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LAA Electrical Isolation for Treatment of Recurrent Atrial Fibrillation

A Meta-Analysis

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ABSTRACT

OBJECTIVES The authors sought to perform a meta-analysis of controlled studies assessing the relationship between left atrial appendage (LAA) electrical isolation (EI) and recurrent atrial fibrillation (AF).

BACKGROUND LAA triggers could play an important role in AF and can be treated with complete EI of the LAA via surgical or percutaneous approaches.

METHODS We conducted a meta-analysis of all controlled studies published as of November 21, 2016, assessing the relationship between LAA EI (LAAEI) and recurrent AF. The primary endpoint was atrial tachycardia (AT) or AF recurrence after the post-procedure blanking period. The association between LAAEI and AT/AF was estimated using random-effects modeling. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the DerSimonian and Laird method.

RESULTS We identified 7 studies including 1,037 patients; LAAEI was performed in 566 patients (55%). LAAEI was associated with a significantly lower rate of AT/AF recurrence in the primary analysis (OR: 0.38; 95% CI: 0.16 to 0.90; $p = 0.02$). The association between LAAEI and recurrent AT/AF was strongest in a sensitivity analysis restricted to studies of percutaneous LAAEI (OR: 0.22; 95% CI: 0.11 to 0.46; $p < 0.001$; 5 studies, n = 623 patients). LAAEI was not associated with thromboembolism (OR: 0.50; 95% CI: 0.18 to 1.39; $p = 0.18$; n = 5 studies, n = 767 patients), although these studies either incorporated LAA occlusion (3 studies, n = 552 patients) or follow-up echocardiography to assess LAA function (2 studies, n = 215 patients) to inform antithrombotic strategies.

CONCLUSIONS LAAEI is associated with a significant reduction in recurrent AT/AF. Randomized trials are required to confirm the efficacy and long-term safety of LAAEI and to determine the optimal concomitant antithrombotic strategy. (J Am Coll Cardiol EP 2017;■:■–■) © 2017 by the American College of Cardiology Foundation.

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AT = atrial tachycardia

CI = confidence interval

LAA = left atrial appendage

LAAEI = left atrial appendage electrical isolation

OR = odds ratio

PV = pulmonary vein

SR = sinus rhythm

TEE = transesophageal echocardiography

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with substantial symptoms, morbidity (heart failure, myocardial infarction, and stroke), and mortality (1). The substantial public health impact of AF has made the development of successful treatment strategies a priority. Early work (2) demonstrated that AF is frequently triggered by ectopic activity originating from the pulmonary veins (PVs); this observation led to the development of the modern AF ablation, which involves the electrical isolation of the PVs from the left atrial chamber. Although PV isolation can achieve long-term maintenance of sinus rhythm (SR), patients with nonparoxysmal AF and structural heart disease experience frequent recurrences of AF, and only ≈50% are AF free after 1 year (3). These recurrences are likely caused by a combination of PV reconnection and non-PV triggers. Many studies (3-7) have assessed adjunctive ablation of fractionated electrograms, rotors, and empiric linear lesions, but to date, the most rigorous studies have not clearly identified the best approach to AF ablation.

Recently, the left atrial appendage (LAA) has received increasing attention as a potentially important source of AF triggers, particularly among patients with structural heart disease, nonparoxysmal AF, and AF recurrence after AF ablation (8,9). LAA electrical isolation (LAAEI) has been proposed as a viable adjunctive strategy to PV isolation, although data are limited. LAAEI can be performed with catheter ablation, surgical excision, or via the LARIAT (SentreHEART, Inc., Redwood City, California) exclusion (which infarcts the LAA). Concerns regarding limited evidence on safety (e.g., thromboembolism) and efficacy have limited the adoption of routine LAAEI at most centers. Herein, we report the results of a meta-analysis assessing LAAEI versus no LAAEI as an adjunctive strategy to PV isolation for maintenance of SR.

METHODS

This meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.

LITERATURE SEARCH. An electronic PubMed literature search was performed by 3 of the study investigators (D.J.F., E.W.B.-M., A.S.B.) on November 21, 2016, using the broad search terms of *atrial fibrillation*, *left atrial appendage*, and *catheter ablation*. No filters were applied. All resulting abstracts were manually screened with subsequent full review of candidate study manuscripts. Clinicaltrials.gov was searched to identify relevant ongoing or unpublished clinical trials. We additionally reviewed the bibliography from each included study to identify relevant studies not identified by other strategies.

STUDY SELECTION. We included all randomized and nonrandomized studies that 1) compared outcomes among patients with and without LAAEI and 2) reported freedom from atrial tachycardia (AT)/AF after a 2- to 3-month blanking period. We included studies in which LAAEI occurred via catheter ablation, LARIAT exclusion, or surgical amputation (**Figure 1**). We excluded case reports, case series, single-armed studies of LAAEI without a comparison group, and studies that included patients with WATCHMAN (Boston Scientific, Natick, Massachusetts) LAA occlusion only, because there is no evidence that WATCHMAN occlusion leads to electrical isolation. We additionally excluded surgical studies in which LAA occlusion was performed via clipping without amputation or heterogeneous or vague methods, because the extent of LAAEI could not be clearly determined in these situations. All studies were reviewed individually by 3 investigators (D.J.F., E.W.B.-M., A.S.B.) and selected on the basis of consensus, with additional consultation, as needed, by a fourth investigator (J.P.P.).

DATA EXTRACTION. All included studies were reviewed by 2 investigators (D.J.F. and E.W.B.-M. or A.S.B.) using a standardized data acquisition form generated specifically for this study by 2 investigators (D.J.F., J.P.P.). Disagreements were resolved through discussion or consultation with a third investigator (J.P.P.). The primary outcome for this study was freedom from AT/AF after a blanking period. Thromboembolism (stroke or transient ischemic attack) was a secondary outcome. When available, periprocedural outcomes were additionally examined. Details regarding post-LAAEI ambulatory monitoring protocols were documented and are reported in **Table 1**.

OUTCOME DEFINITIONS. A recurrence of AT/AF was defined as AT or AF documented on either standardized or clinically driven ambulatory monitoring after a 2- to 3-month post-procedure blanking period. A minimum AT/AF duration of 30 s (11-15) or 32 s (8) was specified in all but 1 study (10). A thromboembolic event was classified clinically by the treating physician, and the definition was not standardized.

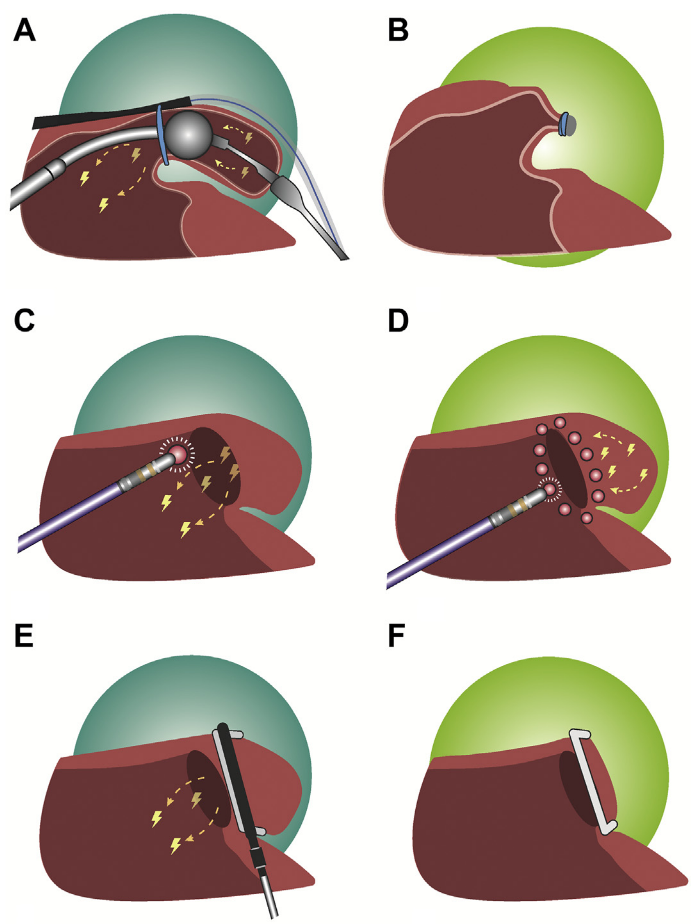
STATISTICAL ANALYSES. We performed random-effects modeling and evaluated the relationship between LAAEI and recurrent AT/AF using the method of DerSimonian and Laird to compute odds ratios (ORs) with 95% confidence intervals (CIs) based on event counts. Sensitivity analyses were performed by serial exclusion of individual studies, with additional analyses based on procedure characteristics, including method of LAAEI and concomitant LAA excision or closure. When no events were observed in both groups, a 1 was added to each group's count to allow for analysis (16); this approach was not possible for the study by Panikker et al. (13) because of differences in the size of the study arms. Heterogeneity between studies was assessed with the I^2 index (17) and τ^2 values. To assess for the possibility of reporting bias, funnel plots were generated by plotting the standard error versus the DerSimonian and Laird log OR for each study. Analyses were conducted with Comprehensive Meta-Analysis Software (BIOSTAT, Englewood, New Jersey). All tests were 2-tailed, and a p value of <0.05 was considered statistically significant.

RESULTS

STUDY SUMMARY. A total of 537 abstracts were identified via PubMed and reviewed. Seven studies were identified that reported on AT/AF recurrence after LAAEI and did not meet any exclusion criteria (**Figure 2**): 6 were identified from the PubMed search (8,10,12-15) and 1 was from a bibliography search (11). LAAEI was achieved via catheter ablation in 4 studies (8,14,13,12), LARIAT exclusion in 1 study (11), and surgical excision in 2 studies (10,15). Two studies were randomized controlled trials (12,15), and the remainder were observational studies with control comparator groups (**Table 1**) (8,10,11,13,14). The ablation strategy in all studies included PV isolation (or reisolation) with adjunctive ablation that varied by study. All studies used arrhythmia monitoring protocols with adjunctive clinically indicated monitoring. Key details regarding each study are presented in **Table 1**.

PATIENT CHARACTERISTICS. A total of 1,037 patients were included; LAAEI was performed in 566 (55%). The majority (60%, n = 623) of patients underwent percutaneous ablation, and 349 patients (34%) were from a randomized trial. Patients were generally older men and had hypertension, nonparoxysmal AF, a preserved ejection fraction, and an enlarged left atrium. The baseline characteristics of the study patients, when stratified by study and LAAEI versus no LAAEI, are detailed in **Table 2**.

FIGURE 1 Procedures Leading to Electrical Isolation of the LAA



(A) Left atrial appendage (LAA) occlusion using the LARIAT is achieved by securing a suture at the neck of the LAA, which results in acute occlusion and infarction of the LAA. **(B)** Suture-induced infarction of the LAA typically results in eventual regression of the LAA, which leaves a small residual LAA stump and sometimes a diminutive LAA remnant. Circumferential radiofrequency ablation around the LAA ostium **(C)** can lead to conduction block, with preservation of the distal LAA tissue **(D)**, analogous to when circumferential ablation is performed around the ostia of the pulmonary veins. Successful ablation-based LAAEI is associated with impaired LAA mechanical function, because the atrial depolarization wave front can no longer reach the LAA. Surgical LAA occlusion **(E)** of the LAA with the AtriClip (AtriCure, West Chester, Ohio) leads to acute closure and infarction of the LAA, with a small residual stump **(F)**. Surgical LAA occlusion can cause electrical isolation of the LAA with other approaches, including oversewing and amputation (not shown).

RECURRENT ATRIAL ARRHYTHMIAS AFTER LAAEI. Recurrent AT/AF was significantly less common among patients who received LAAEI than among those who did not (OR: 0.375; 95% CI: 0.164 to 0.895; p = 0.02) (**Figure 3**). Heterogeneity was noted for the primary endpoint ($I^2 = 87.1$; $\tau^2 = 1.054$). A plot of the standard error versus the DerSimonian and Laird log OR for the primary endpoint for each study suggested the possibility of bias (Online Figure 1). In a series of

TABLE 1 Controlled Studies Comparing LAAEI vs. No LAAEI for Maintenance of SR

First Author	Year	LAAEI (n)	Control (n)	Study Design	Study Description	Arrhythmia Follow-Up Protocol	Arrhythmia Endpoint	Mean Follow-Up (Months)
Di Biase (8)*	2010	167	43	Retrospective observational	Patients with LAA triggers during redo AF ablation managed with no ablation, LAAEI, or focal ablation	Holter (48 h or 7 d) was obtained at 3, 6, 9, 13, and 15 months after ablation. Pts had event recorder for 5 months and had periodic asymptomatic transmissions per protocol	AT/AF >32 s after 2-month blanking period	12
Lee (10)	2014	119	119	Retrospective observational study with propensity matching	Mitral valve surgery with cryomaze ± LAA excision at the surgeon's discretion	ECG at 1, 3, 6, 12, 24, and 36 months. Holter used for asymptomatic patients, but use was not standardized	AF/AT after 3-month blanking period†	62
Lakkireddy (11)	2015	69	69	Prospective observational with matched control subjects	Prospective arm underwent LARIAT LAA occlusion followed by AF ablation during a separate procedure	2-month event monitor beginning 2 weeks post procedure, 7-day monitor at 6- and 12-month visits, or additionally as clinically indicated. Device interrogation (when applicable) at 2-, 6-, and 12-month clinic appointments	AT/AF >30 s after 2-month blanking	12
Di Biase (12)	2016	85	88	Randomized trial	LAAEI vs. no LAAEI at the time of AF ablation	Holter (48 h or 7 d) at 3, 6, 9, 12, and 15 months post ablation with event recorder for symptomatic evens and periodic asymptomatic transmissions	AT/AF >30 s after 12-week blanking period	24
Panikker (13)	2016	20	40	Prospective observational with matched control subjects	LAAEI with WATCHMAN occlusion at the time of AF ablation compared to AF ablation alone	7-d continuous ECG monitoring at 3, 6, 9, and 12 months	AT/AF >30 s after 3-month blanking period	12
Park (14)‡	2016	18	24	Retrospective observational	Stepwise approach to AF ablation, with reporting of those with and without LAAEI at the conclusion of the procedure	Holter monitoring (48 h) at 3, 6, 9, and 12 months after ablation	>30 s AT/AF after 3-month blanking period	21
Romanov (15)	2016	88	88	Randomized trial	Surgical AF ablation (PV isolation, box lesion, ganglionated plexi ablation) ± LAA excision	Holter at 3, 6, 9, 12, and 18 months with implantable monitors in ≈80%	>30 s recurrent atrial arrhythmia after 3-month blanking period	18

Value are n. *Study included a third arm with focal ablation of left atrial appendage (LAA) triggers (i.e., without complete isolation) that was not included in the current study. †Minimum arrhythmia duration was not specified. ‡Study included a third arm with delayed (but ongoing) LAA conduction (i.e., without complete isolation) that was not included in the current study.

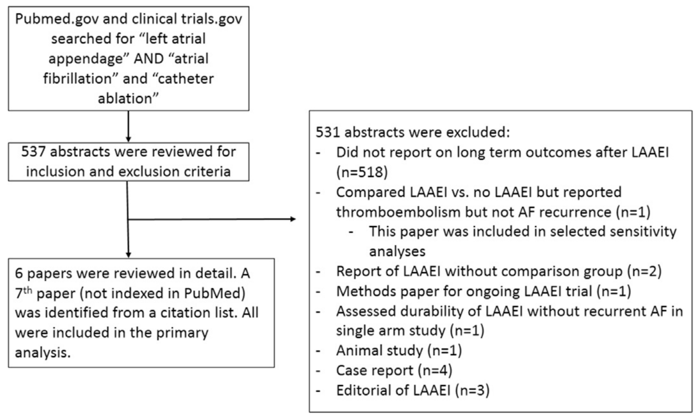
AF = atrial fibrillation; AT = atrial tachycardia; LAAEI = left atrial appendage electrical isolation; Pts = patients; PV = pulmonary vein; SR = sinus rhythm.

sensitivity analyses with sequential removal of individual studies, the results were consistent with the primary analysis (Online Figure 2). In a subgroup analysis of percutaneous LAAEI (8,11-14) (5 studies, n = 623), LAAEI was associated with a substantially lower risk of recurrent AT/AF (OR: 0.223; 95% CI: 0.108 to 0.463; $p < 0.001$) (Online Figure 3). Results were consistent, but not statistically significant, when we exclusively considered the 2 randomized trials (12,15) (OR: 0.507; 95% CI: 0.187 to 1.377; p = 0.183).

THROMBOEMBOLISM AFTER LAAEI. Thromboembolism during follow-up was reported in 6 studies and was rare. Overall, there were 18 thromboembolic events among 977 patients (across both arms) from 6 studies (10-15). There was no association between LAAEI and thromboembolism (OR: 0.5; 95% CI: 0.18 to 1.389; p = 0.184) (**Figure 4**), and no heterogeneity was noted ($I^2 = 0\%$, $\tau^2 = 0$). Notably, among the 6 studies that reported long-term thromboembolism, the LAA was either occluded or excised in 4 studies (11,13-15), and follow-up transesophageal echocardiography (TEE) was performed to assess LAA mechanical function in the other 2 studies (12,14) and might have influenced antithrombotic strategies, including LAA occlusion. A sensitivity analysis restricted to studies with concomitant LAA occlusion or excision (3 studies, n = 552) (Online Figure 4) demonstrated consistent results. A study by Rillig et al. (18) reported rates of thromboembolism among patients with LAAEI versus no LAAEI but did not report on arrhythmia recurrence and therefore did not meet inclusion criteria for the current study; inclusion of the results from that study in a sensitivity analysis of LAAEI and thromboembolism did not change the results (Online Figure 5). In an analysis that included studies without LAA occlusion or excision (12,14,18) (3 studies, n = 315), there was no association with thromboembolism, although the CIs were wide and the upper bound was >21 (OR: 1.451; 95% CI: 0.10 to 21.138; p = 0.785) (Online Figure 6).

PERIPROCEDURAL COMPLICATIONS. The heterogeneous approaches to LAAEI in this study preclude a comparison of periprocedural outcomes among all studies. Among the individual surgical studies (10,15), there was no difference in periprocedural reoperation for bleeding or periprocedural mortality among patients with and without LAAEI. Among the studies with LAAEI via radiofrequency ablation (8,12-14), there were no reports of phrenic nerve damage or circumflex artery injury; there were insufficient data by treatment group to determine whether LAAEI was associated with different rates of pericardial effusion and tamponade.

FIGURE 2 PRISMA Algorithm



AF = atrial fibrillation; LAAEI = left atrial appendage electrical isolation; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

DISCUSSION

This meta-analysis demonstrates a number of important findings. First, LAAEI was associated with a significantly lower risk of recurrent AF/AF, and this association was particularly dramatic among studies in which LAAEI was performed percutaneously. Second, although there was no significant association between LAAEI and thromboembolic events, all studies either occluded or excised the LAA or used echocardiographic follow-up to determine the intensity of antithrombotic therapy. Finally, periprocedural complications were not consistently reported across studies, which precludes meaningful analysis and conclusions regarding safety.

The LAA has been known to be a site of AT and ectopic activity that could trigger AF, although the contribution of the LAA to the development and maintenance of AF has been unclear. Although some studies have demonstrated that LAA triggers are common among patients undergoing AF ablation (8,9,19), others suggest that LAA triggers are rare (20-22). The results from this meta-analysis support the role of the LAA in recurrent AF, particularly among patients with persistent AF. However, this analysis cannot determine whether the observed association is attributable to isolation of triggers, elimination of rotors or rotational propagation, debulking of an arrhythmogenic substrate, ganglionic plexus ablation, or a combination thereof. The inferiority of LAA trigger ablation compared with LAAEI suggests the antiarrhythmic effect of LAAEI could be more complicated than simply abolishing a trigger (8). It is also important to consider that ablation aimed at isolation of the LAA could lead to more extensive ablation or isolation of the adjacent ligament of Marshall, which contains extensive autonomic innervation and is an important source of focal AF in certain patients (23). The antiarrhythmic effect of LAAEI in the BELIEF (LAA Isolation in Patients With Longstanding Persistent AF Undergoing Catheter Ablation) trial (12) is unexpected given the high reported rates of LAA reconnection, which supports the hypothesis that catheter ablation around the base of the LAA, but not durable LAAEI per se, could be the minimum requirement for benefit. Finally, the majority of LAA tachycardias appear to originate from the base of the LAA (24); this suggests that adjunctive ablation might be necessary when there is a residual stump after surgical or LARIAT-based LAA occlusion (see **Figure 1** for an overview of the different approaches to LAAEI).

Several studies have documented the acute impact of LAAEI on the electrical substrate. One study of 68 patients undergoing LARIAT occlusion demonstrated that suture tightening led to an acute reduction in unipolar and bipolar voltages and an inability to capture LAA tissue in the majority of patients (25). Another study of 15 patients undergoing LARIAT occlusion reported acute significant decreases in P-wave duration, the PQ interval, and P-wave dispersion, which were stable during short-term

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TABLE 2 Baseline Characteristics Stratified by Study and Treatment

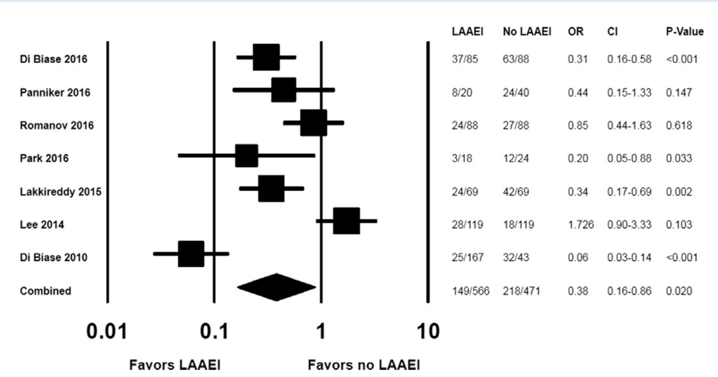
	Di Biase et al. (8)		Lee et al. (10)		Lakkireddy et al. (11)		Romanov et al. (15)		Panikker et al. (13)		Di Biase et al. (12)		Park et al. (14)	
	LAAEI	No LAAEI	LAAEI	No LAAEI	LAAEI	No LAAEI	LAAEI	No LAAEI	LAAEI	No LAAEI	LAAEI	No LAAEI	LAAEI	No LAAEI
N	167	43	119	119	69	69	88	88	20	40	85	88	18	24
Age, mean (yrs)	64	61	53	54	67	67	57	58	68	67	64	64	57	56
Male (%)	73	74	38	41	70	70	81	77	65	65	88	83	83	88
HTN (%)	47	40	19	19	74	78	52	47	N/A	N/A	68	68	33	38
DM (%)	8	7	8	8	29	26	11	9	N/A	N/A	20	21	6	4
Nonparoxysmal AF (%)	87	72	91	91	100	100	100	100	100	100	100	100	83	88
EF, mean (%)	59	58	57	57	53	53	58	56	N/A	N/A	54	55	51	52
LA size, mean (mm)	43	41	59	60	50	48	47	47	46	45	48	48	41	44

Values are N, or n (%).
DM = diabetes mellitus; EF = ejection fraction; HTN = hypertension; LA = left atrium; N/A = not available; other abbreviations as in Table 1.

follow-up (26). In contrast, PV isolation, when performed after LARIAT LAAEI, did not cause an acute change in P-wave duration or P-wave dispersion (27). The acute antiarrhythmic potential of LAAEI has been emphasized by a report of 162 patients with ≥3 months of continuous AF undergoing LARIAT LAAEI. With LAAEI, 13 patients (12 had continuous AF >1 year) converted from AF to SR. Eight of these patients converted to SR during the procedure; 5 converted to SR within 2 days (28).

Antiarrhythmic benefit of LAAEI is invariably dependent on the extent to which the mechanism of an individual's AF depends on triggers or substrate within the LAA. Patients with paroxysmal AF, which is most commonly caused by PV triggers, are unlikely to benefit from LAAEI. In contrast, patients with longer-standing AF and patients with recurrences after AF ablation might be more likely to have LAA-dependent AF. These hypotheses are supported by a study demonstrating that LAAEI was associated with decreased AF burden and that the magnitude of association was strongest among those with nonparoxysmal and those with known LAA triggers (29). Notably, among the studies in this meta-analysis, those with a higher proportion of patients with longstanding persistent AF were the studies that demonstrated the most favorable association between LAAEI and AF recurrence.

FIGURE 3 OR (LAAEI vs. No-LAAEI) for AT/AF Recurrence Among All Studies (n = 7)



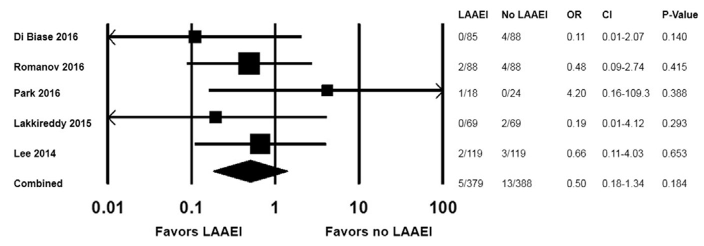
AT = atrial tachycardia; CI = confidence interval; OR = odds ratio; other abbreviations as in Figure 2.

Thromboembolism after LAAEI is a key concern and safety consideration. The data from Rillig et al. (18) are concerning, because they found that 10 of 50 patients had evidence of LAA thrombus on TEE imaging after LAA isolation despite oral anticoagulation in 9 of those 10 patients. Electrical isolation of the LAA would be expected to lead to decreased contractile function, increased stasis, and increased risk of thrombus formation, at least among patients without concomitant LAA occlusion or excision. In the overall analysis, there was no association between LAAEI and clinical thromboembolism. Although the subgroup analysis limited to studies without LAA occlusion or excision (12,14,18) (3 studies, n = 315) demonstrated no statistically significant association with thromboembolism, the CIs were wide, and we were unable to exclude the possibility of a several-fold increased risk of thromboembolism (given the upper bound of the CI). It is possible that the frequent occurrence of LAA reconnection (12) led to an underestimate of the potential risk for thromboembolism associated with durable LAAEI.

Follow-up TEE was reported in a number of studies to assess LAA function and asymptomatic thrombus formation after LAAEI (8,12,14,18). A TEE was performed in 204 patients who were in SR 6 months after first-time LAAEI (as index or follow-up procedure) in the study by Di Biase et al. (8); although qualitatively poor LAA contractility was noted in 47% of patients, no thrombus was identified. Of note, Di Biase et al. (8) did not report rates of thromboembolism, LAA function, or rates of asymptomatic thrombus among those in AF during follow-up. Sixteen (of 18) patients with LAAEI in a study by Park et al. (14) underwent follow-up TEE 1 month after the index procedure. Although 50% of patients had qualitatively poor LAA contractility and 1 patient had LAA orifice stenosis, no asymptomatic thrombus or spontaneous echocardiographic contrast was noted. The BELIEF trial investigators performed routine TEE in the 62 patients who underwent LAAEI and were in SR at 6 months; 56.5% of patients had impaired LAA function, 1 patient with a subtherapeutic international normalized ratio had an LAA thrombus, and 1 patient had spontaneous LAA contrast despite therapeutic warfarin (12). In the BELIEF trial, LAA function and the presence of asymptomatic thrombi were not reported for patients who remained in AF after catheter ablation. None of the above studies compared LAA function among patients with and without LAAEI. Rillig et al. (18) compared LAA function among patients with and without LAAEI. TEE was performed in 47 of 50 cases and 50 of 50 matched control subjects. Patients with LAAEI (vs. control subjects) demonstrated reduced LAA flow velocity after ablation (0.2 m/s vs. 0.5 m/s; $p < 0.01$) and increased rates of spontaneous echocardiographic contrast in the LAA (41% vs. 18%; $p = 0.012$) and thromboembolism or asymptomatic thrombus (26% vs. 0%; $p < 0.01$; due to 10 asymptomatic thrombi and 3 thromboembolic events in the LAAEI group). Of note, 9 of the 50 patients had evidence of LAA thrombus despite oral anticoagulation. A retrospective analysis from the same group reported 10% of patients (7 of 71) undergoing LAAEI had an asymptomatic LAA thrombus identified by TEE before a subsequent left atrial procedure; interpretation of these findings is difficult because anticoagulation use was not reported (30).

The occasional finding of preserved LAA function after isolation is intriguing and suggests durable LAAEI is often not achieved. Among patients in the BELIEF study who underwent LAAEI and required a repeat procedure, LAA reconnection was observed in 37% of patients (12). A recent study reported a 27% reconnection rate after LAAEI; however, patients in that report underwent LAAEI through a wide-area isolation approach, typically using linear and or complex fractionated electrogram ablation to achieve isolation, often after several procedures (30). The LAA can be activated via both endocardial propagation and through the distal extensions of the Bachmann bundle (31); incomplete ablation of this

FIGURE 4 OR (LAAEI vs. no-LAAEI) for Thromboembolism (n = 5 Studies)



Thromboembolism was not reported in 1 study (8) and did not occur in another study with asymmetrical arms (12), which precluded the substitution of a 1 count in each arm (16). Abbreviations as in **Figures 2 and 3**.

epicardial component of the specialized conduction system could be an important barrier to durable LAAEI.

STUDY LIMITATIONS. This meta-analysis has several limitations. The majority of the studies were observational, which raises the possibility that residual confounding influenced the results (8,10,11,13,14). Moreover, the studies included in the meta-analysis had different designs, thus limiting the specificity of the findings. Accordingly, we conducted a series of sensitivity analyses, which generally supported the main analyses. Although the funnel plot suggests the possibility of underreporting, the primary results reassuringly remained robust in a series of sensitivity analyses, including analyses that excluded studies with the most statistically significant association between LAAEI and recurrent AT/AF. We observed heterogeneity among the studies used in the primary analysis, likely because of several factors, including 1 study (8) that studied only patients with known LAA triggers, which resulted in a relatively larger effect size. We included studies with a variety of approaches to AF ablation and LAAEI, which improved the overall generalizability of our findings but limits the precision with which we can estimate clinical benefit for a specific type of patient undergoing a specific procedure. There was uncertainty regarding the exact ablation approach used in the intervention arm of certain studies (8,10,11,13,14). Specifically, it was not clear whether ablation in the interventional arm only differed based on performance of LAAEI. Only 1 study (15) was blinded, which raises the possibility of bias. One study included patients with incidentally noted LAAEI (14). Finally, there were several important differences in the patient populations across the various studies, including differences in AF subtype, AF duration, and left atrial size.

The infrequency of thromboembolism and the relatively short follow-up intervals might have limited the ability to detect differences in these outcomes among patients who did and did not receive LAAEI. Additionally, the wide CIs observed in the analysis assessing the association between LAAEI without occlusion and thromboembolism suggest these analyses were limited by relatively low power to detect a difference. Periprocedural complications were not uniformly recorded, which precludes robust analyses on periprocedural safety. Finally, the incidence rates for our primary and secondary outcomes were infrequently available, and therefore, raw event counts were used for all statistical analyses.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS. The current study suggests that the LAA plays an important role in certain types of AF and that LAAEI might reduce AF recurrence. Although LAAEI does not appear to be associated with increased risk of thromboembolism among patients with concomitant LAA occlusion or excision, there are insufficient data to determine whether this strategy is safe among patients managed exclusively with oral anticoagulation.

The ongoing aMAZE trial (LAA Ligation Adjunctive to PVI for Persistent or Longstanding Persistent Atrial Fibrillation) is rigorously testing the antiarrhythmic effect of LARIAT-based LAAEI by randomizing up to 600 patients (2:1) with nonparoxysmal AF to standard AF ablation with LARIAT LAA exclusion versus standard AF ablation alone (32). Additional randomized trials are necessary to confirm LAAEI efficacy, define procedural safety, and determine the best concomitant antithrombotic strategies and optimal method for LAAEI.

CONCLUSIONS

LAAEI is associated with a significant reduction in recurrent AT/AF; however, the data also raise concern for potential increased risk of LAA stasis and long-term risk of thromboembolic events. Randomized trials are required to confirm safety and efficacy and to determine the best treatment regimen to prevent thromboembolic events after LAAEI.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The LAA plays a critical role in atrial fibrillation pathogenesis in certain patients with atrial fibrillation. Electrical isolation of the LAA is associated with a significant reduction in recurrent atrial fibrillation among patients undergoing atrial fibrillation ablation.

TRANSLATIONAL OUTLOOK: Future studies are needed to understand the anatomic and electrophysiological determinants of successful LAA electrical isolation to optimize the safety and efficacy of this promising albeit controversial adjunctive strategy.

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KEY WORDS ablation, atrial fibrillation, left atrial appendage

APPENDIX For supplemental figures, please see the online version of this article.