

CLINICAL REVIEW

Left atrial appendage isolation in atrial fibrillation catheter ablation: A meta-analysis

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Abstract

A significant proportion of patients' experience recurrence of atrial fibrillation (AF) despite pulmonary venous isolation (PVI), especially those with persistent AF. Isolation of the left atrial appendage (LAA) may reduce AF recurrence. The aim of this study was to assess the efficacy of LAA isolation in addition to PVI compared with PVI alone. We conducted a comprehensive search of electronic databases, up to April 21st, 2017, for all studies comparing the effect LAA electrical isolation or ligation in addition to PVI, as opposed to PVI alone, on the recurrence of atrial fibrillation after catheter ablation. We used random-effects meta-analysis models to summarize the studies. One RCT and four observational studies enrolling 781 patients were retained. Four studies assessed the added effect of LAA catheter ablation, and one study evaluated the effect of LAA ligation with the aim of LAA electrical isolation. Four studies exclusively enrolled patients with persistent atrial fibrillation and one study predominantly enrolled patients with persistent atrial fibrillation. Follow-up ranged from 12 to 15 months. The addition of LAA isolation to PVI reduced AF recurrence compared with the latter alone (odds ratio (OR) = 0.19; 95% confidence intervals (CI) = 0.10-0.37; $P < 0.00001$). Left atrial appendage isolation was also associated with a reduction in AF recurrence after repeat ablation (OR = 0.40; CI = 0.25-0.65; $P = 0.0003$). The addition of LAA isolation to PVI was associated with a decrease in AF recurrence in patients with persistent AF. Further studies are needed to assess the effect on long-term risk of stroke.

KEYWORDS

atrial fibrillation, catheter ablation, left atrial appendage isolation, meta-analysis, pulmonary vein isolation

1 | INTRODUCTION

Catheter ablation is an established therapeutic modality for rhythm control of symptomatic atrial fibrillation (AF).¹⁻³ Electrical isolation of

the pulmonary veins (PVI) is effective in improving symptoms^{4,5} and is the cornerstone of AF catheter ablation.^{1,2} Despite improvements in catheter ablative techniques, the AF recurrence rate remains relatively high.^{6,7} This is especially true in patients with persistent AF

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where recurrence rates of 34% at 1 year and 52% at 2-year follow-up have been shown.^{8,9} Strategies targeting other AF triggers have thus far proven to be of limited success.^{9–12}

The left atrial appendage (LAA) represents a potential arrhythmic substrate. Takahashi et al¹³ originally identified the LAA as a trigger and substrate for AF maintenance after pulmonary vein isolation (PVI), with several case reports and case series confirming this proarrhythmic role.^{14–16} Studies have demonstrated the feasibility of targeting the LAA during catheter ablation^{17,18} and during surgical ablation^{19,20} with current guidelines recommending closure of the LAA during surgical AF ablation.²¹ Ligation of the LAA by the LAR-IAT suture delivery device has also been shown to reduce LAA voltage and capture during pacing²² as well as AF burden.²³ Similar to surgical ligation, LAA ligation may alter the ganglionated plexi of the autonomic nervous system in the epicardial fat which may reduce atrial fibrillation paroxysms.²⁴ In addition, epicardial ligation of the LAA is associated with lower levels of neurohormonal activation and systemic blood pressure of compared to endocardial LAA closure.²⁵ Mechanistically, ischemic necrosis of the LAA will develop leading to its electrical isolation.²² This contrasts with surgical isolation in which tissue ingrowth leads to encapsulation from adjacent structures, a more prolonged process.²⁶ Catheter ablation of the LAA is undertaken by either radiofrequency or cryoablation and should be performed with caution given the thin wall of the LAA that may be prone to perforation.²⁷ Ligation of the LAA has the advantage of decreasing thrombus formation in the LAA.²⁸

The electrical isolation of the LAA by catheter ablation as well as percutaneous-based LAA ligation represents potential options to improve freedom from AF recurrence. The aim of this study was to assess the efficacy and safety of LAA isolation, through catheter ablation or ligation. To this end, we performed a systematic review and meta-analysis.

2 | METHODS

2.1 | Data sources and searches

This systematic review was performed according to the guidelines described in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement²⁹ and the MOOSE checklist.³⁰ We systematically searched, with no language restriction, PubMed, the Cochrane Library, Web of Science and Scopus and MEDLINE for articles published from inception through April 21st, 2017. We used permutations of the terms atrial fibrillation, left atrial appendage, catheter ablation and electrical isolation to identify potential studies for inclusion. Hand searching with cross-references of retrieved publications, review articles and guidelines was also performed to ensure the inclusion of all relevant studies.

2.2 | Study selection

Two authors (A.A.T. and A.D.) independently performed the initial screening of titles and abstracts to identify potentially relevant

articles. Review articles, case reports, meeting abstracts and duplicates were excluded. In addition, articles assessing the surgical ligation of the LAA were also excluded as this topic has been relatively well studied and is beyond the scope of this study. The full text of selected articles was independently assessed by two authors (A.A.T. and A.D.) to determine relevance for inclusion. Conflicts were resolved by discussion between the assessors, and it was arranged that any disagreement is resolved by discussion with the senior author (V.E.).

Eligibility criteria for included studies were decided a priori. RCT and cohort studies were included if they fulfilled all the following criteria: (a) assessed the effect of LAA isolation or ligation; (b) included a comparator arm of PVI; and (c) reported AF-free survival in both groups.

2.3 | Data extraction

Two investigators (A.A.T. and A.D.) independently extracted information on study characteristics (author, study type and publication year), duration of follow-up (mean, median or maximum number of follow-up), sample size, sex, mean age, atrial fibrillation type and duration, left atrial size or diameter, diabetes mellitus, hypertension, coronary artery disease, and mean left ventricular ejection fraction (LVEF). Disagreements were resolved by consensus.

Outcomes of interest were:

1. Recurrence of atrial tachycardia/atrial fibrillation after initial ablation
2. Recurrence of atrial tachycardia/atrial fibrillation after repeat ablation
3. All reported periprocedural adverse events
4. Periprocedural and long-term thromboembolic events

2.4 | Quality assessment

We used the Newcastle-Ottawa Scale to evaluate the quality of the included studies on three broad perspectives: selection of the study groups, the comparability of the groups, and the ascertainment of exposure and outcome of interest. Nine points were available to be awarded based on (a) representativeness of the exposed cohort, (b) selection of nonexposed cohort, (c) exposure ascertainment, (d) the absence of the outcome of interest at study onset, (e) study controls for left atrial size, (f) study controls for other factors, (g) assessment of outcome, (h) follow-up long enough for outcomes to occur, and (h) outcome of controls adequacy. Studies were categorized as either: (a) high quality: seven to nine points; (b) fair quality: four to six points; or (c) poor quality: zero to three points.

2.5 | Statistical analysis

We calculated odds ratios and 95% confidence intervals for all studies. The odds ratios were then pooled using a DerSimonian and Laird random-effects model.³¹ Peto odds ratio was used if there were less

than ten events in both groups. Publication bias was assessed visually using a funnel plot and quantified using Egger's test for small study effects. Heterogeneity among studies was examined with the I^2 test. Statistical analyses were carried out using StatsDirect version 3 (England: StatsDirect Ltd. 2013). We conducted an influence analysis with sequential exclusion of individual studies.

3 | RESULTS

3.1 | Study selection

The search strategy led to the retrieval of 3030 citations from electronic database and manual searches as shown in Figure S1. We reviewed 19 citations for full-text articles; five full-text articles were included in final analysis.^{27,32–35} Of the five included studies, one was a randomized clinical trials,³² three were prospective cohort studies,^{27,33,34} and one was a retrospective cohort study.³⁵

3.2 | Quality assessment

Four studies were classified as high quality, and one was classified as fair quality using the nine parameters of the Newcastle-Ottawa scale (Table S1).

3.3 | Baseline characteristics

Four studies compared LAA isolation in addition to PVI compared to PVI alone.^{27,32,34,35} Nonpulmonary triggers, such as the posterior wall of the left atrium, the coronary sinus and the superior vena cava, were similarly ablated in both groups at the operators' discretion. Three studies required further entry criteria in the form of firing from the LAA²⁷ and at least one risk factor for stroke.^{33,34,36} One study also involved occlusion of the LAA in addition to PVI to reduce stroke risk.³⁴ Lakkireddy et al³³ examined the effect of LAA ligation in addition to PVI vs PVI alone, on AF recurrence. LAA isolation by catheter ablation was not performed in this study. Non-PV triggers were also similarly ablated in both groups.

In the five included studies, 781 patients were enrolled. There was a total of 441 patients in the PVI + LAA isolation/ligation arm and 340 patients in the PVI alone arm. Baseline characteristics in all studies were comparable in both groups. Study and baseline patient characteristics in the individual studies are shown in Tables 1 and 2, respectively. Four studies included patients with predominantly LSPAF,^{27,32–34} one study was conducted in predominantly persistent AF.³⁵ The duration of follow-up ranged from 12 to 15 months. The average duration of AF pre-intervention ranged from 25 to 90 months in PVI + LAAI group and 24–83 months in PVI-alone group. Of the four studies that used LAA isolation, three were performed using radiofrequency ablation^{27,32,34} and one using cryoballoon ablation.³⁵ In the study by Panniker et al,³⁴ LAA isolation was followed by occlusion of the LAA using the WATCHMAN device.

3.4 | Arrhythmia recurrence

The addition of LAA isolation to PVI reduced AF recurrence compared to the latter alone at 12- to 15-month follow-up (odds ratio (OR) = 0.23; 95% confidence intervals (CI) = 0.14–0.38; $P < 0.00001$; Cochran $Q = 7.54$, $P = 0.11$; $I^2 = 46\%$) as demonstrated in Figure 1. There was no difference in the results after influence analysis (Table S2). One study, which included patients with paroxysmal AF and was the only study with fair quality, caused the heterogeneity but there was no difference in the final results with its exclusion.²⁷ Two studies provided data on AF recurrence after repeat catheter ablation.^{32,33} The addition of LAA isolation was associated with a reduction in AF recurrence after repeat ablation (OR = 0.40; CI = 0.25–0.65; $P = 0.0003$) (Figure 2). There was no asymmetry in the funnel plot to suggest publication bias, and Egger's test was not significant for publication bias (Figure S2).

3.5 | Complications

One periprocedural ischemic stroke event occurred in all LAA intervention groups compared to two periprocedural transient ischemic attacks and six periprocedural ischemic strokes in the PVI only

TABLE 1 Baseline study characteristics

Study first author (y)	Type	Procedure	Comparator	Follow-up (mo)	Primary endpoint	Mode of Follow-up
Di Biase (2010)	Prospective cohort	LAAI + PVI	PVI	15	AF recurrence	Holter monitor and event recorder
Di Biase (2016)	Randomized clinical trial	LAAI + PVI	PVI	12	AF recurrence	Holter monitor and event recorder
Lakkireddy (2015)	Prospective cohort	LAA ligation (LARIAT) + PVI	PVI	12	AF recurrence	History, ECG and event recorder
Panniker (2016)	Prospective cohort	LAAI + LAA Occlusion (WATCHMAN) + PVI	PVI	12	Successful LAA electric isolation and occlusion. (AF recurrence was a secondary end point)	Holter monitor
Yorgun (2017)	Retrospective cohort	LAAI + PVI (CB)	PVI (CB)	12	AF recurrence	History, ECG and Holter monitor

LAAI, left atrial appendage isolation; PVI, pulmonary vein isolation; AF, atrial fibrillation; ECG, electrocardiogram; CB, cryoballoon.

TABLE 2 Baseline patient characteristics

Study first author	Number		Age (y)		Male		Mean LVEF		AF type		AF duration		LA diameter/ Size		CAD (%)		HTN (%)		DM (%)	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Di Biase (2010)	167	43	64	61	73	74	59	58	PAF 13 PER 23 LSP 64	PAF 28 PER 23 LSP 49	90	83	43	41	-	-	47	40	8	7
Di Biase (2016)	85	88	64	64	75	73	54	55	LSP 100	LSP 100	-	-	48	48	20	19	58	60	17	18
Lakkireddy (2015)	69	69	67	67	48	48	53	53	LSP 100	LSP 100	52	52	50	48	20	12	51	54	20	18
Panikker (2016)	20	40	68	67	65	65	-	-	PER/LSP 100	PER/LSP 100	25	24	46	45	-	-	-	-	-	-
Yorgun (2017)	100	100	57	57	48	49	65	65	PER 90 LSP 10	PER 91 LSP 9	60	60	44	43	16	15	33	36	20	18

A = left atrial appendage isolation + pulmonary vein isolation.

B = pulmonary vein isolation alone.

LVEF, left ventricular ejection fraction; AF, atrial fibrillation; LA, left atrium; CAD, coronary artery disease; HTN, hypertension; DM, diabetes mellitus; PAF, paroxysmal atrial fibrillation; PER, persistent; LSP, long-standing persistent.

Recurrence of atrial fibrillation after catheter ablation in persistent atrial fibrillation

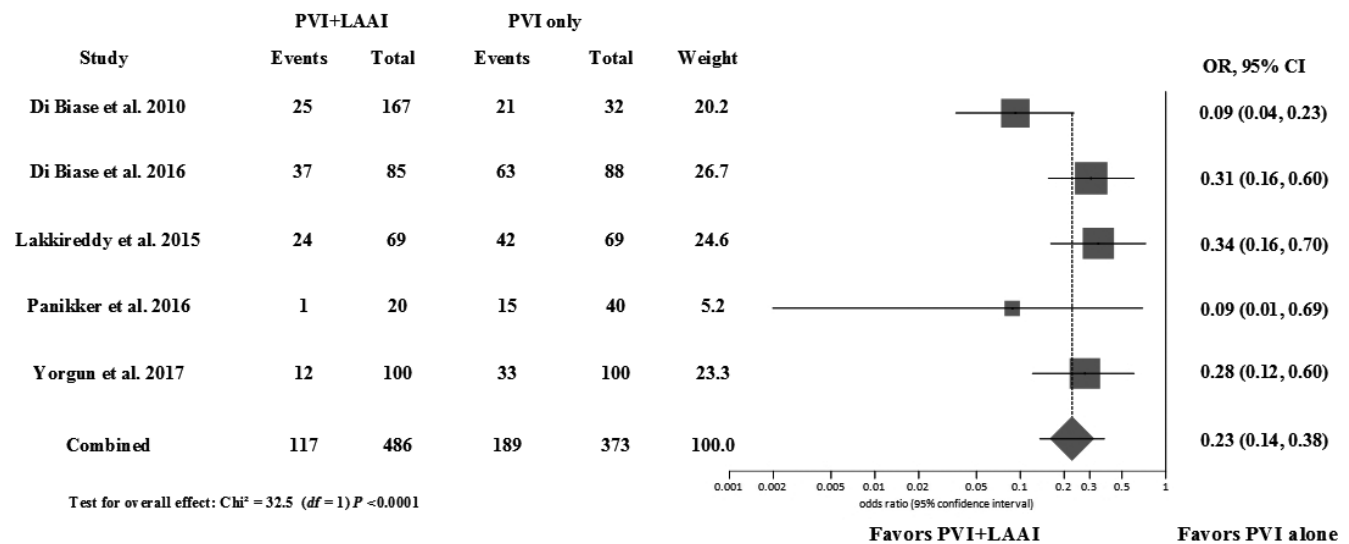


FIGURE 1 Forest plot of recurrence events of atrial fibrillation at 12- to 15-mo follow-up comparing PVI + LAA isolation/ligation vs PVI alone. PVI, pulmonary vein isolation; LAAI, left atrial appendage isolation; OR, odds ratio; CI, confidence interval

group. LAA isolation with PVI was associated with less periprocedural cerebrovascular (transient ischemic attack and ischemic stroke) events than PVI alone (Peto: OR, 0.21; 95% CI, 0.06-0.78; $P = 0.02$; $I^2 = 0\%$; Figure 3). None of the included studies reported on long-term cerebrovascular events. All reported adverse events are summarized in Table 3. The difference between the 2 groups was not statistically significant (Peto: OR, 0.39; 95% CI, 0.13-1.10; $P = 0.07$; $I^2 = 14\%$; Figure 3).

4 | DISCUSSION

We found that the addition of LAA isolation by catheter ablation or ligation to PVI is associated with an 80% reduction in the odds of AF

recurrence in patients with persistent and LSPAF. This approach may help reduce AF recurrence after PVI in persistent AF.^{9,10} Our analysis demonstrates a robust benefit as shown in the influence analysis despite relatively small sample sizes. All studies demonstrated more than 65% reduction in the odds of AF recurrence.^{27,32-35}

Current guidelines give a class 2A recommendation for catheter ablation of persistent AF in patients who remain symptomatic despite antiarrhythmic drug therapy.^{2,37} This meta-analysis demonstrates a significant reduction in AF recurrence in patients with persistent AF who underwent LAA isolation in addition to PVI. In a worldwide survey, over 40% of patients undergoing ablation for persistent or LSPAF had lower success rates as compared to patients with paroxysmal AF (PAF).³⁸ Given that at least 30% of patients with persistent AF have identifiable triggers in the LAA region,³⁹ these

Recurrence of atrial fibrillation after repeat catheter ablation

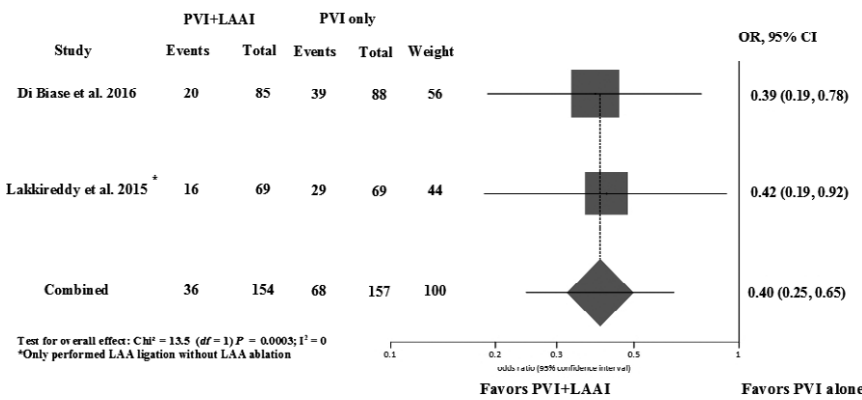
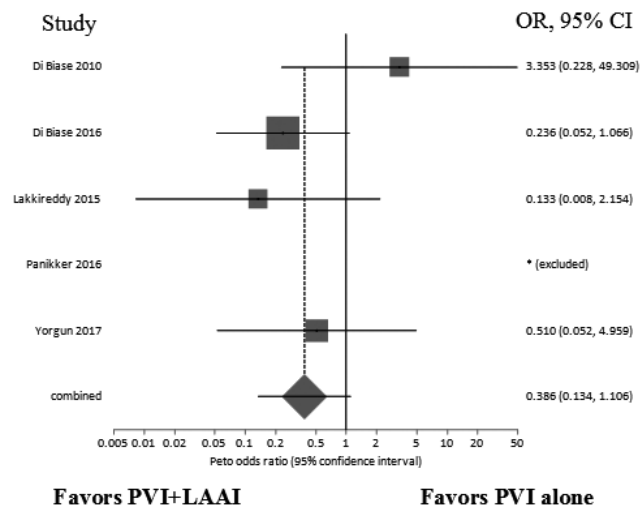


FIGURE 2 Forest plot of recurrence of AF comparing PVI + LAA isolation/ligation vs PVI alone after repeat procedures. PVI, pulmonary vein isolation; LAAI, left atrial appendage isolation; OR, odds ratio; CI, confidence interval

Total adverse events



Thromboembolic events

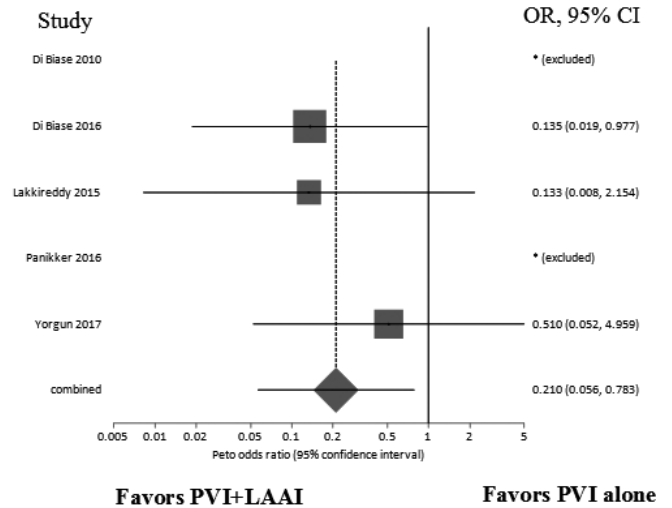


FIGURE 3 Forest plots of reported thromboembolic events and all reported adverse events in PVI + LAA isolation/LAA ligation vs PVI alone. PVI, pulmonary vein isolation; LAAI, left atrial appendage isolation; OR, odds ratio; CI, confidence interval

TABLE 3 Adverse events

Study first author	Reported adverse events	
	PVI + LAAI	PVI alone
Di Biase (2010)	4 (1.8%) pericardial effusions requiring pericardiocentesis	No reported complications
Di Biase (2016)	1 (1%) pericardial effusions	4 (4.5%) patients had ischemic stroke 1 (1%) pericardial effusions 1 (1%) gastrointestinal bleed
Lakkireddy (2015)	No reported complications	Two (3%) patients had a transient ischemic attack
Panikker (2016)	No major periprocedural complications	No major periprocedural complications
Yorgun (2017)	1 (1%) patients had ischemic stroke	2 (2%) patients had ischemic stroke

LAAI, left atrial appendage isolation; PVI, pulmonary vein isolation.

LAA triggers may be an important source of recurrent AF in patients with persistent AF at index and repeat ablation procedures.¹⁷

The benefit of LAA ligation is in line with the benefits of LAA isolation seen in the other included studies and the overall meta-analysis, indicating the effectiveness of this technique in isolating the LAA. Lakkireddy et al³³ demonstrated a reduction in AF recurrence as well as a decreased need for repeat ablation in the LAA group. LAA ligation leads to an acute infarct of the tissue and eventual fibrosis of the LAA²² which results in the electrical isolation of the LAA from the rest of the left atrium. The aMAZE trial is an ongoing study to assess the incremental benefit of catheter-based LAA ligation procedure as an adjunctive therapy to PVI for persistent or LSPAF (NCT02513797).

This meta-analysis shows that the benefits attained with LAA isolation occur without an increase in acute complications. However, none of the studies reported the long-term risk of thromboembolic events. The major concerns of the use of LAA ablation are increased thromboembolic risk, perforation, and phrenic nerve injury.⁴⁰ LAA

isolation may lead to the formation of thrombus in the LAA due to decreased contractility.^{18,41} At odds with this hypothesis, Di Biase et al³² and Park et al¹⁸ showed that 50% of patients have flow velocity in the LAA that is within the normal range after LAA isolation. Di Biase et al²⁷ also demonstrated an absence of LAA thrombus after distal LAA isolation on TEE after 3 and 6 months postisolation. Distal isolation is performed by circumferential ablation at the ostium of the LAA. Furthermore, a large proportion of these patients have an ongoing indication for anticoagulation due to their CHADS-VASc score >2 regardless of having undergone LAA isolation.⁴¹ In contrast, Rillig et al found that 21% of patients developed an LAA thrombus after LAA ablation despite 90% of patients receiving oral anticoagulation at the time. However, LAA ablation in this study included electrical isolation of the LAA base using bidirectional block of both an anterior and mitral isthmus line, which may explain the increased stroke risk.⁴² On the other hand, all studies included in this meta-analysis made use of distal LAA isolation. Anticoagulation should be continued after the procedure, although concomitant ligation of the LAA may provide the added benefit of preventing thrombus formation and reducing the need for anticoagulation.⁴⁰ Given the theoretical increased risk of stroke due to decreased contraction of the LAA, transesophageal echocardiography is usually performed around 6 months after the ablation to rule out the presence of thrombus.^{6,41} Reassuringly, there were no transient ischemic attacks or strokes in the LAA isolation groups, although long-term follow-up was limited.

Electrical isolation of the LAA may be technically challenging. Given the thin wall of the LAA, there is a risk of perforation with subsequent pericardial effusion which was seen in 1.8% of cases in the study by Di Biase et al²⁷ Acute reconnections requiring further intraprocedural ablation are not uncommon occurring in 85% of patients in the study by Panikker et al³⁴ However, in patients with arrhythmia recurrence requiring redo ablation, none showed recurrence of firing in the LAA.³⁴

Caution must be taken in the interpretation of these results. Most of the studies included were observational, had a very limited number of participating centers, and had the procedure performed at the hands of very experienced operators. The findings of this study should therefore be considered hypothesis generating and highlight the need for multicenter, randomized studies with blinded adjudication of endpoints. Our results are consistent with an earlier meta-analysis that included studies assessing surgical excision of the LAA, which represents a distinct therapeutic approach for a different patient population, as well as a study evaluating left atrial anterior wall ablation.⁴³

4.1 | Limitations

There are several potential limitations to our meta-analysis. First, there is only one randomized study included, and therefore, the major effect seen is from observational studies with a variation in design. Second, the number of studies as well as the number of patients included in each of the studies is small and there were differences between baseline characteristics in the different studies,

although characteristics were similar in comparative groups. Third, intraprocedural differences related to operators' experience may have occurred between studies and centers. In addition, there was some uncertainty regarding the actual ablation approaches in some studies. Fourth, although no clear publication bias was demonstrable, the current tools for the assessment of publication bias are likely underpowered given the small number of studies. Finally, long-term follow-up, especially with regard to stroke risk, is needed to demonstrate the safety of this technique.

5 | CONCLUSIONS

The addition of LAA isolation to PVI was associated with decreases in AF recurrence in patients with persistent AF. Large, multicenter randomized studies are needed to confirm this benefit. Future research is required to elucidate the impact of LAA isolation on long-term risk of stroke.

CONFLICT OF INTERESTS

Dr Essebag has received honoraria from Abbott, Biosense Medical, Boston Scientific, and Medtronic.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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