b). Furthermore, sensitivity analysis was conducted in order to study the impact of individual studies on overall risk estimates. The results showed that the overall risk of OR estimates were consistent and not significantly volatile, with a range from 0.76 (0.44–1.30) to 1.21(0.83–1.77) (Table 3).

### 3.3 Secondary outcomes

Four studies were involved in the analysis of acute PVI [12, 13, 18, 19]. The percentage of acute PVI in the CB-2 group was 99.5% (1076/1081), and 99.68% (936/939) in the CF-RF group. There were no statistical differences in acute PVI between the CB-2 and CF-RF groups (RR = 1.0; 95%CI = 0.99–1.01;  $P = 0.92$ ;  $I^2 = 0\%$ ). A single study did not influence the overall risk estimate.

Four studies were included in the analysis of serious complications [12, 17–19], and one study did not mention the occurrence of complications in the article [13]. The occurrence of complications in all participants was 6.34%, and the occurrence of serious complications was 3.34% and 2.94% in the CB-2 arm and CF-RF arm, respectively. There were no statistical differences between the two arms (RD = 0.0; 95%CI = -0.04–0.03;  $P = 0.87$ ;  $I^2 = 47\%$ ) (Fig. 4b). The removal of a single study did not influence the overall risk estimate, and there were no deaths in any of the involved studies. In the CB-2 arm, phrenic nerve palsy was the most common complication (1.67%), and the incidence of

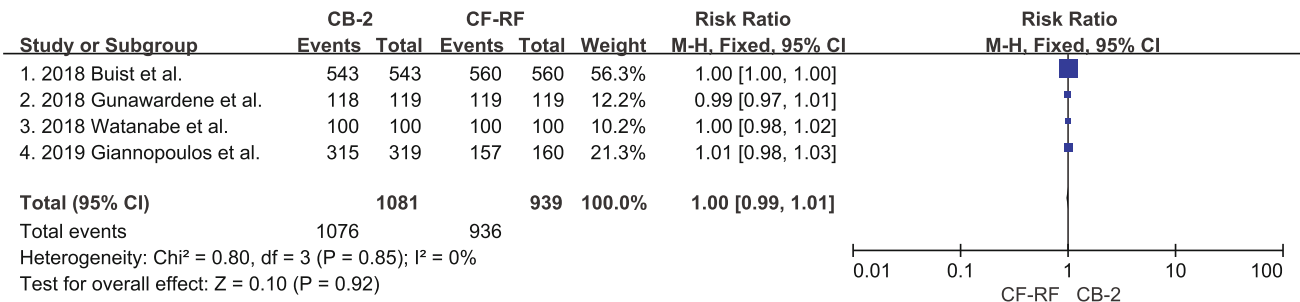
**Table 4** Summary of complications

Studies	Group	Temporary PNP	Death	Vascular access	Permanent PNP	Pericarditis	Pericardial effusion	Pneumonia/bronchitis	TIA	Coronary events	Hematoma requiring intervention	Esophageal perforation	Esophageal Injury	Acute pulmonary infarction
2018 Buist et al.	CB-2	4	0	3	0	1	0	0	0	0	0	0	0	0
	CF-RF	0	0	3	0	2	1	1	1	1	0	0	0	0
2018 Gunawardene et al.	CB-2	1	0	5	0	0	0	0	0	0	0	0	0	0
	CF-RF	0	0	4	0	0	0	0	0	0	0	0	0	0
2018 Watanabe et al.	CB-2	NA	0	NA	0	0	0	0	0	0	0	0	0	0
	CF-RF	NA	0	NA	0	0	0	0	0	0	0	0	0	0
2019 Giannopoulos et al.	CB-2	NA	0	NA	NA	NA	NA	NA	NA	NA	0	0	0	0
	CF-RF	NA	0	NA	NA	NA	NA	NA	NA	NA	0	0	0	0
2019 Andrade et al.	CB-2	NA	0	0	3	3	1	1	2	1	0	0	1	1
	CF-RF	NA	0	1	0	2	1	0	0	0	1	1	0	0

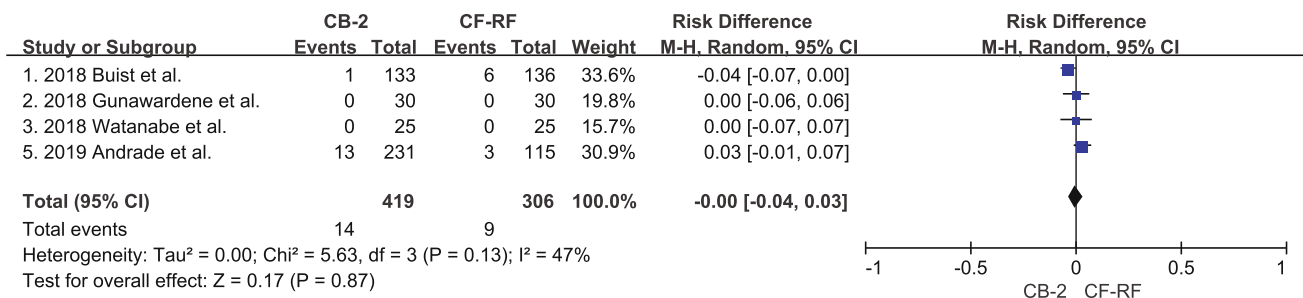
PNP phrenic nerve palsy, TIA transient stroke, CB-2 second-generation cryoballoon, CF-RF contact-force radiofrequency ablation catheter



**a Acute PVI**

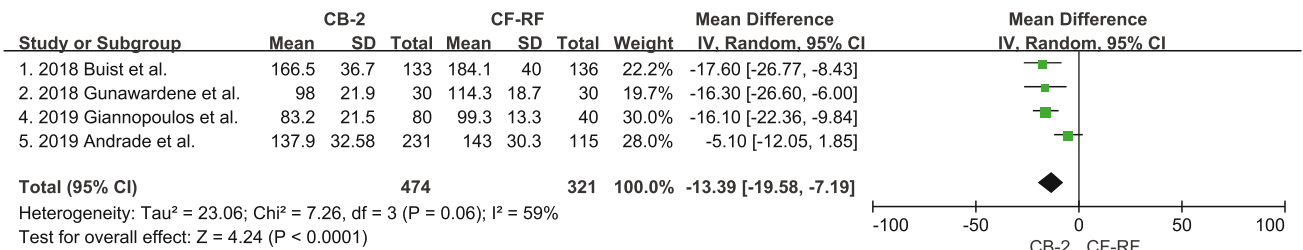


**b Serious Complications**

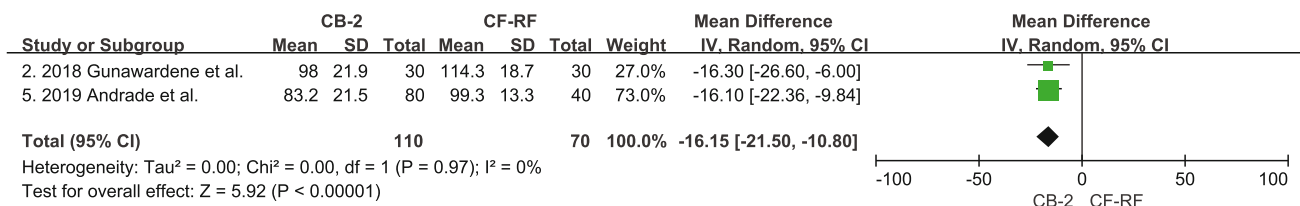


**c Procedure Duration**

(1)



(2)



**Fig. 4** Secondary outcomes. **a** Analysis of occurrence of acute PVI; **b** analysis of occurrence of serious complications; **c** analysis of procedure duration, a subgroup analysis was conducted based on whether there was a waiting process during the evaluation of the ablation endpoint. AF atrial

fibrillation, CF-RF contact force sensing radiofrequency ablation, CB-2 second-generation cryoballoon ablation, PVI acute pulmonary vein isolation

permanent phrenic nerve palsy was 0.72% during second-generation cryoballoon ablation. Table 4 summarizes the incidence of complications in the involved studies.

Four studies were available for the analysis of procedure duration [12, 13, 17, 18]. The results showed that in the CB-2

group, the procedure duration was shorter than that in the CF-RF group (MD = -13.39; 95% CI = -15.58-7.19; P < 0.0001; I<sup>2</sup> = 59%). Moderate heterogeneity was found (I<sup>2</sup> = 59%), and as a result, subgroup analysis was conducted based on whether there was a waiting process during the



**Table 5** The quality of evidence measured by GRADE system

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Recurrence of AF	Study population 286 per 1000	326 per 1000 (250 to 415)	OR 1.21 (0.83 to 1.77)	576 (5 studies)	3 ⊕⊕⊕⊕ moderate <sup>1</sup>
	Medium risk population 275 per 1000	315 per 1000 (239 to 402)			
Acute PVI	Study population 997 per 1000	997 per 1000 (987 to 1000)	RR 1 (0.99 to 1.01)	202 (4 studies)	⊕⊕⊕⊕high
	Medium risk population 1000 per 1000	1000 per 1000 (990 to 1000)			
Serious complications	Study population 29 per 1000	26 per 1000 (− 10 to 59)		725 (4 studies)	⊕⊕⊕⊕moderate <sup>1</sup>
	Medium risk population 13 per 1000	12 per 1000 (− 5 to 26)			
Duration		The mean duration in the intervention groups was 13.39 lower (19.58 to 7.19 lower)		795 (4 studies)	⊕⊕⊕⊕low <sup>1,2</sup>
No waiting process		The mean No waiting process in the intervention groups was 16.15 lower (21.5 to 10.8 lower)		180 (2)	

\*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

CI confidence interval, OR odds ratio, RR risk ratio

GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate

<sup>1</sup> Events less than 300

<sup>2</sup> I<sup>2</sup> greater than 50%

evaluation of the ablation endpoint. The results are shown in Fig. 4c.

High heterogeneity was found in the analysis of fluoroscopy time, and for sample sensitivity analysis, all I<sup>2</sup> values were greater than 85% (Table s1); thus, the analysis of this indicator was abandoned. The high heterogeneity may be due to different habits of fluoroscopy and different levels of operator experience in different medical centers. Based on the available evidence, our study cannot draw valid conclusions.

Table 5 shows the quality of evidence measured by the GRADE system.

### 4 Discussion

To our knowledge, our study is the first meta-analysis to compare CB-2 with CF-RF catheter ablation in patients with AF by focusing on published RCTs. We demonstrated that there were comparable recurrences of AF after ablation, with a similar incidence of serious complications in the CB-2 and CF-RF groups. Furthermore, our results showed that the procedure

duration in the CB-2 group was shorter than that in the CF-RF group.

The incidence of recurrence of AF in our study was 30.3% in the CB-2 arm and 29.2% CF-RF arm. It seemed that, similar to the first generation of cryoballoon and non-contact RF ablation catheters, CB-2 and CF-RF had similar therapeutic efficacy in patients with AF [11]. Furthermore, it appears that the advanced generation ablation catheters did not improve the effectiveness of AF ablation, since a previous meta-analysis review on first-generation cryoballoon ablation and non-contact force irrigate radiofrequency catheter ablation for AF reported that the incidence of recurrence of AF after single procedure ablation was 28.3% and 30.9%, retrospectively [20]. These findings are consistent with those of Zhao et al., who reported that first-generation and second-generation cryoballoon catheters showed similar efficacy for paroxysmal AF ablation [21]. Furthermore, Kajiyama et al. reported that the anatomy of PV could influence acute PVI during the process of second-generation cryoballoon catheter ablation [22]. In our study, we showed that acute PVI was not affected by the anatomy of the PV, as there was only one involved study

that screened the anatomy of PVs before ablation [19], and removing that study did not affect the result of acute PVI and recurrence of AF in the study. Therefore, it was considered that screening the anatomy of the PV did not affect the effectiveness of AF ablation of CB-2. A similar low incidence of serious complications was found in the CB-2 and CF-RF groups (3.34% and 2.94%, respectively), but no deaths occurred in the included RCTs. More phrenic nerve palsy was found in the CB-2 arm (1.67%) than in the CF-RF arm (0%). Most patients with phrenic nerve palsy recovered, and the incidence of permanent phrenic nerve palsy was just 0.72%. In the CF-RF arm, pericardial effusion and vascular access complications were more common. The incidence of complications in our research was much lower than that of previous studies [20]. The reason for the difference in the incidence of complications may be due to the use of advanced generation catheters and the growth of the experience of the operator in involved studies of our research. Generally, CB-2 and CF-RF are safe techniques for patients with AF and have comparable efficacy.

Consistent with previous studies [7, 23, 24], the procedure duration in the CB-2 group was shorter compared with the CF-RF group. The shorter time needed in the CB-2 group may be due to the “single shot” manner used during the process of PVI. Inconsistent with previous research [25, 26], we could not draw valid conclusions about fluoroscopy times in the CB-2 arm vs. CF-RF arm because high heterogeneity was found during sample sensitivity analysis, in which all  $I^2$  values were greater than 85%. The high heterogeneity may be due to different levels of experience and habits of fluoroscopy in different medical centers, since it was reported that the fluoroscopy time would be reduced by increased experience during ablation of AF [23].

Since CB-2 and CF-RF had efficacy and safety in the first ablation of AF patients according to our research, both advanced generation catheters should be equally recommended to patients with AF. However, other aspects need to be considered. Indeed, it has been demonstrated that cryoballoon ablation was performed in a “single shot” manner with a faster learning curve compared to radiofrequency ablation [27]. Thus, less experienced electrophysiologists would benefit from this technique. It has been reported that cryoballoon ablation is better tolerated than point-by-point radiofrequency ablation [20, 28]. Therefore, future studies are needed to investigate if a specific subgroup of AF patients would benefit more from CB-2 or CF-RF ablation [20].

Some limitations of this study should be considered. Although the selected studies are all RCT studies comparing the effects of CB-2 and CF-RF in AF patients, it should be noted that there were still some differences in randomly assigned patterns, the ablation process, protocols, and strategies, and the methods of follow-up in the individual CB-2 and CF-RF groups as shown in

Tables 1 and 2. And because of the nature of meta-analysis review, comorbidities and risk factors are not always known in the present research, as shown in Table 2. Another limitation of this study was that we could not draw valid conclusions about fluoroscopy times in the CB-2 arm vs. the CF-RF arm based on current evidence. In addition to those, the cost-effectiveness of the two competing technologies was also not compared in our research. Further investigations and more data are needed. Perhaps, the two ongoing multicenter RCTs (The FIRE AND ICE II randomized outcome trial and the ABLANSAF study) will help to solve those confusions [11, 29].

## 5 Conclusion

Our study demonstrated that CB-2 and CF-RF had comparable recurrences of AF and similar incidences of serious complications during the ablation process of AF patients. Since the efficacy and safety of the first ablation of AF patients in the CB-2 and CF-RF groups were comparable, both of the advanced generation catheters should be recommended equally as the first approach for ablation of AF.

**Funding** This study was sponsored by the Natural Science Foundation of Shandong Province of China (ZR2019PH036) and the Key Research and Development Plan of Jinan Shandong Province of China (201805056).

**Data availability** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. Roy D. Rationale and design of a study assessing treatment strategies of atrial fibrillation in patients with heart failure: the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial. *Am Heart J*. 2002;144(4):597–607.
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Rev Esp Cardiol*. 2017;70(1):50. <https://doi.org/10.1016/j.rec.2016.11.033>.
3. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace*. 2012;14(4):528–606. <https://doi.org/10.1093/europace/eus027>.
4. Hakalahti A, Biancari F, Nielsen JC, Raatikainen MJ. Radiofrequency ablation vs. antiarrhythmic drug therapy as first

- line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. *Europace*. 2015;17(3):370–8. <https://doi.org/10.1093/europace/euu376>.
5. Mulder BA, Al-Jazairi MIH, Arends BKO, Bax N, Dijkshoorn LA, Sheikh U, et al. Pulmonary vein anatomy addressed by computed tomography and relation to success of second-generation cryoballoon ablation in paroxysmal atrial fibrillation. *Clin Cardiol*. 2019;42(4):438–43. <https://doi.org/10.1002/clc.23163>.
  6. Bhatti S, Saliaris AP. Atrial fibrillation ablation in the era of cryoballoon and force-sensing catheters: freeze or burn? *Curr Treat Options Cardiovasc Med*. 2015;17(4):374. <https://doi.org/10.1007/s11936-015-0374-1>.
  7. Zhou X, Lv W, Zhang W, Ye Y, Li Y, Zhou Q, et al. Comparative efficacy and safety of contact force-sensing catheter and second-generation cryoballoon ablation for atrial fibrillation: a meta-analysis. *Braz J Med Biol Res*. 2017;50(9):e6409. <https://doi.org/10.1590/1414-431X20176409>.
  8. Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med*. 2016;374(23):2235–45. <https://doi.org/10.1056/NEJMoal602014>.
  9. Kuck KH, Furnkranz A, Chun KR, Metzner A, Ouyang F, Schluter M, et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. *Eur Heart J*. 2016;37(38):2858–65. <https://doi.org/10.1093/eurheartj/ehw285>.
  10. Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hormann P, et al. Cryoballoon versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation: the prospective, randomized, controlled, Noninferiority FreezeAF Study. *Circulation*. 2015;132(14):1311–9. <https://doi.org/10.1161/CIRCULATIONAHA.115.016871>.
  11. Kuck KH, Brugada J, Schluter M, Braegelmann KM, Kueffer FJ, Chun KRJ, et al. The FIRE AND ICE Trial: what we know, what we can still learn, and what we need to address in the future. *J Am Heart Assoc*. 2018;7(24):e010777. <https://doi.org/10.1161/JAHA.118.010777>.
  12. Buist TJ, Adiyaman A, Smit JJJ, Ramdat Misier AR, Elvan A. Arrhythmia-free survival and pulmonary vein reconnection patterns after second-generation cryoballoon and contact-force radiofrequency pulmonary vein isolation. *Clin Res Cardiol*. 2018;107(6):498–506. <https://doi.org/10.1007/s00392-018-1211-9>.
  13. Giannopoulos G, Kossyvakis C, Vrachatis D, Aggeli C, Tsitsinakis G, Letsas K, et al. Effect of cryoballoon and radiofrequency ablation for pulmonary vein isolation on left atrial function in patients with nonvalvular paroxysmal atrial fibrillation: a prospective randomized study (Cryo-LAEF study). *J Cardiovasc Electrophysiol*. 2019;30(7):991–8. <https://doi.org/10.1111/jce.13933>.
  14. Squara F, Zhao A, Marijon E, Latcu DG, Providencia R, Di Giovanni G, et al. Comparison between radiofrequency with contact force-sensing and second-generation cryoballoon for paroxysmal atrial fibrillation catheter ablation: a multicentre European evaluation. *Europace*. 2015;17(5):718–24. <https://doi.org/10.1093/europace/euv060>.
  15. Propadalo I, Tranfic M, Vuka I, Barcot O, Pericic TP, Puljak L. In Cochrane reviews, risk of bias assessments for allocation concealment were frequently not in line with Cochrane's Handbook guidance. *J Clin Epidemiol*. 2019;106:10–7. <https://doi.org/10.1016/j.jclinepi.2018.10.002>.
  16. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135. <https://doi.org/10.1186/1471-2288-14-135>.
  17. Andrade JG, Champagne J, Dubuc M, Deyell MW, Verma A, Macle L, et al. Cryoballoon or radiofrequency ablation for atrial fibrillation assessed by continuous monitoring: a randomized clinical trial. *Circulation*. 2019;140(22):1779–88. <https://doi.org/10.1161/CIRCULATIONAHA.119.042622>.
  18. Gunawardene MA, Hoffmann BA, Schaeffer B, Chung DU, Moser J, Akbulak RO, et al. Influence of energy source on early atrial fibrillation recurrences: a comparison of cryoballoon vs. radiofrequency current energy ablation with the endpoint of unexcitability in pulmonary vein isolation. *Europace*. 2018;20(1):43–9. <https://doi.org/10.1093/europace/euw307>.
  19. Watanabe R, Sairaku A, Yoshida Y, Nanasato M, Kamiya H, Suzuki H, et al. Head-to-head comparison of acute and chronic pulmonary vein stenosis for cryoballoon versus radiofrequency ablation. *Pacing Clin Electrophysiol : PACE*. 2018;41(4):376–82. <https://doi.org/10.1111/pace.13293>.
  20. Murray MI, Arnold A, Younis M, Varghese S, Zeiher AM. Cryoballoon versus radiofrequency ablation for paroxysmal atrial fibrillation: a meta-analysis of randomized controlled trials. *Clin Res Cardiol*. 2018;107(8):658–69. <https://doi.org/10.1007/s00392-018-1232-4>.
  21. Zhao A, Squara F, Marijon E, Thomas O. Two-year clinical outcome after a single cryoballoon ablation procedure: a comparison of first- and second-generation cryoballoons. *Arch Cardiovasc Dis*. 2017;110(10):543–9. <https://doi.org/10.1016/j.acvd.2017.01.015>.
  22. Kajiyama T, Miyazaki S, Matsuda J, Watanabe T, Niida T, Takagi T, et al. Anatomic parameters predicting procedural difficulty and balloon temperature predicting successful applications in individual pulmonary veins during 28-mm second-generation cryoballoon ablation. *JACC Clin Electrophysiol*. 2017;3(6):580–8. <https://doi.org/10.1016/j.jacep.2017.01.004>.
  23. Matta M, Anselmino M, Ferraris F, Scaglione M, Gaita F. Cryoballoon vs. radiofrequency contact force ablation for paroxysmal atrial fibrillation: a propensity score analysis. *J Cardiovasc Med*. 2018;19(4):141–7. <https://doi.org/10.2459/JCM.0000000000000633>.
  24. Yokokawa M, Chugh A, Latchamsetty R, Ghanbari H, Crawford T, Jongnarangsin K, et al. Ablation of paroxysmal atrial fibrillation using a second-generation cryoballoon catheter or contact-force sensing radiofrequency ablation catheter: a comparison of costs and long-term clinical outcomes. *J Cardiovasc Electrophysiol*. 2018;29(2):284–90. <https://doi.org/10.1111/jce.13378>.
  25. Chen CF, Gao XF, Duan X, Chen B, Liu XH, Xu YZ. Comparison of catheter ablation for paroxysmal atrial fibrillation between cryoballoon and radiofrequency: a meta-analysis. *J Interv Card Electrophysiol*. 2017;48(3):351–66. <https://doi.org/10.1007/s10840-016-0220-8>.
  26. Jourda F, Providencia R, Marijon E, Bouzeman A, Hireche H, Khoueiry Z, et al. Contact-force guided radiofrequency vs. second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation—a prospective evaluation. *Europace*. 2015;17(2):225–31. <https://doi.org/10.1093/europace/euu215>.
  27. Koller ML, Schumacher B. Cryoballoon ablation of paroxysmal atrial fibrillation: bigger is better and simpler is better. *Eur Heart J*. 2009;30(6):636–7. <https://doi.org/10.1093/eurheartj/ehp031>.
  28. Defaye P, Kane A, Jacon P, Mondesert B. Cryoballoon for pulmonary vein isolation: is it better tolerated than radiofrequency? Retrospective study comparing the use of analgesia and sedation in both ablation techniques. *Arch Cardiovasc Dis*. 2010;103(6–7):388–93. <https://doi.org/10.1016/j.acvd.2010.06.004>.
  29. Nct. Changes in cardiac autonomic nervous system following atrial fibrillation ablation. <https://clinicaltrials.gov/show/NCT03811639> 2019.