Journal of Interventional Cardiac Electrophysiology (2019) 54:237–245
https://doi.org/10.1007/s10840-018-0474-4

REVIEWS

Comparison of efficacy and safety of laser balloon and cryoballoon ablation for atrial fibrillation—a meta-analysis

Yue Wei[1] · Ning Zhang[1] · Qi Jin[1] · Wenqi Pan[1] · Yucai Xie[1] · Kang Chen[1] · Tianyou Ling[1] · Changjian Lin[1] · Yangyang Bao[1] · Qingzhi Luo[1] · Chaofan Xing[1] · Liqun Wu[1]

Received: 9 July 2018 / Accepted: 11 October 2018 / Published online: 20 October 2018

Abstract

Background Laser balloon (LB) and cryoballoon (CB) ablation are two balloon-based catheter ablation technologies used for atrial fibrillation (AF) ablation in recent years. However, the efficacy and the safety of LB ablation in comparison to CB ablation remained indeterminate. We sought to compare these two technologies by conducting meta-analysis of previous studies using both the CB and LB ablation systems for AF ablation.

Methods We searched electronic scientific databases for studies of LB vs. CB ablation in AF patients. The procedural efficacy was assessed by the success of acute pulmonary vein isolation (PVI) and the 12-month recurrence of any atrial arrhythmia, and the safety was evaluated by the risk of procedure-related complications.

Results A total of 595 participants (LB, $n = 292$ vs. CB, $n = 303$) from eight studies were included in this meta-analysis. Risk of acute PVI failure (risk ratio, RR 95% confidence interval [95% CI] = 2.55 [0.86–7.56], $P = 0.09$) and atrial arrhythmia recurrence in 12 months (RR [95% CI] = 0.91 [0.64–1.28], $P = 0.59$) were comparable between LB vs. CB ablation, and LB ablation tended to be more effective than CB ablation in paroxysmal AF patients (RR [95% CI] = 0.70 [0.47–1.03], $P = 0.07$). Risk of procedure-related complications was similar while LB ablation showed slightly higher risk without statistic significance (LB 13.9% vs. CB 9.3%, RR [95% CI] = 1.52 [0.88–2.64], $P = 0.14$). Compared with CB ablation, LB ablation led to longer procedure duration (weighted mean differences WMD [95% CI] =29.7 [15.8–43.7], $P < 0.001$) while similar fluoroscopy duration was observed between these two ablation devices (WMD [95% CI] = − 1.99[− 6.46–2.47], $P = 0.38$).

Conclusions LB ablation has a trend toward higher procedural efficacy compared with CB ablation in paroxysmal AF patients. However, longer procedure duration and a statistically non-significant trend of more procedure-related complications were also observed in patients ablated by LB. Further larger comparative randomized trials are warranted to disclose the impact of LB compared with CB for ablation of AF.

Keywords Atrial fibrillation · Catheter ablation · Laser balloon · Cryoballoon

1 Background

Atrial fibrillation (AF) is one of the most common sustained form of cardiac arrhythmia. For symptomatic AF refractory to anti-arrhythmic drugs, catheter ablation of AF is recommended as optimal therapeutic strategy by guidelines [1]. Pulmonary vein isolation (PVI) is the corner stone of catheter ablation of AF, which alone has been demonstrated to have similar therapeutic efficacy compared with PVI with extensive lesions [2].

To simplify PVI procedures, balloon-based catheter ablation technologies were developed in recent years. The cryoballoon (CB) ablation system, using cryoenergy for ablation, has been shown excellent efficacy and safety in a number of trials [3, 4]. In recent years, a newly invented laser balloon (LB) ablation system, consisting of a compliant balloon adjustable in size from 9 to 35 mm and a miniature endoscope allowing for visually guided segment-by-segment ablation,

Yue Wei and Ning Zhang contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10840-018-0474-4) contains supplementary material, which is available to authorized users.

✉ Liqun Wu
wuliqun8907@163.com

[1] Department of Cardiology, Shanghai Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Ruijin No. 2 Road, Shanghai 201204, China

has also been shown favorable feasibility and durable PVI in several multicenter trials [5–7].

Several studies were conducted to compare these two balloon-based catheter ablation. However, reported results are variable in terms of ablation efficacy, procedural parameters and complications. Thus, we sought to conduct this meta-analysis to resolve discrepancies among studies and to derive comprehensive estimates of safety and efficacy of LB ablation by comparing to CB ablation for AF treatment.

2 Methods

The present review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA). The protocol for our study was registered in the international prospective register of systematic reviews (PROSPERO), with the registration number CRD42018093332 (available from https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=93332).

2.1 Literature search

Scientific databases such as PubMed, EMBASE, Web of Science, the Cochrane library, and other electronic databases were searched for studies comparing cryoballoon or laser balloon ablation for AF. The following key words and the corresponding Medical Subject Heading (MeSH) terms were used: "AF," "pulmonary vein isolation," "cryoballoon," "cryoablation," "laserballoon". The reference list of all eligible items was checked for identification of further relevant studies.

2.2 Study selection and quality assessment

Studies that were included in our meta-analysis should meet the following criteria: (1) randomized or non-randomized prospective studies and retrospective studies enrolling consecutive patients; (2) studies comparing patients undergoing "PVI-only" using laser balloon or cryoballoon; (3) studies including patients with AF and/or paroxysmal AF (PAF) and/or persistent AF (Per AF). Non-comparative trials, abstract-only articles, case reports, editorials, and reviews as well as studies containing no adequate outcomes of interest were excluded from this study.

Two investigators (Y. W and N. Z) independently screened each citation for inclusion. Two reviewers (Y. W and N. Z) independently reviewed the full-text articles of potentially relevant studies to determine their eligibility. Discrepancies between them were resolved by discussion with the entire group. We extracted the following data from the included studies: publication year, the first author, geographic area, number of patients, the baseline characteristics of the study population, features of the study design, and the data we need in our meta-analysis.

2.3 Outcome variables and definitions

The primary efficacy outcome of our study was the achievement of acute PVI after balloon-based ablation alone and the 1-year recurrence of any atrial arrhythmia 3 months after ablation procedure without the administration of anti-arrhythmic drugs. The primary safety outcome was the procedure-related complications, including groin complication, embolic events, phrenic nerve palsy (PNP) unresolved until discharge, cardiac tamponade, and new asymptomatic embolic cerebral lesion. Secondary outcomes were procedure duration and fluoroscopy duration.

2.4 Statistical analysis

Data were pooled using random effects models, according to the Mantel–Haenszel model. Fixed effect model was also tested and results reported only if different from random effects. Dichotomous outcome data were expressed as risk ratios (RRs) with 95% confidence intervals (CIs) and continuous outcome data as weighted mean differences (WMDs) with 95% CIs. The present study assessed the heterogeneity between studies using the Cochran's Q statistic and the I^2 index. I^2 values of $< 25\%$, 25–50%, or $> 50\%$ indicated low, moderate, or high heterogeneity. Sensitivity analysis was performed to check the consistency of the overall effect estimate. The presence of publication bias was evaluated by the use of funnel plots, Egger test, and Begg test. All statistical testing was two-tailed with a statistical significance set at $P < 0.05$. Statistical analysis was performed with RevMan 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

3 Results

3.1 Literature search

The electronic search yielded 120 potentially relevant abstracts. After removing duplicates and ineligible abstracts, we reviewed the full text of 24 reports. Of these reports, 16 reports were excluded for respective reasons. Consequently, eight studies were finally selected in this meta-analysis [8–15]. The results of the search and selection process are shown in Fig. 1.

3.2 Study characteristics

Supplementary Table S1 summarizes the characteristics of included studies. In all studies, patients were sufficiently anticoagulated and an activating clotting time was maintained between 300 and 350 s. LB ablation was all performed with visually guided laser ablation catheter (HeartLight™, CardioFocus). Laser energy level was applied between 5.5 and 12 W according to the degree of tissue exposure for 20 to 30 s in order to achieve PVI in most studies. CB ablation was performed mostly with 28-mm second-generation CB (Arctic Front Advance™, Medtronic). In all studies, cryoablation for 240 to 300 s were applied after obtaining optimal pulmonary vein occlusion and a single bonus application was delivered after PVI.

The main clinical characteristics of participants included in the meta-analysis were reported in Table 1. Of the 595 patients included in this analysis, 292 patients underwent LB ablation and 303 underwent CB ablation. Types of AF were predominantly PAF, but three studies included a small portion of Per AF (especially short-standing Per AF) and one study enrolled only Per AF. Cases were mainly males (69%), with a mean age of 62.4 years old, 11% diabetics, 57% hypertensive, 16% coronary arterial disease, a mean LVEF of 60.8% and a mean LA diameter of 41.1 mm.

3.3 Primary outcomes

The failure of PVI was available for six studies, in total of 489 patients (LB, $n = 239$ vs. CB, $n = 250$). PVI failure occurred in 24 patients (24/239, 10.0%) in LB arm and 19 patients (19/250, 7.6%) in CB arm (RR [95% CI] = 0.84 [0.61–1.14], $P = 0.25$) but it exists a medium heterogeneity with $I^2 = 48\%$ and P for heterogeneity (Phet) = 0.09. This may be due to dissimilar patient populations, different ablation catheter, and ablation experience of operator. In Casella study, a large portion of CB patients were ablated with first generation CB catheter, which showed a significant increase of PVI failure (RR [95% CI] = 0.08 [0.01–1.32]). Therefore, we excluded this study in the analysis and found a trend of higher rate of PVI failure with LB catheter (LB 24/219, 11.0% vs. CB 9/215, 4.2%; RR [95% CI] = 2.55 [0.86–7.56], $P = 0.09$; $I^2 = 24\%$, Phet = 0.26). It was noted that by using fixed effect model, PVI failure with LB catheter was higher than with CB catheter (RR [95% CI] = 2.55 [1.22–5.34], $P = 0.01$).

The recurrence of any atrial arrhythmia in 1 year was available for six studies, in a total of 446 patients (LB, $n = 208$ vs. CB, $n = 238$). Recurrence occurred in 118 patients (26%), and the risk of recurrence in total did not differ between patients treated with LB ablation and those with CB ablation (LB 25% vs. CB 27%; RR [95% CI] = 0.91 [0.64–1.28], $P = 0.55$; $I^2 = 11\%$, Phet = 0.35). When stratifying the results according to AF type, the risk of recurrence tended to be lower in the LB group than in the CB group if only PAF were included (LB 20% vs. CB 27%; RR [95% CI] = 0.70 [0.47–1.03], $P = 0.07$; $I^2 = 0\%$, Phet = 0.92). In the subgroup of studies including Per AF, risk of recurrence was comparable between two studies (LB 40% vs. CB 27%; RR [95% CI] = 1.48 [0.87–2.51], $P = 0.15$; $I^2 = 0\%$, Phet = 0.75) (Fig. 2).

In terms of safety, procedure-related complications were occurred in 35 patients (13.9%) treated with LB ablation and 23 patients (9.3%) treated with CB ablation. The risk of overall complication showed no significant difference (RR [95% CI] = 1.52 [0.88–2.64], $P = 0.14$; $I^2 = 5\%$, P for heterogeneity (Phet) = 0.39).

Groin complication (LB 4.0% vs. CB 2.1%; RR [95% CI] = 1.80 [0.55–5.91], $P = 0.33$; $I^2 = 0\%$, Phet = 0.67), cardiac tamponade (LB 2.8% vs. CB 0.6%; RR [95% CI] = 2.85 [0.56–14.47], $P = 0.21$; $I^2 = 0\%$, Phet = 0.89), PNP (LB 3.8% vs. CB 3.8%; RR [95% CI] = 0.96 [0.38–2.42], $P = 0.93$; $I^2 = 0\%$, Phet = 0.78) and new asymptomatic embolic brain lesion (LB 23.6% vs. CB 20.0%; RR [95% CI] = 1.46 [0.62–3.44], $P = 0.39$; $I^2 = 0\%$, Phet = 0.64) did not show significant differences between patients treated with LB ablation and those treated with CB ablation (Fig. 3).

Three studies with 270 patients reported only one embolic events in LB-ablated patients, two studies with 200 patients reported only 1 esophageal injury in LB-ablated patients, two studies with 160 patients reported only 2 gastroparesis in CB-ablated patients and three studies with 270 patients reported 0 death. We were unable to conduct analysis for those complications due to the low event number.

3.4 Secondary outcomes

Mean procedure duration was 168 min in LB arm and 141 min in CB arm, which was available for seven studies. Longer procedure duration was observed with LB compared with CB (Range 141–201 min vs. 103–185 min, WMD [95% CI] = 29.7 [15.8–43.7], $P < 0.001$). There was high heterogeneity for this risk estimate ($I^2 = 83\%$, Phet < 0.001). A comparable fluoroscopy duration was observed between LB and CB (Range 12–28 min vs. 14–36 min, WMD [95% CI] = −1.99[−6.46–2.47], $P = 0.38$) with high heterogeneity ($I^2 = 89\%$, Phet < 0.001) (Fig. 4).

3.5 Small study effects and publication bias

Funnel plot distribution of primary efficacy outcomes, primary safety outcomes, and secondary outcomes showed no publication bias after visual estimation. Additionally, Egger test and Begg test were performed for PVI failure, arrhythmia recurrence, procedure-related complications, and procedure parameters respectively and no publication bias was found. Sensitivity test showed that no single study significantly

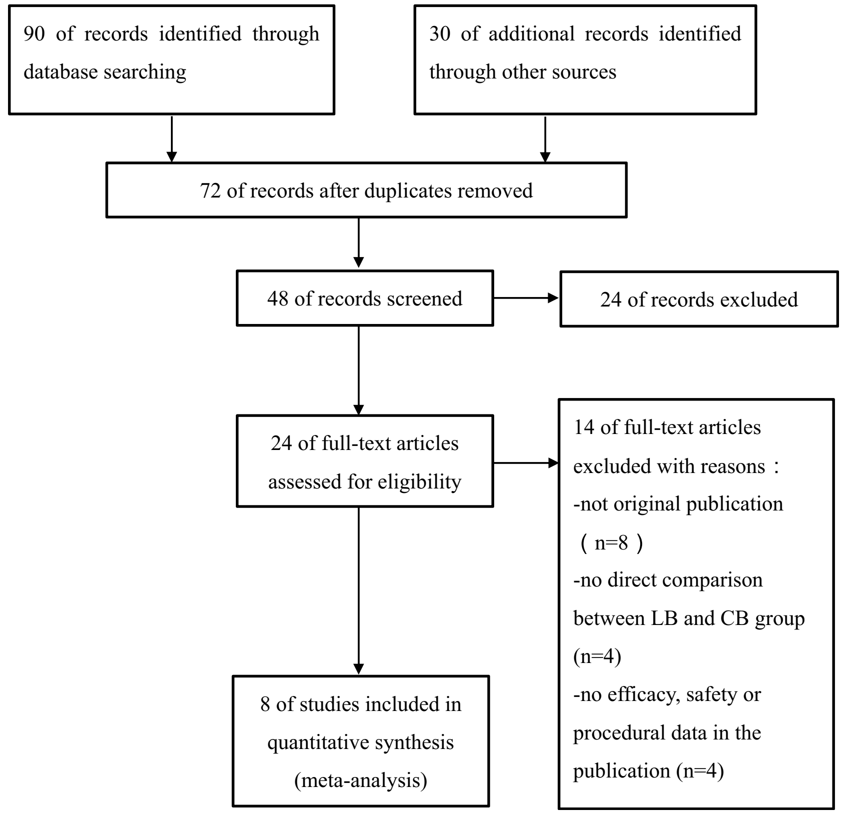

Fig. 1 Flow chart of the systematic literature research for the meta-analysis

altered the summary RR for primary and secondary outcomes (see supplementary material online, Table S2, Fig. S1).

4 Discussion

4.1 Principal findings

This was the first meta-analysis which investigated efficacy and safety of LB vs. CB ablation for PVI in AF patients. The main findings are as follows: (i) LB ablation seems to be associated with higher risk of PVI failure but more effective than CB ablation in PVI for paroxysmal AF in terms of 1-year outcome; (ii) LB ablation shows a non-significant trend for more procedure-related complications; and (iii) procedure duration of LB ablation was longer.

4.2 Efficacy

In the present analysis, LB ablation was essentially compared with CB, thus a comparison of "single-shot" and "segment-by-segment" balloon-based PVI ablation. Although a trend of higher PVI failure using LB ablation was observed, the 12-month success rate was comparable between two groups. PV

Table 1 Main clinical characteristics of participants included in the meta-analysis

Study	Patients, *n*	Type of AF	Mean age (years)	Males (%)	DM (%)	HTA (%)	CAD (%)	Mean LVEF (%)	Mean LAD (mm)
Bordignon 2013	140	PAF	63.0 ± 10.6	66	12	62	10	63.0 ± 5.1	39.9 ± 4.4
Schmidt 2013	66	PAF	65.5 ± 9.1	N/A	6	25	17	60.0 ± 6.1	40.0 ± 5.0
Kumar 2014	60	PAF and Per AF	58.3 ± 7.0	73	N/A	13	6	57.7 ± 5.4	N/A
Wissner 2014	64	PAF or short-standing Per AF	62.4 ± 9.0	67	5	69	10	64.0 ± 7.0	42.4 ± 4.7
Casella 2014	55	PAF	57.6 ± 10.7	73	N/A	N/A	N/A	61.8 ± 7.0	41.8 ± 5.1
Tsyganov 2015	100	PAF	62.5 ± 10.1	63	16	64	N/A	N/A	43.0 ± 5.9
Stockigt 2016	70	Pers AF	65.2 ± 10.0	77	19	79	43	55.2 ± 13.5	N/A
Perotta 2017	40	PAF or short-standing Per AF	66.5 ± 9.5	73	5	88	20	62.0 ± 4.1	40.0 ± 4.5

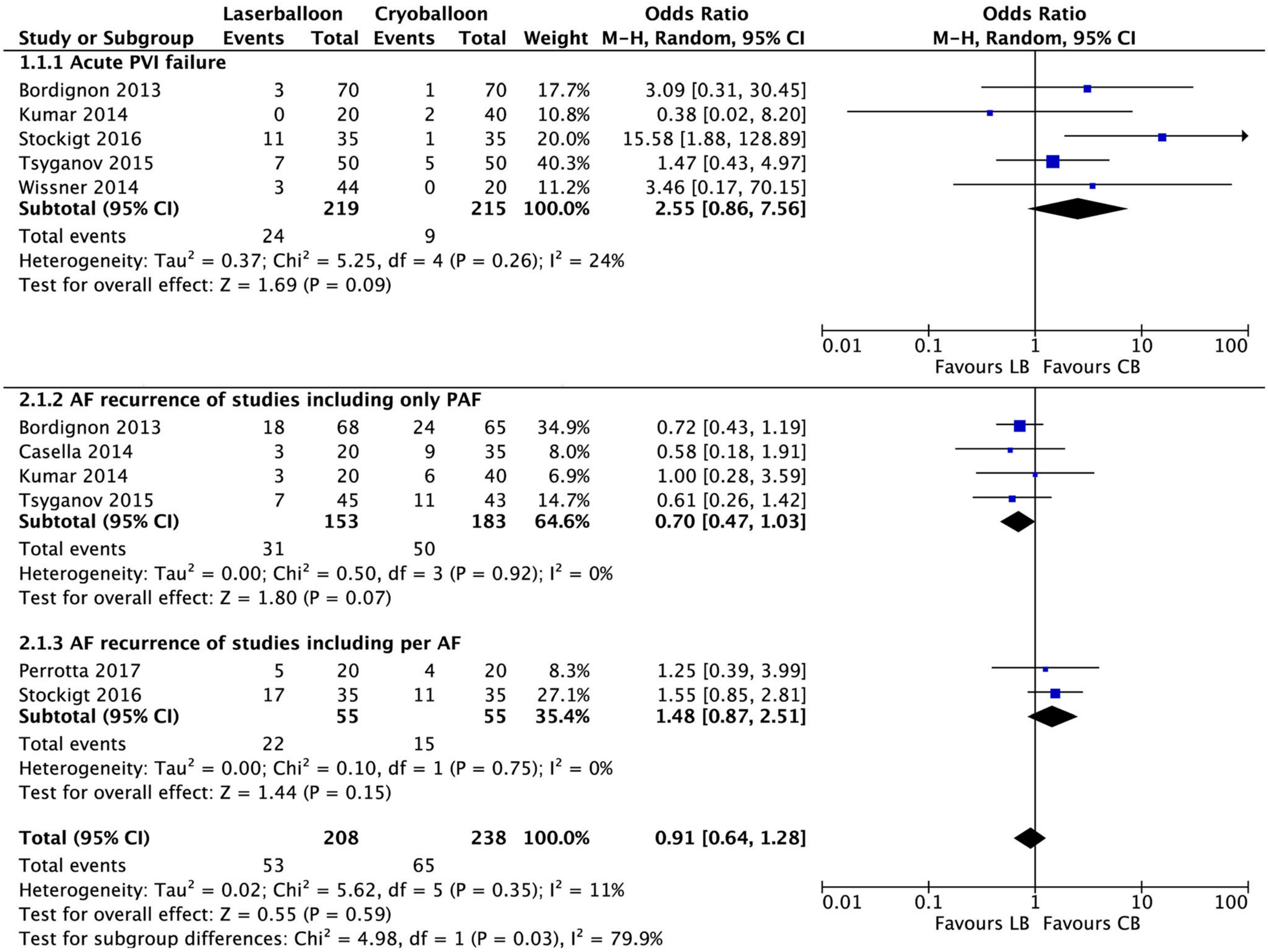

Fig. 2 Risk estimates of the primary efficacy outcome of LB vs. CB ablation. PVI, pulmonary vein isolation; AF, atrial fibrillation; LB, laser balloon, CB, cryoballoon

anatomical factors might contribute to PVI failure. Right inferior PV (RIPV) was known to cause poor alignment of the balloon, resulting in poor contact of balloon at the ostium, which caused most isolation failure compared to other PVs [8, 13]. In addition, unfavorable orientation of PV has been linked to worse long-term efficacy. Gal [16] discovered that ventral-caudal orientation of left inferior PV (LIPV) was associated with lower 1-year AF-free survival after LB ablation compared with dorsal-cranial orientation of LIPV. This may be caused by the non-fluent deployment of LB in ventral-caudal-oriented LIPV. Proximity of extra-cardiac structures such as the esophagus or the phrenic nerve seems to be another reason. Stöckigt [14] reported that LB procedures were prematurely interrupted predominantly due to excessive esophageal temperature rise, resulting in incomplete PV isolation (especially LIPV) in three patients. Learning curve effect influence acute PVI success as well. It was demonstrated in several studies that number of incompletely isolated PVs, incidence of complications, procedure duration and fluoroscopy duration declined over time [5, 14, 17]. Further large-scale studies are warranted to disclose the impact of LB catheter compared with CB catheter on acute PVI success.

LB ablation tended to have lower acute PV isolation rate than CB; however, both ablation devices showed similar long-term efficacy in the total population. The overall 1-year AF-free rate was 75.1% after LB ablation and 73.5% after CB ablation, which is coherent with previous study [7]. Additionally, AF recurrence seemed to be lower after ablation therapy by LB compared with CB in paroxysmal AF patients. A potential reason was the durable lesion created by LB, as 86% PVs remained isolation 3 months after LB isolation [18]. In Bordignon study [8], repeat procedure was performed in patients experiencing AF recurrence and it was found that 68% PV previously isolated by CB and 42% PV isolated by LB showed reconduction to the LA, resulting in a risk reduction of 37% to have PV reconduction during repeat procedure. Figueras [19] reported that laser balloon ablation achieved more complete anatomical PVI and less LA scar extension compared with radio-frequency ablation using late-gadolinium-enhanced cardiac magnetic resonance. However, energy titration in LB ablation affects acute and

Study or Subgroup	Laserballoon Events	Laserballoon Total	Cryoballoon Events	Cryoballoon Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Procedure related complication						
Bordignon 2013	9	70	6	70	28.8%	1.50 [0.56, 3.99]
Kumar 2014	4	20	5	40	19.7%	1.60 [0.48, 5.31]
Schmidt 2013	8	33	6	33	30.9%	1.33 [0.52, 3.42]
Stockigt 2016	7	35	1	35	7.1%	7.00 [0.91, 53.95]
Tsyganov 2015	1	50	4	50	6.4%	0.25 [0.03, 2.16]
Wissner 2014	6	44	1	20	7.0%	2.73 [0.35, 21.18]
Subtotal (95% CI)		**252**		**248**	**100.0%**	**1.52 [0.88, 2.64]**
Total events	35		23			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.25$, df = 5 (P = 0.39); $I^2 = 5\%$						
Test for overall effect: Z = 1.49 (P = 0.14)						
2.1.2 Groin complications						
Bordignon 2013	4	70	2	70	51.1%	2.00 [0.38, 10.57]
Kumar 2014	1	20	1	40	19.1%	2.00 [0.13, 30.34]
Stockigt 2016	2	35	0	35	15.7%	5.00 [0.25, 100.53]
Tsyganov 2015	0	50	1	50	14.0%	0.33 [0.01, 7.99]
Subtotal (95% CI)		**175**		**195**	**100.0%**	**1.80 [0.55, 5.91]**
Total events	7		4			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.55$, df = 3 (P = 0.67); $I^2 = 0\%$						
Test for overall effect: Z = 0.96 (P = 0.33)						
2.1.3 Tamponade						
Bordignon 2013	1	70	0	70	26.0%	3.00 [0.12, 72.40]
Casella 2014	1	20	0	35	26.5%	5.14 [0.22, 120.62]
Kumar 2014	0	20	0	40		Not estimable
Stockigt 2016	2	35	1	35	47.5%	2.00 [0.19, 21.06]
Subtotal (95% CI)		**145**		**180**	**100.0%**	**2.85 [0.56, 14.47]**
Total events	4		1			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.22$, df = 2 (P = 0.89); $I^2 = 0\%$						
Test for overall effect: Z = 1.27 (P = 0.21)						
2.1.4 Phrenic nerve palsy						
Bordignon 2013	3	70	4	70	40.1%	0.75 [0.17, 3.23]
Kumar 2014	1	20	3	40	17.7%	0.67 [0.07, 6.01]
Perotta 2017	1	44	0	20	8.6%	1.40 [0.06, 32.95]
Stockigt 2016	3	35	0	35	10.0%	7.00 [0.37, 130.69]
Tsyganov 2015	1	50	2	50	15.2%	0.50 [0.05, 5.34]
Wissner 2014	1	44	0	20	8.6%	1.40 [0.06, 32.95]
Subtotal (95% CI)		**263**		**235**	**100.0%**	**0.96 [0.38, 2.42]**
Total events	10		9			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.46$, df = 5 (P = 0.78); $I^2 = 0\%$						
Test for overall effect: Z = 0.09 (P = 0.93)						
2.1.5 New asymptomatic embolic brain lesion						
Schmidt 2013	8	33	6	33	83.0%	1.33 [0.52, 3.42]
Wissner 2014	5	44	1	20	17.0%	2.27 [0.28, 18.21]
Subtotal (95% CI)		**77**		**53**	**100.0%**	**1.46 [0.62, 3.44]**
Total events	13		7			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.21$, df = 1 (P = 0.64); $I^2 = 0\%$						
Test for overall effect: Z = 0.86 (P = 0.39)						

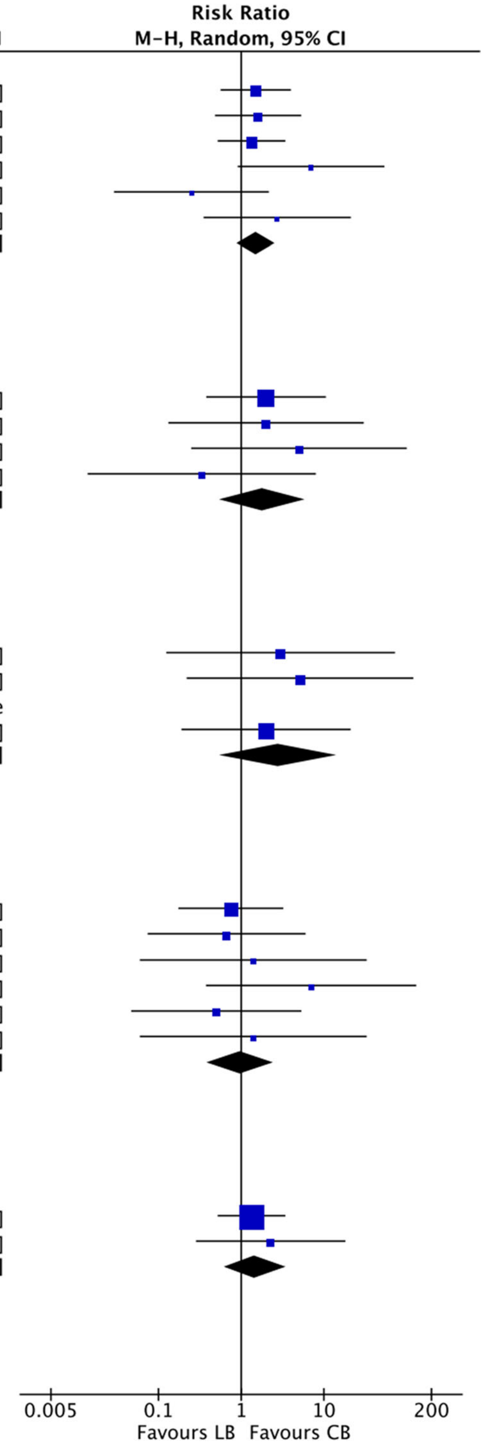

Fig. 3 Risk estimates of the primary safety outcome of LB vs. CB ablation. LB, laser balloon, CB, cryoballoon

chronic outcomes. Compared with low dose ablation (5.5–8.5 W), high-dose ablation (> 8.5 W) showed better acute PVI rate (89% vs. 69%), higher proportion of patients in whom all PVs were isolated after a single ablation circle (70% vs. 39%) as well as a lower recurrence rate after a follow-up of 311 days (17% vs. 40%) [20]. To date, LB ablation showed non-inferior long-term efficacy to CB ablation, and further studies are still needed to draw the conclusion of the impact of LB on long-term outcome.

4.3 Safety

Regarding the safety outcome, though in this analysis LB ablation showed slightly higher risk of procedure-related

Study or Subgroup	Laserballoon Mean	Laserballoon SD	Laserballoon Total	Cryoballoon Mean	Cryoballoon SD	Cryoballoon Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 Procedure duration								
Bordignon 2013	144	33	70	136	30	70	14.3%	8.00 [-2.45, 18.45]
Fassini 2015	190.3	47.3	40	148.2	40.5	50	12.2%	42.10 [23.64, 60.56]
Kumar 2014	180	44	20	185	47	40	10.6%	-5.00 [-29.17, 19.17]
Perrotta 2017	141	31	20	103	24	20	12.5%	38.00 [20.82, 55.18]
Schmidt 2013	149	34	33	129	29	33	13.1%	20.00 [4.75, 35.25]
Stockigt 2016	158.5	37.9	35	110.9	26.5	35	13.1%	47.60 [32.28, 62.92]
Tsyganov 2015	201.2	53.2	50	147	37.4	50	12.3%	54.20 [36.17, 72.23]
Wissner 2014	195	48	44	164	29	20	12.0%	31.00 [11.96, 50.04]
Subtotal (95% CI)			**312**			**318**	**100.0%**	**29.73 [15.79, 43.67]**
Heterogeneity: $Tau^2 = 326.58$; $Chi^2 = 40.25$, df = 7 ($P < 0.00001$); $I^2 = 83\%$								
Test for overall effect: Z = 4.18 ($P < 0.0001$)								
3.1.2 Fluoroscopy duration								
Bordignon 2013	15	6	70	21	9	70	22.0%	-6.00 [-8.53, -3.47]
Kumar 2014	25	10	20	36	16	40	15.6%	-11.00 [-17.62, -4.38]
Perrotta 2017	12	3	20	14	5	20	22.0%	-2.00 [-4.56, 0.56]
Stockigt 2016	28.4	11.1	35	23.5	9.4	35	18.5%	4.90 [0.08, 9.72]
Tsyganov 2015	20.4	7.7	50	17.8	5.2	50	21.9%	2.60 [0.02, 5.18]
Subtotal (95% CI)			**195**			**215**	**100.0%**	**-1.99 [-6.46, 2.47]**
Heterogeneity: $Tau^2 = 21.94$; $Chi^2 = 36.62$, df = 4 ($P < 0.00001$); $I^2 = 89\%$								
Test for overall effect: Z = 0.87 (P = 0.38)								

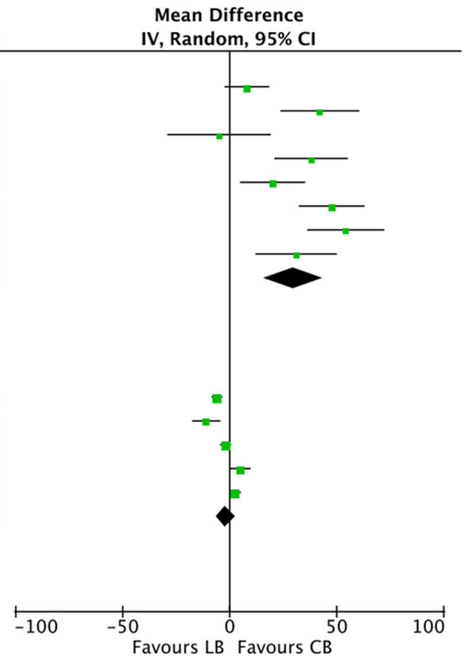

Fig. 4 Risk estimates of the secondary outcome of LB vs. CB ablation. LB, laser balloon, CB, cryoballoon

complications, both ablation techniques showed comparable safety profile. PNP was a common periprocedural complication of balloon-based ablation for AF probably because of the distortion of right superior PV anatomy due to balloon dilation and decreasing of the distance to PN [21]. In all cases PNP recovered during follow-up and risk for PNP showed no difference between two ablation devices. One remarkable point was that 4 out of 5 patients who experienced cardiac tamponade in the present analysis were ablated by LB despite of lack of statistical significance. A recent meta-analysis including 1188 AF patients treated by LB showed that the pooled risk of cardiac perforation or tamponade was 1.1% [22]; however, much lower incidence was found in CB group in Fire and Ice study [3] (0.3% postprocedural pericarditis and tamponade). Those results implied that LB-ablated atrium might be more susceptible to cardiac tamponade than to other kinds of complication. This may be attributed to: first, LB is not delivered through a guidewire as is CB; second, low number of catheter manipulations with CB compared with segment-by-segment ablation with LB; third, inexperience of operators using LB catheter. Further larger comparative randomized trials are needed to determine the influence of these factors on periprocedure complications.

4.4 Secondary endpoints

In the present analysis, it was shown that procedure duration was longer in LB ablation than in CB ablation while fluoroscopy duration was similar. Balloon catheters were designed for anatomic ablation, and therefore PV anatomy is important for ablation strategy. As CB size is fixed, sometimes switching balloons (between 28 and 23 mm CB) is inevitable due to insufficient PV occlusion [23, 24].This might extend procedure time. In contrast, LB is sizable and compatible with all different sizes of PV. However, the mode of "segment-by-segment" LB ablation would offset its advantage in size-compatibility and consume more procedure time than "single shot" CB ablation [25]. Additionally, CB ablation system contains the integrated circular mapping catheter (Achieve catheter) allowing real-time recording of PV potentials, which can be less time-consuming than LB ablation system using additional lasso catheter for PV isolation validation. Inexperience of operators using LB could be another reason. Mean procedure duration for CB ablation was 371 min in STOP AF trial as was 124 min in FIRE AND ICE study [3, 4]. Hence, procedure duration may decrease with the accumulation of experience in using LB. Fluoroscopy time tends to be shorter as LB system using endoscope allowing for a visual control of balloon for lesion deployment while CB system requires serial angiogram for optimal PV occlusion, but in the present analysis, no significant difference was found between two groups. Nevertheless, a high heterogeneity was observed while no publication bias was found and sensitivity test showed no positive results. It may be related to the small sample size and considerably discrepant cumulative experiences at individual centers.

5 Limitations

The current study has a number of limitations. First of all, only two of eight qualified trials were performed in a randomized design. Although randomized trials can minimize bias and are regarded as the gold standard for quantifying effect estimates, they may not reflect AF treatment in general clinical practice. Second, the total sample size of the present analysis is relatively small. Considering LB catheter is a new technology used for AF ablation, it is not unexpected that studies comparing LB and CB were small-scale studies. Third, subgroup analysis was not performed due to the relatively small sample size. Four, data on major complications such as tamponade or stroke were limited in our analysis. Fifth, inexperience may affect the result of the analysis as one study reported the influence of learning curve effect. Sixth, patients included were all Caucasians from European countries limited the generalizability of our findings, reinforcing the future validation in other ethnics is needed. Finally, as with all meta-analyses, despite a low probability of publication bias in this meta-analysis, selection bias cannot be completely excluded, since we merely identified articles from the English journals and published trials. Further large-scale randomized clinical trials are warranted to confirm or refute our findings.

6 Conclusion

LB ablation has a trend toward higher procedural efficacy compared with CB ablation in paroxysmal AF patients. However, longer procedure duration and a statistically non-significant trend of more procedure-related complications were also observed in patients ablated by LB. Further larger comparative randomized trials are warranted to disclose the impact of LB compared with CB for ablation of AF.

Funding This work was supported by the Science and Technology Commission of Shanghai Municipality (no. 16140904602) and National Natural Science Foundation of China (81470450, 81470451, 81600270).

Compliance with ethical standards

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

Ethical approval Ethical approval was not required for this study design.

References

1. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace. 2018;20(1):e1–e160. https://doi.org/10.1093/europace/eux274.
2. Verma A, Jiang C-Y, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015;372(19):1812–22. https://doi.org/10.1056/NEJMoa1408288.
3. Kuck K-H, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KRJ, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med. 2016;374(23):2235–45. https://doi.org/10.1056/NEJMoa1602014.
4. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation. J Am Coll Cardiol. 2013;61:1713–23. https://doi.org/10.1016/j.jacc.2012.11.064.
5. Dukkipati SR, Cuoco F, Kutinsky I, Aryana A, Bahnson TD, Lakkireddy D, et al. Pulmonary vein isolation using the visually guided laser balloon: a prospective, multicenter, and randomized comparison to standard radiofrequency ablation. J Am Coll Cardiol. 2015;66(12):1350–60. https://doi.org/10.1016/j.jacc.2015.07.036.
6. Dukkipati SR, Woollett I, Mc EH, Bohmer MC, Doshi SK, Gerstenfeld EP, et al. Pulmonary vein isolation using the visually guided laser balloon: results of the U.S. feasibility study. J Cardiovasc Electrophysiol. 2015;26:944–9. https://doi.org/10.1111/jce.12727.
7. Schmidt B, Neuzil P, Luik A, Osca Asensi J, Schrickel JW, Deneke T, et al. Laser balloon or wide-area circumferential irrigated radiofrequency ablation for persistent atrial fibrillation: a multicenter prospective randomized study. Circ Arrhythm Electrophysiol. 2017;10(12):e005767. https://doi.org/10.1161/CIRCEP.117.005767.
8. Bordignon S, Chun KR, Gunawardene M, Fuernkranz A, Urban V, Schulte-Hahn B, et al. Comparison of balloon catheter ablation technologies for pulmonary vein isolation: the laser versus cryo study. J Cardiovasc Electrophysiol. 2013;24(9):987–94. https://doi.org/10.1111/jce.12192.
9. Schmidt B, Gunawardene M, Krieg D, Bordignon S, Furnkranz A, Kulikoglu M, et al. A prospective randomized single-center study on the risk of asymptomatic cerebral lesions comparing irrigated radiofrequency current ablation with the cryoballoon and the laser balloon. J Cardiovasc Electrophysiol. 2013;24(8):869–74. https://doi.org/10.1111/jce.12151.
10. Kumar N, Blaauw Y, Timmermans C, Pison L, Vernooy K, Crijns H. Adenosine testing after second-generation balloon devices (cryothermal and laser) mediated pulmonary vein ablation for atrial fibrillation. J Interv Card Electrophysiol. 2014;41(1):91–7. https://doi.org/10.1007/s10840-014-9921-z.
11. Wissner E, Metzner A, Neuzil P, Petru J, Skoda J, Sediva L, et al. Asymptomatic brain lesions following laserballoon-based pulmonary vein isolation. Europace. 2014;16(2):214–9. https://doi.org/10.1093/europace/eut250.
12. Casella M, Dello Russo A, Russo E, Al-Mohani G, Santangeli P, Riva S, et al. Biomarkers of myocardial injury with different energy sources for atrial fibrillation catheter ablation. Cardiol J. 2014;21:516–23. https://doi.org/10.5603/CJ.a2013.0153.
13. Tsyganov A, Petru J, Skoda J, Sediva L, Hala P, Weichet J, et al. Anatomical predictors for successful pulmonary vein isolation using balloon-based technologies in atrial fibrillation. J Interv Card Electrophysiol. 2015;44(3):265–71. https://doi.org/10.1007/s10840-015-0068-3.
14. Stockigt F, Kohlmann AT, Linhart M, Nickenig G, Andrie RP, Beiert T, et al. Laserballoon and cryoballoon pulmonary vein isolation in persistent and longstanding persistent atrial fibrillation. Pacing Clin Electrophysiol. 2016;39(10):1099–107. https://doi.org/10.1111/pace.12929.
15. Perrotta L, Konstantinou A, Bordignon S, Fuernkranz A, Dugo D, Chun KJ, et al. What is the acute antral lesion size after pulmonary vein isolation using different balloon ablation technologies? Circ J. 2017;81(2):172–9. https://doi.org/10.1253/circj.CJ-16-0345.
16. Gal P, Ooms JF, Ottervanger JP, Smit JJ, Adiyaman A, Ramdat Misier AR, et al. Association between pulmonary vein orientation and atrial fibrillation-free survival in patients undergoing

endoscopic laser balloon ablation. Eur Heart J Cardiovasc Imaging. 2015;16(7):799–806. https://doi.org/10.1093/ehjci/jeu321.
17. Perrotta L, Bordignon S, Dugo D, Furnkranz A, Chun KJ, Schmidt B. How to learn pulmonary vein isolation with a novel ablation device: learning curve effects using the endoscopic ablation system. J Cardiovasc Electrophysiol. 2014;25(12):1293–8. https://doi.org/10.1111/jce.12491.
18. Dukkipati SR, Neuzil P, Kautzner J, Petru J, Wichterle D, Skoda J, et al. The durability of pulmonary vein isolation using the visually guided laser balloon catheter: multicenter results of pulmonary vein remapping studies. Heart Rhythm. 2012;9(6):919–25. https://doi.org/10.1016/j.hrthm.2012.01.019.
19. Figueras IVRM, Margulescu AD, Benito EM, Alarcon F, Enomoto N, Prat-Gonzalez S, et al. Postprocedural LGE-CMR comparison of laser and radiofrequency ablation lesions after pulmonary vein isolation. J Cardiovasc Electrophysiol. 2018;29(8):1065–72. https://doi.org/10.1111/jce.13616.
20. Bordignon S, Chun KR, Gunawardene M, Urban V, Kulikoglu M, Miehm K, et al. Energy titration strategies with the endoscopic ablation system: lessons from the high-dose vs. low-dose laser ablation study. Europace. 2013;15(5):685–9. https://doi.org/10.1093/europace/eus352.
21. Okumura Y, Henz BD, Bunch TJ, Dalegrave C, Johnson SB, Packer DL. Distortion of right superior pulmonary vein anatomy by balloon catheters as a contributor to phrenic nerve injury. J Cardiovasc Electrophysiol. 2009;20(10):1151–7. https://doi.org/10.1111/j.1540-8167.2009.01495.x.
22. MRA-Ohoo R, Zheng Q, Doros G. Laser balloon ablation for AF: a systematic review and meta-analysis. J Cardiovasc Electrophysiol. 2018. https://doi.org/10.1111/jce.13698.
23. Neumann T, Vogt J, Schumacher B, Dorszewski A, Kuniss M, Neuser H, et al. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol. 2008;52(4):273–8. https://doi.org/10.1016/j.jacc.2008.04.021.
24. Straube F, Dorwarth U, Vogt J, Kuniss M, Heinz Kuck K, Tebbenjohanns J, et al. Differences of two cryoballoon generations: insights from the prospective multicentre, multinational FREEZE Cohort Substudy. Europace. 2014;16(10):1434–42. https://doi.org/10.1093/europace/euu162.
25. Metzner A, Wissner E, Lin T, Ouyang F, Kuck KH. Balloon devices for atrial fibrillation therapy. Arrhythm Electrophysiol Rev. 2015;4(1):58–61. https://doi.org/10.15420/aer.2015.4.1.58.