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ORIGINAL ARTICLE

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Efficacy and safety of pulsed-field versus conventional thermal ablation for atrial fibrillation: A systematic review and meta-analysis

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Abstract

Background: Pulsed-field ablation (PFA) has emerged as an innovative alternative to radiofrequency (RF) and cryoablation because it selectively targets myocardial tissue. Thus, we aim to estimate the efficacy and safety of PFA versus thermal ablation for atrial fibrillation (AF) ablation.

Methods: A systematic review and meta-analysis were retrieved from PubMed, WOS, SCOPUS, EMBASE, and CENTRAL through September 2023. We used RevMan V. 5.4 to pool dichotomous data using risk ratio (RR) and continuous data using mean difference (MD) with a 95% confidence interval (CI). PROSPERO ID: CRD42023480321

Results: We included 17 studies with a total of 2255 patients. PFA was significantly associated with a decreased incidence of AF recurrence (RR: 0.66 with 95% CI [0.51, 0.87], $p = .003$). However, there was no significant difference between PFA and thermal ablation in arrhythmia recurrence (RR: 0.92 with 95% CI [0.74, 1.46], $p = .42$). PFA was significantly associated with decreased total procedure time (MD: −15.15 with 95% CI [−20.23, −10.07], $p < .00001$), decreased heart rate change (MD: −7.39 with 95% CI [−12.16, −2.62], $p = .002$), decreased phrenic nerve palsy (RR: 0.38 with 95% CI [0.15, 0.98], $p = .05$), and reduced esophageal lesions (RR: 0.09 with 95% CI [0.01, 0.69], $p = .02$). On the contrary, PFA was significantly associated with increased pericardial tamponade (RR: 6.14 with 95% CI [1.43, 26.33], $p = .01$).

Conclusion: PFA was significantly associated with decreased AF recurrence, total procedure time, heart rate change, phrenic nerve palsy, esophageal lesion, and increased incidence of pericardial tamponade compared with thermal ablation.

KEYWORDS
ablation, atrial fibrillation, pulsed-field

1 | INTRODUCTION

Atrial fibrillation (AF) is a global health concern, affecting around 60 million individuals worldwide and causing over 8 million disability-adjusted life years. The risk of developing AF during one's lifetime is about 33%, though this risk can vary based on age, gender, race, and clinical risk factors.[1] In the United States, AF affects at least three to 6 million people, and projections suggest that this number could increase to approximately 6 to 16 million by the year 2050.[2]

AF catheter ablation creates scar tissue in the left atrium to block chaotic electrical activity. The current methods include radiofrequency (RF) and cryoablation catheters. These thermal ablation techniques risk collateral damage to adjacent tissues because of the heat generated, potentially causing complications like nerve damage or injury to vital structures. Incomplete treatment is also a concern, as variations in tissue composition and blood flow can affect the distribution of thermal energy, potentially leaving residual disease. Additionally, postprocedural pain associated with thermal ablation can significantly impact the patient's quality of life, requiring further management strategies.[3–7]

Cryoablation for AF is a minimally invasive medical procedure for treating abnormal heart rhythms. Performed by electrophysiologists, this technique involves threading a catheter through blood vessels to the heart. The catheter's tip releases extremely cold temperatures, typically using nitrous oxide, to create scar tissue in the heart areas, contributing to AF. Freezing these specific areas disrupts abnormal electrical pathways, restoring a regular heart rhythm. Compared with radiofrequency ablation, which uses heat, cryoablation may cause less pain and discomfort and is less likely to damage surrounding tissues.[3]

Nonthermal ablation methods, like pulsed-field ablation (PFA), use high-voltage electrical fields in microsecond pulses to precisely target cardiac tissue while minimizing damage to surrounding structures. This precision reduces the risk of collateral damage and offers a controlled, reproducible means of tissue destruction. PFA addresses the limitations of thermal ablation, potentially providing safer and more tailored treatments, especially important for preserving healthy tissues and ensuring successful patient outcomes.[8]

PFA is an innovative and safe alternative to traditional ablation methods for treating AF. It uses a catheter to deliver controlled electrical pulses to the heart, creating precise lesions that block abnormal electrical pathways. PFA effectively treats AF with minimal complications.[8–10]

This systematic review and meta-analysis investigate the efficacy and safety outcomes from randomized and nonrandomized clinical studies of PFA versus thermal ablation for AF. This meta-analysis aims to compare the techniques used for AF ablation and could have substantial implications for approaching AF in clinical settings, potentially influencing how AF is treated.

2 | METHODOLOGY

2.1 | Protocol registration

The study's protocol was registered in PROSPERO under ID CRD42023480321 following the Preferred Reporting Items for Systematic Review and Meta-analysis of Interventional Studies (PRISMA) statement[11] and the Cochrane Handbook for Systematic Reviews and Meta-Analysis[12] guidelines.

2.2 | Data sources and search strategy

Databases, including PubMed, CENTRAL, Web of Science, SCOPUS, and EMBASE were searched by two reviewers (A.M.A. and M.T.A.) through September 2023 without any restrictions. The strategy was made using [all fields] for searching studies that assess “pulsed field” ablation in “atrial fibrillation” Patients. More details are in (Table S1).

2.3 | Eligibility criteria

Randomized controlled trials and nonrandomized comparative studies that met all of our PICO criteria were included: population (P): patients with paroxysmal or persistent AF underwent first or repeat ablation; intervention (I): PFA; comparison (C): thermal ablation including RF ablation or cryoballoon ablation; outcomes (O): Our primary outcomes were the number of patients suffering from AF recurrence and the number of patients suffering from arrhythmia recurrence (any tachyarrhythmia recurrence (AF, atrial tachycardia [AT], atrial flutter [AFL])). Our secondary outcomes were procedural outcomes, including total procedure time and fluoroscopy time. In contrast, safety outcomes, including heart rate, any complications, all-cause mortality, phrenic nerve palsy, pericardial tamponade, esophageal lesions, stroke/transient ischemic attack (TIA), and systemic thromboembolism have been assessed. Exclusion criteria were duplicate publications, reviews, and conference abstracts.

2.4 | Study selection

Three reviewers (H.E., A.A., and M.E.) independently screened the titles and abstracts using the Covidence platform. After excluding the duplicates, the three reviewers independently screened the full texts in accordance with the previous eligibility criteria mentioned. Any conflicts have been resolved by (A.M.A. and M.T.A.).

2.5 | Data extraction

Four reviewers (H.E., A.A., M.E., and M.A.) independently extracted data from the eligible studies using an Excel sheet. A.M.A. and M.T.A. resolved any conflicts.

This sheet encompassed: (1) a summary sheet (study design, country, number of centers, recruitment duration, source of data, total participants, intervention used, control used including description of the control with the type of energy, primary outcome, and follow-up duration); (2) baseline information (Number of patients in each group, gender (male), age (years), body mass index (BMI), CHA_2DS_2-VASc score, left atrium diameter, left ventricular ejection fraction (LVEF), AF type (paroxysmal or persistent), comorbidities, which include hypertension, diabetes mellitus, ischemic heart disease (IHD) or coronary artery disease, dyslipidemia, and stroke/TIA); and (3) study outcomes (AF recurrence, atrial arrhythmia recurrence, total procedure time, fluoroscopy time, heart rate change, high sensitive troponin-I (hsTnI) change, high sensitive troponin-T (hsTnT) change, S100 concentration change, left superior pulmonary vein (LSPV) ablation area, left inferior pulmonary vein (LIPV) ablation area, right superior pulmonary vein (RSPV) ablation area, right inferior pulmonary vein (RIPV) ablation area, and total posterior ablation area). We also included safety data, which included any complications, phrenic nerve palsy, stroke/TIA, pericardial tamponade, all-cause mortality, systemic thromboembolism, and esophageal lesions. Conflicts were discussed and resolved by consensus.

2.6 | Risk of bias

Four reviewers (H.E., A.A., M.E., and M.A.) independently used the Cochrane RoB 2 tool[13] and Cochrane ROBINS-I tool[14] for quality assessment of randomized controlled trials (RCTs) and nonrandomized studies, respectively. RoB 2 tool was used to assess the risk of bias in RCTs by judging five domains: randomization process, deviation from intended intervention, missing outcome data, how the outcomes were measured, and selection of the reported results, while ROBINS-1 tool was used to assess the risk of bias in nonrandomized studies by judging seven domains: confounding bias, bias arising from selection of the participants, bias in classification of the interventions, bias due to deviation from intended interventions, bias due to missing outcomes, bias in measurement of the outcomes, and bias in selection of the reported results. The reviewers resolved any conflicts by consensus.

2.7 | Statistical analysis

RevMan v5.3 was used to run the statistical analysis.[15] To pool the results of dichotomous outcomes, we used the risk ratio (RR), while for the continuous outcomes, we used the mean difference (MD), both with a 95% confidence interval (CI). We performed both the chi-squared and I-square tests to evaluate heterogeneity, where the chi-squared test detects the presence of heterogeneity, and the I-square test evaluates its degree. I-square was interpreted in accordance with the Cochrane Handbook (chapter nine)[12] as follows: heterogeneity is not significant for 0%–40%, moderate for 30%–60%, substantial for 50%–90%, and considerable for 75%–100%. We considered an alpha level below 0.1 for the chi-squared test to detect significant heterogeneity. A leave-one-out sensitivity analysis was employed to resolve the heterogeneity by excluding each study one time from the pooled analyzed studies. We used Stata MP Version 17 (Stata Corp) to create funnel plots and conduct Egger's test to detect publication bias in outcomes reported by 10 studies or more.

3 | RESULTS

3.1 | Search results and study selection

After searching the following databases (PubMed, CENTRAL, Embase, Web of Science, and Scopus), our search strategy resulted in 1160 records. After duplicate removal, we reached 622 for title and abstract screening and 54 records eligible for full-text screening. Finally, we included 17 studies by our eligibility criteria (Figure 1).

3.2 | Characteristics of included studies

We included 17 studies (one RCT[16] and 16 nonrandomized studies[17–32]) with 2255 patients, with 1051 patients in the PFA group and 1204 in the thermal group. For the PFA group, all included studies have used the FARAPULSE™ system (Boston Scientific)[16–28,30–32] except Reddy et al., which has used the HexaPulse System (Affera, Inc).[29] More details about the characteristics of included studies and enrolled patients are summarized in Tables 1 and 2; Table S2.

3.3 | Risk of bias

We used Cochrane RoB 2 and ROBINS-1 to evaluate the risk of bias. One study had an overall high risk of bias,[29] while nine studies had an overall some concerns.[17,18,20–23,26,28,31] RoB results are shown in Figure 2. In addition, the RoB decisions for each domain are outlined in Tables S3 and S4.

3.4 | Primary outcomes: AF Recurrence and arrhythmia recurrence

PFA was significantly associated with a low incidence of AF recurrence (RR: 0.66 with 95% CI [0.51, 0.87], $p = .003$) (Figure 3A). However, there was no significant difference between PFA and

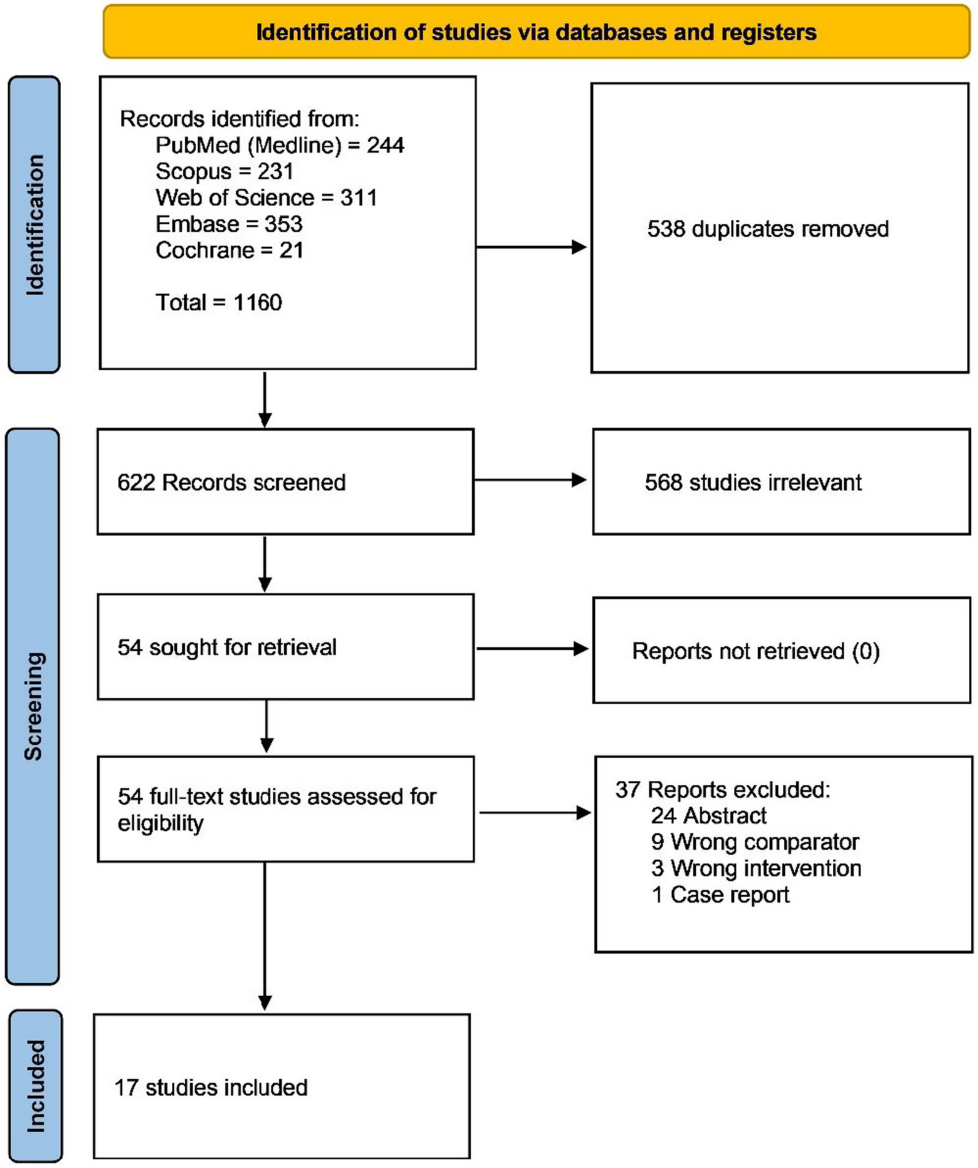


FIGURE 1 PRISMA flowchart of the screening process.

thermal ablation in the incidence of atrial arrhythmia recurrence (RR: 0.92 with 95% CI [0.74, 1.13], $p = .42$) (Figure 3B). Regarding AF recurrence and atrial arrhythmia recurrence, the pooled studies were homogenous ($I^2 = 0\%$, $p = .55$) and ($I^2 = 21\%$, $p = .28$), respectively.

3.5 | Secondary outcomes

3.5.1 | Procedural outcomes

PFA was significantly associated with decreased total procedure time (MD: −15.15 with 95% CI [−20.23, −10.07], $p < .00001$) (Figure 4A). However, there was no significant difference between PFA and thermal ablation in fluoroscopy time (MD: 2.83 with 95% CI [−0.38, 6.04], $p = .08$) (Figure 4B).

Pooled studies were heterogeneous in total procedure time ($I^2 = 78\%$, $p < .00001$) and fluoroscopy time ($I^2 = 97\%$, $p < .00001$). Regarding total procedure time and fluoroscopy time, heterogeneity was not resolved by leave-one-out sensitivity analysis (Table S5).

A funnel plot was used to detect possible publication bias. Regarding total procedure time, we did not find significant asymmetry by inspection, indicating no significant publication bias (Egger's p-value = .68) (Figure S2). Moreover, we did not find significant asymmetry by inspection regarding fluoroscopy time, suggesting no significant publication bias (Egger's p-value = .42) (Figure S3).

3.5.2 | Safety outcomes

PFA was significantly associated with decreased heart rate change (MD: −7.39 with 95% CI [−12.16, −2.62], $p = .002$) (Figure S1), decreased incidence of phrenic nerve palsy (RR: 0.38 with 95% CI [0.15, 0.98], $p = .05$), and reduced incidence of esophageal lesions (RR: 0.09 with 95% CI [0.01, 0.69], $p = .02$). However, there was no significant difference between PFA and thermal ablation in the incidence of any complications (RR: 0.90 with 95% CI [0.80, 1.02], $p = .10$), the incidence of stroke/TIA (RR: 0.52 with 95% CI [0.14, 1.91], $p = .32$), the incidence of systemic thromboembolism (RR: 0.33 with 95% CI [0.01, 8.01], $p = .50$), and all-cause mortality (RR: 0.33 with 95% CI [0.01, 8.07], $p = .50$). On the contrary, PFA was significantly associated with an increased incidence of pericardial tamponade (RR: 6.14 with 95% CI [1.43, 26.33], $p = .01$) (Figure 5).

The pooled studies were homogenous in the incidence of any complications ($I^2 = 17\%$, $p = .29$), phrenic nerve palsy ($I^2 = 0\%$, $p = .80$), stroke/TIA ($I^2 = 0\%$, $p = .72$), pericardial tamponade ($I^2 = 0\%$, $p = .85$), and esophageal lesions ($I^2 = 0\%$, $p = .38$). However, pooled studies were heterogeneous in heart rate change ($I^2 = 86\%$, $p < .0001$). Regarding heart rate change, heterogeneity was best resolved by excluding Schipper et al. ($I^2 = 0\%$, $p = .96$) (Table S5).

4 | DISCUSSION

Catheter ablation has proven to be a highly effective intervention for addressing AF. Traditional thermal ablation methods, such as RF and cryoablation, have shown reasonable efficacy over the years. However, these approaches have limitations, including the potential for collateral tissue damage (like the esophagus and phrenic nerve) and prolonged application times ranging from seconds to minutes.[33–36]

PFA introduces a novel approach by utilizing a rapid, nonthermal mechanism of cell death. The goal was to improve the efficiency, safety, and, potentially, the overall effectiveness of cardiac ablation procedures. PFA aims to minimize collateral damage that has occurred with thermal ablation while still achieving the desired therapeutic effects.[35,37]

Although injuries to the esophagus, phrenic nerve, and PVs are relatively rare with thermal ablation, they present a risk to patients. Based on preclinical data, PFA appears to have a preferential impact on cardiac cells, sparing pulmonary venous tissue, esophageal cells, and myelinated nerve cells.[36] Promisingly, intentional overablation of these collateral tissues with pulsed fields in preclinical studies did not result in substantial injury, and initial human pilot data have shown encouraging results.[36]

However, making direct comparisons between PFA technologies and traditional thermal ablation methods is challenging due to differences in the execution and endpoints of clinical studies.

In individuals experiencing persistent AF, the ongoing structural and electrical remodeling of the heart creates a complex foundation for initiating and perpetuating the arrhythmia that leads to recurrent AF. More extensive ablation approaches have been implemented, including targeting complex fractionated electrograms, rotors, or voltage-based ablation. However, the procedural complexity during persistent AF ablation raises the risk of complications due to the increased number of lesions required, emphasizing the importance of establishing lasting lesions.[38] PFA has also been applied in the treatment of persistent AF patients. A recent study presented findings on the safety and durability of lesions created by PFA for both PVI and left atrial posterior wall (LAPW) ablation in cases of persistent AF. Notably, acute PVI and LAPW ablation were successfully achieved in all patients. Subsequent examinations, including esophagogastroduodenoscopy and repeat cardiac computed tomography, revealed no mucosal lesions or PV narrowing. Invasive remapping further demonstrated the enduring isolation of targeted areas.[38]

The theoretical proposition suggests that PFA could yield more comprehensive lesions, penetrating the entire thickness of the myocardium. This could decrease the likelihood of PV reconnection, a crucial factor in the recurrence of AF. However, an associated concern arises from the hypothesis that PFA may have a subdued impact on nervous tissue, leading to inadequate ablation of the adjacent ganglionated plexi.[38] These ganglionated plexi play a significant role in the pathogenesis of AF by interacting with the sympathetic and parasympathetic nervous systems. Suppose the effect of PFA on the nervous tissue is attenuated. In that case, it may compromise the efficacy of ablating these critical structures, potentially leaving behind substrates that could contribute to the persistence or recurrence of AF. An intriguing aspect supporting this hypothesis is the notable absence of PV reconnections observed during follow-up mapping post-PFA procedures. This explains the decreased incidence of recurrent AF after PFA compared with thermal ablation.[38]

PFA employs microsecond, high-voltage electrical fields to induce irreversible electroporation, enhancing cell membrane permeability and subsequent cell death. Various factors, such as cell characteristics, pulse parameters, and electrode distance, influence the reversibility of membrane hyperpermeability. PFA lesions maintain homogeneity, preserving extracellular matrix architecture, microvascular structures, and nerves. The brief duration and pulses ($< 100\,\mu s$) enable high-energy delivery with minimal thermal impact, potentially reducing collateral damage to surrounding tissue. PFA was significantly associated with decreased total procedure time.[4,28,39–41] However, there was no significant difference between PFA and thermal ablation in fluoroscopy time. This may be attributed to operator inexperience and the widespread use of nonfluoroscopic electro-anatomical mapping systems with thermal ablation. Anticipated decreases in fluoroscopy time are expected with growing familiarity with PFA and the integration of mapping systems in the future.[42]

As mentioned in the results, PFA was significantly associated with a low incidence of AF recurrence. PFA was significantly associated with decreased heart rate change, decreased incidence of phrenic nerve palsy, and decreased incidence of esophageal lesions.[39] However, there was no significant difference between PFA

TABLE 1 Summary characteristics of the included studies.

Study ID	Study design	Country	Total participants	Intervention
Badertscher et al.[17]	Prospective, single-center, cohort study	Switzerland	115	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Blockhaus et al.[18]	Retrospective, single-center, cohort study	Germany	43	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Cochet et al.[19]	Prospective, single-center, cohort study	France	41	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Kawamura et al.[20]	Retrospective, multi-center, cohort study	Czech Republic and USA	59	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Krisai et al.[21]	Prospective, multi-center, cohort study	Switzerland	60	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Kupusovic et al.[22]	Retrospective, single-center, cohort study	Germany, Canada, Austria	26	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Kuroki et al.[23]	Retrospective, multi-center, cohort study	Czech Republic, USA	80	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Lemoine et al.[24]	Prospective, single-center, cohort study	Germany, UK	91	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Maurhofer et al.[25]	Prospective, single-center, cohort study	Switzerland	200	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Musikantow et al.[26]	Retrospective and Prospective, single-center, Cohort Study	USA	120	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
My et al.[27]	Prospective, single-center, cohort study	Germany	60	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Nakatani et al.[28]	Retrospective, single-center, cohort study	France	41	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Reddy et al.[29]	Retrospective and Prospective, multi-center, Cohort Study	Czech Republic and Lithuania	107	Pulsed-field ablation HexaPulse System (Affera, Inc)
Reddy et al. (ADVENT)[16]	Randomized controlled trial (RCT)	USA	607	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Schipper et al.[30]	Retrospective, single-center, cohort study	Germany	108	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Tohoku et al.[31]	Prospective, single-center, cohort study	Germany	97	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).
Urbanek et al.[32]	Retrospective, single-center, cohort study	Germany	400	Pulsed-field ablation FARAPULSE™ System (Boston Scientific).

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; NA, not available; PET/CT, positron emission tomography/computed tomography; PVI, pulmonary vein isolation; PVs, pulmonary veins.

and thermal ablation in the incidence of any complications, the incidence of stroke/TIA, the incidence of systemic thromboembolism, and all-cause mortality. On the contrary, PFA was significantly associated with an increased incidence of pericardial tamponade.

Using thermal and distal PV ablation can result in the depletion of the collagen matrix, potentially leading to PV stenosis. In contrast, the innovative PFA system, employing nonthermal irreversible electroporation, demonstrated no association with PV stenosis in animal studies and initial clinical applications.[35,43–45] Due to rare findings of stenosis, it is difficult to assess by this data analysis.

Considering the esophagus's proximity to the left atrium's rear wall, preventing esophageal injury has become a significant focus

Control	Are patients undergoing their first ablation or repeat ablation?	Primary outcome	Follow-up duration
Single-catheter high-power short-duration radiofrequency ablation	First ablation	Efficiency, safety, myocardial injury, and mid-term outcomes	214 [107–380] days
Cryoballoon ablation	NA	Characterization of the antral lesion size	12 months
Radiofrequency and cryoballoon ablation	First ablation	Assess injury on the esophagus, descending aorta, and Phrenic nerve	3 months
Thermal energy ablation (radiofrequency, cryo, or laser)	NA	Level of pulmonary vein isolation	2.5 months
Thermal energy ablation (radiofrequency, cryo)	First ablation	Troponin release after pulmonary vein isolation	24 h
Cryoballoon ablation	NA	Fibroblast activation using 68GaFAPI PET/CT after pulmonary vein isolation	6 months
Radiofrequency ablation	NA	Ostial dimensional changes	3 months
Cryoballoon ablation	First ablation	Neurocardiac damage after PVI	Minutes after PVI
Radiofrequency and cryoballoon ablation	First ablation	Recurrence of any atrial tachyarrhythmia	1 year
Cryoballoon ablation and radiofrequency ablation	NA	Assess the impact of pulsed-field ablation on the cardiac Ganglionated plexi in patients undergoing PVI	3 months
Radiofrequency balloon multielectrode catheter	NA	Acute lesion extension of PVI obtained by pulsed-field ablation and radiofrequency balloon after 3D mapping measured the postprocedural troponin release	NA
Radiofrequency or cryoablation ablation	First ablation	Compare the left atrial (LA) structural and mechanical characteristics after pulsed-field ablation vs. thermal ablation	9 ± 4 months
Radiofrequency Ablation	First ablation	The composite occurrence of major adverse events within 7 days. The primary efficacy endpoint was the electrical isolation of all PVs	At least 1 month (most >3 months)
Radiofrequency ablation or cryoballoon ablation	First ablation	Freedom from a composite of initial procedural failure, documented atrial tachyarrhythmia after a 3-month blanking period, antiarrhythmic drug use, cardioversion, or repeat ablation. The primary safety endpoint included acute and chronic device- and procedure-related serious adverse events	12 months
Cryoballoon ablation	NA	Primary endpoints included procedural data, reported postprocedural discomfort, and arrhythmia-free survival	12 months
Cryoballoon ablation	NA	To reveal the clinical impact of pulsed-field ablation on ICANS by investigating the serum S100 increase (DS100), a well-known denervation-relevant biomarker	6 months
Cryoballoon ablation	NA	Documented recurrence of atrial tachyarrhythmias >30 s after a 3-month blanking period	12 months

during PVI procedures.[8] Using thermal ablation has caused various esophageal alterations ranging from redness to fistulas have been documented, with an atrio-esophageal fistulas being particularly problematic due to their strong association with serious health complications and mortality.[8] Importantly, PFA has not been shown to cause esophageal damage.

PFA has been proposed to reduce phrenic nerve injury during AF ablation. The precise and controlled nature of the electrical fields generated in PFA may contribute to a lower risk of damage to adjacent structures such as the phrenic nerve.[8,37,39] The primary advantage of PFA is its precision and reduced collateral damage to surrounding tissues, such as the pericardium. This characteristic

TABLE 2 Baseline characteristics of the participants.

	Number of patients in each group		Age (years), mean (SD)		BMI, mean (SD)		CHA2DS2VAS, mean (SD)	
Study ID	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Badertscher et al.[17]	52	63	65 (10)	65 (10)	NA	NA	NA	NA
Blockhaus et al.[18]	23	20	57.13 (10.32)	59.1 (8.96)	28.13 (3.6)	26.27 (3.78)	1.52 (1.1)	1.65 (1.35)
Cochet et al.[19]	18	23	58 (9)	59 (9)	NA	NA	NA	NA
Kawamura et al.[20]	20	39	56.9 (11.0)	66.1 (9.3)	NA	NA	NA	NA
Krisai et al.[21]	20	40	NA	NA	NA	NA	NA	NA
Kupusovic et al.[22]	15	11	65.3 (10.2)	65.1 (9.40)	28.8 (4.9)	27.9 (4.5)	2.6 (1.2)	2.4 (1.5)
Kuroki et al.[23]	37	43	58.9 (10.1)	61.9 (9.4)	NA	NA	NA	NA
Lemoine et al.[24]	51	40	68 (12)	63 (13)	27 (5)	28 (5)	2.7 (1.7)	2.3 (1.6)
Maurhofer et al.[25] (PFA vs. RFA)	40	80	62.6 (9.6)	62.4 (10.8)	25.9 (4.1)	25.9 (3.7)	NA	NA
Maurhofer et al.[25] (PFA vs. CBA)	40	80	62.6 (9.6)	62.7 (12.1)	25.9 (4.1)	26.3 (4.5)	NA	NA
Musikantow et al.[26] (PFA vs RFA)	40	40	59.1 (10.3)	61.1 (8.3)	NA	NA	NA	NA
Musikantow et al.[26] (PFA vs CBA)	40	40	59.1 (10.3)	59.9 (12.5)	NA	NA	NA	NA
My et al.[27]	28	32	69 (12)	65 (13)	NA	NA	NA	NA
Nakatani et al.[28]	18	23	56 (9)	60 (8)	26 (4)	26 (3)	0.5 (0.8)	0.7 (0.8)
Reddy et al.[29]	36	71	60.7 (8.9)	NA	30.2 (4.2)	NA	NA	NA
Reddy et al. (ADVENT)[16]	305	302	62.4 (8.7)	62.5 (8.5)	28.3 (4.6)	29 (4.8)	1.7 (1.2)	1.7 (1.2)
Schipper et al.[30]	54	54	69 (11)	67 (13)	27.8 (5.0)	28.1 (4.5)	3.0 (1.8)	2.7 (1.7)
Tohoku et al.[31]	54	43	69 (9)	69 (9)	28 (5)	28 (6)	NA	NA
Urbanek et al.[32]	200	200	70 (11.1)	67.6 (6.6)	27.3 (5.2)	27 (5.2)	2.7 (1.5)	2.7 (2.2)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CBA, cryoballoon ablation; LA, left atrium; LVEF, left ventricular ejection fraction; N, number; NA, not available; FA, pulsed-field ablation; RFA, radiofrequency ablation; SD, standard deviation.

theoretically reduces the risk of complications, which are more common in thermal ablation techniques that can cause extensive heat-related damage.

However, despite these advantages, there is a notable incidence of cardiac tamponade associated with PFA procedures. This complication may be attributed to the relative inexperience of operators with PFA devices. As this technology is relatively new, practitioners may not have the familiarity and nuanced understanding necessary to minimize risks effectively. With more experience and refined techniques, it is expected that the incidence of such complications will decrease. Another contributing factor could be body movement during the delivery of PFA. Movement can potentially cause the PFA device to inadvertently ablate unintended areas, leading to damage and complications such as cardiac tamponade. Ensuring patient immobility during the procedure and improving device stability might help mitigate this risk.[16,46]

Nonthermal complications such as cerebral events and vascular complications are not exclusive to either thermal ablation or PFA. In contrast, thermal ablation can be associated with specific issues like PV stenosis, esophageal lesions, and phrenic nerve palsy.[8] Specialized techniques commonly used in thermal ablation, like esophageal deviation, temperature monitoring, and phrenic nerve pacing, are not consistently applied in PFA procedures. Complications unique to PFA, such as coronary vasospasm, were not thoroughly evaluated in the included studies, representing a limitation in the safety analysis. This becomes more concerning when additional ablation lesions are delivered close to coronary arteries, possibly contributing to the observed high rates of transient hypotension and bradycardia/asystole events requiring right ventricular pacing in certain studies. While coronary vasospasm has been mostly subclinical and treatable with nitroglycerin, postablation cardiac magnetic resonance imaging indicated no esophageal injury in PFA patients, contrasting with evidence of such injuries in thermal ablation patients.[4,36,39] Studies with routine postablation cardiac imaging also showed a more significant narrowing of PV ostia in thermal ablation patients, possibly due to less chronic fibrosis with PFA. Although PFA in the included studies did not result in reported atrio-esophageal fistula, PV stenosis, or phrenic nerve injury, the sample sizes were insufficient to

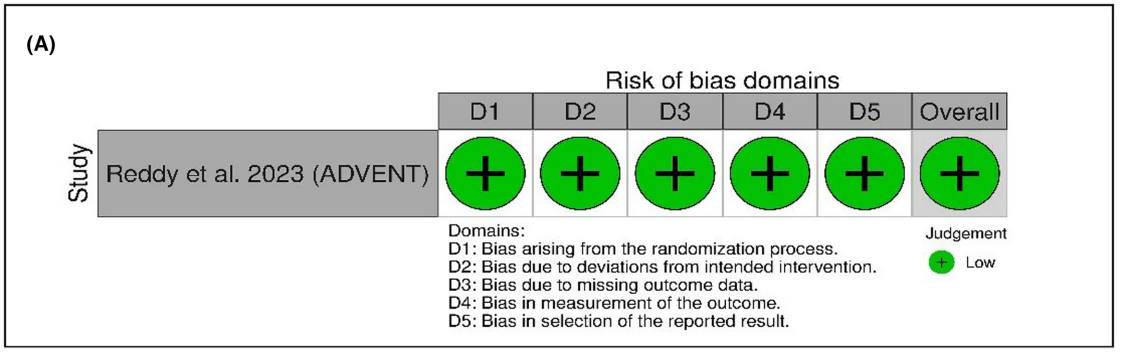
LVEF, mean (SD)		LA diameter (mm), mean (SD)		AF type N. (%)			
				Paroxysmal		Persistent	
Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
56 (11)	56 (11)	NA	NA	29 (56)	35 (56)	23 (44)	28 (44)
55.65 (7.60)	55 (8.1)	41.22 (3.14)	41 (2.77)	12 (52.18)	10 (50)	11 (47.8)	10 (50)
62 (6)	61 (8)	NA	NA	18 (100)	23 (100)	0 (0)	0 (0)
63.6 (3.7)	60.8 (7.5)	41.7 (5.0)	41.1 (6.0)	20 (100)	39 (100)	0 (0)	0 (0)
NA	NA	NA	NA	11 (56.7)	23 (56.7)	9 (43.3)	18 (43.3)
52.7 (8.8)	55.2 (5.7)	NA	NA	9 (60.0)	4 (36.4)	6 (40)	7 (64.6)
63.0 (3.4)	60.4 (5.8)	41.2 (3.9)	37.9 (7.0)	37 (100)	43 (100)	0 (0)	0 (0)
52 (12)	53 (9)	NA	NA	21 (41)	19 (47)	30 (59)	21 (53)
58.3 (3.8)	58.3 (3.8)	41.7 (5.4)	41 (7.2)	40 (100)	80 (100)	0 (0)	0 (0)
58.3 (3.8)	60.3 (6.9)	41.7 (5.4)	41.7 (5.3)	40 (100)	80 (100)	0 (0)	0 (0)
63.1 (5.4)	64.3 (4.8)	44 (4)	42 (4)	40 (100)	40 (100)	0 (0)	0 (0)
63.1 (5.4)	57.6 (12.7)	44 (4)	48 (11)	40 (100)	40 (100)	0 (0)	0 (0)
47.4 (12.9)	57.6 (4.8)	NA	NA	17 (60.7)	25 (78.1)	11 (39.3)	7 (21.9)
62 (6)	61 (8)	NA	NA	18 (100)	23 (100)	0 (0)	0 (0)
59.4 (6.1)	NA	43.6 (5.8)	NA	26 (72)	NA	10 (28)	NA
NA	NA	38.8 (5.7)	39.6 (5.8)	305 (100)	302 (100)	0 (0)	0 (0)
53.3 (10.9)	54.9 (10.6)	38.8 (5.8)	39.6 (6.1)	16 (30)	17 (31)	38 (70)	37 (69)
60.8 (7.2)	59.1 (13.4)	40.5 (5.9)	39.5 (7.0)	32 (59)	25 (58)	22 (41)	18 (42)
NA	NA	41.3 (6.7)	40 (6)	116 (58)	127 (63.5)	84 (42)	73 (36.5)

detect significant differences. Larger-scale studies with thousands of patients are essential to uncover proper distinctions in these rare complications, particularly considering the low reported risks for atrio-esophageal fistula, severe PV stenosis, and phrenic nerve injury after thermal ablation procedures.[42]

Our study showed a significant association between cardiac tamponade and PFA compared with catheter-based ablation. During PFA, pulsed electric fields are applied to targeted cardiac tissue to create lesions and interrupt aberrant electrical pathways. However, unintended effects on surrounding structures, particularly the pericardium, may lead to cardiac tamponade. Cardiac tamponade arises when there is damage to the pericardium. The pulsed electric fields employed in PFA can induce cellular injury, potentially extending beyond the intended ablation zone. Clinical manifestations of cardiac tamponade include hypotension, tachycardia, and signs of inadequate perfusion. The occurrence of cardiac tamponade highlights the importance of refining PFA techniques and ensuring meticulous procedural execution to minimize the risk of complications.[47,48]

Our study found a significant difference in heart rate changes associated with PFA compared to catheter-based ablation. The observed decrease in heart rate changes after PFA compared with thermal ablation may be attributed to the fundamental differences in how these two ablation methods affect cardiac tissue.[8,38,39] Heat is generated during thermal ablation, such as RF or cryoablation, to create lesions in the targeted tissue. The rise in temperature can stimulate the cardiac nerves and potentially lead to increased sympathetic nervous system activity, which might result in transient changes in heart rate. In contrast, PFA utilizes electric fields to induce nonthermal irreversible electroporation, causing cell membrane disruption and cell death without substantial heat generation. This approach may have a more selective impact on the cellular structures involved in arrhythmogenic pathways while minimizing unintended stimulation of cardiac nerves. As a result, the sympathetic nervous system may be less activated, leading to a more stable heart rate profile compared to thermal ablation methods.[8,39]

PFA is an emerging technology in cardiac ablation that is being closely compared with more established thermal ablation



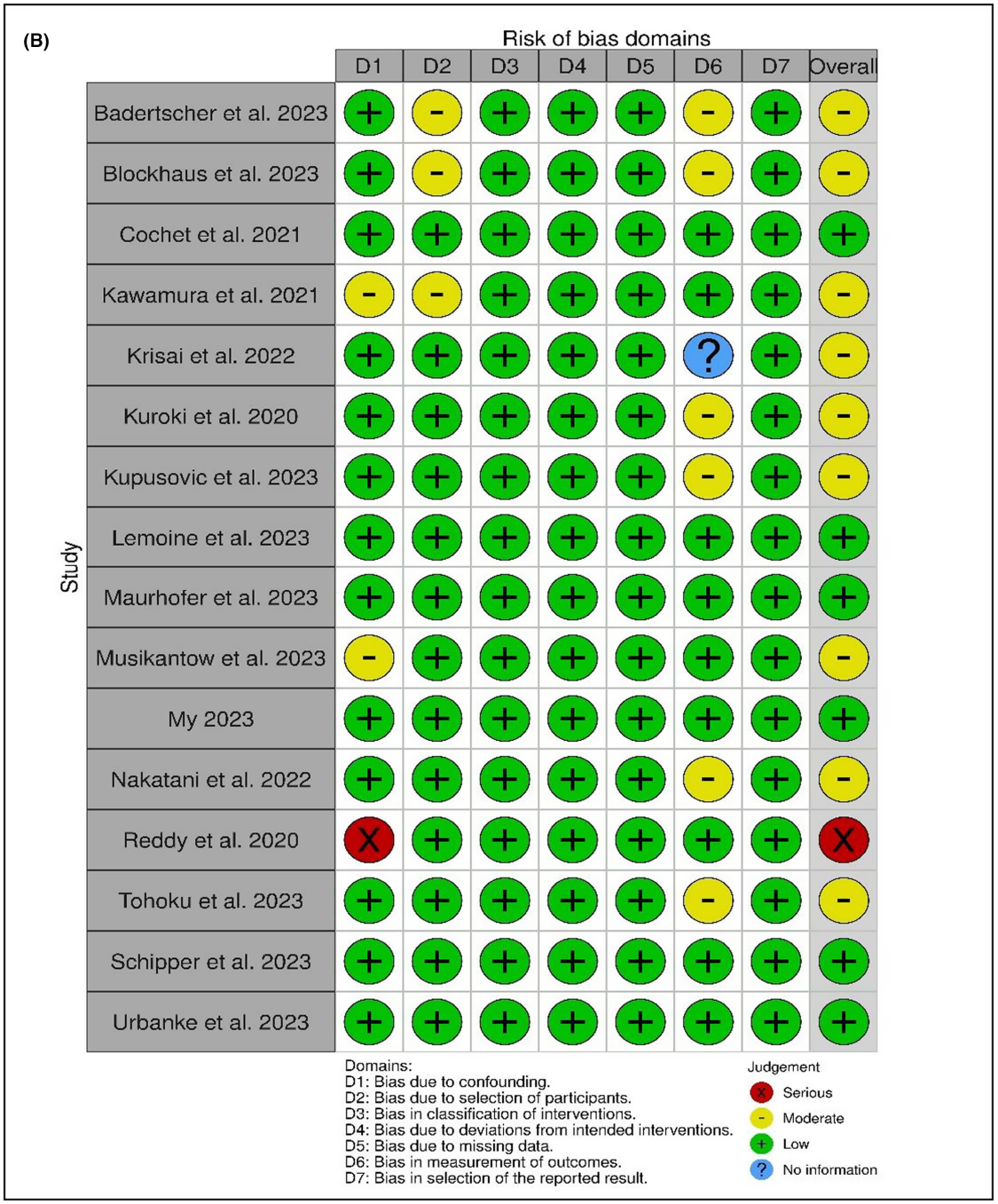


FIGURE 2 Quality assessment of the risk of bias (ROB) for the included trials (A) ROB assessment for randomized controlled trials (ROB-2 tool); (B) ROB assessment for nonrandomized trials (ROBINS-1).

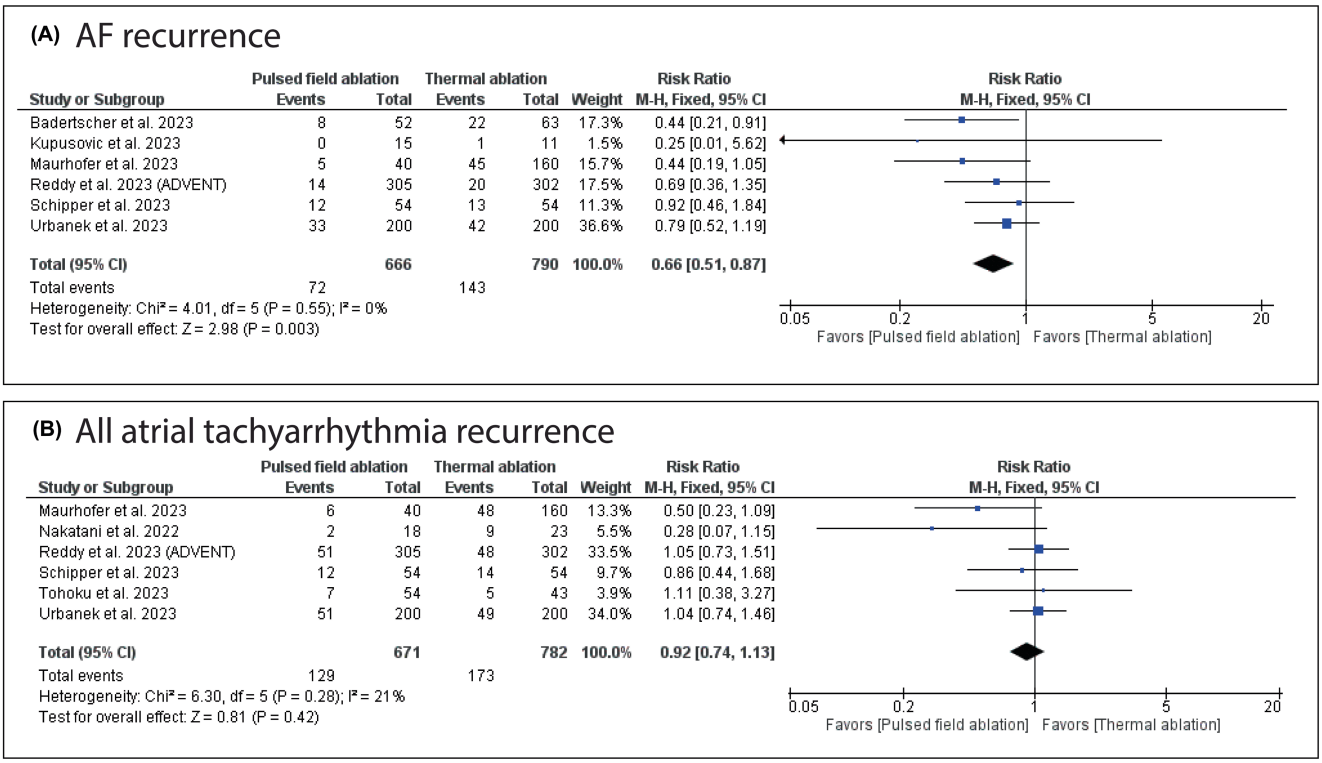


FIGURE 3 Forest plot of the primary outcomes A) AF recurrence and B) All atrial tachyarrhythmia recurrence. RR, risk ratio; CI, confidence interval.

procedures, such as radiofrequency (RF) and cryoablation. Initial studies comparing these techniques revealed some challenges and higher complication rates associated with PFA. For instance, the MANIFEST-PF trial, published in 2022, reported a tamponade rate of 0.97%. This higher incidence of complications raised concerns about the safety and efficacy of early PFA techniques.[49]

However, as the technology has matured and operators have gained more experience, significant improvements have been observed. The MANIFEST-17K trial, which included a larger cohort of 17,642 patients and was presented at the American Heart Association (AHA) conference in 2023, demonstrated a dramatic reduction in the tamponade rate to 0.36%. This substantial decrease highlights the rapid advancements in PFA technology and technique, resulting in better safety profiles and fewer complications. Similar improvements have been noted in other types of complications associated with PFA. As operators become more skilled and technology evolves, the incidence of adverse events continues to decline.[50] This trend suggests that PFA may become a more reliable and safer alternative to thermal ablation methods in the future. Despite these promising developments, it is important to cautiously approach systematic reviews and meta-analyses. The rapid evolution of PFA technology means that earlier studies may not accurately reflect the current state of the technique. Consequently, making definitive conclusions based on these early comparisons may be misleading and premature. Furthermore, some studies' relatively small sample sizes, with around 1000 patients in each group, may not provide sufficient data to draw comprehensive conclusions. Larger, long-term studies and continuous monitoring of outcomes are necessary to fully understand the benefits and potential risks of PFA compared to traditional thermal ablation methods.[50]

In summary, while PFA is an exciting and promising technology in cardiac ablation, ongoing advancements, and increasing operator experience are crucial for its continued success. As the technology improves, PFA has the potential to offer a safer and more effective alternative to thermal ablation. Still, it is essential to remain cautious in making definitive conclusions based on early data. More extensive studies and further research will clarify PFA's long-term efficacy and safety.

5 | STRENGTHS AND LIMITATIONS

This systematic review and meta-analysis have notable limitations that warrant acknowledgment. First, the comparative studies exhibited heterogeneity in populations, study designs, and ablation protocols, potentially restricting the generalizability of the findings. Significant heterogeneity existed in using various devices at different intervals, introducing potential variations in the complication assessment across studies. Also, all included studies employed the same PFA catheter, which may constrain the broader

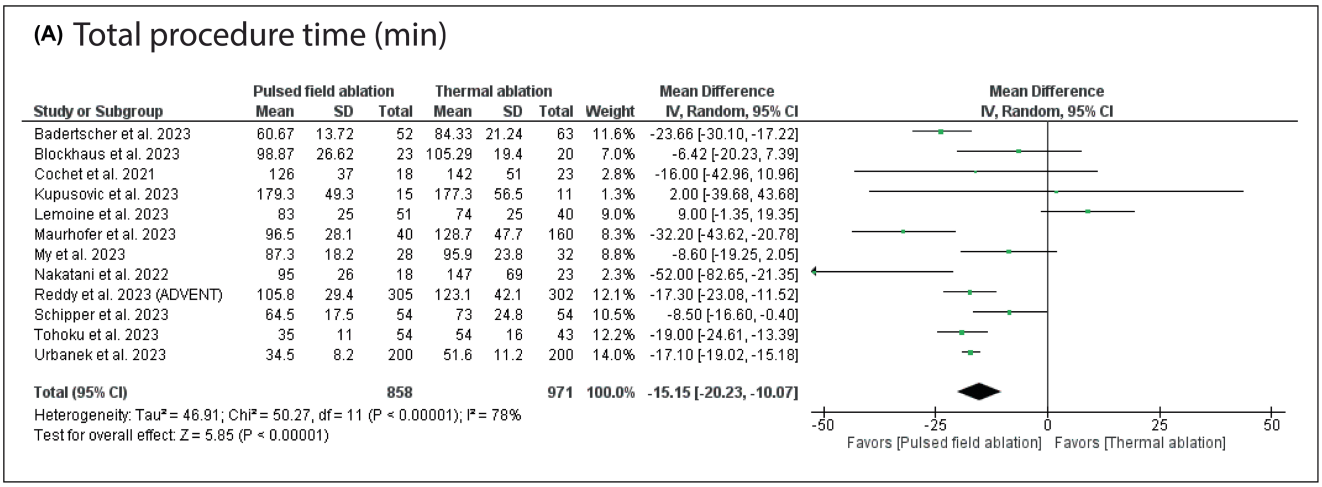


FIGURE 4 Forest plots of the secondary outcomes A) total procedure time and B) fluoroscopy time. MD, mean difference; CI, confidence interval.

applicability of the results. Second, some patients are included in more than one study simultaneously because some studies were conducted at the same center, and some studies used some patients' data from the same trials. Third, some studies' relatively small sample sizes, with approximately 1000 patients per group, may not offer enough data to make definitive conclusions. Larger, long-term studies and ongoing outcome monitoring are essential to thoroughly evaluate PFA's benefits and potential risks compared to traditional thermal ablation methods. Fourth, due to the limited availability of data for most outcomes, it was not possible to analyze subgroups based on radiofrequency and cryoablation separately. Therefore, our study aimed to estimate the efficacy and safety of PFA compared to all types of thermal ablation. Fifth, the majority of the included studies were nonrandomized, making it inevitable that there are biases related to patient backgrounds. Finally, our analysis of the outcomes of mortality and systemic embolism is limited due to the presence of only one event in total between the two groups, making these results need to be interpreted cautiously. Despite these limitations, our study stands as the first meta-analysis comparing AF ablation with PFA versus thermal energy sources, providing valuable insights into the outcomes of PFA as an innovative ablation energy source compared to the current standard of care.

6 | IMPLICATION FOR FUTURE RESEARCH

As various PFA systems emerge with distinct features, forthcoming research may clarify differences in the clinical performance of these systems. To understand PFA technologies comprehensively, conducting more extended studies, including durability evaluations after repeat ablation and randomized trials, is essential. The creation of extensive PFA lesions around the PVs may form narrow channels on the left atrial posterior wall, potentially serving as an isthmus for roof-dependent atrial tachycardia. This potential arrhythmogenic effect warrants further investigation, and awareness of this effect might influence the selection of catheter size in PFA.[8,51] Subsequent studies should explore whether variations in catheters or waveforms could be linked to insufficient PVI or if acute markers of reversible electroporation during the index procedure can predict more

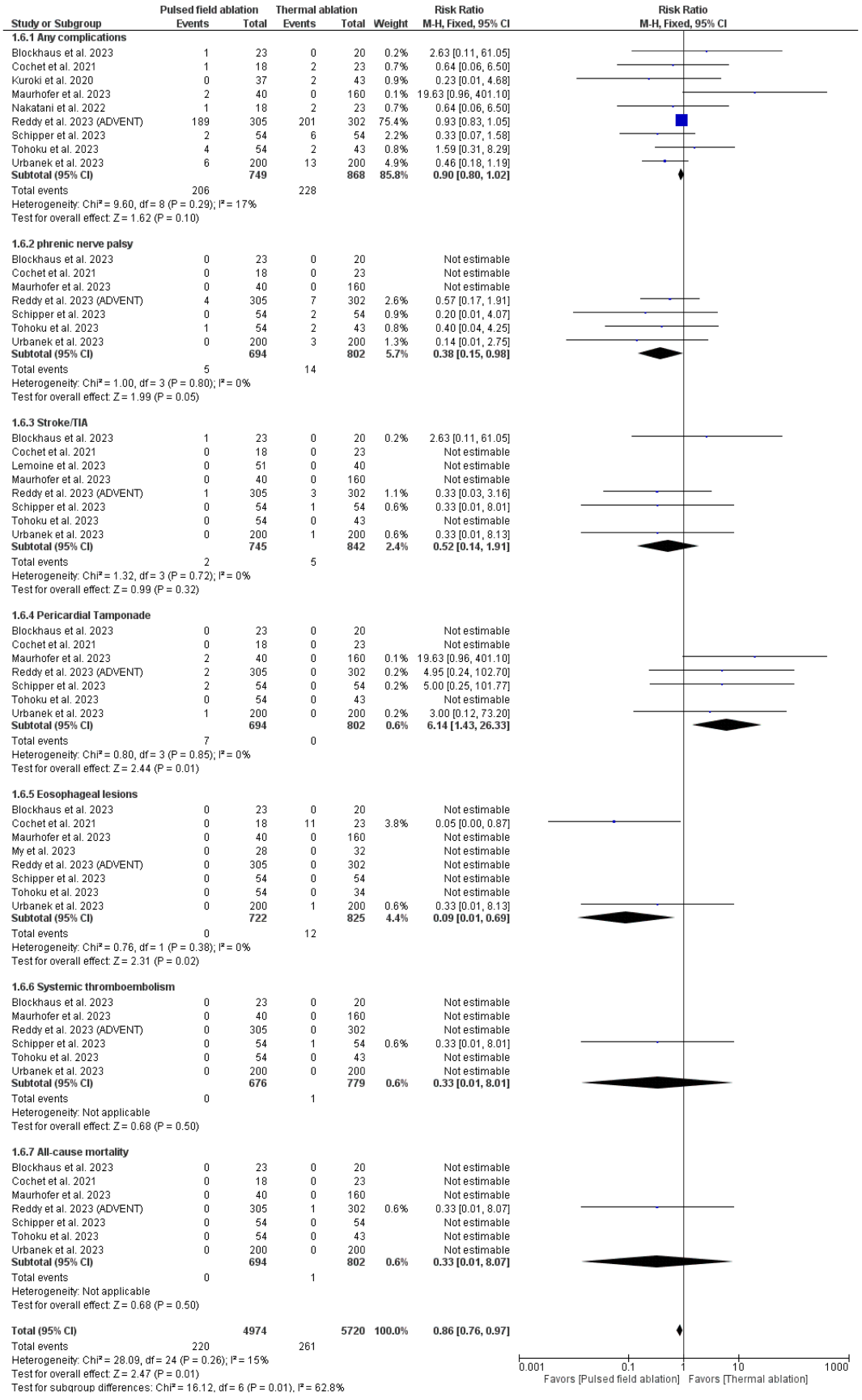


FIGURE 5 Forest plot of the safety outcomes. RR, risk ratio; CI, confidence interval.

durable ablation with PFA. Unlike thermal ablation, which has been extensively studied regarding catheter types, ablation duration, power settings, and lesion sets, PFA is still in its early stages, and the optimal ablation strategy remains unknown.

7 | CONCLUSION

This meta-analysis indicates that compared with thermal energy ablation, PFA is associated with shorter procedural times but no difference in fluoroscopy times, with discernible differences in the incidence of phrenic nerve palsy and esophageal lesions. However, PFA is associated with a high incidence of pericardial tamponade.

Additionally, PFA is associated with lower incidence in rates of recurrent AF during follow-up with no difference in atrial arrhythmia recurrence. However, larger randomized controlled trials with extended follow-up periods comparing PFA to thermal ablation are essential for a more comprehensive evaluation.

AUTHOR CONTRIBUTIONS

M.T.A. conceived the idea. A.M.A. and M.T.A. designed the research workflow. A.M.A. and M.T.A. searched the databases. H.E., A.A., M.E., M.T., and M.A. screened the retrieved records, extracted relevant data, assessed the quality of evidence, and B.A. resolved the conflicts. A.M.A. and A.A.I. performed the analysis. A.M.A., A.N., and M.T.A. wrote the final manuscript. B.A. and M.T. supervised the project. All authors have read and agreed to the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Disclosures for Dr. Annabelle S. Volgman (October 2023) Consulting—Sanofi, Pfizer, Janssen; Clinical Trials: Janssen, Novartis and NIH Clinical Trials; Stock: Apple, Inc while the other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Not applicable.

PATIENT CONSENT STATEMENT

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

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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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