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REVIEW

Comparative Safety of Pulsed Field Ablation and Cryoballoon Ablation Technologies for Pulmonary Vein Isolation in Patients with Paroxysmal Atrial Fibrillation: A Critical Literature Review and Indirect Treatment Comparison

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ABSTRACT

Introduction: Cryoballoon ablation (CBA) is a standard catheter ablation technology with demonstrated clinical effectiveness for the treatment of paroxysmal atrial fibrillation (PAF); however, it can be associated with major adverse events, including phrenic nerve paralysis. Pulsed field ablation (PFA) is a novel, minimally thermal technology with comparable effectiveness and low safety risk. This study aimed to compare the safety profiles of PFA and CBA through critical analyses of the literature and indirect treatment comparisons.

Methods: Studies were identified by searching the MEDLINE database and the Clinicaltrials.gov registry. Registered clinical trials and/or Food and Drug Administration Investigation Device Exemption (FDA IDE) studies evaluating PFA or CBA in adult patients with drug-refractory PAF between January 2008 and March 2023 were selected. Comparative safety between PFA and CBA was assessed for major and prespecified adverse events. Indirect comparisons were conducted using the proportion of patients experiencing adverse events and confirmed with single-arm meta-analyses and sensitivity analyses.

Results: Data were extracted from three PFA publications including a total of 497 patients and six CBA studies including a total of 1113 patients. The analysis revealed that PFA was associated with significantly lower risk of major adverse events {risk difference − 4.3% [95% confidence interval (CI) − 5.8, − 2.8]; risk ratio 0.16 [95% CI 0.07, 0.45]} and prespecified adverse events [risk difference − 2.5% (95% CI − 4.4, − 0.5); risk ratio 0.53 (95% CI 0.31, 0.96)]. Meta-analyses confirmed the lower rate of major adverse events for PFA [0.4% (95% CI 0.0, 1.3)] vs. CBA [5.6% (95% CI 2.6, 8.6)] and prespecified adverse events for PFA [2.7% (95%

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CI 1.2, 4.1)] vs. CBA [5.8% (95% CI 2.7, 9.0)]. Sensitivity analyses exploring heterogeneity across studies confirmed robustness of the main analyses.

Conclusion: The findings of this study show that PFA has a more favorable safety profile than CBA, with significantly lower risks of major and prespecified adverse events. These indirect comparisons help contextualize the safety of PFA compared to CBA for the treatment of drug-refractory PAF in the absence of head-to-head studies.

Keywords: Pulsed field ablation; Cryoballoon; Cryoablation; Paroxysmal atrial fibrillation; Pulmonary vein isolation

Key Summary Points
Pulsed field ablation (PFA) is a novel, minimally thermal technology for treating paroxysmal atrial fibrillation (PAF), with effectiveness comparable to cryoballoon ablation (CBA) and low safety risk.
With limited direct evidence, the current study aimed to compare the safety profiles of PFA and CBA through indirect treatment comparison.
PFA was associated with significantly lower risk of major adverse events and prespecified adverse events (risk ratios of 0.16 and 0.53, respectively).
The findings of this study show that PFA has a more favorable safety profile than CBA, providing further insight into treatment strategies for patients with drug-refractory PAF.

INTRODUCTION

Atrial fibrillation (AF) is the most common type of cardiac arrythmia, affecting ~ 3% of the adult population across the world [1]. Atrial fibrillation is associated with a considerable impact on patient quality of life and substantial risk of cardiovascular events, leading to an increased risk of morbidity and mortality among patients [1, 2]. In addition, AF places considerable burden on the healthcare system [2].

Guidelines have recommended using anti-arrhythmic drugs (AADs) as an initial treatment of paroxysmal AF (PAF). Among patients who are drug-refractory or intolerant to AADs, pulmonary vein isolation (PVI) using catheter ablation is recommended. The use of catheter ablation has been increasing in its frequency over the past decade, with higher efficiency rates and better safety profile [3]. Cryoballoon ablation (CBA) is a thermal-based catheter ablation technology that uses cryo, or freezing, energy to freeze tissue and isolate the pulmonary veins to prevent aberrant electrical signals that are responsible for AF [4]. This technology has demonstrated lower recurrence rate and improved quality of life compared to AADs as a treatment of PAF [5]. Despite these clinical advantages, CBA is associated with increased risk of atrio-esophageal injury/fistula [6, 7], phrenic nerve injuries [8, 9], and/or pulmonary vein stenosis [10].

Pulsed field ablation (PFA) is a novel, minimally thermal catheter ablation technology that creates lesions in myocardial tissue through irreversible electroporation [11]. It is currently limited to high-volume centers, but its adoption rate continues to grow for smaller centers. Several single-arm clinical trials have shown the effectiveness of PFA in patients with drug-refractory PAF, with freedom from atrial arrhythmias ranging from 66.2% to 87.4% one year after PVI [12–15]. Because of the highly selective nature of PFA for myocardial tissue, PFA may prevent potential damage to adjacent tissues [16]. Evidence from clinical trials support favorable safety profiles of PFA, with incidence rates ranging from 0% to 2.5% for early-onset serious adverse events, including phrenic nerve injury, atrio-esophageal fistula, pulmonary vein stenosis, and vascular complications [12, 13].

Most clinical trials assessing PFA technology in patients with drug-refractory PAF are single-arm trials, and head-to-head trials comparing PFA to CBA are limited [17]. Indirect treatment

comparisons pooling data from multiple clinical trials present a robust alternative option to compare these technologies. The objective was to conduct a critical literature review and an indirect treatment comparison to evaluate the comparative safety of PFA and CBA for PVI in patients with drug-refractory PAF.

METHODS

Search Strategy

Literature searches were conducted in the MEDLINE (PubMed) database and the Clinicaltrials.gov registry from January 2008 to March 2023. Searches were performed using combinations of the following keywords: "pulsed field ablation", "PFA", "cryoballoon", or "cryoablation", together with "atrial fibrillation". Only English-language articles were reviewed for eligibility. Identified studies were critically evaluated for inclusion in the final indirect comparison following best reporting practices from PRISMA guidelines [18], based on a qualitative assessment of study design, patient eligibility, patient baseline characteristics, and outcomes criteria.

Study Eligibility

Eligible studies had one of the following study designs: (1) FDA IDE (the Food and Drug Administration Investigation Device Exemption) studies; (2) first-in-human studies; or (3) registered clinical trials. Only the clinical trials that were registered on a clinical trial registry (i.e., clinicaltrials.gov) were considered. Studies had to involve adult patients with PAF who were drug-refractory to at least one class of AAD and received either PFA or CBA. Studies were excluded if they included patients with persistent AF, were not registered on a clinical trial registry, or were observational studies or conference abstracts. Studies were screened by an independent reviewer and checked for accuracy by a second reviewer.

Outcomes

The primary outcome was the composite of major procedure- or device-related adverse events reported at up to 30 days post-procedure. Major procedure- or device-related adverse events included cardiac tamponade or perforation, major vascular access complication or bleeding, myocardial infarction (MI), pericardial effusion, pericarditis, phrenic nerve paralysis, stroke, cerebrovascular accident (CVA), thromboembolism, transient ischemic attack (TIA), atrio-esophageal fistula, device- or procedure-related death, and pulmonary vein (PV) stenosis. Of note, PV stenosis and atrio-esophageal fistula were included in the primary outcome regardless of the timepoint. These events were identified as known potential risks across multiple clinical trials of AF ablation devices [12, 13, 15, 19–24], and as per guidance of the 2017 expert consensus statement from the Heart Rhythm Society (HRS) [25]. The secondary outcome was the composite of several prespecified adverse events reported at any timepoint.

Data Extraction and Feasibility Assessment

Data on study design, patient baseline characteristics, treatments, and safety outcomes were extracted into a standardized template by a single reviewer and checked for accuracy by a second reviewer. Cross-trial heterogeneity may contribute to bias within indirect treatment comparisons [26]. To ensure that studies were similarly sufficient for indirect comparison, a qualitative assessment of study design, eligibility criteria, patient baseline characteristics, treatments, and outcome definitions across the studies was conducted in accordance with best practices [27–29]. Studies that were deemed sufficiently similar based on clinical opinion were included in the analysis.

Statistical Analyses

Comparative safety between PFA and CBA was assessed through an unadjusted indirect

treatment comparison and confirmed through single-arm meta-analyses. The proportion of patients experiencing an adverse event was calculated, and the results were presented using risk differences and risk ratios. Corresponding 95% confidence intervals (95% CI) were calculated using the Wald and the adjusted-log procedures, respectively. Sensitivity analyses were conducted by using other methods (i.e., Katz-log [30], Bailey [31], Noether [32], and Koopman [33]) to estimate the 95% CI.

Single-arm meta-analyses on PFA and CBA were performed separately to confirm the results from the indirect comparison. The overall weighted proportion of patients experiencing an adverse event within the eligible studies was estimated and presented in forest plots. Random effects model was used to account for potential heterogeneity between studies. Heterogeneity between study results was assessed using the τ^2 statistic, and the percentage of total variation across studies was assessed using the inconsistency index, I^2. Fixed effect meta-analyses were also conducted.

Analyses were conducted using the R packages *DescTools* [34] and *meta* [35] for single proportions. All analyses were conducted using the R software version 3.6.1.

Sensitivity Analyses

Sensitivity analyses were performed to assess the impact of cross-trial heterogeneity on the primary outcome. CBA studies with notable outlier values in the baseline characteristics were excluded one at a time from the primary analysis. PFA studies were not excluded to ensure a sufficient sample for analyses.

Statement of Ethics Compliance

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Study Inclusion and Feasibility Assessment

A total of 170 PFA and 158 CBA studies were identified as potentially relevant from literature searches (Fig. 1). After excluding the studies that did not meet the eligibility criteria, a total of three PFA studies representing five trials (InspIRE [12], IMPULSE, PEFCAT, PEFCAT II [13], and PULSED AF [15]) and six CBA studies representing six trials (Cryo versus RF [20], SUPIR [24], plusONE [19], STOP AF Post-Approval Study [21], FreezeAF [23], and Fire and Ice [22]) were deemed eligible for inclusion.

All included studies were registered clinical trials (Table 1). All PFA trials were prospective, multi-center, single-arm trials with 12 months of follow-up. Four of the six CBA trials were prospective, randomized controlled trials with 12–18 months follow-up. The remaining two CBA trials were prospective, single-arm trials with 3.4 months (median) and 34.3 (mean) months of follow-up, respectively.

In total, the PFA studies consisted of 497 patients and the CBA studies consisted of 1113 patients. The distribution of baseline characteristics including age, gender, body mass index (BMI), left atrial diameter (LAD), and left ventricular ejection fraction (LVEF) were comparable across the studies (Table 2). The mean age of patients in the included studies ranged between 56 and 64 years. The distribution of male population was between 57.5% and 73.6% across the studies. A slightly lower male proportion (42.9%) was reported for the SUPIR study. The mean LAD values were 38.0–42.0 mm, and the mean LVEF was 57.9–64.2% across studies.

Medical characteristics for the patients were also comparable among the PFA and CBA trials (Table 2). The ranges of proportion for different comorbidities were as follows: diabetes (4.8–16.0%); hypertension (34.6–61.5%); coronary artery disease (CAD; 0.7–20.7%), and stroke/TIA (2.1–9.0%). Overall, the included studies were deemed sufficiently similar by clinical opinion to conduct an unanchored

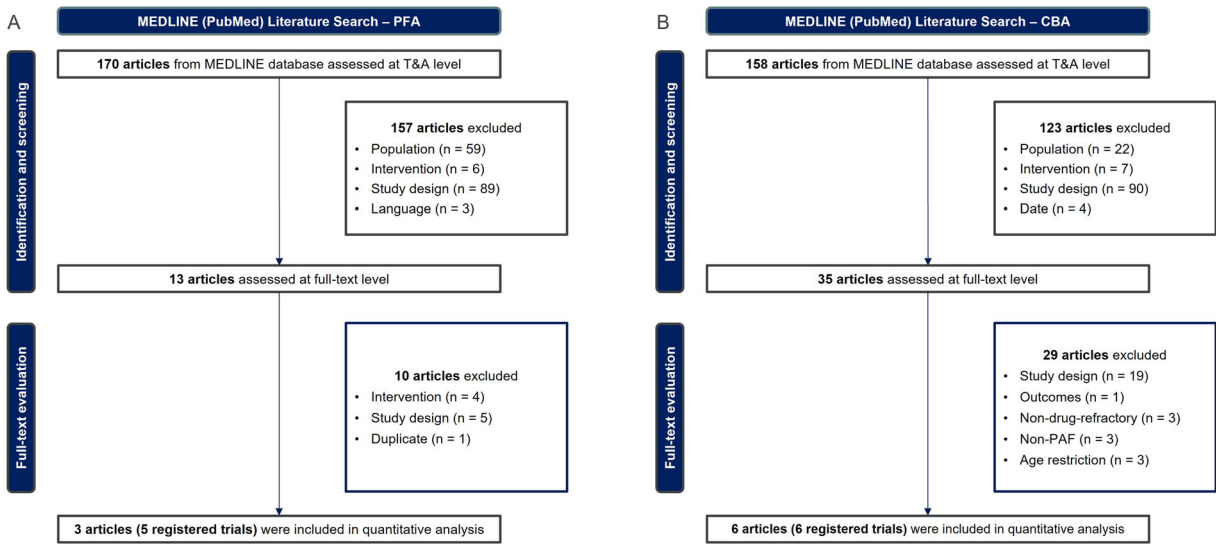

Fig. 1 PRISMA flow diagram of the targeted literature review for **A** pulsed field ablation and **B** cryoballoon ablation. *CBA* cryoballoon ablation, *PAF* paroxysmal atrial fibrillation, *PFA* pulsed field ablation, *T&A* title and abstract

indirect treatment comparison for safety outcomes.

Comparative Safety of PFA and CBA

Composite of Major Adverse Events

The indirect comparison revealed that PFA was associated with a statistically significantly lower risk of major adverse events than CBA, with a risk difference of − 4.3% (95% CI − 5.8, − 2.8) and a risk ratio of 0.16 (95% CI 0.07, 0.45) (Table 3).

Results were confirmed in single-arm meta-analyses, which showed that 0.4% (95% CI 0.0, 1.3) of patients who underwent PFA experienced major adverse events, in contrast to 5.6% (95% CI 2.6, 8.6) of patients who underwent CBA (Table 3, Supplementary Fig. 1). Higher risk of major adverse events with CBA was primarily driven by phrenic nerve paralysis (PFA: 0 event vs. CBA: 33 events) and major vascular access complication or bleeding (PFA: 1 event vs. CBA: 12 events) (Table 4).

Composite of Prespecified Adverse Events

The indirect comparison showed that PFA was associated with a statistically significantly lower risk of prespecified adverse events than CBA, with a risk difference of − 2.5% (95% CI − 4.4, − 0.5) and a risk ratio of 0.53 (95% CI 0.31, 0.96) (Table 3).

Results were confirmed in single-arm meta-analyses, which showed that 2.7% (95% CI 1.2, 4.1) of patients who underwent PFA experienced an adverse event, in contrast to 5.8% (95% CI 2.7, 9.0) of patients who underwent CBA (Table 3, Supplementary Fig. 2).

Sensitivity Analyses

Four studies were identified with potential heterogeneity in baseline patient characteristics: SUPIR (duration of AF), plusONE (CAD and duration of AF), FreezeAF (hypertension), and Fire and Ice (hypertension) (Table 2). Exclusion of these studies one-at-a-time from the main analysis showed statistically significantly lower risk of major adverse events with PFA than with CBA (Supplementary Table 1).

DISCUSSION

Pulsed field ablation (PFA) is emerging as an alternative to thermal-based catheter ablation technologies such as CBA, and multiple PFA systems have demonstrated their clinical effectiveness in single-arm clinical trials [12–15]. With limited head-to-head evidence comparing

Table 1 Overview of key study characteristics in PFA and CBA clinical trials

Device	Trial name (NCT #) Author (Year)	Sample size (relevant arm)	Study design	Intervention	Comparator (control)	Follow-up
Pulsed field ablation	InspIRE (Wave II) (NCT04524364) InspIRE (Wave I) Duytschaever et al. (2023)	226	Prospective, multi-center, single-arm trial	VARIPULSE® Catheter and TRUPULSE™ Generator, Biosense Webster	None	12 months
	IMPULSE / PEFCAT / PEFCAT II (NCT03700385 / NCT03714178 / NCT04170608) Reddy et al. (2021)	121 (40/71/10)[a]	Prospective, multi-center, single-arm trial	Farapulse, Boston Scientific	None	12 months
	PULSED AF (NCT04198701) Verma et al. (2023)	150	Prospective, multi-center, single-arm trial	PulseSelect, Medtronic	None	12 months
Cryoballoon ablation	Cryo Versus RF (NCT01038115) Hunter et al. (2015)	78	Prospective, single-center, randomized, controlled trial	Arctic Front™ cryoablation catheter, Medtronic	RFA	12 months
	SUPIR (NCT01645917) Reddy et al. (2015)	21	Prospective, single-center, single-arm trial	Arctic Front™ cryoablation catheter, Medtronic	None	3.4 (2.9–4.1) months Median (range)
	plusONE (NCT02789358) Ferrero-de Loma-Osorio et al. (2017)	140	Prospective, multi-center, randomized, controlled trial	Arctic Front™ cryoablation catheter, Medtronic	CBA (new protocol)	12.29 (2.99) months, mean (SD)
	STOP AF PAS (NCT01456949) Knight et al. (2019)	344	Prospective, multi-center, single-arm trial	Arctic Front™ cryoablation catheter, Medtronic	None	34.3 (7.4) months, mean (SD)
	FreezeAF (NCT00774566) Luik et al. (2015)	156	Prospective, randomized, controlled, non-inferiority study	Arctic Front™ cryoablation catheter, Medtronic	RFA	12 months
	Fire and ice (NCT01490814) Kuck et al. (2016)	374	Prospective, randomized, controlled trial	Arctic Front™ cryoablation catheter, Medtronic	RFA	18 months (mean); 33 months (maximum)

Abbreviations: *CBA* Cryoballoon ablation, *IQR* interquartile range, *PFA* pulsed field ablation, *RFA* radiofrequency ablation, *SD* standard deviation

[a]Number of patients in IMPULSE/PEFCAT/PEFCAT II, respectively

Table 2 Overview of patient baseline characteristics in PFA and CBA clinical trials

Device	Trial name (NCT #) Author (Year)	Sample size (*n*)	PAF (%)	Age (year)	Male (%)	BMI (kg/m^2)	LAD mm	LVEF (%)	CHA_2DS_2 VASc	Atrial flutter (%)	Diabetes (%)	CAD (%)	Stroke /TIA (%)	Hyper-tension (%)	CHF (NYHA Class I or II) (%)	# Failed AADs	Previous AAD (%)	Duration of AF (months)
Pulsed field ablation	InspIRE (Wave II) (NCT04524364)	226	100	59.4 (10.2)	70.4	27.6 (4.3)	39.4 (5.3)	60.8 (5.8)	1.3 (1.2)	2.2	7.0	5.9		46.2	2.2	1.4 (0.6)	100	60.1 (12.0–81.2)[a]
	Duytschaever et al. (2023)																	
	InspIRE (Wave I)		100	58.4 (10.9)	57.5	27.4 (4.3)	38.0 (5.1)	57.9 (4.7)	1.8 (1.5)	5.0	10.0	15.0		52.5	12.5	1.6 (0.7)	100	76.9 (22.5–83.7)[a]
	(NCT04524364)																	
	Duytschaever et al. (2023)																	
	IMPULSE / PEFCAT / PEFCAT II	121	100	57.4 (10.3)	73.6		40.5 (4.5)	62.5 (5.7)			9.1	3.3	5.0	56.2			97.5	13.8 (8.0–46.2)[a]
	(NCT03700385 / NCT03714178 / NCT04170608)																	
	Reddy et al. (2021)																	
	PULSED AF (NCT04198701)	150	100	63.4 (9.9)	64.0	28.6 (5.9)	38.7 (5.8)	60.3 (4.8)			16.0	20.7	4.0	48.7		1.3 (0.6)	100	45.6 (74.4)
	Verma et al. (2023)																	
Cryo-balloon ablation	Cryo Versus RF (NCT01038115)	78	100	56 (11)	71.8		42 (4)				5.1		9.0	34.6		2.4 (1.0)	100	56.4 (24–120)[a]
	Hunter et al. (2015)																	
	SUPIR (NCT01645917)	21	100	60 (11)	42.9	29.0 (4.8)				19.0	4.8	4.8	4.8	42.9			100	32.7 (29.5)
	Reddy et al. (2015)																	
	plusONE (NCT02789358)	140	100	56 (11)	67.9	24.5 (8.5)		64.2 (8.5)		25.7	9.3	0.7	2.1	40.0		1.57 (0.8)	100	75.6 (28.8)
	Ferrero-de Loma-Osorio et al. (2017)																	
	STOP AF PAS (NCT01456949)	344	100	60.2 (10.4)	66.3	29.9 (6.1)	39.8 (5.6)				10.2	9.6		48.8	20.9	1.3 (0.5)	100	54 (64.8)
	Knight et al. (2019)																	
	FreezeAF (NCT00774566)	156	100	61 (54–66)[a]	64.1						9.0	12.2	7.7	61.5			100	
	Luik et al. (2015)																	
	Fire and Ice (NCT01490814)	374	100	59.9 (9.8)	59.1	28.0 (4.7)	40.8 (6.5)		1.9 (1.4)		9.9	8.3	4.3	57.5	29.4		100	55.2 (61.2)
	Kuck et al. (2016)																	

Values are presented as proportion of patients (%) or mean (SD) unless noted otherwise.
CHA_2DS_2VASc score is used to estimate the risk of stroke in AF patients, taking the following into consideration: congestive heart failure, hypertension, age (≥ 75 years), diabetes mellitus, prior stroke/transient ischemic attack/embolism, vascular disease, age (65–74 years), and sex category (i.e., female sex)
AAD antiarrhythmic drug, *AF* atrial fibrillation, *BMI* body mass index, *CAD* coronary artery disease, *CBA* Cryoballoon ablation, *CHF* congestive heart failure, *IQR* interquartile range, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *PAF* paroxysmal atrial fibrillation, *PFA* pulsed field ablation, *SD* standard deviation, *TIA* transient ischemic attack
[a]Median (IQR)

Table 3 Summary of indirect treatment comparison and single-arm meta-analyses of composite adverse events between PFA and CBA trials

Outcome	Indirect comparison		Single-arm meta-analyses	
	PFA vs. CBA risk difference % (95% CI)	PFA vs. CBA risk ratio (95% CI)	PFA events % (95% CI)	CBA events % (95% CI)
Composite of major adverse events (primary)	**− 4.3 (− 5.8, − 2.8)**	**0.16 (0.07, 0.45)**	0.4 (0.0, 1.3)	5.6 (2.6, 8.6)
Composite of prespecified adverse events (secondary)	**− 2.5 (− 4.4, − 0.5)**	**0.53 (0.31, 0.96)**	2.7 (1.2, 4.1)	5.8 (2.7, 9.0)

Statistically significant results are in bold. Composite of major adverse events include cardiac tamponade or perforation, major vascular access complication or bleeding, myocardial infarction (MI), pericardial effusion, pericarditis, phrenic nerve paralysis, stroke, cerebrovascular accident (CVA), thromboembolism, transient ischemic attack (TIA), atrio-esophageal fistula, device- or procedure-related death, and pulmonary vein (PV) stenosis. Composite of prespecified adverse events include all of the major AEs and the following additional events: silent cerebral lesion (SCL), coronary artery spasm, microvascular obstruction, ST-segment elevation, sinus pause, and asystole episodes

CBA cryoballoon ablation, *CI* confidence interval, *PFA* pulsed field ablation

PFA to CBA available, an indirect treatment comparison of PFA and CBA was conducted to evaluate the comparative safety for PVI in patients with drug-refractory PAF. The present analysis shows that PFA has a significantly favorable safety profile compared to CBA. PFA was associated with 84% lower risk of major adverse events and 47% lower risk of prespecified adverse events than CBA. Results were driven by higher rates of major vascular access complication or bleeding, phrenic nerve injury, and pericardial effusion with CBA. Notably, there were no phrenic nerve injuries observed in the PFA trials included in the present study. Events of atrio-esophageal fistula or PV stenosis were also not observed in the included PFA trials. To the authors' knowledge, this is the first indirect comparison of the safety profile between these two technologies using high-quality data from FDA IDE studies and registered clinical trials.

The evidence base supporting PFA in the treatment of drug-refractory PAF is evolving. ADVENT is the first randomized controlled trial to compare the effectiveness and safety of PFA (FARAPULSE; Boston Scientific, USA) ($n = 301$) or thermal ablation ($n = 296$) in adults with drug-refractory PAF [17]. Patients randomized to thermal ablation received either CBA ($n = 132$) or radio-frequency catheter ablation ($n = 164$), with each method planned to constitute approximately 50% of the aggregated control group [17]. The ADVENT trial showed that PFA was non-inferior to thermal ablation for the primary safety endpoint of acute- and chronic device-related and procedure-related serious adverse events (2.1% vs. 1.5% in thermal ablation, with posterior probability of non-inferiority > 0.999) [17]. In contrast, results from the current indirect comparison that pooled safety events from multiple PFA and CBA studies showed an improved safety profile with PFA relative to CBA, driven by phrenic nerve injury. Interestingly, no phrenic nerve injury was reported with thermal ablation in the ADVENT trial. Results from a real-world, retrospective, observational study comparing PFA ($n = 200$) and CBA ($n = 200$) also showed that PFA had an improved safety profile compared to CBA, with a numerically lower overall complication rate than CBA (3.0% vs. 6.5%; $p = 0.1$) that was driven by a higher rate of phrenic nerve injury with CBA (7.5% vs. 1.0%; $p = 0.001$) [36].

Overall, safety events across multiple novel PFA systems are reportedly low, with the rates of primary adverse events (assessed at 7 and

Table 4 Number of events for individual safety outcomes in pooled PFA and CBA trials

Events	Pulsed field ablation (n = 497 patients)	Cryoballoon ablation (n = 1113 patients)
Composite major adverse events	**4**	**57**
Cardiac perforation	0	NR
Cardiac tamponade	1	1
Pericardial effusion	1	6
Pericarditis	0	NR
Stroke or cerebrovascular accident (CVA)	1	1
Thromboembolism	0	NR
Transient ischemic attack (TIA)	0	2
Major vascular access complication / bleeding[a]	1	12
Myocardial Infarction	0	NR
Phrenic nerve paralysis	0	33
Atrio-esophageal (AE) fistula	0	0
Device- or procedure-related death	0	0
Pulmonary vein (PV) stenosis	0	2
Composite prespecified adverse events	**10**	**2**
Silent cerebral lesion (SCL)	10	NR
Coronary artery spasm	0	NR
Microvascular obstruction	NR	NR
ST-segment elevation	0	2
Sinus pause	NR	NR
Asystole episodes	NR	NR
Composite major and prespecified adverse events	14	59

AV arteriovenous, *CBA* cryoballoon ablation, *NR* not reported, *PFA* pulsed field ablation

[a]Major vascular access complications include hematoma, AV fistula or pseudoaneurysm which requires intervention (such as surgical repair or transfusion), prolongs the hospital stay, or requires hospital admission. Major bleeding events are defined as events that "requires and/or treated with transfusion or results in a 20% or greater fall in hematocrit"; ST-segment elevation is defined as abnormally high ST-segment trace above the baseline on an electrocardiogram. NR (not reported) indicates that there was no trial addressing or evaluating the event

30 days after ablation) as low as zero for the VARIPULSE catheter and TRUPULSE generator system (Biosense Webster, USA) [12], 0.7% for PulseSelect (Medtronic, USA) [15], and up to 2.5% for FARAPULSE (Boston Scientific) [13]. Exceptionally low rates of major adverse events such as cardiac tamponade, pericardial effusion, and vascular complications have been reported with the PulseSelect and FARAPULSE systems, while no events were observed with the VARIPULSE/TRUPULSE system [12].

The current indirect comparison provides meaningful insight into the comparative safety profile of PFA and CBA. A strength of this analysis is that it only included patients with PAF who were drug-refractory to at least one AAD from a high-quality evidence base of registered clinical trials. Indirect treatment comparisons rely on the assumption that trials are sufficiently similar such that any underlying differences in patient populations would not bias the comparative effect estimate. A qualitative assessment of cross-trial heterogeneity was conducted a priori, the results of which showed sufficiently similar baseline characteristics across the trials. This was supported by clinical opinion. Nevertheless, this analysis was associated with limitations inherent to naïve indirect comparisons, including increased susceptibility to potential bias stemming from cross-trial heterogeneity. The impact of cross-trial heterogeneity on the analysis was explored in meta-analyses and sensitivity analyses. The results from meta-analyses using the random-effects model to account for cross-trial differences within PFA and CBA studies aligned with those from the indirect comparison. Additionally, the results for major adverse events were robust to excluding studies with outlier baseline patient characteristics one at a time in sensitivity analyses. However, cross-trial heterogeneity could not be fully explored within PFA studies owing to the need for a sufficient sample to conduct analyses. Anchored comparisons were not feasible due to limited randomized trials with a common comparator. Further, the ADVENT trial, which compared PFA to thermal ablation, was published outside the literature search window and therefore not considered for inclusion in this analysis.

CONCLUSION

Overall, the indirect treatment comparison and meta-analyses of the safety profile of PFA and CBA showed that PFA had significantly lower risks of major and prespecified procedure- or device-related adverse events than CBA, mainly driven by the higher rates of phrenic nerve palsy and vascular complications with CBA. These findings imply that PFA may be a reasonable alternative to CBA for PVI in patients with drug-refractory PAF.

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Data Availability. The datasets generated during and/or analyzed during the current

study are available from the corresponding author on reasonable request.

Declarations

Conflicts of Interest. Donghyun D. Lee and Anja Haltner are employees of EVERSANA^{TM}. EVERSANA^{TM} receives consultancy fees from major pharmaceutical and device companies, including Biosense Webster. Sonia Maccioni, Rahul Khanna, and Reecha Sharma are employees of Johnson & Johnson. Johan Vijgen reports research funding from Daiichi-Sackyo, BMS-Pfizer, Bayer, Biotronik, Boston Scientific, Medtronic, and Abbott. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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