Pulsed-field ablation versus thermal ablation for atrial fibrillation: A meta-analysis

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BACKGROUND Pulsed-field ablation (PFA) is an alternative to thermal ablation (TA) in patients with atrial fibrillation (AF) receiving catheter-based therapy for pulmonary vein isolation (PVI). However, its efficacy and safety have yet to be fully elucidated.

OBJECTIVE The purpose of this study was to compare the acute and long-term efficacies and safety of PFA and TA.

METHODS We performed a systematic review and meta-analysis of randomized and nonrandomized controlled trials comparing PFA and TA in patients with AF undergoing their first PVI ablation. The TA group was divided into cryoballoon (CB) and radiofrequency subgroups. AF patients were divided into paroxysmal atrial fibrillation (PAF) and persistent atrial fibrillation (PersAF) subgroups for further analysis.

RESULTS Eighteen studies involving 4998 patients (35.2% PFA) were included. Overall, PFA was associated with a shorter procedure time (mean difference [MD] −21.68; 95% confidence interval [CI] −32.81 to −10.54) but longer fluoroscopy time (MD 4.53; 95% CI 2.18–6.88) than TA. Regarding safety, lower (peri-)esophageal injury rates (odds ratio [OR] 0.17; 95% CI 0.06–0.46) and higher tamponade rates (OR 2.98; 95% CI 1.27–7.00) were observed after PFA. In efficacy assessment, PFA was associated with a better first-pass isolation rate (OR 6.82; 95% CI 1.37–34.01) and a lower treatment failure rate (OR 0.83; 95% CI 0.70–0.98). Subgroup analysis showed no differences in PersAF and PAF. CB was related to higher (peri)esophageal injury, and lower PVI acute success and procedural time.

CONCLUSION Compared to TA, PFA showed better results with regard to acute and long-term efficacy but significant differences in safety, with lower (peri)esophageal injury rates but higher tamponade rates in procedural data.

KEYWORDS Cryoballoon ablation; Paroxysmal atrial fibrillation; Persistent atrial fibrillation; Pulmonary vein isolation; Pulsed-field ablation; Radiofrequency ablation; Thermal ablation

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Introduction

Atrial fibrillation (AF), the most prevalent cardiac arrhythmia, is commonly treated using catheter ablation. This minimally invasive procedure involves the passage of a thin, flexible catheter through blood vessels to the heart to disrupt abnormal electrical pathways in the cardiac tissue, which causes irregular heartbeats.[1] Conventionally, thermal ablation (TA) involving radiofrequency (RF) or cryothermal energy is used to achieve pulmonary vein isolation (PVI).[2] The European Society of Cardiology recommends catheter ablation in patients with paroxysmal atrial fibrillation (PAF) who do not respond to medication.[3] American College of Cardiology/American Heart Association recommends catheter ablation for patients who remain symptomatic after an adequate trial of antiarrhythmic therapy and for whom a rhythm control strategy remains desired.[4]

Pulsed-field ablation (PFA) has emerged as a new and promising alternative to TA for the treatment of PAF and persistent atrial fibrillation (PersAF). In PFA, microsecond electrical pulses destabilize cell membranes by forming nanopores in irreversible electroporation, resulting in cell death.[2] PFA seems to preferentially ablate heart tissue with

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KEY FINDINGS

- Pulsed-field ablation (PFA) procedures were shorter than thermal ablation (TA) procedures, but fluoroscopy time was longer in PFA procedures.
- PFA was related to a significantly lower treatment failure rate compared to TA. No significant differences were observed in <1-year and >1-year follow-up subgroup analyses.
- PFA was related to higher rates of tamponades and lower rates of periesophageal and esophageal injuries. No significant differences were observed regarding overall periprocedural complications between groups.
- In subgroup analysis, there were no significant differences in efficacy and safety outcomes between patients with paroxysmal atrial fibrillation or persistent atrial fibrillation. However, the cryoballoon subgroup was related to all (peri-)esophageal injuries of the TA group but with shorter procedural time compared to the radiofrequency group.

minimal or no damage to surrounding structures, such as the esophageal and phrenic nerve, and no pulmonary vein stenosis, all of which can be induced by TA.[2,3,5]

To date, PFA has met noninferiority criteria in terms of primary efficacy and point of freedom from a composite of initial procedural failure, documented atrial tachyarrhythmia after a 3-month blanking period, antiarrhythmic drug use, cardioversion, and repeat ablation, and in terms of the primary safety endpoint of device- and procedure-related serious adverse events at 1 year among patients with PAF receiving catheter-based therapy. However, the short- and long-term success and safety of PFA have not yet been fully determined, in contrast to the well-established cryoballoon (CB) and RF ablation techniques.[3,5]

The present study aimed to answer the question: Does PFA have superior short- and long-term outcomes and fewer procedural complications than TA in patients with AF?

Materials and methods

This systematic review and meta-analysis was performed according to the recommendations of the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines.[6] The protocol was registered with PROSPERO (CRD420234 72160).

Eligibility criteria

The following studies were included in the meta-analysis: (1) randomized and nonrandomized controlled trials; (2) studies that reported any of the outcomes of interest; (3) studies that compared PFA and TA for PVI in patients with PAF and/or PersAF; and (4) studies with patients undergoing their first PVI ablation. The following studies were excluded: (1) case reports; (2) editorials; (3) reviews; (4) expert opinions; (5) studies with no control groups; (6) conference abstracts; and (7) research letters/brief communications.

Search strategy and study selection

We systematically searched the databases of PubMed, Cochrane Library, Embase, and Cochrane Central Register of Controlled Trials from inception to February 2024.The following search terms were used: “pulse field ablation,” “pulsed field ablation,” “PFA,” “PF ablation,” “pulmonary vein isolation,” “PVI,” "PV ablation," “atrial fibrillation,” “AF,” “thermal ablation,” “radiofrequency,” “cryoballoon,” “RF,” “CB,” with the incorporation of the Boolean operators AND and OR. This search strategy identified all potentially relevant studies by manually reviewing the reference lists of the included studies and therefore was considered valid. Two reviewers (MC, RD) independently screened all retrieved records’ titles and abstracts to identify potentially eligible studies. The same 2 reviewers then assessed the full texts, and any disagreements were discussed with a third reviewer (VR).

Data extraction

Data from the included studies were independently extracted by 2 reviewers (MC, VR) using specifically designed electronic standardized data extraction. The data extracted included the study author, publication year, sample size, sample demographics, percentage of PAF patients, follow-up time, treatment failure, procedural data, procedural complications, and procedural acute success. Any disagreements were resolved through discussion with a third reviewer (AM). Any essential data missing or available in the study were calculated when possible, using the Cochrane Handbook.[7] We contacted the authors via e-mail to obtain the required information.

Endpoints and subanalyses

Primary outcomes were as follows: (1) rate of treatment failure after 3 months of blanking period and by any reason reported, such as any atrial tachyarrhythmia recurrence, including AF, atrial tachycardia, and atrial flutter, repeat ablation, use of antiarrhythmic drugs, and cardioversion; (2) acute success of PVI and first-pass isolation; and (3) overall periprocedural complications. Secondary outcomes were as follows: (1) procedural data, including procedure and fluoroscopy times; (2) tamponade; (3) (peri-)esophageal injuries, including temporary or permanent phrenic nerve palsy, phrenic nerve injury, esophageal injury, and atrioesophageal fistula; (4) high-sensitivity troponin levels; (5) vascular access complications, including groin hematoma, false aneurysm, bleeding, air embolism, and arteriovenous fistula; and (7) systemic embolic events, including stroke, transient ischemic attack, or any reported thromboembolism event. We also extracted data and analyzed the following

subgroups: (1) patients treated with CB; (2) patients treated with RF; (3) patients with PAF; and (4) patients with PersAF.

Quality assessment

Two reviewers (VR, JP) used the Cochrane Collaboration's risk of bias in nonrandomized studies of interventions (ROBINS-I)[8] tool to analyze 7 domains (confounding, selection, classification of intervention, deviation, missing data, measurement, and reporting bias) and classified nonrandomized studies as having a low, moderate, serious, or critical risk of bias. The revised tool for risk of bias in randomized trials (ROB2)[9] was used to analyze 5 domains (randomization, deviation, missing data, measurement, and reporting bias) and classify randomized controlled trials (RCTs) as having low concerns or high risk of bias. Publication bias was assessed using funnel plot analysis of point estimates according to study weights and Egger's regression asymmetry test.

Statistical analysis

Data were extracted from individual studies as odds ratios (ORs) to preserve time-to-event data from each study. The treatment effects for the binary endpoints were compared using ORs with 95% confidence intervals (CIs). Weighted mean differences (MDs) were used to pool continuous outcomes. Heterogeneity was evaluated using the Cochran Q test and Higgins I^2 statistic. $P < .10$ and $I^2 > 25\%$ were considered significant for heterogeneity. A sensitivity analysis was performed using the generic variance inversion method. The decision to use a random-effects model (the DerSimonian-Laird method) was made after critically appraising all included studies. R statistical software Version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

Results

The initial systematic literature search yielded 1122 results (Figure 1). After duplicate records and ineligible studies were removed, 28 remained and were fully reviewed to establish whether they met the inclusion criteria. Of these studies, 18 (2 RCTs and 16 nonrandomized prospective and retrospective cohort studies) met the inclusion criteria and were included in the meta-analysis.

Study selection and characteristics

These randomized and nonrandomized trials included a total of 4998 patients (62.5% of whom were male) with similar reported characteristics, such as age (median age 64 years), left atrial diameter (median 41 mm), left ventricular ejection fraction (median 56.6%), body mass index (median 27.6 kg/m^2), and CHA_2DS_2-VASc score (median 2.2 points). Most of the patients (66.2%) had PAF; 1761(35.2%) underwent PFA, and 3237(64.8%) underwent TA (71% CB, 28.9% RF). The characteristics of the study population are summarized in Table 1.

Procedural data

PFA procedures had a significantly shorter duration than TA procedures (MD –21.68; 95% CI –32.81 to –10.54; $P < .01$; $I^2 = 95\%9$) (Figure 2A).[2,3,10–25] However, fluoroscopy time was significantly shorter in TA procedures than in PFA procedures (MD 4.53; 95% CI 2.18–6.88; $P < .01$; $I^2 = 97\%$) (Figure 2B).[2,3,10–14,17–24] After sensitivity testing, the heterogeneity of both procedural and fluoroscopy times remained high ($I^2 > 90\%$) (Supplemental Figures S1A and S1B).

Subgroup analysis revealed that procedural time was significantly longer in the RF group than in the PFA group (MD –41.35; 95% CI –66.09 to –16.60; $P < .01$; $I^2 = 98\%$) (Figure 2C), with significant differences between the CB and RF subgroups ($P = .02$) (Figure 2C). However, although fluoroscopy time was significantly shorter in both CB and RF ablations ($P = .04$ and $P < .01$, respectively) (Figure 2D), there was no significant difference between them ($P = .08$) (Figure 2D).

Acute and long-term efficacy

Regarding acute efficacy, there was no statistically significant difference between PFA and TA in terms of initial PVI success (OR 1.62; 95% CI 0.21–12.36; $P = .64$; $I^2 = 49\%$) (Figure 3A),[2,3,10–12,15,17,18,20–25] but there was a significant difference in the rate of first-shot PVI (OR 6.82; 95% CI 1.37–34.01; $P = .02$; $I^2 = 96\%$) (Figure 3B).[2,3,10,12] These results were unchanged by the sensitivity analysis, which decreased the heterogeneity by omitting Reddy et al[2] from the initial PVI success data (OR 5.50; 95% CI 0.63–47.76; $P = .12$; $I^2 = 0\%$) (Supplemental Figure S1C) and the rate of first-shot PVI data (OR 12.15; 95% CI 3.96–44.57; $P < .01$; $I^2 = 88.7\%$) (Supplemental Figure S1D).

Subgroup analysis showed no statistical difference in acute PVI success when comparing PFA to CB ($P = .61$) (Supplemental Figure S2A). All studies that reported comparison to PFA and RF had 100% acute PVI success. Additionally, there was no significant difference in first-pass isolation between CB and RF subgroups ($P = .22$) (Supplemental Figure S2B).

To assess long-term efficacy, a 12-lead electrocardiogram or a 24-hour Holter electrocardiogram was used to identify any recurrence of atrial tachyarrhythmia, and patients were monitored using Holter monitoring in our studies. We observed a significantly lower treatment failure rate in the PFA group than in the TA group (OR 0.83; 95% CI 0.70–0.98; $P = .03$; $I^2 = 0\%$) (Figure 3C).

Subgroup testing for treatment failure revealed no significant difference <1 year after the procedure or >1 year after the procedure ($P = .97$) (Figure 3C); (2) no significant difference in PFA vs CB or RF patients ($P = .22$) (Figure 3D); (3) no significant difference in patients with PAF or PersAF ($P = .63$) (Figure 4A); (4) no significant difference in CB or RF ablations in patients with PAF ($P = .25$) (Figure 4B); and (5) no

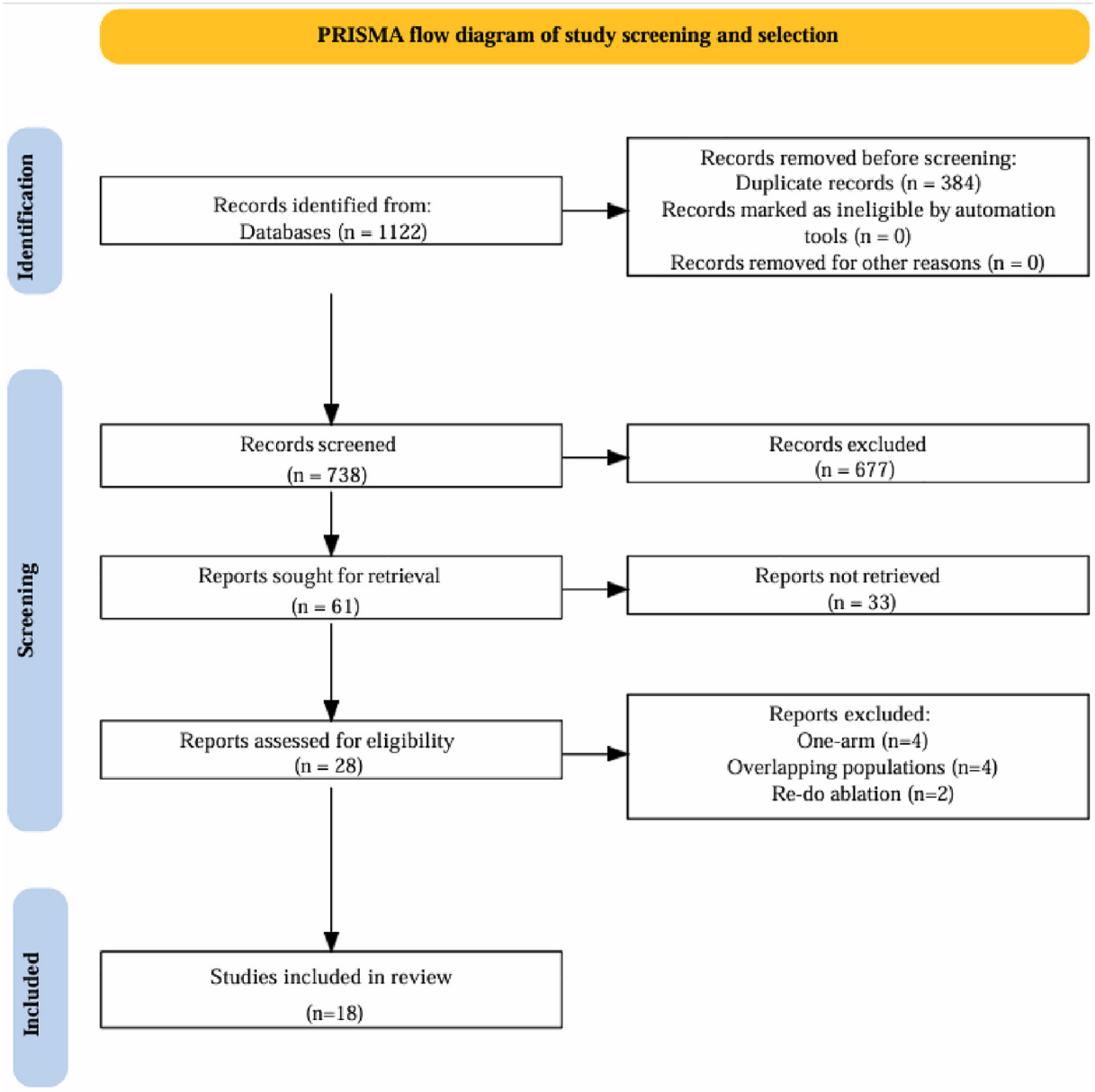

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of search results and reasons for exclusion of studies.

significant difference in PFA vs CB or RF ablations in patients with PersAF (P = .43) (Figure 4C).

Safety and adverse effects

There was no significant difference between the PFA and TA groups in terms of overall periprocedural complications (OR 0.79; 95% CI 0.47–1.33; P = .38; I^2 = 37%) (Figure 5A).[2,3,10–12,14–16,18–24] However, PFA showed significantly fewer periprocedural complications than TA after omitting the study by Popa et al[20] during the sensitivity analysis (OR 0.59; 95% CI 0.39–0.88; $P \leq .01$; I^2 = 0%) (Supplemental Figure S1E). In subgroup analysis, no significant difference was shown in CB or RF patients (P = .09) (Figure 5B).

There were significantly lower rates of periesophageal and esophageal injuries in the PFA group than in the TA group (OR 0.17; 95% CI 0.06–0.46; $P \leq .01$; I^2 = 0%) (Figure 5C).[2,3,10–12,14–16,19,21–23] However, the tamponade rate was significantly increased after PFA compared to TA (OR 2.98; 95% CI 1.27–7.00; P = .01; I^2 = 0%) (Figure 5D),[2,3,10,12,18] as were high-sensitivity troponin levels[10,17,19,20] after omitting Osmancik et al[19] during the sensitivity analysis (MD 421.42; 95% CI 251.49–591.35; $P \leq .01$; I^2 = 77.1%) (Supplemental Figure S1F).

No significant differences were found between the PFA and TA groups with regard to the specific complications of vascular access complications (OR 0.91; 95% CI 0.54–1.54; P = .73; I^2 = 0%) (Supplemental Figure S2C)[2,3,10–12,15,16,18–24] or systemic embolic events

Table 1 Summary of the included studies

Data/study	Design	Patients PFA/CB/RF	PAF (%) PFA/TA	Male (%) PFA/TA	Age (y) PFA/TA	BMI (kg/m^2) PFA/TA	HTN (%) PFA/TA	DM (%) PFA/TA	CAD (%) PFA/TA	LAd (mm) PFA/TA	LVEF (%) PFA/TA	CHA_2DS_2-VASc score† PFA/TA	Follow-up (d)
Osmancik et al[19]	RCT	33/0/32	61/63	64/78	61/64	29/31	67/69	18/31	12/6	42/44	59/58	2.4/2.3	NA
Badertscher et al[10]	Non-RCT	106/75/0	61/51	63/64	65/64	27/27	60/47	11/8	9/8	41/40	57/58	NA	404 ± 150
Maurhofer et al[14]	Non-RCT	40/80/80	100	30/76	62/62	26/26	65/61	8/11	20/15	42/41	60/60	NA	381 ± 20
My et al[17]	Non-RCT	28/0/32	61/78	60/53	69/65	NA	NA	NA	NA	NA	47/58	NA	NA
Kupusovic et al[13]	Non-RCT	15/11/0	60/36	67/100	65/65	29/28	80/91	13/9	33/36	NA	53/55	2.6/2.4	180
Schipper et al[22]	Non-RCT	54/54/0	30/31	69/69	69/67	28/28	72/69	17/17	31/26	39/40	53/55	3.0/2.7	273 ± 129
Wahedi et al[23]	Non-RCT	50/50/0	72/58	64/58	67/65	26/29	60/70	6/16	18/22	42/43	NA	2.2/2.4	NA
Wormann et al[24]	Non-RCT	57/0/57	30/30	33/40	67/67	28/27	65/60	16/14	25/19	40/38	56/56	3/3	90
Reddy et al[2]	RCT	305/135/167	100	34/35	62/62	28/29	57/52	11/11	10/17	NA	NA	1.7/1.7	360
Yang et al[25]	Non-RCT	36/0/36	58/53	72/64	68/65	NA	53/44	0/8	28/17	35/34	59/59	2.8/2.7	180
Urbanek et al[3]	Non-RCT	200/200/0	58/63	59/54	71/68	27/27	66/70	14/16	14/13	41/40	NA	2/3	374 ± 134
Nakatani et al[18]	Non-RCT	18/7/16	100	83/74	56/60	26/26	22/17	6/0	6/9	NA	62/61	0.5/0.6	270 ± 105
Rattka et al[21]	Non-RCT	94/47/0	56/51	62/74	63/64	44/57	78/55	17/32	NA	NA	NA	3/3	365
Van de Kar et al[16]	Non-RCT	473/1241/0	61/66	64/69	65/64	27/27	NA	9/7	NA	NA	55/55	NA	180
Della Rocca et al[12]	Non-RCT	174/348/348	100	63/63	62/63	27/27	45/43	9/8	6/7	42/42	59/58	2/2	360 ± 69
Popa et al[20]	Non-RCT	35/0/144	100	69/60	62/63	27/27	40/54	3/8	23/19	NA	59/58	1.7/1.9	180
Blockhaus et al[11]	Non-RCT	23/20/0	52/50	65/80	57/59	28/26	65/40	NA	9/25	41/41	56/55	1.5/1.7	NA
Grosse Meininghaus et al[15]	Non-RCT	20/33/24	35/44	70/53	72/66	28/29	80/93	5/16	NA	46/44	NA	NA	269 ± 22/786 ± 120

BMI = body mass index; CAD = coronary artery disease or vascular disease; CB = cryoballoon; DM = diabetes mellitus; HTN = hypertension; LAd = left atrial diameter; LVEF = left ventricular ejection fraction; NA = not available; PAF = paroxysmal atrial fibrillation; PFA = pulsed-field ablation; RCT = randomized controlled trial; RF = radiofrequency; TA = thermal ablation.

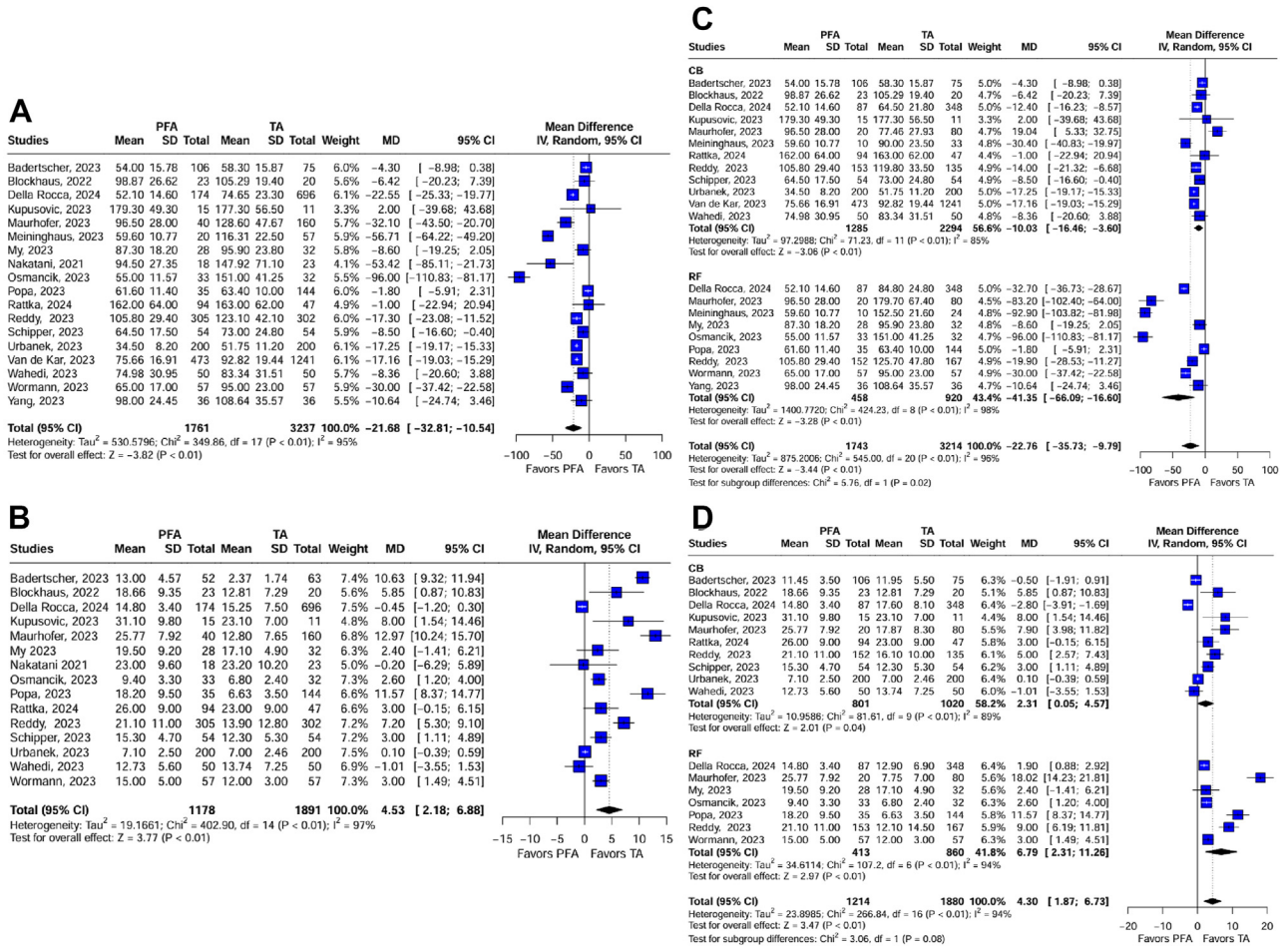

Figure 2 Mean difference (MD) and funnel plots for procedural data. **A:** Procedural time (minutes). **B:** Fluoroscopy time (minutes). **C:** Procedural time subgroup analysis (minutes): pulsed-field ablation (PFA) vs cryoballoon (CB) or radiofrequency (RF) **D:** Fluoroscopy time subgroup analysis (minutes): PFA vs CB or RF. Size of data markers in the forest plot indicate the weight of the study in the pooled analysis. Markers in the funnel plot indicate the distribution of studies around the estimated effect size. CI = confidence interval; IV = inverse variation.

(OR 1.52; 95% CI 0.57–4.07; P = .40; I^2 = 0%) (Supplemental Figure S2D).[2,3,10–12,14–16,20–23]

When performing subgroup testing, there was no significant difference between CB and RF subgroups with regard to tamponade rate (P = .87) (Supplemental Figure S2E), vascular access complications (P = .67) (Supplemental Figure S2F), or systemic embolic events (P = .31) (Supplemental Figure S2G). However, it was revealed that all (peri-)esophageal injuries occurred during CB ablations (Supplemental Figure S2H). All the adverse events reported in the studies included in this meta-analysis are given in Supplemental Figure S3.

Quality assessment

Appraisal of the individual non-RCTs is shown in Supplemental Figure S4A. Two observational studies were evaluated as having a severe risk of confounding bias due to the heterogeneous distribution of essential patient characteristics between the PFA and TA groups, with no reported statistical analysis of possible confounding factors.[15,17] The other 3 studies were evaluated as also having a severe risk of selection of patients.[11,20,21] Both RCTs were found to have a low risk of bias in all domains (Supplemental Figure S4B). Supplemental Figure S5A shows evidence of publication bias due to the asymmetric distribution of weighted studies in the treatment failure analysis, which was confirmed using Egger's regression test (P = .012). Supplemental Figure S5B is also asymmetric, with an Egger's regression test of P = .035. The other outcomes were not found to suggest publication bias using either the funnel plot analysis or Egger's regression test (procedural time, P = .52) (Supplemental Figure S5C; overall periprocedural complications = 0.34) (Supplemental Figure S5D).

Discussion

This systematic review and meta-analysis of 18 studies and 4998 patients compared PFA with TA for the treatment of AF. The significant findings of our meta-analysis were as follows. (1) PFA showed better rates of first-shot isolation and lower rates of treatment failure. (2) Fluoroscopy times were shorter in TA than in PFA procedures, but overall procedural times were longer for TA than for PFA, especially using RF.

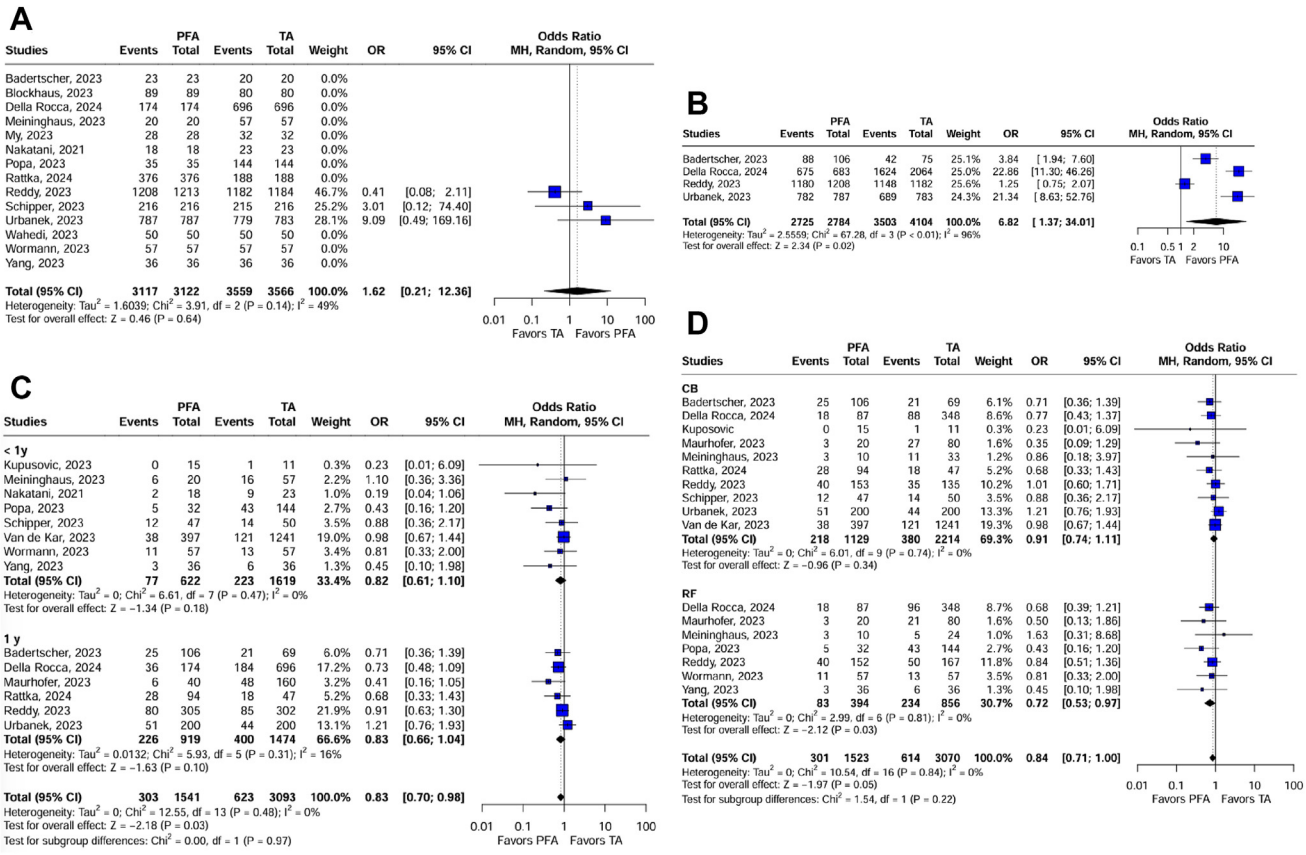

Figure 3 Odds ratios (ORs) and funnel plots for acute and long-term procedural efficacy. **A:** Acute Success pulmonary vein isolation. **B:** First-pass Isolation. **C:** Treatment failure was defined as <1 year and >1 year of follow-up. **D:** Treatment failure in PFA vs CB or RF patients. Size of data markers indicate the weight of the study in the pooled analysis. Markers in the funnel plot indicate the distribution of the studies around the estimated effect size. MH = Mantel-Haenszel; other abbreviations as in Figure 2.

(3) After sensitivity analysis, PFA ablations resulted in lower periprocedural complications than TA ablations. (4) PFA was associated with a higher rate of tamponade and higher levels of high-sensitivity troponin than those observed following TA. (5) PFA had a lesser impact than TA on the esophageal area. (5) PFA demonstrated efficacy in both patients with PAF and PersAF, with no significant difference between them. Furthermore, atrioesophageal fistula, the most serious complication of TA, was not observed in any of the studies analyzed due to its rarity; therefore, it could not offer any value to the analysis (Supplemental Figure S3).

PFA involves the application of high-voltage electrical fields for a period of microseconds to induce irreversible electroporation, which leads to increased cell membrane permeability and cell death.[26–30] A wide range of parameters can affect the potential for reversal of transmembrane hyperpermeability. Koruth et al[31] identified these parameters as cell size, shape, orientation, pulse width and amplitude, the number of pulses, monophasic or biphasic waveforms, pulse cycle duration, and the distance between the tissue and delivery electrodes. Because PFA lesions are homogeneous, the architecture of the extracellular matrix, microvascular systems, and nerves remains intact.[31,32] Although PFA transmits large quantities of energy into tissues, it has little effect on tissue temperature because of the short duration of each pulse. Rubinsky et al[27] suggested that this might reduce the amount of collateral damage to the surrounding tissue.

PVI caused by TA can damage the esophagus. Grosse Meininghaus et al[15] found that PFA, with its better tissue selectivity, might reduce esophageal and periesophageal damage and reduce or eliminate the risk of the potentially fatal complication of atrioesophageal fistula. Additionally, the inspIRE study (Study for Treatment of Paroxysmal Atrial Fibrillation [PAF] by Pulsed Field Ablation [PFA] System With Irreversible Electroporation [IRE]) assessed the safety and efficacy of a fully integrated biphasic PFA device with a variable-loop circular catheter for drug-refractory paroxysmal AF. This technique proved safe for paroxysmal AF ablation with no significant side effects, esophageal damage, or pulmonary vein stenosis. The 12-month effectiveness was equivalent to that of early RF ablation technology.[33]

Our meta-analysis found that PFA was associated with an increased incidence of pericardial tamponade, possibly because of the exceptionally rigid guidewire used to deliver the PFA catheter. Inadvertent left atrial appendage perforation by the guidewire occurred in 4 patients while attempting to engage the PV. The clinical sites involved universally transitioned to using a J-tip wire, and no subsequent cases of

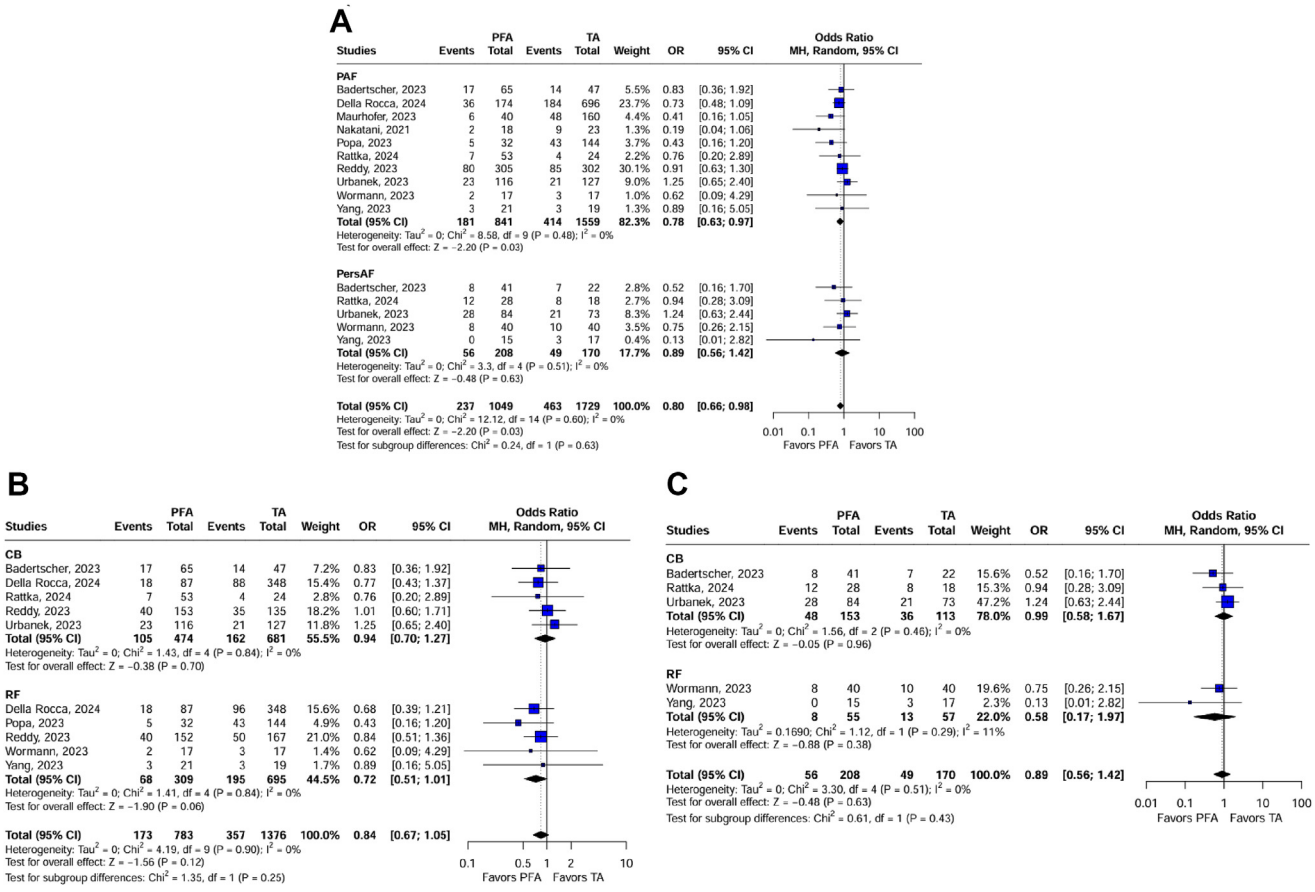

Figure 4 Odds ratio and funnel plot long-term procedure efficacy, subgroup analysis with paroxysmal atrial fibrillation (PAF) and persistent atrial fibrillation (PersAF) patients. **A:** Treatment failure in patients with PAF and PersAF. **B:** Treatment failure in patients with PAF compared to CB vs RF ablation. **C:** Treatment failure in patients with PersAF compared with CB vs RF ablations **D:** Treatment failure in patients with PersAF compared to CB vs RF ablation. Size of data markers indicates weight of study in the pooled analysis. Markers in funnel plot indicate the distribution of the studies around the estimated effect size. Abbreviations as in Figures 2 and 3.

pericardial tamponade were observed. The tight locking mechanism between the dilator and sheath also means that dilator unlocking could lead to sudden unintentional forward motion of the sheath.[34]

Our study also showed that PFA was associated with elevated high-sensitivity troponin levels. However, the result was not significant due to the large discrepancy brought about by Osmancik et al,[19] who reported an exceptional high-sensitivity troponin release 10 times higher in the PFA group than in the TA group, much higher than that reported by other included studies. A previous study by Krisai et al[35] found high-sensitivity troponin release after PFA to be approximately 1.6 times higher than that after RF and 1.9 times more than that after CB. It has been suggested that this is due to the larger and more advanced lesions induced by the floral shape of the PFA catheter. However, recent research has found that PVIs induced by PFA and TA have comparable magnitudes and shapes.[35,36] The increase in high-sensitivity troponin levels after PFA suggests that more complete ablation has been achieved; however, whether these elevated high-sensitivity troponin levels lead to improved lesion durability with time or affect safety requires investigation in future prospective studies.[35] Regardless of the type of ablation, serious adverse effects have been shown to occur in <1% of patients,[36] which is consistent with the findings of our study.

It is essential to note that although our studies did not identify them, various adverse effects, notably acute kidney injury, warrant attention. Several patients who underwent PFA exhibited hemoglobinuria within 24 hours after catheter ablation. Although it is recognized that high-voltage pulses may induce hemolysis, future discussions should consider their potential impact on renal function in patients.[37,38] Moreover, Venier et al[38] attributed 2 cases of acute kidney injury to acute and severe hemolysis after a PFA procedure, likely related to the frequency of its applications.

Conversely, PFA offers promising advantages, particularly its tissue specificity, which benefits cardiomyocytes because of its lower threshold in these fields. However, reproducible coronary spasm during PFA of the cavotricuspid isthmus (CTI) or mitral isthmus has been reported.[39–41] The proximity of PFA to the coronary arteries increases the risk of vasospasm, and focal PFA to the CTI induces subclinical coronary spasm when applied near the right coronary artery (RCA).[42] During a study involving RCA angiography concurrent with PFA of the CTI, severe RCA

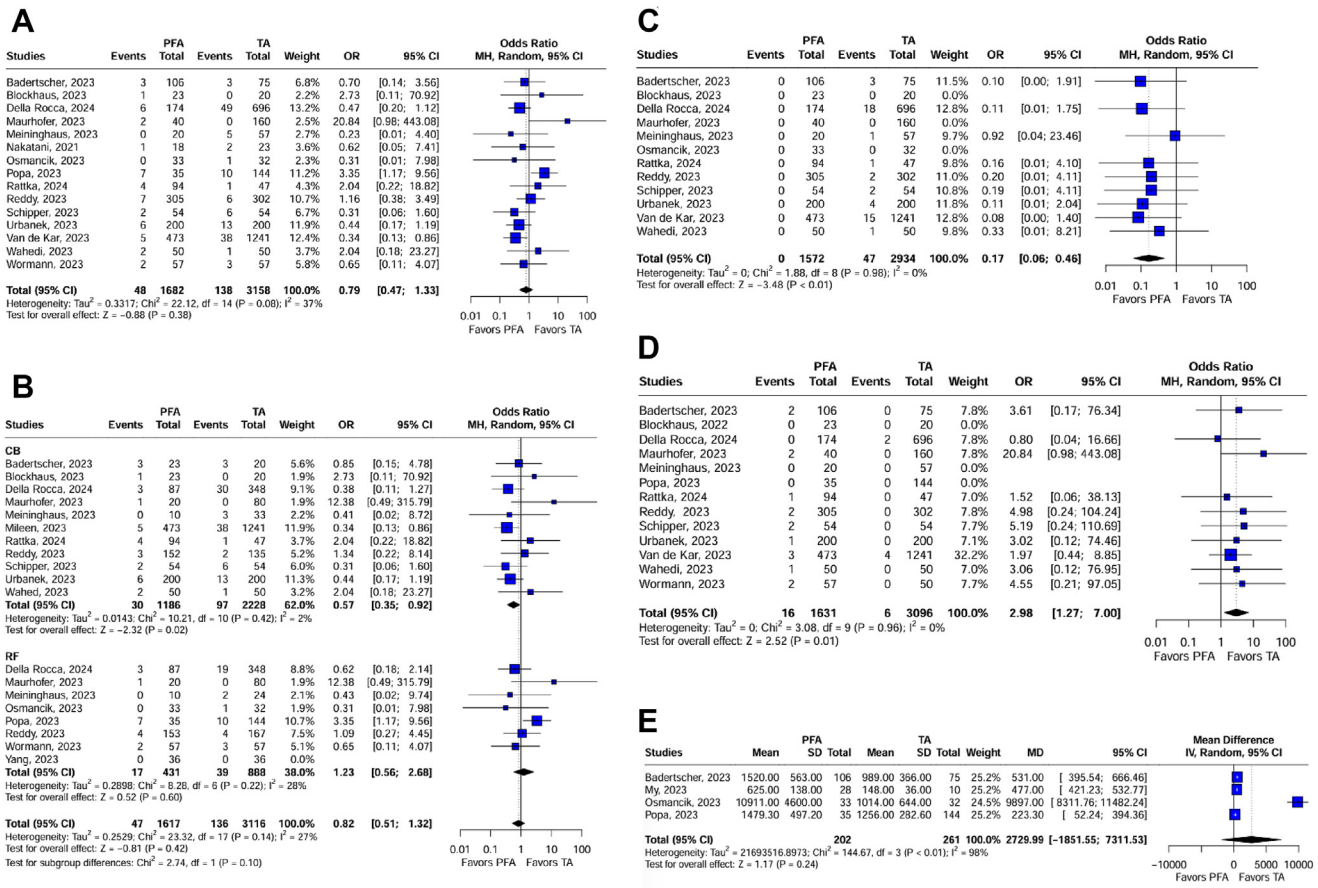

Figure 5 Odds ratios and funnel plots for procedural adverse events. **A:** Overall periprocedural complications. **B:** Subanalysis of periprocedural complications in PFA vs CB or RF. **C:** (Peri-)esophageal injuries. **D:** Tamponades. **E:** High-sensitivity troponin levels. Size of data markers indicate the study's weight in the pooled analysis. Markers in the funnel plot indicate the distribution of the studies around the estimated effect size. Abbreviations as in Figures 3 and 4.

spasms were universally observed. The reason for vasospastic response to PFA (vs TA) remains unclear. However, recent data indicate that the incidence and severity of vasospasm are significantly higher with PFA (nearly 100% incidence and severity) than with RF ablation (15% incidence and mild severity), suggesting a functionally and qualitatively distinct difference from PFA.[43] Nitroglycerin can be used prophylactically.[41,44]

The cost-effectiveness of FARAPULSE (Boston Scientific, Marlborough, MA) PFA is another topic of discussion. An analysis considering the clinical benefits, additional life-years gained, and perspective of the Social Security Institution (SGK) suggests that the system offers economic and social benefits in the reimbursement coverage for patients with PAF in Turkey.[45] Additionally, new techniques in PFA, such as a simplified workflow with direct transseptal access, could be used to shorten procedural times and reduce costs.[46] However, more comprehensive discussions are required to establish a firm understanding of these aspects.

It should also be noted that, in our study, despite longer fluoroscopy times in PFA compared to TA procedures, the overall procedural times were shorter for PFA, particularly when using RF. PFA could further optimize laboratory utilization and procedural times without compromising safety through a structured protocol that includes ketamine for sedation due to its advantageous pharmacologic properties in mitigating adverse effects. Factors such as shorter procedural times, patient satisfaction, and brief hospital stays are crucial for hospitals when selecting a sedation protocol and warrant further analysis.[47]

Recently, significant sinus pauses and/or atrioventricular block with PFA within the pulmonary vein antra adjacent to the cardiac ganglionated plexuses have been documented. Vagal responses have been mitigated by atrial and/or ventricular pacing or administration of atropine, but there might be some limitations regarding those strategies, such as potential side effects related to systemic anticholinergic activity.[48] PFA's mechanism and effect on the adjacent intrinsic cardiac autonomic nervous system are unclear. However, PVI with the PFA system is associated with only transitory and short-lasting vagal effects on the intrinsic cardiac autonomic nervous system, which recover almost completely within a few minutes after ablation.[49] Although more research should be conducted on this matter, these observations align with the lower nervous tissue destruction of PFA compared with TA.[50,51]

Additional research is needed to explore the association between catheter or waveform variations and inadequate

PVI. It also is vital to determine whether any acute markers of reversible electroporation can predict long-term reconnection, thereby improving long-term ablation success after PFA. Because PFA is still in the developmental stages, optimizing the ablation approach remains a work in progress. Although current evidence is promising, randomized and larger trials are necessary to comprehensively evaluate PFA safety and effectiveness in treating AF.

Comparisons to previous meta-analysis

A previous meta-analysis published in 2023 had significant flaws, including a small number of included publications involving only 1012 patients.[52] Only 1 of the 6 studies had a 2-arm design protocol, 2 of the included studies were conducted at the same center, and the study only included patients with PAF. In addition, 2 of the studies had a follow-up period of only 3 months. In contrast, we included patients with both PersAF and PAF, and we conducted subgroup and sensitivity analyses and Egger's tests to reduce bias and demonstrate the effects of heterogeneity. Our study included 3 times as many studies as the previous meta-analysis and involved almost 5 times the number of patients. Moreover, a meta-analysis published in 2024 included 1 RCT, 12 observational studies, 2 research letters, and 1 brief communication, and aimed to compare PFA with only CB ablations.[53] Their efficacy and safety had similar outcomes with those we found in our study. However, our outcomes also compare RF ablations with PFA and analyze some different periprocedural complications, such as vascular access complications and systemic embolic events. Additionally, we excluded research letters and brief communications from our analysis to reduce bias and improve the reliability of our results.

Study limitations

First, studies with different follow-up periods were included in the analysis. However, subgroup analyses were performed to evaluate differences in treatment failure rates. Moreover, the other reported outcomes, such as procedural data and periprocedural complications, did not have much influence during the follow-up period. Second, 2 included studies might have some overlapping PFA populations as they were both performed in the exact center and during the same period (Supplemental Figure S6).[22,24] However, their population characteristics revealed some important baseline differences, especially= the male proportion, and the control group differed between the studies. Therefore, both were included in the analysis. Third, the included populations were heterogeneous, resulting from the inclusion of only 2 RCTs. Finally, some outcomes showed heterogeneity and asymmetry that could not be corrected using sensitivity or subgroup analyses, representing a possible bias.

Conclusion

This meta-analysis found statistically significant differences between PFA and TA with regard to acute and long-term effectiveness and safety in both techniques. PFA procedures were related to better first-shot isolation rates and lower treatment failure rates than TA. PFA was also related to higher tamponade rates but less damage to the esophageal area. Moreover, these non-TAs had shorter durations than TAs, especially RF ablations, but fluoroscopy time was longer for PFA. The results of this meta-analysis suggest that PFA can be considered a faster and more efficient option for patients with PAF or PersAF than CB and RF TA. However, PFA has reported important safety differences from TA, raising the need to assess PFA myocardium-related complications and higher fluoroscopy exposure in further studies.

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Ethics Statement: This systematic review and meta-analysis was performed according to the recommendations of the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2024.04.012.

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