Interventional procedure overview of pulsed field ablation for atrial fibrillation

Contents

Table 1 Abbreviations

Abbreviation	Definition
AE	Adverse event
AF	Atrial fibrillation
AFEQT	Atrial Fibrillation Effect on Quality-of-life questionnaire
CBA	Cryoballoon ablation
CHA_2DS_2-VaSc	Score for atrial fibrillation stroke risk
EQ-5D	European Quality of life – 5 Dimensions
EQ-VAS	European Quality of life – Visual Analogue Scale
GA	General anaesthesia
HR	Hazard ratio
MD	Mean difference
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OR	Odds ratio
PAF	Paroxysmal atrial fibrillation
PersAF	Persistent atrial fibrillation
PFA	Pulsed field ablation
PV	Pulmonary vein
PVI	Pulmonary vein isolation
RCT	Randomised controlled trial
RFA	Radiofrequency ablation
RR	Risk ratio
SAE	Serious adverse event
TA	Thermal ablation

Indications and current treatment

AF is an irregular contraction of the upper chambers of the heart (atria) and often causes the heart to beat rapidly. This makes the heart less effective at moving blood from the upper to the lower chambers of the heart. Symptoms of AF include palpitations, dizziness, shortness of breath, fatigue and chest pain. It can have a substantial effect on quality of life. Complications of AF include stroke and

heart failure. AF can be transient (paroxysmal), lasting longer than 30 seconds but only up to 7 days (PAF) or persistent, lasting more than 7 days (PersAF).

Standard treatments for symptomatic AF include lifestyle modification, drug therapy and procedural interventions. The aim of treatment is to prevent complications like stroke and alleviate symptoms. Drug treatments include anticoagulants to reduce the risk of stroke, and antiarrhythmics to restore or maintain the normal heart rhythm or to slow the heart rate. When medications for AF do not work or are unsuitable, other treatments like catheter ablation procedures may be used. The current standard catheter ablation techniques are RFA and CBA. Laser balloon ablation is rarely used in the NHS.

Unmet need

AF is the most common heart rhythm disorder, affecting about 2% of the adult population. The prevalence is likely increasing because it is associated with age, underlying heart disease, diabetes, obesity and hypertension, which are also increasing in prevalence in the UK population. If left untreated, AF is a significant risk factor for stroke, other morbidities and mortality. When standard medications for AF do not work or are unsuitable, catheter ablation procedures are commonly offered. Most catheter ablation methods use thermal energy, by either burning (in RFA) or freezing (in CBA) heart tissue that conducts the irregular electrical impulses. Thermal ablation carries a risk of damaging neighbouring tissues. PFA uses electrical instead of thermal energy. Heart cells are very sensitive to electrical energy. So, PFA may be able to target heart tissue more precisely than thermal ablation, which may reduce the risk of damaging surrounding tissues like the oesophagus, nerves, and blood vessels.

What the procedure involves

PFA is a catheter ablation technique that uses electrical energy to destroy the heart cells that transmit abnormal electrical impulses. In the NHS, the procedure is usually done under GA but deep sedation is often used in other countries. As in other catheter ablation procedures for AF, a catheter is inserted via the femoral vein and advanced into the left atrium through a trans-septal puncture. The PFA catheter delivers rapid, high-voltage pulsed electrical energy to the tissue it is applied to. This causes pores to form in myocardial cells, so the cells die (irreversible electroporation). Most commonly, PFA is used for isolation of abnormal electrical activity transmitted through the PV cells at the entrance to the left atrium, but it can be used on other structures like the left atrial posterior wall. The aim is targeted destruction and scar formation in the tissue it is applied to, to disrupt the transmission of abnormal electrical impulses that cause AF, whilst avoiding damage to surrounding tissues such as nerves and blood vessels.

Outcome measures

The main outcomes included acute treatment success, recurrence of AF or other atrial arrhythmia, reintervention, composite scores of treatment success and quality of life. Most outcomes were measured with physiological assessment.

Acute treatment success was generally defined as PVI success rate. Composite scores that represented longer-term treatment success were described in Table 3 with the results. Standardised outcome measures were used for quality of life and in some studies for symptoms or risk of stroke.

Quality of life outcome measures

- AFEQT is a patient-reported measure of AF effect on quality of life. It gives an overall score comprised from scores for symptoms, daily activities,

treatment concerns, and treatment satisfaction. Overall scores range from 0 (complete disability) to 100 (no disability).

- EQ-5D is a patient-reported measure of health-related quality of life. It is not specific to AF. It has 5 domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and each domain has 5 levels (no problems, slight problems, moderate problems, severe problems and extreme problems). Scores are weighted to adjust for societal context.
- EQ-VAS is a patient-reported outcome measure of self-rated health. It is not specific to AF. It is measured on a vertical visual analogue scale where the endpoints are labelled 'The best health you can imagine' (scored 100) and 'The worst health you can imagine' (scored 0).

Stroke and cerebral lesion symptom or risk measures

- mRS is a clinician-completed measure that represents the degree of dependence or disability in daily activity caused by stroke or neurological impairment. Symptoms are scored from 0 (no symptoms) to 6 (death).
- NIHSS is a clinician-completed measure of impairment caused by stroke. It is comprised of 11 items measuring alertness, visual function, muscle strength (in the face, arms, and legs), sensory function, coordination, and language comprehension and production. Scores range from 0 (no stroke symptoms) to 42 (severe stroke).
- CHA_2DS_2-VaSc is a clinical prediction rule for stroke risk in people with AF. Risk scores are calculated from factors including congestive heart failure, hypertension, age, diabetes, prior history of stroke or thromboembolism, vascular disease and sex.

- Mental Status Examination is a clinician-completed assessment of appearance, attitude, behaviour, mood and affect, speech, thought process, thought content, perception, cognition, insight, and judgment.

Evidence summary

Population and studies description

The identified publications were stratified by technology and then prioritised to select the key evidence that is representative of this procedure. Evidence was prioritised for 5 technologies. Key evidence for other technologies is presented in the first section of appendix B, table 5.

This interventional procedures overview is based on 12 studies reported in 17 publications. They are presented in table 2 and table 3, and 100 other relevant studies are presented in appendix B, table 5. The publications include about 30,000 people of whom about 24,850 had PFA, from the UK, EU, Israel, US, Canada, Australia and China. Most studies reported outcomes up to 12 months. One study reported acute outcomes within 48 hours as the focus was on prevention of a common periprocedural adverse event (Mohanty 2024). One study of 17,642 people had average follow up of 15 months and data up to 25 months (Ekanem 2024). The UK analysis of 707 people comparing PFA with RFA and CBA (Calvert 2024) reported findings at a median of 7.6 months.

The selected evidence included 2 systematic review and meta-analyses (de Campos 2024, Amin 2024), mostly comprised of evidence from the Farawave catheter (Boston Scientific, see Procedure technique for more information on the different technologies in the prioritised evidence). De Campos (2024) included 18, mostly non-randomised comparative studies with 4,998 people (1,761 had PFA), and Amin (2024) included 17 mostly non-randomised comparative studies with 2,255 people (1,051 had PFA). Both publications compared PFA with TA

(RFA and CBA) and both included evidence from across the globe. Eight studies were included in both systematic review and meta-analyses. The differences in included studies was likely due to de Campos (2024) having a more recent search date and because they only included studies done in people having first-time ablation. Also, Amin (2024) did not have an exclusion criteria around repeat ablation procedures.

Other prioritised evidence done with the Farawave catheter was from a US 3-arm multicentre RCT comparing PFA with RFA and CBA (ADVENT trial, Reddy 2023a, Patel 2024), a UK single-arm real-world study of 707 people comparing RFA with PFA and CBA (Calvert, 2024), an EU retrospective analysis of a prospective registry of 1,568 people across 24 centres (MANIFEST-PF study, Turagam 2023, Turagam 2024), a centre-level study done across 101 centres in the EU and Israel including 17,642 people (MANIFEST-17K study, Ekanem 2024), a prospective case series of 191 people who all had PFA with deep sedation (Schmidt 2022), and a retrospective case series of 103 people focusing on avoidance of a common adverse event (Mohanty 2024).

Prioritised evidence from the Varipulse catheter (Biosense Webster Inc.) was from an EU and Canada prospective single-arm trial of 226 people across 13 centres (inspIRE study, Duytschaever 2023, de Potter 2024, Grimaldi 2023).

Prioritised evidence for the PulseSelect catheter (Medtronic) was from an international prospective single-arm trial of 300 people across 41 centres (PULSED AF, Verma 2023a, Verma 2023b).

Prioritised evidence for the Sphere-9 catheter (Affera Inc, Medtronic) was from a publication that combined evidence from 2 prospective single-arm trials which together had 178 people across 3 EU centres (Reddy 2023b).

Prioritised evidence for the CENTAURI PFA generator (Galvanize therapeutics) was from a prospective, single-arm trial of 84 people from 2 EU centres (Anić 2023).

Most studies included a mixture of people who had PAF, PersAF and some also reported including people with longstanding PersAF. Some studies did separate analyses for these subgroups. The ADVENT RCT comparing PFA with RFA and CBA (Reddy 2023a, Patel 2024) and the inspIRE single arm trial of 226 people (Duytschaever 2023, de Potter 2024, Grimaldi 2023), only included people with PAF.

The evidence included a mixture of people having first-time PFA and people having repeat procedures. The systematic review and meta-analysis of 18 studies comparing PFA with TA only included people having first-time PVI ablation (de Campos 2024). The systematic review and meta-analysis of 17 studies comparing PFA with TA included studies of people having both first-time and repeat ablation procedures but the proportion of each was not reported (Amin 2024). Most of the remaining studies only included people having first-time procedures. The EU-PORIA centre-level registry study did not exclude people that had had previous ablation procedures (Schmidt 2023), but most people (96%) had first time ablation, and inclusion criteria with respect to repeat procedures was unclear in Mohanty (2024). Most studies reported need for repeat ablation procedure after the index PFA procedure as an outcome.

This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. Table 2 presents study details.

Figure 1 Flow chart of study selection

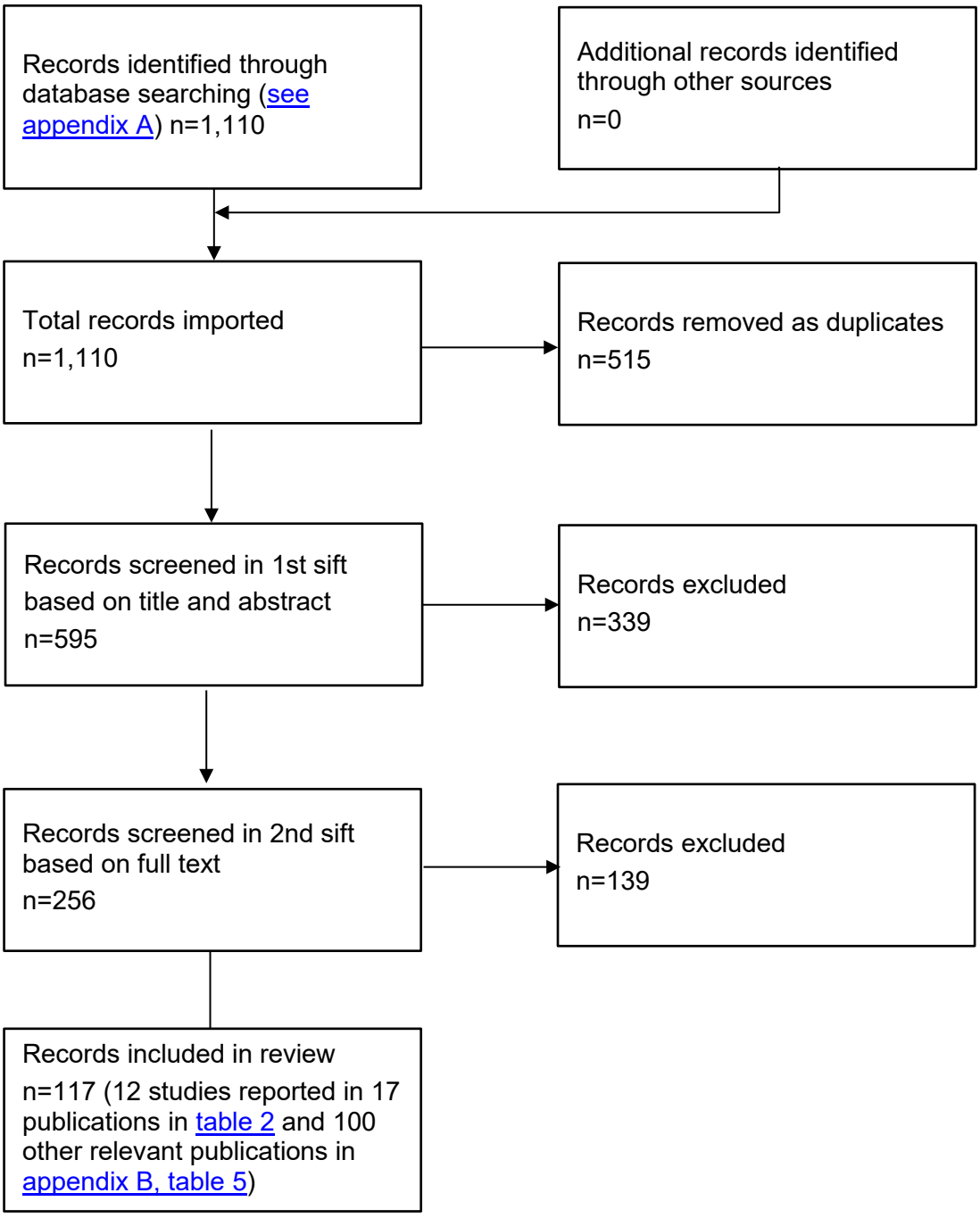

Table 2 Study details

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
Systematic review and meta-analysis evidence						
1	de Campos, 2024 Included studies were done in Switzerland, US, Germany, China, Czech Republic, Brussels, Italy, Netherlands and France.	18 studies including 2 RCTs and 16 non-randomised studies. n=4,998 people, of whom 1,761 (35%) had PFA • 66% had PAF, 34% PersAF • All first-time ablation • 63% male • Median age: 64 years • Median BMI: 27.6 kg/m^2	Systematic review and meta-analysis. Databases were searched until February 2024.	Inclusion criteria: • randomised and non-randomised controlled trials in people with PAF or PersAF • studies that compared PFA with thermal ablation • studies that reported outcomes of interest • first PVI ablation Exclusion criteria: • case reports • editorials • reviews • expert opinions • no control group • conference abstracts	PFA compared with thermal ablation, including CBA and RFA. 17 of 18 studies used the Farawave catheter (Boston Scientific), 1 study used LEAD-PFA catheter (Sichuan Jinjiang Electronic Technology Co.)	Maximum follow up in an included study was 404 days (plus or minus 150). Treatment failure rate was summarised at before 1 year and after 1 year.

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
				• research letters and brief communications		
2	Amin, 2024 Included studies were done in US, Switzerland, Germany, France, Czech Republic, Canada, Austria and UK	17 studies including 1 RCT and 16 non-randomised studies n=2,255 people of whom 46% (1,051 people) had PFA • The proportion of people with PAF and PersAF was not reported • The proportion of people having first time compared with repeat ablation was not reported • Mean age ranged from 56 to 70 in the included studies	Systematic review and meta-analysis. Databases were searched until September 2023.	Inclusion criteria: • randomised and non-randomised controlled trials • done in people with PAF or PersAF • people having first or repeat ablation • compared with TA • reported outcomes interest Exclusion criteria: • Duplicates, reviews and conference abstracts	PFA compared with thermal ablation, including CBA and RFA. 16 of 17 studies used the Farawave catheter (Boston Scientific), 1 study used Sphere-9 (Afferra, Medtronic)	Up to 12 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		• Mean BMI ranged from 25.9 to 30.2 in the included studies				
Farawave catheter studies						
3	ADVENT trial, NCT04612244 (2 publications) US **Main RCT report:** • Reddy, 2023a **Additional publications:** • Patel, 2024	**Full RCT sample (Reddy, 2023a)** 607 people (305 had PFA, 302 had TA including 167 RFA and 135 CBA) • All people had PAF • All first time ablation • 66% male in PFA, 65% male in TA • Mean age was 62 in PFA and 63 in TA • Mean BMI was 28 in PFA and 29 in TA	**Full RCT sample (Reddy, 2023a)** 3-arm, patient and end-point assessor blind, multicentre, non-inferiority RCT and post-hoc sub-analyses between March 2021 and June 2022. 30 centres with 65 operators **Patel (2024)** Sub-group analysis of 6 of 30 centres in the ADVENT trial. People in this sub-	**Full RCT sample (Reddy, 2023a)** Inclusion criteria: • Age 18 to 75 years • Symptomatic PAF that was refractory to 1 or more antiarrhythmic drug • First time ablation. There were many exclusion criteria listed in the supplementary material. These mainly listed common contraindications for catheter ablation and PFA. **Patel (2024)**	PVI only using PFA (Farawave PFA catheter, Boston Scientific), compared with TA, including CBA and RFA	**Full RCT sample (Reddy, 2023a)** 12 months **Patel (2024)** 3 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		Patel (2024) n=71 (34 had PFA, 37 had TA including 20 RFA and 17 CBA) • 50% female in PFA, 29.7% female in TA • Mean age (61 years) was similar between groups • Mean BMI (28.7) was similar between groups	study had MRI after PFA.	Consecutive patients at each of the 6 centres in the sub-study had MRI scans.		
4	Calvert, 2024 UK	n=707 (208 had PFA, 499 had TA including 325 CBA and 174 RFA) • 56% PAF, 44% PersAF • All first time ablation • 33 to 36% female across arms	Single-centre, retrospective real-world observational study of consecutive patients between June 2022 and December 2023.	Consecutive people with PAF or PersAF, who had first time ablation with one of the following procedures: • Point by point RFA • CBA • Single-shot PFA with the Farapulse catheter People who had the following were	PVI with operator discretion additional lesion sets using PFA (Farawave PFA catheter, Boston Scientific), compared with TA, including CBA and RFA	Median was 7.6 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		• Median age 63 to 64 across arms • Median BMI was 29 in all 3 arms		excluded from the analysis: • Procedure was part of another research study • Redo procedures Patient selection for each procedure was unclear.		
5	MANIFEST-PF Registry study (2 publications) Europe (24 centres) **Primary publication:** Turagam, 2023 **Additional publications:** Turagam, 2024	**Full analysis (Turagam, 2023)** n=1568 people • 65% had PAF, 32% had PersAF, 3% had long-standing PersAF • All first-time ablation • Mean age 64.5 years • Mean BMI 28.1 • 35% female **Turagam (2024)**	Retrospective analysis of a prospective, multicentre, patient-level registry study. Procedures were done between March 2021 and May 2022.	**Full analysis (Turagam, 2023)** Consecutive people ages 18 or older who had first-time ablation for PAF, PersAF or long-standing PersAF. People were excluded if they had previous left atrial ablation. **Turagam (2024)** A subset of the Turagam (2023) sample were selected for analysis. Only people who had PFA	**Full analysis (Turagam, 2023)** PVI with operator discretion additional lesion sets using PFA (Farawave PFA catheter, Boston Scientific) • 28% (439 of 1568 people) had additional lesion sets. This included 11% (173 of 1568 people) who had left	1 year

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		n=547 • 131 had PVI plus left atrial posterior wall ablation, 416 had PVI only • Mean age 66.3 (SD 2.6) • 30.2% female • Mean BMI 28.9 (SD 5.2) • People who had left atrial posterior wall ablation were on average younger, had lower stroke risk and less likely to have had coronary artery disease than the PVI only group.		for PersAF or longstanding PersAF were included. People with PAF were excluded.	atrial posterior ablation. 76% of those had PersAF or longstanding PersAF. **Turagam (2024)** • Of the 131 people who had PVI plus left atrial posterior wall ablation, 16.8% (22) had additional ablation. • Of the 416 people who had PVI only, 11.5% had additional ablation, not including left atrial posterior wall ablation. • This was not a statistically	

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
					significant difference (p=0.14).	
6	MANIFEST-17K (1 publication) 19 European countries and Israel (106 centres) Ekanem (2024)	n=17,642 people • 58% PAF, 35% PersAF, 6% longstanding PersAF, 1% atrial flutter or tachycardia • Proportion of first time ablation procedures not reported. • Mean age 64 • 35% female	Multicentre, centre-level retrospective observational study. Procedures were done between early 2022 and for most centres, until June 2023. Data from MANIFEST-PF was excluded.	All centres doing post-approval PFA with Farawave were invited to participate (n=116 centres). Data that was used in the MANIFEST-PF study was excluded. No patient-level inclusion and exclusion criteria were applied.	Farawave PFA catheter, Boston Scientific)	Average 15 months (range 3 to 25 months)
7	Schmidt, 2022 Germany (1 centre)	n=191 • 62% PAF, 38% PersAF • All first-time ablation • All had deep sedation	Prospective, single-centre case series of consecutive people recruited between March and August 2021.	All people aged 18 to 85 people with symptomatic, drug refractory AF. Exclusion criteria: • Previous PVI or non-PVI ablation	PVI with PFA using a deep sedation protocol (Farawave PFA catheter, Boston Scientific)	6 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		• Mean age 69 (SD 12) • 58% male • Mean BMI 28 (SD 5)		done during the procedure • Ineligible for oral anticoagulation • Intracardiac thrombus • Moderate or severe mitral valve disease		
8	Mohanty, 2024 US	n=103 (Group 1, n=28: people had little or no hydration immediately after the procedure, Group 2, n=75: people who had planned fluid infusion) • Group 1: 46% PAF, 50% PersAF, 4% longstanding PersAF, Group 2: 77.3% PAF, 20% PersAF, 2.7%	Retrospective case series of consecutive people. The purpose of the study was to assess the effects of hydration on haemoglobinuria and acute kidney injury after PFA.	Consecutive people who had PFA for all AF types between mid-2022 and mid-2023. People with estimated glomerular filtration rates of less than 45 ml per minute per 1.73 m^2 were excluded.	PVI with operator discretion to do additional lesions using PFA (Farawave PFA catheter, Boston Scientific)	48 hours post-procedure

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		longstanding PersAF • No information on whether anyone had previous ablative procedures • Mean age 62.9 in group 1, 65.0 group 2 • 75% male in group 1, 71% male in group 2 • Mean BMI 27.3 in group 1, 26.7 in group 2.				
Varipulse catheter						
9	inspIRE study NCT04524364 (3 publications) Europe, Canada (13 centres)	n=226 (40 in wave 1, 186 in wave 2) • All people had PAF • All people were having first time ablation	Prospective, single-arm multicentre trial between 2020 and 2022. This comprised of 2 waves (Wave 1 feasibility study, wave 2 pivotal	People aged 18 to 75 with drug refractory symptomatic PAF and for whom PVI was suitable. Exclusion criteria:	PVI with Varipulse PFA catheter (Biosense Webster, Inc.)	12 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
	Primary publication: Duystchaever, 2023 **Additional publications**: de Potter, 2024 Grimaldi, 2023	• Similar age in wave 1 (mean 58.4) and wave 2 (mean 59.4, p=0.58) • Higher proportion of men in wave 2 (70%) than wave 1 (58%, p=0.11) • Similar BMI in wave 1 (mean 27.4) and wave 2 (mean 27.6, p=0.8) **Grimaldi (2023)** n=29, mean age 55, 72% male, mean BMI 26	study). Findings of the early interim analysis are presented. **de Potter (2024)** Reported complete follow-up data for 12-month outcomes and an analysis of predictors of outcomes. **Grimaldi (2023)** Reported a deep sedation protocol and outcomes in the subgroup of people that had this instead of GA.	• Previous AF surgery or ablation • Persistent AF • Anticipated need for ablation other than PVI • AF secondary to non-cardiac or reversible causes. **Grimaldi (2023)** Selection of patients for a deep sedation protocol instead of GA was unclear.		
PulseSelect catheter						
10	PULSED AF trial NCT04198701 (2 publications)	n=300 people in primary analysis cohort	Prospective, multicentre, single-arm trial. People were enrolled between	People aged 18 to 80, with drug refractory PAF or PersAF, or for whom drug treatment was not suitable to	PVI with PulseSelect Pulsed Field Ablation System (Medtronic)	12 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
	US, Canada, Japan, Netherlands, Austria, Belgium, Australia, France, Spain (41 centres) **Primary publication:** Verma, 2023a **Additional publications:** Verma, 2023b	• 50% PAF and 50% PersAF (of 300 people) • All first-time procedures • Mean age was 63 in the PAF arm and 66 in the PersAF arm • 64% of people were male in the PAF arm and 75% were male in the PersAF arm. • Mean BMI was 28.6 (SD 5.9) in the PAF arm and 30.9 (SD 6.8) in the PersAF arm.	March and November 2021. **Verma (2023b)** Reported a secondary analysis of atrial arrhythmia burden and its association with clinical outcomes including health-related quality of life and reintervention.	treat recurrent symptomatic PAF or PersAF. There were many exclusion criteria listed in the supplementary material, including PersAF that has been sustained for 12 months or more. Other criteria mainly listed common contraindications for catheter ablation and PFA.		
Sphere-9 catheter						
11	Reddy, 2023b Reports aggregated data from 2	n=178 (79 people had RFA and PFA, 99 people had PFA only)	Combined data from 2 prospective, single arm trials to have a multicentre	People with symptomatic PAF or PersAF, aged 18 or over, were resistant to antiarrhythmic drugs,	PVI and linear lesion ablation with the Sphere-9 PFA catheter (Affera Inc/Medtronic).	12 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
	trials NCT04141007 and NCT04194307 Czech Republic, Lithuania (3 centres)	• 39.3% PAF, 60.7% PersAF. • All first-time procedures • Mean age was 59.7 (SD 9.4) • 72% were male • Mean BMI was 30 (SD 4.2) • The 2 cohorts (RFA/PFA, PFA only) were relatively well matched in clinical characteristics, including a similar distribution of PAF and PersAF.	dataset. Recruitment and study period was not reported.	planned for a first AF ablation procedure were included. People were only included if they had a left atrial anteroposterior dimension of 5.5 cm or less, and a left ventricular ejection fraction of more than 40%. Additional inclusion and exclusion criteria were reported in the supplementary material.	This technology can do both RFA and PFA ablation through the same catheter. This study compared effects between a combined RFA and PFA approach with a PFA only approach.	
CENTAURI generator						
12	Anić, 2023 ECLIPSE AF trial	n=84 enrolled (82 in per protocol analysis)	Prospective, single-arm, multicentre study. People were	People with symptomatic PAF or PersAF who were resistant to antiarrhythmic drugs,	PVI with the CENTAURI PFA generator (Galvanize Therapeutics) used	12 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
	NCT04523545 Croatia, Belgium (2 centres)	• 51.2% PAF, 48.8% PersAF • All first-time PVI • Mean age was 61 (SD 9.1) • 74.4% were male • Mean BMI 29.1 (SD 4.2)	enrolled between 2020 and 2022.	had left ventricular ejection fraction more than 35% and left anteroposterior diameter of 50 or less. People were excluded if they had implanted cardiovascular devices and New York Heart Association class 3 or 4 heart failure.	with 3 commercially available ablation catheters and mapping systems: • TactiCath SE and EnSite Precision • IntellaNav StablePoint and RHYTHMIA • ThermoCool ST and CARTO3.	

Table 3 Study outcomes

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
De Campos, 2024	**Treatment failure rate** Defined as 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. Statistically significant lower treatment failure rate for PFA than TA (14 studies, OR 0.83, 95% CI 0.70 to 0.98, p=0.03, I^2=0%). Subgroup analyses indicated this finding was not driven by whether it was measured before 1 year or after 1 year, whether PFA was compared with RFA or CBA, or whether the studies were done in people with PAF or PersAF. • No statistically significant difference in findings between PFA and TA when subgroup analysis was done for before 1 year (8 studies), or after 1 year (8 studies, p>0.97). • No statistically significant difference if PFA was compared with RFA (7 studies) or CBA (10 studies, p=0.22).	**Overall periprocedural complications** No statistically significant difference between the PFA and TA groups in overall periprocedural complication rate (15 studies, OR 0.79, 95% CI 0.47 to 1.33, p=0.38, I^2 =37%). • In sensitivity analyses, removal of 1 study did result in a statistically significant difference. Heterogeneity reduced to 0% and fewer periprocedural complications were reported in PFA studies than TA if Popa et al (2023) was removed (14 studies, OR 0.59, 95% CI 0.39 to 0.88, p<0.01). • There was no statistically significant difference in findings if PFA was compared with CBA (11 studies) or RFA (8 studies, p=0.09). **Peri-oesophageal injury rate** Statistically significantly lower rates of peri-oesophageal and oesophageal injuries were seen in the PFA group than in the TA group (12 studies, OR 0.17, 95% CI 0.06 to 0.46, p<0.01, I^2=0%). • All peri-oesophageal events in the TA arm were from the CBA group.

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	• No significant difference if compared between people with PAF (10 studies) or PersAF (5 studies, p=0.63). **Acute procedural success** No statistically significant difference between PFA and TA on initial procedural success (14 studies, OR 1.62, 95% CI 0.21 to 12.4, p=0.64, I^2 49%). • Sensitivity analysis reduced heterogeneity and confirmed the results (13 studies, OR 5.5, 95% CI 0.63 to 47.8, p=0.12, I^2 0%). Any signal of difference was likely driven by comparisons with RFA. • There was no statistically significant difference in procedural success rates between PFA and CBA (p=0.61) • All studies comparing PFA with RFA had 100% success rate in the PFA arm. **Procedural time** Overall, PFA had statistically significant shorter procedural duration than TA (18 studies, MD -21.7 minutes, 95% CI -32.8 to -10.5, p<0.01, I^2=95%). • Heterogeneity was high and remained high in sensitivity analyses.	**Tamponade rate** Tamponade rate was statistically significantly higher after PFA compared with TA (5 studies, OR 2.98; 95% CI 1.27 to 7.00, p=0.01; I^2=0%). • No statistically significant difference in findings if PFA was compared with RFA or CBA (p=0.87). **High-sensitivity troponin** High-sensitivity troponin levels, which can indicate heart damage, were statistically significantly higher for PFA than TA after omitting 1 study during the sensitivity analysis (3 studies, MD 421.4, 95% CI 251.5 to 591.4, p<0.01, I^2=77%). **Vascular access complications** No statistically significant difference between PFA and TA in vascular access complications (14 studies, OR 0.91, 95% CI 0.54 to 1.54, p=0.73, I^2=0%). • No statistically significant difference in findings if PFA was compared with RFA or CBA (p=0.67). **Systemic embolic events**

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	The findings were likely driven by longer procedure time in the RFA group, although heterogeneity was high. • Procedure time was statistically significantly longer for RFA than PFA (9 studies, MD -41.4 minutes, 95% CI -66.1 to -16.6, p<0.01, I^2=98%) • Procedure time was statistically significantly longer for CBA than PFA (12 studies, MD -10.3 minutes, 95% CI -16.5 to -3.6, p<0.01, I^2=85%).	No statistically significant difference between PFA and TA in systemic embolic events (12 studies, OR 1.52, 95% CI 0.57 to 4.07, p=0.40, I^2=0%). • No statistically significant difference in findings if PFA was compared with RFA or CBA (p=0.31). **Other adverse events reported in PFA and not covered by comparative analysis above** Across the 18 included studies (with 1,761 people who had PFA), the following adverse events were also reported in the PFA group: • Death (1 event) • ST segment changes (1 event) • Stroke or transient ischaemic attack (8 events) • Bleeding (1 event) • Pericarditis (2 events) • Pseudoaneurysm or arteriovenous fistula (7 events) • Pulmonary oedema (1 event) The following event rates were reported in the thermal ablation group (3,273 people) but none were seen in the PFA group: • Haemoptysis (1 event)

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
		• Transient phrenic nerve palsy (19 events) • Permanent phrenic nerve palsy (27 events) • Pulmonary vein stenosis (1 event)
Amin, 2024	**AF recurrence** AF recurrence was statistically significantly lower in PFA compared with TA (RR 0.66, 95% CI 0.51 to 0.87, p=0.003, 6 studies I^2=0%). **Atrial arrhythmia recurrence** There was no statistically significant difference between PFA and TA in rate of atrial arrhythmia recurrence (RR 0.92, 95% CI 0.74 to 1.13, p=0.42, 6 studies I^2=21%). **Procedure time** Procedure time was statistically significantly shorter in PFA compared with TA (MD -15.15 minutes, 95% CI -20.2 to -10.1, p<.00001, 12 studies, I^2=78%). High heterogeneity in this finding was not resolved by leave one out sensitivity analysis and there was no indication of publication bias.	**All complications** There was no statistically significant difference between PFA and TA in the incidence of any complications (RR 0.9, 95% CI 0.80 to 1.02, p=0.10, 9 studies, I^2= 17%). **All-cause mortality** There was no statistically significant difference in all-cause mortality between PFA and TA (RR 0.33, 95% CI 0.01 to 8.07, 7 studies). **Stroke and transient ischaemic attack** There was no statistically significant difference between PFA and TA in the incidence of stroke or transient ischaemic attack (RR 0.52, 95% CI 0.14 to 1.91, p=0.32, 8 studies, I^2=0%). **Phrenic nerve palsy** Incidence of phrenic nerve palsy was statistically significantly lower in PFA than TA (RR 0.38, 95% CI 0.15 to 0.98, p=0.05, 7 studies, I^2= 0%).

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
		Oesophageal lesions Incidence of oesophageal lesions was statistically significantly lower in PFA than TA (RR 0.09, 95% CI 0.01 to 0.69, p=0.02, 8 studies, I^2=0%). **Pericardial tamponade** Incidence of pericardial tamponade was statistically significantly higher in PFA than TA (RR 6.14, 95% CI 1.43 to 26.3, p=0.01, 7 studies, I^2=0%). **Thromboembolism** There was no statistically significant difference between PFA and TA in the incidence of systemic thromboembolism (RR 0.33, 95%CI 0.01 to 8.01, p=0.50, 6 studies). **Heart rate change** PFA had significantly lower heart rate change than TA (MD -7.39 beats per minute, 95% CI -12.2 to -2.62, p=0.002, 4 studies, I^2= 86%). Leave one out analysis resolved heterogeneity with removal of Schipper et al (2023), after which MD -9.78 (95% CI -11.8 to -7.7, p<0.00001, 3 studies I^2=0%).
Farawave studies		

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
ADVENT trial (Farawave, Farapulse PFA system, Boston Scientific) Reported in Reddy (2023a) unless otherwise stated.	All outcomes were estimated using Bayesian statistical analysis. Non-inferiority hypothesis testing and associated probabilities were only done for primary efficacy and safety outcomes (treatment success, percent of people with at least 1 primary serious adverse event end-point). **Treatment success** Defined as freedom from: • failure to achieve PVI • atrial tachyarrhythmia lasting 30 seconds or more at 3 months • use of class 1 or 3 antiarrhythmic drugs • cardioversion after 3 months • use of amiodarone at any time • repeat ablation at 1 year Estimated probability of treatment success was 73.3% for PFA arm and 71.3% for TA. Probability of treatment success for PFA was not statistically inferior to TA (MD 2.0, 95% CI -5.2 to 9.2, posterior probability >0.999). The difference did not reach the threshold to show statistical superiority (posterior probability=0.708).	**Device and procedural SAE** PFA was non-inferior to TA for incidence of device and procedural serious adverse events (serious adverse events were classed as those happening within 7 days of the procedure except for atrio-oesophageal fistula and pulmonary vein stenosis which were included as regardless of the timing of occurrence) (MD 0.6%, 95% CI -1.5 to 2.8, posterior probability >0.999). • PFA procedure related SAE: 23 events in 20 of 305 people (6.6%) • TA procedure-related SAE: 11 events in 9 of 302 people (3%) • PFA device-related SAE: 4 events in 4 of 305 people (1.3%) • TA device-related SAE: 0 events in 302 people. **Stroke** 1 person in the TA (RFA) arm had clinical stroke related to the procedure. **Tamponade** Pericardial tamponade was seen in 2 of 305 people who had PFA (0.6%). In 1 of the 2 people,

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	Need for repeat ablation because of recurrence of AF Repeat ablation was done for clinical recurrence: • 14 of 305 people who had PFA (4.6%) • 20 of 302 people who had TA (6.6%). **Quality of life** Quality of life improved in both PFA and TA at 1 year. No clear difference between PFA and TA on 3 quality of life scores (no statistical test): • AFEQT: difference between PFA and TA in change from baseline was 2.3 points (-1.2 to 5.9) • EQ-5D: difference between PFA and TA in change from baseline was 0.01 (−0.02 to 0.03) • EQ-VAS: difference between PFA and TA in change from baseline was 1.2 (−1.0 to 3.4) **Procedure time** Procedure time was shorter in the PFA arm than TA arm on average (statistical significance was not tested). • PFA mean 106 minutes (SD 29)	emergency sternotomy and resuscitation were needed and the person died after 10 days. **Persistent phrenic nerve injury** 2 people who had TA (CBA) had persistent phrenic nerve injury. **Pulmonary vein stenosis** No people in either the PFA or TA groups had symptoms of pulmonary vein stenosis. Mean change in pulmonary vein cross-sectional area was superior in PFA to TA (mean relative difference 11.0%, 95% CI 8 to 14.1%, posterior probability of superiority >0.999). **Silent cerebral events and lesions (data from Patel, 2024)** No significant difference in rate of silent cerebral events and lesions detected on MRI between 12 and 48 hours after treatment (p=0.10): • Seen in 3 of 34 who had PFA. All 3 were female and had higher BMI than the cohort average. • Seen in 0 of 37 people who had TA.

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	• TA mean 123 minutes (SD 42)	Neurological findings for all 3 people were normal at predischarge and day 90 assessments along with mRS and NIHSS scores of 0 at each timepoint.
Calvert, 2024 (Farawave, Farapulse PFA system, Boston Scientific)	**Acute procedural success** Acute success was statistically significantly higher in PFA (205 of 208 people, 98.6%) and RFA (173 of 174 people, 99.4%) than CBA (309 of 325 people, 95.1%) (p=0.008) **Arrhythmia recurrence** Kaplan-Meier estimates showed no statistically significant difference in rate of 12-month arrhythmia freedom after a 2-month blanking period (p=0.34): • 51% (95% CI 42 to 60%) in PFA • 54% (95% CI 47 to 62%) in CBA • 60% (95% CI 51 to 71%) in RFA Cox proportional hazard ratios found no statistically significant difference in risk of recurrence between groups: • Adjusted HR of CBA compared with PFA was 1.35 (95% CI 0.87 to 2.09, p=0.177) • Adjusted HR of RFA compared with PFA was 1.18 (95% CI 0.79 to 1.76, p=0.417)	**Major complications** No statistically significant difference in rate of major complications between groups (p=0.553): • 1 in PFA (0.5%) • 5 in CBA (1.5%) • 1 in RFA (0.6%) No periprocedural tamponade, stroke, or deaths were seen. **Phrenic nerve palsy or injury** There were 8 phrenic nerve palsy events in the CBA arm (5 transient, 1 partial recovery, 2 persistent). No phrenic nerve injury was seen in the PFA or RFA arms. **Myocardial infarction** There was 1 suspected myocardial infarction event in the CBA arm. No events were seen in the PFA or RFA arm. **Vascular injury**

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	Reintervention There was no statistically significant difference between groups for reintervention at a median of 9 months (p=0.856): • 38 people (18.4%) in the PFA group • 55 people (17.7%) in the CBA group • 28 people (16.3%) in the RFA group **Posterior wall isolation** Posterior wall isolation was done in 19 PFA procedures (9.1%) and 2 RFA procedures (2.3%). **Length of stay** People who had CBA had higher rate of same day discharge (58.5%) than people who had PFA (45.2%) or RFA (24.7%) (p<0.001). This could be explained by a higher rate of PFA and RFA procedures done in the afternoon than CBA. **Procedure time** Procedure time was statistically significantly shorter in the PFA arm (median 102 minutes) than CBA (median 122 minutes) and RFA arms (median 123 minutes, p<0.001).	There were 3 serious vascular injuries: • 2 in the CBA arm (1 needing surgical intervention, 1 managed conservatively) • 1 in the RFA arms needing surgical intervention

First author, date **Or** **Study name, author, date**	**Efficacy outcomes**	**Safety outcomes**
MANIFEST-PF registry study (Farawave, Farapulse PFA system, Boston Scientific) Reported in Turagam (2023) unless otherwise stated	**Composite treatment success summary** • Kaplan-Meier estimates of freedom from AF, atrial flutter or atrial tachycardia and freedom from antiarrhythmic drugs, or any need for redo ablation was 70.8% (95%CI 68.4 to 73%). This outcome was better for people with PAF (73.8%) than people with PersAF (65.1%, p=0.001). • Turagam's (2024) subgroup analysis of people with PersAF or longstanding PersAF reported that there was no statistically significant difference in 1-year Kaplan-Meier estimates of freedom from atrial arrhythmias and freedom from antiarrhythmic drugs, or any need for redo ablation between people who had PVI plus left atrial posterior wall ablation (59.5%, 95% CI 50.6 to 68%) and people who had PVI only (66.8%, 95% CI 62.1 to 71.3%, p=0.77). **Acute treatment success** PVI was achieved in 99.2% (1,556 of 1,568 people). **Recurrence of AF, atrial flutter or atrial tachycardia**	**Overall complication rate** • 1.9% (30 of 1,568 people) had a major complication (detailed below). • 4% (63 of 1,568 people) had a minor complication. Acute minor complications included: pericardial effusion without intervention (0.3%), pericarditis (0.06%), air embolism (0.3%), transient ischaemic attack (0.1%), transient phrenic nerve injury (0.4%), vascular access complications including haematoma, arteriovenous fistula (0.3%) and pseudoaneurysm (0.1%), deep vein thrombosis (0.6%), and respiratory related AEs (0.3%). • There were no oesophageal complications (including no atrio-oesophageal fistula, oesophageal ulcerations or oesophageal dysmotility disorders). • There were no incidents of PV stenosis. **Cardiac tamponade** Cardiac tamponade was the most common major AE. This happened in 1.1% (18 of 1,568 people). • 14 of 18 people had percutaneous drainage • 2 of 18 people had surgical drainage.

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	At a median of 367 days (289 to 421), Kaplan-Meier estimates for freedom from AF, atrial flutter or atrial tachycardia was 78.1% (95% CI 76.0 to 80.0%). Median time to recurrence was 180 days (129 to 266). • Recurrence rates were statistically significantly better in people with PAF (81.6%) than people with PersAF (71.5%, p=0.001). Cox regression estimated that likelihood of recurrence failure was increased by 39% (HR 1.39, 95% CI 1.26 to 1.53, p<0.001). • There was no statistically significant difference in recurrence rate between people with PersAF and longstanding PersAF (p=0.15). • Other risk factors associated with higher risk of recurrence were: being aged 65 or older (HR 1.57, 95% CI 1.41 to 1.76, p<0.001), left atrial diameter greater than 45 mm (HR 1.33, 95% CI 1.21 to 1.46, p<0.001), procedure time of more than 60 minutes (HR 1.30, 95% CI 0.68 to 0.90, p<0.001). • Turagam's (2024) analysis of people with PersAF or longstanding PersAF reported that there was no statistically significant difference in 1-year Kaplan-Meier estimates of freedom from atrial arrhythmias in people who had PVI plus left atrial posterior wall ablation (66.4%,	**Stroke** Stroke was the second most common major complication. This happened in 0.4% (11 of 1,568 people). **Persistent phrenic nerve injury** 1 person (of 1,568, 0.6%) had persistent phrenic nerve injury. This was classed as a major complication. **Death** 1 person (of 1,568, 0.6%) died during the study. This person had a sustained stroke. **Coronary spasm** 0.1% (2 of 1,568 people) had coronary spasm. This was classed as a major complication. **Vascular complications requiring surgery** 0.1% (2 of 1,568 people) had vascular access complications requiring surgery. This was classed as a major complication. **Safety outcomes reported in Turagam (2024) subgroup analysis**

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	95% CI 57.6 to 74.4%) compared with people who had PVI only (73.1%, 95% CI 68.5 to 77.2%). A propensity score-matched cohort sensitivity analysis of 184 people also found no statistically significant difference on this outcome (p=34). There was also no statistically significant difference in median time to recurrence (PVI plus left atrial posterior wall 207 days compared with 178 days for PVI only, p=0.68). • Outcomes in the full sample (Turagam, 2023) did not vary by centre level volume of procedures. **Reintervention** 9.3% (147 of 1,568 people) had a redo procedure. Of the 147 people, 59.2% (87 people) had PAF, 37.2% (55 people) had PersAF and 3.4% (5 people) had longstanding PersAF. • 72.6% of PVs were durably isolated in 45.5% (67 of 147) people. Turagam's (2024) analysis of people with PersAF or longstanding PersAF reported that likelihood of repeat ablation did not differ between people who had left atrial posterior wall ablation (13.7%) than people who had PVI only (10.1%, p=0.26).	• Major adverse event rate was 2.2% (3 of 131 people) in people who had PVI plus left atrial posterior wall ablation and 1.4% (6 of 416 people) in people who had PVI only (p=0.51). • Minor complication rate was 6.8% in people who had PVI plus left atrial posterior wall ablation and 3.6% in people who had PVI only. • Transient phrenic nerve injury happened in 1 person who had PVI plus left atrial posterior wall ablation. • Coronary spasm happened in 1 person who had PVI plus left atrial posterior wall ablation. • Complications related to catheter manipulation happened in 1 person who had PVI plus left atrial posterior wall ablation and 1.2% (5 of 416 people) in people who had PVI only. • Stroke happened in 1 person who had PVI plus left atrial posterior wall ablation and 1 person who had PVI only. • No deaths happened in this subgroup analysis. • As in the full trial analysis sample, there were no instances of PFA-related oesophageal complications, including no atrio-oesophageal fistula, oesophageal ulcerations, or oesophageal dysmotility. There were no

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	Procedure time Mean procedure time was 61 minutes (IQR 40 to 90). Turagam's (2024) analysis of people with PersAF or longstanding PersAF reported that: • procedure time was statistically significantly longer in the group who had left atrial posterior wall ablation (80 minutes), than the PVI only group (61 minutes, p<0.001). • time from first to repeat ablation did not statistically significantly differ between the group who had left atrial posterior wall ablation (220 days), and the PVI only group (202 days, p=0.92).	instances of symptomatic PV stenosis or persistent phrenic nerve injury.
MANIFEST-17K study (Farawave, Farapulse PFA system, Boston Scientific) Reported in Ekanem (2024)	Efficacy outcomes were not reported in this study.	**Major complications** Major complication rate was 1% of 17,642 people, most commonly vascular issues (0.3%). There were no incidents of oesophageal complications including no atrio-oesophageal fistula or dysmotility disorders, no myocardial infarction and no PV stenosis. **Phrenic nerve injury** There were no instances of sustained phrenic nerve palsy but 0.1% (11 of 17,642 people) had

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
		transient phrenic paresis that recovered by the next day. **Coronary spasm** 0.1% (25 of 17,642 people) had coronary spasm. Most were proximal to the lesion (88%), 20% (5 of 25 people) had hypotension and nitroglycerin was given to 84% (21 of 25 people) Clinical sequalae were seen in 4 people: (1) one person had atrioventricular block and ventricular fibrillation during PFA of the cavotricuspid isthmus. They had resuscitation and defibrillation, (2) 2 people had chest pain in the post-procedure recovery area and both resolved with nitroglycerin, (3) 2 people had anterior ST elevation, polymorphic premature ventricular contractions and subsequent ventricular fibrillation after PFA at the right inferior PV. They had resuscitation, defibrillation and intravenous nitroglycerin. **Pericardial tamponade** 0.4% (63 of 17,642 people) had pericardial tamponade. Most instances (56 of 63 people) were managed with percutaneous pericardiocentesis. The other 7 people had surgery.

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
		Stroke 0.1% (22 of 17,642 people) had stroke. The most common cause was catheter exchanges or sheath management in the events that a cause could be determined. **Silent cerebral events** In a subset of 96 people at 8 centres who had routine post-procedural MRI, abnormalities were seen in 9 people (9.4%). **Haemolysis and acute kidney failure** 5 people (0.3%) had haemolysis with acute kidney failure with creatine level increase of 100% within a day of the procedure. Symptoms included haemoglobinuria, nausea and oliguria, beginning either immediately post-procedure or the next day. Transient haemodialysis improved renal function by the time of hospital discharge. All 5 had PFA for Pers AF, with a complex lesion set with a high number of PF applications (143 ± 27 per procedure). 1 other person had haemolysis without acute kidney injury and the authors reported that several people at 1 centre had 'dark urine or haemoglobinuria' either immediately post-

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
		procedure or the next day. But there was no reported kidney injury or drop in red cell count. **Vascular complications** 2.5% (441 of 17,642 people) had vascular complications, of which 0.3% were major complications. Rate of major vascular complication was statistically significantly higher in centres that dud not routinely use ultrasound guidance (p=0.046). **Death** 0.03% (5 of 17,642 people) died during the study of which 2 were classed as procedure-related: 1 person died from complications from cardiac tamponade, and 1 person died from post-procedure cardiogenic shock in a person with cardiomyopathy and decompensated heart failure. **Minor complications** Minor complication rate was 3.2% of 17,642 people, most commonly vascular issues (2.2%). Other minor adverse events were pericardial effusion not requiring intervention (0.3%), transient ischaemic attack (0.1%), pericarditis (0.2%) and

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
		phrenic palsy that recovered before hospital discharge (0.1%) Other complications Other complications happened in 57 people, including: • 0.07% (12 of 17,642 people) had a pacemaker implant and 3 (0.02%) had lead malfunction or dislocation • 0.06% (10 of 17,642 people) had air emboli without clinical sequalae • 0.02% (3 of 17,642 people) had haemoptysis • 0.02% (3 of 17,642 people) had atrioventricular block • 0.02% (3 of 17,642 people) had migraine • 0.01% (2 of 17,642 people) had anaesthesia related hypotension • 0.01% (2 of 17,642 people) had heart failure • 0.01% (2 of 17,642 people) had pneumonia • 0.01% (2 of 17,642 people) had gastritis • 0.09% (15 of 17,642) people had 'miscellaneous' events
Schmidt, 2022	**Sedation**	The safety of PFA with deep sedation protocol was explored in this study.

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
(Farawave, Farapulse PFA system, Boston Scientific)	All people had deep sedation. No switches to GA or mechanical ventilation were needed. **Acute procedural success** 100% of all PVs were isolated with the PFA device. In total, a mean of 32 (SD 1) applications were delivered for each person. **Atrial tachyarrhythmia recurrence** At 3 months, 11% (13 of 119 people) had symptomatic recurrence of atrial tachyarrhythmia. At 6 months, 5.8% (4 of 69 people) had symptomatic recurrence of atrial tachyarrhythmia. **Repeat ablation** 5 people had a repeat procedure (4 had atrial tachyarrhythmia recurrence, 1 person was scheduled for left atrial appendage closure). Of 20 PVs that were remapped, 2 showed reconduction within the same person. **Procedure time** Mean procedure time was 39 minutes (SD 14). statistically significant shorter procedure time was observed in the streamline phase (38 minutes, SD	**Oesophageal injury** In the subgroup of 52 people who had oesophageal endoscopy as part of planned study data collection, there were no incidents of thermal injury. **Stroke** 2 people had stroke. They were both in the validation phase of the study. In 1 person, symptoms had resolved within 4 weeks. In the other person, symptoms had resolved by 3 months. **Silent cerebral injury** In 53 people who had diffusion weighted MRI within 24 hours of the ablation as part of planned study data collection, acute asymptomatic injury was seen in 19% (10 people). All of these procedures were done in the streamline phase of the study. None of the people had symptoms. **Transient phrenic nerve palsy** 1% (2 of 191 people) had phrenic nerve palsy with loss of diaphragmatic contraction; 1 was in the validation phase, 1 was in the streamline phase. In

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	14) compared with the validation phase (46 minutes, SD 14, p=0.004).	both cases, phrenic nerve function recovered within 1 minute. **Pericardial effusion** 1 person (of 191, 0.5%) had cardiac perforation with pericardial effusion, in the streamline phase of the study. They had pericardiocentesis and anticoagulation reversal and were discharged within 2 days. **Vascular access complication** 2.1% (4 of 191 people) had a vascular access complication; 2 were in the validation phase, 2 were in the streamline phase. These were major groin haematomas and resolved with conservative management.
Mohanty, 2024 (Farawave, Farapulse PFA system, Boston Scientific)	No efficacy outcomes were reported in this study as the focus of this study was on the effects of hydration on post PFA haemoglobinuria.	Note: more people in the group who had no or minimal postablation hydration (group 1) had PersAF than in the group with planned post-ablation hydration (group 2). **Haemoglobinuria** Group 1: 75% (21 of 28 people) had haemoglobinuria within 24 hours post-PFA. All people with haemoglobinuria were successfully treated with hydration before discharge. Group 2: no incidence of haemoglobinuria.

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
		Haemolysis Group 1: there was a statistically significant increase in bilirubin, indicating haemolysis (p=0.002). Group 2: there was no statistically significant change in bilirubin (p=0.62). **Acute kidney injury** Hydration (p<0.01) and number of PFA applications (p<0.01) were found to be statistically significant, independent predictors of renal injury. Group 1: • all 21 people with haemoglobinuria had statistically significantly increased serum creatinine levels post-ablation (p<0.001). All 21 people had normal baseline renal function. • 4 (19%) people had serum creatinine levels that met diagnostic criteria for acute kidney injury. All 4 with renal kidney injury had haemoglobinuria after the procedure, and had statistically significantly more PFA applications than the other 17 people (p<0.001).

First author, date **Or** **Study name, author, date**	**Efficacy outcomes**	**Safety outcomes**
		• Serum creatinine was in the normal range for people without haemoglobinuria (n=7), and they had statistically significantly fewer PFA applications than people who had haemoglobinuria (p=0.019). Group 2: • No statistically significant change in Serum creatinine (p=0.18). **Oliguria** All 4 people who met diagnostic criteria for acute kidney injury were oliguric (less than 400mL per day).
Varipulse studies		
inspIRE trial (Varipulse, Biosense Webster) Reported in Duytschaever (2023) unless otherwise stated	In Duytschaever (2023, primary publication), an interim analysis with incomplete follow-up was reported because it met an effectiveness threshold. So, 39 of 40 people in wave 1 and 83 of 186 people from wave 2 were included in the 12-month clinical effectiveness outcome in this publication. De Potter (2024, subsequent publication) reported complete 12-month data for wave 2 only. **Acute treatment success**	**Primary adverse events** There were no primary adverse events (defined as pericarditis, myocardial infarction, cardiac tamponade or perforation, thromboembolism, stroke or cerebrovascular accident, transient ischemic attack, phrenic nerve paralysis, or major vascular access complication or bleeding, as well as death, PV stenosis, and atrio-oesophageal fistula that occurred later than 7 days post-procedure). This met a posterior probability that the primary AE rate was less than 14% (p>0.975).

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	Confirmed PV entrance block was seen in 100% (n=226) of people in wave 1 and 2. PVI without acute reconnection was seen in 96% of veins in wave 1 and 97.1% of veins in wave 2. **Primary effectiveness** Primary effectiveness was defined as freedom from documented asymptomatic or symptomatic atrial arrhythmia episodes of 30 seconds or more, after a 3-month blanking period. This outcome met the statistical effectiveness threshold in wave 2: • 70.9% of 186 people were estimated to meet the primary effectiveness criteria with Kaplan-Meier estimation at 12 months (99.5% CI 59.6 to 82.2%), although note that only 83 people had 12-month follow-up data available for this analysis • Posterior probability that effectiveness proportion was more than 50% was >0.0998). Follow-up continued and more favourable results were reported in de Potter (2024), wave 2 data only: • 75.6% of 186 people met the primary effectiveness criteria (95% CI 69.5 to 81.8%)	**Cerebral lesions (wave 1 cohort only)** Silent cerebral lesions were found 4 of the first 6 of the wave 1 cohort. After workflow enhancements, 4 silent cerebral lesions were found in the following 33 people. All lesions were asymptomatic and transient (resolved by 3 months). All participants had National Institutes of Health Stroke Scale score of 0 by 3-month follow-up. **Urinary retention (reported in de Potter, 2024)** Urinary retention was reported as a serious procedure-related adverse event. It was resolved completely. **Other procedure-related adverse events** In Grimaldi (2023), they reported that 2 people had a procedure-related complication (pseudoaneurysm of right femoral artery resolved using manual compression). **Deep sedation safety outcomes (reported in Grimaldi, 2023)** Deep sedation was used without side effects in all 29 people:

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	AF recurrence (clinical effectiveness 12-month endpoint) Clinical effectiveness was defined as 12-month freedom from symptomatic AF recurrence: • Wave 1 Kaplan-Meier estimates showed 76.9% (95% CI 63.7 to 90.1%) met clinical effectiveness • Wave 2 Kaplan-Meier estimates showed 78.9% of people (95% CI 71.9 to 85.9%) met clinical effectiveness Follow-up continued and more favourable results were reported in de Potter (2024), wave 2 data only: • 81.7% of 186 people had clinical success (95% CI 76.1 to 87.2%). Simulation modelling of real-world outcomes estimated higher estimates for freedom from all recurrence (85.5%) and freedom from symptomatic recurrence (94.0%). **Reintervention** Freedom from repeat ablation at 12 months after a 3-month blanking period was reported: • Wave 1: 92.5% (3 people, 95% CI 84.3 to 100%); 90% (9 of 10) previously isolated PVs were electrically reconnected.	• no significant sedation-related hypotension • no muscular fasciculations or cough during PFA • 18 of 29 people scored -4 or -5 on the Richmond agitation-sedation scale (range 4 to -5), indicating near or total unarousal, 2 people scored 0 indicating they were calm and alert, and the other 9 people scored -1 to -3 indicating their arousal level was in between these states. • 22 of 29 people scored 0 indicating no pain on the visual analogue scale (range 0 to 10), 1 person scored 1, 1 person scored 2, 3 people scored 3 and 2 people scored 4. • The authors reported that most people gave positive responses to a Likert scale questionnaire which asked about satisfaction with pain management and the experience of having deep sedation for the procedure.

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	• Wave 2: 92.3% (10 people, 95% CI 87.6 to 96.9%); 69.2% (27 of 39) previously isolated PVs were electrically reconnected. Follow-up continued and similar results were reported in de Potter (2024), wave 2 data only: • 92.4% (14 people, 95% CI 88.5 to 96.2%); PV reconnections in 72.5% of previously isolated PVs. De Potter (2024) reported that left ventricular ejection fraction of less than 60%, and having less than 48 valid PFA applications around the PV were independent, statistically significant predictors of 12-month success failure ($p<0.05$), each predicting about 70% reduction in treatment success odds ratio at 12 months. **Procedure time** • In wave 1, mean procedure time was 82.4 minutes (SD 20.0) • In wave 2, mean procedure time was 70.1 minutes (SD 27.7). • de Potter (2024) reported that conscious sedation resulted in slightly higher procedure time (+4.24 minutes) compared with GA.	

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	• Grimaldi (2023) reported that the mean procedure time for deep sedation protocol was 68 minutes (SD 22).	
PulseSelect studies		
PULSED AF trial (PulseSelect, Medtronic) Reported in Verma (2023a) unless otherwise stated.	**Acute treatment success** Acute isolation of PVs with the PFA catheter was 100%. **Composite treatment success** Treatment success was defined as freedom from acute procedural failure (inability to isolate all PVs, or any left atrium using a non-study device during the index procedure), arrhythmia recurrence or antiarrhythmic escalation at 12 months, excluding a 90-day blanking period. A checklist of criteria is listed in the publication. • In the PAF group: 100 of 150 people (66.7%) met the primary effectiveness endpoint. 1-year Kaplan-Meier estimate 66.2% (95%CI 57.9 to 73.2%). • In the PersAF group: 83 of 150 people (55.3%) met the primary effectiveness endpoint. 1-year Kaplan-Meier estimate 55.1% (95% CI 46.7 to 62.7%). **AF recurrence**	**Primary safety endpoint** The primary safety endpoint was a composite of serious procedure and device-related AEs. • 1 person with PAF and 1 person with PersAF of 150 people in each group met the primary safety endpoint at 6 months. • 6-month Kaplan-Meier estimates were 0.7% (95% CI 0.1 to 4.6%) in both groups. **Pulmonary vein stenosis** No moderate or severe pulmonary vein stenosis was observed on imaging between baseline and 3-months (63 people). **Oesophageal injury** No reports of atrio-oesophageal fistula, other oesophageal injury. Optional oesophageal temperature monitoring demonstrated a 0.3 (plus or minus 0.4 degree Celsius change from baseline, n=140 people).

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	No statistical comparison was made but recurrence of atrial fibrillation was the most common reason for classification of treatment failure in both groups, with similar proportions (20% of people with PAF including 30 of 50 treatment failures in this arm, 26% of people with PersAF including 39 of 67 treatment failures). AF recurrence rate was 20% in the PAF cohort and 26% in the PersAF. **Atrial arrhythmia recurrence** • 69.5% of people with PAF had freedom from any atrial arrhythmia after the 90-day blanking period, and 79.7% had freedom from symptomatic arrhythmia. • 62.3% of people with PersAF had freedom from any atrial arrhythmia after the 90-day blanking period and 80.8% had freedom from symptomatic arrhythmia. Verma (2023b) reported further detail on atrial arrhythmia burden after the blanking period. Burden definition was calculated as the higher of 1) percentage of atrial arrhythmia on total Holter time; or (2) percentage of weeks with 1 or more transtelephonic monitoring with symptomatic atrial arrhythmia, out of all weeks with 1 or transtelephonic monitoring:	**Cerebrovascular accident** 1 person (of 150) with PAF had a cerebrovascular accident on the same day as the procedure. They had lower leg numbness and mild dysphagia. It was resolving at the end of the study. **Silent cerebral lesions** 45 people had cerebral MRI before and after the procedure. 4 of 45 people (8.9%) showed a new silent cerebral lesion. But, change in Mental State Examination scores only changed by 0.4 (SD 1.8). **Pericardial effusion** 1 person with PersAF had pericardial effusion needing drainage **Death** 1 person with PAF died during follow-up: they had a history of cirrhosis, a CT scan showed liver masses and they died of liver failure. 1 PersAF died during the follow-up: they had a cardiopulmonary arrest within 2 weeks of dofetilide initiation. **Other adverse events**

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	• 87.1% of people with PAF experienced less than 10% burden, and excluding those with 0 burden, median burden was 7.1% • 81.8% of people with PersAF experienced less than 10% burden, and excluding those with 0 burden, median burden was 8.7% **Reintervention** • 8% of people with PAF (12 of 150) had repeat ablation after the blanking period • 9.3% of people with PersAF (14 of 150) had repeat ablation after the blanking period Verma (2023b) reported that atrial arrhythmia burden was statistically significantly associated with repeat ablation and cardioversion in both PAF and PersAF ($p<0.01$). **Quality of life** Both groups showed statistically significant and clinically meaningful improvements in quality of life at 12 months compared to baseline: • In PAF, mean AFE-QT improvement was 29.4 (95%CI 25.8 to 33.1) and mean EQ-5D improvement was 0.05 (95% CI 0.02 to 0.08). Verma (2023b) reported that people with 0 atrial arrhythmia burden experienced	No reports of myocardial infarction or phrenic nerve injury related to the pulsed field ablation procedure. Other important adverse events, such as coronary artery spasm or incidental ST-segment elevation, were not detected.

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	significantly higher AFE-QT scores than those with some burden (32.1 versus 23.1 points, p=0.03). • In PersAF, mean AFE-QT improvement was 29.0 (95% CI 25.5 to 32.5) and mean EQ-5D improvement was 0.06 (95% CI 0.04 to 0.09). Verma (2023b) reported no statistically significant difference between people with 0 atrial arrhythmia burden and those with some burden on AFE-QT scores (30.5 versus 26.8 points, p=0.32). • Verma (2023b) reported that clinically relevant AFE-QT score improvement was only seen in people with PAF with less than 10% atrial arrhythmia burden. But, irrespective of atrial arrhythmia burden, AFE-QT showed clinically meaningful improvement for all people with PersAF. **Procedure time** Mean time between first and last application was 58 minutes (SD 28 minutes) in the PAF group and 64 (SD 28) in the PersAF group. This included a 20 minute waiting period and post-ablation mapping.	
Sphere-9 studies		

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
Reddy (2023b) (Sphere-9, Medtronic)	3 different waveforms were used in this study and not all people had only PFA with the catheter. **Acute procedure success** In 100% of 356 PV pairs, PVI was achieved; 55.6% of these people had PFA only. **Linear ablation procedure success (acute)** Successful linear lesion block was achieved in 100% of attempts across the mitral isthmus line, roof line, posterior inferior line and cavotricuspid isthmus line, but combinations of RFA and PFA were used in most cases. **PV lesion durability** At 96 days (SD 43), 58% of 122 people showed PVI durability. Per-vein durability was 75%. Durability improved with waveform used. In an optimised waveform protocol, there was no statistically significant difference in PV durability rate between RFA combined with PFA (97%) and PFA only (96%, p=0.74). The per-patient PV durability rate was 90% in the optimised waveform group. **Linear lesion durability**	**Primary safety endpoint** Primary safety endpoint was a composite rate of device-related serious AEs within 7 days of the procedure: • Event rate was 0.6% (1 of 178 people). 1 person who had combined RFA and PFA was hospitalised 20 days after the procedure for inflammatory pericardial effusion. It was managed with anti-inflammatory medication. • no death, myocardial infarction, persistent diaphragmatic paralysis, stroke or transient ischaemic attack or thromboembolism, cardiac tamponade or perforation, pneumothorax, major vascular complications, pulmonary oedema, hospitalisation or heart block. Note that PV stenosis, atrio-oesophageal fistula were not included in this assessment period. **Procedure-related SAEs** There were 4 procedure-related SAEs. • 1 groin haematoma requiring surgical intervention • 1 groin puncture bleeding treated with compression • 1 pericardial effusion related to transeptal puncture

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	Overall durability for the roof line, mitral isthmus, and cavotricuspid isthmus lines were 82%, 68%, and 87%, respectively. Linear lesion durability improved with waveform evolution. Because various combinations of RFA and PFA were used for most linear lesions, only the roof line data can be used to understand PFA effects alone. The roof line was largely created using PF energy, durability improved from 63% for early waveforms to 100% with the optimised waveform. **Atrial arrhythmia recurrence** Kaplan-Meier estimates of freedom from atrial arrhythmia recurrence at 348 (SD 52) days was 78.1% (SD 3.2%) across the whole cohort, with similar findings for PAF and PersAF. • For PVI, 1-year Kaplan Meier estimate for PFA only was 77.3% (SD 4.3%) and 79.1% (SD 4.6%) for RFA and PFA combined. • In the optimised waveform group only, at mean 324 days the Kaplan-Meier estimate of freedom from atrial arrhythmia was 84.8% (SD 4.9%). **Procedure time**	• 1 transient ST-segment elevation following atropine administration in a person with prior myocardial infarction and unknown residual right coronary arterial stenosis later requiring angioplasty and stenting. **Oesophageal thermal injury** Low level heating (around 2.3 degrees Celsius) was seen when PFA was done along the left atrial posterior wall. Post-procedure oesophagogastroduodenoscopy showed 3 instances (8.3% of 36 people) of asymptomatic minor mucosal thermal injury in a subgroup of people who had RFA and PFA. There were no injuries in the PFA only group. **Silent cerebral events and lesions** At mean of 1.2 days post-procedure: • 7.9% (7 of 89 people) had diffusion weighted imaging-positive but fluid attenuated inversion recovery-negative silent cerebral events • 6.7% (6 of 89 people) had diffusion weighted imaging-positive and fluid attenuated inversion recovery-positive silent cerebral lesions. **PV stenosis**

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	Mean total procedure time was 99 minutes (SD 34).	No evidence of any PV stenosis in all 122 people who had invasive remapping. At 129 (SD 93) days, 43.3% (77 of 178 people), cardiac computed tomography scans indicated no evidence of PV stenosis.
CENTAURI studies		
Anić, 2023 ECLIPSE-AF trial of the CENTAURI PFA generator	There were 5 cohorts in this analysis that used different procedure techniques and catheters with the CENTAURI system. The authors classified cohorts 1 and 2 as the workflow development cohorts, and cohorts 3 to 5 as the optimised PFA cohorts. The catheters used with CENTAURI were as follows: cohorts 1 to 3 used TactiCath SE, cohort 4 used StablePoint and cohort 5 used ThermoCool ST. **Acute treatment success** Across all cohorts, 100% (82 of 82) people and PVs had confirmed PV isolation after PFA. **Durability** At a mean of 98 (SD 25) days, workflow development cohorts had per-patient isolation rate of between 26 and 38% with PV isolation rate between 47 and 53%.	**Primary SAE endpoint** The primary SAE endpoint was incidence of predefined system-related and procedure-related SAEs within 30 days of ablation. The event rate was 4.9% (4 events in 4 of 82 people), and all were related to the procedure. • 3 vascular access complications led to haemorrhagic events needing hospitalisation • 1 non-embolic cerebrovascular accident caused by exacerbated cardiac tamponade secondary to ablation catheter perforation. There were no incidences of AE fistula, diaphragmatic paralysis, myocardial infarction, pericarditis, thromboembolism, PV stenosis, TIA, or death **Silent cerebral events** A subgroup of 35 people had MRI within 72 hours post-procedure. People with abnormal findings at 72 hours returned for 30 day follow up MRI.

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
	In the optimised PFA groups, per-patient isolation rate was between 60 and 81% with a PV isolation rate of 84 to 92%. **Procedure time** Across all cohorts, mean procedure time was 140 minutes (SD 42.4). This was only slightly reduced in the final cohort (mean 137.1, SD 40.4).	• 11.4% of people had silent cerebral events detected on diffusion weighted imaging (4 of 35 people), but not on Fluid-attenuated inversion recovery (0%). All 4 people had ablation with the StablePoint catheter. • All findings were resolved at 30 days with no incidence of neurological dysfunction, increase in National Institute of Health Stroke Scale or detectable microbubbles. **Cardiac effusion and tamponade** 2 events of catheter perforation were seen in 2 people, which led to cardiac effusion or tamponade: • In 1 person, it was resolved with pericardiocentesis and they were discharged after an overnight stay. • In 1 person, the effusion and tamponade was treated with cardiac surgery. The event was resolved but because of a delay in treatment it caused a non-embolic cerebrovascular event (this was also recorded as a primary SAE endpoint). **Oesophageal lesions**

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
		2.7% (2 people of 75) had mild oesophageal lesions, seen on endoscopy within 72 hours, but these were the only people who also had oesophageal temperature probe placed during the procedure. No temperature rise was seen in relation to PFA and both events were resolved without sequalae. **Phrenic nerve injury** No phrenic nerve injury was seen in 80 people who were monitored. **PV narrowing** Mean percent narrowing was 2.3% for the left superior PV, 0.9% for left inferior PV, 3.6% for the right superior PV, 3% for the right inferior PV, and 0.5% for all other PV types indicating no chronic effect to PV diameters after PFA. **No incidents of microbubbles and ST elevation** 61 procedures were monitored with intracardiac echocardiography to detect microbubbles caused by gaseous emboli, and ST-segment changes were also monitored in all procedures. Microbubbles were not observed at any time during the 61 ICE-monitored procedures, and there

First author, date Or Study name, author, date	Efficacy outcomes	Safety outcomes
		were no incidences of ST elevation during any PEF applications for PVI.

Procedure technique

Each PFA technology has unique design and properties, briefly described below. Some studies only used GA, whilst others used a mixture of GA and conscious or deep sedation. Schmidt (2022) and the inspIRE sub study (Grimaldi 2023) both used deep sedation only. Some studies only applied PFA for PVI whilst others included people who had PFA for other lesion sets (like left atrial posterior wall ablation), at the operator's discretion. Typically, uninterrupted oral anticoagulation was used. Use of 3D mapping systems was used variably within and between studies, whilst some procedures were done under fluoroscopic guidance only. One study explicitly reported differences in haemoglobinuria and acute kidney injury outcomes when post-procedure hydration was or was not used (Mohanty 2024).

Farawave

The Farawave catheter was used in 6 studies. These were the ADVENT RCT (Reddy 2023a, Patel 2024), the UK real-world study of 707 people comparing RFA with PFA and CBA (Calvert, 2024), the MANIFEST-PF EU retrospective analysis of a prospective registry of 1,568 people across 24 centres (Turagam 2023, Turagam 2024), the MANIFEST-17K centre-level study of 101 centres with 17,642 people (Ekanem 2024), the prospective case series of 191 people (Schmidt 2022) and retrospective case series of 103 people (Mohanty 2024).

This catheter is referred to as a 'single shot' technology. It is available in 2 sizes, 31 mm or 35 mm diameter. It delivers a bipolar, biphasic waveform. A standard procedure protocol has been developed for this technology. The PFA catheter is used in a basket configuration to deliver 2 sets of PFA lesions, then rotated to deliver two additional PFA lesions, then changed to a flower configuration to deliver two more PFA lesions, and finally rotated again to deliver two final PFA lesions, for a minimum total of 8 PFA applications per PV. Each application is

5 pulse trains, delivered over 2.5 seconds. The lesions may be delivered at 1800, 1900 or 2000 volts.

In the ADVENT RCT (Reddy 2023a, Patel 2024), GA or deep sedation was used at the operator's discretion. In the UK real-world study of 707 people (Calvert, 2024) and the retrospective case series of 103 people (Mohanty 2024), GA only was used. In MANIFEST-PF(Turagam 2023, Turagam 2024), the authors described that intravenous moderate sedation or GA was used. In MANIFEST-17K (Ekanem 2024), procedures were done with deep sedation without intubation in 53% of people but the authors did not report what was done for the rest of the group. In prospective case series of 191 people (Schmidt 2022), all people had deep sedation.

Varipulse

In inspIRE (Duytschaever 2023, de Potter 2024, Grimaldi 2023), the Varipulse catheter was used. This catheter is referred to as a 'single shot' technology. The authors describe that this catheter has a bidirectional circular tip that can be expanded and contracted to fit PVs of different sizes. PFA with Varipulse is applied in a bipolar configuration with an energy of 1800 V and each application has microsecond-long square-wave biphasic pulses, for a total application duration of about 250 milliseconds. In this study, procedures were done under conscious sedation, deep sedation or GA. Deep sedation outcomes were reported in Grimaldi (2023). A mapping system was used and 12 applications of PFA were done per PV.

PulseSelect

In PULSED AF (Verma 2023a, Verma 2023b), the PulseSelect catheter was used. This catheter is referred to as a 'single shot' catheter. Each application was 4 biphasic, bipolar pulse trains, each lasting 100 to 200 milliseconds at 1400 to 1500 V measured from baseline to peak (2800 to 3000 V measured peak to peak). After each application, the catheter was rotated circumferentially to a new

position to achieve full circumferential isolation. No system or waveform modifications were made during the trial. In this study, all procedures were done under conscious sedation or GA. Mapping systems were only used with operator discretion.

Sphere-9

In the publication that combined evidence from 2 prospective single-arm trials which together had 178 people across 3 EU centres (Reddy 2023b), the Sphere-9 catheter was used. This catheter is referred to as a 'point-by-point' catheter. Unlike other catheters, the system has a dual generator design so operators can toggle between RFA and PFA. During PFA applications, a biphasic monopolar PF waveform is delivered from the entire lattice tip. Waveforms consist of a train of microsecond-scale pulses delivered over 3 to 5.5 seconds, driven with up to plus or minus 2 kV. The length of lesion application time developed over time in this study. All procedures were done under GA. A mapping system was used in all procedures. PFA was used for all posterior left atrial applications lesion sets, but the anterior applications were done using either RFA or PFA. Outcomes were reported separately.

CENTAURI

In ECLIPSE-AF (Anic 2023) the CENTAURI generator was used. Unlike the other technologies, CENTAURI is a generator of PFA energy and it can be used with commercially available catheters and mapping systems, like those used for RFA. The CENTAURI generator delivers biphasic, monopolar pulsed electric field energy at three selectable energy settings (19, 22, and 25 A). During the study, workflows were optimised in phases, and with different catheters and mapping systems. Mapping systems were used in this study. The following catheters were used with the CENTAURI generator sequentially as the workflows developed: TactiCath SE, INTELLANAV STABLEPOINT, and THERMOCOOL SMARTTOUCH. Standard wide antral circumferential ablation was done with

sufficient overlap of each lesion. A mixture of GA and deep sedation were used in this study.

Procedure details in the systematic review and meta-analyses

In the meta-analysis comparing PFA with thermal ablation (de Campos 2024) 17 of 18 studies used the Farawave catheter and 1 study used the 8F disposable cardiac PFA catheter (PFA8D18L). In the systematic review and meta-analysis of 17 studies comparing PFA with TA (Amin 2024), Farawave was used in all studies. No further procedure details were reported in either publication.

Efficacy

Composite scores of treatment success or failure

Four studies reported a composite score of treatment success or failure. These represented conservative estimates by combining status or response on several desirable clinical outcomes. Point estimates for treatment success were reported in 3 studies. Rates were between 71 and 73% in 2 studies but as low as 55% in the other, and conclusions about comparative effectiveness between PFA and TA differed between comparative studies. In 2 studies, findings were more favourable in people with PAF than PersAF but this was not corroborated by the systematic review findings. The differences in conclusions are likely primarily driven by differences in definitions of treatment success or failure.

In the systematic review and meta-analysis of 18 studies comparing PFA with TA (de Campos 2024), data from studies were combined to measure overall treatment failure. The authors defined this as 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. They found a statistically significant, lower treatment failure rate for PFA than thermal ablation (OR 0.83, 95% CI 0.70 to 0.98, p=0.03). Subgroup analyses indicated this finding

was not driven by whether it was measured before 1 year or after 1 year (p>0.97), whether PFA was compared with RFA or CBA (p=0.22), or whether the studies were done in people with PAF or PersAF (p=0.63).

In the ADVENT RCT that compared PFA with RFA and CBA (Farawave, Reddy 2023a, Patel 2024), composite score of treatment success was freedom from:

- failure to achieve PVI
- atrial tachyarrhythmia lasting 30 seconds or more at 3 months
- use of class 1 or 3 antiarrhythmic drugs
- cardioversion after 3 months
- use of amiodarone at any time
- repeat ablation at 1 year.

By this definition, estimated probability of treatment success was 73% for PFA and 71% for TA. Probability of treatment success for PFA was not statistically inferior to TA (posterior probability was more than 0.999). The difference did not reach the threshold to show superiority (posterior probability=0.708). All people had PAF in this study.

In MANIFEST-PF (Farawave), the EU retrospective analysis of a prospective registry of 1,568 people across 24 centres (Turagam 2023, Turagam 2024), Kaplan-Meier estimates of freedom from AF, atrial flutter or atrial tachycardia and freedom from antiarrhythmic drugs, or any need for redo ablation at 1 year was 71% (95% CI 68 to 73%). This outcome was statistically significantly better for people with PAF (74%) than people with PersAF (65%, p=0.001).

In PULSED-AF (PulseSelect), the international prospective single-arm trial of 300 people across 41 centres (Verma 2023a, Verma 2023b), treatment success was defined as freedom from acute procedural failure (inability to isolate all PVs, or any left atrium lesion using a non-study device during the index procedure), arrhythmia recurrence or antiarrhythmic escalation at 12 months, excluding a 90 day blanking period. A more detailed checklist of criteria is listed in the publication. In the PAF group, 67% of people met the primary effectiveness endpoint and the 1-year Kaplan-Meier estimate was 66% (95%CI 58 to 73%). In the PersAF group, 55% of people met the primary effectiveness endpoint and the 1-year Kaplan-Meier estimate was 55% (95% CI 47 to 63%). Recurrence of atrial fibrillation was the most common reason for classification of treatment failure in both groups. No statistical comparison was made between PAF and PersAF.

Recurrence of AF

Recurrence of AF was reported in 3 studies. In the systematic review and meta-analysis of 17 studies comparing PFA with TA (Amin 2024), AF recurrence was statistically significantly lower in people who had PFA compared with TA (RR 0.66, 95% CI 0.51 to 0.87, p=0.003). No other comparative evidence with TA was included in the key evidence.

In inspIRE (Varipulse), the EU and Canada prospective single-arm trial of 226 people across 13 centres (Duytschaever 2023, de Potter 2024, Grimaldi 2023), people in the wave 1 cohort had 12-month freedom from AF recurrence Kaplan-Meier estimates of 77% (95% CI 64 to 90%, Duytschaever 2023). In the most complete wave 2 (pivotal phase study cohort, de Potter 2024), 82% of 186 people had 12-month freedom from AF recurrence (95% CI 76.1 to 87.2%). Simulation modelling of real-world outcomes gave even higher estimates for freedom from all recurrence (86%) and freedom from symptomatic recurrence (94%). The increase in freedom from recurrence rates indicates there may be a

learning curve effect as procedural workflows and operator experience becomes established.

In the PULSED-AF (PulseSelect) international prospective single-arm trial of 300 people across 41 centres (Verma 2023a, Verma 2023b), AF recurrence was reported separately for people with PAF and people with PersAF. No statistical comparison was made but recurrence of atrial fibrillation was the most common reason for classification of treatment failure in both groups, with similar proportions. AF recurrence rate was 20% in the PAF cohort and 26% in the PersAF cohort.

Recurrence of atrial arrhythmia

Recurrence of atrial arrhythmia, not just AF, was reported in 7 studies.

In the systematic review and meta-analysis of 17 studies comparing PFA with TA (Amin 2024) there was no statistically significant difference in atrial arrhythmia recurrence (RR 0.92, 95% CI 0.74 to 1.13, p=0.42). Other comparative evidence from the UK real-world study of 707 people comparing RFA with PFA and CBA (Farawave, Calvert, 2024) had similar findings. Kaplan-Meier estimates showed no statistically significant difference between PFA and TA in rate of 12-month arrhythmia freedom after a 2-month blanking period (p=0.34), and adjusted HRs of comparisons between PFA and CBA and RFA also found no statistically significant difference (p=0.177, p=0.417 respectively).

Across all studies, the highest rate of recurrence of atrial arrhythmia was in the UK real-world study of 707 people (Farawave, Calvert, 2024). In this study, 51% of people that had PFA had freedom from arrhythmia at 12 months. This was only after a 2-month blanking period whereas most studies defined recurrence after a 3-month blanking period. The lowest recurrence of arrhythmia outcomes were reported in the prospective case series of 191 people (Farawave, Schmidt 2022). This study reported that 6% of people had symptomatic recurrence of

atrial tachyarrhythmia, although this was among only 69 people and reported at 6 months, whereas most studies reported this at 12 months. Also, this was symptomatic recurrence not any detected recurrence, as in some other studies.

Among the other 4 studies that reported it, atrial arrhythmia freedom rates ranged between 62% in people with PersAF (any symptomatic or asymptomatic atrial arrhythmia detected in the PULSED-AF trial- PulseSelect, Verma 2023a) to 85% in people with PersAF or PAF who had an optimised treatment protocol (Reddy 2023b, a publication that combined 2 prospective single-arm trials totalling 178 people in 3 EU centres). Findings across the 4 studies varied based on some factors. When PAF and PersAF were compared, people with PAF tended to have better outcomes (see comparisons in MANIFEST-PF- Farawave, Turagam 2023, Turagam 2024 and PULSED-AF- PulseSelect, Verma 2023a,b). Outcomes were more favourable if only symptomatic arrhythmia recurrence, rather than any arrhythmia detected with Holter monitoring was considered (see comparisons in PULSED-AF- PulseSelect, Verma 2023a, Verma 2023b).

Health-related quality of life

Two studies reported health-related quality of life outcomes. The ADVENT RCT (Farawave, Reddy 2023a, Patel 2024) found no difference in health-related quality of life outcomes between PFA and TA at 1 year. This was across 3 patient-reported measures, including 1 AF specific questionnaire (AFEQT). No statistical test was reported. In PULSED-AF, the international prospective single-arm trial of 300 people across 41 centres (PulseSelect, Verma 2023a), people with both PAF and PersAF showed statistically significant and clinically meaningful improvements in quality of life at 12 months compared to baseline. This was across 2 patient-reported measures, including 1 AF specific questionnaire (AFEQT). Additional analyses in Verma (2023b) found that most benefit in people with PAF was seen if they had no atrial arrhythmia burden at

12 months, and clinically relevant improvements were driven by people with PersAF and people with PAF with less than 10% atrial arrhythmia burden.

Reintervention

Six studies reported reintervention rates. Lowest rates were reported in the prospective case series of 191 people (Farawave, Schmidt 2022), in which 5 of 191 people had a repeat procedure. But, follow-up was only until 6 months in this study and most studies measured this at 12 months. Low rates of need for reintervention were also reported in the ADVENT RCT (Farawave, Reddy 2023a, Patel 2024), in which 5% of people who had PFA and 7% of people who had TA had reintervention for clinical recurrence of AF. Not all studies restricted reintervention outcomes just to reintervention for AF, some included reintervention for all atrial arrhythmia, which may explain higher rates of reintervention in other studies compared to ADVENT. Highest reintervention rates were reported in the UK real-world study of 707 people comparing RFA with PFA and CBA (Farawave, Calvert, 2024), in which 19% of people who had PFA had reintervention at a median of 9 months. This was similar to rates in the comparison arms of this study, with 18% of people who had CBA and 16% of people who had RFA also having reintervention.

The remaining 3 studies reported reintervention rates of between 8 and 9% up to 12 months (MANIFEST-PF- Farawave, Turagam 2023, Turagam 2024, inspIRE-Varipulse, Duytschaever 2023, de Potter 2024, Grimaldi 2023, and PULSED-AF-PulseSelect, Verma 2023a, Verma 2023b).

Acute procedural success

Acute procedural success was reported in 8 studies and defined in terms of acute isolation of target lesion sites. The systematic review and meta-analysis of 18 studies comparing PFA with TA (de Campos 2024) found no statistically significant difference between PFA and thermal ablation (OR=1.62, p=0.64). Any signal of difference was likely driven by comparisons with RFA. There was no

statistically significant difference in procedural success rates between PFA and CBA (p=0.61). All studies comparing PFA with RFA had 100% success rate in the PFA arm.

In contrast, the UK real-world study of 707 people comparing RFA with PFA and CBA (Farawave, Calvert, 2024) found acute success was statistically significantly higher in PFA (99%) and RFA (99%) than CBA (95%, p=0.008).

In the non-comparative studies, lowest rates of PVI without acute reconnection was seen in 96% of veins in wave 1 and 97% of veins in wave 2 of inspIRE (the EU and Canada prospective single-arm trial of 226 people across 13 centres- Duytschaever 2023, de Potter 2024, Grimaldi 2023). Rates were between 99% and 100% in all other studies.

Procedure time

Procedure time was reported in 10 studies. Both systematic review and meta-analyses (de Campos 2024, Amin 2024) found PFA procedure time was statistically significantly shorter than thermal ablation (MD -21.7 minutes, p<0.01 and MD -15.2 minutes, p<0.0001 in each study respectively), although heterogeneity was high. The de Campos (2024) subgroup analysis found that the effect size was probably driven by comparisons with RFA; the mean procedure time was 41 minutes longer in the RFA arm than PFA (p<0.01). Other comparative studies found PFA procedure time to be shorter than TA comparators (ADVENT RCT- Farawave, Reddy 2023a Patel 2024; UK real-world study of 707 people- Farawave, Calvert 2024). Average procedure time across all studies that reported it ranged from 39 minutes (SD 14) as reported in the prospective case series of 191 people (Farawave, Schmidt 2022), to 140 minutes (SD 42, CENTAURI, Anić, 2023).

Procedure time may be affected by technology characteristics (‘point-by-point’ PFA may take longer than ‘single-shot’ catheters), learning curve and procedure

protocol establishment (see Schmidt 2022, inspIRE- Duytschaever 2023 and also Anić 2023), use of sedation or GA (see inspIRE- de Potter 2024, Grimaldi 2023) use of additional lesion sets (see MANIFEST-PF- Turagam 2023, Turagam 2024), or procedures done in people with PAF compared with PersAF (see PULSED-AF- Verma 2023a, Verma 2023b).

Length of stay

One study, the UK real-world study of 707 people comparing RFA with PFA and CBA (Farawave, Calvert, 2024), reported length of stay outcomes. They found that people who had CBA had a higher rate of same day discharge (59%) than people who had PFA (45%) or RFA (25%) ($p<0.001$). The authors explained this may be because more PFA and RFA procedures were done in the afternoon than CBA.

Use of additional lesion sets for linear ablation and outcomes

Many studies included people who had additional lesion sets at the operator's discretion using PFA in addition to PVI, but only 3 studies reported data relating to this.

In terms of prevalence of this practice in the UK, the UK real-world study of 707 people comparing RFA with PFA and CBA (Farawave, Calvert, 2024) reported that posterior wall isolation was done in 19 PFA procedures (9%) and 2 RFA procedures (2%).

A sub study of MANIFEST-PF (Farawave, EU retrospective analysis of a prospective registry of 1,568 people across 24 centres) did an analysis in people with PersAF or longstanding PersAF (Turagam 2024). Time from first to repeat ablation did not differ between the group who had left atrial posterior wall ablation in addition to PVI (220 days) and the PVI only group (202 days, $p=0.92$). Also, this study found that likelihood of repeat ablation did not differ between people who had left atrial posterior wall ablation (14%) and people who had PVI only

(10%, p=0.26). They reported that there was no statistically significant difference in 1-year Kaplan-Meier estimates of freedom from atrial arrhythmias in people who had PVI plus left atrial posterior wall ablation (66%, 95% CI 58 to 74%) compared with people who had PVI only (73%, 95% CI 69 to 77%). A propensity score-matched cohort sensitivity analysis of 184 people also found no statistically significant difference on this outcome (p=0.34). There was also no statistically significant difference in median time to recurrence (PVI plus left atrial posterior wall 207 days compared with 178 days for PVI only, p=0.68).

In the publication that combined evidence from 2 prospective single-arm trials which together had 178 people across 3 EU centres (Sphere-9, Reddy 2023b), linear lesion block was reported. Because various combinations of RFA and PFA were used for most linear lesions, only the roof line data can be used to understand PFA effects alone. On roof line ablations, durability was between 63% for early waveforms to 100% with the optimised waveform.

Safety

Key safety events are presented below. Other minor events and events that were reported but not discussed in reference to the procedure are presented in table 3.

Overall complication rate

Both systematic review and meta-analyses reported overall complication rates. Both studies compared PFA with TA (de Campos 2024, Amin 2024), and in primary analyses, neither found any statistically significant difference in complication rates. In de Campos (2024), the OR was 0.79 (95% CI 0.47 to 1.33, p=0.38, I^2 =37%). But, sensitivity analyses did result in a statistically significant difference; heterogeneity reduced to 0% and fewer periprocedural complications were reported in the PFA than thermal ablation arms of the studies in 1 leave-one-out scenario (OR 0.59, 95% CI 0.39 to 0.88, p<0.01). In Amin (2024), no

statistically significant difference was seen between PFA and TA (RR 0.9, 95% CI 0.80 to 1.02, p=0.10, 9 studies, I^2= 17%).

Major complications (SAEs)

Four primary research studies done with the Farawave catheter and 1 with the Sphere-9 catheter reported summaries and comparisons of SAE rates.

Comparative studies found PFA to be either non-inferior or to have no statistically significant difference in SAE rate compared with TA (RFA and CBA) (Farawave- Reddy 2023a, Patel 2024, Calvert 2024). The rate of SAEs in the PFA arm ranged from 0.5% at a median of 7.6 months in the UK real-world study (Calvert, 2024), to 7% at 12 months for procedure-related events in the ADVENT RCT (Reddy 2023a, Patel 2024).

The ADVENT RCT (Reddy 2023a, Patel 2024) reported procedure-related and device-related SAEs for the Farawave catheter at 12 months separately. Device SAE rate was lower than procedure-related SAE rate for both PFA and TA (procedure related: 7% for PFA and 3% for TA; device related: 1% for PFA and no events for TA).

In the 2 large studies based mainly in the EU, similar event rates were reported with the Farawave catheter, up to 12 months. In the full analysis of MANIFEST-PF (Turagam 2023), 2% had a major complication. In MANIFEST-17K (Ekanem 2024) 1% had a major complication, which were most commonly vascular issues.

The publication that combined evidence from 2 prospective single-arm trials which together had 178 people across 3 EU centres (Sphere-9, Reddy 2023b) reported 4 procedure-related SAEs (2%).

Oesophageal lesions and injury

Eight studies reported incidence of oesophageal lesions, injury and atrio-

oesophageal fistula. The primary studies were done with Farawave, PulseSelect, Sphere-9 and CENTAURI.

Both systematic reviews found lower oesophageal lesion rates in PFA than TA. In the systematic review and meta-analysis of 18 studies comparing PFA with TA (de Campos 2024), there were statistically significantly lower rates of peri-oesophageal and oesophageal injuries in the PFA group than in the thermal ablation group (OR 0.17, 95% CI 0.06 to 0.46, p<0.01). In the systematic review and meta-analysis of 17 studies comparing PFA with TA (Amin 2024), incidence of oesophageal lesions was statistically significantly lower in PFA than TA (RR 0.09, 95 CI% 0.01 to 0.69, p=0.02).

There were no instances of oesophageal injury or complications in 3 studies done with Farawave and 1 done with PulseSelect. In MANIFEST-PF, the EU retrospective analysis of a prospective registry of 1,568 people across 24 centres (Farawave, Turagam 2023) reported there were no oesophageal complications, including no atrio-oesophageal fistula, oesophageal ulcerations or oesophageal dysmotility disorders. In MANIFEST-17K, the centre-level study of 101 centres with 17,642 people (Farawave, Ekanem 2024), there were no incidents of oesophageal complications including no atrio-oesophageal fistula or dysmotility disorders. In the prospective case series of 191 people (Farawave, Schmidt 2022), 52 people had oesophageal endoscopy and there were no incidents of thermal injury. In PULSED-AF, the international prospective single-arm trial of 300 people across 41 centres (PulseSelect, Verma 2023a, Verma 2023b), there were no reports of atrio-oesophageal fistula, or other oesophageal injury. Optional oesophageal temperature monitoring demonstrated a 0.3 (plus or minus 0.4 degrees) Celsius change from baseline (140 people).

Mild oesophageal lesions were seen on invasive post-procedure monitoring in 2 studies. In the publication that combined evidence from 2 prospective single-arm trials done with the Sphere-9 catheter (178 people across 3 EU centres;

Reddy 2023b) low level heating (around 2.3 degrees Celsius) was seen when PFA was done along the left atrial posterior wall. Post-procedure oesophagogastroduodenoscopy showed 3 instances (8% of 36 people) of asymptomatic minor mucosal thermal injury in a subgroup of people who had RFA and PFA. There were no injuries in the PFA only group. In the prospective, single-arm trial done with the CENTAURI generator in 84 people from 2 EU centres (Anić 2023) 3% (2 people of 75) had mild oesophageal lesions, seen on endoscopy within 72 hours, but these were the only people who also had oesophageal temperature probe placed during the procedure. No temperature rise was seen in relation to PFA and both events were resolved without sequalae.

Phrenic nerve injury

Seven studies reported on phrenic nerve injury. Most data was from the Farawave catheter and 1 study was done with the CENTAURI generator.

The systematic review and meta-analysis of 17 studies comparing PFA with TA (Amin 2024) found the incidence of phrenic nerve palsy was statistically significantly lower in PFA than TA (RR 0.38, 95% CI 0.15 to 0.98, p=0.05).

In 2 comparative studies with the Farawave catheter, no instances of phrenic nerve injury were seen in the PFA arm but these were seen in the CBA arm (ADVENT RCT Reddy 2023a, Patel 2024 and the UK real-world study - Calvert, 2024).

Rates between 0 and 1% were reported in the single-arm data collected in studies done with Farawave and CENTAURI. No phrenic nerve injury was seen in 80 people who were monitored in the prospective, single-arm trial done with the CENTAURI device in 84 people from 2 EU centres (Anić 2023). In MANIFEST-PF, the EU retrospective analysis of a prospective registry of 1,568 people across 24 centres (Farawave, Turagam 2023, Turagam 2024), 1 person had persistent phrenic nerve injury. This was classed as a major

complication. In Turagam (2024), transient phrenic nerve injury happened in 1 person who had PVI plus left atrial posterior wall ablation. In MANIFEST-17K, the centre-level study of 101 centres with 17,642 people (Farawave, Ekanem 2024), there were no reported instances of sustained phrenic nerve palsy but 0.1% (11 of 17,642 people) had transient phrenic paresis that recovered by the next day. In the prospective case series of 191 people (Schmidt 2022) 1% (2 of 191 people) had phrenic nerve palsy with loss of diaphragmatic contraction; 1 was in the validation phase, 1 was in the streamline phase of the study. In both cases, phrenic nerve function recovered within 1 minute.

Pericardial tamponade, perforation and effusion

Eleven studies reported on pericardial tamponade, perforation and effusion, across all technologies included in the prioritised evidence.

Both systematic review and meta-analyses found that rate of tamponade was statistically significantly higher than TA. The systematic review and meta-analysis of 18 studies comparing PFA with TA (de Campos 2024) reported OR of 2.98 (95% CI 1.27 to 7.00, p=0.01; I^2=0%). The systematic review and meta-analysis of 17 studies comparing PFA with TA (Amin 2024) reported a RR of 6.14 (95% CI 1.43 to 26.3, I^2= 0%).

Among the studies with the Farawave technology, tamponade rates ranged from 0 (in the UK real-world study - Calvert, 2024) to 1% (in MANIFEST-PF, Turagam 2023). Some events did results in complications and death. The ADVENT RCT (Reddy 2023a, Patel 2024) reported pericardial tamponade was seen in 2 of 305 people who had PFA (0.6%). In 1 of the 2 people, this was fatal. In MANIFEST-PF (Turagam 2023, Turagam 2024), tamponade rate was 1%. Turagam (2023) reported this was the most common major AE. In both studies some people required surgical drainage to treat symptoms. Pericardial effusion, classed as a minor AE and without need for intervention, was also seen in 0.3% of people in this study. In MANIFEST-17K, the centre-level study of 101 centres

with 17,642 people (Ekanem 2024), 0.4% (63 of 17,642 people) had pericardial tamponade. Most instances (56 of 63 people) were managed with percutaneous pericardiocentesis. The other 7 people had surgery and 1 person died from complications. In the prospective case series of 191 people (Schmidt 2022), 1 person had cardiac perforation with pericardial effusion, in the streamline phase of the study. They had pericardiocentesis and anticoagulation reversal and were discharged within 2 days.

In inspIRE (Varipulse), the EU and Canada prospective single-arm trial of 226 people across 13 centres (Duytschaever 2023, de Potter 2024, Grimaldi 2023), there were no incidents of cardiac tamponade or perforation.

In PULSED-AF (PulseSelect), the international prospective single-arm trial of 300 people across 41 centres (Verma 2023a, Verma 2023b) 1 person with PersAF had pericardial effusion needing drainage.

In the publication that combined evidence from 2 prospective single-arm trials which together had 178 people across 3 EU centres (Sphere-9, Reddy 2023b) there was 1 pericardial effusion event related to transeptal puncture. But, the authors reported no events of tamponade or perforation.

In the prospective, single-arm trial of 84 people from 2 EU centres (CENTAURI, Anić 2023) 2 events of catheter perforation were seen in 2 people, which led to cardiac effusion or tamponade. In 1 person, it was resolved with pericardiocentesis and they were discharged after an overnight stay. In 1 person, the effusion and tamponade was resolved with cardiac surgery. The event was resolved but because of the delay in treatment it caused a non-embolic cerebrovascular event (this was also recorded as a primary SAE endpoint).

Stroke, transient ischaemic attack

Eight studies reported on stroke and transient ischaemic attack events, across the Farawave, PulseSelect and Sphere-9 technologies.

In the systematic review and meta-analysis of 17 studies comparing PFA with TA (Amin 2024), there was no statistically significant difference between PFA and TA in the incidence of stroke or transient ischaemic attack (RR 0.52, 95% CI 0.14 to 1.91, p=0.32).

Absolute estimates of the rate and transient ischaemic attack were low, between 0 and 1% but did sometimes result in death. No events happened in the PFA groups reported in the ADVENT RCT (Reddy 2023a, Patel 2024), UK real-world study (Calvert, 2024) or the publication that combined evidence from 2 prospective single-arm trials with 178 people across 3 EU centres (Reddy 2023b). In MANIFEST-PF, the EU retrospective analysis of a prospective registry of 1,568 people across 24 centres (Turagam 2023, Turagam 2024), stroke was the second most common major complication. This happened in 0.4% (11 of 1,568 people). They also reported that 1 person died during the study from a sustained stroke. In MANIFEST-17K, the centre-level study of 101 centres with 17,642 people (Ekanem 2024), 0.1% (22 of 17,642 people) had stroke. The most common cause was catheter exchanges or sheath management in the events that a cause could be determined. In the prospective case series of 191 people (Schmidt 2022), 2 people had stroke. They were both in the validation phase of the study. In 1 person, symptoms had resolved within 4 weeks. In the other person, symptoms had resolved by 3 months. In PULSED-AF, the international prospective single-arm trial of 300 people across 41 centres (Verma 2023a, Verma 2023b), 1 person (of 150) with PAF had a cerebrovascular accident on the same day as the procedure. They had lower leg numbness and mild dysphagia. It was resolving at the end of the study.

Silent cerebral events

Seven studies reported findings on silent cerebral events and lesions. These tended to be done in subgroups of the full study sample and studies were done

with the Farawave, Varipulse, PulseSelect, Sphere-9 and CENTAURI technologies.

Across all 6 studies, silent cerebral event rates were very high in some analyses of some studies. Comparative evidence from the ADVENT RCT (Reddy 2023a, Patel 2024) found no statistically significant difference in rate of silent cerebral events and lesions detected on MRI when compared to TA (p=0.10). Neurological findings for all 3 people who had silent cerebral events in the PFA arm were normal at predischarge and day 90 assessments, and mRS and NIHSS scores were 0 at each timepoint indicating no neurological deficit. In MANIFEST-17K, the centre-level study of 101 centres with 17,642 people (Farawave, Ekanem 2024), a subset of 96 people at 8 centres had routine post-procedural MRI. Abnormalities were seen in 9 people (9%). In the prospective case series (Varipulse, Schmidt 2022) 53 of 191 people in the study had diffusion weighted MRI within 24 hours of the ablation. Acute asymptomatic injury was seen in 19% (10 people). All of these procedures were done in the procedure development phase of the study. None of the people had symptoms. In inspIRE (Farawave), the EU and Canada prospective single-arm trial of 226 people across 13 centres (Duytschaever 2023, de Potter 2024, Grimaldi 2023), silent cerebral lesions were found 4 of the first 6 of the wave 1 cohort. After workflow enhancements, 4 silent cerebral lesions were found in the following 33 people. All lesions were asymptomatic and transient (resolved by 3 months). All participants had National Institutes of Health Stroke Scale score of 0 by 3-month follow-up. In PULSED-AF (PulseSelect), the international prospective single-arm trial of 300 people across 41 centres (Verma 2023a, Verma 2023b), 45 people had cerebral MRI before and after the procedure and 4 of 45 people (9%) showed a new silent cerebral lesion. But, change in Mental State Examination scores only changed by 0.4 (SD 1.8). In the publication that combined evidence from 2 prospective single-arm trials centres (Sphere-9, Reddy 2023b), 8% (7 of 89 people) had diffusion weighted imaging-positive but fluid attenuated inversion recovery-negative silent

cerebral events and 7% (6 of 89 people) had diffusion weighted imaging-positive and fluid attenuated inversion recovery-positive silent cerebral lesions at a mean of 1.2 days post-procedure. In the prospective, single-arm trial of 84 people from 2 EU centres (CENTAURI, Anić 2023), a subgroup of 35 people had MRI within 72 hours post-procedure. People with abnormal findings at 72 hours returned for 30 day follow up MRI. 11% of people had silent cerebral events detected on diffusion weighted imaging (4 of 35 people), but not on fluid-attenuated inversion recovery (0%). All findings were resolved at 30 days with no incidence of neurological dysfunction, increase in National Institute of Health Stroke Scale or detectable microbubbles.

Systemic embolic events

Both systematic review and meta-analyses and 1 primary study reported on systemic embolic events. The systematic review and meta-analysis of 18 studies comparing PFA with TA (de Campos 2024) found no statistically significant difference between PFA and thermal ablation in systemic embolic events (12 studies, OR 1.52, 95% CI 0.57 to 4.07, p=0.40). Similarly, the systematic review and meta-analysis of 17 studies comparing PFA with TA (Amin 2024) found there was no statistically significant difference between PFA and TA in the incidence of systemic thromboembolism (RR 0.33, 95% CI 0.01 to 8.01, p=0.50, 6 studies).

The publication that combined evidence from 2 prospective single-arm trials done in the Sphere-9 catheter, which together had 178 people across 3 EU centres (Reddy 2023b) reported that no thromboembolic events were seen.

Myocardial infarction

In the UK real-world study of 707 people comparing RFA with PFA and CBA (Farawave, Calvert, 2024) there was 1 suspected myocardial infarction event in the CBA arm. No events were seen in the PFA or RFA arm.

Three studies done with Farawave, CENTAURI and Sphere-9 reported no myocardial infarction events were seen (MANIFEST-17K- Ekanem 2024, Anić 2023, Reddy 2023b).

PV stenosis

Six studies reported on PV stenosis across the Farawave, PulseSelect, Sphere-9 and CENTAURI technologies. All 5 studies reported no evidence of PV stenosis. Some evaluated this in terms of symptomatic PV stenosis whilst others did invasive mapping.

The ADVENT RCT comparing PFA with RFA and CBA (Reddy 2023a, Patel 2024) reported that no people in either the PFA or TA groups had symptoms of pulmonary vein stenosis. Mean change in pulmonary vein cross-sectional area was superior in PFA to TA (mean relative difference 11%, 95% CI 8 to 14%, posterior probability of superiority >0.999). In MANIFEST-PF, the EU retrospective analysis of a prospective registry of 1,568 people across 24 centres (Turagam 2023, Turagam 2024), they reported there were no incidents of PV stenosis. In MANIFEST-17K, the centre-level study of 101 centres with 17,642 people (Ekanem 2024), there were no reported events of PV stenosis. In PULSED-AF, the international prospective single-arm trial of 300 people across 41 centres (Verma 2023a, Verma 2023b) there were no moderate or severe pulmonary vein stenosis was observed on imaging between baseline and 3 months (63 people). In the publication that combined evidence from 2 prospective single-arm trials across 3 EU centres (Reddy 2023b), there was no evidence of any PV stenosis in all 122 people who had invasive remapping. Cardiac computed tomography scans were done on everyone at 129 days (SD 93); 43% (77 of 178 people) indicated no evidence of PV stenosis. In the prospective, single-arm trial of 84 people from 2 EU centres (Anić 2023), they found that between baseline and 90 days, mean narrowing was between 0.5% and 3.6% across PVs which indicated no chronic effect.

Coronary artery spasm

Both MANIFEST studies done with Farawave reported coronary spasm events. In MANIFEST-PF, (Turagam 2023, Turagam 2024), coronary spasm happened in 0.1% (2 of 1,568 people). This was classed as a major complication. This included 1 person who had PVI plus left atrial posterior wall ablation. Both events were resolved with intracoronary nitroglycerin. In MANIFEST-17K, the centre-level study of 101 centres with 17,642 people (Ekanem 2024), 0.1% (25 of 17,642 people) had coronary spasm. Most were proximal to the lesion (88%), 20% (5 of 25 people) had hypotension and nitroglycerin was given to 84% (21 of 25 people). Clinical sequalae were seen in 4 people; 1 person had atrioventricular block and ventricular fibrillation during PFA of the cavotricuspid isthmus and they had resuscitation and defibrillation, 2 people had chest pain in the post-procedure recovery area and both resolved with nitroglycerin, and 2 people had anterior ST elevation, polymorphic premature ventricular contractions and subsequent ventricular fibrillation after PFA at the right inferior PV. They had resuscitation, defibrillation and intravenous nitroglycerin.

In PULSED-AF (PulseSelect), the international prospective single-arm trial of 300 people across 41 centres (Verma 2023a, Verma 2023b), they reported there were no coronary artery spasm events.

Pericarditis

Four studies reported pericarditis outcomes across the Farawave, Varipulse and CENTAURI technologies.

In the systematic review and meta-analysis of 18 studies comparing PFA with TA (de Campos 2024), they reported that across the 18 included studies (with 1,761 people who had PFA), 2 events of pericarditis were reported.

In MANIFEST-PF (Turagam 2023, Turagam 2024), 1 person had pericarditis classed as a minor complication.

Both inspIRE (Varipulse), the EU and Canada prospective single-arm trial of 226 people across 13 centres (Duytschaever 2023, de Potter 2024, Grimaldi 2023), and the prospective, single-arm trial of 84 people from 2 EU centres (CENTAURI, Anić 2023) reported there were no pericarditis events.

Haemoglobinuria, haemolysis and acute kidney injury

Two studies reported on acute kidney injury and associated safety events. They were both done with Farawave.

One study explicitly reported differences in haemoglobinuria, haemolysis and acute kidney injury depending on periprocedural hydration (Mohanty, 2024). In this study, group 1 (28 people) had little or no hydration immediately after the procedure and group 2 (75 people) had planned fluid infusion. Procedures in this study were done with the Farawave technology.

In group 1, 75% had haemoglobinuria within 24 hours post-PFA and there was a statistically significant increase in bilirubin, indicating haemolysis ($p=0.002$). Also, all 21 people with haemoglobinuria had statistically significantly increased serum creatinine levels post-ablation ($p<0.001$), and 19 people had serum creatinine levels that met diagnostic criteria for acute kidney injury. All 4 with renal kidney injury had haemoglobinuria after the procedure and had statistically significantly more PFA applications than the other 17 people ($p<0.001$). Serum creatinine was in the normal range for people without haemoglobinuria, and they had statistically significantly fewer PFA applications than people who had haemoglobinuria ($p=0.019$). All people with haemoglobinuria were successfully treated with hydration before discharge.

In group 2, there was no incidence of haemoglobinuria, no statistically significant change in bilirubin ($p=0.62$) and no statistically significant change in serum creatinine ($p=0.18$).

In MANIFEST-17K, the centre-level study of 101 centres with 17,642 people (Ekanem 2024), 5 people (0.3%) had haemolysis with acute kidney failure with creatine level increase of 100% within a day of the procedure. Symptoms included haemoglobinuria, nausea and oliguria, beginning either immediately post-procedure or the next day. Transient haemodialysis improved renal function by the time of hospital discharge. All 5 had PFA for PersAF, with a complex lesion set with a high number of PF applications. One other person had haemolysis without acute kidney injury and the authors reported that several people at 1 centre had 'dark urine' or haemoglobinuria either immediately post-procedure or the next day. But there was no reported kidney injury or drop in red cell count in these people.

High sensitivity troponin level

The systematic review and meta-analysis of 18 studies comparing PFA with TA (de Campos 2024) reported a summary of high-sensitivity troponin levels, which can indicate heart damage. They found results were statistically significantly higher in PFA than TA in the sensitivity analysis (3 studies, MD 421.4, 95% CI 251.5 to 591.4, $p<0.01$, $I^2=77\%$).

Vascular access complications

Eight studies reported findings on vascular access complications across the Farawave, Varipulse, Sphere-9 and CENTAURI technologies.

The systematic review and meta-analysis of 18 studies comparing PFA with TA (de Campos 2024) found no statistically significant difference between PFA and thermal ablation in vascular access complications (OR 0.91, 95% CI 0.54 to 1.54, p=0.73).

Among studies done with Farawave, vascular access complications happened in 2% or less of people. In the UK real-world study of 707 people comparing RFA with PFA and CBA (Calvert, 2024), there were 3 serious vascular injuries but only

1 in the RFA arm, which needed surgical intervention. In MANIFEST-PF, the EU retrospective analysis of a prospective registry (Turagam 2023, Turagam 2024), 0.1% (2 of 1,568 people) had vascular access complications requiring surgery. This was classed as a major complication. In MANIFEST-17K, the centre-level study of 101 centres with 17,642 people (Ekanem 2024), 3% (441 of 17,642 people) had vascular complications, of which 0.3% were major complications. Rate of major vascular complication was statistically significantly higher in centres that did not routinely use ultrasound guidance (p=0.046). In the prospective case series of 191 people (Schmidt 2022), 2% (4 of 191 people) had a vascular access complication; 2 were in the validation phase, 2 were in the streamline phase. These were major groin haematomas and resolved with conservative management.

In inspIRE (Varipulse), the EU and Canada prospective single-arm trial of 226 people across 13 centres (Duytschaever 2023, de Potter 2024, Grimaldi 2023), there were no primary adverse events which included major vascular access complication or bleeding.

In the publication that combined evidence from 2 prospective single-arm trials which together had 178 people across 3 EU centres (Sphere-9, Reddy 2023b), there were 2 vascular access SAEs, including 1 groin haematoma requiring surgical intervention and 1 groin puncture bleeding treated with compression. This study also reported there were no major vascular complications.

In the prospective, single-arm trial of 84 people from 2 EU centres (CENTAURI, Anić 2023), 3 vascular access complications led to haemorrhagic events needing hospitalisation.

Heart rate change and ST segment changes

The systematic review and meta-analysis of 17 studies comparing PFA with TA (Amin 2024) reported change in heart rate findings. PFA had significantly lower

heart rate change than TA (MD -7.39 beats per minute, 95% CI -12.2 to -2.62, p=0.002, 4 studies, I^2= 86%). Leave one out analysis resolved heterogeneity with removal of 1 study, after which MD was -9.78 (95% CI -11.8 to -7.7, p<0.00001, 3 studies I^2=0%).

ST-segment change events were rare. The systematic review and meta-analysis of 18 studies comparing PFA with TA (de Campos 2024) reported that across the 18 included studies (with 1,761 people who had PFA), there was 1 event of ST segment change. The publication that combined evidence from 2 prospective single-arm trials which together had 178 people across 3 EU centres (Reddy 2023b) reported 1 transient ST-segment elevation following atropine administration in a person with prior myocardial infarction and unknown residual right coronary arterial stenosis later requiring angioplasty and stenting. In MANIFEST-17K (Ekanem 2024), 2 people had anterior ST elevation, polymorphic premature ventricular contractions and subsequent ventricular fibrillation after PFA at the right inferior PV. This was considered a clinical sequalae to coronary spasm. They had resuscitation, defibrillation and intravenous nitroglycerin. Both PULSED-AF, the international prospective single-arm trial of 300 people across 41 centres (Verma 2023a, Verma 2023b) and the prospective, single-arm trial of 84 people from 2 EU centres (Anić 2023) found there were no incidences of ST elevation during any PFA applications.

Death

Ten studies reported mortality outcomes across Farawave, Varipulse, PulseSelect, Sphere-9 and CENTAURI technologies.

The systematic review and meta-analysis of 17 studies comparing PFA with TA (Amin 2024) found there was no statistically significant difference in all-cause mortality between PFA and TA (RR 0.33, 95% CI 0.01 to 8.07, 7 studies). The systematic review and meta-analysis of 18 studies comparing PFA with TA (de

Campos 2024) did not do comparative analysis but reported 1 death among the 1,761 people who had PFA.

In 4 studies, the UK real-world study (Farawave, Calvert, 2024), the inspIRE EU and Canada prospective single-arm trial (Duytschaever 2023, de Potter 2024, Grimaldi 2023), the publication that combined evidence from 2 prospective single-arm trials (Sphere-9, Reddy 2023b) and the prospective single-arm trial (CENTAURI, Anić 2023) no deaths were reported.

In the ADVENT RCT (Reddy 2023a, Patel 2024) 1 person in the PFA arm had pericardial tamponade; emergency sternotomy and resuscitation were needed and the person died after 10 days. In MANIFEST-PF, the EU retrospective analysis of a prospective registry (Farawave, Turagam 2023, Turagam 2024), 1 person died during the study. This person had a sustained stroke. In MANIFEST-17K, the centre-level study of 101 centres with 17,642 people (Ekanem 2024), 0.03% (5 of 17,642 people) died during the study of which 2 deaths were classed and procedure-related: 1 person died from complications from cardiac tamponade, and 1 person died from post-procedure cardiogenic shock in a person with cardiomyopathy and decompensated heart failure. In PULSED-AF (PulseSelect), the international prospective single-arm trial of 300 people (Verma 2023a, Verma 2023b) 1 person with PAF died during follow-up who had a history of cirrhosis, a CT scan showed liver masses and they died of liver failure and 1 person with PersAF died from cardiopulmonary arrest within 2 weeks of dofetilide initiation.

Composite safety outcomes

Four studies defined a primary safety endpoint which could be met if one of a selection of predefined SAEs was seen. These were in studies done with 4 technologies (Varipulse, PulseSelect, Sphere-9 and CENTAURI). Authors reported that events were selected as part of the composite because they are known procedure or device-related events, although their definitions were not

homogeneous across studies. Between 0 and 4 people met safety endpoints in each of the 4 studies.

In inspIRE (Varipulse), the EU and Canada prospective single-arm trial of 226 people across 13 centres (Duytschaever 2023, de Potter 2024, Grimaldi 2023), there were no primary adverse events (defined as pericarditis, myocardial infarction, cardiac tamponade or perforation, thromboembolism, stroke or cerebrovascular accident, transient ischemic attack, phrenic nerve paralysis, or major vascular access complication or bleeding, as well as death, PV stenosis, and atrio-oesophageal fistula that occurred later than 7 days post-procedure).

In PULSED-AF (PulseSelect), the international prospective single-arm trial of 300 people across 41 centres (Verma 2023a, Verma 2023b), the primary safety endpoint was a composite of serious procedure and device-related AEs. One person with PAF and 1 person with PersAF of 150 people in each group met the primary safety endpoint at 6 months, and the 6-month Kaplan-Meier estimates were 0.7% (95% CI 0.1 to 4.6%) in both groups.

In the publication that combined evidence from 2 prospective single-arm trials of the Sphere-9 catheter, which together had 178 people across 3 EU centres (Reddy 2023b), 1 person met the primary safety endpoint. This was device-related serious adverse events within 7 days of the procedure. The person had combined RFA and PFA was hospitalised 20 days after the procedure for inflammatory pericardial effusion. It was managed with anti-inflammatory medication. There were no instances of death, myocardial infarction, persistent diaphragmatic paralysis, stroke or transient ischaemic attack or thromboembolism, cardiac tamponade or perforation, pneumothorax, major vascular complications, pulmonary oedema, hospitalisation or heart block. Note that PV stenosis, atrio-oesophageal fistula were not included in this assessment period.

In the prospective, single-arm trial of the CENTAURI generator, with 84 people from 2 EU centres (Anić 2023), the event rate was 5% (4 events in 4 of 82 people). The SAE endpoint was predefined system-related and procedure-related SAEs within 30 days of ablation. These included 3 vascular access complications led to haemorrhagic events needing hospitalisation and 1 non-embolic cerebrovascular accident caused by exacerbated cardiac tamponade secondary to ablation catheter perforation. There were no incidences of AE fistula, diaphragmatic paralysis, myocardial infarction, pericarditis, thromboembolism, PV stenosis, TIA, or death.

Differences in safety for PVI compared with PVI plus left atrial posterior wall ablation

In the substudy of MANIFEST-PF, (Turagam 2024), they found no statistically significant difference (p=0.51) in the major adverse event rate between people who had just PVI (2%; 3 of 131 people) compared with people who had PVI plus left atrial posterior wall ablation (1%; 6 of 416 people). The minor complication rate was 7% in people who had PVI plus left atrial posterior wall ablation and 4% in people who had PVI only. Transient phrenic nerve injury happened in 1 person who had PVI plus left atrial posterior wall ablation. Coronary spasm happened in 1 person who had PVI plus left atrial posterior wall ablation. Stroke happened in 1 person who had PVI plus left atrial posterior wall ablation and 1 person who had PVI only. No deaths happened in either group. As in the full trial analysis sample, there were no instances of PFA-related oesophageal complications, including no atrio-oesophageal fistula, oesophageal ulcerations, or oesophageal dysmotility. There were no instances of symptomatic PV stenosis or persistent phrenic nerve injury.

MHRA safety alert

An MHRA safety alert was issued for a series of lot numbers for Varipulse

(Biosense Webster Inc) in April 2024. A polymer used to bind the catheter electrodes to the catheter (Polyurethane) had overrun over the electrodes.

In summary, the alert states that this may increase the risk of a cerebrovascular event. Five complaints were reported of people treated with Varipulse catheters from the listed lots. The report states that in all cases, the ablation procedures were completed successfully, and the patients were discharged home and the complaints are being investigated to determine if they are related to this issue. Healthcare providers who have treated people using the specific lots subject to this removal should continue to follow those patients pursuant to their standard of care.

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or Royal College. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

All theoretical and anecdotal events reported by professional experts were reported in the key evidence.

Ten professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

- Professional expert feedback has informed NICE that rollout of PFA technologies is currently highly controlled and monitored in the NHS. The Cardiac Rhythm Management (CRM) Device Working Group has oversight on

this and have established the MINTAC Programme (Monitored introduction of New Technologies – Ablation and CRM), which has initiated a series of light-touch registries for each PFA technology. See more information in the section reporting ongoing trials (UK registries).

- Twelve studies reported in 17 publications, which together included about 30,000 people of whom about 24,850 had PFA, were presented in the key evidence. Follow up was up to 12 months in most studies, but safety data in 17,642 people were reported with an average of 15 months follow up. The studies were chosen to be representative of evidence across 5 PFA technologies (Farawave, Varipulse, PulseSelect and Sphere-9 catheters and CENTAURI generator). Most of the key evidence, including all comparative evidence from primary studies, was done in the Farawave catheter. One randomised study was included, and this was done in the Farawave technology. Evidence for all other technologies was from single-arm studies. All prioritised evidence that was done in the UK was done using the Farawave catheter. Key evidence for technologies other than those included in the main overview are presented in section 1 of appendix B.

- Generally, findings indicate that PFA for AF is as efficacious as other ablative techniques that are currently used in the NHS. Acute procedural success rates were high, with most studies showing 99 to 100% acute PVI, and comparative analysis showed this was likely to be similar to other ablative techniques. Composite scores of treatment effectiveness indicated desirable clinical outcomes happened in up to 73% of people and comparative evidence suggested that this was as good as or better than other ablative techniques. Rates of AF recurrence only were lower than overall treatment failure estimates and systematic review level evidence suggested that PFA was superior to other ablative techniques on this outcome. But, the rate of AF recurrence depended on whether symptomatic recurrence or all recurrence

was considered. Also, rate of all atrial arrhythmia recurrence did not show such positive effects. Findings with respect to health-related quality of life at 1 year were mixed. There was a consistent signal that PFA procedures are likely to have shorter procedure time than other ablative techniques, although absolute estimates of procedure time varied widely and most evidence was from a technology that does 'single-shot' PFA, not point-by-point PFA. Also, this could be affected by a range of other factors.

- Often, sub-group analyses found that people with PersAF had worse efficacy outcomes than people with PAF.

- All theoretical and anecdotal adverse events reported to NICE by professional experts were reported on in the evidence, and whilst complications could be very serious, most SAEs happened in few people. Comparative evidence suggests there is no difference in overall complication rates between PFA and other TA techniques for AF, and rates ranges between less than 1% to 7%. Comparative evidence indicates that oesophageal lesion and phrenic nerve palsy rate may be lower in PFA than TA. But, the evidence suggests that rates of cardiac tamponade may be higher in PFA than TA, and complications of cardiac tamponade were sometimes fatal. Comparative evidence was from one technology and mostly non-randomised. Haemoglobinuria, haemolysis and acute kidney injury appeared to be avoided with planned fluid infusion immediately post-procedure (Mohanty, 2024).

- Experts indicated that PFA may be particularly useful if operators wish to do additional ablation lesion sets, not just PVI. UK and EU analysis suggested that additional ablation sites may be targeted in PFA in up to 19% of people (Calvert 2024, Schmidt 2023). Whilst many of the prioritised studies included people who had operator discretion additional lesion sets which commonly

included left atrial posterior wall ablation, Turagam (2024) explicitly compared efficacy and safety outcomes between people who had PVI only and people who had this in addition to PVI. This was a sub study of the MANIFEST-PF registry study and included 547 people with PersAF; 131 had PVI plus left atrial posterior wall ablation, 416 had PVI only. Their conclusions were that the addition of left atrial posterior wall ablation to PVI did not improve freedom from atrial arrhythmia at 12 months, it did not improve secondary arrhythmic recurrence outcomes for use of antiarrhythmic drugs, need for redo ablation was not significantly different, and there were no differences in complication rate. An ongoing prospective study is exploring this use case in more detail (ADVANTAGE-AF, NCT05443594).

- Whilst most evidence was prospectively collected, efficacy and adverse event rates would be detected more readily in clinical trials with close monitoring. For example, one of the large EU prospective registry studies (MANIFEST PF, Turagam, 2023) noted that 1 case of phrenic nerve injury was detected because of ongoing symptoms, and the authors noted that missed rhythm monitoring and the use of intermittent rather than continuous monitoring may have resulted in an overestimation of treatment success. Some studies actively screened for efficacy and adverse events. Issues with event detection should not affect relative differences in comparisons done between groups within studies. Both systematic reviews only included comparative evidence and did not do indirect comparisons, but this may have been a source of heterogeneity in effect size estimates.

- Each PFA technology has unique design and properties. The application of Farawave for PVI was uniform across studies that used it. But other aspects of the procedure and workflow varied within and between studies. Some studies only used GA, whilst others used a mixture of GA and conscious or deep sedation. Schmidt (2022) and the inspIRE substudy (Grimaldi 2023) both used

deep sedation only. Typically, uninterrupted oral anticoagulation was used, which may be contraindicated in some people. Some studies only applied PFA for PVI whilst others included people who had PFA for other lesion sets (like left atrial posterior wall ablation), at the operator's discretion. Mapping systems were also used variably between and within studies.

- In the systematic review and meta-analysis by de Campos (2024), 11 of 18 studies were prospective including 2 randomised studies that were considered low risk of bias on the ROB2 tool. Five of 18 studies were considered high risk of bias on the ROBINS-I tool. All main analyses comparing PFA with thermal ablation underwent 1-way sensitivity analyses to observe if effects of individual studies affected the overall findings. Also, subgroup analyses assessed if any differences in findings were driven by key study characteristics, like comparison group (RFA or CBA). Procedure time and treatment failure analyses may have been affected by publication bias, according to funnel plot analysis. No conflicts of interest were reported, although evidence from the authors' own publications was included.

- In the systematic review and meta-analysis by de Amin (2024), 10 of 17 studies were prospective including 1 randomised study (ADVENT RCT, Reddy 2023a). The authors assessed this RCT as high risk of bias on the ROB2 tool because of issues with confounding. Six of the remaining 16 studies were considered low risk of bias on the ROBINS-I tool, and all others were considered moderate risk. Leave-1-out sensitivity analyses were used to resolve issues with heterogeneity. No direct financial conflicts of interest were reported.

- Various author conflicts of interest were reported across the other studies and some were funded by the manufacturers. The ADVENT trial (Reddy 2023a) was funded by the manufacturers of Farawave (Boston Scientific) and several authors reported financial conflicts of interest. The UK analysis of 707 people

(Calvert, 2024) reported no funding conflicts but some financial conflicts with Boston Scientific were disclosed for some authors. Many financial conflicts were reported for the MANIFEST-PF trial (Turagam 2023, Turagam 2024), including that Boston Scientific funded data collection but were not involved in design or analysis or authoring of publication. MANIFEST-17K (Ekanem 2024) received no external funding but a range of conflicts were reported for the author list. Financial conflicts were reported for authors of the prospective case series of 191 people (Schmidt 2022) and the retrospective case series of 103 people focusing on avoidance of a common adverse event (Mohanty 2024). The inspIRE trial (Duytschaever, 2023) was funded by the manufacturer and several authors declared financial conflicts of interest. The PULSED AF study (Verma 2023a,b) was funded by the manufacturer and authors reported financial conflicts. The publication that combined evidence from 2 prospective single-arm trials which together had 178 people across 3 EU centres (Reddy 2023b) was funded by the manufacturer and authors reported financial conflicts. The ECLIPSE-AF study (Anic, 2023) was funded by the manufacturer and several financial conflicts of interest were reported.

Any ongoing trials

UK registries

Professional experts informed NICE that there are ongoing UK registries (attached to the MINTAC Programme) dedicated to each technology in current NHS usage. The registries collect information on acute efficacy, safety, and resource utilisation, including a single 3-month follow up to look for late complications. At the moment, the Farawave technology is the most used in the NHS, with over 1,000 procedures done and collected in the MINTAC Farawave registry. Other technologies currently in this programme are PulseSelect and Sphere-9, Varipulse and CENTAURI. Experts on the CRM device working group said that compliance with the registries is a mandatory requirement for centres selected to have access to the technologies, and compliance is 100% to date.

The registries are individual to each technology and do not have ethics committee oversight so cannot be recommended for use in NICE guidance. But, the group intend to publish reports on the data they are collecting.

NICOR were also contacted for data relating to PFA for AF. They do not currently have a field to indicate whether the ablative technique was done with PFA. So, this registry is currently inappropriate for NICE to recommend its use. But, NICOR have been made aware and expressed intentions to update the database.

Farapulse

NCT05072964 The FARAPULSE FARA-Freedom Trial A Prospective Open Label Single Arm Post Market Clinical Follow-Up Trial of the FARAPULSE Pulsed Field Ablation System in Patients With Paroxysmal Atrial Fibrillation https://clinicaltrials.gov/study/NCT05072964, n=180, EU. Expected completion: 07/2024

NCT05493852 A RWS of the FARAPULSE in A Chinese Population With PAF https://clinicaltrials.gov/study/NCT05493852 n=30, China. Expected completion: 31/12/2024

NCT06175234 Feasibility Study on the FARAVIEW Technology (NAVIGATE PF) https://clinicaltrials.gov/study/NCT06175234 Estimated n=30 Expected completion: 15/07/2024

NCT05159492 Ground-Breaking Electroporation-based Intervention for PAROXysmal Atrial Fibrillation Treatment (BEAT PAROX-AF) https://clinicaltrials.gov/study/NCT05159492 n=292, EU. Expected completion: 01/02/2025

NCT05443594 A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation (ADVANTAGE AF) https://clinicaltrials.gov/study/NCT05443594 n=669, US, Canada, EU. Expected completion: 03/2025.

NCT05418725 Ground-Breaking Electroporation-based Intervention for PERSistent Atrial Fibrillation Treatment (BEAT PERS-AF) https://clinicaltrials.gov/study/NCT05418725?term=NCT05418725&rank=1 , n=78, EU. Expected completion: 05/2025.

NCT06128174 LS-PersAFone: Pulsed Field Ablation for Long-Standing Persistent Atrial Fibrillation (LS-PersAFone) https://clinicaltrials.gov/study/NCT06128174?term=NCT06128174&rank=1 n=25, US. Expected completion: 06/2025

NCT05940597 Pulsed Field Ablation vs Cryoablation In Paroxysmal Atrial Fibrillation (FACIL AF) https://clinicaltrials.gov/study/NCT05940597 Estimated n=350, France. Expected completion: 09/2026

NCT06335082 A Registry Based Collaborative to Measure Efficiency, Effectiveness, and Safety of Farapulse PFA Technology for AF (DISRUPT-AF) https://clinicaltrials.gov/study/NCT06335082 n=2000, US. Expected completion: 30/01/2027

NCT05534581 Single Shot Pulmonary Vein Isolation: Comparison of Cryoballoon vs. Pulsed Field Ablation in Patients With Symptomatic Paroxysmal Atrial Fibrillation - A Multi-Center Non-Inferiority Design Clinical Trial (The SINGLE SHOT CHAMPION Trial) https://clinicaltrials.gov/study/NCT05534581 Estimated n=210, Switzerland. Expected completion: 01/2027

NCT05501873 Real World Data Collection in Subjects Treated With the FARAPULSE Pulsed Field Ablation System (FARADISE) https://clinicaltrials.gov/study/NCT05501873. n=1173, global including UK. Expected completion: 08/2027

NCT06096337 Pulsed Field Ablation (PFA) Vs Anti-Arrhythmic Drug (AAD) Therapy As a First Line Treatment for Persistent Atrial Fibrillation (AVANTGUARD) https://clinicaltrials.gov/study/NCT06096337 n=520, global. Expected completion: 12/2027

NCT06199180 Pulsed Field Ablation Versus Conventional Radiofrequency Catheter Ablation for Repeat PVI in Patients With Paroxysmal AF (REPEAT-AF)

https://clinicaltrials.gov/study/NCT06199180 Estimated n=154, Netherlands. Expected completion: 07/2028

NCT06364215 Posterior Wall Substrate Modification Using Irreversible Electroporation for Paroxysmal Atrial Fibrillation (SMILE-AF) https://clinicaltrials.gov/study/NCT06364215, Estimated n=450, US. Expected completion: 10/2028

Varipulse

NCT06099730 Safety and Effectiveness of Pulmonary Vein Isolation and Posterior Wall Ablation with Pulsed Field Energy in Patients With Paroxysmal and Persistent AF (POLARIS) https://clinicaltrials.gov/study/NCT06099730 Estimated n=360, US. Expected completion: 11/2024

NCT06056557 Versatility of a Circular Multielectrode Catheter in the Individualized Recognition & Treatment of Atrial Fibrillation and Related Arrhythmias Using Pulsed Field Energy (VIRTUE) https://clinicaltrials.gov/study/NCT06056557 Estimated n=141, US. Expected completion: 31/12/2024

NCT05552963 A Study of Multi-electrode Circular Irreversible Electroporation (IRE) Catheter and Multi-Channel IRE Generator in Paroxysmal Atrial Fibrillation (AFIRE) https://clinicaltrials.gov/study/NCT05552963 Estimated n=147, China. Expected completion: 31/12/2024

NCT05971693 A Study For Treatment of Paroxysmal Atrial Fibrillation (PAF) With the OMNYPULSE Catheter and the TRUPULSE Generator (Omny-IRE) https://clinicaltrials.gov/study/NCT05971693?term=NCT05971693&rank=1 n=188, Canada, EU. Estimated completion: 04/2025

NCT06455098 A Study of Assessment on Safety and Effectiveness of BWI Pulsed Field Ablation With OMNYPULSE Catheter for the Treatment of Paroxysmal Atrial Fibrillation (PAF) (OMNY-AF) https://clinicaltrials.gov/study/NCT06455098 n=440, US, Australia. Estimated completion: 05/2026

NCT06014996 Comparison of PFA vs. RFA in Patients With Symptomatic Paroxysmal Atrial Fibrillation (InsightPFA)

https://clinicaltrials.gov/study/NCT06014996 Estimated:292, China. Expected completion: 31/12/2026

Sphere-9
NCT05120193 Treatment of Persistent Atrial Fibrillation with Sphere-9 Catheter and Affera Mapping and Ablation System (SPHERE Per-AF). https://clinicaltrials.gov/study/NCT05120193 n=477, US and EU. Estimated completion: 10/01/2024.

Globe, Kardium
NCT05462145 Safety and Effectiveness of the Globe® Pulsed Field System for Treating Patients With Symptomatic Paroxysmal or Persistent Atrial Fibrillation (PULSAR) https://clinicaltrials.gov/study/NCT05462145 n=449, US, Canada, EU. Expected completion: 02/2025

THERMOCOOL STSF with TRUPULSE Generator
NCT06144632 A Study of the THERMOCOOL SMARTTOUCH Surround Flow (SF) Catheter With the TRUPULSE Generator for Treatment of Drug Refractory Symptomatic PAF (SMARTPULSE PAF). https://clinicaltrials.gov/study/NCT06144632 Estimated n=250, US. Expected completion: 16/06/2025

NCT06272981 A Study of the THERMOCOOL SMARTTOUCH Surround Flow (SF) Catheter With the TRUPULSE Generator for Treatment of Drug Refractory Symptomatic PAFOUS (PulseSmart) https://clinicaltrials.gov/study/NCT06272981 Estimated n=135, Australia, Canada. Expected completion: 29/08/2025

No technology named
NCT05328882 Early Recurrences of Atrial Arrhythmias and Their Impact on Late Recurrence After Pulmonary Vein Isolation With Pulsed Field Ablation of Paroxysmal Atrial Fibrillation https://clinicaltrials.gov/study/NCT05328882 Estimated n=40, Croatia. Expected completion: 17/05/2024

NCT06039722 Clinical Trial of the Pulse Field Ablation System for the Treatment of Paroxysmal Atrial Fibrillation in 11 Centers in China https://clinicaltrials.gov/study/NCT06039722 n=166, China. Expected completion: 17/08/2024

NCT06160076 Inflammatory Response Following " Pulsed Field Ablation " vs. Radiofrequency Ablation-2 (RIPAF-2)
https://clinicaltrials.gov/study/NCT06160076 Estimated n=60, France. Expected completion: 16/12/2024

NCT06307860 Comparison of Different Ablation Surgeries on Left Atrial Reverse Remodelling in Patients With Atrial Fibrillation
https://clinicaltrials.gov/study/NCT06307860
Estimated n=120, China. Expected completion: 01/03/2025

NCT05618340 PFA for Paroxysmal Atrial Fibrillation
https://clinicaltrials.gov/study/NCT05618340, n=149, China. Expected completion: 01/09/2025

NCT06166524 Pulsed-field Ablation for Patients With Asymptomatic Non-paroxysmal Atrial Fibrillation https://clinicaltrials.gov/study/NCT06166524.
Estimated n=124, Czechia. Expected completion: 31/12/2025

Existing assessments of this procedure

No existing guidelines were identified in standard searches. Topic experts corroborated that there are no guidelines specific to PFA yet, but noted the following:

- Heart Rhythm Society position statement (North America): “In the context of regulatory approval of PFA by multiple competent authorities across the world (including the FDA), HRS believes that this novel treatment modality should be made available to patients based on the best clinical judgment of the treating physician. Controlled clinical trials and real-world evidence registries have demonstrated that PFA is a safe and effective treatment for arrhythmia conditions including AF. Adoption of this technology could lead to improved cardiovascular outcomes and quality of life with reduced costs associated with recurrent hospitalizations and the need for additional

procedures. The Society recommends that payors apply the same coverage criteria for PFA as those established for thermal ablation of AF."

- Section 6.2.3. of a consensus statement from the US Heart Rhythm Society and its EU, Asia and Pacific, and Latin America equivalents describes mostly preclinical data but includes information on differences in properties of PFA between different manufacturers which may affect safety and efficacy.

    - Tzeis S, Gerstenfeld EP, Kalman et al (2024). 2024 European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on catheter and surgical ablation of atrial fibrillation. EP Europace 26: euae043.

Related NICE guidance

Interventional procedures

Percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation (2016) NICE Interventional procedures guidance 563 (Recommendation: standard arrangements)

Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation (2012) NICE Interventional procedures guidance 427 (Recommendation: standard arrangements)

Percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for atrial fibrillation (2009) NICE Interventional procedures guidance 294 (Recommendation: special arrangements)

Thoracoscopic epicardial radiofrequency ablation for atrial fibrillation (2009) NICE Interventional procedures guidance 286 (Recommendation: special arrangements)

Percutaneous radiofrequency ablation for atrial fibrillation (2006) NICE Interventional procedures guidance 168 (Recommendation: standard arrangements)

Microwave ablation for atrial fibrillation in association with other cardiac surgery (2005) NICE Interventional procedures guidance 122 (Recommendation: standard arrangements)

Cryoablation for atrial fibrillation in association with other cardiac surgery (2005) NICE Interventional procedures guidance 123 (Recommendation: standard arrangements)

Medical technologies

TactiCath Quartz catheter for percutaneous radiofrequency ablation in atrial fibrillation (2016) NICE medtech innovation briefing MIB60

ThermoCool SmartTouch catheter for percutaneous radiofrequency ablation in atrial fibrillation (2016) NICE Medtech innovation briefing MIB61

NICE guidelines

Atrial fibrillation: diagnosis and management (2021) NICE guideline NG196

Professional societies

- Society of Cardiothoracic Surgeons of Great Britain and Ireland (SCTS)
- British Cardiovascular Interventional Society (BCIS)
- British Cardiovascular Society (BCS)
- British Heart Rhythm Society

- Royal College of Physicians
- Royal College of Physicians and Surgeons of Glasgow
- Royal College of Physicians of Edinburgh
- NHS England
- NHS Scotland

Evidence from people who have had the procedure and patient organisations

NICE received 1 submission from a patient organisation about PFA for AF.

The views of people who have had the procedure were consistent with the published evidence and the opinions of the professional experts.

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 4 completed submissions. These were considered by the interventional procedures technical team and any relevant points have been taken into consideration when preparing this overview.

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9. Schmidt B, Bordignon S, Tohoku S et al. (2022). 5S Study: Safe and Simple Single Shot Pulmonary Vein Isolation With Pulsed Field Ablation Using Sedation. Circulation: Arrhythmia and Electrophysioology 15: e01817.
10. Mohanty S, Casella M, Compagnucci P, et al. (2024). Acute Kidney Injury Resulting From Hemoglobinuria After Pulsed-Field Ablation in Atrial Fibrillation: Is it Preventable? JACC: Clinical Electrophysiology 10: 709-715.
11. Duytschaever M, de Potter T, Grimaldi M et al. (2023). 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. Circulation: Arrhythmia and Electrophysiology 16: e011780.
12. de Potter T, Grimaldi M, Duytschaever M et al. (2024). Predictors of Success for Pulmonary Vein Isolation With Pulsed-field Ablation Using a Variable-loop Catheter With 3D Mapping Integration: Complete 12-month Outcomes From inspire. Circulation: Arrhythmia and Electrophysiology 17: e012667.
13. Grimaldi M, Quadrini F, Caporusso N et al. (2023). Deep sedation protocol during atrial fibrillation ablation using a novel variable-loop biphasic pulsed field ablation catheter. Europace 25: 1-4.

14. Verma A, Haines DE, Boersma LV et al. (2023a). Pulsed Field Ablation for the Treatment of Atrial Fibrillation: PULSED AF Pivotal Trial. Circulation: 147: 1422-1432.
15. Verma A, Haines DE, Boersma LV et al. (2023b). Influence of monitoring and atrial arrhythmia burden on quality of life and health care utilization in patients undergoing pulsed field ablation: A secondary analysis of the PULSED AF trial. Heart Rhythm 20: 1238-1245.
16. Reddy VY, Peichl P, Anter E et al. (2023b). A Focal Ablation Catheter Toggling Between Radiofrequency and Pulsed Field Energy to Treat Atrial Fibrillation. JACC: Clinical Electrophysiology 9: 1786-1801.
17. Anic A, Phlips T, Breskovic T et al. (2023). Pulsed field ablation using focal contact force-sensing catheters for treatment of atrial fibrillation: acute and 90-day invasive remapping results. Europace 25: 1-11.

Appendix A: Methods and literature search strategy

Methods and literature search strategy

NICE has identified studies and reviews relevant to PFA for AF from the medical literature.

Search strategy design and peer review

This search report is informed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension (PRISMA-S).

A NICE information specialist ran the literature searches on 26/07/2024. See the search strategy history for the full search strategy for each database. Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The principal search strategy was developed in MEDLINE ALL (Ovid interface). It was adapted for use in each of the databases listed in table 4a, taking into account the database's size, search functionality and subject coverage. The MEDLINE ALL strategy was quality assured by a NICE senior information specialist. All translated search strategies were peer reviewed to ensure their accuracy. The quality assurance and peer review procedures were adapted from the Peer Review of Electronic Search Strategies (PRESS) 2015 evidence-based checklist.

Review management

The search results were managed in EPPI-Reviewer version 5 (EPPI-R5). Duplicates were removed in EPPI-R5 using a 2-step process. First, automated deduplication was done using a high-value algorithm. Second, manual deduplication was used to assess low-probability matches. All decisions about inclusion, exclusion and deduplication were recorded and stored.

Limits and restrictions

The search was not limited by date or language.

The CENTRAL database search removed trial registry records and conference material. The Embase search excluded conference material.

The limit to remove animal studies in the searches is standard NICE practice, which has been adapted from Dickersin K, Scherer R, Lefebvre C (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ 309(6964): 1286.

Main search

1 Table 4a Main search results

Database	Date searched	Database platform	Database segment or version	Number of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	26/07/24	Wiley	Issue 7 of 12, May 2024	43
Cochrane Database of Systematic Reviews (CDSR)	26/07/24	Wiley	Issue 7 of 12, June 2024	7
Embase	26/07/24	Ovid	1974 to 2024 July 25	577
INAHTA International HTA Database	26/07/24	https://database.inahta.org/	n/a	0
MEDLINE ALL	26/07/24	Ovid	1946 to 2024 July 25	537

Search strategy history

MEDLINE ALL search strategy

1. atrial fibrillation/ 75313

2.((atrial or atria or atrium or auricular or persistent or paroxsymal) adj4 fibrillat*).tw. 98009

3. AF.tw. 56955

4. *Arrhythmias, Cardiac/ 42698

5. (Cardiac adj4 (arrhythmia* or dyrrhymthia*)).tw. 25220

6. *Pulmonary Veins/ 12985
7. ((pulmonary vein* adj4 isolat*) or PVI or PVAI).tw. 7565
8. or/1-7 192830
9. (Puls* adj4 field adj4 ablat*).tw. 509
10. PFA.tw. 3534
11. Farapulse.tw. 25
12. PulseSelect.tw. 2
13. (Sphere-9 or Sphere9).tw. 7
14. Varipulse.tw. 3
15. (("Kardium Globe" or "Acutus" or "Biosense Webster") and ablat*).tw. 288
16. or/9-15 4079
17. 8 and 16 553
18. animals/ not humans/ 5207441
19. 17 not 18 522

Embase search strategy

1. atrial fibrillation/ 127378
2. ((atrial or atria or atrium or auricular or persistent or paroxsymal) adj4 fibrillat*).tw. 176472
3. AF.tw. 108893
4. *heart arrhythmia/ 46145
5. (Cardiac adj4 (arrhythmia* or dyrrhymthia*)).tw. 37059
6. *Pulmonary Vein/ 5067
7. ((pulmonary vein* adj4 isolat*) or PVI or PVAI).tw. 16300
8. or/1-7 315889
9. (Puls* adj4 field adj4 ablat*).tw. 1006
10. PFA.tw. 6118
11. Farapulse.tw. 99
12. PulseSelect.tw. 4
13. (Sphere-9 or Sphere9).tw. 41
14. Varipulse.tw. 8
15. (("Kardium Globe" or "Acutus" or "Biosense Webster") and ablat*).tw. 1104

16. or/9-15 7551
17. 8 and 16 1457
18. nonhuman/ not human/ 5499852
19. 17 not 18 1375
20. (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5991436
21. 19 not 20 537

Cochrane Library (CDSR and CENTRAL) search strategy

#1. MeSH descriptor: [Atrial Fibrillation] explode all trees 7292
#2. ((atrial or atria or atrium or auricular or persistent or paroxsymal) near/4 fibrillat*) 17311
#3. AF 18625
#4. MeSH descriptor: [Arrhythmias, Cardiac] explode all trees 13729
#5. (Cardiac near/4 (arrhythmia* or dyrrhymthia*)) 5090
#6. MeSH descriptor: [Pulmonary Veins] explode all trees 694
#7. ((pulmonary vein* near/4 isolat*) or PVI or PVAI) 2205
#8. {or #1-#7} 36342
#9. (Puls* near/4 field near/4 ablat*) 54
#10. PFA 414
#11. Farapulse 12
#12. PulseSelect 1
#13. (Sphere 9 or Sphere9) 308
#14. Varipulse 2
#15. ((Kardium Globe or Acutus or Biosense Webster) and ablat*) 91
#16. {or #9-#15} 824
#17. #8 and #16 147
#18. "conference":pt or (clinicaltrials or trialsearch):so 765632
#19. #17 not #18 51

INAHTA HTA Database search strategy

1. "Atrial Fibrillation"[mh] 159

2. ((atrial or atria or atrium or auricular or persistent or paroxsymal) and fibrillat*) 192
3. "Arrhythmias, Cardiac"[mh] 55
4. (Cardiac and (arrhythmia* or dyrrhymthia*)) 87
5. "Pulmonary Veins"[mh] 10
6. ((pulmonary vein* and isolat*) or PVI or PVAI) 12
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6 295
8. PFA 0
9. Farapulse 0
10. PulseSelect 0
11. (Sphere 9 or Sphere9) 6
12. Varipulse 0
13. ((Kardium Globe or Acutus or Biosense Webster) and ablat*) 0
14. (Puls* and field*) 12
15. #9 or #10 or #11 or #12 or #13 or #14 18
16. #7 and #15 0

Inclusion criteria

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, letters and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology.
- Study design: Case reports were excluded. For the Farawave technology, studies less than 30 people were excluded.
- People with atrial fibrillation.
- Intervention or test: pulsed field ablation.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in Appendix B: Other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Appendix B: Other relevant studies

Other potentially relevant studies that were not included in the main evidence summary (tables 2 and 3) are listed in table 5 below.

Table 5 additional studies identified

Study	Technology, study design, number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Key studies for other identified technologies that were not prioritised			
Chen B, Chang L, Cui Y et al (2024). A pilot clinical assessment of biphasic asymmetric pulsed field ablation catheter for pulmonary vein isolation. Frontiers in Cardiovascular Medicine 11: 1266195.	PFA catheter from Tianjin Intelligent Health Co., Ltd. (Tianjin). Prospective, single-centre feasibility study (ChiCTR2100051894) n=10 12 months	The focus of the study is on PVI and included people with PAF and PersAF. At 12 months, there were no recurrences, PV stenosis or other SAEs.	This technology is not yet in use in the UK. Larger studies with technologies used in the UK and more robust design were included in the prioritised evidence as representative of this class of procedure.
Duytschaever M, Račkauskas G, de Potter T et al (2024). Dual energy for pulmonary vein isolation using dual-energy focal ablation technology integrated with a three-dimensional mapping system: SmartfIRE 3-	Dual energy smarttouch SF (DE STSF) catheter (Biosense Webster) Prospective, multicentre, single arm clinical study (SmartFIRE	This catheter can also deliver RFA energy, and both energies were applied during the procedure. Both PVI and linear ablation were done. All people had PAF. Acute procedure success rate was 100%. Primary adverse event rate was 4.4%, including 2 PV stenoses, 2 cardiac tamponade or perforation, 1 stroke and 1 pericarditis. PVI durability,	This technology is not yet in use in the UK. Larger studies with technologies used in the UK and with longer follow-up and more robust design were included in the

month results. Europace 26.	study, NCT05752487) n=140 75 days (SD 15)	assessed in 30 people, was 60%.	prioritised evidence as representative of this class of procedure.
Sanders P, Healy S, Emami M et al (2024). Initial clinical experience with the balloon-in-basket pulsed field ablation system: acute results of the VOLT CE mark feasibility study. Europace 26: euae118.	Volt PFA Catheter Sensor Enabled, Abbott Prospective, multicentre, single arm study (VOLT CE mark study, NCT06106594) n=32 30 days	Both people with PAF and PersAF were included. Only PVI was done. Acute success was seen in 99.2% of PVs in 96.9% of people. Procedure time was 124.6 minutes. At 30 days, there were no incidences of phrenic nerve injury, pulmonary vein stenosis, or oesophageal lesions causally related to the PFA system. 3 people had silent cerebral lesions (9.4%). There were no primary serious adverse events	This technology is not yet in use in the UK. Larger studies with technologies used in the UK, with more robust design were included in the prioritised evidence as representative of this class of procedure.
Turagam MK, Neuzil P, Petru J et al (2024). AF ablation using a novel "single-shot" map-and-ablate spherical array pulsed field ablation catheter: 1-Year outcomes of the first-in-human PULSE-EU trial. Heart Rhythm 21: 1218-1226.	Globe G4 catheter (Kardium Inc.) Prospective, single centre, single arm study (PULSE-EU study, NCT05164107) n=48 12 months	Both people with PAF and PersAF were included. Both PVI and linear ablation were done. Acute success of lesions was 100% for PVI and posterior wall, and 91% of mitral isthmuses. 93.5% of PVs were durably isolated at 3 months. 1 person had drug-responsive pericarditis. The 1-year Kaplan-Meier estimates of freedom from atrial arrhythmia were 84% (PAF) and 80% (PersAF).	This technology is not yet in use in the UK. Larger studies with technologies used in the UK, with more robust design were included in the prioritised evidence as representative of this class of procedure.
Wang Y, Lai HL, Chen Q et al (2024). Application of a circular-shaped pulsed field	LEAD-PFA (Sichuan Jinjiang Electronic Medical Device	This study only assessed PVI. All people had PAF. 100% PVI was achieved with the PFA system. 4 of 11 people who had deep sedation for the procedure	This technology is not yet in use in the UK. Larger studies with

ablation catheter with magnetic sensors for pulmonary vein isolation: a multi-centre clinical study report. Europace 26: 1-9.	Technology Co. Ltd) Prospective, multicentre, single arm clinical study (ESPFA-CN21 study, NCT05400928) n=151 15 months	had transient vagal responses. No severe periprocedural complications. During follow-up, 3 people had atrial flutter, 11 had AF recurrence. The estimated 12-month Kaplan–Meier of freedom from arrhythmia was 88.4%.	technologies used in the UK, with more robust design were included in the prioritised evidence as representative of this class of procedure.
Wang Z, Tang M, Reddy VY et al (2024). Efficacy and safety of a novel hexaspline pulsed field ablation system in patients with paroxysmal atrial fibrillation: the PLEASE-AF study. Europace 26: euae174.	CardiPulse (Hangzhou Dinova EP Technology Co) Prospective, multicentre, single arm clinical study (PLEASE-AF, NCT05114954) n=143 12 months	All people had PAF. Main focus was on PVI but additional ablation was at the surgeon's discretion. 100% of PVs were successfully isolated. Freedom from any atrial arrhythmia lasting at least 30s at 12 months was 86.7%. One person had a small pericardial effusion 1 month after the procedure. No intervention was needed.	This technology is not yet in use in the UK. Larger studies with technologies used in the UK, with more robust design were included in the prioritised evidence as representative of this class of procedure.
Systematic reviews, meta-analyses and cross-study comparison analyses that were not included in the prioritised evidence			
Aldaas OM, Malladi C, Han FT et al (2024). Pulsed field ablation versus thermal energy ablation for atrial fibrillation: a systematic review and meta-analysis of procedural efficiency, safety,	Systematic review and meta-analysis n=6 studies (n=441 people had PFA, n=571 had TA) Up to 12 months	All studies used the Farawave catheter. People predominantly had PAF. Only comparative evidence was included. No statistically significant differences between PFA and TA in periprocedural complications or recurrence of atrial tachyarrhythmias. Procedure time was shorter for PFA. The	The findings of this meta-analysis align with the findings of meta-analysis level evidence in the main evidence. More detailed outcomes were reported

and efficacy. Journal of Interventional Cardiac Electrophysiology 67: 639-648.		authors state more RCT evidence is needed.	in the MA included in the prioritised evidence.
Aldaas OM, Malladi C, Aldaas AM et al (2023). Safety and acute efficacy of catheter ablation for atrial fibrillation with pulsed field ablation vs thermal energy ablation: A meta-analysis of single proportions. Heart Rhythm 0^2 4: 599-608.	Systematic review and meta-analysis n=24 studies (n=2841 had PFA, 2361 had TA) Up to 1 year	This meta-analysis synthesised evidence on PFA and compared outcomes from key trials of TA. It included people with both PAF and PersAF. Statistically significantly less periprocedural complications were seen in the PFA group than TA (p<0.001). Recurrence up to 1 year was not statistically significantly lower, but there was a trend that favoured PFA (p=0.132).	More recent systematic review and meta-analyses were included in the main evidence. More detailed outcomes were reported in the MA included in the prioritised evidence.
Messori A, Mamone D, Rivano M et al (2024). Pulsed-field ablation for paroxysmal atrial fibrillation: An indirect comparison of effectiveness among three proprietary devices conducted in the absence of randomized trials. International Journal of Cardiology 406: 132025.	Review and indirect comparison analysis n=9 studies (n=1916 people) Up to 12 months	This analysis only included evidence from people with PAF. Study selection was not systematic. Farawave (according exclusively to the results of the ADVENT RCT), PulseSelect, and Varipulse showed a similar time-course of their respective outcomes with no significant difference. The single-arm trials using Farawave showed better outcomes than the randomised trial using Farawave and the pivotal trials using PulseSelect and Varipulse.	The findings of this study align with the prioritised evidence. A systematic review and meta-analysis with more robust methods for finding and selecting studies was also prioritised.
Qamar U, Agarwal S, Krishnan S et al (2023). Efficacy and safety of pulsed field ablation for atrial fibrillation: A	Systematic review and meta-analysis n=26 studies (n=2561 people)	This study included evidence from people with PAF and PersAF. Acute isolation of all PVs was achieved in 99.7%. Mean total procedure time was 83.0 minutes. Overall rate of arrhythmia recurrence	The findings of this study align with a meta-analysis included in the main evidence. A

systematic review and meta-analysis. Pacing Clin Electrophysiol 47: 474-480.	Up to 12 months	after the blanking period was 17.3%. Overall post-procedure complication rate was 2.8%, including vascular access complications, cardiac tamponade, ischaemic attack and phrenic nerve injury. There were no cases of oesophageal injury, atrio-oesophageal fistula, and pulmonary vein stenosis in the included studies. One death was reported among all the included studies.	systematic review and meta-analysis with more robust methods and reporting was prioritised.
Rivano M, Cancanelli L, Brunoro R et al (2024). Radiofrequency ablation, cryotherapy ablation, or pulsed-field ablation to treat paroxysmal atrial fibrillation unresponsive to pharmacological treatments: interpreting efficacy through reconstruction of individual patient data from randomized trials. Cureus 16: e65113	Comparative analysis of RCTs 3 RCTs Minimum of 12 months	This study selected 1 RCT as representative of recurrence outcomes from each of CBA, RFA and PFA. Heterogeneity analysis indicated it was appropriate to pool findings. Results indicated superiority of pulsed-field ablation versus thermal ablation for recurrence. The authors said findings must be interpreted with caution because the people given pulsed-field ablation were limited, and their follow-up was shorter than that of patients receiving thermal ablation.	Only comparative outcomes on recurrence was assessed in this study. The RCT of people with pulsed field ablation was included in the prioritised evidence, and this included within-trial comparisons with both CBA and RFA.
Rudolph I, Mastella G, Bernlochner I et al (2024). Efficacy and safety of pulsed field ablation compared to cryoballoon ablation in the treatment of atrial	Review and meta-analysis n=11 studies (n=3805 people) Follow-up not reported.	This study included people with PAF and PersAF. There was a focus on PVI and compared with CBA. PFA had statistically significantly lower recurrence of AF and atrial tachycardia compared with CBA, and fewer periprocedural complications. The lower complication rate	There is near-complete overlap in studies included in this meta-analysis with de Campos (2024), which is included in

fibrillation: a meta-analysis. European Heart Journal Open 4: oeae044		was driven by fewer phrenic nerve injuries, but there were more cardiac tamponades after PFA. Total procedure time was statistically significantly shorter in PFA.	the prioritised evidence. This study only compared with CBA. De Campos (2024) systematic review and meta-analysis had more robust methods and reporting was prioritised. The findings of this study align de Campos (2024).
Serban T, Mannhart D, Abid Q et al (2023). Durability of pulmonary vein isolation for atrial fibrillation: a meta-analysis and systematic review. Europace 25: 1-10.	Systematic review and meta-analysis n=19 studies (n=1050 people) 2 to 7 months	The focus of this study was on PVI durability in people with PAF and PersAF. Pooled across PFA, RFA, laser balloon ablation and CBA 99.7% of PVs were isolated during the procedure and 75.5% of PVs in 51% of people were persistently isolated at follow-up. Higher durability percentages were reported in PVs ablated with laser-balloon (84%) and PFA (87%, 95% CI 84 to 90, 2 studies).	This study only included 2 studies with people who had PFA. The findings of this study align with a meta-analysis included in the main evidence that had more of a focus on PFA outcomes.
Shaheen N, Shaheen A, Ramadan A & Nashwan AJ (2022). Efficacy and safety of novel pulsed field ablation (PFA) technique for atrial fibrillation: A systematic review	Systematic review and meta-analysis n=16 studies (n=485 people) 12 months	The study included people with both PAF and PersAF. They only included studies in people having first time ablation. Isolation of all pulmonary veins was 100% Overall recurrence rate of arrhythmia was 2.84%. Complications were detected during or after the PFA procedure at a rate of 2.23%.	The studies included in this systematic review are mainly small, early studies on PFA, indicated by the low number of

and meta-analysis. Health Science Reports 6: e1079.			people included across all 16 studies. A systematic review and meta-analysis with more robust evidence and reporting was prioritised. The findings of this meta-analysis are more favourable on recurrence outcomes.
Shtembari J, Shrestha DB, Pathak BD et al (2023). Efficacy and safety of pulsed field ablation in atrial fibrillation: a systematic review. J. Clin. Med. 12: 719.	Systematic review n=6 studies (1897 people) 9 months (SD 3)	Acute PVI was between 99.9 and 100% in 5 of 6 studies. Major complications were rare, and included pericardial tamponade, vascular complications requiring surgery and stroke. The atrial arrhythmia recurrence was higher in the thermal group than in the PFA group (39% versus 11%).	The searches for this study were completed in mid-2022 meaning many of the more recent, larger comparative studies were not included.
Wan Y, Zeng S, Liu FW et al (2024). Comparison of therapeutic effects between pulsed field ablation and cryoballoon ablation in the treatment of atrial fibrillation: a systematic review and meta-analysis	Systematic review and meta-analysis n=9 studies (n=1105 PFA, 1770 CBA) Up to 12 months	In this study comparing PFA and CBA, PFA had statistically significantly reduced rate of perioperative complications (RR 0.52, p=0.02). There was no statistically significant difference in recurrence rate during follow-up (RR 0.95, p=0.57).	This study only looked at comparisons with 1 of the current standard treatments. The findings of this study align with a meta-analysis included in the main evidence.

Zhang H, Zhang H, Lu H et al (2023). Meta-analysis of pulsed-field ablation versus cryoablation for atrial fibrillation. Pacing Clin Electrophysiol. 47: 603-613.	Systematic review and meta-analysis n=15 studies (n=1,880 people) Up to 12 months	In this study comparing PFA and CBA, there were no statistically significant differences in recurrences of atrial arrhythmia (OR 0.83), or periprocedural complication (OR 0.78). Procedure time was statistically significantly shorter in PFA (MD -7.17 minutes). PFA had statistically significantly more cardiac tamponade, higher release of troponin, but statistically significantly less incidence of phrenic nerve palsy.	This study only looked at comparisons with 1 of the current standard treatments. The findings of this study align with a meta-analysis included in the main evidence.
All other deprioritised studies			
Badertscher P, Mannhart D, Weidlich S, et al. (2024). Left atrial posterior wall isolation using pulsed-field ablation: procedural characteristics, safety, and mid-term outcomes. J Interv Card Electrophysiol 67: 1359–136.	Prospective observational study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=100 12 months	This study assessed the safety and outcomes of pulsed-field ablation (PFA) for posterior wall isolation (PWI) in 100 patients with persistent atrial fibrillation. PWI was achieved in all cases with no major complications. During a median follow-up of 144 days, 15% had recurrent AF. The results suggest PFA-PWI is safe and effective, with promising mid-term outcomes, though further trials are needed.	This was a single centre study from Switzerland. Evidence from larger, multicentre or UK based real-world studies has been included in the prioritised evidence.
Badertscher P, Weidlich S, Knecht S, et al (2023). Efficacy and safety of pulmonary vein isolation with pulsed field ablation vs. novel cryoballoon ablation system for atrial fibrillation. EP Europace 25: 1905–1913.	Prospective comparative clinical study, single centre Farawave, Farapulse (Boston Scientific) PFA system vs Cryo (Boston Scientific) n=181	This study compared PFA and cryoballoon for pulmonary vein isolation in 181 patients with atrial fibrillation. Procedure times, fluoroscopy times, and complications were similar between the two groups. After a median follow-up of 404 days, AF recurrence rates were also comparable (24% for PFA vs. 30% for CBA), indicating similar efficacy and safety for both techniques.	Evidence from larger, multicentre or UK based real-world studies has been included in the prioritised evidence. This study was also included in the systematic

	12 months		review and meta-analysis by de Campos (2024) in the main evidence.
Bejinariu AG, Spieker M, Makimoto H, Augustin N, Kelm M, Rana OR (2024). A zero-exchange approach for left atrial access in pulmonary vein isolation with pulsed field ablation. J Cardiovasc Electrophysiol.	Prospective clinical study, single arm Farawave, Farapulse PFA system (Boston Scientific) n=166 48 hours	This study evaluated the safety and feasibility of direct transeptal puncture (TSP) using a Faradrive sheath for pulmonary vein isolation with PFA in 166 people with AF. The procedure was completed in a median of 60 minutes, with a median fluoroscopy dose of 595 cGy × cm², with one patient experiencing pericardial tamponade, managed with puncture.	This was a single centre study. Evidence from larger, multicentre or UK based real-world studies has been included in the prioritised evidence.
Bianchini L, Schiavone M, Vettor G, et al. (2024). Hybrid-convergent procedure or pulsed field ablation in long-standing persistent atrial fibrillation. JACC: Clinical Electrophysiology 10: 1700-1710.	Prospective comparative clinical study, single-centre. Farawave, Farapulse PFA system (Boston Scientific) n=93 12 months	This study compared the efficacy and safety of the hybrid-convergent RF vs PFA of PVs and left atrial posterior wall in long-standing persistent atrial fibrillation (LSPAF). Hybrid-convergent and PFA share comparable arrhythmic outcomes in LSPAF. However, PFA showed a better safety profile with a lower rate of major periprocedural complications compared with hybrid ablation (12% vs 0%; p=0.028).	Larger multicentre studies were included in the main evidence.
Bisignani A, Schiavone M, Solimene F et al. (2024). National workflow experience with pulsed field ablation for atrial fibrillation: learning curve,	Prospective observational study, multicentre Italy Farawave, Farapulse PFA system (Boston Scientific)	The study evaluated the learning curve for PFA in AF. Among 752 patients, procedural efficiency significantly improved after 10 PFA cases, with reduced time to pulmonary vein isolation (PVI) and fluoroscopy ($p<0.0001$ and $p=0.0045$, respectively). Compared to	The is based ATHENA registry is structured to stratify data based on the learning curve of practitioners involved.

efficiency, and safety. J Interv Card Electrophysiol.	n=752 3 months	prior RF and cryoablation times, PFA was faster in 62.4% of cases and showed no major complications, highlighting rapid procedural improvements and acute effectiveness.	Notably, it does not include comparative analyses with other ablation techniques.
Blockhaus C, Guelker JE, Feyen L et al. (2023) Pulsed field ablation for pulmonary vein isolation: real-world experience and characterization of the antral lesion size compared with cryoballoon ablation. J Interv Card Electrophysiol 66, 567–575.	Retrospective comparative clinical study, single-centre Farawave, Farapulse PFA system (Boston Scientific) n=43 12 months	In this cohort study of 43 people (23 PFA, 20 CBA), PFA demonstrated no early vein reconnection and a low complication rate, with no nerve injury or bleeding, though one stroke (4.34%) and episodes of transient hypotension and bradycardia requiring pacing were noted. PFA shows promise in treating AF with a high acute PVI success rate (100%) and larger antral lesions compared to CBA (67.03% compared to 57.39%, p=0.01).	This was a single centre comparative study. Evidence from larger, multicentre or UK based real-world studies has been included in the prioritised evidence. This study was also included in both systematic review and meta-analyses in the main evidence.
Boersma LVA, Natale A, Haines D et al (2024). Prevalence, timing, and impact of early recurrence of atrial tachyarrhythmias after pulsed field ablation: A secondary analysis of the PULSED AF trial. Heart Rhythm: 1-7.	Secondary analysis of a prospective, multicentre, single arm trial (PULSED-AF) PulseSelect (Medtronic) n=294 12 months	This study explored the relationship between early recurrence (within the blanking period) of atrial tachyarrhythmias and late recurrence (after the blanking period) after PFA. They found early recurrence predicted late recurrence, but the association was weak; about 1 third of people with early recurrence go on to develop late recurrence.	This is a secondary analysis of the PULSED-AF trial. The main publication is included in the prioritised evidence. This study does not add to the discussion of safety and efficacy of the

			procedure so was deprioritised.
Bohnen M, Weber R, Minners J, et al. (2023). Characterization of circumferential antral pulmonary vein isolation areas resulting from pulsed-field catheter ablation. EP Europace, 25(1), 65–73.	Retrospective observational study, single-centre Farawave, Farapulse PFA system (Boston Scientific) n=40 Follow up: 6 months	In this study, PFA for PVI in AF patients was examined using high-density voltage mapping. Among 40 patients (62.5% with paroxysmal AF), insufficient isolation areas were frequently found in the left anterior antral PV segments (62.5 to 77.5% of cases), with the largest gaps in segments 2, 5, and 8. Additionally, enlarged isolation areas were observed on the posterior wall and roof in nearly all patients (89.5 to 100%), extending beyond the antral segments.	This primary aim of this study was visualising areas, rather than assessing the safety or efficacy of the device.
Chaumont C, Hayoun C, Savoure A. et al. (2024). Pentaspline pulsed field ablation catheter versus cryoballoon for atrial fibrillation ablation: results from a prospective comparative study journal of the American Heart Association 13(6): e033146.	Prospective comparative study, multicentre Farawave, Farapulse PFA system vs CB n=301 1 year	This study compared PFA and CBA for PVI in AF patients. Among 301 people, complete PVI was achieved in 96% of the CBA group and 100% of the PFA group (p=0.01). The CBA group had a longer procedure time and experienced phrenic nerve injuries (10%), which were absent in the PFA group. After one year, freedom from atrial arrhythmia was higher in the PFA group (87.9% compared to 77.7%; adjusted HR 0.53, 95% CI 0.30 to 0.96; p=0.037), suggesting PFA's potential for greater safety and long-term efficacy.	This was a multicentre comparative study. Evidence from larger, multicentre or UK based real-world studies has been included in the prioritised evidence.
Chaumont C., McDonnell E., Boveda S, et al. (2024). Prospective 1-year results of atrial fibrillation ablation using the	Prospective clinical study, single arm Farawave, Farapulse PFA	This multicentre study evaluated PFA in 311 patients with AF across three French centres. The cohort included 53% with paroxysmal AF, 35% with persistent AF, and 11% with long-standing persistent AF. After 1 year,	This was a single arm multicentre study. Evidence from larger, multicentre or UK based

pentaspline pulsed field ablation catheter: The initial French experience. Archives of cardiovascular diseases.	system (Boston Scientific) n=311	the overall freedom from arrhythmia recurrence was 77.6%, with significantly higher rates in paroxysmal AF patients (88.4%) compared to persistent AF (69.7%, p<0.001) and long-standing persistent AF (49.0%, p<0.001). Additional non-pulmonary vein ablation was performed in 104 patients. Major complications occurred in 2.6% of patients (4 tamponades, 2 strokes, and 1 coronary spasm). Factors predictive of recurrence included left atrium size, CHA2DS2-VASc score, AF type, and the presence of AF at the start of the procedure, with the latter independently associated with recurrence (HR 2.04, 95% CI 1.10 to 3.77).	real-world studies has been included in the prioritised evidence.
Cochet H, Nakatani Y, Sridi-Cheniti S et al. (2021). Pulsed field ablation selectively spares the oesophagus during pulmonary vein isolation for atrial fibrillation. Europace 23(9): 1391-1399.	Prospective clinical study, comparative Farawave, Farapulse PFA system (Boston Scientific) n=41 3 months	This study compared extra-atrial injuries after PVI using PFA versus thermal methods (radiofrequency and cryoballoon) in 41 paroxysmal AF patients. Cardiac magnetic resonance (CMR) imaging before, acutely (less than 3 hours), and 3 months post-ablation assessed oesophageal, aortic, and phrenic nerve injuries. Thermal methods caused a high rate of oesophageal lesions (43%) due to direct contact with the oesophagus, while no oesophageal lesions occurred with PFA (0%, p<0.001), despite similar contact rates. Aortic lesions were observed in 43% of thermal ablation patients and 33% of PFA patients (p=0.52). Three-month follow-	This was a small comparative clinical study. Evidence from larger, multicentre or UK based real-world studies has been included in the prioritised evidence. This study was also included in the systematic review and meta-analysis by Amin (2024) in the

		up showed complete resolution of oesophageal and aortic injuries with no clinical complications in any patient.	main evidence.
Davong B, Adeliño R, Delasnerie H et al. (2023). Pulsed-field ablation on mitral isthmus in persistent atrial fibrillation. JACC: Clinical Electrophysiology 9: 1070-1081.	Prospective single arm preliminary data study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=45 Mean 107.8 days (3.5 months)	This study evaluated the feasibility and safety of mitral isthmus (MI) ablation in addition to PVI and PW ablation with PFA. Everyone achieved complete MI block. Three people presented with complications, including 2 cases (4.4%) of reversible and nonfatal coronary spasm.	Comparative evidence from larger multicentre studies was included in the main evidence.
De Becker B, Haddad M, De Smet M, et al. (2024). Procedural performance and outcome after pulsed field ablation for pulmonary vein isolation: comparison with a reference radiofrequency database. European Heart Journal Open 4: 1-8.	Retrospective, propensity score matched study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=322 6 months	This study evaluated the procedural performance, efficacy, safety, and durability of PFA compared with a dataset of patients receiving optimised RFA. Pulsed field ablation–guided PVI was obtained in everyone with a procedure time of 47 minutes (compared to 71 minutes in RFA, p<0.0001) and a fluoroscopy time of 15 minutes (compared to 11 minutes in RFA, p<0.0001).	Prospective comparative and randomised evidence with longer follow up was included in the main evidence.
Della Rocca DG, Marcon L, Magnocavallo M et al (2024). Pulsed electric field, cryoballoon, and	Retrospective, propensity score-matched study n=1572	PVI-only ablation outcomes were compared with CBA and RFA in people with PAF. First pass isolation of PVs was statistically significantly higher in PFA (98.8%), compared with CBA (81.5%) and RFA	This study was only based in Italy and used retrospective propensity score-

radiofrequency for paroxysmal atrial fibrillation ablation: a propensity score-matched comparison. Europace 26: 1-10.	Mean 12.3 months Farawave, Farapulse PFA system (Boston Scientific)	(73.1%, p<0.001). Overall complication rates approached statistical significance in favour of PFA (3.4%), compared with CBA (8.6%) and RFA (5.5%, p=0.052). No statistically significant difference in 1-year estimates of freedom from any atrial arrhythmia in PFA (79.3%), CBA (72.4%) and RFA (72.4%, p=0.24).	matched data. EU-wide registry data and UK-based real-world evidence was included in the prioritised evidence. This study was also included in the systematic review and meta-analysis by de Campos (2024) in the main evidence.
Dello Russo A, Tondo C, Schillaci, V et al. (2023). Intracardiac echocardiography-guided pulsed-field ablation for successful ablation of atrial fibrillation: a propensity-matched analysis from a large nationwide multicenter experience. Journal of interventional cardiac electrophysiology 67: 1257–1266	Retrospective propensity-matched analysis n= 556 Farawave, Farapulse PFA system (Boston Scientific) Follow up not reported.	This study aimed to assess whether the use of intracardiac echocardiography could improve procedural parameters in a people having PAF. No major procedure-related adverse events were reported. The authors conclude that use of intracardiac echocardiography to guide PFA was not associated with an improvement in procedural metrics.	Larger studies with prospective registry or randomised evidence for this technology was included in the key evidence.
Dello Russo A, Compagnucci P, Anselmino M, et	Retrospective propensity-matched	This study compared PFA with very high-power short-duration RFA for the	Larger prospective studies that

al. (2024). Pulsed field vs very high-power short-duration radiofrequency ablation for atrial fibrillation: Results of a multicenter, real-world experience. Heart Rhythm 21: 1526-1536.	analysis study of prospectively collected data, multi-centre Farawave, Farapulse PFA system (Boston Scientific) n=534 Median 12 months	treatment of paroxysmal or persistent AF. PFA was associated with more common use of general anaesthesia (p<0.001), shorter procedural times (70 minutes for PFA; 100 minutes for RFA; p<0.001), and longer fluoroscopy exposure (15 minutes for PFA; 7 minutes for RFA; p<0.001) compared with very high-power short-duration RFA ablation. The 12-month survival free from recurrent atrial tachyarrhythmia was similar between groups, both overall (75% for PFA; 76% for RFA; log-rank p=0.73) and in propensity score-matched people (n=342; 75% for PFA; 77% for RFA; log-rank p=0.980).	compared with current NHS standard of care were included in the main evidence.
Del Monte A, Fernández C, Vetta M, et al. (2023). Quantitative assessment of transient autonomic modulation after single-shot pulmonary vein isolation with pulsed-field ablation. Journal of Cardiovascular Electrophysiology 34: 2393-2397.	Prospective clinical study, comparative, single centre Farawave, Farapulse PFA system (Boston Scientific) n=76 Periprocedural outcomes	This study sought to investigate the degree and acute vagal modulation induced during PVI compared with single-shot thermal ablation. The vagal response after PVI almost disappeared in the thermal ablation group but persisted in the PFA group. Intraprocedural vagal reactions occurred more frequently with PFA than thermal ablation (70% compared to 28%, p=0.001). Heart rate 24 hours post-PVI increased more with thermal ablation than with PFA (16.5 vs 2.6 bpm, p<0.001). PVI with the Farapulse system is associated with only transitory and short-lasting vagal effects which recover almost completely within a few minutes after ablation.	Larger prospective and randomised clinical studies for this technology were included in the main evidence. Clinical outcomes at longer follow ups were also reported in the studies in the main evidence.

Del Monte A, Giovanni Della Rocca D, Pannone L, et al (2024). Pulsed field ablation of the right superior pulmonary vein prevents vagal responses via anterior right ganglionated plexus modulation. Heart Rhythm 21: 780-787.	Prospective clinical study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=76 Median 8 months	This study aimed to assess whether PFA-induced transient anterior-right ganglionated plexus modulation when targeting the right superior PV before any other PVs effectively prevents intraprocedural vagal responses. It was concluded that PVI with PFA frequently induced vagal responses when initiated from the left superior PV. It was also noted that a right superior PV-first approach promoted transient heart rate increase and reduced vagal response occurrence.	Larger prospective or randomised studies with longer follow up and more clinical outcomes were included in the main evidence.
Ekanaem E, Reddy VK, Schmidt B et al (2022). Multi-national survey on the methods, efficacy, and safety on the post-approval clinical use of pulsed field ablation (MANIFEST-PF). Europace 24: 1256 -1266.	Retrospective survey study (part of the MANIFEST-PF study) n=1758 Follow-up not reported Farawave, Farapulse PFA system (Boston Scientific)	There were no oesophageal complications or phrenic nerve injuries reported in this centre-level analysis of 24 EU centres. Major complication rate was 1.6%, including pericardial tamponade (1%), stroke (0.4%), and stroke-related death. Minor complications were primarily vascular. Rare complications included coronary artery spasm, haemoptysis and dry cough.	This was a centre-level analysis of the 24-centres included in the MANIFEST-PF study. A more recent, patient-level analysis of the same centres was included in the prioritised evidence.
Erhard N, Englert F, Prommersberger S, et al. (2024). Focal pulsed field ablation in complex atrial tachycardia: First clinical experience and 1-year outcome. Heart Rhythm: 1-8	Retrospective single arm study, single centre Centauri PFA system with TactiCath catheter (Abbott) or INTELLANAV STABLEPOINT	This study assessed the feasibility, safety, and long-term outcome of focal PFA for ablation of complex atrial tachycardia (AT). Focal PFA of complex AT substrates was found to be safe and efficient. Acute procedural success was accomplished in everyone. Mean procedural duration was 102.7 minutes, with left atrial dwell time of	A larger prospective study with this technology was included in the main evidence.

	catheter (Boston Scientific) n=34 12-month	75.0 minutes. Mean fluoroscopy duration was 8.7 minutes. No complications occurred and recurrence of any AT occurred in 15 people (44.1%).	
Falasca Zamponi A, Olsen J, Scheel S et al. (2024). Procedural efficiency is enhanced combining the pentaspline pulsed field ablation catheter with three-dimensional electroanatomical mapping system for pulmonary vein isolation. Journal of interventional cardiac electrophysiology.	Retrospective comparative analysis Farawave, Farapulse PFA system n=248 Periprocedural outcomes only	This study aimed to evaluate the effects of integration of 3D-electroanatomical mapping with PFA during PVI, compared with conventional fluoroscopic guidance. There was no statistically significant difference in overall procedure time between groups (p=0.22). Acute procedural success was achieved in all people and there were no major complications in either group.	Larger, prospective studies with more clinical outcomes and longer follow up were included in the main evidence.
Futing A, Reinsch N, Höwel D (2022). First experience with pulsed field ablation as routine treatment for paroxysmal atrial fibrillation. Europace 24: 1084–1092.	Prospective single arm clinical study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=30 90 days	This study was the first-in-human study of PVI using this CE-marked PFA system and assessed phrenic nerve function, both pre and post ablation. It was observed that PVI using PFA for PAF appears to be safe and feasible. Procedure times were found to be homogeneous (median 116 minutes), and Left atrial dwell time short (median 29 minutes) with a median fluoroscopy time of 26 minutes. There were no in-hospital and 30-day follow up adverse events and 97% of patients were in sinus rhythm after 90 days.	Larger, more recent prospective and randomised studies with longer follow up were included in the main evidence.

Futing A, Reinsch N, Brokkaar L, et al. (2023). Bronchial safety after pulsed field ablation for paroxysmal atrial fibrillation. Circulation: Arrhythmia and Electrophysiology 16: 191-196.	Prospective single arm clinical study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=30 30 days	This study aimed to assess the bronchial effects after pulmonary vein isolation using PFA for paroxysmal atrial fibrillation. Pulmonary vein isolation using PFA for paroxysmal atrial fibrillation was not found to cause thermal lesions in the bronchial system. It was identified that use of a straight-tip, extra stiff guide wire for the over-the-wire PFA catheter can lead to asymptomatic bleeding in the bronchial system without clinical relevance at 30-day follow-up (experienced by 12 of 30 patients). However, all patients were asymptomatic with clinically stable haemoglobin levels at 30-days.	Larger, prospective studies with longer follow up were included in the main evidence.
Gerstenfeld EP, Mansour M, Whang W et al (2024). Autonomic effects of pulsed field vs thermal ablation for treating atrial fibrillation: Subanalysis of ADVENT. JACC: Clinical Electrophysiology 7: 1634-1644.	Secondary analysis of an RCT (ADVENT) n=379 12 months Farawave, Farapulse PFA system (Boston Scientific)	This study explored the relationship between heart rate, heart rate variability and autonomic function after PFA compared with TA. They found the effect of PFA on the autonomic nervous system was attenuated compared with TA but the relationship with long-term freedom from AF and symptomatic bradycardia/pauses after AF ablation could not be answered with this study.	This is a secondary analysis of the ADVENT RCT. The main publication is included in the prioritised evidence. This study does not add to the discussion of safety and efficacy of the procedure so was deprioritised.
Gunawardene M, Frommeyer G, Ellermann C, et al (2023). Left atrial posterior wall	Prospective clinical study, multi-centre Farawave, Farapulse PFA	This study explored the efficacy and safety of left atrial posterior wall isolation performed by non-thermal pulsed field ablation in	Larger prospective and randomised clinical

isolation with pulsed field ablation in persistent atrial fibrillation. J. Clin. Med 12: 6304 - 6322	system (Boston Scientific) n=79 Mean 354 days	catheter ablation for persistent atrial fibrillation. The authors identified no difference regarding acute procedural and clinical outcome compared to the PVI-only cohort. Left atrial posterior wall isolation was performed successfully in everyone, only two minor complications occurred, and freedom from atrial arrhythmias was reported among 79.3% of people. From these findings, left atrial posterior wall isolation guided by PFA was reported to be feasible and safe in people undergoing catheter ablation for persAF and demonstrate favourable outcomes.	studies for this technology were included in the main evidence.
Gunawardene M, Harloff T, Jularic M, et al. (2024). Contemporary catheter ablation of complex atrial tachycardias after prior atrial fibrillation ablation: pulsed field vs. radiofrequency current energy ablation guided by high-density mapping. Europace 26: euae072.	Prospective propensity score matched clinical study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=56 Median 401 days	This study aimed to explore the efficacy of PFA vs RFA in people undergoing repeat catheter ablation. It was reported that PFA of post-ablation left atrial tachycardia using a pentaspline catheter is feasible, safe (no major complications), and faster (PFA: 121 vs. RFA: 190 minutes, $p<0.0001$) but less effective (arrhythmia free survival PFA for 63% compared to 87% for RFA [HR 2.91, p=0.0473]) compared to standard RFA ablation after one year of follow-up.	Larger, randomised studies in this technology have been included in the main evidence.
Guo F, Wang J, Deng Q, et al. (2023). Effects of pulsed field ablation on autonomic nervous system in paroxysmal atrial	Prospective pilot clinical study, single centre LEAD-PFA system (Jinjiang Electronic	This study evaluated the effect of a PFA system for performing PVI on the autonomic nervous system. It was reported that PFA does not induce nerve injury during pulmonary vein isolation for paroxysmal AF. Acute	This technology was not prioritised into the main evidence as it is not used in the UK yet.

fibrillation: A pilot study. Heart Rhythm 20: 329-338.	Science and Technology Co.) n=18 8 months	electrical isolation was achieved in 100% of people. Mean procedural time was 64.1 minutes, and mean fluoroscopy time was 12.3 minutes. Serum nerve injury biomarkers did not show any changes either immediately, or 24 hours post procedure ($p>0.05$), and heart rate variability did not differ pre or post-ablation ($p>0.05$).	Larger, randomised studies with longer follow up for other technologies were included.
Katov L, Teumer Y, Bothner C, et al. (2024). Pulmonary vein isolation with pulsed field ablation and size-adjustable cryo-balloon: a comparative procedural analysis of first-time use. J. Clin. Med 13: 3113.	Prospective comparative clinical study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=100 24 hours	This study compared the procedural data and safety of two new PVI techniques in first-time users – the thermal size-adjustable CBA and PFA system. It was concluded that both systems demonstrate good effectiveness (acute PVI was achieved in all cases for both PFA and CBA) and safety (PFA 0% complications compared to CBA 4%, $p=0.213$) during PVI. However, the PFA group had a significantly shorter procedure duration (59 minutes for PFA compared to 76.5 minutes for CBA).	Larger, randomised studies for this technology with longer follow up were included in the main evidence.
Kawamura I, Neuzil P, Shivamurthy P, et al. How does the level of pulmonary venous isolation compare between pulsed field ablation and thermal energy ablation (radiofrequency, cryo, or laser)? EP Europace. 2021;23(11):1757-1766	Propensity score matched study Farawave, Farapulse PFA system (Boston Scientific) n=59 75 days	This study compared PVI success between PFA and TA. After 75 days, there was no statistically significant difference in isolation success in the left and right sided PV areas. The authors conclude that catheter-based PVI with PFA creates chronic PV antral isolation areas as encompassing as thermal energy ablation.	Prospective, large registry or randomised evidence was prioritised for this technology. This study was also included in the systematic review and meta-analysis by de Amin (2024) in the

			main evidence.
Kordic L, Jurišić Z, Brešković T, et al. (2024). Safety and effectiveness of additional left atrial posterior wall ablation using pulsed field ablation for persistent and long-standing persistent atrial fibrillation patients. J. Cardiovasc. Electrophysiol 35: 1525–1535.	Retrospective observational study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=94 Median 13 months	This study assessed the long-term freedom from atrial fibrillation, atrial flutter, and atrial tachycardia, as well as the safety and feasibility of left atrial posterior wall PFA. It was concluded that the addition of posterior wall ablation to PVI using multipolar PFA was safe and did not significantly influence the ablation time. The acute ablation success rate was 100%. The best outcomes were observed in people without extensive LA fibrosis.	Prospective, large registry or randomised evidence was prioritised for this technology.
Kueffer T, Baldinger S, Servatius H, et al. (2022). Validation of a multipolar pulsed-field ablation catheter for endpoint assessment in pulmonary vein isolation procedures. Europace 24: 1248–1255.	Prospective registry study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=56 3.2 months	This study aimed to validate the performance of a multipolar PFA catheter compared to a standard pentaspline 3D mapping catheter for endpoint assessment of PVI. It was concluded that the PFA catheter allows reliable endpoint assessment for PVI. Acute PVI was achieved in 100% of PVs and the accuracy of PV assessment with the PFA catheter after the standard ablation protocol was 91%.	Prospective comparative evidence from larger registry or randomised studies were prioritised for this technology.
Kueffer T, Madaffari A, Thalmann G, et al (2023). Eliminating transseptal sheath exchange for pulsed field ablation procedures using a direct over-the-needle transseptal access with the	Prospective clinical study, multi-centre Farawave, Farapulse PFA system (Boston Scientific) n=100	This study aimed to evaluate the feasibility and safety of a simplified workflow using the PFA sheath. It was concluded that an over-the-needle transseptal puncture directly with the PFA sheath proved feasible (successfully performed in all patients) and safe (no observed complications). It was noted that the simplified workflow has the potential to reduce	Larger, comparative and randomised evidence for this technology was prioritised.

Faradrive sheath. Europace 25: 1500–1502.	Follow-up NR	the risk of air embolism, shorten procedure time, and reduce costs.	
Kueffer T, Bordignon S, Neven K et al (2024). Durability of pulmonary vein isolation using pulsed-field ablation: results from the multicenter EU-PORIA registry. JACC: Clinical Electrophysiology 10: 698-708.	Secondary analysis of EU-PORIA n=144 Median 5 months Farawave, Farapulse PFA system (Boston Scientific)	This study reported PVI durability in people who had redo procedures after index PFA (median 7 months after first procedure; subgroup of EU-PORIA Registry). Durable isolation was observed in 71% of the pulmonary veins during the redo procedure, and 38% of all people showed durable isolation of all pulmonary veins.	Most outcomes reported in this study were reported in Schmidt (2023) in the main evidence. This study does not add to the discussion of safety and efficacy of the procedure so was deprioritised.
Kueffer T, Stefanova A, Madafari A, et al (2024). Pulmonary vein isolation durability and lesion regression in patients with recurrent arrhythmia after pulsed-field ablation. Journal of Interventional Cardiac Electrophysiology 67: 503–511.	Retrospective observational study, single centre Farapulse PFA system (Boston Scientific) n=341 12 months	This study aimed to assess PVI durability on a per-vein and per-person level. In those people with arrhythmia recurrence after PFA PVI using a first-generation PFA device, durable isolation was observed in 63% of the veins and 21% of the people showed durable isolation of all previously isolated veins. Reconnection was not different with different catheter sizes, with observations of 5/18 (28%) reconnections for the 35 mm device and 35/92 (38%) reconnections for the 31 mm device (p=0.575).	Prospective evidence from larger, randomised studies with this technology were prioritised.
Kueffer T, Stettler R, Maurhofer J et al (2024). Pulsed-field vs cryoballoon vs radiofrequency ablation:	Prospective registry study (single centre, Switzerland) Farawave, Farapulse PFA	In this study, people with persistent AF had PVI with PFA, RFA or CBA. There was no statistically significant difference in acute safety events: 2.3%, 2.6% and 0.8% of PFA, CBA and RFA	This was a single centre study. Evidence from larger, multicentre or UK based

Outcomes after pulmonary vein isolation in patients with persistent atrial fibrillation. Heart Rhythm 21: 1227-1235.	system (Boston Scientific) n=533 12 months	groups, respectively. Estimated freedom from atrial arrhythmia at 1 year was 62.1%, 55.3% and 48.3% for CBA, PFA and PFA, respectively. There was a statistically significant difference favouring PFA (p=0.010) and CBA (p=0.009) over RFA but no statistically significant difference between CBA and PFA (p=0.79)	real-world studies has been included in the prioritised evidence.
Kueffer T, Tanner H, Madaffari A, et al. (2024). Posterior wall ablation by pulsed-field ablation: procedural safety, efficacy, and findings on redo procedures. Europace 26: 1–10.	Retrospective observational study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=215 12 months	This study aimed to provide data on the safety and efficacy of pulsed-field ablation for posterior wall ablation. It was concluded that posterior wall ablation with the pentaspline PFA catheter can be safely and efficiently performed, with a high durability observed during redo procedures. Posterior wall ablation was successful in everyone and 1-year arrhythmia-free outcome was 53%. Severe adverse events (cardiac tamponade and vascular access complication) were observed in 1 person (0.9%) and 26 people (12%) had redo procedures.	Prospective evidence from larger, randomised studies with this technology were prioritised.
Kuroki K, Whang W, Eggert C, et al. (2020). Ostial dimensional changes after pulmonary vein isolation: Pulsed field ablation vs radiofrequency ablation. HeartRhythm 17: 1528-1535.	Retrospective observational study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=80 3 months	This study compared the effect of PFA compared to RFA on the incidence and severity of PV narrowing or stenosis. It was concluded that the incidence and severity of PV narrowing or stenosis after PV isolation is virtually eliminated with PFA. PV ostial diameters decreased significantly (p<0.001) less with PFA than with RFA. Mild, moderate or severe narrowing was not	Prospective evidence from larger, randomised studies with this technology were prioritised. This outcome was also reported in detail in other

		observed in any of the PV cohort after PFA compared with between 1.2% and 9% of the RFA cohort (p<0.001).	prioritised studies.
Lee X, Freeman B, Gunthorpe N, et al. (2024). Pulsed field ablation of atrial fibrillation: an initial Australian single centre experience. Heart, Lung and Circulation 33: 46-54.	Prospective clinical study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=97 6 months	This study aimed to present an initial single-centre Australian experience of PFA for AF ablation. It was concluded that pulsed field ablation can be performed safely and efficiently, with encouraging efficacy in early follow-up. All pulmonary veins were successfully isolated acutely. The median procedure time was 74 minutes and two (2%) pseudoaneurysm vascular access complications occurred.	Prospective evidence from larger, randomised studies with longer follow up for this technology were prioritised.
Lemoine M, Fink T, Mencke C, et al. (2023). Pulsed-feld ablation-based pulmonary vein isolation: acute safety, efficacy and short-term follow-up in a multi-center real world scenario. Clinical Research in Cardiology 112: 795–806.	Prospective single arm observational study, multi centre Farawave, Farapulse PFA system (Boston Scientific) n=138 12 months	This study aimed to assess the efficacy, safety and follow-up of PFA-based PVI in an early adopter routine care setting. It was concluded that PFA-based PVI is acutely highly effective and associated with a beneficial safety and low recurrence rate. PVI was achieved in all everyone with a mean procedure time of 78 minutes. The 1-year follow-up showed freedom of arrhythmia in 90% in people with paroxysmal AF and 60% with persistent AF (p=0.015).	Prospective evidence from larger, randomised studies with this technology were prioritised. This study was also included in the systematic review and meta-analysis by de Campos (2024) in the main evidence.
Magni F, Mulder B, Groenveld H, et al. (2022). Initial experience with pulsed field ablation for atrial	Prospective single arm clinical study, single centre	This study aimed to describe procedural findings and acute safety and efficacy in the first 100 people treated with the PFA catheter. It was concluded that use of the	Prospective evidence from larger, randomised studies with this

fibrillation. Front. Cardiovasc. Med 9:01-09.	Farawave, Farapulse PFA system (Boston Scientific) n=100 12 months	PFA catheter for pulmonary vein isolation (PVI) is safe, fast, and easy to learn. In everyone (100%), all PVs were confirmed to be isolated, no difference in procedure times was observed between senior and junior operators (46.9 compared to 45.9 minutes), and the only complications observed were 2 cases of bleeding at the site of percutaneous access.	technology were prioritised.
Malyshev Y, Neuzil P, Petru J, et al. (2024). Nitroglycerin to ameliorate coronary artery spasm during focal pulsed-field ablation for atrial fibrillation. JACC: Clinical Electrophysiology 10: 885 – 896.	Prospective single arm clinical study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=39 Follow up NR	This study aimed to assess the vasospastic potential of a focal PFA catheter with a narrower electrical field and develop a preventive strategy with nitroglycerin. It was concluded that ablation of the Cavo tricuspidisthmus using a focal PFA catheter routinely provokes right coronary vasospasm, with moderate-severe vasospasm observed in 80% of people who were treated without nitroglycerin. Pretreatment with high doses of parenteral nitroglycerin prevents severe spasm, with no observed cases of severe spasm and only 20% of people experiencing mild-moderate vasospasm.	Prospective evidence from larger, randomised studies with this technology were prioritised.
Mansour M, Gerstenfeld EP, Patel et al (2024). Pulmonary vein narrowing after pulsed field versus thermal ablation. Europace 26: 1-9.	Secondary analysis of an RCT (ADVENT) n=607 12 months Farawave, Farapulse PFA system (Boston Scientific)	This study explored methods of measuring PV narrowing after PFA. Almost half of all PFA PV diameters did not decrease, but the majority (80%) of RF PVs decreased, regardless of PV anatomic location.	PV narrowing outcomes were already reported in the primary publication from this RCT, and this has been included in the prioritised evidence. This is an

			exploratory analysis.
Maurhofer J, Tanner H, Kueffer T, et al. (2024). Pulsed-field ablation for repeat procedures after failed prior thermal ablation for atrial fibrillation. Heart Rhythm 5: 257-265.	Prospective single arm clinical study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=186 12 months	This study aimed to summarise the initial experiences of people undergoing repeat procedures using PFA. The authors concluded that PFA is a versatile and safe option for repeat procedures after failed prior thermal ablation. Major complications occurred in 1 person (transient ischemic attack 0.5%) and freedom from arrhythmia recurrence in Kaplan-Meier-analysis was 78% after 6 months and 54% after 12 months.	Prospective evidence from larger, randomised studies with this technology were prioritised.
Maurhofen J, Kueffer T, Madaffari A, et al. (2024). Pulsed-field vs. cryoballoon vs. radiofrequency ablation: a propensity score matched comparison of one-year outcomes after pulmonary vein isolation in patients with paroxysmal atrial fibrillation. Journal of Interventional Cardiac Electrophysiology 67:389–397.	Propensity score matched registry study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=200 12 months	This study compared procedural and 1-year follow-up data of people with paroxysmal atrial fibrillation (AF) undergoing PVI using PFA, cryoballoon ablation (CBA) and radiofrequency ablation (RFA). It was concluded that freedom from any atrial tachyarrhythmia 1 year after PVI using PFA was favourable and at least as good as for PVI with CBA or RFA (85% for PFA compared to 66.2% for CBA and 73.8% for RFA).	Prospective evidence from larger registries or randomised studies with this technology were prioritised. This study was also included in both of the systematic review and meta-analyses in the main evidence.
Metzner A, Fiala M, Vijgen J, et al. (2024). Long-term outcomes of the pentaspline pulsed-field ablation catheter	Prospective clinical study, multi centre Farawave, Farapulse PFA	This study aimed to evaluate the long-term efficacy and safety of PFA using the pentaspline catheter for PAF. It was concluded that PVI using a pentaspline PFA catheter was effective in	Prospective evidence from larger, randomised studies with this technology

for the treatment of paroxysmal atrial fibrillation: results of the prospective, multicentre FARA-Freedom Study. Europace 26: 1-6.	system (Boston Scientific) n=180 12 months	treating PAF (all PVs were successfully isolated) and also demonstrated favourable safety (safety endpoints were only demonstrated in 2 people (1%), including 1 tamponade and 1 transient ischaemic attack).	were prioritised.
Musikantow D, Neuzil P, Petru J, et al. (2023). Pulsed field ablation to treat atrial fibrillation. JACC: Clinical Electrophysiology 9: 481-493.	Combined retrospective and prospective clinical study, multi centre Farawave, Farapulse PFA system (Boston Scientific) n=120 3 months	This study aimed to assess the impact of pulsed field ablation on the ganglionated plexi in patients undergoing PVI. It was concluded that PFA has minimal effect on GP. Unlike with thermal ablation, the mechanism by which PFA treats atrial fibrillation is mediated solely by durable PVI.	Prospective evidence from larger, randomised studies with longer follow up done with this technology were prioritised. This study was also included in the systematic review and meta-analysis by Amin (2024) in the main evidence.
My I, Lemoine M, Butt M, et al. (2023). Acute lesion extension following pulmonary vein isolation with two novel single shot devices: Pulsed field ablation versus multielectrode radiofrequency balloon. J Cardiovasc Electrophysiol 34: 1802–1807.	Prospective clinical study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=60 12 months	This study aimed to compare the acute lesion extent after PVI induced by PFA and RF balloon ablation (RFB). It was concluded that PFA delivers larger acute lesion areas and higher troponin release upon successful PVI than multielectrode RFB-based PVI in this single-centre series. Acute PVI was achieved in everyone in both groups. The total posterior ablation area was significantly larger in PFA than RFB (20.7 cm^2 vs. 7.1 cm^2; $p<0.001$). The posterior	Prospective evidence from larger, randomised studies with this technology were prioritised. This is not a comparator that is used routinely in the NHS. This study was also included in

		ablation area for each PV resulted in larger lesions after PFA versus RFB.	both the systematic review and meta-analyses (2024) in the main evidence.
Nakatani Y, Sridi-Cheniti S, Cheniti G, et al. (2021). Pulsed field ablation prevents chronic atrial fibrotic changes and restrictive mechanics after catheter ablation for atrial fibrillation. Europace 23: 1767-1776.	Prospective clinical study, multi centre Farawave, Farapulse PFA system (Boston Scientific) n=63 9 months	This study aimed to compare the left atrial structural and mechanical characteristics after PFA compared to thermal ablation. It was concluded that pulsed field ablation induces large acute late gadolinium enhancement without microvascular damage or intramural haemorrhage. In the acute stage, late gadolinium enhancement volume was 60% larger after PFA vs. thermal ablation ($p<0.001$), and oedema on T2 imaging was 20% smaller ($p=0.002$). In the chronic stage, most acute late gadolinium enhancement had disappeared after PFA, whereas most late gadolinium enhancement persisted after thermal ablation.	Prospective evidence from larger, randomised studies with more clinical outcomes for this technology were prioritised. This study was also included in both the systematic review and meta-analyses in the main evidence.
Ollitrault P, Chaumont C, Font J, et al. (2024). Superior vena cava isolation using a pentaspline pulsed-field ablation catheter: feasibility and safety in patients undergoing atrial fibrillation catheter ablation. Europace 26: 1-7.	Prospective clinical study, multi centre Farawave, Farapulse PFA system (Boston Scientific) n=105 3 months	This study aimed to assess the feasibility and safety of PFA-based superior vena cava isolation. It was concluded that superior vena cava isolation using a pentaspline PFA catheter is feasible and safe. Acute superior vena cava isolation was achieved in everyone. Transient high-degree sinus node dysfunction occurred in 5 out of 105 (4.7%) people, with no recurrence, and at the	Prospective evidence from larger, randomised studies with longer follow up and broader scope for this technology were prioritised.

		3-month follow-up visit, no complication occurred.	
Orczykowski M, Urbanek P, Bodalski R, et al. (2024). Acute safety and efficacy of pulsed field ablation for atrial fibrillation in a Polish cohort of patients. Polish Heart Journal (Kardiologia Polska) 82: 658-659.	Prospective cohort study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=150 6 months	This study aimed to assess acute safety, efficacy, and feasibility of ablation with the use of PFA in a high-volume Polish centre. It was concluded that the procedure is safe, feasible and effective. The procedure was not observed to entail any serious complications. Most pulmonary veins were successfully isolated (99.3%) and first-pass PVI was achieved using the multispline PFA catheter in most people (96.6%), with a mean time of 25 minutes between first and last ablation.	Prospective evidence from larger, multicentre randomised studies with longer follow up for this technology were prioritised.
Osmancik P Bacova B, Hozman M, et al. (2024). Myocardial damage, inflammation, coagulation, and platelet activity during catheter ablation using radiofrequency and pulsed-field energy. JACC: Clinical Electrophysiology 10: 463-474.	Prospective randomised controlled trial, single centre Farawave, Farapulse PFA system (Boston Scientific) n=65 24 hours	This study aimed to compare the systemic response in people undergoing pulmonary vein isolation using pulsed-field and radiofrequency energy. It was concluded that pulsed-field ablation was associated with a similar degree of platelet/coagulation activation (more than 50%), and slightly lower inflammatory response than people undergoing PVI using radiofrequency. However, pulsed-field ablation was associated with increased myocardial damage.	Prospective evidence from larger, randomised studies with longer follow up and more clinical outcomes for this technology were prioritised. This study was also included in the systematic review and meta-analysis by de Campos (2024) in the main evidence.
Osmancik P, Bacova B,	Prospective observational	This study aimed to compare the potential for haemolysis	Prospective evidence from

Herman D, et al. (2024). Periprocedural intravascular hemolysis during atrial fibrillation ablation. JACC: Clinical Electrophysiology 10: 1660-1671.	clinical study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=70 1 day	during PVI with PFA vs RFA. It was concluded that PFA is associated with significant periprocedural haemolysis but the likelihood of significant renal injury is uncommon. At 24 hours with PFA, the concentration of lactate dehydrogenase and indirect bilirubin increased, whereas haptoglobin decreased significantly (all p<0.001), whereas RFA caused only small changes in lactate dehydrogenase and haptoglobin concentrations (p=0.03) and no change in bilirubin.	larger, randomised studies with longer follow up and more clinical outcomes for this technology were prioritised. Also Mohanty (2024) in the main evidence explored the same research question around haemolysis and acute kidney injury.
Plank K, Bordignon S, Urbanek L, et al. (2023). Early recurrences predict late therapy failure after pulsed field ablation of atrial fibrillation. J. Cardiovasc. Electrophysiol 34: 2425–2433.	Retrospective analysis, single centre Farawave, Farapulse PFA system (Boston Scientific) n=231 Median 367 days	This study aimed to report the rate of early recurrences and their effect on clinical midterm outcomes following PFA-based PVI. It was concluded that was an independent predictor for LR and was recorded in 21% of people after PFA-PVI (HR 3.370: p<0.001). No difference in the rate of LRs among people experiencing early recurrence of atrial tachycardia before or after 45 days was observed.	Prospective evidence from larger, randomised studies for this technology were prioritised.
Popa M, Bahlke F, Kottmaier M, et al. (2023). Myocardial injury and inflammation following pulsed field ablation and very high-power short-duration ablation for atrial	Retrospective analysis, single centre Farawave, Farapulse PFA system (Boston Scientific)	This study aimed to determine the extent of myocardial injury and systemic inflammation following PFA, high power short duration, and standard RFA using established biomarkers. It was concluded that PFA was associated with the highest myocardial injury	Prospective evidence from larger, randomised studies with more clinical outcomes for this technology were

fibrillation. J. Cardiovasc. Electrophysiol 35: 317-327.	n=179 12 months	and the lowest inflammatory reaction among the investigated ablation techniques. Post ablation high sensitivity cardiac troponin release was significantly higher with PFA ($p<0.001$), creatine kinase and creatine kinase-MB release increased significantly with PFA compared to RFA ($p<0.001$), and PFA was associated with the lowest elevation in white blood cell count ($p<0.001$).	prioritised. This study was also included in the systematic review and meta-analysis by de Campos (2024) in the main evidence.
Rattka M, Mavrakis E, Vlachopoulou D, et al. (2024). Pulsed field ablation and cryoballoon ablation for pulmonary vein isolation: insights on efficacy, safety and cardiac function. Journal of Interventional Cardiac Electrophysiology 67: 1191–1198.	Prospective case control study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=114 12 months	This study aimed to compare outcomes of people undergoing either PFA or CBA for primary PVI. It was concluded that CBA and PFA for PVI are of similar efficacy when it comes to AF recurrence after 12 months (PFA: 70% compared to CBA: 61% free from AF/AT; $p=0.470$). However, PFA rather than CBA might induce left atrial reverse remodelling thereby contributing to left ventricular systolic function.	Evidence from larger, randomised studies for this technology were prioritised. This study was also included in the systematic review and meta-analysis by de Campos (2024) in the main evidence.
Reddy V, Neuzil P, Koruth J, et al. (2019). Pulsed field ablation for pulmonary vein isolation in atrial fibrillation. Journal of the American College of Cardiology 74: 315-326.	Prospective clinical study, multicentre Farawave, Farapulse PFA system (Boston Scientific) n=81 12 months	This study aimed to determine whether PFA allows durable PVI without damage to collateral structures. It was concluded that PFA preferentially affected myocardial tissue, allowing facile ultra-rapid PV isolation with excellent durability and chronic safety. All PVs were acutely isolated with an average procedure time of 92.2 minutes and a	Prospective evidence from larger, randomised studies for this technology were prioritised.

		fluoroscopy time of 13.1 minutes. Only 1 procedure-related pericardial tamponade was observed, with no other additional primary adverse events, and a 12-month freedom from arrhythmia estimate of 87.4%.	
Reddy V, Rackauskas G, Peich P, et al. (2020). Lattice-tip focal ablation catheter that toggles between radiofrequency and pulsed field energy to treat atrial fibrillation. Circ Arrhythm Electrophysiol 13: 483-495.	Prospective single arm clinical study, multi centre Sphere-9 Affera n=76 12 months	This study aimed to assess the capability of the lattice-tip catheter to permit focal PFA. It was concluded that the novel lattice-tip catheter could safely and rapidly ablate atrial fibrillation using either a combined RF/PF approach or an entirely PF approach. All lesion sets were acutely successful and no device-related complications were observed. However, postprocedural esophago-gastroduodenoscopy revealed minor mucosal thermal injury in 2 of 36 people with RF/PF.	A more recent publication of the same trials, but with more data was included in the main evidence for this technology. This study was also included in the systematic review and meta-analysis by Amin (2024) in the main evidence.
Reddy V, Dukkipati S, Neuzil P, et al. (2021). Pulsed field ablation of paroxysmal atrial fibrillation. JACC: Clinical Electrophysiology 7: 614-627.	Prospective single arm clinical study analysis, multi centre Farawave, Farapulse PFA system (Boston Scientific) n=121 12 months	This study sought to determine whether durable PVI using pulsed field ablation PFA translates to freedom from atrial fibrillation recurrence without an increase in adverse events. It was concluded that PVI with a “single-shot” PFA catheter results in excellent PVI durability and acceptable safety with a low 1-year rate of atrial arrhythmia recurrence. PVI was achieved in 100% of PVs with PFA alone. Primary adverse events occurred in 2.5% of people (2 pericardial effusions	Prospective evidence from larger, randomised studies for this technology were prioritised.

		or tamponade, 1 haematoma); with 1 transient ischaemic attack. Kaplan-Meier estimates for freedom from any atrial arrhythmia at 12-months were 78.5% for the entire cohort and 84.5% for the optimised biphasic energy PFA waveform cohort.	
Reinsch N, Futing A, Howel D, et al. (2022). Cerebral safety after pulsed field ablation for paroxysmal atrial fibrillation. Heart Rhythm 19: 1813-1818.	Prospective clinical study, single centre Farawave, Farapulse PFA system (Boston Scientific) n=30 30 days	This study aimed to investigate the occurrence of neurological deficits and SCL and/or SCE after PFA in paroxysmal atrial fibrillation. It was concluded that the incidence of MRI-detected asymptomatic thromboembolic cerebral events or lesions was as low as 3% among people treated with PFA for symptomatic paroxysmal AF. No neurological deficits occurred. Cerebral MRI scans were normal in 97% of people. While a single 7-mm cerebellar lesion was observed among 1 person (3%), the lesion had completely regressed at follow-up.	Prospective evidence from larger, randomised studies for this technology were prioritised. Data focusing on cerebral events has been covered in the prioritised publications.
Reinsch N, Futing A, Hartl S, et al. (2024). Pulmonary vein isolation using pulsed field ablation vs. high-power short-duration radiofrequency ablation in paroxysmal atrial fibrillation: efficacy, safety, and long-term follow-up (PRIORI	Retrospective analysis, single centre Farawave, Farapulse PFA system (Boston Scientific) n=410 12 months	This study aimed to the efficacy of PFA-PVI versus. high power short duration-RF PVI in terms of single-procedure arrhythmia-free outcome and safety in a real-world setting. It was concluded that both PFA and high-power short duration-RF were highly efficient and effective in achieving PVI in paroxysmal AF. The arrhythmia-free survival is comparable between treatments (PFA: 85%	Evidence from larger, studies for this technology were prioritised.

study). Europace 26: 2-7.		compared to high power short duration-RF: 79%; p=0.160). The PV reconnection rate was not different (PD: 30% compared to high power short duration-RF: 38%; p=0.372).	
Ruwald, Martin H, Johannessen, Arne, Hansen, Morten Lock et al. (2024). Focal pulsed field ablation and ultrahigh-density mapping - versatile tools for all atrial arrhythmias? Initial procedural experiences Journal of interventional cardiac electrophysiology 67(1): 99-109.	Prospective single arm clinical study n=51 14 days CENTAURI, Galvanize	This study included people with a range of atrial arrhythmias not just AF. First pass PVI rate was 97%, 100% isolation for any isthmus and 82% for left atrial posterior wall. One person had transient ST segment elevation, and 1 person had transient atrioventricular block.	Studies with focus on only atrial fibrillation were included in the main evidence. Studies with longer follow up and comparative evidence were also included in the main evidence.
Ruwald MH, Johannessen A, Hansen M et al. (2023). Pulsed field ablation in real-world atrial fibrillation patients: clinical recurrence, operator learning curve and re-do procedural findings. Journal of interventional cardiac electrophysiology 66(8): 1837-1848.	Prospective cohort study n=121 Mean 308 days Farawave, Farapulse PFA system	PVI was achieved with PFA-only in 119 (98%). 1 person had phrenic nerve palsy with only partial remission at follow-up. 18.2% of people had clinically significant recurrence or started anti-arrhythmic drugs. Kaplan–Meier event-free estimate at 365 days was 80% (88% for paroxysmal versus 69% for persistent).	Larger, randomised studies for this technology were included in the main evidence.
Schiavone M, Solimene F, Moltrasio M et al. (2024). Pulsed field ablation	Prospective single arm trial n= 249	All people in this analysis had left atrial posterior wall isolation during a redo procedure in a single centre. The authors reported that this	A larger, subgroup analysis of a multicentre registry study

technology for pulmonary vein and left atrial posterior wall isolation in patients with persistent atrial fibrillation. Journal of cardiovascular electrophysiology 35: 1101-1111.	Median 273 days Farawave, Farapulse PFA system	approach with PFA was feasible, and safe in real world practice, and was a viable alternative for people with PersAF. No major complications occurred. During a median follow-up of 273 days 17% of people had arrhythmic recurrence.	that focused on left atrial posterior wall isolation, with comparative and longer-term evidence was included in the main evidence.
Schipper, Jan-Hendrik, Steven, Daniel, Luker, Jakob et al. (2023). Comparison of pulsed field ablation and cryoballoon ablation for pulmonary vein isolation. Journal of cardiovascular electrophysiology 34: 2019-2026.	Retrospective comparative study n=108 Mean 273 days Farawave, Farapulse PFA system	This study compared outcomes from PFA and CBA. 1 person had transient phrenic nerve palsy in the CBA group. PFA procedures were shorter on average but this wasn't statistically significant (p=0.07). Two cardiac tamponades occurred in the PFA group (p= 0.495). There was no statistically significant difference in pain, assessed by amount of analgesic prescribing (p=0.598). Atrial arrhythmia freedom was 74% in PFA and 72% in CBA after 273 days on average. The PFA group had statistically significantly higher heart rate after 3 months (p=0.008).	Larger, prospective studies with longer follow-up were included in the key evidence. This study was also included in both the systematic review and meta-analyses in the main evidence.
Schmidt B, Bordignon S, Neven K et al (2023). EUropean real-world outcomes with Pulsed field ablatiOn in patients with symptomatic atRIAl fibrillation: lessons from the multi-centre EU-PORIA registry.	Retrospective centre-level registry study n=1233 Median 365 days Farawave, Farapulse PFA system	This publication reports findings from the multi-centre EUropean Real World Outcomes with Pulsed Field AblatiOn in Patients with Symptomatic AtRIAl Fibrillation (EU-PORIA) registry study. Median procedure time was 58 minutes, Major complication rate was 1.7%, including pericardial tamponade (1.1%), transient ischaemic attack or stroke (0.6%), of which 1 was fatal.	A registry study of similar size which collected data prospectively and at a patient-level, was included in the main evidence (MANIFEST-PF). The findings of this study

Europace 25: 1-11.		1-year Kaplan-Meier estimates of arrhythmia free survival was 74%, but differed depending on whether people had PAF (80%) or PersAF (66%). Reintervention was needed for recurrence of AF in 12% of people.	align with the findings of MANIFEST-PF.
Soubh N, Gronwald J, Haarmann H et al. (2024). Next-generation atrial fibrillation ablation: clinical performance of pulsed-field ablation and very high-power short-duration radiofrequency. Journal of interventional cardiac electrophysiology.	Retrospective comparative study n=82 6 months Farawave, Farapulse PFA system	RFA was compared with high-power short-duration radiofrequency ablation. At 6 months, there was no statistically significant difference in AF recurrence between groups (p=0.138), and both groups had statistically significant improvements in AF symptoms. Procedure time was statistically significantly shorted in the PFA group (p<0.001). There were no statistically significant differences in complications (p=0.366).	Larger, prospective studies with longer follow-up were included in the main evidence for this technology.
Stojadinovic P, Wichterle D, Peichl P et al. (2022). Autonomic changes are more durable after radiofrequency than pulsed electric field pulmonary vein ablation. JACC. Clinical Electrophysiology 8(7): 895-904.	Prospective comparative observational study n=31 Periprocedural outcomes only Sphere-9, Affera	This study investigated whether PVI with PFA compared with RFA had less effect on the cardiac autonomic nervous system. The response of the sinoatrial and atrioventricular node to extracardiac high-frequency, high-output, right vagal nerve stimulation was assessed at baseline and during and at the end of the ablation procedure. PFA caused significantly weaker and less durable suppression of cardiac autonomic regulations.	Larger studies with longer follow up and more clinical outcomes were included in the main evidence.
Tilz, RR, Vogler J, Kirstein B et al. (2023). Pulsed field ablation-based pulmonary	Prospective single arm clinical study	100% acute PVI rate was seen. Mean procedure time was 27.4 minutes and time to ambulation was 3.3 hours. No severe complications were	Larger, randomised studies with longer follow-up and more

vein isolation using a simplified single-access single-catheter approach - the fast and furious PFA study. Circulation journal 87(12): 1722-1726.	n=50 Mean 6.5 months Farawave, Farapulse PFA system	seen. At a mean of 6.5 months, 82% had maintained sinus rhythm.	clinical outcomes were included in the main evidence.
Tilz RR, Heeger CH, Vogler J et al. (2023). Wide antral circumferential vs. ostial pulmonary vein isolation using pulsed field ablation- the butterfly effect. Frontiers in cardiovascular medicine 10: 1217745.	Prospective comparative study n=30 12 months Farawave, Farapulse PFA system	This study compared outcomes between wide angle circumferential ablation compared with ostial PVI. The wide angle circumferential approach was associated with neither increased procedure nor statistically significant differences in 1-year rhythm outcome.	Larger, randomised studies with more clinical outcomes were included in the main evidence for this technology.
Tohoku S, Bordignon S, Schaack D et al. (2024). Initial real-world data on catheter ablation in patients with persistent atrial fibrillation using the novel lattice-tip focal pulsed-field ablation catheter. Europace 26: euae129.	Prospective observational single arm study n=28 90 days Sphere-9, Affera	This study presents early real world data on the Sphere-9 catheter. PVI was successful in acute phase for 100%. Median procedure time was 97 minutes and early recurrent AF within 90 days was seen in 15%. No major or minor AEs were seen.	Larger studies with longer follow-up for this technology were included in the key evidence.
Tohoku S, Schmidt B, Schaack D et al (2023). Impact of pulsed-field ablation on intrinsic cardiac autonomic	Prospective non-randomised comparative study n=97	The impact of PFA compared with CBA on the intrinsic cardiac nervous system was assessed with a biomarker in this study (s100). Statistically significantly lower S100 release following PFA PVI vs CBA ($p<0.0001$). Vagal	Larger, randomised studies reporting more clinical outcomes at longer follow up were

nervous system after pulmonary vein isolation. JACC Clinical electrophysiology 9: 1864-1875.	6 months Farawave, Farapulse PFA system	response during PFA was not associated with S100 release. This indicated lower nervous tissue destruction with PFA than CBA.	included in the main evidence. This study was also included in the systematic review and meta-analysis by de Amin (2024) in the main evidence.
Tohoku S, Chun KRJ, Bordignon S et al (2023). Findings from repeat ablation using high-density mapping after pulmonary vein isolation with pulsed field ablation. Europace 25: 433-440.	Retrospective observational study n=360 Mean 4.8 months Farawave, Farapulse PFA system (Boston Scientific)	25 of 360 people had repeat ablation within 6.1 months; 16 had atrial tachycardia, 8 had AF and 1 atrial flutter.	Larger prospective studies with longer follow up and more clinical outcomes were included in the main evidence.
Turagam MK, Neuzil P, Petru J et al (2023). PV isolation using a spherical array PFA catheter: application repetition and lesion durability (PULSE-EU Study). Jacc: Clinical Electrophysiology. 9: 638-648.	Prospective single arm trial Globe PF System (Kardium) n=21 Mean 93 days	This was a first in human trial of the Globe PFA catheter. They found 100% acute PVI, and 62.5% durability in people who had 1 application versus 100% in people who had 3 PFA applications. No stroke, transient ischaemic attack, pericardial effusion, phrenic nerve injury or oesophageal complications. Asymptomatic brain lesions were seen on MRI for 3 of 16 people.	This is a small study with short follow-up in a catheter that is not currently in use in the UK.
Turagam MK, Neuzil P, Schmidt B et al (2023). Clinical outcomes by sex after	Secondary retrospective analysis of a	This study aimed to explore whether there were differences in outcome after PFA by sex because of mixed findings in the literature about	This was a secondary analysis of the MANIFEST-

pulsed field ablation of atrial fibrillation. JAMA Cardiology 8: 1142-1151.	registry (MANIFEST PF) n=1568 1 year Farawave, Farapulse PFA system (Boston Scientific)	other ablative methods for AF. The study concluded there were no significant sex differences in clinical effectiveness or safety events.	PF registry. Two publications with patient level outcomes from this registry were included in the prioritised evidence. The findings of this study do not substantially add to the overall conclusions for this assessment.
Turagam MK, Neuzil P, Schmidt B et al (2024). Safety and effectiveness of pulsed field ablation for atrial fibrillation in patients with heart failure: a MANIFEST-PF sub-analysis. JACC. Clinical electrophysiology 10: 1675-1686.	Secondary retrospective analysis of a registry (MANIFEST PF) n= 1381 1 year Farawave, Farapulse PFA system (Boston Scientific)	This is a sub analysis of the MANIFEST-PF study. This study focused on the efficacy of PFA in heart failure. The authors concluded that PFA appears to be safe and effective in AF with heart failure. Freedom from atrial arrhythmia post-PFA was higher in people without a history of heart failure.	This was a secondary analysis of the MANIFEST-PF registry. Two publications from this registry were included in the prioritised evidence. The findings of this study do not substantially add to the overall conclusions for this assessment.
Urbanek L, Bordignon S, Schaack D et al (2023). Pulsed field versus	Retrospective comparative cohort study n=400	This study compared RFA with CBA. Acute PVI was achieved in 100% of people with PFA and 98% of CBA (p=0.123). Median procedure	Larger, multicentre prospective, randomised studies were

cryoballoon pulmonary vein isolation for atrial fibrillation: efficacy, safety, and long-term follow-up in a 400-patient cohort. Circulation: Arrhythmia and Electrophysiology 16: e011920.	12 months Farawave, Farapulse PFA system	time was statistically significantly shorter in PFA (p<0.001). Overall complications did not differ statistically (p=0.1). There were more incidents of phrenic nerve palsy in the CBA arm. Freedom from AF was similar for CBA and PFA but rates were higher for both groups in the PAF group (CBA 83.1%, PFA 80.3%; p=0.724) than PersAF (CBA 71%, PFA 66.8%, p=0.629)	included in the main evidence for this technology. This study was also included in both the systematic review and meta-analyses in the main evidence.
van de Kar MRD, Slingerland SR, van Steenbergen GJ et al (2024). Pulsed field versus cryoballoon ablation for atrial fibrillation: a real-world observational study on procedural outcomes and efficacy. Neth Heart J 32: 167-172.	Retrospective comparative cohort study n=1714 6 months Farawave, Farapulse PFA system	PFA was compared with CBA in this study. People who had CBA had higher incidence of phrenic nerve palsy than the PFA group (p=0.02). Procedure duration was shorter in PFA (p<0.001).	Prospectively collected EU real world evidence with longer follow up was included in the main evidence. This study was also included in the systematic review and meta-analysis by de Campos (2024) in the main evidence.
Verma A, Boersma L, Haines DE et al. (2022). First-in-human experience and acute procedural outcomes using a novel pulsed field ablation system: the PULSED AF	Prospective single arm pilot trial (PULSED AF) n=38 30 days	This is the pilot trial associated with the PULSED AF study included in the main evidence. They found that acute PVI was achieved in 100%. Average procedure time was 160 minutes and no serious adverse events, including phrenic nerve injury, oesophageal injury, stroke, or death were observed.	This is the pilot trial associated with the PULSED AF study included in the main evidence.

pilot trial. Circulation. Arrhythmia and electrophysiology 15: e010168.	PulseSelect, Medtronic		
Wahedi R, Willems S, Feldhege J et al (2023). Pulsed-field versus cryoballoon ablation for atrial fibrillation—Impact of energy source on sedation and analgesia requirement. J. Cardiovasc. Electrophysiol 35: 162-170.	Prospective comparative study n=100 Follow-up was not reported. Farawave, Farapulse PFA system	This study compared outcomes for people who had deep sedation with either PFA or CBA. Requirement of propofol, midazolam, and sufentanyl was significantly higher in the PFA group compared to CBA ($p<0.002$ across outcomes). Sedation and non-sedation-associated complications did not differ between both groups ($p>0.99$)	Larger, randomised studies with more clinical outcomes were included in the main evidence. Studies in the main evidence did include deep sedation protocols. This study was also included in the systematic review and meta-analysis by de Campos (2024) in the main evidence.
Wenzel JP, Lemoine MD, Rottner L. et al (2023). Repeat pulmonary vein isolation and anterior line ablation using a novel point-by-point pulsed-field ablation system. Heart Rhythm 21: 250-257.	Prospective single arm study n=24 Follow up was not reported but appears to be peri-procedural only. Centauri PFA system with THERMOCOOL	This study assessed feasibility, safety, and lesion characteristics of point-by-point PFA in consecutive people undergoing repeat ablation of atrial fibrillation (AF). 100% of PVs were successfully reisolated. Anterior line ablation was done in 19 people and acute reconduction rate was 42%. No major or minor complications were seen.	Larger, comparative studies with longer follow-up and more clinical outcomes reported were included in the key evidence.

	SMARTTOUCH catheter		
Weyand S, Adam V, Biehler P et al (2024). Focal pulsed field ablation for atrial arrhythmias: efficacy and safety under deep sedation. Journal of Clinical Medicine 13: 576.	Retrospective observational study n=30 30 days. Centauri NAVISTAR SMARTTOUCH, Biosense Webster/ TACTICATH QUARTZ, Abbott Laboratories	This study assessed outcomes from PFA under deep sedation. Not everyone had AF. The authors concluded that focal PFA is an effective approach for complex left atrial ablations under deep sedation, offering both high efficacy and efficiency with a reliable safety profile.	Not all people in this study were being treated for AF. Follow-up was short and few people were included in the study.
Wormann J, Schipper JH, Luker J et al (2023). Comparison of pulsed-field ablation versus very high power short duration-ablation for pulmonary vein isolation. J. Cardiovasc. Electrophysiol 34: 2417-2424.	Retrospective comparative study n=114 12 months Farawave, Farapulse PFA system	This study compared PFA with CHPSD ablation. PVI was successful in 100% of people. PFA has statistically significantly shorter procedure duration ($p<0.01$). There was no statistically significant difference in atrial arrhythmia at a median of 125 days ($p=0.819$).	Larger studies, and prospective randomised comparative evidence for this technology was included in the key evidence. This study was also included in the systematic review and meta-analysis by de Campos (2024) in the main evidence.
Yang M, Wang P, Hao Y et al (2023). A	Case-control study compared with RFA	There were no statistically significant differences in recurrence rate between PFA	This was a small study short follow-

real-world case–control study on the efficacy and safety of pulsed field ablation for atrial fibrillation. European Journal of Medical Research 28: 519	n=36 6 months LEAD-PFA catheter (Sichuan Jinjiang Electronic Technology Co.)	and RFA groups at 6 month follow-up. Procedure time was statistically significantly shorter in the PFA group than the RFA group (p<0.001)	up. Larger studies with longer-follow-up were included in the main evidence. This study was also included in the systematic review and meta-analysis by de Campos (2024) in the main evidence.