ESC European Society of Cardiology

Europace (2024) **26**, euae293
https://doi.org/10.1093/europace/euae293

META-ANALYSIS

Multielectrode catheter-based pulsed electric field vs. cryoballoon for atrial fibrillation ablation: a systematic review and meta-analysis

Giampaolo Vetta [1,2†], Domenico Giovanni Della Rocca [1,2,3*†], Antonio Parlavecchio [4], Michele Magnocavallo [2,5], Antonio Sorgente [1], Luigi Pannone [1], Alvise Del Monte [1], Alexandre Almorad [1], Juan Sieira[1], Lorenzo Marcon [1], Ioannis Doundoulakis [1], Sanghamitra Mohanty [3], Charles Audiat [1], Kazutaka Nakasone [1], Gezim Bala [1], Erwin Ströker [1], Stéphane Combes [6], Ingrid Overeinder [1], Stefano Bianchi [5], Pietro Palmisano [7], Pietro Rossi [5], Serge Boveda [6], Marc La Meir[1], Andrea Natale [3], Andrea Sarkozy [1], Carlo de Asmundis [1*‡], and Gian-Battista Chierchia [1‡]

[1]Heart Rhythm Management Centre, Postgraduate Program in Cardiac Electrophysiology and Pacing, Universitair Ziekenhuis Brussel-Vrije Universiteit Brussel, European Reference Networks Guard-Heart, Brussels 1090, Belgium; [2]Mediterranean Consortium for Arrhythmia Research (MediCAR), Rome, Italy; [3]Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, TX 78705, USA; [4]Department of Clinical and Experimental Medicine, Cardiology Unit, University of Messina, Messina, Italy; [5]Arrhythmology Unit, Ospedale Fatebenefratelli Isola Tiberina-Gemelli Isola, Rome, Italy; [6]Heart Rhythm Department, Clinique Pasteur, Toulouse, France; and [7]Cardiology Unit, 'Card. G. Panico' Hospital, Tricase, Italy

Received 9 June 2024; accepted after revision 24 October 2024; online publish-ahead-of-print 23 November 2024

Aims

Pulsed field ablation (PFA) is an innovative technology recently adopted for the treatment of atrial fibrillation (AF). Preclinical and clinical studies have reported a remarkable safety profile, as a result of its tissue-specific effect targeting cardiomyocytes and sparing adjacent tissues. Single-shot pentaspline system was the first PFA device to receive regulatory approval. We performed a meta-analysis to compare the efficacy and safety of PFA with the single-shot pentaspline system vs. currently available second-/third-/fourth-generation cryoballoon ablation (CRYO) technologies.

Methods and results

We systematically searched electronic databases for studies focusing on AF ablation employing the PFA single-shot pentaspline system or second-/third-/fourth-generation CRYO technologies. The primary endpoints were acute procedural success assessed on a vein and patient basis. Safety endpoints included overall periprocedural complications and major periprocedural complications. We also compared procedural, fluoroscopy times, and freedom from atrial tachyarrhythmias (ATs) at follow-up (secondary endpoints). Twenty and 70 studies were included for PFA and CRYO, respectively. Pulsed field ablation demonstrated greater acute procedural success on a vein basis (99.9% vs. 99.1%; $P < 0.001$), as well as per patient (99.5% vs. 98.4%; $P < 0.001$). Pulsed field ablation yielded lower overall periprocedural complications (3.1% vs. 5.6%; $P < 0.001$), shorter procedural time (75.9 min vs. 105.6 min; $P < 0.001$), and fluoroscopy time (14.2 min vs. 18.9 min; $P < 0.001$) compared with CRYO. No differences were found for major periprocedural complications (1.2% vs. 1.0%; $P = 0.46$) and freedom from ATs at 1 year (82.3% vs. 80.3%; log-rank $P = 0.61$).

Conclusion

Pulsed field ablation contributed to higher acute procedural success and safety compared with CRYO. No statistically significant differences in AT recurrence at 1-year follow-up were observed.

* Corresponding authors. *E-mail address*: domenicodellarocca@hotmail.it (D.G.D.R.); *E-mail address*: CarlodeAsmundis@uzbrussel.be (C.A.)

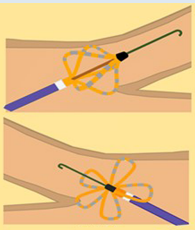
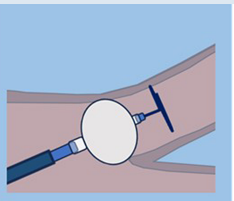
† The first two authors contributed equally to the study.

‡ The last two authors contributed equally to the study.

© The Author(s) 2024. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

Downloaded from https://academic.oup.com/europace/article/26/12/euae293/7907807 by guest on 22 January 2025

Graphical Abstract

	 PFA (*N* = 2481)	 CRYO (*N* = 13 766)	*P*-value
Procedural success (per vein)	**99.9%** (95% CI: 99.8–100)	**99.1%** (95% CI: 98.7–99.5)	***P* < 0.001**
Procedural success (patient basis)	**99.5%** (95% CI: 99.2–99.8)	**98.4%** (95% CI: 97.9–98.9)	***P* < 0.001**
Procedural time	**75.9 min** (95% CI: 59.4–92.3)	**105.6 min** (95% CI: 96.7–114.6)	***P* < 0.001**
Fluoroscopy time	**14.2 min** (95% CI: 11.8–16.6)	**18.9 min** (95% CI: 17.1–20.7)	***P* < 0.001**
Major complications	**1.2%** (95% CI: 0.7–1.7)	**1.0%** (95% CI: 0.8–1.2)	*P* = 0.46
Overall complications	**3.1%** (95% CI: 2.2–4.0)	**5.6%** (95% CI: 4.6–6.6)	***P* < 0.001**

Efficacy and safety of pulse field ablation and cryoballoon ablation for atrial fibrillation ablation. CRYO, cryoballoon ablation; PFA, pulsed field ablation.

Keywords Atrial fibrillation • Ablation • Pulmonary vein isolation • Pulsed field ablation • Cryoballoon ablation • Catheter ablation

Downloaded from https://academic.oup.com/europace/article/26/12/euae293/7907807 by guest on 22 January 2025

What's new?

- Pulsed field ablation via the pentaspline catheter contributed to greater acute procedural success, assessed either on a pulmonary vein and a patient basis, compared with cryoballoon.
- Pulsed field ablation-based procedures showed a shorter procedural time and X-ray exposure.
- Pulsed electric field demonstrated a remarkable safety profile, as demonstrated by a significantly lower incidence of overall complications.
- Freedom from atrial tachyarrhythmias at 1 year was high (>80.0%) and similar between technologies.

Introduction

Catheter ablation (CA) is a highly effective rhythm control strategy for paroxysmal atrial fibrillation (AF),[1–3] with pulmonary vein (PV) isolation (PVI) being the mainstay strategy of any first-time ablation procedure. Pulmonary vein isolation is commonly achieved using thermal energy sources [e.g. radiofrequency (RF), cryothermy and laser] either via point-by-point ablation or single-shot balloon devices. Single-shot technologies have been developed with the aim of simplifying AF ablation and improve its reproducibility; the most common energy source for balloon-based ablation is cryogenic, which has been proven to be non-inferior to RF ablation with respect to safety and efficacy of PVI.[4] However, all above-mentioned thermal energy sources' drawback is their lack of tissue selectivity, as they may elicit varying degrees of collateral damage to adjacent tissues and a non-negligible risk of serious complications [e.g. phrenic nerve (PN) palsy and atrio-oesophageal fistula].[5,6]

Pulsed field ablation (PFA) is an innovative technology recently adopted for the treatment of cardiac arrhythmias, which relies on the application of high-voltage, rapidly alternating electric fields to the heart tissue; pulse delivery results in nanopore development on cardiac cell membrane ultimately leading to apoptosis.[7] Unlike other energy sources, PFA-induced lesion formation occurs in a non-thermal and selective fashion; specifically, waveforms can be tailored to preserve the surrounding tissues and concomitantly improve lesion durability.[8] Preferential myocardial ablation by PFA has been extensively proven in preclinical and clinical studies demonstrating lower vulnerability of nerves, vasculature and oesophageal tissue to PFA. Several single-shot and focal ablation devices with PFA capabilities have been developed in the last years.[9–11] Among them, the single-shot pentaspline has been the first PFA technology to receive regulatory approval (CE-mark). The system efficacy and safety have been described in several clinical studies as well as in a randomized trial.[12–14] Nevertheless, to date, no study proved better safety and efficacy of PFA compared with other systems. In this perspective, we performed a systematic review and meta-analysis to compare the efficacy, safety, and procedural data of the PFA single-shot pentaspline system with available cryoballoon ablation (CRYO) technologies.

Methods

Data sources and searches

We systematically searched Medline, Cochrane, Journals@Ovid, and Scopus electronic databases for studies published from inception to 15 January 2024 and focusing on AF ablation employing the pentaspline Farapulse™ (Boston Scientific Inc., Marlborough, MA, USA) PFA catheter or second-/third-/fourth-generation CRYO (Medtronic: Arctic Front

Advance™, Arctic Front Advance ST™, and Arctic Front Advance Pro™; Boston Scientific: POLARx™ and POLARx FIT™). The Farapulse™ system consists of a 12 F over-the-wire ablation catheter (Farawave™) that is advanced into the left atrium (LA) through a 13.8 F steerable sheath (Faradrive™) and a generator (Farastar™) that creates high-voltage electric fields (1.8–2.0 kV) (see Supplementary material online, *Figure S1*).

Three investigators (D.G.D.R., G.V., and A.P.) independently performed searches including the following terms: atrial fibrillation, pulsed field ablation, cryoballoon, catheter ablation, and pulmonary vein isolation. Detailed information on our literature search strategy is available in the Expanded Methods in Supplementary material.

Study selection and outcomes

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reporting systematic reviews and meta-analyses was used in this study.[15] The predefined protocol was registered into the international prospective registry of systematic reviews PROSPERO (ID: CRD42023460640).

The studies had to fulfil the following criteria to be included in the analysis: (i) use of pentaspline Farapulse™ PFA catheter or second-/third-/fourth-generation CRYO for AF ablation, (ii) adult (>18 years old) study population, and (iii) description of at least one clinical outcome of interest. In case of multiple publications from the same centre, the study period was assessed. In studies with overlapping populations, the study with the largest sample size was included.

Editorials, surveys, case reports, reviews, expert opinions, and non-English studies were excluded.

Data extraction and quality appraisal

Three investigators (D.G.D.R., G.V., and A.P.) extracted data from each study using standardized protocol and reporting forms. Three reviewers (D.G.D.R., G.V., and A.P.) independently assessed the quality items, and disagreements were resolved by consensus.

Individual patient data (IPDs) were retrieved from Kaplan–Meier plots if available. Data were extracted using a two-stage approach as described by Liu *et al.*[16] In the first step, the Kaplan–Meier curves were digitized with a dedicated software (WebPlotDigitizer, https://apps.automeris.io/wpd/), where the axes were defined and the raw data coordinates [time and probability of freedom from atrial tachyarrhythmias (ATs)] were extracted in each of the Kaplan–Meier curves. In the second phase, the data coordinates were processed on the basis of the raw data coordinates from the first phase in combination with the numbers at risk at certain time points and/or the total number of patients and IPDs were reconstructed. Finally, the extracted IPDs from all studies were merged to create the study data set.

The quality of individual studies was assessed by three investigators (D.G.D.R., G.V., and A.P.) using the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies and the Cochrane risk-of-bias tool for randomized clinical trials (RCTs).

Study endpoints

The primary endpoints were acute procedural success assessed on a PV basis, as well as per patient. Procedural success on a PV basis was defined as the number of PVs successfully isolated with the chosen technology, without the need for touch-up applications with another device, divided by the overall number of PVs targeted for isolation. Procedural success per patient was defined as the number of patients with complete successful PVI with a certain technology, without the need for touch-up applications with another device, divided by the number of patients undergoing PVI. Safety endpoints were defined as follows: (i) overall periprocedural complications, which included ST-elevation, oesophageal lesions, stroke and/or transient ischaemic attack (TIA), pericardial tamponade or effusion with or without need for pericardiocentesis, transient or persistent PN palsy, death, and bleeding/vascular complications and (ii) major periprocedural complications, which included stroke and/or TIA, pericardial tamponade or effusion with the need for pericardiocentesis, persistent PN palsy, and death.

Secondary outcomes were procedural time, fluoroscopy time for PVI-only procedures, and freedom from AT recurrences at 12-month follow-up based on the reconstructed IPD in paroxysmal AF patients with only PVI ± cavotricuspid isthmus (CTI) ablation. Recurrence was defined as any documented AT episodes lasting >30 s after a blanking period of 90 days.

Statistical analysis

Descriptive statistics are presented as means and standard deviations for continuous variables or a number of cases (*n*) and percentages (%) for dichotomous and categorical variables.

We used the restricted maximum likelihood method with the random-effects model to combine the untransformed raw proportions. The heterogeneity across studies was evaluated by using the χ^2, τ^2, and Higgins-I^2 statistics. Random-effects models weighted by inverse variance were used because of clinical heterogeneity. The subgroup analyses are reported in Expanded Methods in Supplementary material. Individual patient data were represented through Kaplan–Meier curves and groups were compared with log-rank test. The hazard ratio (HR) with 95% confidence interval (CI) for the difference between the two groups was calculated using the Cox regression. Meta-regression analyses were performed to evaluate the sources of heterogeneity of efficacy endpoint (acute procedural success assessed per patient) and overall complications using Meta Regress command of STATA. Publication bias was assessed by graphical inspection of funnel plots. Statistical significance was defined as a two-tailed *P*-value < 0.05. Statistical analysis was performed using the meta function of STATA version 18.

Results

Study selection

Among 322 screened articles for PFA, 50 full texts were retrieved and reviewed for possible inclusion. A total of 20 studies fulfilled the selection criteria and were included in the final analysis (see Supplementary material online, *Figure S2A*). Among 1990 screened articles for CRYO, 488 full texts were retrieved and reviewed for possible inclusion; a total of 70 studies fulfilled the selection criteria and were included in the final analysis (see Supplementary material online, *Figure S2B*).

Baseline characteristics

The 20 PFA studies enrolled 2481 patients, whereas the 69 CRYO studies included 13 766 patients.

Pulsed field ablation patients were 65.9% (95% CI: 58.3–74.1) males with an average age of 65.3 years (95% CI: 62.7–68.0); 58% (95% CI: 35–81) of them were affected by paroxysmal AF. Cryoballoon ablation patients were 65.8% (95% CI: 63.7–67.9) males with an average age of 62.4 years (95% CI: 60.3–64.5); 76% (95% CI: 70–82) of them had a diagnosis of paroxysmal AF. Pulsed field ablation patients had a mean CHA_2DS_2-VASc score of 2.2 (95% CI: 1.91–2.49), left ventricular ejection fraction (LVEF) of 57.3% (95% CI: 55.9–58.7), and a LA diameter of 41.8 mm (95% CI: 40.8–42.9). Cryoballoon ablation patients showed a CHA_2DS_2-VASc score of 1.81 (95% CI: 1.62–2.01), LVEF of 59.8% (95% CI: 58.9–60.8), and LA diameter of 39.7 mm (95% CI: 38.9–40.6).

Further details on baseline characteristics are reported in Supplementary material online, *Tables S1* and *S2*.

Primary endpoints

Thirteen studies for PFA and 35 others for CRYO reported acute procedural success per vein including 6171 and 21 952 veins, respectively. The PVI confirmation method of PFA studies is reported in Supplementary material online, *Table S3*. Pulsed field ablation demonstrated greater acute PVI success on a PV basis compared with CRYO [99.9% (95% CI: 99.8–100) vs. 99.1% (95% CI: 98.7–99.5); $P < 0.001$; $I^2 = 95.9\%$] (*Figure 1*).

Nineteen studies for PFA and 43 others for CRYO reported acute procedural success on a patient basis including 1910 and 7819 patients, respectively. Pulsed field ablation yielded higher procedural success compared with CRYO [99.5% (95% CI: 99.2–99.8) vs. 98.4% (95%

Downloaded from https://academic.oup.com/europace/article/26/12/euae293/7907807 by guest on 22 January 2025

Study	Number of successes	Total	Proportion with 95% CI	Weight (%)
CRYO				
Abdin *et al.* 2019 <75 years (LXXXI)	732	732	0.999 (0.997, 1.000)	2.25
Abdin *et al.* 2019 ≥75 years (LXXXI)	214	214	0.998 (0.991, 1.000)	2.00
Akkaya *et al.* 2017 (XXIII)	1788	1788	1.000 (0.999, 1.000)	2.27
Aryana *et al.* 2016 2° gen Cryo (XLV)	1003	1009	0.994 (0.989, 0.999)	2.12
Aryana *et al.* 2016 3° gen Cryo (XLV)	407	407	0.999 (0.995, 1.000)	2.19
Buist *et al.* 2017 (LIV)	543	543	0.999 (0.997, 1.000)	2.23
Canpolat *et al.* 2019 (XIX)	1898	1902	0.998 (0.996, 1.000)	2.24
Chen *et al.* 2019 (LXXVI)	579	592	0.978 (0.966, 0.990)	1.55
Chun *et al.* 2016 (LIX)	390	390	0.999 (0.995, 1.000)	2.18
Ekizler *et al.* 2017 bonus freeze (XXXV)	308	312	0.987 (0.975, 1.000)	1.50
Ekizler *et al.* 2017 no bonus freeze (XXXV)	215	217	0.991 (0.978, 1.000)	1.48
Giannopoulos *et al.* 2019 (LX)	315	319	0.987 (0.975, 1.000)	1.52
Gunawerdene *et al.* 2018 (LIII)	118	119	0.992 (0.975, 1.000)	1.20
Hara *et al.* 2020 (XXVI)	713	736	0.969 (0.956, 0.981)	1.49
Heeger *et al.* 2019 2° gen Cryo (XXVII)	217	217	0.998 (0.991, 1.000)	2.00
Heeger *et al.* 2019 3° gen Cryo (XXVII)	217	218	0.995 (0.986, 1.000)	1.79
Heeger *et al.* 2020 (LXXIII)	539	541	0.996 (0.991, 1.000)	2.09
Heeger *et al.* 2021 polarX (XXV)	594	594	0.999 (0.997, 1.000)	2.23
Heeger *et al.* 2022 (LXIX)	1252	1256	0.997 (0.994, 1.000)	2.20
Jourdal et al. 2015 (XXXII)	284	284	0.998 (0.993, 1.000)	2.11
Kardos *et al.* 2016 (LXXIX)	156	157	0.994 (0.981, 1,000)	1.50
Keçe *et al.* 2019 TTI 120s (LVII)	99	99	0.995 (0.981, 1.000)	1.39
Keçe *et al.* 2019 TTI 150s (LVII)	100	100	0.995 (0.981, 1.000)	1.40
Keçe *et al.* 2019 TTI 90s (LVII)	100	100	0.995 (0.981, 1.000)	1.40
Knight *et al.* 2019 (XLIII)	1341	1350	0.993 (0.989, 0.998)	2.14
Kumar *et al.* 2014 (XXIV)	352	358	0.983 (0.970, 0.997)	1.43
Matta *et al.* 2018 (XXXIV)	177	181	0.978 (0.956, 0.999)	0.90
Miyamoto *et al.* 2019 (LXXXIV)	427	438	0.975 (0.960, 0.990)	1.33
Molenaar *et al.* 2018 (LVIII)	874	880	0.993 (0.988, 0.999)	2.07
Mortsell *et al.* 2018 bonus freeze (LVI)	271	271	0.998 (0.993, 1.000)	2.09
Mortsell *et al.* 2018 no bonus freeze (LVI)	267	269	0.993 (0.982, 1.000)	1.68
Nitta *et al.* 2022 (XXXIX)	993	1028	0.966 (0.955, 0.977)	1.61
Reddy *et al.* 2014 (XLVI)	84	84	0.994 (0.978, 1.000)	1.21
Ruiz *et al.* 2019 (LXXVIII)	663	681	0.974 (0.962, 0.986)	1.53
Seidl *et al.* 2021 (XXXI)	88	89	0.989 (0.967, 1.000)	0.88
Seki *et al.* 2020 (XVI)	193	193	0.997 (0.990, 1.000)	1.94
Straube *et al.* 2016 (XXXIII)	673	673	0.999 (0.997, 1.000)	2.24
Tebbenjohanns *et al.* 2016 (XXX)	2 11	211	0.998 (0.991, 1.000)	1.99
Tokuda *et al.* 2019 (XVIII)	837	920	0.910 (0.891, 0.928)	1.06
Urbanek *et al.* 2022 (IX)	779	783	0.995 (0.990, 1.000)	2.10
Watanabe *et al.* 2018 (LXII)	92	100	0.920 (0.867, 0.973)	0.22
Wei *et al.* 2022 (XLI)	974	976	0.998 (0.995, 1.000)	2.21
Wieczorek *et al.* 2019 (XXVIII)	386	390	0.990 (0.980, 1.000)	1.71
Heterogeneity: τ^2 = 0.00, I^2 = 97.17%, H^2 = 35.32			0.991 (0.987, 0.995)	
Test of $\theta_i = \theta_j$: $Q(42)$ = 241.42, P = 0.00				
Test of θ = 0: Z = 513.41, P = 0.00				
PFA				
Bohnen *et al.* 2022 (VII)	160	160	0.997 (0.988, 1.000)	1.82
Futing *et al.* 2022 (VI)	118	118	0.996 (0.984, 1,000)	1.57
Gunawerdene *et al.* 2022 (V)	80	80	0.994 (0.977, 1.000)	1.16
Kueffer *et al.* 2022 (IV)	1301	1303	0.998 (0.996, 1.000)	2.24
Lemoine *et al.* 2022 (XIII)	546	546	0.999 (0.997, 1.000)	2.23
Magni *et al.* 2022 (III)	391	391	0.999 (0.995, 1.000)	2.18
Reddy *et al.* 2020 (I)	96	96	0.995 (0.981, 1.000)	1.36
Reddy *et al.* 2021 (XII)	195	195	0.997 (0.990, 1.000)	1.95
Reddy *et al.* 2023 RCT (XV)	1208	1213	0.996 (0.992, 0.999)	2.18
Tilz *et al.* 2022 (II)	196	196	0.997 (0.990, 1.000)	1.95
Urbanek *et al.* 2022 (IX)	787	787	0.999 (0.998, 1.000)	2.25
Della Rocca *et al.* 2024 (LXXXV)	683	683	0.999 (0.997, 1.000)	2.24
Lee *et al.* 2023 (LXXXVII)	403	403	0.999 (0.995, 1.000)	2.19
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00			0.999 (0.998, 1.000)	
Test of $\theta_i = \theta_j$: $Q(12)$ = 4.59, P = 0.00				
Test of θ = 0: Z = 2193, P = 0.00				
Overall				
Heterogeneity: τ^2 = 0.00, I^2 = 95.86%, H^2 = 24.16				
Test of $\theta_i = \theta_j$: $Q(55)$ = 246.45, P = 0.00				
Test of θ = 0: Z = 744.67, P = 0.00				
Test of group differences: $Q_b(1)$ = 15.61, P = 0.00				

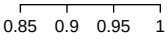


Figure 1 Acute procedural success per vein. Forest plot comparing acute procedural success per vein between PFA and CRYO. References in brackets are reported in Supplementary material. CI, confidence interval; CRYO, cryoballoon ablation; PFA, pulsed field ablation.

Downloaded from https://academic.oup.com/europace/article/26/12/euae293/7907807 by guest on 22 January 2025

CI: 97.9–98.9); $P < 0.001$; $I^2 = 68.5\%$] (*Figure 2*). Subgroup analysis including only studies with PVI without additional lesions in the LA or with entrance and exit block PVI confirmation method confirmed greater procedural success for PFA compared with CRYO on both a patient and PV basis (see Supplementary material online, *Figures S3* and *S4*). Moreover, subgroup analysis including only studies with fourth-generation cryoballoons confirmed greater procedural success for PFA compared with CRYO on a patient basis (see Supplementary material online, *Figure S5*). No reduction in heterogeneity was found in subgroup analyses including only studies with >100 patients or RCTs (see Supplementary material online, *Figures S6* and *S7*).

Meta-regression analysis results were reported in Expanded Results section in Supplementary material.

Safety endpoints

Sixteen studies for PFA and 60 others for CRYO reported overall periprocedural complications in 1611 and 11 326 patients, respectively. Pulsed field ablation demonstrated lower overall periprocedural complications compared with CRYO [3.1% (95% CI: 2.2–4.0) vs. 5.6% (95% CI: 4.6–6.6); $P < 0.001$; $I^2 = 81.2\%$] (*Figure 3*).

The pooled incidence of periprocedural complications in each group is shown in Supplementary material online, *Table S4*. Among PFA patients, the most common complications were bleeding/vascular complication [1.30% (95% CI: 0.60–1.90)], followed by ST-elevation due to coronary spasm or air embolism [0.85% (95% CI: 0.00–2.20)]. Pericardial tamponade or effusion with the need for pericardiocentesis was reported in 0.80% (95% CI: 0.28–1.33) of patients. In addition, stroke and/or TIA occurred in 0.39% (95% CI: 0.00–1.11) while PN palsy in 0.01% (95% CI: 0.00–0.07) of patients.

Among CRYO patients, the most common complications were PN palsy [1.84% (95% CI: 1.58–2.10)] and PN capture monitoring method during right PV ablation is reported in Supplementary material online, *Table S5*. Bleeding/vascular complication and stroke and/or TIA were reported in 1.20% (95% CI: 0.90–1.50) and 0.45% (95% CI: 0.29–0.62) of patients, respectively. In addition, pericardial tamponade or effusion with the need for pericardiocentesis occurred in 0.40% (95% CI: 0.24–0.56) while ST-elevation due to coronary spasm or air embolism in 0.33% (95% CI: 0.03–0.62) of patients. Oesophageal lesions were reported in five studies of the CRYO group, but none of these studies reported an atrio-oesophageal fistula event.

Meta-regression analysis results were reported in Expanded Results section in Supplementary material. Subgroup analysis was performed in the CRYO group to assess the influence of additional/bonus complications on overall complications outcome showing a non-statistically significant difference (Supplementary material online, *Figure S8*). Subgroup analysis including only studies with fourth-generation cryoballoons confirmed lower overall periprocedural complications for PFA compared with CRYO (see Supplementary material online, *Figure S9*).

Sixteen studies for PFA and 40 studies for CRYO reported major periprocedural complications including 1566 and 11 178 patients, respectively. No difference was found between the two ablation strategies [1.2% (95% CI: 0.7–1.7) vs. 1.0% (95% CI: 0.8–1.2); $P = 0.46$; $I^2 = 23.1\%$] (*Figure 4*). No significant reduction in heterogeneity was found in any subgroup analyses (see Supplementary material online, *Figures S6*, *S7*, and *S10*).

Secondary endpoints

Nine studies for PFA and 42 studies for CRYO reported procedural time for PVI-only procedures, including 1371 and 5641 patients, respectively. Pulsed field ablation demonstrated shorter procedural time compared with CRYO [75.9 min (95% CI: 59.4–92.3) vs. 105.6 min (95% CI: 96.7–114.6); $P < 0.001$; $I^2 = 99.8\%$] (*Figure 5*).

Seven studies for PFA and 37 studies for CRYO reported fluoroscopy times for PVI-only procedures, including 1314 and 5781 patients, respectively. Pulsed field ablation demonstrated shorter fluoroscopy time compared with CRYO [14.2 min (95% CI: 11.8–16.6) vs. 18.9 min (95% CI: 17.1–20.7); $P < 0.001$; $I^2 = 99.3\%$] (*Figure 6*). Subgroup analysis including only studies with fourth-generation cryoballoons confirmed lower fluoroscopy time for PFA compared with CRYO (see Supplementary material online, *Figure 11*).

Individual patient data analysis

Five studies for PFA and 21 studies for CRYO presented a Kaplan–Meier curve depicting AT-free survival in paroxysmal AF patients with PVI (±CTI) only procedures. The IPDs of 4076 patients were constructed, 1033 in the PFA group and 3043 in the CRYO one. The follow-up of the studies included in the IPD analysis is reported in Supplementary material online, *Table S6*. Atrial tachyarrhythmia freedom at 1-year follow-up was 82.3% ± 1.4% vs. 80.3% ± 1.7%, respectively (log-rank $P = 0.61$) (*Figure 7*). Neither CRYO nor PFA showed any additional advantages for AT recurrence at Cox regression analysis [HR: 0.96 (95% CI: 0.81–1.13), $P = 0.61$].

Publication bias

A graph and summary of the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies for each observational study and Cochrane risk-of-bias tool for RCTs for PFA and CRYO are reported in Supplementary material online, *Figures 12–15*. The funnel plots for visual inspection of the bias are reported and showed no significant bias in Supplementary material online, *Figure 16*.

Discussion

Herein, we report the first meta-analysis performing a comparison of the efficacy, safety, and acute procedural outcomes of PFA vs. CRYO in AF ablation (*Graphical Abstract*).

The main findings are as follows:

(1) Pulsed field ablation via the pentaspline catheter contributed to greater acute procedural success, assessed either on a PV and a patient basis, compared with CRYO.
(2) Pulsed field ablation-based procedures showed a shorter procedural time and X-ray exposure.
(3) Pulsed electric field (PEF) demonstrated a remarkable safety profile, as demonstrated by a significantly lower incidence of overall complications, with PN palsy, either transient or persistent, being the main determinant of this difference; no difference was found for major periprocedural complications.
(4) Freedom from ATs at 1 year was high (>80.0%) and similar between technologies.

Single-shot, cryogenic-based devices have been developed with the aim of achieving PVI in a simple and reproducible manner, thereby limiting the need for extensive training and the inter-operator variability. Previous studies have confirmed a high safety profile of cryoballoon, as well as non-inferiority compared with focal RF ablation.[4]

Pulsed field ablation is a novel form of non-thermal energy for AF ablation, which relies on rapidly alternating high electric fields and ultimately cell membrane nanopore formation, namely electroporation, to achieve cell death and lesion formation.[8,17–19] Unlike cryogenic energy, PEF can be tailored to improve lesion durability and tissue selectivity, thereby targeting cardiomyocytes and sparing other tissues (e.g. nerves, oesophagus, and blood vessels). The effect on cardiac tissue appears to be long-lasting, as confirmed by remapping data showing a high percentage of long-lasting PVI.[8] The Farapulse™ system is the first PFA device to have received regulatory approval, as well as the only one with 'single-shot' features.

Ours is the first meta-analysis to compare procedural success, safety, and long-term freedom from arrhythmia between cryothermy- vs. PEF-based single-shot devices. Our findings confirm a high success

Downloaded from https://academic.oup.com/europace/article/26/12/euae293/7907807 by guest on 22 January 2025

Study	Number of successes	Total	Proportion with 95% CI	Weight (%)
CRYO				
Ahn *et al.* 2023 (LII)	50	50	0.990 (0.963, 1.000)	1.10
Akhtar *et al.* 2021 (LXIII)	74	74	0.993 (0.975, 1.000)	1.71
Akkaya *et al.* 2017 (XXIII)	457	457	0.999 (0.996, 1.000)	3.23
Andrade *et al.* 2019 2 min Cryo (LXI)	116	116	0.996 (0.984, 1.000)	2.39
Andrade *et al.* 2019 4 min Cryo (LXI)	115	115	0.996 (0.984, 1.000)	2.38
Aryana *et al.* 2016 2° gen Cryo (XLV)	249	253	0.984 (0.969, 1.000)	2.00
Aryana *et al.* 2016 3° gen Cryo (XLV)	102	102	0.995 (0.982, 1.000)	2.21
Baimbetov *et al.* 2022 (XLVIII)	46	50	0.920 (0.845, 0.995)	0.20
Buist *et al.* 2017 (LIV)	136	136	0.996 (0.986, 1.000)	2.59
Choi *et al.* 2022 (LXVI)	198	200	0.990 (0.976, 1.000)	2.17
Chun *et al.* 2016 bonus freeze (LIX)	50	50	0.990 (0.963, 1.000)	1.10
Chun *et al.* 2016 no bonus freeze (LIX)	50	50	0.990 (0.963, 1.000)	1.10
Curnis *et al.* 2017 (XVII)	96	96	0.995 (0.981, 1.000)	2.12
Davies *et al.* 2020 (LXXIV)	194	200	0.970 (0.946, 0.994)	1.30
Ekizler *et al.* 2017 bonus freeze (XXXV)	80	80	0.994 (0.977, 1.000)	1.84
Ekizler *et al.* 2017 no bonus freeze (XXXV)	56	56	0.991 (0.967, 1.000)	1.27
Giannopoulos *et al.* 2019 (LX)	78	80	0.975 (0.941, 1.000)	0.78
Gunawerdene *et al.* 2018 (LIII)	29	30	0.967 (0.902, 1.000)	0.27
Haeger *et al.* 2019 (XXVII)	54	55	0.982 (0.947, 1.000)	0.75
Haeger *et al.* 2020 (LXXIII)	137	139	0.986 (0.966, 1.000)	1.59
Iacopino *et al.* 2019 2° gen Cryo (XLVII)	119	120	0.992 (0.975, 1.000)	1.91
Iacopino *et al.* 2019 3° gen Cryo (XLVII)	120	120	0.996 (0.984, 1.000)	2.43
Iacopino *et al.* 2019 4° gen Cryo (XLVII)	119	120	0.992 (0.975, 1.000)	1.91
Jain *et al.* 2023 (LXX)	119	127	0.937 (0.895, 0.979)	0.56
Jourda *et al.* 2015 (XXXII)	75	75	0.993 (0.975, 1.000)	1.73
Kardos *et al.* 2016 (LXXIX)	39	40	0.975 (0.927, 1.000)	0.44
Keçe *et al.* 2019 TTI 120s (LVII)	25	25	0.981 (0.928, 1.000)	0.38
Keçe *et al.* 2019 TTI 150s (LVII)	25	25	0.981 (0.928, 1.000)	0.38
Keçe *et al.* 2019 TTI 90s (LVII)	25	25	0.981 (0.928, 1.000)	0.38
Knecth *et al.* 2022 (LXVIII)	80	80	0.994 (0.977, 1.000)	1.84
Knight et al.2019 (XLIII)	340	344	0.988 (0.977, 1.000)	2.45
Kobori et al. 2022 (LXV)	243	253	0.960 0.936, 0.984)	1.28
Kumar et al. 2014 (XXIV)	86	90	0.956 (0.913, 0.998)	0.55
Matta *et al.* 2018 (XXXIV)	43	46	0.935 (0.863, 1.000)	0.22
Michaelsen *et al.* 2022 (XLII)	964	983	0.981 (0.972, 0.989)	2.75
Molenaar *et al.* 2018 (LVIII)	216	222	0.973 (0.952, 0.994)	1.47
Mortsell *et al.* 2019 (LVI)	912	980	0.931 (0.915, 0.947)	1.95
Mugnai *et al.* 2015 (XXXVIII)	500	500	0.999 (0.996, 1.000)	3.25
Reddy *et al.* 2014 (XLVI)	21	21	0.977 (0.915, 1.000)	0.28
Ruiz *et al.* 2019 (LXXVIII)	167	172	0.971 (0.946, 0.996)	1.21
Seidl *et al.* 2021 (XXXI)	21	22	0.955 (0.868, 1.000)	0.15
Seki *et al.* 2020 (XVI)	50	50	0.990 (0.963, 1.000)	1.10
Sharma et al. 2017 (XXXVI)	105	122	0.861 (0.799, 0.922)	0.29
Shi *et al.* 2021 (L)	49	52	0.942 (0.879, 1.000)	0.27
Straube *et al.* 2016 (XXXIII)	173	173	0.997 (0.989, 1.000)	2.82
Tanese *et al.* 2023 (XL)	135	137	0.985 (0.965, 1.000)	1.57
Tscholl *et al.* 2018 (LXXVII)	80	80	0.994 (0.977, 1.000)	1.84
Urbanek *et al.* 2023 (IX)	186	200	0.930 (0.895, 0.965)	0.74
Watanabe *et al.* 2018 (LXII)	17	25	0.680 (0.497, 0.863)	0.04
Yokokawa *et al.* 2017 (XXIX)	68	71	0.958 (0.911, 1.000)	0.47
Zhao *et al.* 2017 (XXII)	50	50	0.990 (0.963, 1.000)	1.10
Maurhofer *et al.* 2023 (XC)	80	80	0.994 (0.977, 1.000)	1.84
Heterogeneity: τ^2 = 0.00, I^2 = 79.39%, H^2 = 4.85			0.984 (0.979, 0.989)	
Test of $\theta_i = \theta_j$: $Q(51)$ = 184.80, P = 0.00				
Test of θ = 0: Z = 396.62, P = 0.00				
PFA				
Badertscher *et al.* 2023 (VIII)	52	52	0.991 (0.965, 1.000)	1.15
Bohnen *et al.* 2022 (VII)	40	40	0.988 (0.954, 1.000)	0.80
Davong *et al.* 2023 (X)	45	45	0.989 (0.959, 1.000)	0.95
Futing *et al.* 2022 (VI)	30	30	0.984 (0.940, 1.000)	0.51
Gunawerdene *et al.* 2022 (V)	20	20	0.976 (0.911, 1.000)	0.26
Kueffer *et al.* 2022 (IV)	339	341	0.994 (0.986, 1.000)	2.80
Lemoine *et al.* 2022 (XIII)	138	138	0.996 (0.986, 1.000)	2.60
Magni *et al.* 2022 (III)	100	100	0.995 (0.981, 1.000)	2.18
Reddy *et al.* 2020 (I)	25	25	0.981 (0.928, 1.000)	0.38
Reddy *et al.* 2021 (XII)	49	49	0.990 (0.962, 1.000)	1.07
Reddy *et al.* 2023 RCT (XV)	303	305	0.993 (0.984, 1.000)	2.70
Ruwald *et al.* 2023 (XI)	119	121	0.983 (0.961, 1.000)	1.37
Tilz *et al.* 2022 (II)	50	50	0.990 (0.963, 1.000)	1.10
Urbanek *et al.* 2022 (IX)	200	200	0.998 (0.991, 1.000)	2.93
Della Rocca *et al.* 2024 (LXXXV)	174	174	0.997 (0.989, 1.000)	2.83
Badertscher *et al.* 2024 (LXXXVI)	46	46	0.989 (0.960, 1.000)	0.98
Lee et al. 2023 (LXXXVII)	97	97	0.995 (0.981, 1.000)	2.14
Meininghaus et al. 2023 (LXXXVIII)	20	20	0.976 (0.911, 1.000)	0.26
Wörmann et al. 2023 (LXXXIX)	57	57	0.991 (0.968, 1.000)	1.29
Heterogeneity: τ^2 = 0.00, I^2 = 0.01%, H^2 = 1.00			0.995 (0.992, 0.998)	
Test of $\theta_i = \theta_j$: $Q(18)$ = 4.08, P = 1.00				
Test of θ = 0: Z = 608, P = 0.00				
Overall				
Heterogeneity: τ^2 = 0.00, I^2 = 68.51%, H^2 = 3.18				
Test of $\theta_i = \theta_j$: $Q(70)$ = 188.89, P = 0.00				
Test of θ = 0: Z = 558.97, P = 0.00				
Test of group differences: $Q_b(1)$ = 12.79, P = 0.00a				

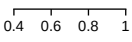


Figure 2 Acute procedural success per patient. Forest plot comparing acute procedural success per patient between PFA and CRYO. References in brackets are reported in Supplementary material. CI, confidence interval; CRYO, cryoballoon ablation; PFA, pulsed field ablation.

Downloaded from https://academic.oup.com/europace/article/26/12/euae293/7907807 by guest on 22 January 2025

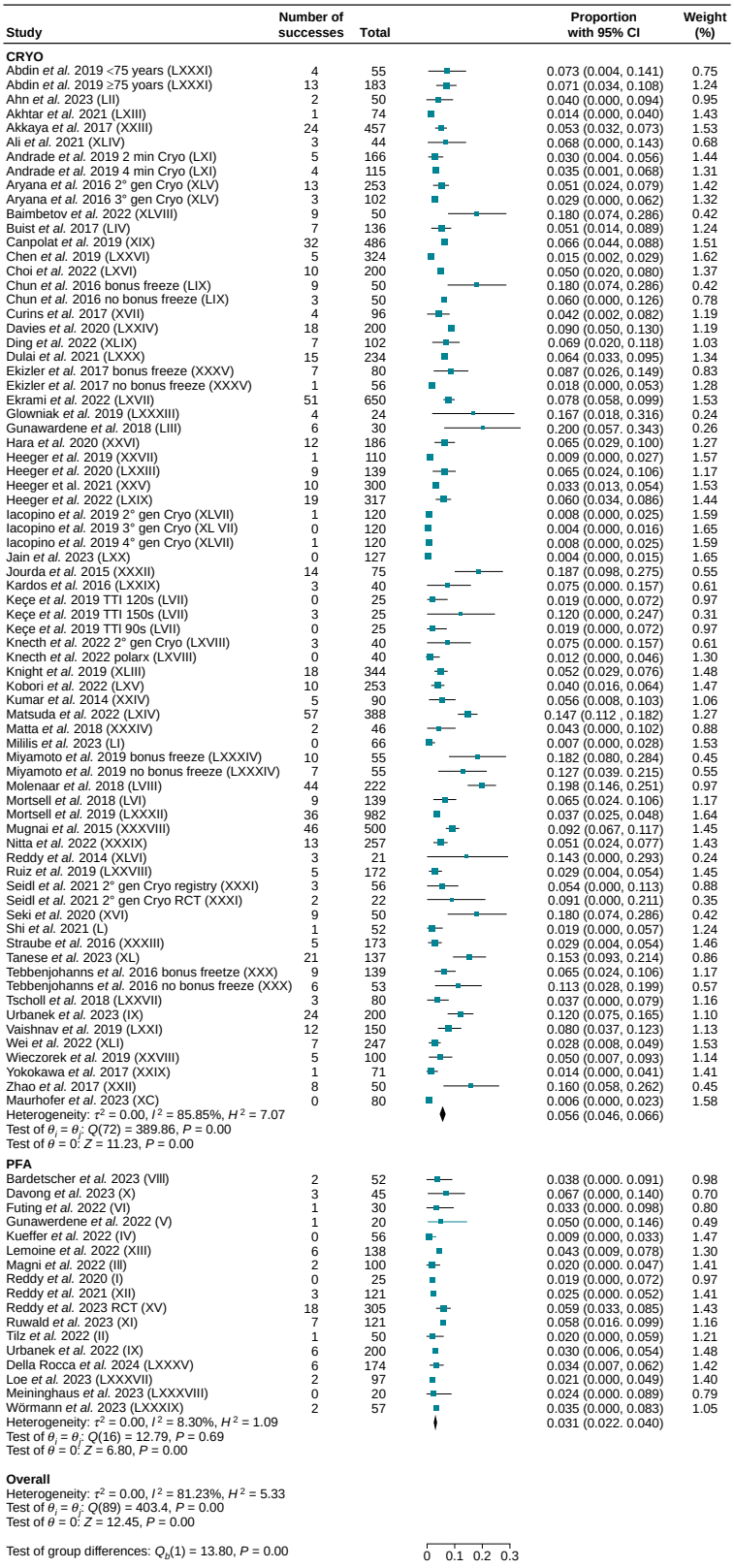


Figure 3 Overall periprocedural complications. Forest plot comparing overall periprocedural complications between PFA and CRYO. References in brackets are reported in Supplementary material.

Downloaded from https://academic.oup.com/europace/article/26/12/euae293/7907807 by guest on 22 January 2025

Study	Number of successes	Total	Proportion with 95% CI	Weight (%)
CRYO				
Mattaa *et al.* 2018 (XXXIV)	0	46	0.011 (0.000, 0.040)	0.44
Abdin *et al.* 2019 <75 years (LXXXI)	2	55	0.036 (0.000, 0.086)	0.16
Abdin *et al.* 2019 ≥75 years (LXXXI)	0	183	0.003 (0.000, 0.010)	3.26
Ahn *et al.* 2023 (LII)	0	50	0.010 (0.000, 0.037)	0.52
Akhtar *et al.* 2021 (LXIII)	1	74	0.014 (0.000, 0.040)	0.54
Akkaya *et al.* 2017 (XXIII)	6	457	0.013 (0.003, 0.024)	2.31
Ali *et al.* 2021 (XLIV)	2	44	0.045 (0.000, 0.107)	0.11
Andrade *et al.* 2019 2 min Cryo (LXI)	2	166	0.012 (0.000, 0.029)	1.20
Andrade *et al.* 2019 4 min Cryo (LXI)	3	115	0.026 (0.000, 0.055)	0.45
Aryana *et al.* 2016 2° gen Cryo (XLV)	2	253	0.008 (0.000, 0.019)	2.18
Aryana *et al.* 2016 3° gen Cryo (XLV)	0	102	0.005 (0.000, 0.018)	1.65
Balmbelov *et al.* 2022 (XLVIII)	1	50	0.020 (0.000, 0.059)	0.26
Buist *et al.* 2017 (LIV)	0	136	0.004 (0.000, 0.014)	2.40
Canpolat *et al.* 2019 (XIX)	6	486	0.012 (0.003, 0.022)	2.48
Chen *et al.* 2019 (LXXVI)	2	324	0.006 (0.000, 0.015)	2.89
Choi et al. 2022 (LXVI)	0	200	0.002 (0.000, 0.009)	3.51
Chun *et al.* 2016 bonus freeze (LIX)	1	50	0.020 (0.000, 0.059)	0.26
Chun *et al.* 2016 no bonus freeze (LIX)	0	50	0.010 (0.000, 0.037)	0.52
Curnls *et al.* 2017 (XVII)	0	96	0.005 (0.000, 0.019)	1.51
Davies *et al.* 2020 (LXXIV)	1	200	0.005 (0.000, 0.015)	2.49
Ding *et al.* 2022 (XLIX)	3	102	0.029 (0.000. 0.062)	0.36
Dulai *et al.* 2021 (LXXX)	3	234	0.013 (0.000, 0.027)	1.49
Eklzler *et al.* 2017 bonus freeze (XXXV)	1	80	0.013 (0.000, 0.037)	0.62
Ekizler *et al.* 2017 no Bonus freeze (XXXV)	1	56	0.018 (0.000, 0.053)	0.32
Ekrami *et al.* 2022 (LXVII)	27	650	0.042 (0.026, 057)	1.35
Glowniak *et al.* 2019 (LXXXIII)	1	24	0.042 (0.000, 0.122)	0.06
Gunawardene *et al.* 2018 (LIII)	0	30	0.016 (0.000, 0.060)	0.20
Hara *et al.* 2020 (XXXVI)	0	186	0.003 (0.000. 0.010)	3.31
Heeger *et al.* 2019 (XXVII)	0	110	0.005 (0.000, 0.017)	1.83
Heeger *et al.* 2020 (LXXIII)	1	139	0.007 (0.000, 0.021)	1.55
Heeger *et al.* 2021 (XXV)	1	300	0.003 (0.000, 0.010)	3.66
Heeger *et al.* 2022 (LXIX)	5	317	0.016 (0.002, 0.029)	1.60
Iacopino *et al.* 2019 2° gen Cryo (XLVII)	0	120	0.004 (0.000, 0.016)	2.06
Iacopino *et al.* 2019 3° gen Crya (XLVII)	0	120	0.004 (0.000, 0.016)	2.06
Iacopino *et al.* 2019 4° gen Cryo (XLVII)	0	120	0.004 (0.000, 0.016)	2.06
Jain *et al.* 2023 (LXX)	0	127	0.004 (0.000, 0.015)	2.21
Jourda *et al.* 2015 (XXXII)	0	75	0.007 (0.000, 0.025)	1.03
Kardos *et al.* 2016 (LXXIX)	0	40	0.012 (0.000, 0.046)	0.35
Keçe *et al.* 2019 TTI 120s (LVII)	0	25	0.019 (0.000, 0.072)	0.14
Keçe *et al.* 2019 TTI 150s (LVII)	1	25	0.040 (0.000, 0.117)	0.07
Keçe *et al.* 2019 TTI 90s (LVII)	0	25	0.019 (0.000, 0.072)	0.14
Knecth *et al.* 2022 2° gen Cryo (LXVIII)	1	40	0.025 (0.000, 0.073)	0.17
Knecth et al. 2022 polarX (LXVIII)	0	40	0.012 (0.000, 0.046)	0.35
Knight *et al.* 2019 (XLIII)	3	344	0.009 (0.000, 0.019)	2.48
Kobori *et al.* 2022 (LXV)	2	253	0.008 (0.000, 0.019)	2.18
Kumar *et al.* 2014 (XXIV)	2	90	0.022 (0.000, 0.053)	0.41
Matsuda *et al.* 2022 (LXIV)	6	388	0.015 (0.003, 0.028)	1.87
Mililis *et al.* 2023 (LI)	0	66	0.007 (0.000. 0.028)	0.84
Miyamoto *et al.* 2019 bonus freeze (LXXXIV)	1	55	0.018 (0.000, 0.053)	0.31
Miyamoto *et al.* 2019 no bonus freeze (LXXXIV)	0	55	0.009 (0.000, 0.034)	0.61
Molenaar *et al.* 2018 (LVIII)	1	74	0.014 (0.000, 0.040)	0.54
Mortsell *et al.* 2018 (LVI)	2	139	0.014 (0.000, 0.034)	0.89
Mortsell *et al.* 2019 (LXXXII)	28	982	0.029 (0.018, 0.039)	2.31
Mugnai *et al.* 2015 (XXXVIII)	13	500	0.026 (0.012, 0.040)	1.56
Nitta *et al.* 2022 (XXXIX)	11	257	0.043 (0.018, 0.068)	0.61
Reddy *et al.* 2014 (XLVI)	1	21	0.048 (0.000, 0.139)	0.05
Ruiz *et al.* 2019 (LXXVIII)	0	172	0.003 (0.000, 0.011)	3.08
Seidl *et al.* 2021 2° gen Cryo RCT (XXXI)	0	22	0.022 (0.000, 0.081)	0.11
Seidl *et al.* 2021 2° gen Cryo registry (XXXI)	0	56	0.009 (0.000, 0.033)	0.63
Seki *et al.* 2020 (XVI)	5	50	0.100 (0.017. 0.183)	0.06
Shi *et al.* 2021 (L)	1	52	0.019 (0.000, 0.057)	0.28
Straube *et al.* 2016 (XXXIII)	3	173	0.017 (0.000, 0.037)	0.92
Tanese *et al.* 2023 (XL)	1	137	0.007 (0.000, 0.022)	1.51
Tebbenjohanns *et al.* 2016 bonus freeze (XXX)	2	139	0.014 (0.000. 0.034)	0.89
Tebbenjohanns *et al.* 2016 no bonus freeze (XXX)	2	53	0.038 (0.000, 0.089)	0.15
Tscholl *et al.* 2018 (LXXVII)	1	80	0.013 (0.000, 0.037)	0.62
Urbanek *et al.* 2023 (IX)	4	200	0.020 (0.001, 0.039)	0.93
Vaishnav *et al.* 2019 (LXXI)	1	150	0.007 (0.000. 0.020)	1.72
Wei *et al.* 2022 (XLI)	1	247	0.004 (0.000, 0.012)	3.11
Wieczorek *et al.* 2019 (XXVIII)	0	100	0.005 (0.000, 0.019)	1.61
Yokokawa *et al.* 2017 (XXIX)	1	71	0.014 (0.000, 0.041)	0.50
Zhao *et al.* 2017 (XXII)	0	50	0.010 (0.000. 0.037)	0.52
Maurhofer *et al.* 2023 (XC)	0	80	0.006 (0.000, 0.023)	1.14
Heterogeneity: τ^2 = 0.00, I^2 = 28.52%, H^2 = 1.40			0.010 (0.008, 0.012)	
Test of $\theta_i = \theta_j$: $Q(72)$ = 88.69, P = 0.09				
Test of θ = 0: Z = 8.59, P = 0.00				
PFA				
Bardetscher *et al.* 2023 (VIII)	2	52	0.038 (0.000, 0.091)	0.15
Futlng *et al.* 2022 (VI)	1	30	0.033 (0.000, 0.098)	0.10
Gunawerdene *et al.* 2022 (V)	0	20	0.024 (0.000, 0.089)	0.10
Kueffer et al. 2022 (IV)	0	56	0.009 (0.000, 0.033)	0.63
Lemoine *et al.* 2022 (XIII)	2	138	0.014 (0.000, 0.034)	0.88
Magni *et al.* 2022 (111)	0	100	0.005 (0.000, 0.019)	1.61
Reddy *et al.* 2020 (I)	0	25	0.019 (0.000, 0.072)	0.14
Reddy *et al.* 2021 (XII)	2	121	0.017 (0.000. 0.039)	0.71
Reddy et a l. 2023 RCT (XV)	4	305	0.013 (0.000, 0.026)	1.77
Ruwald *et al.* 2023 (XI)	3	121	0.025 (0.000. 0.052)	0.49
Urbanek *et al.* 2022 (IX)	3	200	0.015 (0.000, 0.032)	1.17
Tilz *et al.* 2022 (II)	0	50	0.010 (0.000, 0.037)	0.52
Della Rocca *et al.* 2024 (LXXXV)	2	174	0.011 (0.000, 0.027)	1.29
Lee *et al.* 2023 (LXXXVII)	0	97	0.005 (0.000, 0.019)	1.54
Meininghaus *et al.* 2023 (LXXXVIII)	0	20	0.024 (0.000, 0.089)	0.10
Wörmann *et al.* 2023 (LXXXIX)	2	57	0.035 (0.000, 0.083)	0.18
Heterogeneity: τ^2 = 0.00, I^2 = 0.01%, H^2 = 1.00			0.012 (0.007, 0.017)	
Test of $\theta_i = \theta_j$: $Q(15)$ = 5.85, P = 0.98				
Test of θ = 0: Z = 4.38, P = 0.00				
Overall				
Heterogeneity: τ^2 = 0.00, I^2 = 23.08%, H^2 = 1.30				
Test of $\theta_i = \theta_j$: $Q(88)$ = 96.05, P = 0.26				
Test of θ = 0: Z = 9.59, P = 0.00				
Test of group differences: $Q_b(1)$ = 0.55, P = 0.46				

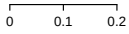


Figure 4 Major periprocedural complications. Forest plot comparing major periprocedural complications between PFA and CRYO. References in brackets are reported in Supplementary material. CI, confidence interval; CRYO, cryoballoon ablation; PFA, pulsed field ablation.

Downloaded from https://academic.oup.com/europace/article/26/12/euae293/7907807 by guest on 22 January 2025

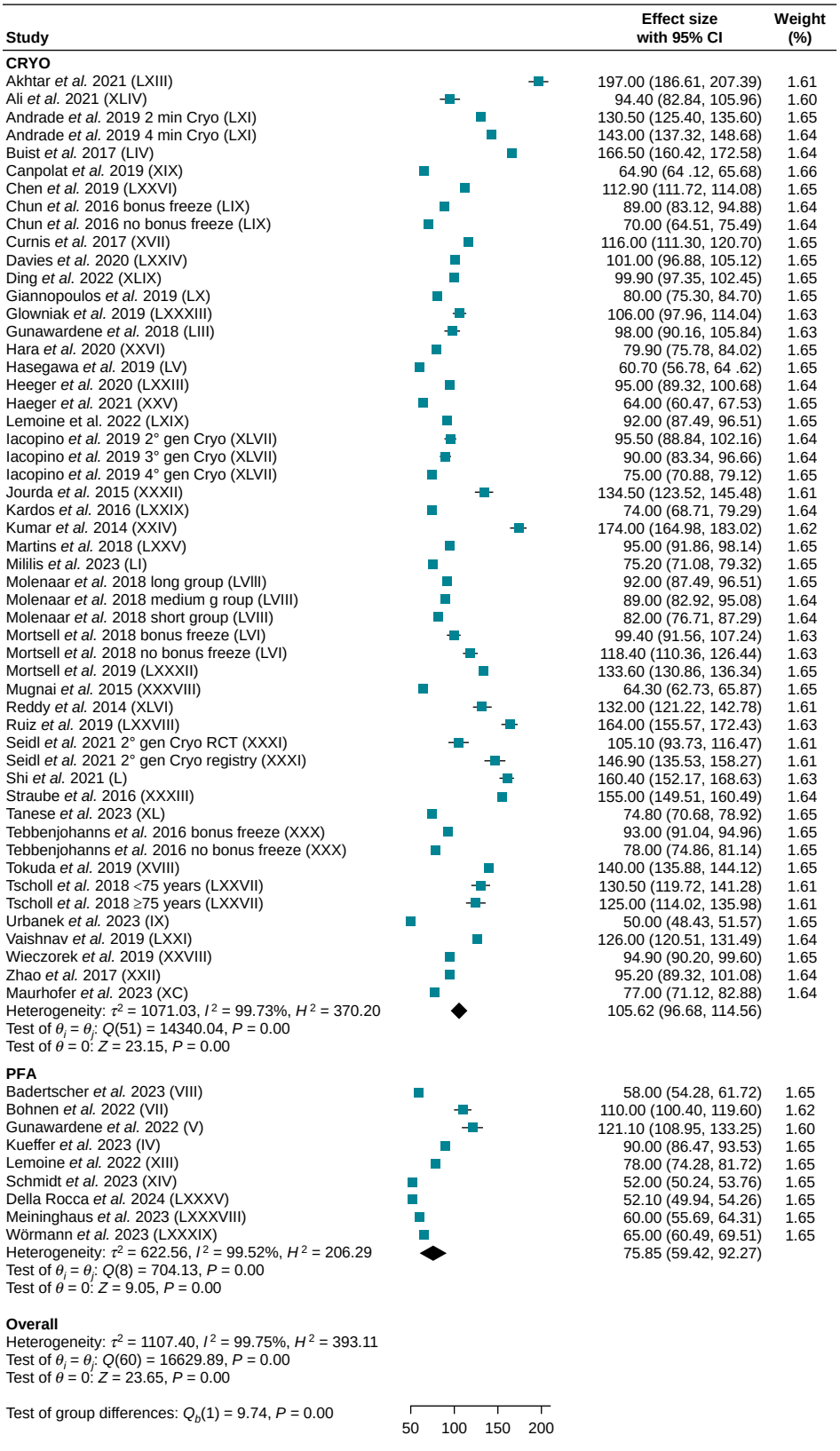


Figure 5 Procedural time. Forest plot comparing procedural time between PFA and CRYO. References in brackets are reported in Supplementary material. CI, confidence interval; CRYO, cryoballoon ablation; PFA, pulsed field ablation.

Downloaded from https://academic.oup.com/europace/article/26/12/euae293/7907807 by guest on 22 January 2025

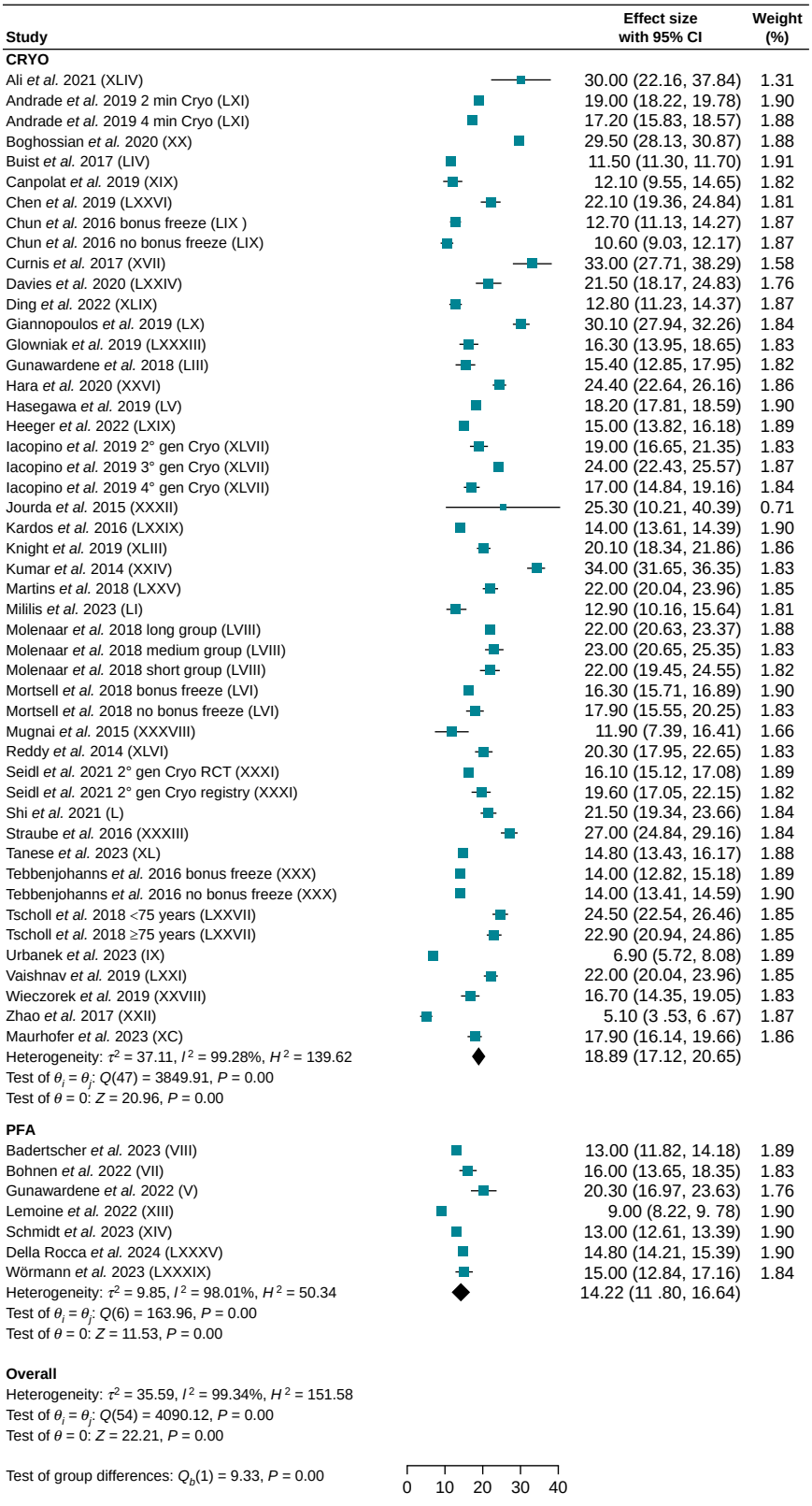


Figure 6 Fluoroscopy time. Forest plot comparing fluoroscopy time between PFA and CRYO. References in brackets are reported in Supplementary material. CI, confidence interval; CRYO, cryoballoon ablation; PFA, pulsed field ablation.

Downloaded from https://academic.oup.com/europace/article/26/12/euae293/7907807 by guest on 22 January 2025

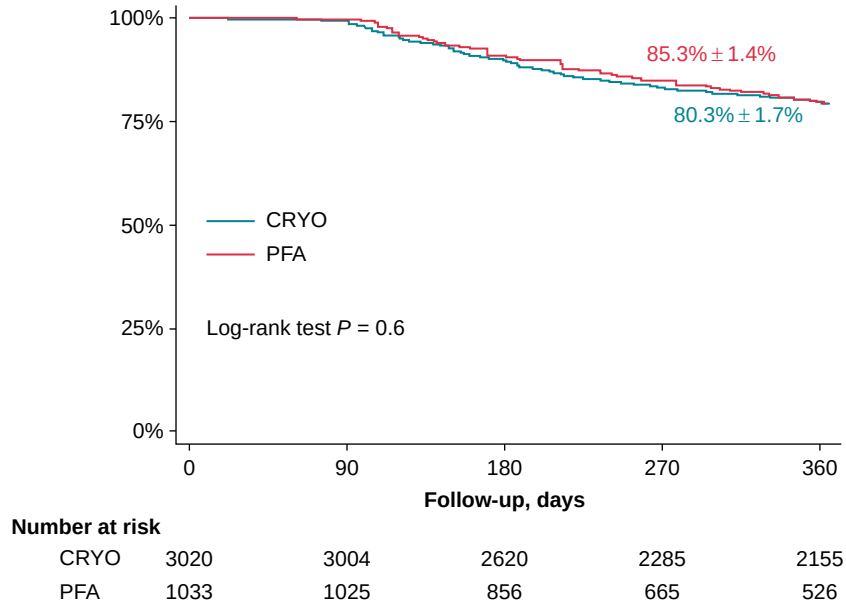


Figure 7 Kaplan–Meier survival estimates for atrial tachycardia recurrences comparing PFA and CRYO. CRYO, cryoballoon ablation; PFA, pulsed field ablation.

rate of acute PVI for both techniques; however, this is the first study to demonstrate greater acute procedural success with PFA compared with CRYO. Acute procedural success was assessed either on a PV basis as well as per patient and referred to a successful PV isolation without the need to adopt a different ablation technology. Even if the difference in acute procedural success on PV basis was only ≈1%, this may lead to a clinically meaningful issue requiring a switch to another ablation system with increased procedural costs and time. The superior acute efficacy of PFA may be explained by a greater adaptability of the Farapulse™ system to the variable PV anatomy compared with the CRYO, as a result of the dual configuration of basket and flower.[20] The flower configuration allows for a wide antral circumferential area of the lesion, as evidenced by ultra-high-density mapping studies showing greater coverage even in PVs with complex anatomy.[21] For these reasons, studies have shown a smooth transition from cryoballoon to PFA and a steep learning curve for operators who are new to single-shot technologies.[20,22]

Achieving isolation of the right PVs with cryoballoon may be hindered by the vicinity of the PN, with PN palsy, either transient or persistent, being the most common periprocedural complication in such procedures.[23–25] Periprocedural PN palsy is a potential cause of incomplete right PV isolation requiring point-by-point ablation. In patients treated with PFA, the incidence of transient PN palsy is extremely rare (0.3%–0.46%), whereas PFA-related persistent PN injury has been reported only once in the literature.[13,26]

Our findings also underlined the remarkable safety profile of PFA, as suggested by a significantly lower rate of overall periprocedural complications compared with CRYO (3.1% vs. 5.6%); this difference was mainly due to the rate of PN injury in the CRYO group (1.84% vs. 0.01%). Although the rate of major periprocedural complications was similar, it is important to highlight that PEF does not pose any risks of thermal lesions to the oesophagus, thereby completely eliminating the risk of the dreaded and life-threatening atrio-oesophageal fistula.[6]

Our meta-analysis also demonstrated shorter procedural (75.9 min vs. 105.6 min) and fluoroscopy (14.2 min vs. 18.9 min) times with PFA. A reduction in procedure times was also demonstrated in the ADVENT with PFA compared with conventional thermal energy, but this was mainly due to the use of electroanatomical mapping and longer ablation times in the point-by-point RF ablation subgroup.[14] In contrast with our findings, the ADVENT trial reported a longer fluoroscopy time with PFA, but, again, this was probably related to the ubiquitous use of non-fluoroscopic electroanatomical mapping systems with RF ablation.[14] As a matter of fact, CRYO showed significantly higher X-ray exposure when compared with RF in the FIRE AND ICE randomized trial.[4] Operator experience was proven to decrease fluoroscopy time with PFA; therefore, the integration of the Farapulse™ system with 3D mapping will soon provide an alternative for catheter localization during PFA.[27]

Limitations

Our meta-analysis has several limitations. (i) Observational studies were included in this analysis, which introduced all the inherent limitations and biases related to their design. In particular, studies of cryoablation and PFA were non-contemporaneous, and each study examined only one ablation modality or the other. None of the studies included in this meta-analysis provided a head-to-head comparison of the two modalities. (ii) High levels of heterogeneity for efficacy and safety outcomes were observed. (iii) Data on acute procedural success per vein were available only in a limited number of studies, and the strategy to confirm PV isolation was not uniform among them. (iv) A large registry such as MANIFEST-PF[28] was excluded from this study due to overlap with data from the EU-PORIA registry. (v) The studies available for PFA report data from a first experience with PFA and not from operators with long experience, as for CRYO. This factor may have impacted procedural duration, as well as major complication rates. Similarly, the CRYO group includes studies published since 2014; improved materials and technologies might have contributed to shorter procedural and dwelling times in recent years. (vi) Finally, in our meta-analysis, we showed a higher number of persistent AF in the PFA group than in the CRYO group (76% vs. 58%). The reason for the higher number of persistent AF patients in the PFA group is due

Downloaded from https://academic.oup.com/europace/article/26/12/euae293/7907807 by guest on 22 January 2025

to the capability of the Farapulse™ catheter with the flower shape to perform not only PVI but also posterior wall isolation and posterior mitral line ablation.

Conclusions

In our meta-analysis, PFA contributed to greater acute procedural success and a better safety profile than CRYO. In addition, PFA led to shorter procedural and fluoroscopy times.

Supplementary material

Supplementary material is available at *Europace* online.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: The authors of this manuscript have the following competing interests. A.N. received speaker honoraria from Boston Scientific, Biosense Webster, Abbott, Biotronik, and Medtronic and is a consultant for Biosense Webster, Abbott, and Janssen. G.-B.C. received compensation for teaching purposes and proctoring from Medtronic, Abbott, Biotronik, Boston Scientific, and Acutus Medical. C.d.A. receives research grants on behalf of the centre from Biotronik, Medtronic, Abbott, LivaNova, Boston Scientific, AtriCure, Philips, and Acutus. The other authors have declared that no competing interests exist.

Data availability

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

Appendix

HRMC Investigators: Alvise Del Monte, MD; Sahar Mouram, MD; Cinzia Monaco, MD; Ilenia Lombardo, MD; Roberto Scacciavillani, MD; Kazutaka Nakasone, MD; Maria Cespon Fernandez, MD, PhD.

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C *et al.* 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498.
2. Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J *et al.* Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med* 2021;**384**:305–15.
3. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A *et al.* Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**:1305–16.
4. Kuck K-H, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KRJ *et al.* Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med* 2016;**374**:2235–45.
5. Del Monte A, Chierchia GB, Della Rocca DG, Pannone L, Sorgente A, Bala G *et al.* Posterior wall isolation via a multi-electrode radiofrequency balloon catheter: feasibility, technical considerations, endoscopic findings and comparison with cryoballoon technologies. *J Interv Card Electrophysiol* 2023;**67**:273–83.
6. Della Rocca DG, Magnocavallo M, Natale VN, Gianni C, Mohanty S, Trivedi C *et al.* Clinical presentation, diagnosis, and treatment of atrioesophageal fistula resulting from atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2021;**32**:2441–50.
7. Reddy VY, Anic A, Koruth J, Petru J, Funasako M, Minami K *et al.* Pulsed field ablation in patients with persistent atrial fibrillation. *J Am Coll Cardiol* 2020;**76**:1068–80.
8. Reddy VY, Neuzil P, Koruth JS, Petru J, Funosako M, Cochet H *et al.* Pulsed field ablation for pulmonary vein isolation in atrial fibrillation. *J Am Coll Cardiol* 2019;**74**:315–26.
9. Verma A, Boersma L, Haines DE, Natale A, Marchlinski FE, Sanders P *et al.* First-in-human experience and acute procedural outcomes using a novel pulsed field ablation system: the PULSED AF pilot trial. *Circ Arrhythm Electrophysiol* 2022;**15**:e010168.
10. Turagam MK, Neuzil P, Petru J, Funasako M, Koruth JS, Reinders D *et al.* PV isolation using a spherical array PFA catheter: application repetition and lesion durability (PULSE-EU study). *JACC Clin Electrophysiol* 2023;**9**:638–48.
11. Duytschaever M, De Potter T, Grimaldi M, Anic A, Vijgen J, Neuzil P *et al.* Paroxysmal atrial fibrillation ablation using a novel variable-loop biphasic pulsed field ablation catheter integrated with a 3-dimensional mapping system: 1-year outcomes of the multicenter inspIRE study. *Circ Arrhythm Electrophysiol* 2023;**16**:e011780.
12. Della Rocca DG, Marcon L, Magnocavallo M, Menè R, Pannone L, Mohanty S *et al.* Pulsed electric field, cryoballoon, and radiofrequency for paroxysmal atrial fibrillation ablation: a propensity score-matched comparison. *Europace* 2024;**26**:euae016.
13. Ekanem E, Reddy VY, Schmidt B, Reichlin T, Neven K, Metzner A *et al.* Multi-national survey on the methods, efficacy, and safety on the post-approval clinical use of pulsed field ablation (MANIFEST-PF). *Europace* 2022;**24**:1256–66.
14. Reddy VY, Gerstenfeld EP, Natale A, Whang W, Cuoco FA, Patel C *et al.* Pulsed field or conventional thermal ablation for paroxysmal atrial fibrillation. *N Engl J Med* 2023;**389**:1660–71.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700.
16. Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published Kaplan–Meier survival curves. *BMC Med Res Methodol* 2021;**21**:111.
17. Bradley CJ, Haines DE. Pulsed field ablation for pulmonary vein isolation in the treatment of atrial fibrillation. *J Cardiovasc Electrophysiol* 2020;**31**:2136–47.
18. Boersma L. New energy sources and technologies for atrial fibrillation catheter ablation. *Europace* 2022;**24**:ii44–51.
19. Boersma L, Andrade JG, Betts T, Duytschaever M, Pürerfellner H, Santoro F *et al.* Progress in atrial fibrillation ablation during 25 years of Europace journal. *Europace* 2023;**25**:euad244.
20. Cespón-Fernández M, Della Rocca DG, Almorad A, Magnocavallo M, Pannone L, Koopman P *et al.* Versatility of the novel single-shot devices: a multicenter analysis. *Heart Rhythm* 2023;**20**:1463–5.
21. Gunawardene MA, Schaeffer BN, Jularic M, Eickholt C, Maurer T, Akbulak RÖ *et al.* Pulsed-field ablation combined with ultrahigh-density mapping in patients undergoing catheter ablation for atrial fibrillation: practical and electrophysiological considerations. *J Cardiovasc Electrophysiol* 2022;**33**:345–56.
22. Schmidt B, Bordignon S, Tohoku S, Chen S, Bologna F, Urbanek L *et al.* 5S study: safe and simple single shot pulmonary vein isolation with pulsed field ablation using sedation. *Circ Arrhythm Electrophysiol* 2022;**15**:e010817.
23. Chierchia G-B, Mugnai G, Hunuk B, Ströker E, Velagić V, Saitoh Y *et al.* Impact on clinical outcome of premature interruption of cryoenergy delivery due to phrenic nerve palsy during second generation cryoballoon ablation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2015;**26**:950–5.
24. Heeger C-H, Sohns C, Pott A, Metzner A, Inaba O, Straube F *et al.* Phrenic nerve injury during cryoballoon-based pulmonary vein isolation: results of the worldwide YETI registry. *Circ Arrhythm Electrophysiol* 2022;**15**:e010516.
25. Tokuda M, Yamashita S, Sato H, Oseto H, Ikewaki H, Yokoyama M *et al.* Long-term course of phrenic nerve injury after cryoballoon ablation of atrial fibrillation. *Sci Rep* 2021;**11**:6226.
26. Schmidt B, Bordignon S, Neven K, Reichlin T, Blaauw Y, Hansen J *et al.* EUropean real-world outcomes with Pulsed field ablatiOn in patients with symptomatic atRIAl fibrillation: lessons from the multi-centre EU-PORIA registry. *Europace* 2023;**25**:euad185.
27. Ruwald MH, Johannessen A, Hansen ML, Haugdal M, Worck R, Hansen J. Pulsed field ablation in real-world atrial fibrillation patients: clinical recurrence, operator learning curve and re-do procedural findings. *J Interv Card Electrophysiol* 2023;**66**:1837–48.
28. Turagam MK, Neuzil P, Schmidt B, Reichlin T, Neven K, Metzner A *et al.* Safety and effectiveness of pulsed field ablation to treat atrial fibrillation: one-year outcomes from the MANIFEST-PF registry. *Circulation* 2023;**148**:35–46.

Downloaded from https://academic.oup.com/europace/article/26/12/euae293/7907807 by guest on 22 January 2025