Direct Comparison Between Second-Generation Cryoballoon Ablation Versus Contact Force-Sensing Radiofrequency Ablation in Paroxysmal Atrial Fibrillation Patients: A Systematic Review and Meta-Analysis Study

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Research Article

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Abstract

Background

Pulmonary vein isolation (PVI) is the main ablation approach for paroxysmal atrial fibrillation (AF). The superiority of the second-generation cryoballoon (2G-CB) ablation over contact force-sensing radiofrequency (CF-RF) ablation is unclear. Therefore, we sought to investigate the superiority of 2G-CB ablation over CF-RF ablation in paroxysmal AF patients.

Methods

A systematic review and meta-analysis study was conducted. We included 12 studies involving 1419 patients. The overall effects were quantified using pooled odds ratio (OR) or mean difference (MD) for categorical or continuous variables.

Results

Freedom from atrial tachyarrhythmias (ATAs) (OR = 0.88; 95% confidence interval [CI] = 0.68 to 1.15; p = 0.35), freedom from AF (OR = 0.93; 95% CI = 0.64 to 1.34; p = 0.7), and acute PVI (OR = 1.00; 95% CI = 1.00 to 1.00; p = 0.99) between 2G-CB ablation and CF-RF ablation were not different. The 2G-CB ablation took shorter procedure time (MD = -18.78 minutes; 95% CI = -27.72 to -9.85 minutes; p < 0.01) and relative similar fluoroscopy time (MD = 2.66 minutes; 95% CI = -0.52 to 5.83 minutes; p = 0.10). Phrenic nerve paralysis was higher in 2G-CB ablation group (OR = 7.25; 95% CI = 2.37 to 22.16; p < 0.005).

Conclusion

The 2G-CB ablation was not superior to CF-RF ablation in paroxysmal AF in terms of acute PVI, freedom from ATAs, and freedom from AF. The 2G-CB ablation procedure can be performed faster than CF-RF ablation, although correlated with a higher phrenic nerve paralysis.

Background

In daily clinical practice, the most common arrhythmia encountered by the physician is atrial fibrillation (AF) [1, 2]. AF is strongly correlated with significant morbidity, mortality, and decreased quality of life [3–6]. The ectopic beats of the pulmonary veins (PVs) origin are responsible for the initiation of paroxysmal AF [7, 8]. Based on the latest guideline from the European Society of Cardiology (ESC), pulmonary vein isolation (PVI) using catheter ablation is recommended for rhythm control strategy [9]. The complete PVI can be achieved by the radiofrequency or cryoballoon ablation approach. However, several randomized control trials (RCTs) demonstrated conflicting data [10–13]. A meta-analysis of RCTs revealed equal efficacy between them [14].

Until now, either “freezing” or “burning” approaches are still being debated, and innovations are always being made to improve the efficiency and effectiveness of the PVI procedure. The second-generation cryoballoon (2G-CB) catheter was introduced in 2012 to gain more uniform freezing over the whole distal hemisphere of the balloon [15, 16]. Compared to the first-generation cryoballoon (1G-CB) catheter, ablation using 2G-CB catheter demonstrated a similar procedure-related complications rate, reduced fluoroscopy time, shorter procedure time, and higher procedural success rate [17, 18]. On the other hand, the contact force-sensing radiofrequency (CF-RF) catheter was released in 2014. It was equipped with the specific ability to measure the real-time catheter-tissue contact force to guide ablation more precisely [19, 20]. Compared with non-contact force-sensing radiofrequency (non-CF-RF) ablation, CF-RF ablation revealed lower acute PV reconnection [21], and one-year AF recurrence [22]. Through this systematic review and meta-analysis, we needed to know the superiority of 2G-CB ablation over CF-RF ablation for PVI in paroxysmal AF patients.

Method

Literature search

The present systematic review and meta-analysis study was performed under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [23]. Up to January 2021, relevant articles comparing 2G-CB ablation and RF-CF ablation for paroxysmal AF recorded in the scientific electronic database such as ClinicalTrials.gov, Cochrane, ProQuest, PubMed, and ScienceDirect, were collected and identified according to the eligibility criteria. These keywords: “ablation” or “catheter ablation,” AND “pulmonary vein isolation” or “PVI,” AND “second-generation cryoballoon” or “2nd generation cryoballoon,” AND “contact force radiofrequency,” or “contact force-sensing radiofrequency,” AND “paroxysmal atrial fibrillation” or “paroxysmal AF” were used to collect the relevant articles. The potentially relevant articles from the reference list of the assessed articles were also collected and identified.

Eligibility criteria

The inclusion criteria included: (1) articles comparing 2G-CB ablation and CF-RF ablation for PVI in paroxysmal AF patients; (2) articles written in English; (3) catheter ablation aimed for rhythm control strategy; (4) sample size had to be at least 20 patients in each study arm; (5) follow-up duration had to be more than three months; (6) clear information about arrhythmia detection method; and (7) articles provided the detailed relevant data on the outcomes of
each study arm. Articles were excluded if they: (1) were duplicates; (2) were sub-study of the involved studies; (3) included non-paroxysmal AF patients; (4) had incomparable treatment group and control group; (5) did not report the outcomes of interest.

**Exposure and outcomes**

In this systematic review and meta-analysis study, the intervention was the ablation strategy. Based on the ablation strategy, patients were divided into two groups, the "2G-CB group" and the "CF-RF group." Freedom from atrial tachyarrhythmias (ATAs) after a single catheter ablation procedure was the primary outcome of this study. The secondary outcome involved: (1) freedom of AF after a single catheter ablation procedure; (2) all procedural complications; (3) pericardial effusion; (4) phrenic nerve palsy; (5) vascular complications; (6) procedure time; and (7) fluoroscopy time.

**Quality assessment and data extraction**

Our study included RCTs and cohort studies comparing 2G-CB ablation and CF-RF ablation. The quality assessment of RCTs was performed using the modified Jadad scale, which has eight variables [24]. The total modified Jadad scale ranged from 0 to 8. RCTs with a modified Jadad score of 4 to 8 were considered high-quality [25]. Quality assessment was done using the Methodological Index for Non-randomized Studies (MINORS) for cohort studies. MINORS has 12 variables [26]. The comparative cohort studies with MINORS score of 19 to 24 were considered high-quality [27]. We involved high-quality studies only to minimizing the risk of bias. All essential information about: (1) the first author name; (2) publication date; (3) study design; (4) 3D mapping system; (5) cryoballoon ablation (CBA) strategy; (6) radiofrequency ablation (RFA) strategy; (7) blanking period; (8) follow up period; (9) antiarrhythmic drugs (AADs) treatment during follow-up period; (10) arrhythmia detection method; (11) treatment arms; (12) number of patients; (13) age; (14) sex; (15) comorbid diseases such as hypertension, coronary artery disease (CAD), heart failure, sleep apnea, diabetes mellitus (DM), stroke, or transient ischemic attack (TIA); and (16) echocardiographic variables such as left ventricular ejection fraction (LVEF), left atrial volume index (LAVI), and left atrial diameter (LAD), were extracted from each article. The categorical and continuous data are presented as mean ± standard deviation (SD) and number (percentage), respectively. For continuous data, we also calculated mean ± SD from the median and interquartile range (IQR) [28-30].

**Statistical analysis**

We followed the standard guideline to conduct the statistical analysis [31]. Heterogeneity among the involved studies was assessed using Cochran's Q test [32]. The p-value of Cochran's Q test <0.1 was considered as the presence of heterogeneity [33,34]. The fixed or random-effect analysis models were applied in the absence or presence of heterogeneity, respectively [35,36]. The pooled effects were presented as odds ratio (OR) or mean difference (MD) for dichotomous or continuous outcomes, respectively. We also estimated their 95% confidence interval (CI). Statistically significant was considered if the p-value <0.05. We used the combination of Egger's test and Begg's test to identify the publication bias. A p-value of <0.05 of Egger's and Begg's test indicated publication bias [37,38]. The statistical analysis was performed by two investigators using a combination of Review Manager (RevMan) version 5.3 (Cochrane, Copenhagen, Denmark) and Comprehensive Meta-Analysis (CMA) version 3.0 (Biostat, New Jersey, United States).

**Results**

**Study selection process**

Of the initial 752 collected articles, 12 studies were eligible to be included in this systematic review and meta-analysis [39-50]. The flowchart describing the study selection process is demonstrated in Figure 1.

**Baseline characteristics**

Our current systematic review and meta-analysis study including one multicenter RCT [39], two single-center RCTs [40,48], six single-center cohort studies [41-44,47,50], and three multicenter cohort studies [45,46,49]. The Electroanatomical mapping was conducted using CARTO 3 in nine studies [39-45,48,49]. While in three studies, the electroanatomical mapping was performed using CARTO 3 or EnSite [46,47,50]. Cryoballoon ablation procedures were conducted using the 28-mm 2G-CB catheter in almost all studies [39-45,47-50] Only study from Squara et al. that used the 23 or 28-mm 2G-CB catheter [46]. Cryoballoon ablation procedures were conducted 1 to 2 times for each pulmonary vein, with the duration ranged from 180 to 240 seconds. Radiofrequency ablation procedures were conducted using the CF-RF catheter [39-50]. In most studies, the pulmonary veins were isolated using the low-power and/or long-duration radiofrequency ablation approach [40-44,46-50]. Most of the studies had the 3-month blanking period [40-45,47,49,50]. The shortest follow-up period was six months [39]. The AADs were stopped in the majority of studies [39-41,43,44,46,47,49,50]. Arrhythmia detection methods in all studies were conducted using ambulatory cardiac monitoring devices [39–50]. We summarized the baseline characteristic of the included studies in Table 1.

A total 1419 of patients, including 734 patients in the 2G-CB group and 685 patients in the CF-RF group, were involved in this study. Around 65.3% of the study population were male. The mean age of the patients was 60.8 ± 1.1 years old. The prevalence of comorbid conditions such as hypertension, CAD, heart failure, sleep apnea, DM, and stroke or TIA were 45.6%, 9.9%, 4.0%, 7.4%, 9.1%, and 6.6%, respectively. The mean LVEF was 62 ± 1.3 % and the mean LAD was 40.0 ± 1.1 mm. The data about LAVI were available in the study from Jourda et al [43]. The mean LAVI was 40.7 ± 2.1 mL/m2. Table 2 presents the summary of baseline characteristics of patients from the involved studies.

**Heterogeneity and publication bias**

- Statistical analysis
  - Study selection process
  - Baseline characteristics
  - Exposure and outcomes
  - Quality assessment and data extraction
The heterogeneity was found in procedure time and fluoroscopy time (p-value of heterogeneity was <0.1). Therefore, the pooled effect was estimated using random-effect analysis models. For the other outcomes, we did not find any heterogeneity. We did not find any publication bias as the p-value for the Begg’s test and Egger’s test were ≥ 0.05 for all outcomes (Table 3 and Table 4).

Primary outcome

The primary outcome of freedom from ATAs was not significantly different between 2G-CB and CF-RF ablation (OR = 0.88; 95% CI = 0.68 to 1.15; p = 0.35) (Figure 2 and Table 3).

Secondary outcomes

From the efficacy aspect, we did not find a significant different of freedom from AF after single ablation procedure between two groups (OR = 0.93; 95% CI = 0.64 to 1.34; p = 0.7) (Figure 2 and Table 3). The procedure time was shorter in 2G-CB ablation group compared to CF-RF ablation group (MD = -18.78 minutes; 95% CI = -27.72 to -9.85 minutes; p < 0.01). However, both groups need similar fluoroscopy time (MD = 2.66 minutes; 95% CI = -0.52 to 5.83 minutes; p = 0.10) (Figure 3, Table 3, and Table 4). No difference in acute success of PVI between groups (OR = 1.00; 95% CI = 1.00 to 1.00; p = 0.99). From the safety aspect, the incidence of all-procedural complications (OR = 1.35; 95% CI = 0.82 to 2.23; p = 0.24), pericardial effusion (OR = 0.28; 95% CI = 0.07 to 1.16; p = 0.24), and vascular complications (OR = 0.76; 95% CI = 0.35 to 1.69; p = 0.24) in both groups were not significantly different. However, 2G-CB ablation was correlated with greater incidence of phrenic nerve paralysis (OR = 7.25; 95% CI = 2.37 to 22.16; p = < 0.005) (Figure 4 and Table 3).

Discussions

There are several main findings from our study. First, our study revealed that 2G-CB ablation had similar efficacy with CF-RF ablation for paroxysmal AF in terms of acute PVI, freedom from ATAs, and freedom from AF. Second, the 2G-CB ablation procedure can be performed faster than CF-RF ablation, even though the fluoroscopy time between both groups was similar. Third, 2G-CB ablation was correlated with a higher phrenic nerve paralysis rate. Moreover, all phrenic nerve paralysis complications happened in the 2G-CB group.

Today’s paradigm is that electrical isolation of the pulmonary veins from the left atrium is the fundamental of most catheter-based ablation strategies in paroxysmal AF. However, there are no specific recommendations from the recent guidelines regarding the choice of CBA or RFA [9, 51, 52]. Until now, the largest RCT comparing CBA and RFA in paroxysmal AF is the FIRE AND ICE trial. The study revealed that CBA was not inferior to RFA regarding the efficacy. The overall safety of both procedures was not significantly different. In the FIRE AND ICE trial, the CBA procedures were conducted using 1G-CB or 2G-CB catheters. Moreover, the data of CF-RF catheter were not reported in that trial [13]. The FreezeAF study also revealed the noninferiority of CBA than RFA for rhythm control in paroxysmal AF patients [12]. A meta-analysis of RCTs from Murray et al. comparing CBA using 1G-CB or 2G-CB catheters and RFA demonstrated that CBA and RFA shared equal efficacy. However, that meta-analysis did not provide information about the use of CF-RF catheters [14]. A meta-analysis from Jiang et al. revealed that 2G-CB ablation effectively decreased the recurrence rate of ATAs compared to RFA in paroxysmal AF patients specifically [53].

Buist et al. conducted RCT to compare 2G-CB ablation and CF-RF ablation in AF patients. However, that study included both paroxysmal AF and persistent AF. That study demonstrated that 2G-CB ablation provided better ATAs-free survival and lower repeat ablation than CF-RF ablation [54]. The CIRCA-DOSE study revealed that 2G-CB ablation and CF-RF ablation resulted in similar efficacy for paroxysmal AF during a one-year follow-up duration [55]. However, the study was compared longer and shorter application time of cryoballoon (CB) ablation to CF-RF ablation, which causes the CG group to be non-uniform. A meta-analysis from Ravi et al., including RCT and cohort studies comparing 2G-CB ablation and CF-RF ablation, revealed that the efficacy between both groups was similar [56]. Another meta-analysis from Wang et al. that included RCTs showed that AF recurrence rate between 2G-CB ablation and CF-RF ablation were comparable [57]. However, the meta-analysis study from Ravi et al. and Wang et al. involved both paroxysmal AF and persistent AF patients [56, 57]. Compared to the prior meta-analysis, our study specifically compared 2G-CB ablation and CF-RF ablation in patients with paroxysmal AF. Our study also revealed a similar success rate of acute PVI between groups. This result supported the previous study by Wang et al [57].

Our study demonstrated that 2G-CB ablation in paroxysmal AF could be completed faster than CF-RF ablation. Our result was consistent and supported the previous meta-analysis study from Ravi et al. [56] and Wang et al [57]. The 2G-CB ablation can be conducted faster because of its “single-shot” characteristic used throughout the PVI. On the other hand, CF-RF ablation needs a longer procedure time because of its “point-by-point” approach [11]. Previous meta-analysis demonstrated that fluoroscopy time was longer in 2G-CB ablation than CF-RF ablation [56]. However, in our study, both groups revealed no significantly different fluoroscopy time. We found significant heterogeneity while conducting data analysis of procedure time and fluoroscopy time. That was because of the diverse habit and experience of fluoroscopy utilization among different heart rhythm centers. The increased experience of the operator to perform AF ablation could reduce the fluoroscopy time [45]. The high power and short-duration (HPSD) radiofrequency ablation is now being conducted to reduce the overall procedure time in CF-RF ablation. A study from Baher et al. revealed that compared to the conventional method (35 W power for 10 to 30 seconds), the HPSD approach (50 W for 5 seconds) took a shorter procedure time (149 ± 65 minutes vs. 251 ± 101 minutes; p < 0.001) [58]. Until now, no study specifically compared the 2G-CB ablation and HPSD CF-RF ablation in paroxysmal AF patients. Moreover, almost all CF-RF ablation procedures in this meta-analysis were conducted using the conventional method (25 to 35 W power for at least 20 seconds) [40–44, 46–50].

From the safety aspect, our study revealed that 2G-CB ablation and CF-RF ablation had not significantly different rates of all-procedural complication, pericardial effusion, and vascular complications. Our results supported the findings of prior studies. However, those meta-analyses did not provide the data about pericardial effusion and vascular complications [56–57]. Our result revealed that the incidence of pericardial effusion was not significantly
different in both groups. However, in a prior meta-analysis from Jiang et al., CF-RF ablation had a higher rate of pericardial tamponade than RFA [53]. The possible explanation was: (1) The meta-analysis from Jiang et al. included RFA using the non-CF-RF catheter and CF-RF catheter [53]; (2) Our meta-analysis only included CF-RF ablation; (3) In our meta-analysis, almost all studies used the low-power and/or long-duration radiofrequency strategy in the CF-RF group [41, 44, 46, 50] and (4) CF-RF catheter provides efficient transfer of heat energy to the ablation target [19]. The risk of phrenic nerve paralysis in our meta-analysis was higher in the 2G-CB group than in the CF-RF group. Our result was similar and supported the findings of the prior meta-analysis studies [53, 56].

To the best of our knowledge, our study is the first systematic review and meta-analysis study comparing 2G-CB ablation and RF-CF ablation for paroxysmal AF patients specifically. We also did not find any publication bias in this study. The studies involved in this systematic review and meta-analysis were mainly cohort studies [41–47, 49, 50]. However, we only involved the high-quality study in this meta-analysis.

We recognized several limitations in this meta-analysis. First, the data about the specific comorbidities were not always completely available in most studies [39–44, 46–50]. Second, freedom of ATAs definition among the included studies was varied [39–50]. Third, even though almost all included studies used 12 lead ECG and Holter-monitor as the arrhythmia detection methods [39–49], two studies used additional methods such as external loop recorder and auto-triggered event monitor [47, 50]. The last, the differences in blanking period or follow-up durations and the use of AADs during those periods. Those limitations could be the essential confounders that would affect the final results.

Conclusions

In conclusion, the 2G-CB ablation was not superior to CF-RF ablation of paroxysmal AF in terms of acute PVI, freedom from ATAs, and freedom from AF. The 2G-CB ablation procedure can be performed faster than CF-RF ablation, although the fluoroscopy time between both groups was not significantly different. The 2G-CB ablation was also associated with a higher rate of phrenic nerve paralysis than CF-RF.

Abbreviations

1G-CB: first-generation cryoballoon; 2G-CB: second-generation cryoballoon; AAD: antiarrhythmic drugs; AF: atrial fibrillation; ATA: atrial tachyarrhythmia; CAD: coronary artery disease; CBA: cryoballoon ablation; CF-RF: contact force-sensing radiofrequency; CI: confidence interval; CMA: Comprehensive Meta-Analysis; DM: diabetes mellitus; ESC: European Society of Cardiology; IQR: interquartile range; HPSD: high power and short-duration; LAD: left atrial diameter; LAVI: left atrial volume index; LVEF: left ventricular ejection fraction; MD: mean difference; MINORS: Methodological Index for Non-randomized Studies; non-CF-RF: non-contact force-sensing radiofrequency; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PV: pulmonary vein; PVI: pulmonary vein isolation; RCT: randomized controlled trial; RevMan: Review Manager; RFA: radiofrequency ablation; SD: standard deviation; TIA: transient ischemic attack.

Declarations

Ethical approval and consent to participate

Ethical approval was not applicable for this systematic review and meta-analysis.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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No funding was obtained for this study.

Authors’ contributions

YW contributed to the study idea, study design, literature search, study quality assessment, data extraction, data analysis, data interpretation, and manuscript preparation. AR contributed to the study design, literature search, study quality assessment, data extraction, data analysis, data interpretation, and manuscript preparation. YY contributed to the study conceive, supervision, data interpretation, and manuscript revision. All authors read and approved the final manuscript.

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Tables
| Author                  | Study design | Mapping system | CBA strategy | RFA strategy                  | Blanking period | Follow up period | AADs treatment during follow up period | Arrhythmia detection methods |
|------------------------|--------------|----------------|--------------|-------------------------------|----------------|-----------------|--------------------------------------|-----------------------------|
| Giannopoulos et al., 2019 [39] | RCT – MC     | CARTO 3        | 28-mm 2G-CB  | CF-RF                         | 2 months       | 6 months        | No                                   | 12-lead ECG                 |
|                        |              |                | 240 ◦ 180    |                               |                |                 |                                       | 24-h Holter monitor         |
|                        |              |                | s/vein       |                               |                |                 |                                       |                             |
| Gunawardene et al., 2018 [40] | RCT – SC     | CARTO 3        | 28-mm 2G-CB  | CF-RF                         | 3 months       | 10.3 ± 2.1 months | No                                   | 12-lead ECG                 |
|                        |              |                | 1 x 240 s/vein|                               |                |                 |                                       | 24-h Holter monitor         |
| Hasson et al., 2020 [41] | Cohort – SC  | CARTO 3        | 28-mm 2G-CB  | CF-RF                         | 3 months       | 12 months       | No                                   | 12-lead ECG                 |
|                        |              |                | 2 x 240 s/vein| CF-RF FR 17–20 mL/min         |                |                 |                                       | 24-h Holter monitor         |
|                        |              |                |              |                               |                |                 |                                       |                             |
| Hisazaki et al., 2019 [42] | Cohort – SC  | CARTO 3        | 28-mm 2G-CB  | CF-RF                         | 3 months       | 20 ± 6 months   | No/Yes                               | 12-lead ECG                 |
|                        |              |                | 2 x 180 s/vein| CF-RF Power ≤ 35 W            |                |                 |                                       | 24-h Holter monitor         |
|                        |              |                |              | CF ≥ 10 g                     |                |                 |                                       |                             |
| Jourda et al., 2015 [43] | Cohort – SC  | CARTO 3        | 28-mm 2G-CB  | CF-RF                         | 3 months       | 12 months       | No                                   | 12-lead ECG                 |
|                        |              |                | 2 x 240 s/vein| CF-RF FR 17–20 mL/min         |                |                 |                                       | 24-h Holter monitor         |
|                        |              |                |              |                               |                |                 |                                       |                             |
| Kardos et al., 2016 [44] | Cohort – SC  | CARTO 3        | 28-mm 2G-CB  | CF-RF                         | 3 months       | 24 months       | No                                   | 12-lead ECG                 |
|                        |              |                | ≥ 1 x 240 s/vein| CF-RF Power ≤ 35 W        |                |                 |                                       | 24-h Holter monitor         |
|                        |              |                |              |                               |                |                 |                                       |                             |

AADs = antiarrhythmic drugs; 2G-CB = second generation cryoballoon ablation; CBA = cryoballoon ablation; CF = contact force; CF-RF = contact force sensing radiofrequency ablation; ECG = electrocardiogram; FR = flow rate; FTI = force-time integral; MC = multicenter; NA = not available; RCT = randomized controlled trial; SC = single center.
| Author                  | Study design | Mapping system | CBA strategy | RFA strategy | Blanking period | Follow up period | AADs treatment during follow up period | Arhythmia detection methods |
|-------------------------|--------------|----------------|--------------|--------------|-----------------|-----------------|----------------------------------------|-----------------------------|
| Matta et al., 2018 [45] | Cohort – MC  | CARTO 3        | 28-mm 2G-CB  | CF-RF        | 3 months        | 12 ± 5 months   | No/Yes                                | 12-lead ECG                 |
|                         |              |                |              | CF 5–15 g    |                 |                 | 24 to 48-h Holter monitor             |                             |
|                         |              |                | 180 s × 240 s/vein |             |                 |                 |                                        |                             |
| Squara et al., 2015 [46]| Cohort – MC  | CARTO 3        | 23 or 28-mm 2G-CB | CF-RF        | 1 months       | 12 (10–18) months | No                                    | 12-lead ECG                 |
|                         |              | EnSite         | 2 × 240 s/vein | Power 30–35 W|                 |                 | 24-h Holter monitor                   |                             |
|                         |              |                |              | Duration 20–40 W|                 |                 |                                        |                             |
|                         |              |                |              | FTI > 400 gs |                 |                 |                                        |                             |
| Tanaka et al., 2019 [47]| Cohort – SC  | CARTO 3        | 28-mm 2G-CB  | CF-RF        | 3 months       | 2.98 years (median) | No                                    | 12-lead ECG                 |
|                         |              | EnSite         | 2 × 180 s/vein |              |                 |                 | Holter monitor                         |                             |
|                         |              |                |              | Duration ≥ 20s|                 |                 |                                        | External loop recorder         |
|                         |              |                |              | CF ≥ 5 g     |                 |                 |                                        |                             |
|                         |              |                |              | FTI ≥ 150 gs |                 |                 |                                        |                             |
| Watanabe et al., 2018 [48]| RCT – SC    | CARTO 3        | 28-mm 2G-CB  | CF-RF        | NA             | 12 months       | No/Yes                                | 12-lead ECG                 |
|                         |              |                | 2 × 180 s/vein | FR 17 mL/min |                 |                 | 24 to 48-h Holter monitor             |                             |
|                         |              |                |              | Power ≤ 35 W |                 |                 |                                        |                             |
|                         |              |                |              | CF ≥ 10 g    |                 |                 |                                        |                             |
| Xiao et al., 2020 [49]  | Cohort – MC  | CARTO 3        | 28-mm 2G-CB  | CF-RF        | 3 months       | 12 months       | No                                    | 12-lead ECG                 |
|                         |              |                | 1 × ≥ 180 s/vein | FR 17–25 mL/min |                 |                 | 24-h Holter monitor                   |                             |
|                         |              |                |              | Power 25 to 35 W|                 |                 |                                        |                             |
|                         |              |                |              | Temperature ≤ 43°C |                 |                 |                                        |                             |
|                         |              |                |              | CF 10–30 g   |                 |                 |                                        |                             |
| Yokokawa et al., 2017 [50]| Cohort – SC | CARTO 3        | 28-mm 2G-CB  | CF-RF        | 3 months       | 25 ± 5 months   | No                                    | Auto-triggered event monitor |
|                         |              | EnSite         | 1 × 180 or 240 s/vein | FR 30 mL/min |                 |                 | 7-d Holter monitor                    |                             |
|                         |              |                |              | Power ≤ 35 W |                 |                 |                                        |                             |
|                         |              |                |              | Temperature ≤ 40°C |                 |                 |                                        |                             |

AADs = antiarrhythmic drugs; 2G-CB = second generation cryoballoon ablation; CBA = cryoballoon ablation; CF = contact force; CF-RF = contact force sensing radiofrequency ablation; ECG = electrocardiogram; FR = flow rate; FTI = force-time integral; MC = multicenter; NA = not available; RCT = randomized controlled trial; SC = single center.
| Author                  | Group | Patients | Age, years | Male | Hypertension | CAD | Heart failure | Sleep apnea | DM | Stroke or TIA | LVEF, % | LAVI, mL/m² | LAD, mm |
|------------------------|-------|----------|------------|------|--------------|-----|---------------|-------------|----|--------------|---------|-------------|---------|
| Giannopoulos, 2019 [39]| 2G-CB 80 | 61.0±2.5 | NA         | 41   | 6 (7.5)      | 2   | NA            | 9 (11.3)    | NA | 59.9±2.3     | NA      | 41.4±4.3    |
|                        | CF-RF 40 | 58.3±3.0 | NA         | 18   | 2 (5.0)      | 2   | NA            | 6 (15.0)    | NA | 60.0±2.3     | NA      | 39.9±1.4    |
| Gunawardene, 2018 [40] | 2G-CB 30 | 62.0±9.5 | 18 (60.0)  | 16   | NA           | NA  | NA            | NA          | NA | 59.8±4.5     | NA      | NA          |
|                        | CF-RF 30 | 57.4±10.5| 24 (80.0)  | 17   | NA           | NA  | NA            | NA          | NA | 59.2±5.0     | NA      | NA          |
| Hassan et al., 2020 [41]| 2G-CB 25 | 47.9±11.6| 15 (60.0)  | 6    | 2 (8.0)      | 1   | 7 (28.0)      | NA          | NA | 61.2±5.7     | NA      | 41.0±3.8    |
|                        | CF-RF 25 | 45.9±12.4| 17 (68.0)  | 5    | 1 (4.0)      | 2   | NA            | 5 (20.0)    | NA | 62.1±7.8     | NA      | 40.9±5.7    |
| Hisazaki et al., 2019 [42]| 2G-CB 64 | 64.0±12.0| 40 (63.0)  | 32   | NA           | NA  | NA            | NA          | NA | 68.0±8.0     | NA      | 35.0±5.0    |
|                        | CF-RF 22 | 67.0±12.0| 15 (68.0)  | 10   | NA           | NA  | NA            | NA          | NA | 67.0±8.0     | NA      | 36.0±5.0    |
| Jourda, et al., 2015 [43]| 2G-CB 75 | 59.9±10.6| 20 (26.7)  | 26   | NA           | 5   | 9 (12.0)      | 6 (8.0)     | 3  | 4.4±7.4      | 42.8±15.2| NA          |
|                        | CF-RF 75 | 62.5±9.9 | 18 (24.0)  | 36   | NA           | 2   | 4 (5.3)       | 3 (4.0)     | 8  | 65.5±5.6     | 39.5±11.3| NA          |
| Kardos, et al., 2016 [44]| 2G-CB 40 | 59.0±10.0| 27 (67.5)  | 17   | 5 (12.5)     | NA  | NA            | 2 (5.0)     | NA | 61.0±5.0     | NA      | NA          |
|                        | CF-RF 58 | 61.0±9.0 | 38 (66.0)  | 30   | 7 (12.0)     | NA  | NA            | 3 (5.1)     | NA | 41.3±4.0     | NA      | 42.1±4.6    |
| Matta, et al., 2018 [45]| 2G-CB 46 | 59.0±9.0 | 36 (78.0)  | 21   | 3 (7.0)      | 1   | 2 (4.0)       | 3 (7.0)     | 0  | 61.0±6.9     | NA      | NA          |
|                        | CF-RF 46 | 59.0±9.0 | 38 (82.0)  | 21   | 3 (7.0)      | 2   | 3 (7.0)       | 1 (2.0)     | NA | 56.6±7.7     | NA      | NA          |
| Squara, et al., 2015 [46]| 2G-CB 178| 58.4±11.5| 128 (71.9) | 55   | NA           | NA  | NA            | 14 (7.9)    | NA | 56.6±7.7     | NA      | NA          |
|                        | CF-RF 198| 61.0±9.0 | 153 (77.3) | 74   | 13 (6.6)     | NA  | NA            | NA          | NA | 55.8±9.2     | NA      | NA          |
| Tanaka, et al., 2019 [47]| 2G-CB 70 | 64.1±10.1| 52 (74.0)  | 40   | NA           | 1   | 7 (10.0)      | 9 (13.0)    | 68.0±9.1 | 37.1±5.7    |
|                        | CF-RF 61 | 63.4±10.5| 42 (69.0)  | 38   | 2 (3.0)      | NA  | 8 (13.0)      | 4 (7.0)     | 67.1±6.6| 36.9±4.7    |
| Watanabe, et al., 2018 [48]| 2G-CB 25 | 62.0±12.0| 17 (68.0)  | 16   | 2 (8.0)      | NA  | 5 (20.0)      | 2 (8.0)     | 58.0±8.0| 39.0±6.0    |
|                        | CF-RF 25 | 68.0±9.0 | 19 (76.0)  | 14   | NA           | 2   | 5 (20.0)      | 2 (8.0)     | 58.0±8.0| 42.0±5.0    |
| Xiao, et al., 2020 [49] | 2G-CB 30 | 64.5±12.1| 17 (56.7)  | NA   | 7 (23.3)     | NA  | NA            | NA          | NA | 63.1±9.6     | NA      | 41.9±5.2    |

2G-CB = second generation cryoballoon ablation; CAD = coronary artery disease; CF-RF = contact force sensing radiofrequency ablation; DM = diabetes mellitus; NA = not available; LA = left atrium; LAD = left atrial diameter; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.
### Table 3

Summary of the primary outcome and secondary outcomes.

| Parameters                          | Number of studies | 2G-CB Event, n (%) | 2G-CB Total, n | CF-RF Event, n (%) | CF-RF Total, n | Model | OR   | 95% CI        | p-value of heterogeneity | p-value of Begg's test | p-value of Egger's test | p     |
|-------------------------------------|-------------------|--------------------|----------------|-------------------|----------------|-------|------|--------------|-------------------------|------------------------|-------------------------|-------|
| **Primary outcomes**                |                   |                    |                |                   |                |       |      |              |                         |                        |                        |       |
| Freedom from ATAs                   | 12                | 579 (78.9)         | 734            | 548 (80.0)        | 685            | Fixed | 0.88 | 0.68 to 1.00 | 0.68                    | 0.73                   | 0.89                    | 0.35  |
| Secondary outcomes                  |                   |                    |                |                   |                |       |      |              |                         |                        |                        |       |
| Freedom from AF                     | 8                 | 332 (79.8)         | 416            | 270 (79.9)        | 338            | Fixed | 0.93 | 0.64 to 1.34 | 0.95                    | 0.71                   | 0.63                    | 0.70  |
| Acute PVI                           | 12                | 2916 (99.5)        | 2931           | 2722 (99.5)       | 2737           | Fixed | 1.00 | 1.00 to 1.00 | 0.94                    | 0.81                   | 0.08                    | 0.99  |
| All-procedural complications        | 9                 | 38 (6.3)           | 599            | 29 (4.9)          | 590            | Fixed | 1.35 | 0.82 to 2.23 | 0.65                    | 1.00                   | 0.57                    | 0.24  |
| Pericardial effusion                | 5                 | 0 (0.0)            | 360            | 7 (1.7)           | 402            | Fixed | 0.28 | 0.07 to 1.16 | 1.00                    | 0.81                   | 0.06                    | 0.08  |
| Phrenic nerve paralysis             | 7                 | 22 (4.6)           | 478            | 0 (0.0)           | 469            | Fixed | 7.25 | 2.37 to 22.16| 0.88                    | 0.13                   | 0.07 < 0.01             |       |
| Vascular complications              | 5                 | 11 (2.8)           | 400            | 15 (3.5)          | 424            | Fixed | 0.76 | 0.35 to 1.69 | 0.69                    | 0.81                   | 0.79                    | 0.50  |

AF = atrial fibrillation; ATAs = atrial tachyarrhythmia; 2G-CB = second generation cryoballoon ablation; CI = confidence interval; CF-RF = contact force sensing radiofrequency ablation; OR = odds ratio; PVI = pulmonary vein isolation.

### Table 4

Summary of the procedural time and fluoroscopy time.

| Parameters                | Number of studies | 2G-CB, n | CF-RF, n | Model     | MD, minutes | 95% CI minutes | p-value of heterogeneity | p-value of Begg's test | p-value of Egger's test | p   |
|---------------------------|-------------------|----------|----------|-----------|-------------|-----------------|--------------------------|------------------------|-------------------------|------|
| Procedure time            | 11                | 709      | 660      | Random    | -18.78      | -27.72 to -9.85 | < 0.01                   | 0.44                   | 0.89                    | < 0.01|
| Fluoroscopy time          | 11                | 709      | 660      | Random    | 2.66        | -0.52 to 5.83   | < 0.01                   | 0.44                   | 0.19                    | 0.10 |

2G-CB = second generation cryoballoon ablation; CI = confidence interval; CF-RF = contact force sensing radiofrequency ablation; MD = mean difference.
Figure 1

Flowchart of the study selection process. AF = atrial fibrillation.
### A. Freedom from Atrial Tachyarrhythmia

| Study or Subgroup     | G2-CB | CF-RF | Odds Ratio | Odds Ratio |
|-----------------------|-------|-------|------------|------------|
|                       | Events| Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Giannopoulos et al., 2019 | 61    | 80    | 29     | 40     | 7.8% | 1.22 [0.51, 2.99] | |
| Gunawardene et al., 2019 | 24    | 30    | 27     | 30     | 4.6% | 0.44 [0.10, 1.97] | |
| Hassan et al., 2020   | 16    | 25    | 18     | 25     | 5.5% | 0.69 [0.21, 2.38] | |
| Heazuki et al., 2019  | 60    | 64    | 20     | 22     | 1.0% | 1.50 [0.26, 8.82] | |
| Joucla et al., 2015   | 64    | 75    | 66     | 75     | 8.2% | 0.79 [0.31, 2.04] | |
| Kado et al., 2018     | 27    | 40    | 38     | 58     | 8.5% | 1.06 [0.45, 2.57] | |
| Malta et al., 2018    | 36    | 46    | 35     | 46     | 6.4% | 1.12 [0.43, 3.00] | |
| Squire et al., 2015   | 144   | 178   | 161    | 198    | 24.6% | 0.97 [0.58, 1.63] | |
| Tanaka et al., 2019   | 49    | 70    | 54     | 61     | 14.6% | 0.30 [0.12, 0.77] | |
| Watanabe et al., 2018 | 20    | 25    | 20     | 25     | 3.4% | 1.00 [0.25, 4.00] | |
| Xiao et al., 2020     | 27    | 30    | 25     | 30     | 2.1% | 1.60 [0.39, 6.32] | |
| Yokokawa et al., 2017 | 51    | 71    | 55     | 75     | 12.7% | 0.93 [0.45, 1.92] | |

Total (95% CI) 734 \(\pm 100\) 685 \(\pm 100\) 0.68 [0.09, 1.15]

Total events: 579 548

### Heterogeneity

- Chisq = 8.41, df = 11 (P = 0.68); P = 0%
- Test for overall effect: Z = 0.04 (P = 0.35)

### B. Freedom from Atrial Fibrillation

| Study or Subgroup     | G2-CB | CF-RF | Odds Ratio | Odds Ratio |
|-----------------------|-------|-------|------------|------------|
|                       | Events| Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Giannopoulos et al., 2019 | 61    | 80    | 29     | 40     | 15.5% | 1.22 [0.51, 2.96] | |
| Gunawardene et al., 2019 | 24    | 30    | 27     | 30     | 9.1% | 0.44 [0.10, 1.97] | |
| Hassan et al., 2020   | 16    | 25    | 18     | 25     | 10.9% | 0.69 [0.21, 2.38] | |
| Heazuki et al., 2019  | 60    | 64    | 20     | 22     | 3.1% | 1.50 [0.26, 8.82] | |
| Joucla et al., 2015   | 64    | 75    | 66     | 75     | 18.3% | 0.79 [0.31, 2.04] | |
| Malta et al., 2018    | 36    | 46    | 35     | 46     | 12.8% | 1.13 [0.43, 3.00] | |
| Squire et al., 2015   | 144   | 178   | 161    | 198    | 24.6% | 0.97 [0.58, 1.63] | |
| Tanaka et al., 2019   | 49    | 70    | 54     | 61     | 14.6% | 0.30 [0.12, 0.77] | |
| Watanabe et al., 2018 | 20    | 25    | 20     | 25     | 3.4% | 1.00 [0.25, 4.00] | |
| Xiao et al., 2020     | 27    | 30    | 25     | 30     | 2.1% | 1.60 [0.39, 6.32] | |
| Yokokawa et al., 2017 | 51    | 71    | 55     | 75     | 12.7% | 0.93 [0.45, 1.92] | |

Total (95% CI) 416 \(\pm 100\) 338 \(\pm 100\) 0.93 [0.64, 1.34]

Total events: 332 270

### Heterogeneity

- Chisq = 2.11, df = 7 (P = 0.95); P = 0%
- Test for overall effect: Z = 0.39 (P = 0.70)

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**Figure 2**

Forest plot of (A) freedom from atrial tachyarrhythmias and (B) freedom from atrial fibrillation. 2G-CB = second-generation cryoballoon; CF-RF = contact force sensing radiofrequency; CI = confidence interval; M-H = Mantel-Haenszel.
A. Procedure Time

| Study or Subgroup | G2-CB Mean (SD) | CF-RF Mean (SD) | Weight | Mean Difference N(95% CI) | Mean Difference N(95% CI) |
|-------------------|-----------------|-----------------|--------|--------------------------|--------------------------|
|                   | Total            | Total            |        |                          |                          |
| Guaranidó et al., 2015 | 98 (21.6)        | 30 (14.3)        | 10.3   | -12.80 (3.70, -26.86)    | -12.80 (3.70, -26.86)    |
| Harazono et al., 2015 | 171 (21.6)       | 25 (10.5)        | 13.0   | 12.41 (3.7, -20.92)      | 12.41 (3.7, -20.92)      |
| Harazono et al., 2016 | 199 (27.0)       | 64 (21.6)        | 12.0   | 9.06 (3.5, -15.56)       | 9.06 (3.5, -15.56)       |
| Jorgensen et al., 2015 | 144 (21.6)       | 49 (21.6)        | 11.7   | 12.41 (3.7, -20.92)      | 12.41 (3.7, -20.92)      |
| Karani et al., 2016 | 74 (17)          | 40 (49)          | 10.3   | -12.80 (3.70, -26.86)    | -12.80 (3.70, -26.86)    |
| Matsuzaka et al., 2016 | 124 (36)         | 46 (35)          | 11.7   | 12.41 (3.7, -20.92)      | 12.41 (3.7, -20.92)      |
| Squire et al., 2016 | 109 (6.8)        | 178 (122.5)      | 13.0   | 12.41 (3.7, -20.92)      | 12.41 (3.7, -20.92)      |
| Tsuchida et al., 2016 | 141 (20.5)       | 59 (108)         | 12.0   | 9.06 (3.5, -15.56)       | 9.06 (3.5, -15.56)       |
| Xiao et al., 2020 | 163.1 (20.4)     | 30 (104.9)       | 11.7   | 12.41 (3.7, -20.92)      | 12.41 (3.7, -20.92)      |
| Yokel et al., 2017 | 148 (41)         | 71 (207)         | 12.0   | 9.06 (3.5, -15.56)       | 9.06 (3.5, -15.56)       |

Total (95% CI): 738 900 100.0% -15.78 (27.72, -6.85)

B. Fluoroscopy Time

| Study or Subgroup | G2-CB Mean (SD) | CF-RF Mean (SD) | Weight | Mean Difference N(95% CI) | Mean Difference N(95% CI) |
|-------------------|-----------------|-----------------|--------|--------------------------|--------------------------|
|                   | Total            | Total            |        |                          |                          |
| Guaranidó et al., 2015 | 16 (3.7)         | 20 (3.9)         | 15.4   | -16.58 (3.7, -30.65)     | -16.58 (3.7, -30.65)     |
| Hepler et al., 2016 | 58.6 (11.7)      | 20 (36.8)        | 15.4   | -16.58 (3.7, -30.65)     | -16.58 (3.7, -30.65)     |
| Hepler et al., 2019 | 19.8 (64)        | 23 (13.0)        | 15.4   | -16.58 (3.7, -30.65)     | -16.58 (3.7, -30.65)     |
| Jorgensen et al., 2015 | 25.3 (9.9)       | 21.6 (8.0)       | 15.4   | -16.58 (3.7, -30.65)     | -16.58 (3.7, -30.65)     |
| Karani et al., 2016 | 14 (17)          | 16 (35)          | 15.4   | -16.58 (3.7, -30.65)     | -16.58 (3.7, -30.65)     |
| Matsuzaka et al., 2016 | 11 (46)          | 4 (46)           | 15.4   | -16.58 (3.7, -30.65)     | -16.58 (3.7, -30.65)     |
| Squire et al., 2015 | 17.6 (117)       | 10 (13.0)        | 15.4   | -16.58 (3.7, -30.65)     | -16.58 (3.7, -30.65)     |
| Tsuchida et al., 2016 | 4.4 (15)         | 29 (10)          | 15.4   | -16.58 (3.7, -30.65)     | -16.58 (3.7, -30.65)     |
| Xiao et al., 2020 | 21.5 (3.7)       | 27.1 (7.3)       | 15.4   | -16.58 (3.7, -30.65)     | -16.58 (3.7, -30.65)     |
| Yokel et al., 2017 | 30 (12)          | 21 (10)          | 15.4   | -16.58 (3.7, -30.65)     | -16.58 (3.7, -30.65)     |

Total (95% CI): 738 900 100.0% 2.88 (-0.82, 5.58)

C. Acute Pulmonary Vein Isolation

| Study or Subgroup | G2-CB Events (SD) | CF-RF Events (SD) | Weight | Rate Ratio M.H. Fixed, 95% CI | Rate Ratio M.H. Fixed, 95% CI |
|-------------------|-------------------|-------------------|--------|-------------------------------|-------------------------------|
|                   | Total             | Total             |        |                               |                               |
| Guaranidó et al., 2015 | 210 (20.5)        | 231 (219)        | 15.4   | 1.00 (99.99, 1.00)            | 1.00 (99.99, 1.00)            |
| Hepler et al., 2016 | 100 (100)         | 100 (100)        | 15.4   | 1.00 (99.99, 1.00)            | 1.00 (99.99, 1.00)            |
| Hepler et al., 2019 | 250 (250)         | 250 (250)        | 15.4   | 1.00 (99.99, 1.00)            | 1.00 (99.99, 1.00)            |
| Jorgensen et al., 2015 | 300 (300)         | 300 (300)        | 15.4   | 1.00 (99.99, 1.00)            | 1.00 (99.99, 1.00)            |
| Karani et al., 2016 | 100 (100)         | 100 (100)        | 15.4   | 1.00 (99.99, 1.00)            | 1.00 (99.99, 1.00)            |
| Matsuzaka et al., 2016 | 177 (180)         | 180 (182)        | 15.4   | 1.00 (99.99, 1.00)            | 1.00 (99.99, 1.00)            |
| Squire et al., 2015 | 712 (712)         | 752 (752)        | 15.4   | 1.00 (99.99, 1.00)            | 1.00 (99.99, 1.00)            |
| Tsuchida et al., 2016 | 280 (280)         | 280 (280)        | 15.4   | 1.00 (99.99, 1.00)            | 1.00 (99.99, 1.00)            |
| Xiao et al., 2020 | 120 (120)         | 13 (120)         | 15.4   | 1.00 (99.99, 1.00)            | 1.00 (99.99, 1.00)            |
| Yokel et al., 2017 | 282 (282)         | 300 (300)        | 15.4   | 1.00 (99.99, 1.00)            | 1.00 (99.99, 1.00)            |

Total (95% CI): 2521 2737 100.0% 1.00 (99.99, 1.00)

Figure 3

Forest plot of (A) procedure time; (B) fluoroscopy time; and (C) acute pulmonary vein isolation. G2-CB= second-generation cryoballoon; CF-RF = contact force sensing radiofrequency; CI = confidence interval; IV = inverse variance; SD = standard deviation.
A. All Procedural Complications

| Study or Subgroup | Events | Total | CF - RF | Odde Ratio | 95% CI | Odds Ratio | 95% CI |
|-------------------|--------|-------|---------|------------|--------|------------|--------|
| Huang et al. 2016 | 6      | 28    | 4       | 26         | 12.1%  | 9.4%       | 15.4%  |
| Hesmati et al. 2016 | 2 | 25    | 2       | 23         | 7.3%   | 4.9%       | 11.4%  |
| Jorba et al. 2015  | 1      | 75    | 2       | 73         | 7.5%   | 4.6%       | 12.0%  |
| Kan et al. 2016    | 9      | 45    | 1       | 44         | 2.9%   | 5.2%       | 8.3%   |
| Ma et al. 2018     | 3      | 46    | 2       | 44         | 7.1%   | 1.0%       | 30.8%  |
| Squires et al. 2015| 13     | 178   | 14      | 164        | 41.4%  | 10.9%      | 158.7% |
| Torrellas et al. 2019| 7 | 75    | 1       | 74         | 5.6%   | 5.7%       | 55.2%  |
| Total (n=1,479)         | 59     | 589   | 13      | 576        | 10.4%  | 9.8%       | 11.9%  |

Heterogeneity: Chr^2 = 34.96, df = 4 (P = 0.000, F = 0.000)
Not to overall effect: Z = 1.18 (P = 0.24)

B. Pericardial Effusion

| Study or Subgroup | Events | Total | CF - RF | Odds Ratio | 95% CI | Odds Ratio | 95% CI |
|-------------------|--------|-------|---------|------------|--------|------------|--------|
| Han et al. 2020   | 0      | 25    | 1       | 24         | 15.4%  | 9.4%       | 24.6%  |
| Kan et al. 2016   | 0      | 46    | 1       | 45         | 15.4%  | 6.7%       | 33.0%  |
| Ma et al. 2018    | 0      | 46    | 1       | 45         | 15.4%  | 1.0%       | 30.8%  |
| Total (n=1,479)         | 0     | 72    | 2       | 70         | 15.4%  | 9.8%       | 11.9%  |

Heterogeneity: Chr^2 = 5.16, df = 4 (P = 0.18, F = 0.19)
Not to overall effect: Z = 1.18 (P = 0.24)

C. Phrenic Nerve Paralysis

| Study or Subgroup | Events | Total | CF - RF | Odds Ratio | 95% CI | Odds Ratio | 95% CI |
|-------------------|--------|-------|---------|------------|--------|------------|--------|
| Huang et al. 2016 | 1      | 20    | 1       | 19         | 10.8%  | 10.8%      | 10.8%  |
| Han et al. 2020   | 0      | 25    | 0       | 25         | 10.8%  | 10.8%      | 10.8%  |
| Kan et al. 2016   | 0      | 46    | 0       | 46         | 10.8%  | 10.8%      | 10.8%  |
| Total (n=1,479)         | 0     | 72    | 1       | 71         | 10.8%  | 10.8%      | 10.8%  |

Heterogeneity: Chr^2 = 3.35, df = 4 (P = 0.38, F = 0.24)
Not to overall effect: Z = 0.34 (P = 0.73)

D. Vascular Complication

| Study or Subgroup | Events | Total | CF - RF | Odds Ratio | 95% CI | Odds Ratio | 95% CI |
|-------------------|--------|-------|---------|------------|--------|------------|--------|
| Huang et al. 2016 | 1      | 50    | 0       | 50         | 20.5%  | 10.0%      | 43.2%  |
| Torrellas et al. 2019| 7 | 75    | 1       | 74         | 13.7%  | 1.0%       | 152.7% |
| Total (n=1,479)         | 11    | 50    | 1       | 49         | 20.5%  | 10.0%      | 43.2%  |

Heterogeneity: Chr^2 = 4.31, df = 4 (P = 0.37, F = 0.35)
Not to overall effect: Z = 0.34 (P = 0.73)

Figure 4

Forest plot of (A) all-procedural complications; (B) pericardial effusion; (C) phrenic nerve paralysis; and (D) vascular complications. 2G-CB= second-generation cryoballoon ablation; CF-RF = contact force sensing radiofrequency ablation; CI = confidence interval; M-H = Mantel-Haenszel.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 2GCBvsCFRFSUPPLEMENTARYMATERIALS.docx