ORIGINAL ARTICLE

Cryoballoon versus radiofrequency ablation for persistent atrial fibrillation: a systematic review and meta-analysis

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KEY WORDS
cryoballoon ablation, efficacy, persistent atrial fibrillation, radiofrequency ablation, safety

EDITORIAL
by Gul and Verma, see p. 1

ABSTRACT

BACKGROUND Clinical outcomes of catheter ablation for persistent atrial fibrillation (AF) remain discouraging.

AIMS This meta-analysis aimed to compare cryoballoon ablation (CBA) with radiofrequency ablation (RFA) for persistent AF.

METHODS A systematic search of the PubMed, EMBASE, and Cochrane Library databases was performed for studies comparing the outcomes between CBA and RFA. Seven trials including 934 patients were analyzed.

RESULTS There were no differences between groups in terms of freedom from atrial arrhythmia (risk ratio [RR], 1.04; 95% CI, 0.93–1.15; $P = 0.52$; $I^2 = 0\%$), procedural complications (RR, 0.91; 95% CI, 0.52–1.59; $P = 0.74$; $I^2 = 0\%$), atrial fibrillation or atrial tachycardia relapse during the blanking period (RR, 0.73; 95% CI, 0.50–1.06; $P = 0.1$; $I^2 = 9\%$), repeat ablation (RR, 0.74; 95% CI, 0.45–1.21; $P = 0.23$; $I^2 = 62\%$), and vascular complications (RR, 0.98; 95% CI, 0.42–2.27; $P = 0.97$; $I^2 = 0\%$). Cryoballoon ablation increased the incidence of conversion to sinus rhythm during ablation (RR, 1.69; 95% CI, 1.01–2.83; $P = 0.046$; $I^2 = 0\%$) and phrenic nerve palsy (PNP; RR, 3.05; 95% CI, 0.95–9.8; $P = 0.06$; $I^2 = 0\%$), while RFA increased the risk of cardiac tamponade (RR, 0.27; 95% CI, 0.06–1.25; $P = 0.09$; $I^2 = 0\%$). Subanalyses revealed a lower incidence of recurrent atrial arrhythmia and repeat ablation during CBA without touch-up RFA in pulmonary vein isolation.

CONCLUSIONS CBA provides an alternative technique for persistent AF ablation. It might reduce the risk of repeat ablation and cardiac tamponade but increase the risk of PNP.

INTRODUCTION Catheter ablation is an established therapy for drug-refractory atrial fibrillation (AF) according to several guidelines.[1,2] Radiofrequency ablation (RFA) is still the mainstay of AF ablation. In recent years, cryoballoon ablation (CBA) has been widely adopted as an efficacious ablation technique, particularly for paroxysmal AF.[3] However, in about 7.1% of patients per year, paroxysmal AF will develop into persistent AF.[4] Persistent AF was reported to occur in at least 33.3% of patients undergoing AF ablation.[5] There have been few studies, with small sample sizes, comparing the effects of CBA and RFA on persistent AF. Hence, a systematic review and meta-analysis was conducted to assess the efficacy and safety of CBA and RFA in patients with persistent AF.

METHODS The meta-analysis was performed according to the PRISMA 2009 flow diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[6] and was approved by the local institutional review board.

Search strategy and inclusion criteria

PubMed, EMBASE, and Cochrane Library databases were searched between 1966 and April 2019 with the following terms as key concepts: (((((“Radiofrequency Ablation”[Mesh]) OR Ablation, Radiofrequency) OR Ablation, Radio Frequency) OR Radio-Frequency Ablation) OR Ablation, Radio-Frequency) AND (Cryoballoon ablation OR Cryoballoon) AND (((((((“Atrial Fibrillation”[Mesh]) OR Persistent Atrial Fibrillation) OR Atrial Fibrillation, Persistent) OR

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Received: August 20, 2019.
Revision accepted: November 5, 2019.
Published online: November 5, 2019.
Kardiol Pol. 2020; 78 (1): 20-29
doi:10.33963/KP.15048

WHAT'S NEW?

The aim of this meta-analysis was to investigate the differences in efficacy and safety between cryoballoon ablation (CBA) and radiofrequency ablation (RFA) in persistent atrial fibrillation. There were no differences between CBA and RFA in the procedural success rate as well as complications. Cryoballoon ablation might yield a lower incidence of repeat ablation compared with RFA. The results of all subanalyses were similar to the efficacy and safety outcomes between the 2 techniques. The success rate of cryo-pulmonary isolation without touch-up RFA might be higher in patients who underwent CBA compared with those after RFA. Cryoballoon ablation can be considered as an initial technique for recurrent AF ablation in failed RFA for paroxysmal AF.

Atrial Fibrillations, Persistent) OR Fibrillation, Persistent Atrial) OR Fibrillations, Persistent Atrial) OR Persistent Atrial Fibrillations). Conference abstracts were also searched, and references from published meta-analyses, reviews, and identified studies were considered.

Eligible studies in English had to meet the following criteria: 1) patients had persistent AF; 2) data for efficacy and safety for both CBA and RFA were available; 3) the follow-up was at least 12 months; and 4) the first ablation procedure was present. The exclusion criteria were as follows: 1) mixed population; 2) equivocal study design or group allocation; 3) animal studies, case reports, case series, editorials, non-English articles, and review articles.

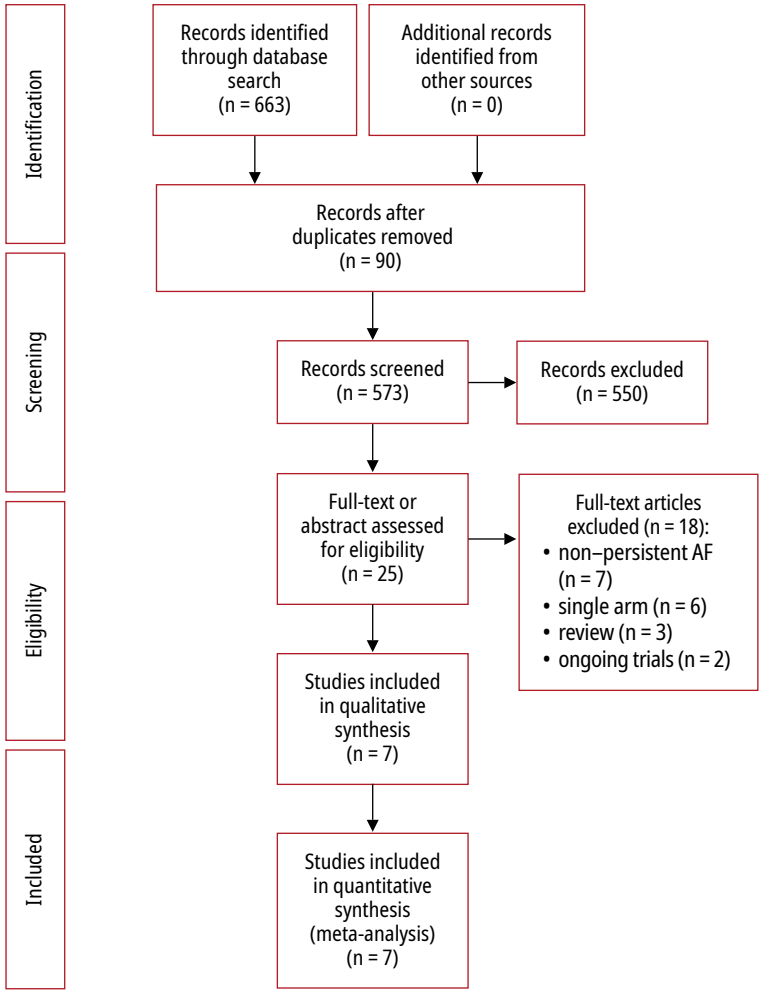

FIGURE 1 PRISMA flow diagram for search strategy and study selection

Abbreviations: AF, atrial fibrillation

Outcomes and data extraction Efficacy outcomes included freedom from AF / atrial tachycardia (AT), AF / AT relapse during the blanking period, conversion to sinus rhythm (SR) during ablation, and repeat ablation. Safety outcomes included procedural complications, cardiac tamponade, phrenic nerve palsy (PNP), and vascular access complications. Two investigators (X-FG and C-LJ) independently extracted specified data from identified studies. All potential disagreement was resolved by consensus.

Quality assessment The quality of the included full-text studies was evaluated according to the following aspects: quality of participant selection, comparability of groups, and outcome adjudication using the Newcastle–Ottawa Scale (C-FC and BC). Each study could be scored a maximum of 9 points. Scores above 6 were regarded as high quality.

Statistical analysis Statistical analyses were performed using the Meta package of R statistics (version 3.5.3; Shanghai, China) by an independent reviewer (X-HL). Risk ratios (RRs) with 95% CIs were calculated. Significant heterogeneity was defined as an I^2 of higher than 50% with a P value of less than 0.1. The fixed effect by the DerSimonian and Laird method[7] was preferred if nonsignificant heterogeneity was identified. Otherwise, a random-effects model was used. Sensitivity analysis was performed to detect a contributing study by excluding each study one by one and recalculating pooled estimates of the remaining studies. The Funnel plot and Peters test were used to investigate publication bias for the outcomes of freedom from AF / AT and procedural complications. The trim-and-fill method was used to help verify the results as needed. Subanalyses were conducted for CBA groups (with or without touch-up RFA in pulmonary vein isolation [PVI]) and RFA groups (with or without the use of a contact force catheter) to evaluate the overall results for freedom from AF / AT, procedural complications, and repeat ablation.

RESULTS Study selection and characteristics

A total of 663 studies were initially screened, of which 90 were duplicates and 550 were excluded after reviewing their titles or abstracts. The remaining 25 studies were further examined, and 7 studies were ultimately included in the analysis: 2 propensity score–matched studies,[8,9] 2 retrospective studies,[10,11] 2 prospective studies,[12,13] and

a conference abstract[14] (FIGURE 1). Two conference abstracts were excluded due to a suspicion of overlapping population. The baseline characteristics of the included studies are summarized in TABLE 1. There was a total of 934 patients, of whom 451 underwent CBA and 483 underwent RFA. For CBA, most studies used a second-generation cryoballoon as an ablation tool, except the study by Boveda et al,[8] which utilized a first-generation cryoballoon. For RFA, a contact force-sensing catheter was employed in 3 studies,[9,12,13] while the remaining studies utilized a standard open irrigated catheter.[10,11] Cryo-PVI in 2 CBA groups was reported with no touch-up RFA.[9,12] Only one CBA group, in the study by Ciconte et al,[12] was treated using the PVI-alone ablation strategy, while the majority of studies showed different extra-PVI ablations in CBA groups. In these studies, a short-term monitoring device was used. Only one study, by Yokokawa et al,[13] employed a long-term device for follow-up monitoring. The Newcastle–Ottawa Scale scores for the included studies are shown in Supplementary material, *Table S1*.

Efficacy outcomes Similar AF-/AT-free survival rates were found between CBA and RFA (58% and 56%, respectively; RR, 1.04; 95% CI, 0.93–1.15; $P = 0.52$; $I^2 = 0\%$; FIGURE 2A). The incidence of AF/AT relapse during the blanking period of CBA did not differ from that of RFA (RR, 0.73; 95% CI, 0.50–1.06; $P = 0.1$; $I^2 = 9\%$; FIGURE 2B). The groups differed in the incidence of conversion to SR during ablation (RR, 1.69; 95% CI, 1.01–2.83; $P = 0.046$; $I^2 = 0\%$; FIGURE 2C). The random-effects model was preferred for a pooled analysis of the incidence of repeat ablation due to its significant heterogeneity (RR, 0.74; 95% CI, 0.45–1.21; $P = 0.23$; $I^2 = 62\%$; FIGURE 2D). Sensitivity analysis found that heterogeneity may be attributed to the study by Kosmidou et al,[11] because its exclusion reduced the heterogeneity to 25% and the difference in repeat ablation became significant (RR, 0.60; 95% CI, 0.44–0.82; $P = 0.001$; Supplementary material, *Figure S1*).

Safety outcomes There were no significant differences in procedural complications (RR, 0.91; 95% CI, 0.52–1.59; $P = 0.74$; $I^2 = 0\%$; FIGURE 3A) or vascular complications (RR, 0.98; 95% CI, 0.42–2.27; $P = 0.97$; $I^2 = 0\%$; FIGURE 3B) between CBA and RFA. The analysis of PNP revealed that it occurred in the CBA group in all 7 studies, and a difference in PNP between the 2 groups tended to be significant (RR, 3.05; 95% CI, 0.95–9.80; $P = 0.06$; $I^2 = 0\%$; FIGURE 3C). Furthermore, a trend to higher incidence of cardiac tamponade was noted during RFA (RR, 0.27; 95% CI, 0.06–1.25; $P = 0.09$; $I^2 = 0\%$; FIGURE 3D).

Publication bias The funnel plots for AF/AT were symmetrical (Supplementary material, *Figure S2*), and the Peters test showed no publication bias ($P = 0.74$). The funnel plots for procedural complications also seemed symmetrical (Supplementary material, *Figure S3*) but were not consistent with the Peters test ($P = 0.03$). None of the studies were added after the trim-and-fill analysis. The adjusted result (RR, 0.92; 95% CI, 0.52–1.62; $P = 0.78$; $I^2 = 0\%$) supported the publication bias and had no influence on the final result.

Subanalyses The subanalyses revealed that patients after cryo-PVI without touch-up RFA in the CBA group more frequently showed freedom from AF/AT (RR, 1.15; 95% CI, 1–1.32) and less often required repeat ablation (RR, 0.49; 95% CI, 0.3–0.79). Patients in the RFA group with the use of contact force-sensing catheter also showed a lower incidence of repeat ablation (RR, 0.65; 95% CI, 0.45–0.93). None of the subanalyses revealed significant differences in procedural complications between groups. Data are presented in FIGURE 4.

DISCUSSION

To the best of our knowledge, this is the first meta-analysis to compare the efficacy and safety between CBA and RFA in persistent AF ablation. The main findings were as follows: 1) CBA showed a similar success rate for maintaining SR for persistent AF as compared with RFA, combined with a similar incidence of procedural complications between groups; 2) CBA might help reduce the need for repeat ablation in persistent AF but with an increased risk of PNP, while RFA might reduce the risk of cardiac tamponade; and 3) subanalyses supported CBA as an initial option for persistent AF in the context of consistent efficacy and safety outcomes.

The success rate of RFA for persistent AF was reported to be approximately 60%,[15,16] which is in agreement with our results both for CBA and RFA. The one-shot mode and the commonly used 28-mm balloon for CBA reinforced the advantage of CBA in creating homogenous and extensive ablation lesions in the pulmonary vein (PV) antrum in comparison with RFA, especially after the advent of second-generation cryoballoons with a wider freezing surface and more injection ports. Higher levels of cardiac troponin I and creatine kinase-MB detected during CBA also reflected a greater degree of lesions during cryoablation.[17] A magnetic resonance imaging study demonstrated that a significantly wider lesion area (mean [SD], 8.2 [2.2] mm vs 5.6 [2.0] mm) and fewer lesion gaps (7% vs 38%) were present after CBA compared with RFA.[18] Consequently, PVI created by CBA was thought to be more beneficial than RFA.

In the recent FREEZE Cohort Study,[19] in which a second- or third-generation cryoballoon was used in 76% of patients undergoing CBA,

TABLE 1 Characteristics of studies included in the meta-analysis (continued on the next page)

Study	Design and type	Group, n	Age[a], y	Male, %	DM, %	Hypertension, %	LVEF[a], %	CHA_2DS_2-VASc[a]	LAD[a], mm	Duration[a]	AF history[a], y	Ablation strategy, n	Antiarrhythmic drugs after BP, %	Monitor strategy
Ciconte et al[12]	Prospective, 2G	CBA (50)	62.4 (9.8)	72	8	52	57.5 (3.7)	1.4 (1.3)	46.0 (7.2)	Follow-up, 12 months	2.7 (3.1)	PVI without touch-up RFA (50)	15	ECG, 24-hour Holter at 1, 3, 6, 12 months
		RFA (50)	62.4 (9.5)	76	14	68	56.3 (4.1)	1.8 (1.2)	47.2 (6.2)	Follow-up, 12 months	2.2 (2)	PVI, CTI (1), adjunctive line (1)		
Boveda et al[8]	Propensity--score matched, 1G	CBA (59)	59.9 (11.6)	83.1	5.1	32.2	NA	1.2 (1.2)	NA	Median, 15.6 months	4.1 (4)	PVI with touch-up RFA (5); CTI by RFA (11)	NA	ECG, 24-hour Holter at 1, 3, 6, 12 months
		RFA (9)	59.8 (9.9)	81.4	5.1	28.8	NA	1.1 (1.0)	NA		3.5 (4.1)	PVI, CFAE (31), RL (40), MI (19), CTI (12)	NA	
Guler et al[10]	Retrospective, 2G	CBA (19)	56.0 (14.2)	50	NA	NA	54.52 (8.4)	NA	42.7 (5.8)	27.2 (7.6) months	5.1 (6.1)	PVI with touch-up RFA (6 veins); all CFAE (5), linear ablation (2), CS ablation (1) by RFA	32	ECG, 24-hour Holter at 1, 3, 6, 12, and 18 months
		RFA (15)	56.2 (12)	47	NA	NA	58.8 (7.1)	NA	40.6 (6.3)		5.6 (4.4)	PVI, CFAE (3), linear ablation (1), CS ablation (1)	34	
Akkaya et al[9]	Propensity--score matched, 2G	CBA (111)	Median (Q1–Q3), 62 (54–69)	69.4	15.3	73	Median (Q1–Q3), 62 (57–62)	1.8 (0.8)	Median (Q1–Q3), 44 (41–48)	Median (Q1–Q3), 22 (12–33) months	Median (Q1– Q3), 3.3 (0.6–6.2)	PVI without touch-up RFA; RL by CBA (48), CTI by RFA (7)	14.4	7-day Holter every 3 months at first year, then every 6 months after first year
		RFA (111)	Median (Q1–Q3), 61 (56–68)	64.9	17.1	76.6	Median (Q1–Q3), 61 (56–62)	2.0 (0.7)	Median (Q1–Q3), 45 (41–49)	Median (Q1–Q3), 27 (15–37) months	Median (Q1– Q3), 2.5 (0.7–8.9)	PVI, RL (49), CTI (14)	28.8	

TABLE 1 Characteristics of studies included in the meta-analysis (continued from the previous page)

Study	Design and type	Group, n	Age[a], y	Male, %	DM, %	Hypertension, %	LVEF[a], %	CHA_2DS_2-VASc[a]	LAD[a], mm	Duration[a]	AF history[a], y	Ablation strategy, n	Antiarrhythmic drugs after BP, %	Monitor strategy
Yokokawa et al[13]	Prospective, 2G	CBA (90)	64 (10)	71	NA	63	NA	2.0 (1.4)	46 (5)	21 (10) months	2.25 (1.75)	PVI with touch-up RFA (3); RL by CBA (33), CTI by RFA (9)	22	Event monitors, implantable loop recorders, 48-hour Holter monitors, ECG, 3 months after the procedure, then every 3–6 months
		RFA (77)	64 (8)	79	NA	69	NA	1.9 (1.2)	46 (6)		2.5 (2.33)	PVI, BOX (77), CTI (2)	14	
Kosmidou et al[11]	Retrospective, NA	CBA (21)	61.7 (7.9)	81	24	67	55.5 (7.6)	NA	42.53 (5.63)	397 (126) days	NA	PVI with touch-up RFA (9 veins); all CFAE (17), MI (6), RL (21), SI (3), CTI (6), CS ablation by RFA (3)	49	ECG at 1, 3 months and every 3 months
		RFA (31)	64.3 (7.6)	81	16	84	51.5 (10.3)	NA	44.17 (5.4)	520 (217) days	NA	PVI, CFAE (27), MI (6), RL (28), SL (10), CTI (9), CS ablation (1)	56	ECG at 1, 3 months and every 3 months
Straube et al[14]	Prospective, 1G/2G	CBA (101)	NA	NA	NA	NA	NA	NA	NA	Median, 418 days	<1	NA	6.5	NA
		RFA (140)	NA	NA	NA	NA	NA	NA	NA	Median, 456 days	<1	NA	15.8	NA

a Data are presented as mean (SD) unless otherwise indicated.

Abbreviations: AF, atrial fibrillation; BOX, isolation of the posterior left atrium; BP, blanking period; CBA, cryoballoon ablation; CFAE, complex fractionated atrial electrogram; CHA_2DS_2-VASc, congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 years, diabetes, thromboembolism or stroke history, vascular disease, age 65–74 years, female sex; CS, coronary sinus; CTI, cavotricuspid isthmus; DM, diabetes mellitus; ECG, electrocardiogram; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; MI, mitral isthmus; NA, not available; PVI, pulmonary vein isolation; Q1, lower quartile; Q3, upper quartile; RFA, radiofrequency ablation; RL, roof line; SL, septal line; 1G, first generation; 2G, second generation

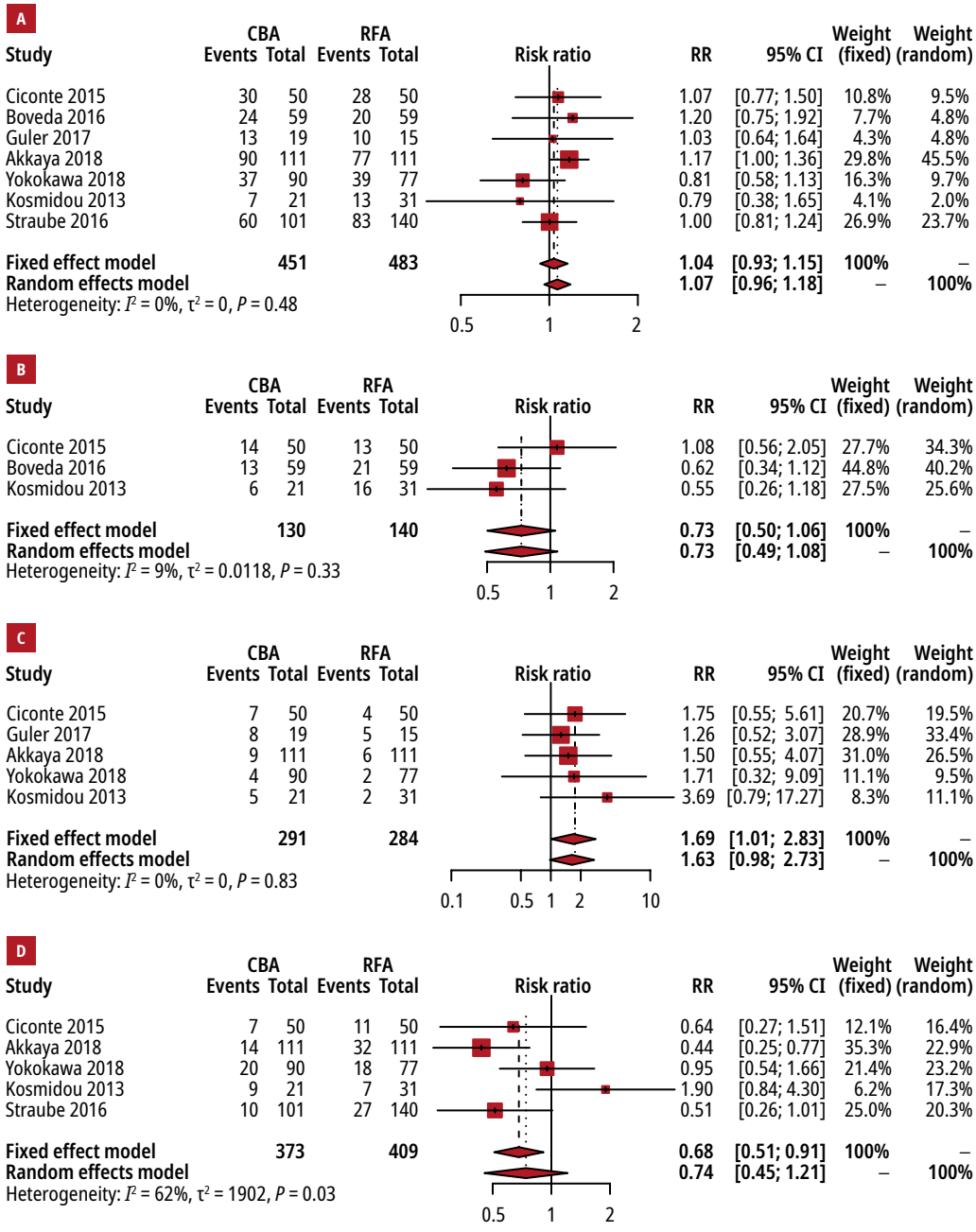

FIGURE 2 Forest plot of freedom from atrial fibrillation or atrial tachycardia (**A**), atrial fibrillation or atrial tachycardia relapse during the blanking period (**B**), conversion to sinus rhythm during ablation (**C**), and repeat ablation (**D**) for cryoballoon ablation vs radiofrequency ablation

Abbreviations: RR, risk ratio; others, see TABLE 1

the persistent AF subanalysis including over 1000 patients showed a consistent and much higher (approximately 65%) success rate between the CBA and RFA groups. However, the duration of persistent AF history in this cohort study was less than 1 year, which is shorter than the duration of more than 2 years in most studies included in this meta-analysis. This could be an important reason for the higher success rate for persistent AF observed in this cohort study. Although the cryo-PVI without touch-up RFA might be related to a better primary outcome as described in the subanalysis, touch-up RFA application was not uncommon in cryo-PVI. The introduction of the second-generation cryoballoon reduced this application by half as compared with the first-generation cryoballoon.[19] Pulmonary vein anatomy might have no obvious influence on the outcome of cryoablation.[20] These findings might support the use of CBA for persistent AF.

In addition, the current analysis for repeat ablation revealed a possibly significant superiority of CBA over RFA after the sensitivity analysis accounted for heterogeneity. In the persistent AF subanalysis of the FREEZE Cohort Study,[19] repeat ablation was nearly halved with CBA as

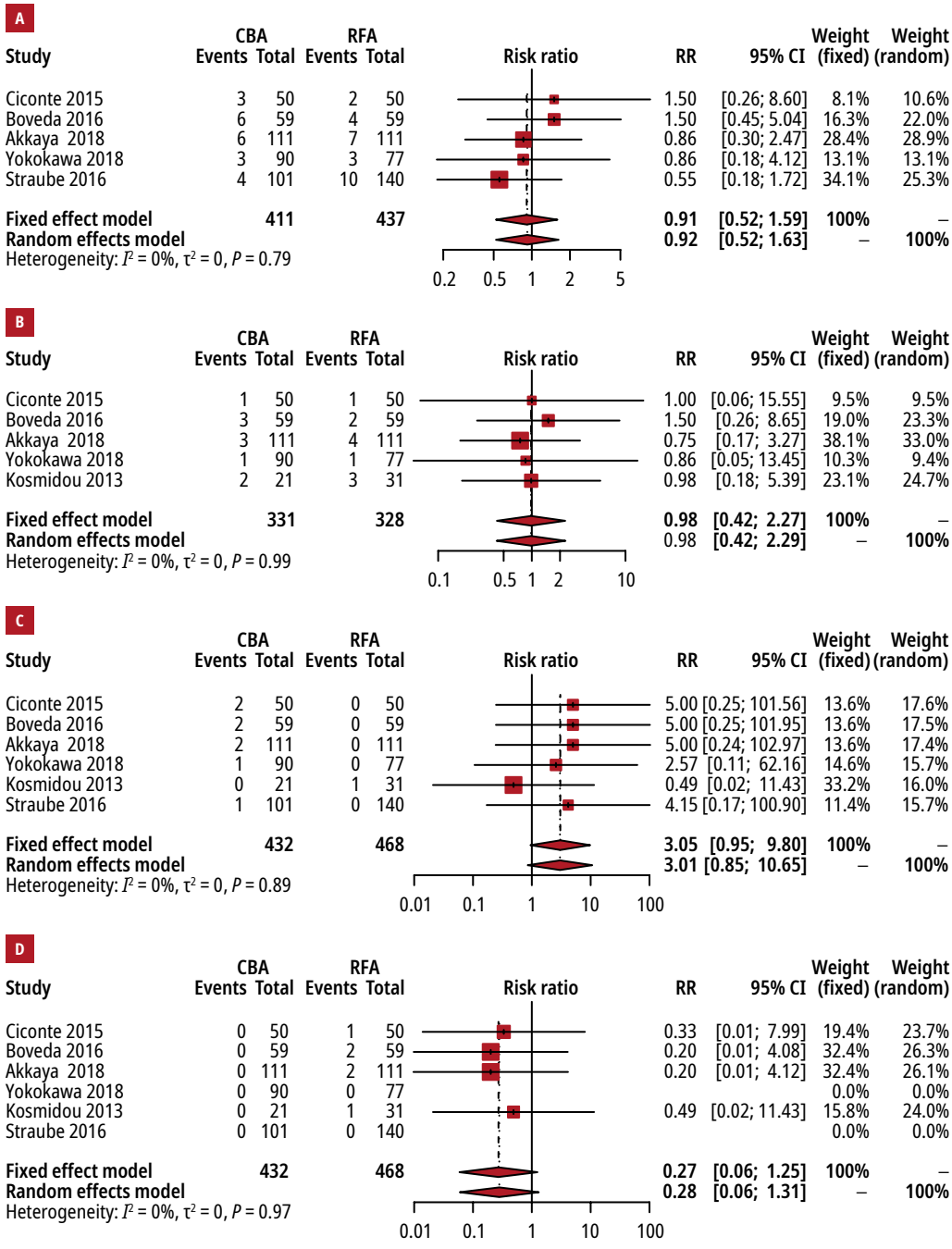

FIGURE 3 Forest plot of procedural complications (**A**), vascular complications (**B**), phrenic nerve palsy (**C**), and cardiac tamponade (**D**) for cryoballoon ablation vs radiofrequency ablation

Abbreviations: see TABLE 1 and FIGURE 2

compared with RFA. Another sizeable real-world registry study found that 11% of patients received a second ablation after RFA and 7.8% after CBA.[21] It should be noted that in terms of the repeated atrial arrhythmia type, the majority of AF cases (96%) were identified by RFA in patients with persistent AF with PVI only,[22] whereas a higher rate of atrial flutter (54.4%) was found with CBA.[23] Studies on repeat ablation identified that extra-PV triggers (63.6%) were predominant in PVI with CBA,[23] while the proportion of PV reconnection via RFA reached a striking 80% in patients undergoing repeat ablation.[22] Therefore, it was assumed that the PVI gap was often related to AF relapse instead of AT and that cryoablation was more capable of creating durable PVI than RFA and is therefore the main advantage of CBA. A small simple randomized study comparing the efficacy of the 2 energy sources in repeat ablation from paroxysmal AF showed no difference in AF recurrence at 1-year follow-up.[24] In summary, it was hypothesized that RFA could be preserved as an initial approach for repeat ablation after failed persistent

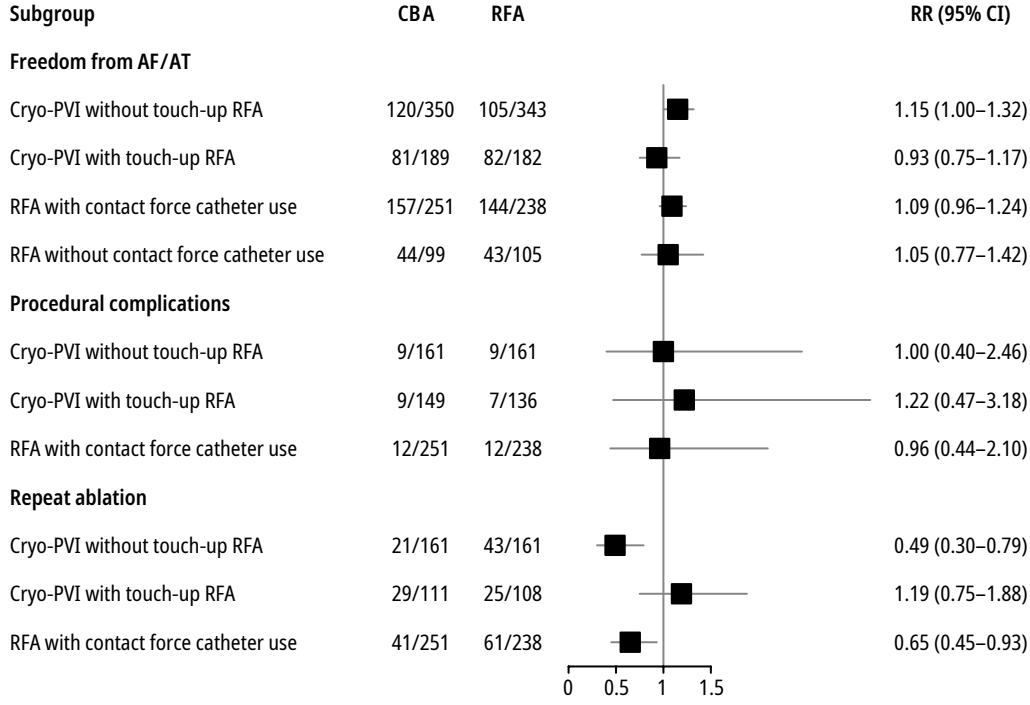

FIGURE 4 Forest plot of subanalyses for cryoballoon ablation with or without touch-up radiofrequency ablation in pulmonary vein isolation and radiofrequency ablation with or without contact-sense catheter use

Abbreviations: see TABLE 1 and FIGURE 2

AF ablation or failed cryoablation for AF, while CBA might be appropriate for recurrent AF in failed RFA for paroxysmal AF, which is commonly driven by PV triggers.

Different from paroxysmal AF, persistent AF was more pronounced in its abnormal substrate of a lower voltage area, slow conduction region, or extra-PV triggers,[25] creating challenges for ablation. Linear ablation was recommended as an adjuvant of PVI for persistent AF ablation to modify the substrate, but not at the same high level as specified in the guidelines[1,2] due to its poor performance in randomized trials.[26] It was speculated that the weak PVI in RFA obscured the benefit of linear ablation, resulting in suboptimal performance.[22] In the current analysis, a number of patients received extra linear ablation via cryoballoon. Akkaya et al[9] reported a significantly higher survival with recurrent arrhythmia in CBA (79.2%) with a cryo-achieved roofline compared with RFA (44.9%) with a fire-achieved roofline. Excitingly, the latest studies have demonstrated the feasibility of cryoballoon in posterior box isolation and improved the 1-year freedom rate from atrial arrhythmia up to about 80% in both initial and repeated ablation in patients with persistent AF.[27,28] The wider, continuous, and homogenous CBA lesions were promising for constructing larger and more reliable substrate lesions during linear ablation. However, testing the bidirectional conduction block, improving the accuracy of the adjuvant line, and establishing safety and stability of contact in linear ablation with cryoballoon remain problematic.

With respect to the safety profile, the risk of procedural and vascular access complications was comparable in CBA and RFA. Similar to paroxysmal AF analysis, an obvious trend for a higher PNP incidence (1.9%) and cardiac tamponade (1.3%) was observed in CBA and RFA groups, respectively. Yet, unlike paroxysmal AF, persistent AF itself might be associated with an enlarged left atrium, complicated substrate, variant PV ostium, increased cryoablation difficulty, or another necessary ablation besides PVI. This contributes to more procedures, longer fluoroscopy time, and higher cryoenergy doses, thus increasing the incidence of complications. Optimization of freezing doses administered during cryoablation has been investigated in several studies, which indicated that the new dosing strategy guided by the time-to-PVI resulted in fewer complications and shorter procedural time without reducing freedom survival rate as compared with conventional strategies.[29-31]

Admittedly, the present meta-analysis failed to indicate the newest advance of RFA in index ablation. A previous animal study showed the efficacy of the ablation index–guided ablation in creating transmural and durable lesions.[32] The PRAISE study (Pulmonary Vein Reconnection Following Ablation Index-guided Ablation: a Success Evaluation) demonstrated that a surprising 95% of patients with persistent AF were in SR after a single PVI with ablation index–guided ablation after 1-year follow-up.[33] In addition, durable PVI

was identified within up to 93% of PVs in a subsequent analysis of repeated ablation, comparable to 91% for CBA in the SUPIR study (Sustained PV Isolation with Arctic Front Advance).[34] This emphasized the importance of durable PVI for persistent AF. Further research is needed to compare the efficacy and safety between ablation guided by the ablation index and cryoablation with the second-generation balloon.

Limitations This meta-analysis has several limitations. First, the small simple size and non-randomized design of the included studies introduced a significant bias. Second, this meta-analysis did not reflect the new technology used in RFA, weakening the reliability of these results. Third, different adjuvant ablation strategies, such as roofline, cavotricuspid isthmus line, and other additional lines, were identified in the included studies, introducing another important bias. Further analyses based on more homogenous ablation strategies are necessary to clarify the difference between the 2 techniques. Finally, the publication bias could not be completely excluded.

Conclusions When considering persistent AF ablation, this meta-analysis demonstrated that CBA is comparable to RFA in the incidence of freedom from AF/AT and procedural complications. Cryoballoon ablation might reduce the incidence of repeat ablation, but with a higher PNP risk. Finally, CBA can be regarded as an initial treatment for patients with persistent AF. However, multicenter randomized clinical trials are needed to further verify the role of CBA in persistent AF ablation.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

ACKNOWLEDGMENTS We appreciate the help from Mr. Bai in figure editing and acknowledge International Science Editing (http://www.internationalscience-editing.com) for editing this manuscript.

CONFLICT OF INTEREST None declared.

HOW TO CITE Liu XH, Gao XF, Jin CL, et al. Cryoballoon versus radiofrequency ablation for persistent atrial fibrillation: a systematic review and meta-analysis. Kardiol Pol. 2020; 78: 20-29. doi:10.33963/KP.15048

REFERENCES

1 Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016; 18: 1609-1678.

2 Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. J Arrhythm. 2017; 33: 369-409.

3 Hindricks G, Sepehri Shamloo A, Lenarczyk R, et al. Catheter ablation of atrial fibrillation: current status, techniques, outcomes and challenges. Kardiol Pol. 2018; 76: 1680-1686.

4 Blum S, Meyre P, Aeschbacher S, et al. Incidence and predictors of atrial fibrillation progression: a systematic review and meta-analysis. Heart Rhythm. 2019; 16: 502-510.

5 Kirchhof P, Calkins H. Catheter ablation in patients with persistent atrial fibrillation. Eur Heart J. 2017; 38: 20-26.

6 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009; 339: b2535.

7 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7: 177-188.

8 Boveda S, Providência R, Defaye P, et al. Outcomes after cryoballoon or radiofrequency ablation for persistent atrial fibrillation: a multicentric propensity-score matched study. J Interv Card Electrophysiol. 2016; 47: 133-142.

9 Akkaya E, Berkowitsch A, Zaltsberg S, et al. Ice or fire? Comparison of second-generation cryoballoon ablation and radiofrequency ablation in patients with symptomatic persistent atrial fibrillation and an enlarged left atrium. J Cardiovasc Electrophysiol. 2018; 29: 375-384.

10 Guler TE, Aksu T, Yalin K, et al. Combined cryoballoon and radiofrequency ablation versus radiofrequency ablation alone for long-standing persistent atrial fibrillation. Am J Med Sci. 2017; 354: 586-596.

11 Kosmidou I, Sumayin K, Deering T, et al. Comparing safety and efficacy of irrigated radiofrequency catheter ablation versus combined cryoballoon and catheter ablation for persistent atrial fibrillation. J Atr Fibrillation. 2013; 6: 924.

12 Ciconte G, Baltogiannis G, de AC, et al. Circumferential pulmonary vein isolation as index procedure for persistent atrial fibrillation: a comparison between radiofrequency catheter ablation and second-generation cryoballoon ablation. Europace. 2015; 17: 559-565.

13 Yokokawa M, Chugh A, Latchamsetty R, et al. Cryoballoon antral pulmonary vein isolation vs contact force-sensing radiofrequency catheter ablation for pulmonary vein and posterior left atrial isolation in patients with persistent atrial fibrillation. Heart Rhythm. 2018; 15: 1835-1841.

14 Straube F, Dorwarth U, Bode F, et al. First-line catheter ablation of persistent atrial fibrillation: Comparison of radiofrequency and cryoballoon ablation. Heart Rhythm. 2016; 13 (suppl): S383.

15 Di Biase L, Burkhardt JD, Mohanty P, et al. Left atrial appendage isolation in patients with longstanding persistent AF undergoing catheter ablation: BELIEF trial. J Am Coll Cardiol. 2016; 68: 1929-1940.

16 Yorgun H, Canpolat U, Kocyigit D, et al. Left atrial appendage isolation in addition to pulmonary vein isolation in persistent atrial fibrillation: one-year clinical outcome after cryoballoon-based ablation. Europace. 2017; 19: 758-768.

17 Casella M, Dello Russo A, Russo E, et al. Biomarkers of myocardial injury with different energy sources for atrial fibrillation catheter ablation. Cardiol J. 2014; 21: 516-523.

18 Kurose J, Kiuchi K, Fukuzawa K, et al. The lesion characteristics assessed by LGE-MRI after the cryoballoon ablation and conventional radiofrequency ablation. J Arrhythm. 2018; 34: 158-166.

19 Hoffmann E, Straube F, Wegscheider K, et al. Outcomes of cryoballoon or radiofrequency ablation in symptomatic paroxysmal or persistent atrial fibrillation. Europace. 2019; 21: 1313-1324.

20 Khoueiry Z, Albenque JP, Providencia R, et al. Outcomes after cryoablation vs. radiofrequency in patients with paroxysmal atrial fibrillation: impact of pulmonary veins anatomy. Europace. 2016; 18: 1343-1351.

21 Mörtsell D, Arbelo E, Dagres N, et al. Cryoballoon vs. radiofrequency ablation for atrial fibrillation: a study of outcome and safety based on the ESC-EHRA atrial fibrillation ablation long-term registry and the Swedish catheter ablation registry. Europace. 2019; 21: 581-589.

22 Fink T, Schluter M, Heeger CH, et al. Stand-alone pulmonary vein isolation versus pulmonary vein isolation with additional substrate modification as index ablation procedures in patients with persistent and long-standing persistent atrial fibrillation: The randomized Alster-Lost-AF Trial (Ablation at St. Georg Hospital for Long-Standing Persistent Atrial Fibrillation). Circ Arrhythm Electrophysiol. 2017; 10: e005114.

23 Chang TY, Lo LW, Te ALD, et al. The importance of extrapulmonary vein triggers and atypical atrial flutter in atrial fibrillation recurrence after cryoablation: Insights from repeat ablation procedures. J Cardiovasc Electrophysiol. 2019; 30: 16-24.

24 Pokushalov E, Romanov A, Artyomenko S, et al. Cryoballoon versus radiofrequency for pulmonary vein re-isolation after a failed initial ablation procedure in patients with paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2013; 24: 274-279.

25 Teh AW, Kistler PM, Lee G, et al. Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease. J Cardiovasc Electrophysiol. 2012; 23: 232-238.

26 Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015; 372: 1812-1822.

27 Nishimura T, Yamauchi Y, Aoyagi H, et al. The clinical impact of the left atrial posterior wall lesion formation by the cryoballoon application for persistent atrial fibrillation: Feasibility and clinical implications. J Cardiovasc Electrophysiol. 2019; 30: 805-814.

28 Iacopino S, Paparella G, Capulzini L, et al. Posterior box isolation as an adjunctive ablation strategy during repeat ablation with the second-generation

cryoballoon for recurrence of persistent atrial fibrillation: 1-year follow-up. J Interv Card Electrophysiol. 2019; 56: 1-7.

29 Ferrero-de-Loma-Osorio Á, García-Fernández A, Castillo-Castillo J, et al. Time--to-effect-based dosing strategy for cryoballoon ablation in patients with paroxysmal atrial fibrillation: results of the plusONE multicenter randomized controlled noninferiority trial. Circ Arrhythm Electrophysiol. 2017; 10: e005318.

30 Aryana A, Kenigsberg DN, Kowalski M, et al. Verification of a novel atrial fibrillation cryoablation dosing algorithm guided by time-to-pulmonary vein isolation: Results from the Cryo-DOSING Study (Cryoballoon-ablation DOSING Based on the Assessment of Time-to-Effect and Pulmonary Vein Isolation Guidance). Heart Rhythm. 2017; 14: 1319-1325.

31 Chun KR, Stich M, Fürnkranz A, et al. Individualized cryoballoon energy pulmonary vein isolation guided by real-time pulmonary vein recordings, the randomized ICE-T trial. Heart Rhythm. 2017; 14: 495-500.

32 Whitaker J, Fish J, Harrison J, et al. Lesion index-guided ablation facilitates continuous, transmural, and durable lesions in a porcine recovery model. Circ Arrhythm Electrophysiol. 2018; 11: e005892.

33 Hussein A, Das M, Riva S, et al. Use of ablation index-guided ablation results in high rates of durable pulmonary vein isolation and freedom from arrhythmia in persistent atrial fibrillation patients. Circ Arrhythm Electrophysiol. 2018; 11: e006576.

34 Reddy VY, Sediva L, Petru J, et al. Durability of pulmonary vein isolation with cryoballoon ablation: results from the Sustained PV Isolation with Arctic Front Advance (SUPIR) study. J Cardiovasc Electrophysiol. 2015; 26: 493-500.