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SYSTEMATIC REVIEW ARTICLE

Cryoballoon Ablation for the Treatment of Atrial Fibrillation: A Meta-analysis

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Abstract: ***Background*:** Ablation therapy is the treatment of choice in antiarrhythmic drug-refractory atrial fibrillation (AF). It is performed by either cryoballoon ablation (CBA) or radiofrequency ablation. CBA is gaining popularity due to simplicity with similar efficacy and complication rate compared with RFA. In this meta-analysis, we compare the recurrence rate of AF and the complications from CBA versus RFA for the treatment of AF.

***Methods*:** We systematically searched PubMed for the articles that compared the outcome of interest. The primary outcome was to compare the recurrence rate of AF between CBA and RFA. We also included subgroup analysis with complications of pericardial effusion, phrenic nerve palsy and cerebral microemboli following ablation therapy.

***Results*:** A total of 24 studies with 3527 patients met our predefined inclusion criteria. Recurrence of AF after CBA or RFA was similar in both groups (RR: 0.84; 95% CI: 0.65, 1.07; I^2=48%, Cochrane p=0.16). In subgroup analysis, heterogeneity was less in paroxysmal AF (I^2=0%, Cochrane p=0.46) compared to mixed AF (I^2=72%, Cochrane p=0.003). Procedure and fluoroscopy time was less by 26.37 and 5.94 minutes respectively in CBA compared to RFA. Complications, pericardial effusion, and silent cerebral microemboli, were not different between the two groups, however, phrenic nerve palsy was exclusively present only in CBA group.

***Conclusion*:** This study confirms that the effectiveness of CBA is similar to RFA in the treatment of AF with the added advantages of shorter procedure and fluoroscopy times.

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1. INTRODUCTION

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia and is a major healthcare concern worldwide. The prevalence is on the rise and it was estimated that 33.5 million patients had AF in 2010 [1]. Given the increase in stroke, cardiomyopathy, and subsequent heart failure associated with AF, an easy, effective treatment option is in tremendous demand. Catheter ablation is a minimally-invasive treatment strategy and a class I indication to resolve drug-refractory AF by means of isolating the pulmonary veins [2]. Pulmonary vein isolation is usually achieved by two commonly used methods, a radiofrequency ablation [3] or cryoballoon ablation (CBA).

RFA uses heat energy produced by alternating the current to ablate, or burn, a specific tissue portion within the electrical conduction system of the heart [4]. CBA uses energy to freeze cardiac tissue rather than heat energy [5] and has become an alternative approach for ablating AF. Due to its simplicity, relative straightforwardness, and reproducibility, CBA is gaining popularity in the clinical setting. In this meta-analysis, we have reviewed available literature to explore the safety profile, effectiveness as well as the procedure and fluoroscopy time with the use of CBA compared to RFA for AF.

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2. METHODS

The current report conforms to standard guidelines according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [6].

2.1. Literature Search

We systematically searched PubMed using terms *"cryosurgery", "cryo", "cryosurg", "cryoballoon"* and *"atrial fibrillation"* in various combinations. The search was conducted in April of 2018. We also manually searched the reference lists of all publications and review articles that would meet inclusion criteria.

2.2. Study Selection

Two authors reviewed all potentially relevant articles in a parallel manner by using *a* pre-defined criteria. A study was deemed eligible with the following inclusion criteria: (1) evaluated the use of CBA in a study; (2) enrolled patients with either paroxysmal or mixed (combination of paroxysmal and persistent) AF; (3) reported data on the clinical success rate or procedure/fluoroscopy time; and (4) was published as a full manuscript in English.

2.3. Data Abstraction

For each included study, two authors (NP and KP) used a standardized data abstraction tool to independently extract all data with disagreements resolved by consensus. The following information was sought from each study: specific data on study characteristics, patient characteristics, intervention details and outcomes. The primary outcome was clinical success rate including subgroup analysis with different types of AF. The secondary measures were fluoroscopic and procedure time, as well as their complications including phrenic nerve palsy, silent cerebrovascular emboli and pericardial effusion.

2.4. Statistical Analysis

All statistical analyses were performed using Review Manager Version 5.3.5 (Reference 1). Continuous variables were reported as mean (standard deviation) or median [7], and categorical variables as *n* (%), weighted for a sample size of each study. Funnel plot analysis was used to evaluate potential publication bias, and Cochran's Q and I^2 statistic were used to investigate heterogeneity among studies and interpreted according to Higgins and Thompson criteria. I^2 values of 25%, 25-50%, or 50% indicated low, moderate, or high heterogeneity, respectively. We pooled data using the fixed effect model when minimal heterogeneity was observed; otherwise, a Hartung-Knapp method random-effects model was used.

3. RESULTS

3.1. Study Outline and Characteristics

The results of our literature search are shown in Fig. (**1**). We identified a total of 24 studies [3, 8-30] including 3,527 patients meeting our inclusion criteria. Baseline characteristics of these studies are included in Table **1**. Most of the studies were conducted in European nations and in non-randomized fashion. Included patients' age were 59.1 and 59.3 years in CBA and RFA group, respectively. Left atrial sizes were comparable in both groups with average around 42mm and left ventricular ejection fraction was 61.6% in CBA and 60.6% in RFA group. Duration of follow up is ranging from 6 to 24 hours and most studies had at least 3 months of further follow up after the procedure.

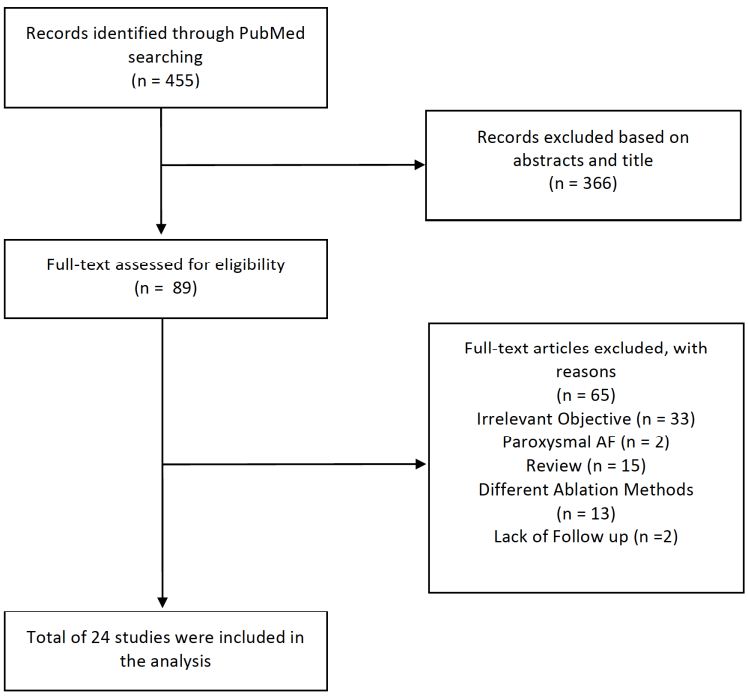

Fig. (1). Flow chart of selected studies.

Table 1. Baseline characteristics of analyzed studies.

Study	Design	CBA Size	n (% Male)		AF Type	Age (years)		LA-D (mm)		LV-EF (%)		Hypertension (%)	Diabetes (%)	AF Surveillance Follow up in Months
			CBA	RF				CBA	RF	CBA	RF			
Linhart *et al*. 2009 [8]	PRS Non-RCT	23 or 28 mm	20 (75)	20 (75)	Paroxysmal	59.9	58.5	NR		59.5	62.5	60	NR	6
Sauren *et al*. 2009 [9]	PRS Non-RCT	28 mm	10 (70)	10 (100)	Mixed but Paroxysmal in CRYO group	58	53	NR		NR		NR	NR	NR
Chierchia *et al*. 2010 [10]	Non-RCT	28 mm	46 (78)	87 (79)	Paroxysmal	56	56	41	41	64	64	24	NR	NR
Kojodjojo *et al*. 2010 [11]	PRS Non-RCT	28 mm	90 (75)	53 (77)	Mixed*	57	59.3	39.6	41.6	65	60.3	47	NR	14.9 /15.6€
Kuhne *et al*. 2010 [12]	Non-RCT	28 mm	18 (88)	25 (84)	Paroxysmal	58	59	41	42	60	58	NR	NR	12
Sorgente *et al*. 2010 [13]	RSP Non-RCT	28 mm	30 (74)	29 (90)	Mixed	56	56.1	40.8	42.4	63.9	64.2	29	NR	12
Gaita *et al*. 2011 [14]	PRS Non-RCT	23 or 28 mm	36 (69)	36 (67)	Paroxysmal	55	57	41	43	63	64	36	NR	NR
Herrera Siklody *et al*. 2011 [15]	PRS RCT	23 or 28 mm	23 (65)	27 (74)	Mixed	61	61	40	42	NR		61	NR	NR
Neumann *et al*. 2011 [16]	Non-RCT	NR	45 (53)	44 (73)	Mixed but Paroxysmal in CRYO group	56	58	51	53	62	58	51	NR	NR
Herrera Siklody *et al*. 2012 [17]	PRS RCT	23 or 28 mm	30 (83)	30 (77)	Mixed	57	56	41.4	40	NR		43	0	NR
Schmidt *et al*. 2012 [18]	Non-RCT	23 or 28 mm	37 (76)	178 (84)	Mixed but Paroxysmal in CRYO group	60	63	46	46	60	58	58	13	NR
Maagh *et al*. 2013 [19]	RSP Non-RCT	28 mm	30 (63)	42 (69)	Mixed	59.9	60.9	38.9	37.5	NR		20	NR	24
Malmborg *et al*. 2013 [20]	PRS RCT	23 or 28 mm	54 (79)	56 (71.4)	Mixed	59	62	40	42	NR		40.7	NR	12
Schmidt *et al*. 2013 [21]	PRS RCT	28 mm	33 (NR)	33 (NR)	Paroxysmal	66	63	40	41	59	58	58	12	NR

(Table 1) Contd…

Study	Design	CBA Size	n (% Male)		AF Type	Age (years)		LA-D (mm)		LV-EF (%)		Hypertension (%)	Diabetes (%)	AF Surveillance Follow up in Months
			CBA	RF				CBA	RF	CBA	RF			
Mugnai *et al* 2014 [22]	RSP Non-RCT	28 mm	136 (NR)	260 (NR)	Paroxysmal	57	58.3	42	42.6	NR				23
Pérez-Castellano *et al*. 2014 [23]	PRS RCT	23 or 28 mm	25 (68)	25 (88)	Paroxysmal	58	56	42	42	NR		24	16	12
Ciconte *et al*. 2015 [1]	PRS Non-RCT	28 mm	50 (72)	50 (76)	Mixed	62.4	62.4	46	47.2	57.5	56.3	52	8	12
Hunter *et al*. 2015 [24]	PRS RCT	23 or 28 mm	78 (56)	77 (61)	Paroxysmal	56	61	42	42	NR		35	5	12
Jourda *et al*. 2015 [25]	PRS Non-RCT	28 mm	75 (74.3)	75 (76)	Paroxysmal	59.9	62.5	NR		64.4	65.5	34.7	8	12
Luik *et al*. 2015 [26]	PRS RCT	23 or 28 mm	156 (64.1)	159 (52.7)	Paroxysmal	61		NR		NR		62.9	9	12
Wasserlauf *et al*. 2015 [27]	PRS Non-RCT	28 mm	101 (66)	100 (69)	Paroxysmal	62.9	60	37	37	58	58.9	44	7	12
Kuck *et al*. 2016 [28]	PRS RCT	NR	374 (59)	376 (63)	Paroxysmal	59.9	60.1	40.8	40.6	NR		57.5	9.9	15
Yokokava *et al*. 2017 [29]	PRS Non-RCT	28 mm	71 (75)	75 (56)	Paroxysmal	63	62	42	42	59	60	56	NR	12
Matta *et al*. 2018 [30]	PRS Non-RCT	NR	46 (78)	46 (82)	Paroxysmal	59	59	70*	69*	61	61	46	7	12

AF, Atrial Fibrillation; CBA, Cryoballoon ablation; LA-D, Left Atrial Diameter; LV-EF, Left Ventricular Ejection Fraction; mm, millimeters; NR, Not Reported; PRS, Prospective; RFA, Radiofrequency Ablation; RCT, Randomized Control Trial; RSP, Retrospective; The value for the column "n" represents the patients in each study

$^{\epsilon}$: Mean follow up in CBA group was 14.9 months compared to 15.6 months in RF group.

*: Left Atrial volume in milliliters.

3.2. Primary Outcome

As shown in Fig. (**2**), sixteen studies [3, 8, 11, 13, 19, 20, 22-30] reported the effectiveness of catheter ablation for AF in 2839 patients. The relative risk of experiencing AF post CBA compared with RFA was 0.84 (95% CI: 0.65, 1.07) with medium heterogeneity detected among the studies (I^2=48%, p=0.16).

Subgroup analysis was performed to confirm the overall effect size and direction. Ten studies [8, 22-30] included patients with paroxysmal AF and six studies [3, 11, 13, 17, 19, 20] included mixed AF patients. The pooled effect did not differ between the two groups. However, sub-grouping was associated with a considerable reduction of the heterogeneity among studies performing paroxysmal AF (I^2=0%, p=0.18; Fig. **2**) and increase in heterogeneity in studies which included patients with mixed AF (I^2=72%, p=0.003; Fig. **2**).

3.3. Secondary Outcome

3.3.1. Procedure Time

The procedure time was reported in twenty-four studies [3, 8-30]. Pooling all the results, the procedure time was, on average, around half an hour lower with CBA in comparison to the RFA (MD=26.37, 95% CI: 14.55, 38.20) and the observed heterogeneity among studies was high (I^2=96%, p<0.01; Fig. **3**).

3.3.2. Fluoroscopy Time

The fluoroscopic time was reported in Twenty studies [3, 8, 11-20, 22-25, 27-30]. Pooling all the results, the

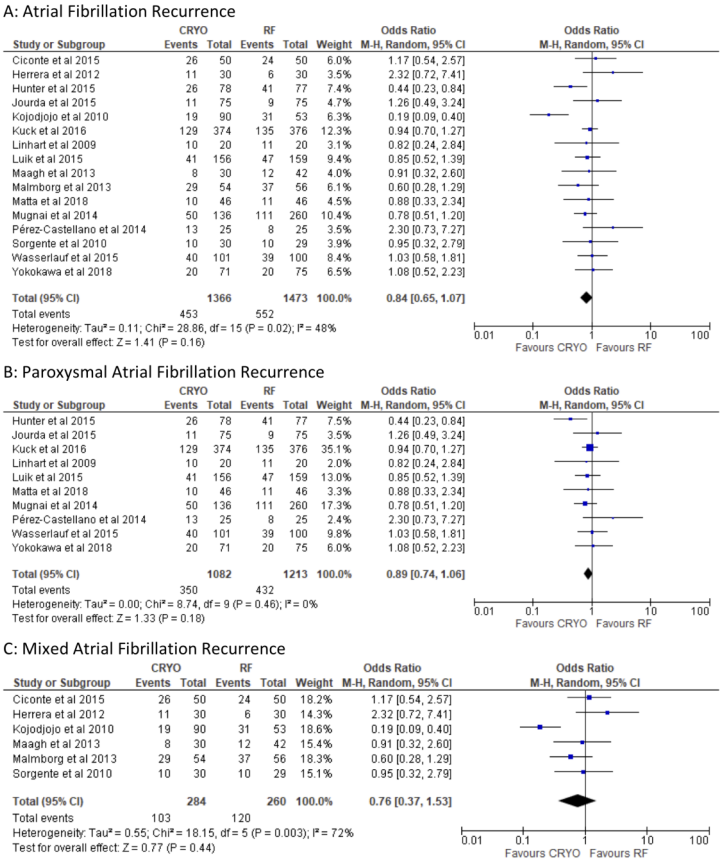

Fig. (2). Forest Plot of incidence of recurrence for atrial fibrillation.

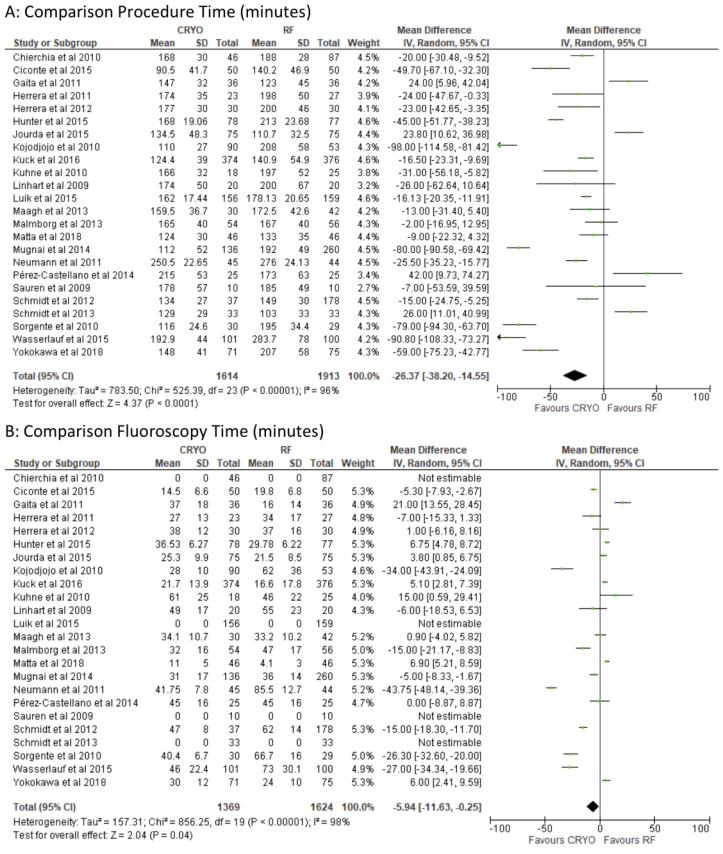

Fig. (3). Forest plot of procedure and fluoroscopy time.

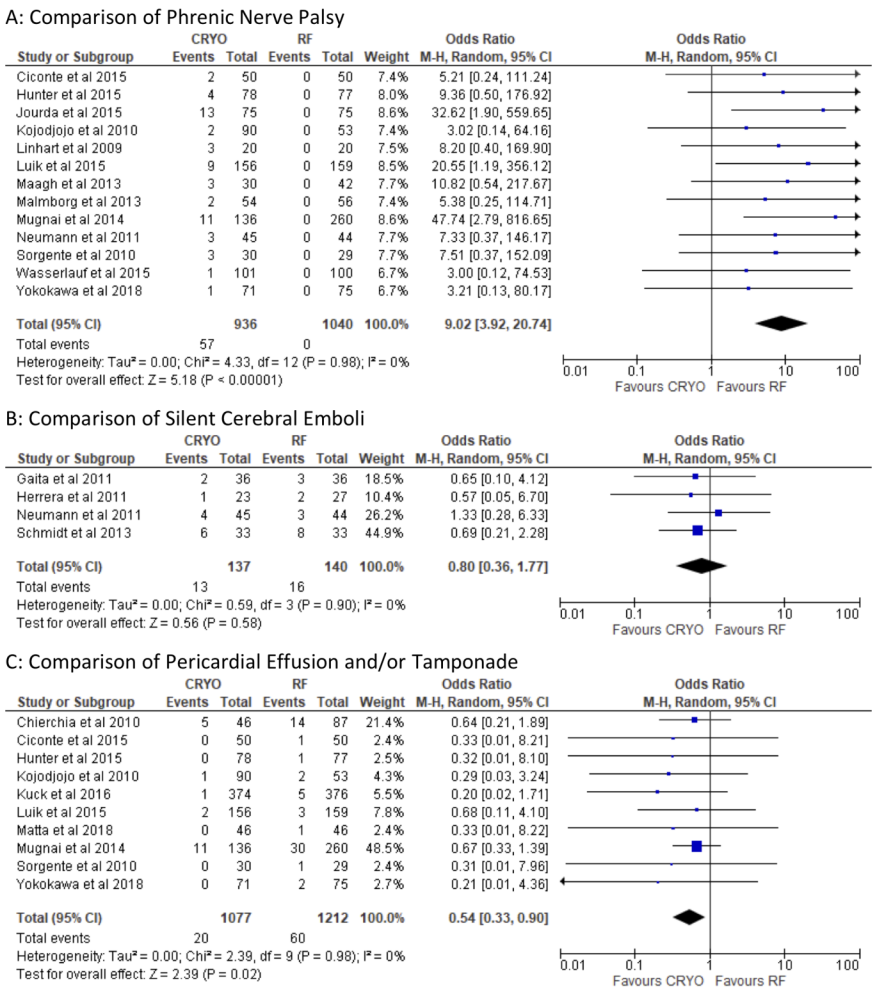

Fig. (4). Forest plot of procedure related complications.

fluoroscopic time was significantly lower in the CBA group compared with the RFA (MD=5.94, 95% CI: 0.25, 11.63) and the observed heterogeneity among studies was high (I^2=98%, p<0.01; Fig. **3**).

Complications:

3.3.3. Phrenic Nerve Palsy

Thirteen studies [3, 8, 11, 13, 16, 19, 20, 22, 24-27, 29] reported phrenic nerve palsy (PNP) in 1976 patients. The pooled relative risk of PNP was RR: 9.02 (95% CI: 3.92, 20.74) time higher in the CBA group, with no heterogeneity detected among the studies (I^2=0%, p=<0.01; Fig. **4**).

3.3.4. Silent Cerebral Emboli

Only four studies [14-16, 21] reported silent cerebrovascular emboli in 277 patients. Overall, 13 of 137 (9%) patients allocated to the CBA had silent cerebrovascular emboli compared with 16 of 140 patients (11%) allocated to RFA. The relative risk with CBA compared to RF was RR: 0.80 (95% CI: 0.36, 1.77), with no heterogeneity detected among the studies (I^2=0%, p=0.58; Fig. **4**).

3.3.5. Pericardial Effusion and/or Tamponade

Ten studies [10, 11, 13, 22, 24, 26, 28-30] reported pericardial effusion or tamponade in 2489 patients. The pooled relative risk of experiencing pericardial effusion with RFA compared with CBA was statistically significant (RR=0.54; 95% CI: 0.33, 0.90) with no heterogeneity detected among the studies (I^2=0%, p=0.98; Fig. **4**).

Publication Bias:

For primary outcome with CBA effectiveness we conducted a funnel plot for publication bias for each study (Fig. **5**).

4. DISCUSSION

Catheter ablation therapy is the treatment of choice in drug-resistant AF [2]. It is achieved by pulmonary vein isolation (PVI) by one of two energy sources - the conventional RFA or the newer CBA. A number of studies have demonstrated similar effectiveness and safety of both of these approaches [31, 32]. In this meta-analysis, we have demonstrated that CBA is non-inferior in treating AF compared to RF with a lesser procedure and fluoroscopy time. This study demonstrated that there is no significant difference in recurrence rate of AF between the two groups with median follow up of 12 months.

CBA catheters are larger than conventional RFA catheters, almost as large as the pulmonary vein. They can apply energy in single application compared to multiple applica-

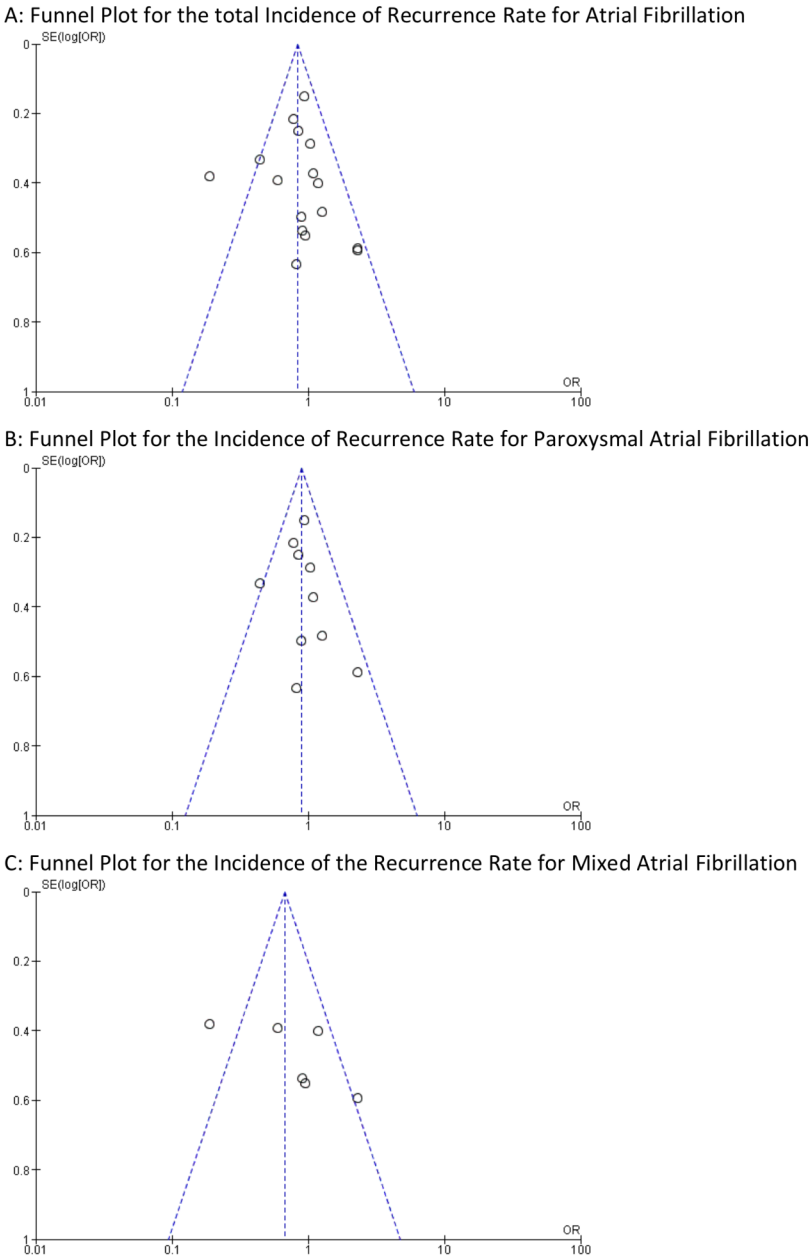

Fig. (5). Funnel plot evaluating publication bias.

tion by RFA catheters by covering larger areas with a more homogeneous ice cap formation resulting in faster achievement of PVI [33]. Due to its technical simplicity, the procedure and fluoroscopy time is significantly less with CBA, this is represented in our analysis as well. The novel third-generation CBA catheters have significantly shorter tips which making the procedure even more simplified with mean procedure time of 71 minutes with similar success rate, as it achieves PVI with a "single shot" [34]. In addition to the catheter features, operator experience also plays a vital role. Since RFA has been around for a longer duration and CBA is a relatively newer procedure, with greater operator experience over time, the procedure and fluoroscopy time will be even lesser among electrophysiologists using CBA.

A common complication of CBA is PNP with a rate of 13.5%, due to the proximity of phrenic nerve to pulmonary vein [35]; however, it is usually transient and not associated with increased mortality, morbidity or hospital stay [36]. In our analysis, PNP was exclusively present in the CBA group. In addition, pericardial effusion is a common complication of catheter ablations with an incidence of 14%. This complication increases with larger CBA catheters [36, 37]. However, Chierchia *et al*. showed that the occurrence of pericardial effusion after ablation is not significantly different between RFA and 28mm CBA. The higher incidence of pericardial effusion in some studies were not associated with an increased hospital stay or mortality [10]. We found that the frequency of pericardial effusion and cardiac tamponade were comparable between both groups.

The most disabling complication of the catheter ablation procedure is cerebral ischemia or stroke, however, asymptomatic or silent cerebrovascular emboli is common with an

incidence of 11-14% and symptomatic events can occur in up to 1.8%-2.0% [16, 38, 39]. We did not find any significant difference in the incidence of silent cerebrovascular emboli in both groups; however, Gaita el al. showed that the risk of 1.48 times higher with duty-cycled radiofrequency generator than irrigated RFA or CBA [14].

A serious complication of artrioesophageal fistula can occur with an incidence of 0.1% to 0.25% after AF ablation [38], more commonly observed in RFA although it has been also reported with CBA [40, 41]. Pulmonary vein stenosis can also occur due to energy application, relatively with lower incidence in CBA of 3.1% [42].

5. LIMITATIONS

Our meta-analysis has several limitations. First, only seven trials were randomized which raises the question of selection bias and methods. Second, nearly all the studies were conducted in European countries and in predominantly males, so the conclusions may not be able to be generalized. Third, follow-up methods and surveillance of AF varied among the studies, therefore it is difficult to draw conclusions about the long-term effectiveness of the procedures in said studies. Fourth, the studies were significantly heterogeneous due to multiple factors. Some studies included mixed AF population but paroxysmal AF was predominant in CBA group compared to RFA, hence same outcome should not be applied to persistent AF. The operator experience varied between the studies and also limited information was available on structural heart disease which could greatly influence the success rate.

CONCLUSION

Our meta-analysis confirms that the effectiveness of CBA is similar to RFA in the treatment of AF with the added advantages of shorter procedure and fluoroscopy times. CBA is a viable alternative to RFA for the definitive treatment for drug-refractory AF.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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