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RESEARCH LETTER

Hybrid ablation for persistent/long-standing persistent atrial fibrillation: a meta-analysis and trial sequential analysis of randomized controlled trials

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Abstract

The efficacy and safety of hybrid ablation (HA) for patients with non-paroxysmal atrial fibrillation (AF) remain unclear. PubMed, Embase, Cochrane, and ClinicalTrials.gov were searched for randomized controlled trials (RCTs) comparing HA (endo-epicardial ablation) versus endocardial ablation (EA) for patients with persistent/long-standing persistent AF. Risk ratios (RRs) and 95% confidence intervals (CIs) were pooled. Our meta-analysis included 3 RCTs comprising 358 patients, of whom 233 (65.1%) were randomized to HA. Compared with EA, HA reduced the recurrence of atrial tachyarrhythmias (RR 0.53; 95% CI 0.41–0.69; $p < 0.01$) but had no subgroup interaction according to AF type ($p = 0.90$). There was no significant difference in major adverse events (RR 1.22; 95% CI 0.46–3.25; $p = 0.68$). Trial sequential analysis indicates that the observed effects can be deemed conclusive. In conclusion, in patients with persistent/long-standing persistent AF, HA substantially reduced the recurrence of atrial tachyarrhythmias. Notably, patients with long-standing persistent AF may benefit more from this ablation strategy.

Abbreviations

AE	Adverse event
AF	Atrial fibrillation
ATA	Atrial tachyarrhythmia
EA	Endocardial ablation
HA	Hybrid ablation
Ls-PeAF	Long-standing persistent atrial fibrillation
PeAF	Persistent atrial fibrillation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomized controlled trial

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1 Introduction

Endocardial catheter ablation (EA) is a cornerstone treatment for atrial fibrillation (AF). Real-world data showed EA to be highly effective for paroxysmal atrial fibrillation (PAF); however, efficacy in persistent AF (PeAF) or long-standing persistent AF (Ls-PeAF) remains a challenge. One-year atrial tachyarrhythmia (ATA) recurrence rates following EA in patients with PeAF and Ls-PeAF ranged from 47 to 69%, urging for new ablation approaches [1, 2]. Hybrid ablation (HA), combining epicardial and endocardial ablation, emerged as a promising ablation strategy [3]. Therefore, we performed a meta-analysis of randomized controlled trials

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(RCTs) comparing HA versus EA for patients with PeAF and Ls-PeAF.

2 Methods

We followed the Cochrane Collaboration Handbook for Systematic Reviews of Interventions [4]. This meta-analysis protocol was registered at the International Prospective Register of Systematic Reviews (CRD42023472858). PubMed, Embase, Cochrane, and ClinicalTrials.gov were searched from inception to October 2023 using the terms: "hybrid," "endo-epicardial," and "atrial fibrillation." Studies were eligible if they were (1) RCTs, (2) enrolled patients with PeAF (≥ 7 days and < 1 year of continuous AF) or Ls-PeAF (≥ 1 year of continuous AF), undergoing *de novo* ablation, and (3) compared HA versus EA. Our efficacy endpoint was a recurrence of documented ATA without antiarrhythmic drugs at 12 months. ATA was defined as a composite of AF, atrial flutter, or atrial tachycardia. Our safety endpoint was major adverse events (AEs), as defined per study. Secondary endpoints were total procedure and fluoroscopy times. We conducted a subgroup analysis for the efficacy endpoint according to AF type and a trial sequential analysis (TSA)

Table 1 Summary of baseline characteristics of the included randomized controlled trials

RCT name	CEASE-AF 2023	HARTCAP-AF 2023	CONVERGE 2020
Randomized controlled trial characteristics			
Trial identification	NCT02695277	NCT02441738	NCT01984346
Design	Multicenter, superiority	Single-center, superiority	Multicenter, superiority
Intervention *Hybrid approach (HA)*	Two-staged HA	Single-staged HA	Single-staged HA
Epicardial approach	Thoracoscopic bipolar RF ablation *PVI + BOXI + LAAO*	Thoracoscopic bipolar RF ablation *PVI + BOXI + LAAO*	Pericardioscopic unipolar RF ablation *PV antrum ablation + PWI*
Endocardial approach	Bipolar RF *PVI + BOXI*	RF *PVI + BOXI*	RF *Completion of PVI + CTI line*
Control *Catheter ablation (CA)*	Bipolar RF *PVI + BOXI*	RF *PVI*	RF *PVI + Roofline*
Sample size (*n*)	HA 102 CA 52	HA 19 CA 22	HA 102 CA 51
AF type	Symptomatic PeAF and long-standing PeAF		
Follow-up *Primary efficacy endpoint*	12 months	12 months	12 months
Monitoring	12-lead ECG and 48-h Holter	12-lead ECG, 24-h Holter, and 7-day Holter	12-lead ECG, 24-h Holter, and 7-day Holter
Patients characteristics			
Age (years), mean	HA 60.8, CA 60.6	HA 64, CA 64	HA 63.7, CA 65.1
Male participants (%)	HA 75.5, CA 73.1	HA 94.7, CA 81.8	HA 78, CA 53
AF classification (%)			
Persistent AF	HA 79.4, CA 82.7	HA 90, CA 91	58
Long-standing PeAF	HA 20.6, CA 17.3	HA 11, CA 9	42
AF duration (years), mean/median	HA 2.9, CA 3.3	HA 1.8, CA 2.8	HA 4.4, CA 4.5
LA size/volume, (†cm or §ml), mean	HA 4.7†, CA 4.7†	HA 114§, CA 101§	HA 4.4†, CA 4.3†
LVEF (%), mean	HA 58.3, CA 57.8	HA 55, CA 54	HA 55.3, CA 55.7
Hypertension (%)	HA 52.9, CA 53.8	HA 53, CA 68	HA 77.5, CA 74.5
AAD class I/III (%)	HA 53.9, CA 57.7	HA 53, CA 36	HA 84, CA 80
Previous ECV (%)	HA 93.1, CA 96.2	HA 95, CA 91	NA

Abbreviations: *AAD* antiarrhythmic drugs, *AF* atrial fibrillation, *BOXI* box isolation, *CA* catheter ablation, *CTI* cavotricuspid isthmus, *ECG* electrocardiogram, *ECV* electrical cardioversion, *HA* hybrid approach, *LA* left atrium, *LAAO* left atrial appendage occlusion, *LVEF* left ventricle ejection fraction, *MI* myocardial infarction, *PV* pulmonary vein, *PVI* pulmonary vein isolation, *RCT* randomized controlled trial, *RF* radiofrequency, *TIA* transient ischemic attack

to assess the risk of random error for the efficacy endpoint. Risk of bias was assessed with the Risk of Bias Tool (RoB 2), and small study effects were assessed with a funnel plot analysis.

We used the Mantel–Haenszel (MH) random-effects model with risk ratios (RR) and 95% confidence intervals (CI) for binary endpoints. A restricted maximum likelihood estimator was used to calculate heterogeneity variance τ^2. We assessed heterogeneity using Cochrane's Q statistic and Higgins and Thompson's I^2 statistic. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant. We used the R software version 4.3.1 and TSA version 0.9.5.10 beta for all statistical analysis.

3 Results

Our systematic search yielded 1139 potential results. After deduplication, initial title, and abstract screening, 28 full-text articles were retrieved and reviewed in full for possible inclusion. Four reports of 3 RCTs met the inclusion criteria and were analyzed [3, 5–7]. Overall, we included 358 patients, of whom 233 (65.1%) were randomized to HA. Mean age ranged from 60.7 to 64.2 years, and 258 (74.1%) were male. In the HARTCAP-AF trial, 42.1% of HA patients underwent touch-up EA, whereas in the CONVERGE trial, 38% required endocardial pulmonary vein touch-ups or ablation of common pulmonary veins. Conversely, in the CEASE-AF trial, the double-stage HA trial, 91.1% received touch-up ablation. All studies employed radiofrequency energy source for EA. Baseline patient and study characteristics are described in Table 1.

Compared with EA, HA significantly reduced the recurrence of ATA at 12 months (RR 0.53; 95% CI 0.41–0.69; $p < 0.01$; $I^2 = 14\%$; Fig. 1A), but there was no significant subgroup interaction according to AF type ($p = 0.90$); notably, in the Ls-PeAF subgroup, there was a lower heterogeneity compared with PeAF subgroup ($I^2 = 0\%$ vs. $I^2 = 64\%$, respectively). No significant difference in major AEs was observed (RR 1.22; 95% CI 0.46–3.25; $p = 0.68$; $I^2 = 5\%$; Fig. 1B).

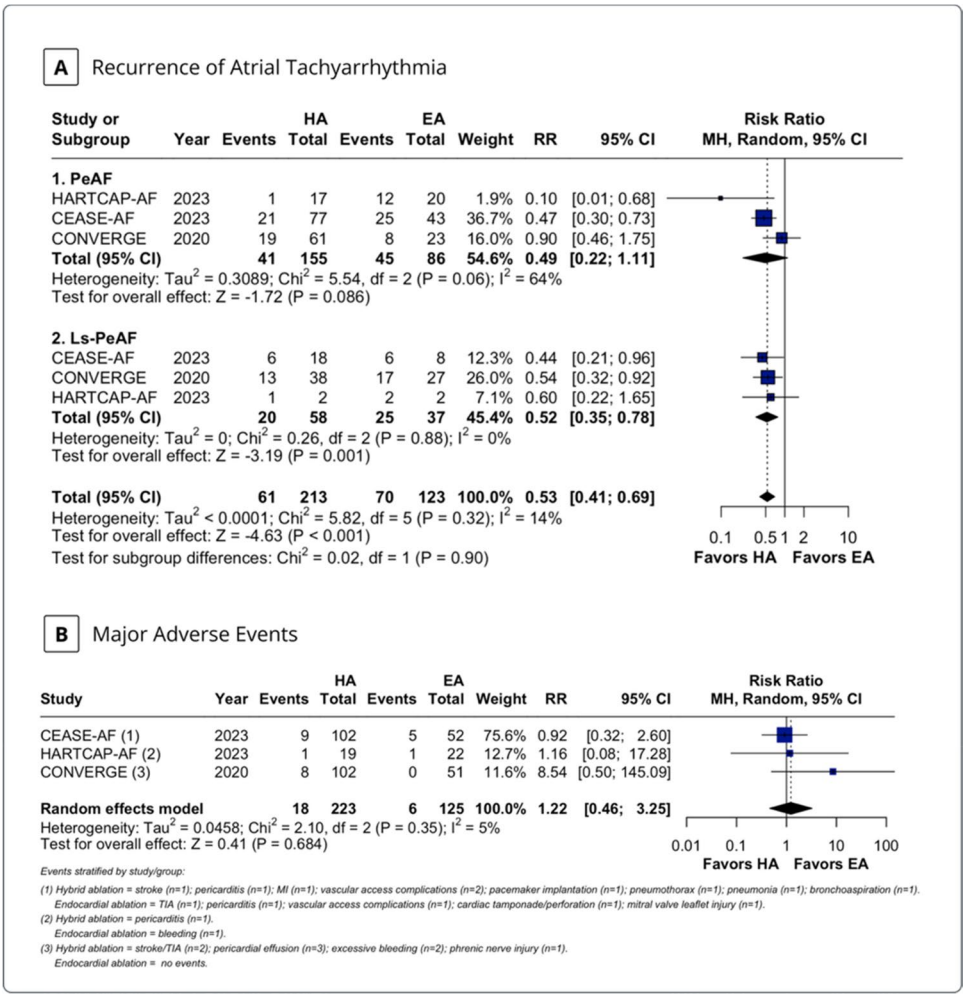

Fig. 1 Hybrid ablation (HA) (**A**) led to a significantly reduced recurrence of atrial tachyarrhythmia (ATA) in patients with persistent/long-standing persistent atrial fibrillation (AF) but had no significant subgroup interaction according to AF type, and **B** HA had similar rates of major adverse events compared with EA

There was a significantly longer total procedural time (MD 105.5 min; 95% CI 76.5–134.4 min; $p < 0.01$; $I^2 = 39\%$), but no significant difference in fluoroscopy time (MD − 6.2 min; 95% CI [− 17.4]–[5.0] min; $p = 0.28$; $I^2 = 80\%$).

In TSA conducted for the recurrence of ATA, the *z*-curve crossed both the conventional boundary and the required information size, indicating that our results can be considered conclusive, with a low risk of type 1 error. Leave-one-out sensitivity analysis showed the robustness of our findings. RoB-2 identified two studies with some concerns of bias [3, 6], while one was considered at low risk [5]. Funnel plot suggested no evidence of small study effects.

4 Discussion

The optimal ablation strategy for persistent/long-standing PeAF is an ongoing debate. Despite the limited effectiveness of EA demonstrated in previous studies, HA appears to mitigate limitations by reducing lesion gaps and producing transmural lesions. This suggests that HA may play a pivotal role in the management of PeAF, particularly in cases of Ls-PeAF. Historically, patients with Ls-PeAF exhibit poor long-term maintenance of sinus rhythm with EA, likely due to contributions from non-pulmonary vein triggers and substrate. Our findings suggest that HA may offer distinct advantages for such patients.

While the HA group exhibited a higher numerical incidence of major AEs, this difference was not statistically significant. The restriction to only RCTs to mitigate confounding variables reinforces our findings, supporting that HA is an efficient strategy. Nonetheless, these findings should be interpreted with caution due to the limited statistical power of the analysis. Further RCTs are warranted to explore the safety profile of HA in these patients. Additionally, extended follow-up of studies to assess long-term outcomes and to compare staged versus concomitant HA in a head-to-head trial, considering that staged HA may be associated with a higher need for endocardial touch-up ablations following the epicardial approach, as seen within the included studies. This may potentially affect efficacy endpoints, although we were unable to assess its impact in the present analysis.

This study has limitations. There was a slight variation in ablation sets and procedures as described in Table 1. Also, the restricted number of studies precluded subgroup and meta-regression analyses. Our analysis may be underpowered to detect a statistically significant difference in major AEs.

5 Conclusion

In this meta-analysis of RCTs, our findings suggest that in patients with persistent and long-standing persistent AF, hybrid ablation substantially reduced the recurrence of atrial tachyarrhythmias at 12 months compared with endocardial ablation. Notably, patients with long-standing persistent AF may have a greater benefit from this ablation strategy.

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Author contribution AR interpreted the data and was involved in the design and draft of the manuscript. MAPB, DMG, and FVM were involved in the acquisition and analysis of data. CMPT, ADF, AHL, and AD critically revised the manuscript. All authors read and approved the final manuscript.

Data availability All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication All the authors consent to publish the paper.

Competing interests The authors declare no competing interests.

Disclosures All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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