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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 drugrefractory 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.

ARTICLE HISTORY

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DOI: 10.2174/1573403X15666181212102419 *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.

Keywords: Atrial fibrillation, cryoballoon ablation, meta-analysis, pericardial effusion, phrenic nerve palsy, radiofrequency ablation, silent cerebral microemboli.

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 minimallyinvasive 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 nonrandomized 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.

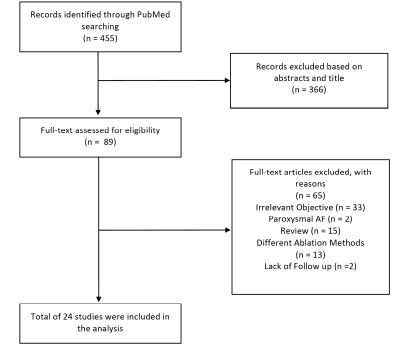


Fig. (1). Flow chart of selected studies.

Table 1. B	aseline charac	teristics of a	nalyzed	studies.
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Study	Design	CBA Size	AF Type		AF Type	AF Type Age (years)			D n)	LV-I (%		Hypertension (%)	Diabetes (%)	AF Surveil- lance Follow
	CBA RF			()				CBA RF		(/*)	(,,,,	up in Months		
Linhart <i>et al.</i> 2009 [8]	PRS Non- RCT	23 or 28 mm	20 (75)	20 (75)	Paroxysmal	59.9	58.5	NF	ł	59.5	62.5	60	NR	6
Sauren <i>et al.</i> 2009 [9]	PRS Non- RCT	28 mm	10 (70)	10 (100)	Mixed but Par- oxysmal in CRYO group	58	53	NF	ł	NR	1	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 <i>et al.</i> 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 <i>et al.</i> 2010 [12]	Non- RCT	28 mm	18 (88)	25 (84)	Paroxysmal	58	59	41	42	60	58	NR	NR	12
Sorgente <i>et al.</i> 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 <i>et al.</i> 2011 [14]	PRS Non- RCT	23 or 28 mm	36 (69)	36 (67)	Paroxysmal	55	57	41	43	63	64	36	NR	NR
Herrera Sik- lody <i>et al.</i> 2011 [15]	PRS RCT	23 or 28 mm	23 (65)	27 (74)	Mixed	61	61	40	42	NR	l	61	NR	NR
Neumann et al. 2011 [16]	Non- RCT	NR	45 (53)	44 (73)	Mixed but Par- oxysmal in CRYO group	56	58	51	53	62	58	51	NR	NR
Herrera Sik- lody <i>et al.</i> 2012 [17]	PRS RCT	23 or 28 mm	30 (83)	30 (77)	Mixed	57	56	41.4	40	NR		43	0	NR
Schmidt <i>et al.</i> 2012 [18]	Non- RCT	23 or 28 mm	37 (76)	178 (84)	Mixed but Par- oxysmal in CRYO group	60	63	46	46	60	58	58	13	NR
Maagh <i>et al.</i> 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 <i>et al.</i> 2013 [21] Table 1) Conte	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 (% N	Male)	АF Туре	AF Type Ag (year		LA- (mn		LV-EF (%)		Hypertension (%)	Diabetes (%)	AF Surveil- lance Follow
			СВА	RF		Q.	~)	СВА	RF	CBA RF				up in Months
Mugnai <i>et al</i> 2014 [22]	RSP Non- RCT	28 mm	136 (NR)	260 (NR)	Paroxysmal	57	58.3	42	42.6	NR				23
Pérez- Castellano <i>et al.</i> 2014 [23]	PRS RCT	23 or 28 mm	25 (68)	25 (88)	Paroxysmal	58	56	42	42	NR		24	16	12
Ciconte <i>et al.</i> 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 <i>et al.</i> 2015 [24]	PRS RCT	23 or 28 mm	78 (56)	77 (61)	Paroxysmal	56	61	42	42	NR		35	5	12
Jourda <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 2017 [29]	PRS Non- RCT	28 mm	71 (75)	75 (56)	Paroxysmal	63	62	42	42	59	60	56	NR	12
Matta <i>et al.</i> 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

 $^{\varepsilon}$ 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 (1^2 =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

Acharrisination		chiec					
	CRY		RF			Odds Ratio	Odds Ratio
Study or Subgroup			Events			M-H, Random, 95% CI	M-H, Random, 95% Cl
Ciconte et al 2015	26	50	24	50	6.0%		
Herrera et al 2012	11	30	6	30	3.5%		
Hunter et al 2015	26	78	41	77	7.4%		
Jourda et al 2015	11	75	9	75	4.7%		
Kojodjojo et al 2010	19	90	31	53	6.3%	0.19 [0.09, 0.40]	_ - _
Kuck et al 2016	129	374	135	376	12.3%	0.94 [0.70, 1.27]	
Linhart et al 2009	10	20	11	20	3.1%		
Luik et al 2015	41	156	47	159	9.4%	0.85 [0.52, 1.39]	
Maagh et al 2013	8	30	12	42	4.0%		
Malmborg et al 2013	29	54	37	56	6.1%	0.60 [0.28, 1.29]	
Matta et al 2018	10	46	11	46	4.5%	0.88 [0.33, 2.34]	
Mugnai et al 2014	50	136	111	260	10.4%	0.78 [0.51, 1.20]	
Pérez-Castellano et al 2014		25	8	25	3.5%	2.30 [0.73, 7.27]	
Sorgente et al 2010	10	30	10	29	3.9%	0.95 [0.32, 2.79]	
Wasserlauf et al 2015	40	101	39	100	8.4%	1.03 [0.58, 1.81]	-
Yokokawa et al 2018	20	71	20	75	6.5%	1.08 [0.52, 2.23]	
Total (95% CI)		1366		1473	100.0%	0.84 [0.65, 1.07]	•
Total events	453		552				
Heterogeneity: Tau ² = 0.11;	Chi ² = 28.86	6, df = 1	5 (P = 0.)	02); I ² =	48%		0.01 0.1 1 10
Test for overall effect: Z = 1.	.41 (P = 0.16)					Favours CRYO Favours RF
: Paroxysmal Atria	al Fibrilla CRY		Recu RF	rreno	ce	Odds Ratio	Odds Ratio
: Paroxysmal Atria Study or Subgroup	CRY	0				Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% Cl
Study or Subgroup	CRY	0	RF			M-H, Random, 95% Cl	
: Paroxysmal Atria Study or Subgroup Hunter et al 2015 Jourda et al 2015	CRY Events 26 11	0 Total 78 75	RF Events 41 9	Total 77 75	Weight 7.5% 3.5%	M-H, Random, 95% Cl 0.44 [0.23, 0.84]	
Study or Subgroup Hunter et al 2015 Jourda et al 2015	CRY Events 26 11 129	D Total 78 75 374	RF Events 41	Total 77	Weight 7.5%	M-H, Random, 95% Cl 0.44 [0.23, 0.84]	
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Kuck et al 2016	CRY Events 26 11 129 10	D Total 78 75 374 20	RF Events 41 9 135 11	Total 77 75 376 20	Weight 7.5% 3.5% 35.1% 2.0%	M-H, Random, 95% CI 0.44 [0.23, 0.84] 1.26 [0.49, 3.24] 0.94 [0.70, 1.27] 0.82 [0.24, 2.84]	
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Kuck et al 2016 Linhart et al 2009	CRY Events 26 11 129	D Total 78 75 374	RF Events 41 9 135	Total 77 75 376	Weight 7.5% 3.5% 35.1%	M-H, Random, 95% CI 0.44 [0.23, 0.84] 1.26 [0.49, 3.24] 0.94 [0.70, 1.27] 0.82 [0.24, 2.84]	
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Kuck et al 2016 Linhart et al 2009 Luik et al 2015	CRY Events 26 11 129 10 41 10	D 78 75 374 20 156 46	RF Events 41 9 135 11 47 11	Total 77 75 376 20	Weight 7.5% 3.5% 35.1% 2.0% 13.0% 3.3%	M-H, Random, 95% Cl 0.44 [0.23, 0.84] 1.26 [0.49, 3.24] 0.94 [0.70, 1.27] 0.82 [0.24, 2.84] 0.85 [0.52, 1.39] 0.88 [0.33, 2.34]	
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Kuck et al 2016 Linhart et al 2009 Luik et al 2015 Matta et al 2018	CRY Events 26 11 129 10 41	D 78 75 374 20 156 46 136	RF Events 41 9 135 11 47 11 111	Total 77 75 376 20 159	Weight 7.5% 3.5% 35.1% 2.0% 13.0%	M-H, Random, 95% Cl 0.44 [0.23, 0.84] 1.26 [0.49, 3.24] 0.94 [0.70, 1.27] 0.82 [0.24, 2.84] 0.85 [0.52, 1.39] 0.88 [0.33, 2.34]	
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Study or Subgroup Hunter et al 2015 Jourda et al 2015 Kuck et al 2016 Lunk at el al 2009 Luik et al 2015 Mugnal et al 2018 Mugnal et al 2018 Pérez-Castellano et al 2014	CRY Events 26 11 129 10 41 10 50 4 13 40	D Total 78 75 374 20 156 46 136 25 101	RF Events 41 9 135 11 47 11 111 8 39	Total 77 75 376 20 159 46 260 25 100	Weight 7.5% 3.5% 35.1% 2.0% 13.0% 3.3% 17.3% 2.4% 9.8%	M-H, Random, 95% Cl 0.44 [0.23, 0.84] 1.26 [0.49, 3.24] 0.94 [0.70, 1.27] 0.82 [0.24, 2.84] 0.85 [0.52, 1.39] 0.88 [0.33, 2.34] 0.78 [0.51, 1.20] 2.30 [0.73, 7.27] 1.03 [0.58, 1.81]	
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Kuck et al 2016 Luik et al 2019 Luik et al 2019 Mugnal et al 2018 Mysserlauf et al 2014 Pérez-Castellano et al 2014	CRY <u>Events</u> 26 11 129 10 41 10 50 4 13	D Total 78 75 374 20 156 46 136 25	RF Events 41 9 135 11 47 11 111 8	Total 77 75 376 20 159 46 260 25	Weight 7.5% 3.5% 35.1% 2.0% 13.0% 3.3% 17.3% 2.4%	M-H, Random, 95% Cl 0.44 [0.23, 0.84] 1.26 [0.49, 3.24] 0.94 [0.70, 1.27] 0.82 [0.24, 2.84] 0.85 [0.52, 1.39] 0.88 [0.33, 2.34] 0.78 [0.51, 1.20] 2.30 [0.73, 7.27] 1.03 [0.58, 1.81]	
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Kuck et al 2016 Luik et al 2016 Julik et al 2019 Mugnai et al 2018 Mugnai et al 2018 Yérez-Castellano et al 2011 Yérekawa et al 2015	CRY Events 26 11 129 10 41 10 50 4 13 40	D Total 78 75 374 20 156 46 136 25 101	RF Events 41 9 135 11 47 11 111 8 39	Total 77 75 376 20 159 46 260 25 100 75	Weight 7.5% 3.5% 35.1% 2.0% 13.0% 3.3% 17.3% 2.4% 9.8%	M-H, Random, 95% CI 0.44 [0.23, 0.84] 1.26 [0.49, 3.24] 0.94 [0.70, 1.27] 0.82 [0.24, 2.84] 0.85 [0.52, 1.39] 0.88 [0.33, 2.34] 0.78 [0.51, 1.20] 2.30 [0.73, 7.27] 1.03 [0.58, 1.81] 1.08 [0.52, 2.23]	
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Study or Subgroup Hunter et al 2015 Jourda et al 2015 Unihart et al 2016 Linhart et al 2009 Matta et al 2015 Matta et al 2015 Matta et al 2016 Pérez-Castelliano et al 2017 Vokokawa et al 2018 Total (95% C1) Total events Heterogeneity, Tau" = 0.00;	CRY <u>Events</u> 26 11 129 10 41 10 50 4 13 40 20 350 ; Chi ^a = 8.74,	D Total 78 75 374 20 156 46 136 25 101 71 1082 df = 9 (RF Events 41 9 135 11 47 11 111 111 8 39 20 432	Total 77 75 376 20 159 46 260 25 100 75 1213	Weight 7.5% 3.5% 2.0% 13.0% 3.3% 17.3% 2.4% 9.8% 6.0% 100.0%	M-H, Random, 95% CI 0.44 [0.23, 0.84] 1.26 [0.49, 3.24] 0.94 [0.70, 1.27] 0.82 [0.24, 2.84] 0.85 [0.52, 1.39] 0.88 [0.33, 2.34] 0.78 [0.51, 1.20] 2.30 [0.73, 7.27] 1.03 [0.58, 1.81] 1.08 [0.52, 2.23]	M.H, Random, 95% Cl
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Jourda et al 2016 Linhart et al 2006 Linhart et al 2019 Matta et al 2015 Matta et al 2015 Matta et al 2014 Verso-Castellano et al 2017 Verso-Castellano et al 2015 Vokokawa et al 2018 Total (95% CI) Total (95% CI) Total events Heterogenetic, Tau" = 0.00; Test for overall effect Z = 1.	CRY Events 26 11 129 10 41 10 41 40 20 4 350 Chi ^a = 8.74, .33 (P = 0.18	D Total 78 75 374 20 156 46 136 25 101 71 1082 df = 9 (RF <u>Events</u> 41 9 135 111 47 111 111 8 39 20 432 P = 0.46]	Total 77 75 376 20 159 46 260 25 100 75 1213	Weight 7.5% 3.5% 2.0% 13.0% 3.3% 17.3% 2.4% 9.8% 6.0% 100.0%	M-H, Random, 95% CI 0.44 [0.23, 0.84] 1.26 [0.49, 3.24] 0.94 [0.70, 1.27] 0.82 [0.24, 2.84] 0.85 [0.52, 1.39] 0.88 [0.33, 2.34] 0.78 [0.51, 1.20] 2.30 [0.73, 7.27] 1.03 [0.58, 1.81] 1.08 [0.52, 2.23]	M-H, Random, 95% Cl
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Jourda et al 2016 Linhart et al 2006 Linhart et al 2019 Matta et al 2015 Matta et al 2015 Matta et al 2014 Verso-Castellano et al 2017 Verso-Castellano et al 2015 Vokokawa et al 2018 Total (95% CI) Total (95% CI) Total events Heterogenetic, Tau" = 0.00; Test for overall effect Z = 1.	CRY Events 26 11 129 41 10 41 10 41 10 41 10 50 0 4 350 c Chi ² = 0.74, .33 (P = 0.18	D Total 78 75 374 20 156 46 136 25 101 71 1082 df = 9 (RF <u>Events</u> 41 9 135 111 47 11 111 8 39 20 432 (P = 0.46) ITTENC	Total 77 75 376 20 159 46 260 25 100 75 1213	Weight 7.5% 3.5% 2.0% 13.0% 3.3% 17.3% 2.4% 9.8% 6.0% 100.0%	M-H, Random, 95% CI 0.44 (0.24), 0.23, 0.84) 1.26 (0.49, 3.24) 0.84 (0.70, 1.23, 0.84) 0.85 (0.52, 1.39) 0.88 (0.32, 2.34) 0.78 (0.51, 1.20) 2.30 (0.73, 7.27) 1.03 (0.58, 1.81) 1.08 (0.52, 2.23) 0.89 (0.74, 1.06)	M-H, Random, 95% Cl
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Linhart et al 2016 Linhart et al 2010 Matta et al 2010 Matta et al 2011 Matta et al 2011 Pérez-Castellano et al 2011 Yokokawa et al 2015 Yokokawa et al 2015 Total (9% CI) Total events Heterogeneits: Tau" = 0.00; Test for overall effect Z = 1.	CRY Events 26 11 129 10 41 1 10 50 4 13 40 20 4 350 5 5 6 17 8.74, 33 (P = 0.18 rillation CRYO	D Total 78 75 374 20 156 46 136 25 101 71 1082 df = 9 () Recu	RF Events 41 9 1355 11 47 111 111 8 39 20 432 P = 0.46 ITTENC RF	Total 77 75 376 20 159 46 260 25 100 75 1213 0; I ² = 0 ⁴ e	Weight 7.5% 3.5% 2.0% 13.0% 3.3% 17.3% 2.4% 9.8% 6.0% 100.0%	M-H, Random, 95% CI 0.44 (0.23, 0.84) 1.26 (0.43, 3.24) 0.94 (0.70, 1.27) 0.92 (0.24, 2.84) 0.95 (0.52, 1.39) 0.88 (0.33, 2.34) 0.78 (0.51, 1.20) 2.30 (0.73, 7.27) 1.03 (0.58, 1.81) 1.08 (0.52, 2.23) 0.89 (0.74, 1.06]	M.H, Random, 95% Cl
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Linhart et al 2010 Linhart et al 2010 Matta et al 2015 Matta et al 2015 Matta et al 2016 Vissorial et al 2017 Vissorial et al 2018 Total (95% CI) Total (95% CI) Test for overall effect Z = 1. Mixed Atrial Fibri Study or Subgroup	CRY Events 26 11 129 10 50 4 13 40 20 20 350 5 ChF = 8.74, .33 (P = 0.18 rillation CRYO vents Tota	D <u>Total</u> 78 75 374 20 156 46 136 25 101 71 1082 df = 9 () Recu	RF Events 41 9 1355 11 47 111 111 8 39 20 432 P = 0.46j ITTENC RF nts Tot	Total 77 75 20 159 46 260 25 100 75 1213); F=0 ⁴ e al We	Weight 7.5% 35.1% 2.0% 13.0% 3.3% 17.3% 6.0% 100.0%	M-H, Random, 95% CI	M-H, Random, 95% Cl
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Jourda et al 2016 Linhart et al 2019 Linhart et al 2019 Matta et al 2015 Matta et al 2015 Matta et al 2014 Pérze-Castellano et al 2011 Yokokawa et al 2018 Total (9% CI) Total events Total overail effect Z = 1. Mixed Atrial Fibli Study or Subgroup Et Ciconte et al 2015	CRY Events 266 11 129 10 41 10 40 20 350 Chi ² = 8.74, .33 (P = 0.18 cRYO cvents Totas 26 5	D Total 78 75 374 200 156 46 136 25 101 71 1082 df = 9 () Recu U Eventor 0	RF Events 41 9 135 11 111 111 111 111 111 20 20 432 20 P = 0.46 39 ITTENCC RF nts Tot 24 5	Total 77 75 376 200 25 100 75 1213 (); (* = 0' e al Wee 50 18	Weight 7.5% 3.5% 35.1% 2.0% 13.0% 3.3% 17.3% 2.4% 9.8% 6.0% 100.0% %	M-H, Random, 95% CI 0.44 (0.23, 0.84) 1.26 (0.43, 3.24) 0.94 (0.70, 1.27) 0.82 (0.24, 2.84) 0.95 (0.52, 1.39) 0.88 (0.33, 2.34) 0.78 (0.51, 1.20) 2.30 (0.73, 7.27) 1.03 (0.58, 1.81) 1.08 (0.52, 2.23) 0.89 (0.74, 1.06] Odds Ratio H, Random, 95% CI 1.17 (0.54, 2.57)	M-H, Random, 95% Cl
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Jourda et al 2016 Linhart et al 2008 Linhart et al 2019 Matta et al 2015 Matta et al 2015 Matta et al 2016 Vesseriauf et al 2015 Yokokawa et al 2018 Total events Heterogeneity: Tau* = 0.00; Test for overall effect Z = 1. Mixed Atrial Fibi Study or Subgroup E Ciconte et al 2015 Herera et al 2015	CRY Events 26 11 129 10 41 10 50 4 13 40 20 20 20 20 20 20 20 20 20 20 20 20 20	D Total 78 75 374 20 156 46 136 25 101 71 1082 df = 9 () Recu 0 0	RF Events 41 9 135 11 111 111 111 111 111 125 432 20 432 P = 0.46j Irrrenc RF nts 24 6	Total 77 75 376 20 159 46 260 25 100 75 1213); F=0' e al Wee 50 18 00 18 10 10 10 10 10 10 10 10 10 11 12 13 14	Weight 7.5% 35.1% 2.0% 13.0% 3.3% 17.3% 2.4% 9.8% 6.0% 100.0%	M-H, Random, 95% CI 0.4 (0) 23, 0.64) 1.2 (0) 49, 0.24) 0.4 (0) 70, 1.27) 0.8 (2) 0.24, 2.84) 0.68 (0) 33, 2.34) 0.78 (0.51, 1.20) 2.30 (0) 73, 7.27) 1.03 (0.56, 1.81) 1.08 (0.52, 2.23) 0.89 (0.74, 1.06] Odds Ratio H, Random, 95% CI 1.17 (0.54, 2.57) 2.32 (0) 72, 7.41]	M-H, Random, 95% Cl
Study or Subgroup Hunter et al 2015 Jourda et al 2015 Jourda et al 2016 Linhart et al 2019 Linhart et al 2019 Matta et al 2015 Matta et al 2015 Matta et al 2014 Pérze-Castellano et al 2011 Yokokawa et al 2018 Total (9% CI) Total events Total overail effect Z = 1. Mixed Atrial Fibli Study or Subgroup Et Ciconte et al 2015	CRY Events 266 11 129 10 41 10 40 20 350 Chi ² = 8.74, .33 (P = 0.18 cRYO cvents Totas 26 5	D <u>Total</u> 78 75 374 20 156 46 136 136 136 136 136 136 46 136 136 46 136 136 46 136 9 () Recu 0 0 0 0 0 0 0 0 0 0 0 0 0	RF Events 9 135 11 135 111 111 111 111 120 432 20 432 20 432 20 432 70 432 70 432 70 432 70 432 70 6 331	Total 77 75 376 20 159 46 260 100 75 1213); = 0' e al Wee 50 18 50 18 53 16	Weight 7.5% 3.5% 35.1% 2.0% 13.0% 3.3% 17.3% 2.4% 9.8% 6.0% 100.0% %	M-H, Random, 95% CI 0.44 (0.23, 0.84) 1.26 (0.43, 3.24) 0.94 (0.70, 1.27) 0.82 (0.24, 2.84) 0.95 (0.52, 1.39) 0.88 (0.33, 2.34) 0.78 (0.51, 1.20) 2.30 (0.73, 7.27) 1.03 (0.58, 1.81) 1.08 (0.52, 2.23) 0.89 (0.74, 1.06] Odds Ratio H, Random, 95% CI 1.17 (0.54, 2.57)	M-H, Random, 95% Cl

 Kojodoje ta 2010
 13
 30
 31
 31
 15.0%
 0.51 (0.52, 2.60)

 Maigh et al 2013
 29
 54
 37
 66
 18.3%
 0.60 (0.22, 1.20)

 Maimborg et al 2013
 29
 54
 37
 66
 18.3%
 0.60 (0.22, 1.20)

 Sorgenet et al 2010
 10
 30
 10
 29
 15.1%
 0.95 (0.52, 2.79)

 Total (95% Cf)
 284
 260
 100.0%
 0.76 [0.37, 1.53]
 100

 Heterogeneity: Tau# = 0.55; Chi#= 18.15, di = 5 (P = 0.003); P = 72%
 10.01
 0.1
 100

 Testfor overail effect: Z = 0.77 (P = 0.44)
 Favours CRYO
 Favours CRYO
 Favours RF

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

A: Comparison Procedure Time (minutes)

		CRYO			RF			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chierchia et al 2010	168	30	46	188	28	87	4.5%	-20.00 [-30.48, -9.52]	
Ciconte et al 2015	90.5	41.7	50	140.2	46.9	50	4.2%	-49.70 [-67.10, -32.30]	
Gaita et al 2011	147	32	36	123	45	36	4.2%	24.00 [5.96, 42.04]	
Herrera et al 2011	174	35	23	198	50	27	3.9%	-24.00 [-47.67, -0.33]	
Herrera et al 2012	177	30	30	200	46	30	4.1%	-23.00 [-42.65, -3.35]	
Hunter et al 2015	168	19.06	78	213	23.68	77	4.6%	-45.00 [-51.77, -38.23]	
Jourda et al 2015	134.5	48.3	75	110.7	32.5	75	4.4%	23.80 [10.62, 36.98]	
Kojodjojo et al 2010	110	27	90	208	58	53	4.3%	-98.00 [-114.58, -81.42]	←
Kuck et al 2016	124.4	39	374	140.9	54.9	376	4.6%	-16.50 [-23.31, -9.69]	
Kuhne et al 2010	166	32	18	197	52	25	3.8%	-31.00 [-56.18, -5.82]	
Linhart et al 2009	174	50	20	200	67	20	3.2%	-26.00 [-62.64, 10.64]	
Luik et al 2015	162	17.44	156	178.13	20.65	159	4.6%	-16.13 [-20.35, -11.91]	-
Maaqh et al 2013	159.5	36.7	30	172.5	42.6	42	4.2%	-13.00 [-31.40, 5.40]	
Malmborg et al 2013	165	40	54	167	40	56	4.3%	-2.00 [-16.95, 12.95]	
Matta et al 2018	124	30	46	133	35	46	4.4%	-9.00 [-22.32, 4.32]	
Mugnai et al 2014	112	52	136	192	49	260	4.5%	-80.00 [-90.58, -69.42]	
Neumann et al 2011	250.5	22.65	45	276	24.13	44	4.5%	-25.50 [-35.23, -15.77]	
Pérez-Castellano et al 2014	215	53	25	173	63	25	3.4%	42.00 [9.73, 74.27]	
Sauren et al 2009	178	57	10	185	49	10	2.7%	-7.00 [-53.59, 39.59]	
Schmidt et al 2012	134	27	37	149	30	178	4.5%	-15.00 [-24.75, -5.25]	
Schmidt et al 2013	129	29	33	103	33	33	4.3%	26.00 [11.01, 40.99]	
Sorgente et al 2010	116	24.6	30	195	34.4	29	4.3%	-79.00 [-94.30, -63.70]	
Wasserlauf et al 2015	192.9	44	101	283.7	78	100	4.2%	-90.80 [-108.33, -73.27]	←
Yokokawa et al 2018	148	41	71	207	58	75	4.3%	-59.00 [-75.23, -42.77]	
Total (95% CI)			1614			1913	100.0%	-26.37 [-38.20, -14.55]	◆
Heterogeneity: Tau ² = 783.50	: Chi ² = 5	25.39.	f= 23	(P < 0.00	001): P	= 96%			ter te te te
Test for overall effect: Z = 4.37									-100 -50 0 50 10
Test for overall effect: Z = 4.37	' (P < 0.0	001)							Favours CRYO Favours RF

100

B: Comparison Fluoroscopy Time (minutes)

	0	RYO			RF			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD.	Total	Mean	SD.	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chierchia et al 2010	0	0	46	0	0	87		Not estimable	
Ciconte et al 2015	14.5	6.6	50	19.8	6.8	50	5.3%	-5.30 [-7.93, -2.67]	-
Gaita et al 2011	37	18	36	16	14	36	4.9%	21.00 [13.55, 28.45]	-
Herrera et al 2011	27	13	23	34	17	27	4.8%	-7.00 [-15.33, 1.33]	
Herrera et al 2012	38	12	30	37	16	30	4.9%	1.00 [-6.16, 8.16]	+
Hunter et al 2015	36.53	6.27	78	29.78	6.22	77	5.3%	6.75 [4.78, 8.72]	•
lourda et al 2015	25.3	9.9	75	21.5	8.5	75	5.3%	3.80 [0.85, 6.75]	+
<ojodjojo 2010<="" al="" et="" td=""><td>28</td><td>10</td><td>90</td><td>62</td><td>36</td><td>53</td><td>4.6%</td><td>-34.00 [-43.91, -24.09]</td><td></td></ojodjojo>	28	10	90	62	36	53	4.6%	-34.00 [-43.91, -24.09]	
kuck et al 2016	21.7	13.9	374	16.6	17.8	376	5.3%	5.10 [2.81, 7.39]	-
Kuhne et al 2010	61	25	18	46	22	25	4.0%	15.00 [0.59, 29.41]	
inhart et al 2009.	49	17	20	55	23	20	4.3%	-6.00 [-18.53, 6.53]	+
uik et al 2015.	0	0	156	0	0	159		Not estimable	
faagh et al 2013	34.1	10.7	30	33.2	10.2	42	5.2%	0.90 [-4.02, 5.82]	+
falmborg et al 2013	32	16	54	47	17	56	5.0%	-15.00 [-21.17, -8.83]	
latta et al 2018	11	5	46	4.1	3	46	5.3%	6.90 [5.21, 8.59]	-
lugnai et al 2014	31	17	136	36	14	260	5.3%	-5.00 [-8.33, -1.67]	+
Veumann et al 2011	41.75	7.8	45	85.5	12.7	44	5.2%	-43.75 [-48.14, -39.36]	-
Pérez-Castellano et al 2014	45	16	25	45	16	25	4.7%	0.00 [-8.87, 8.87]	-
Sauren et al 2009	0	0	10	0	0	10		Not estimable	
Schmidt et al 2012	47	8	37	62	14	178	5.3%	-15.00 [-18.30, -11.70]	+
Schmidt et al 2013	0	0	33	0	0	33		Not estimable	
Sorgente et al 2010	40.4	6.7	30	66.7	16	29	5.0%	-26.30 [-32.60, -20.00]	
Vasserlauf et al 2015	46	22.4	101	73	30.1	100	4.9%	-27.00 [-34.34, -19.66]	
rokokawa et al 2018	30	12	71	24	10	75	5.3%	6.00 [2.41, 9.59]	-
Total (95% CI)			1369			1624	100.0%	-5.94 [-11.63, -0.25]	•
Heterogeneity: Tau ² = 157.31;	Chi ² = 8	56.25	df = 19	(P < 0.	00001): ² = 9	8%		
est for overall effect: Z = 2.04									-100 -50 0 50 10
Test for overall effect Z = 2.04	(1 = 0.0	4)							Favours CRYO Favours RF

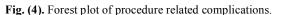
Fig. (3). Forest plot of procedure and fluoroscopy time.

A: Comparison of Phrenic Nerve Palsy

, a companio a				,				O d de Defe	
Study or Subgroup	CRY Events		RI Events		Woight	Odds Ratio M-H, Random, 95% Cl		Odds Ratio M-H, Random, 95% Cl	
Ciconte et al 2015	2	50			0			M-H, Randolli, 55% Cl	
Hunter et al 2015	4	78	-						
Jourda et al 2015	13	70							`
	2	90							
Kojodjojo et al 2010 Linhart et al 2009	3	20							
Luik et al 2009	9	156							
Maagh et al 2013	3	30	-						
Malmborg et al 2013	2	54							
Mugnaietal 2014	11	136	-						
Neumann et al 2014	3	45							
	3	40							
Sorgente et al 2010	1	101	-						
Wasserlauf et al 2015									
Yokokawa et al 2018	1	71	0	75	6.7%	3.21 [0.13, 80.17]			
Total (95% CI)		936		1040	100.0%	9.02 [3.92, 20.74]		•	
Total events	57		0						
Heterogeneity: Tau² = 0	.00; Chi ² =	= 4.33,	df = 12 (i	P = 0.98	3); I ² = 0%		0.01	0.1 1 10	100
Test for overall effect: Z	= 5.18 (P	< 0.00	001)				0.01	0.1 1 10 Favours CRYO Favours RF	100
								Pavouis CICIO Pavouis ICP	
B: Comparison of	f Silent	Cere	ebral E	mbo	li				
•	CRYC)	RF			Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI	
Gaita et al 2011	2	36	3	36	18.5%	0.65 [0.10, 4.12]			
Herrera et al 2011	1	23	2	27	10.4%	0.57 [0.05, 6.70]			
Neumann et al 2011	4	45	3	44	26.2%	1.33 [0.28, 6.33]			
Schmidt et al 2013	6	33	8	33	44.9%	0.69 [0.21, 2.28]			
Total (95% CI)		137		140	100.0%	0.80 [0.36, 1.77]		-	
Total events	13		16						
Heterogeneity: Tau ² = 0		= 0.59		= 0.90) [.] I ² = 0.%		—		
Test for overall effect: Z				- 0.00	/,1 = 0.0		0.01	0.1 1 10 Favours CRYO Favours RF	100
								Favours CRTO Favours RF	
C: Comparison of	f Perica	ardia	l Effus	ion a	nd/or	Tamponade			
	CRYC)	RF			Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% CI	
Chierchia et al 2010	5	46	14	87	21.4%	0.64 [0.21, 1.89]			
Ciconte et al 2015	0	50	1	50	2.4%	0.33 [0.01, 8.21]			
Hunter et al 2015	ŏ	78	. 1	77	2.5%	0.32 [0.01, 8.10]			
Kojodjojo et al 2010	1	90	2	53	4.3%	0.29 [0.03, 3.24]	-		
Kuck et al 2016	1	374	5	376	5.5%	0.20 [0.02, 1.71]	_		
Luik et al 2015	2	156	3	159	7.8%	0.68 [0.11, 4.10]			
Matta et al 2018	Ô	46	1	46	2.4%	0.33 [0.01, 8.22]			
Mugnai et al 2014	11	136	30	260	48.5%	0.67 [0.33, 1.39]		_ _	
Sorgente et al 2010	0	30	1	200	2.4%	0.31 [0.01, 7.96]			
Yokokawa et al 2018	0	71	2	75	2.4%	0.21 [0.01, 4.36]	←		
Total (95% CI)		1077		1212	100.0%	0.54 [0.33, 0.90]		•	
Total events	20		60						

 Total events
 20
 60

 Heterogeneity: Tau² = 0.00; Chi² = 2.39, df = 9 (P = 0.98); l² = 0%
 Test for overall effect: Z = 2.39 (P = 0.02)



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 (l^2 =0%, p=0.98; Fig. 4).

Eavours CRYO Eavours R

100

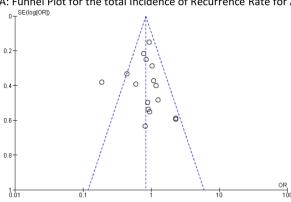
Publication Bias:

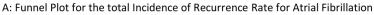
For primary outcome with CBA effectiveness we conducted a funnel plot for publication bias for each study (Fig. 5).

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-





B: Funnel Plot for the Incidence of Recurrence Rate for Paroxysmal Atrial Fibrillation

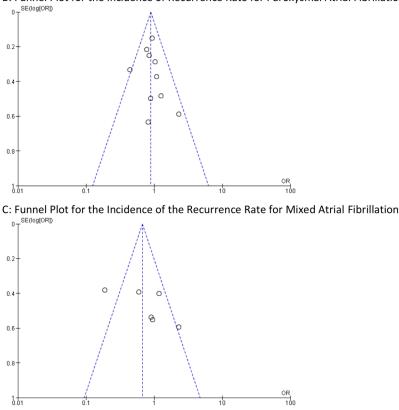


Fig. (5). Funnel plot evaluating publication bias.

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 thirdgeneration 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

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CONFLICT OF INTEREST

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