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# Adjunctive low-voltage area ablation for patients with atrial fibrillation: An updated meta-analysis of randomized controlled trials

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**Disclosures**: None.

## Abstract

**Background:** The efficacy and safety of adjunctive low-voltage area (LVA) ablation on outcomes of catheter ablation (CA) for atrial fibrillation (AF) remains uncertain.

**Methods:** PubMed, Embase, Cochrane Library, and ClinicalTrials.gov were searched for randomized controlled trials (RCTs) comparing CA with versus without LVA ablation for patients with AF. Risk ratios (RR) with 95% confidence intervals (CI) were pooled with a random-effects model. Our primary endpoint was recurrence of atrial tachyarrhythmia (ATA), including AF, atrial flutter, or atrial tachycardia. We used R version 4.3.1 for all statistical analyses.

**Results:** Our meta-analysis included 10 RCTs encompassing 1780 patients, of whom 890 (50%) were randomized to LVA ablation. Adjunctive LVA ablation significantly reduced recurrence of ATA (RR 0.76; 95% CI 0.67–0.88; $p < .01$) and reduced the number of redo ablation procedures (RR 0.54; 95% CI 0.35–0.85; $p < .01$), as compared with conventional ablation. Among 691 (43%) patients with documented LVAs on baseline substrate mapping, adjunctive LVA ablation substantially reduced ATA recurrences (RR 0.57; 95% CI 0.38–0.86; $p < .01$). There was no significant difference between groups in terms of periprocedural adverse events (RR 0.78; 95% CI 0.39–1.56; $p = .49$).

**Conclusions:** Adjunctive LVA ablation is an effective and safe strategy for reducing recurrences of ATA among patients who undergo CA for AF.

**KEYWORDS**

atrial fibrillation, atrial fibrosis, catheter ablation, low-voltage area, pulmonary vein isolation, substrate modification

**Abbreviations:** AAD, antiarrhythmic drugs; AF, atrial fibrillation; ATA, atrial tachyarrhythmias; CA, catheter ablation; CI, confidence interval; ESC, European Society of Cardiology; HR, hazard ratio; LAD, left atrial diameter; LVA, low-voltage area; LVEF, left ventricular ejection fraction; MD, mean difference; NNH, number needed to harm; NNT, number needed to treat; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; PVI, pulmonary vein isolation; RCT, randomized controlled trial; RoB-2, Risk of Bias Assessment Tool 2.

  

## 1 | INTRODUCTION

More than 59 million people suffer from atrial fibrillation (AF) worldwide.[1] Recently, first-line catheter ablation (CA) was found to be superior to antiarrhythmic drugs (AAD) in terms of atrial tachyarrhythmias (ATA) recurrences, symptomatic AF, and hospitalizations.[2,3]

Pulmonary vein isolation remains the standard of care for AF ablation; however, its effectiveness remains constrained. Many adjunctive ablation strategies in addition to pulmonary vein isolation have been explored. However, this initial enthusiasm has been dampened by the limited efficacy shown in randomized controlled trials (RCTs).[4–6] Thus, these negative results were reflected in the Class 2 A recommendations in recent guidelines.[2] These strategies could be limited to the empirical selection of ablation targets. In contrast, the correlation between maintenance of AF and atrial fibrosis has been well established and the presence of low-voltage areas (LVAs) on substrate mapping has emerged as a robust predictor of ATA recurrence.[7–11]

Prior meta-analyses showed a significant reduction of ATA recurrences associated with LVA ablation. However, these studies had important limitations.[12] Several recent RCTs were published showing controversial results.[13,14] Moreover, approximately 57% of the patient population had no LVAs on baseline substrate mapping and were not submitted to the LVA ablation. Therefore, we performed an updated systematic review and meta-analysis of RCTs assessing the adjunctive LVA ablation on efficacy and safety outcomes.

## 2 | MATERIALS AND METHODS

This systematic review and meta-analysis were performed and reported following the Cochrane Collaboration Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement guidelines (Supporting Information: Methods 1).[15,16] The prospective meta-analysis protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO; CRD42023453779).

### 2.1 | Data source and search strategy

We systematically searched PubMed, Embase, Cochrane, and ClinicalTrials.gov from inception to July 2023. The search terms used included "low voltage" and "atrial fibrillation". The complete search strategy is provided in Supporting Information: Methods 2. Two authors (A. R. and M. A. P. B.) independently screened titles and abstracts and evaluated the articles in full for eligibility based on prespecified criteria. Discrepancies were resolved in a panel discussion with a third author (C. M. P. T.). Moreover, we used backward snowballing (i.e., review of references) to identify relevant texts from articles identified in the original search.

### 2.2 | Eligibility criteria

There was no restriction concerning the publication date, status, or language. We considered studies eligible for inclusion if they (1) were RCTs; (2) compared conventional ablation plus adjunctive LVA ablation (LVA group) versus conventional ablation alone (non-LVA group); (3) enrolled patients with any AF type (paroxysmal, persistent, or long-standing persistent AF); (4) included patients undergoing de novo ablation; and (5) reported any prespecified efficacy or safety outcome of interest.

### 2.3 | Data extraction

Three authors (A. R., D. M. G., and P. E. P. C.) independently extracted the data for each study using a standardized study form to determine: authors, enrollment period, study publication year, main exclusion criteria, sample size, follow-up period, baseline patient characteristics, substrate mapping device and timing, endpoint definitions, and the methods used to confirm electrical isolation during ablation (Supporting Information: Methods 3-6). Any discrepancies were resolved by consensus among the authors after examining the complete text of the article and eligibility criteria.

### 2.4 | Endpoints

Our primary efficacy endpoint was ATA recurrence. ATA was defined as a composite of AF, atrial flutter, or atrial tachycardia. Prespecified secondary efficacy endpoints were (1) recurrence of ATA after a single ablation procedure; (2) recurrence of ATA after a single ablation procedure without AAD; (3) the need for redo ablation procedure; and (4) atrial tachycardia/atrial flutter recurrence. Our prespecified safety endpoint was periprocedural adverse events, including pericardial effusion and/or cardiac tamponade, and stroke. Detailed endpoint definitions for each included study are presented in Supporting Information: Methods 7-8.

### 2.5 | Subgroup, sensitivity, and meta-regression analyses

We conducted prespecified subgroup analyses based on (1) AF type (paroxysmal vs. persistent AF vs. long-standing persistent AF); (2) overall risk of bias; (3) timing of substrate mapping (during AF vs. sinus rhythm); and (4) control group (PVI only vs. PVI plus stepwise ablation). Additionally, prespecified sensitivity analyses for the primary efficacy endpoint were restricted to: (1) patients with LVAs on baseline substrate mapping; (2) patients with long-standing persistent AF; (3) RCTs reporting time-to-events outcomes as hazard ratios (HR). The subgroup analysis on AF type included only studies reporting outcomes on each AF type separately. In addition, we performed an absolute risk estimate

and calculated the number needed to treat (NNT) and number needed to harm (NNH) for the primary efficacy and safety endpoints. To assess potential confounders, we performed a sub analysis of ATA recurrence among patients with and without LVA on baseline substrate mapping with a trial sequential analysis (TSA).

Univariable meta-regression analyses were performed to assess for interactions between the primary outcome and study-patient characteristics, including (1) AF duration (i.e., duration from the AF diagnosis to ablation date); (2) left atrial diameter (LAD); (3) mean age of patients; (4) proportion of females; (5) left ventricular ejection fraction (LVEF); and (6) mean body mass index (BMI). TSA was used to assess the risk of random error for primary endpoint. Thresholds for the Z score was based on the O'Brien–Fleming alpha spending function. A type-1 error of 0.05 and a type-2 error of 0.20 were allowed to estimate the required information size. The pooled risk ratio (RR) and the heterogeneity estimated by the diversity ($D^2$) in the included trials were also considered.

### 2.6 | Quality assessment

Two independent authors (P. E. P. C and A. N. P.) assessed the risk of bias in the included RCTs using the Cochrane tool for assessing the risk of bias in randomized trials (RoB-2).[17] Any disagreements were resolved by a third author (A. R.). We explored the potential for publication bias by visual inspection of the comparison-adjusted funnel plots and Egger's test for the primary efficacy endpoint.

### 2.7 | Statistical analysis

We used the Mantel-Haenszel (MH) random-effects model for all outcomes. We employed RR and 95% confidence interval (CI) as the measure of effect size for binary endpoints and weighted mean differences (MD) and 95% CI to pool continuous endpoints. Whenever available, we aggregate outcomes maintaining time-to-event analyses as HR. Exploratory absolute estimates were calculated with risk differences (RD) with 95% CIs, NNTs, and NNHs. The restricted maximum likelihood estimator was used to calculate heterogeneity variance $\tau^2$. We assessed heterogeneity with Cochrane's Q statistic and Higgins and Thompson's $I^2$ statistic, with $p \leq .10$ indicating statistical significance. We determined the consistency of the studies based on $I^2$ values of 0%, ≤25%, ≤50%, and >50%, indicating no observed, low, moderate, and substantial heterogeneity, respectively. All tests were two-tailed, and a $p$ Value of <0.05 was considered statistically significant. If necessary, means and standard deviations were estimated.[18] All statistical analyses were performing using R version 4.3.1 with the extension package "meta" and TSA version 0.9.5.10 beta (Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet).[19]

## 3 | RESULTS

### 3.1 | Study selection and characteristics

Our systematic search yielded 764 potential results. After deduplication and initial title and abstract screening, 43 full-text articles were retrieved and reviewed in full for possible inclusion. Ten RCTs met all the inclusion criteria and were included in the analysis.[13,14,20–27] Overall, 1780 patients were included, of whom 890 (50%) were randomized to LVA group and 890 (50%) to non-LVA group. Comprehensive details of the study selection are detailed in Figure 1.

In this pooled analysis, the mean age was 64.7 years (range, 57.4–75) and 37.3% were females (range, 14%–71%). Mean LAD varied from 39 to 49 mm and mean AF duration from 8.7 to 62.3 months. All included studies defined LVAs as regions with <0.5 millivolts (mV) on substrate mapping. Among studies reporting this characteristic, 691 (43%) patients had documented LVAs on substrate mapping. Radiofrequency ablation was the preferred energy source. Baseline patient and study characteristics are detailed in Table 1 and Supporting Information: Table 1. In addition, the method used to confirm LVA ablation in each study and a description of ablation protocol is reported in Supporting Information: Methods 5 and 9, respectively.

### 3.2 | Efficacy endpoints

Compared with conventional ablation, adjunctive LVA ablation significantly reduced ATA recurrence (RR 0.76; 95% CI 0.67–0.88; $p < .01$; $I^2 = 0\%$; Figure 2A). These results were consistent after a single procedure (RR 0.75; 95% CI 0.65–0.85; $p < .01$; $I^2 = 0\%$; Figure 2B) and after a single procedure without AAD (RR 0.75; 95% CI 0.63–0.88; $p < .01$; $I^2 = 0\%$; Figure 2C). Among patients with LVAs on baseline substrate mapping, the benefit of adjunctive LVA ablation was also present (RR 0.73; 95% CI 0.66–0.88; $p < .01$; $I^2 = 0\%$; Figure 2D). Additionally, LVA ablation reduced the need for redo ablation procedures (RR 0.54; 95% CI 0.35–0.85; $p < .01$; $I^2 = 0\%$; Supporting Information: Figure 1A). There was no significant difference in atrial tachycardia/atrial flutter recurrence (RR 0.56; 95% CI 0.27–1.17; $p = .12$; $I^2 = 37\%$; Supporting Information: Figure 1B). Among patients with long-standing persistent AF, LVA ablation substantially reduced ATA recurrence (RR 0.57; 95% CI 0.38–0.86; $p < .01$; $I^2 = 0\%$; Supporting Information: Figure 1C).

### 3.3 | Meta-analysis of time-to-event data

In time-to-event analysis, adjunctive LVA ablation significantly reduced ATA recurrence in the overall population (HR 0.69; 95% CI 0.56–0.86; $p < .01$; $I^2 = 0\%$; Supporting Information: Figure 2A), in patients undergoing a single procedure (HR 0.69; 95% CI 0.55–0.87; $p < .01$; $I^2 = 0\%$; Supporting Information: Figure 2B), and especially among patients with LVAs on baseline substrate mapping (HR 0.59;

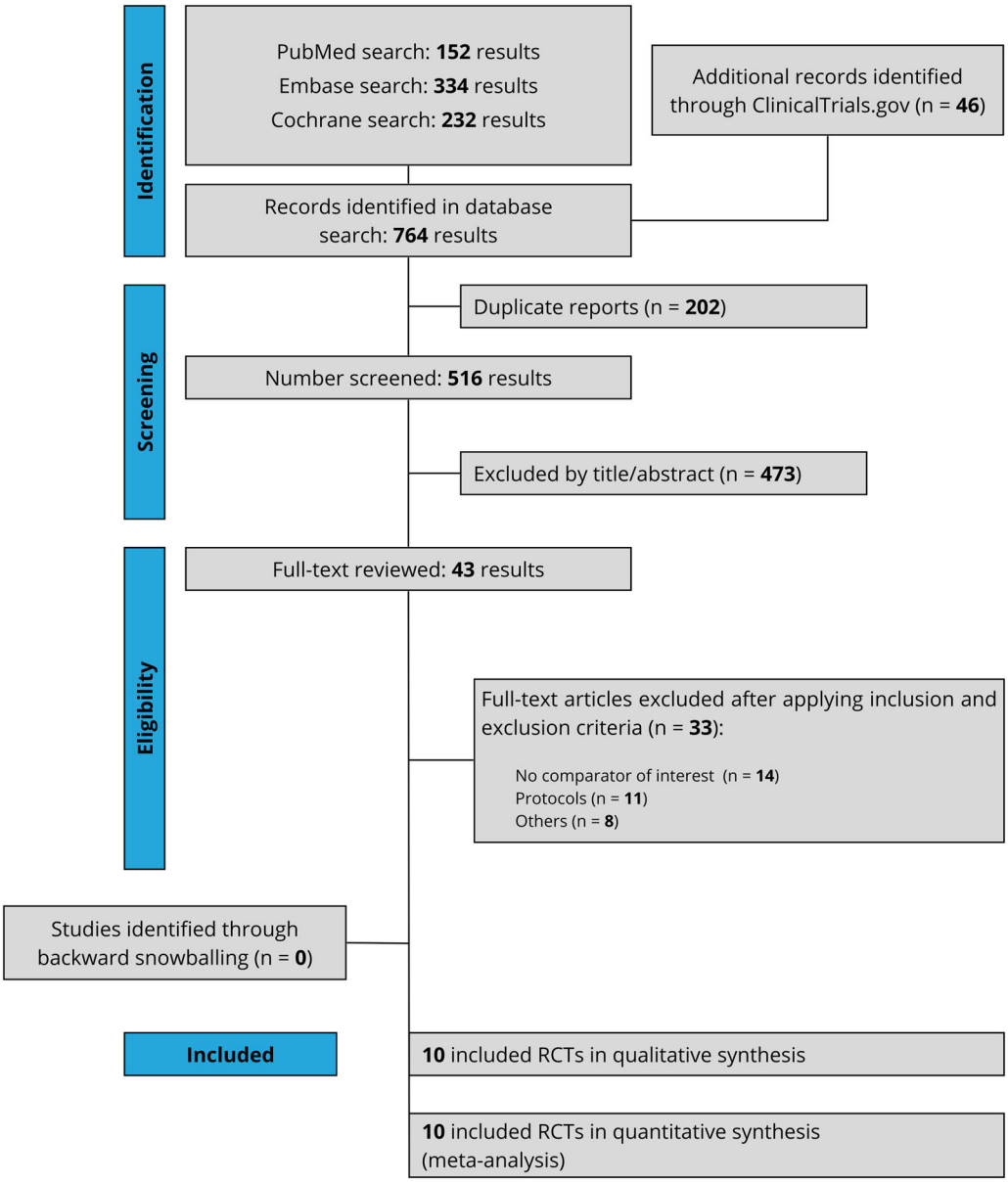


**FIGURE 1** PRISMA flow diagram of study screening and selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT, randomized controlled trial.

95% CI 0.40–0.86; $p < .01$; $I^2 = 0\%$; Supporting Information: Figure 2C).

## 3.4 | Sensitivity analyses and TSA

In an absolute risk assessment, there was a significant reduction in ATA recurrence (RD 0.08; 95% CI [−0.13] to [0.04]; $p < .01$; $I^2 = 0\%$; Supporting Information: Figure 3A) with a NNT of 12.5, but no significant difference in periprocedural adverse events (RD 0.00; 95% CI [−0.02] to [0.01]; $p = .66$; $I^2 = 16\%$; Supporting Information: Figure 3B) with a NNH of −297.3.

TSA results for the primary efficacy endpoint indicate that both the required information size and conventional statistical benefit boundaries were crossed (Figure 3). This suggests that the observed effects can be deemed conclusive, with a low risk of type 1 error. Further study on this ablation strategy would likely be redundant.

There was a significant reduction in ATA recurrence in patients with (RR 0.73; 95% CI 0.66–0.88; $p < .01$; $I^2 = 0\%$) and without LVA on baseline substrate mapping (RR 0.76; 95% CI 0.58–1.00; $p = .05$; $I^2 = 7\%$; Supporting Information: Figure 4) compared with non-LVA ablation. However, in TSA, the analysis in patients with baseline LVA crossed both conventional boundary and required information size, which may be a conclusive finding. Conversely, in the analysis of patients without LVA, the z-curve did not cross the required information size, conventional, and monitoring boundaries, precluding definitive conclusions given the risk of random error.

**TABLE 1** Baseline characteristics of included studies.

| Study, year | Number of patients LVA/Non-LVA | Intervention group | Control group | Mean Age (years) LVA/Non-LVA | Male (%) LVA/Non-LVA | AF duration (months) LVA/Non-LVA | CHA2DS2-VASc score LVA/Non-LVA | Baseline LVA *n* (%) LVA/Non-LVA | AF type | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|---|---|
| ERASE-AF[25] | 161/163 | PVI plus LVA ablation | PVI only | 65 ± 10<br>66 ± 10 | 69.5<br>63.8 | 31 (8–77)<br>31 (12–77) | 3 (2–4)<br>3 (2–4) | 54 (34)<br>64 (39) | Persistent or long-standing persistent AF | 12 |
| Hwang et al.[22] | 25/25 | PVI plus LVA ablation[a] | PVI only | 58.8 ± 9.3/<br>57.9 ± 9.8 | 80.0<br>92.0 | 21.4 ± 26.2<br>27.1 ± 19.2 | 1.8 ± 1.4<br>1.4 ± 1.4 | NA | Persistent AF | 12 |
| Kaiser et al.[21] | 50/50 | PVI plus LVA ablation | PVI plus stepwise ablation | 65.2 ± 8.9/<br>67.5 ± 10.8 | 66.0/72.0 | NA<br>NA | 2.7 ± 1.6<br>2.6 ± 1.7 | 20 (40)<br>25 (50) | Persistent AF | 17.6 ± 4.5 |
| Kircher et al.[23] | 62/62 | PVI plus LVA ablation | PVI plus stepwise ablation | 62 ± 10/<br>63 ± 9 | 58.1 | 54 (24–87)<br>60 (36–111) | 2 (1–3)<br>2 (1–3) | 16 (26)<br>19 (33) | Paroxysmal or persistent AF | 12 ± 3 |
| Kumagai et al.[27] | 31/22 | BOXI plus LVA ablation | BOXI only | 65 ± 8/<br>65 ± 10 | 75.8/66.6 | NA<br>NA | NA<br>NA | 33 (100)<br>21 (100) | Persistent or long-standing persistent AF | 24 ± 9 |
| STABLE-SR[20] | 114/115 | PVI plus LVA ablation | PVI plus stepwise ablation | 57.1 ± 9.5/<br>57.6 ± 8.4 | 80.7/73.7 | 18.9 ± 29<br>15.9 ± 33 | NA<br>NA | 52 (45.6)<br>NA | Persistent or long-lasting persistent AF[b] | 18 |
| STABLE-SR II[14] | 134/142 | PVI plus LVA ablation | PVI only | 60.6 ± 9.4<br>60.4 ± 9.6 | 66.2/69.7<br>69.7 | 6.0 (2.0-15.5)<br>6.0 (1.0-12.0) | NA<br>NA | 71 (54.6)<br>62 (45.9) | Persistent or long-standing persistent AF | 18 |
| STABLE-SR III (2023) | 219/219 | PVI plus LVA ablation | PVI only | 70.2 ± 4.7/<br>70.7 ± 4.1 | 50.7/49.3 | 24.0 (6.0-48.0)<br>14 (4.0-48.0) | 2.3 ± 0.8<br>2.5 ± 1.0 | 88 (40.4)<br>93 (42.5) | Paroxysmal AF | 23 |
| VOLCANO[24] | 30/32 | PVI plus LVA ablation | PVI only | 75.3 ± 7.2/<br>74.7 ± 8.0 | 30.0/28.1 | 4 (2-14)<br>5 (2-23) | 3.6 ± 1.2<br>3.3 ± 1.3 | 30 (100)<br>32 (100) | Paroxysmal AF | 12 |
| Wang et al.[26] | 64/60 | PVI plus LVA ablation | PVI plus stepwise ablation | 62.8 ± 10.5/<br>62.2 ± 5.7 | 64.1/58.3<br>58.3 | 40.8 ± 38.1<br>32.8 ± 15.8 | NA<br>NA | 11 (17.8)<br>NA | Long-standing persistent AF | 12 |

*Note*: The data are presented as mean ± SD or median (IQR).

Abbreviations: AF, atrial fibrillation; BOXI, box isolation; LAD, left atrial diameter; LVEF, left ventricle ejection fraction; LVA, low-voltage area.

[a]This study targeted LVAs within complex fractionated atrial electrograms;

[b]Defined as AF lasting > 1 year and <3 years.

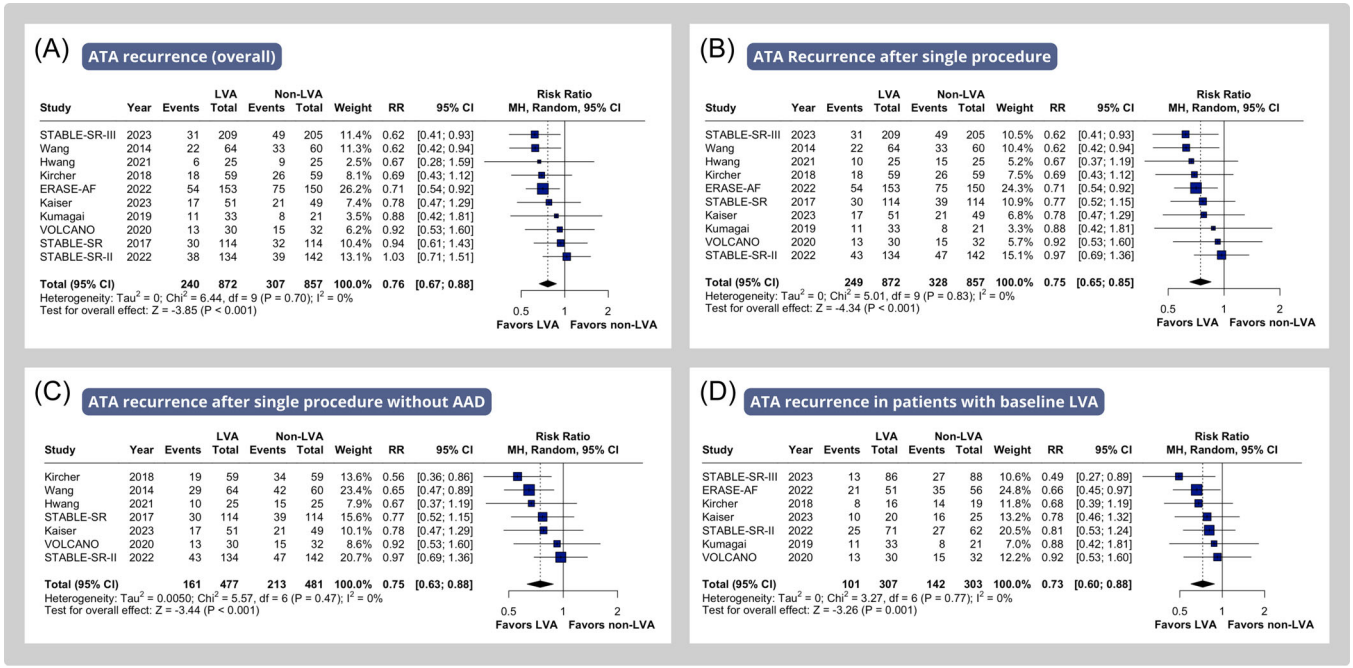


**FIGURE 2** Meta-analysis of efficacy endpoints in patients with atrial fibrillation (AF) undergoing CA with adjunctive LVA ablation. *Caption*: Forest plots presenting the RR and 95% CI for each treatment strategy on ATA recurrence (A) in the overall population, (B) after a single ablation procedure, (C) after a single ablation procedure and without AAD, and (D) in patients with documented LVAs on baseline substrate mapping. AAD, antiarrhythmic drugs; ATA, atrial tachyarrhythmia; CA, catheter ablation; CI, confidence interval; LVA, low-voltage area; MH, Mantel-Haenszel; RR, risk ratio.

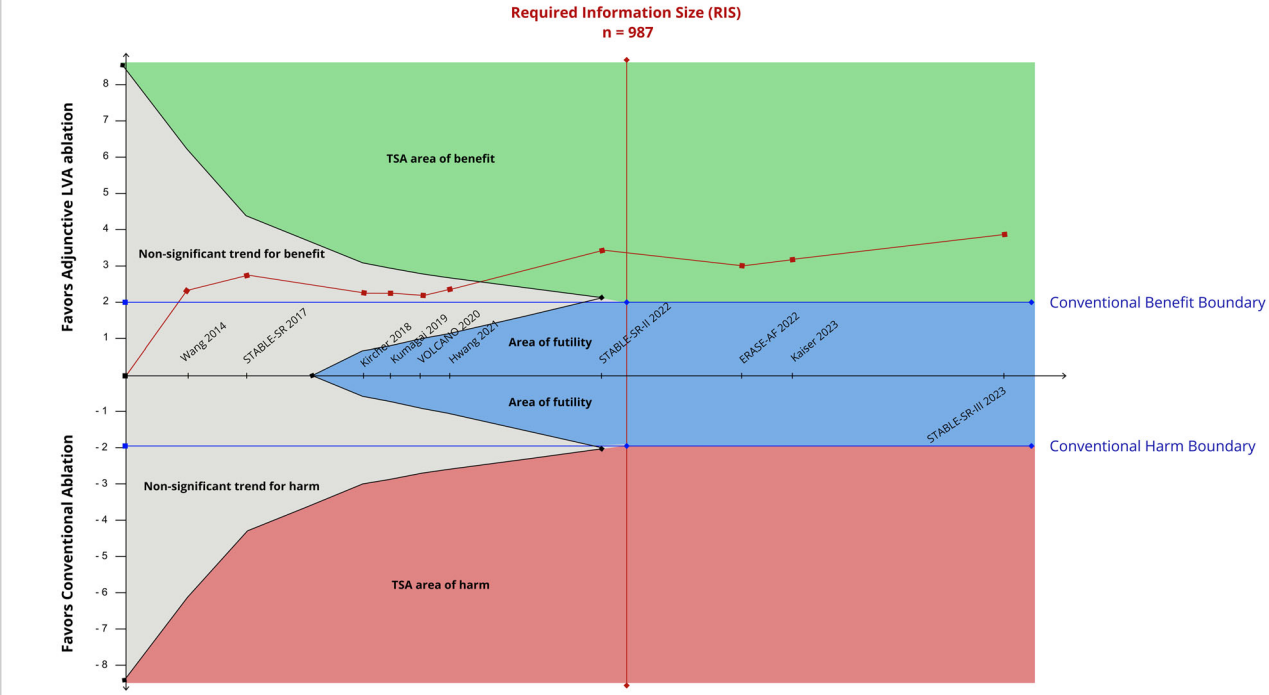


**FIGURE 3** TSA of adjunctive LVA ablation for the primary efficacy endpoint. TSA indicating that both the required information size and conventional statistical benefit boundaries were crossed. LVA, low-voltage area; TSA, trial sequential analysis.

### 3.5 | Subgroup and meta-regression analysis

Results remained similar when stratified by AF type (paroxysmal vs. persistent vs. long-standing persistent AF) ($p = .52$; Figure 4), overall risk of bias ($p = .79$; Supporting Information: Figure 5A), substrate mapping time ($p = .93$; Supporting Information: Figure 5B), and control group ($p = .97$; Supporting Information: Figure 5C).

In meta-regression analysis, there was no significant correlation between the primary endpoint effect size and the covariates of AF duration, mean age, proportion of females, LVEF, mean BMI, and mean LAD (Supporting Information: Figure 6).

### 3.6 | Safety endpoint

There were no significant differences between groups in periprocedural adverse events (RR 0.78; 95% CI 0.39–1.56; $p = .49$; $I^2 = 15\%$; Figure 5). Atrioesophageal fistula occurred in one patient in the non-LVA group.

### 3.7 | Quality assessment

Individual RCT appraisal is detailed in Supporting Information: Figure 7. The Cochrane Collaboration RoB-2 tool identified five RCTs with some concerns for bias and five at low risk of bias. Funnel plot analysis and Egger regression test for the primary efficacy endpoint did not detect evidence of publication bias ($p = .68$; Figure 6).

## 4 | DISCUSSION

This comprehensive meta-analysis of 10 RCTs enrolling 1780 patients assessed the adjunctive LVA ablation in patients with AF. Our main findings were as follows. First, LVA ablation reduced recurrence of ATA rates and reduced redo ablation procedures. Second, LVA ablation was also superior for recurrence of ATA after a single procedure with and without AAD. Third, patients with documented LVAs on baseline substrate mapping had a more pronounced reduction in recurrence of ATA rates with LVA ablation. And fourth, there was no significant difference in periprocedural adverse events.

Atrial fibrosis plays a crucial role in the initiation and maintenance of AF. It separates myocardial bundles, diminishes cell coupling, and causes slow and anisotropic conduction in the atria.[28–30] Several techniques have been developed to identify and target these fibrotic areas. Magnetic resonance imaging (MRI) has proven effective in detecting fibrosis; however, when applied to AF

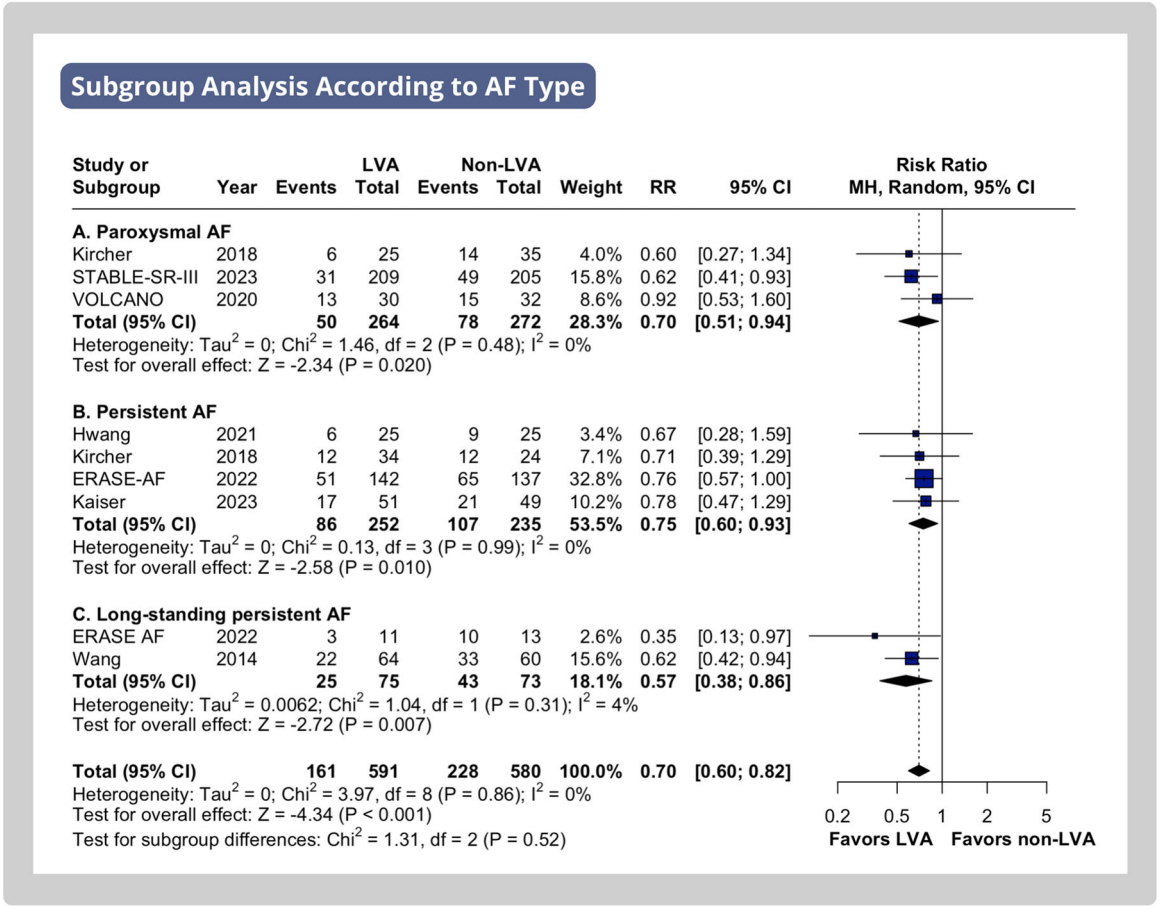


**FIGURE 4** Subgroup analysis of recurrence of ATA showed no significant interaction when stratified by AF type (paroxysmal vs. persistent vs. long-standing persistent AF). ATA, atrial tachyarrhythmia; CI, confidence interval; LVA, low-voltage area; MH, Mantel-Haenszel; RR, risk ratio.

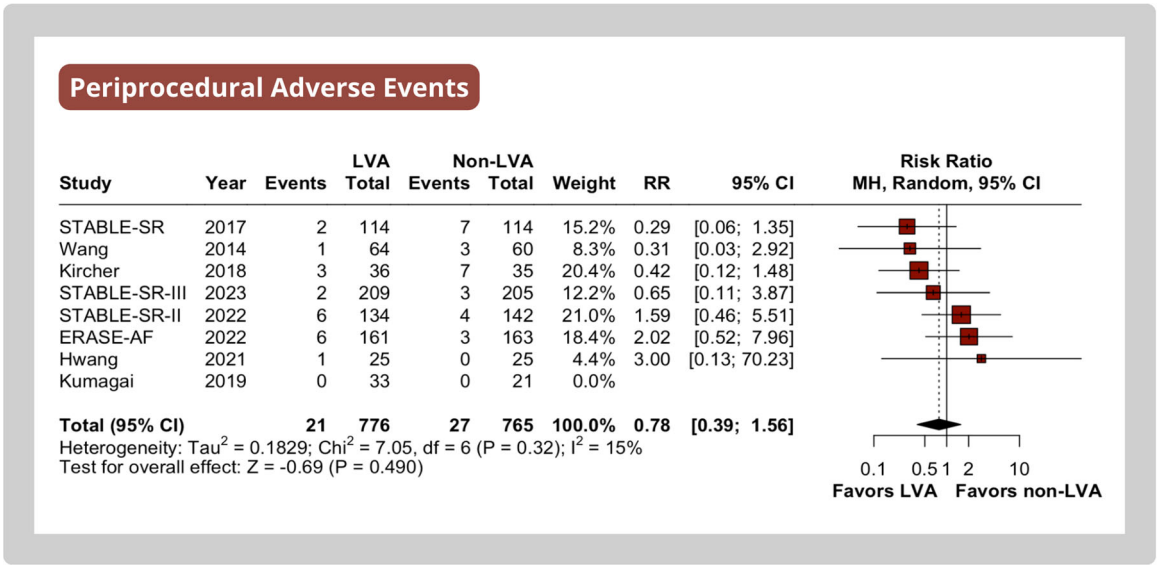


**FIGURE 5** Meta-analysis of the primary safety endpoint in patients with atrial fibrillation (AF) undergoing CA with adjunctive LVA ablation. Forest plots presenting the RR and 95% CI for each treatment strategy on periprocedural adverse events. CA, catheter ablation; CI, confidence interval; LVA, low-voltage area; MH, Mantel-Haenszel; RR, risk ratio.

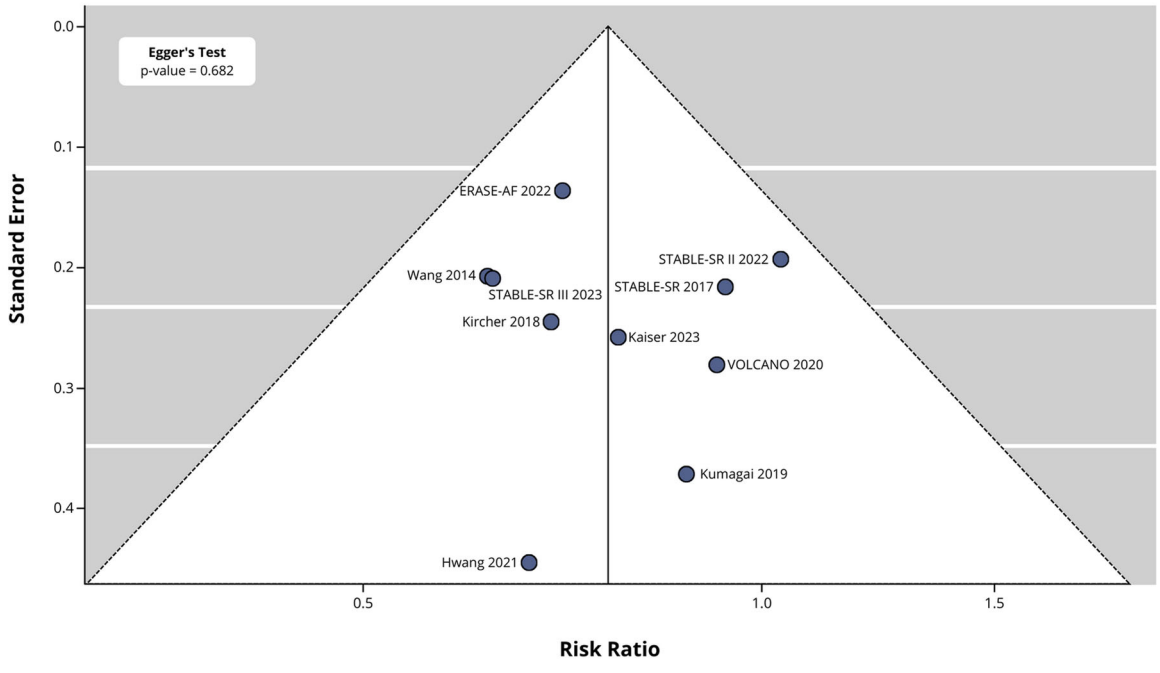


**FIGURE 6** Funnel plot and Egger's regression test suggested no evidence of publication bias for recurrence of ATA. ATA, atrial tachyarrhythmias.

ablation, its utility was limited.[4] This limitation could be attributed to the current challenges of MRI in detecting true electrophysiological substrates within the thin atrial wall. In contrast, substrate mapping has emerged as a promising alternative. This technology effectively identifies regions associated with atrial fibrosis by pinpointing areas with <0.5 mV (i.e., LVAs). Moreover, several studies consistently demonstrated a strong correlation between LVAs and ATA recurrence following CA.[7,9,11] These findings raise the hypothesis that LVA

ablation could serve as an adjunctive strategy to enhance the efficacy of AF ablation procedures.

In addition, LVA ablation may potentially select patients with a heightened risk of ATA recurrence, sparing them from empirical ablation and associated dangers of excessive interventions. Notably, within the LVA ablation group, approximately 56.6% of patients did not exhibit LVAs on baseline substrate mapping and were not subjected to LVA ablation. To address this issue and avoid misinterpretation of our findings, we performed a sensitivity analysis restricting LVA ablation for patients with documented LVAs on baseline substrate mapping and found a substantial reduction in recurrence of ATA in these patients with a low risk of type 1 error on TSA. Furthermore, by restricting the analysis to only studies reporting HR for patients with documented LVAs on baseline substrate mapping, we found a substantial 41% reduction of ATA recurrence (HR 0.59; 95% CI 0.40–0.86). Importantly, this finding was derived from only three RCTs ($n = 552$) and exhibited no statistical heterogeneity.

Remarkably, we found no significant differences in periprocedural adverse events between LVA and non-LVA groups. This finding suggests that the implementation of LVA ablation may not expose patients to elevated complication rates, underscoring the potential enhancement in the overall efficacy of CA. Furthermore, there was only one event of atrioesophageal fistula, accounting for 0.06% of cases, within the non-LVA group. The rarity of this event precluded us from conducting a meta-analysis to assess LVA ablation impact in this important outcome. Ongoing RCTs will help to confirm these findings.[31,32]

Our study builds upon the previous meta-analysis that found a benefit of adjunctive LVA ablation.[12] First, we included five RCTs, yielding 1187 patients not considered in the prior meta-analysis. Second, due to this data availability, we were able to perform several additional analyses including a sensitivity analysis restricted to patients with LVAs on baseline substrate mapping, bringing insightful findings. Third, we limited inclusion to RCTs to minimize confounding variables in our analysis.[33] Fourth, we performed several sensitivity analyses, detecting higher relative efficacy of adjunctive LVA ablation compared with conventional ablation in patients with long-standing persistent AF. And lastly, there was no subgroup interaction regarding the substrate mapping created during sinus rhythm or AF on ATA recurrence.

### 4.1 | Study limitations

This study has some limitations. First, there was a heterogenous ablation protocol among studies, however in a subgroup analysis, there was no interaction regarding the control group for ATA recurrence. Second, the inclusion of patients with paroxysmal and persistent, and long-standing persistent AF resulted in a substantial variation in mean AF duration among studies. Despite the heterogeneity, we found no statistical subgroup interaction between these subsets. Third, the primary efficacy endpoint reported was based on the current standard of 30 s of arrhythmia recurrence. However, the AF burden has recently been increasingly considered a more clinically meaningful endpoint than the conventional recurrence definition.[34] Regrettably, the AF burden was not assessed among studies. Thus, performing a meta-analysis of AF burden as an endpoint was impossible. Fourth, all studies implemented a 0.5 mV cut-off for defining low voltage, which precluded the exploration of the potential effect of varying cut-offs thresholds, as optimal threshold remains undetermined. Fifth, we found a significant reduction of ATA recurrence in the LVA ablation group among patients without LVA on baseline substrate mapping. To assess the random error in this analysis, we conducted a TSA for this endpoint, which suggested a high risk of random error, precluding definitive conclusions on the hypothesis of potential confounders in the present analysis. Lastly, the absence of patient-level data precluded a more granular assessment of factors potentially related to the relative efficacy of an adjunctive LVA ablation versus conventional ablation, such as age and sex differences.

## 5 | CONCLUSION

In this meta-analysis of RCTs, adjunctive LVA ablation significantly reduced ATA recurrence. This benefit was sustained after a single procedure with and without AAD and was even more pronounced among patients with LVAs and with long-standing persistent AF. Our findings support the routine use of adjunctive LVA ablation on patients with LVAs on baseline substrate mapping.

### AUTHOR CONTRIBUTION

**André Rivera**: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, writing—original draft preparation. **Douglas M. Gewehr**: Formal analysis, methodology, visualization, writing—review and editing. **Marcelo A. P. Braga**: Data curation. **Pedro E. P. Carvalho**: Data curation, methodology. **Alexandre N. Pantaleao**: Data curation and methodology. **Caique M. P. Ternes**: Methodology, writing—review and editing. **Daniela Hincapie**: Writing—review and editing. **Frans Serpa**: Methodology and writing—review and editing. **Jorge E. Romero**: Methodology and writing—review and editing. **André d'Avila**: Supervision and writing—review and editing.

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### DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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## SUPPORTING INFORMATION

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

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