54TH PHA ANNUAL CONVENTION and SCIENTIFIC MEETING
SYNERGY
UNITING EXPERTS, ADVANCING TECHNOLOGY

Pulsed-Field Ablation in Atrial Fibrillation

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Declaration

- I have no disclosure.

Outline

- Introduction
- Catheter ablation of AF: Thermal vs Non-thermal
- Mechanism of Irreversible Electroporation (IRE)
- Available evidence of PFA for clinical practice
- Challenges & Advancements
- Conclusion

Introduction

- Most common & medically significant cardiac arrhythmia
- Increasing morbidity, mortality & medical expense, significant negative impact on public health
- Deeper understanding of mechanisms of AF, successfully applying knowledge to clinical practice, utilizing development of technologies improve AF management
- Principal goals of AF Mx : to improve the quality of life (symptom control) & to prevent associated morbidity & mortality (prevention of thromboembolism)

Catheter Ablation of AF

- Widespread acceptance as an initial treatment producing better CV outcomes & quality of life than AAD
- Can be associated with severe complications, dependent on types of AF, its complexity, PVI alone or more ablation, patient's comorbidities, experience of the performing centers
- RF ablation in conjunction with an Electro-Anatomical Mapping (EAM) is a gold standard
- Alternative energy sources for PVI : balloon based ablation; Cryo & Pulsed Field ablation (PFA) are highlighted during 2023.

Thermal vs Non-thermal ablation

- Traditional thermal ablation may be complicated by adverse events such as esophageal injury, phrenic nerve injury, and pulmonary vein stenosis.

- In contrast, pulsed field ablation creates lesions in cardiac tissue nonthermally and within milliseconds through the mechanism of irreversible electroporation.

- Pulsed-field ablation has received considerable interest for catheter ablation of AF to improve safety by decreasing collateral damage and improving lesion durability.

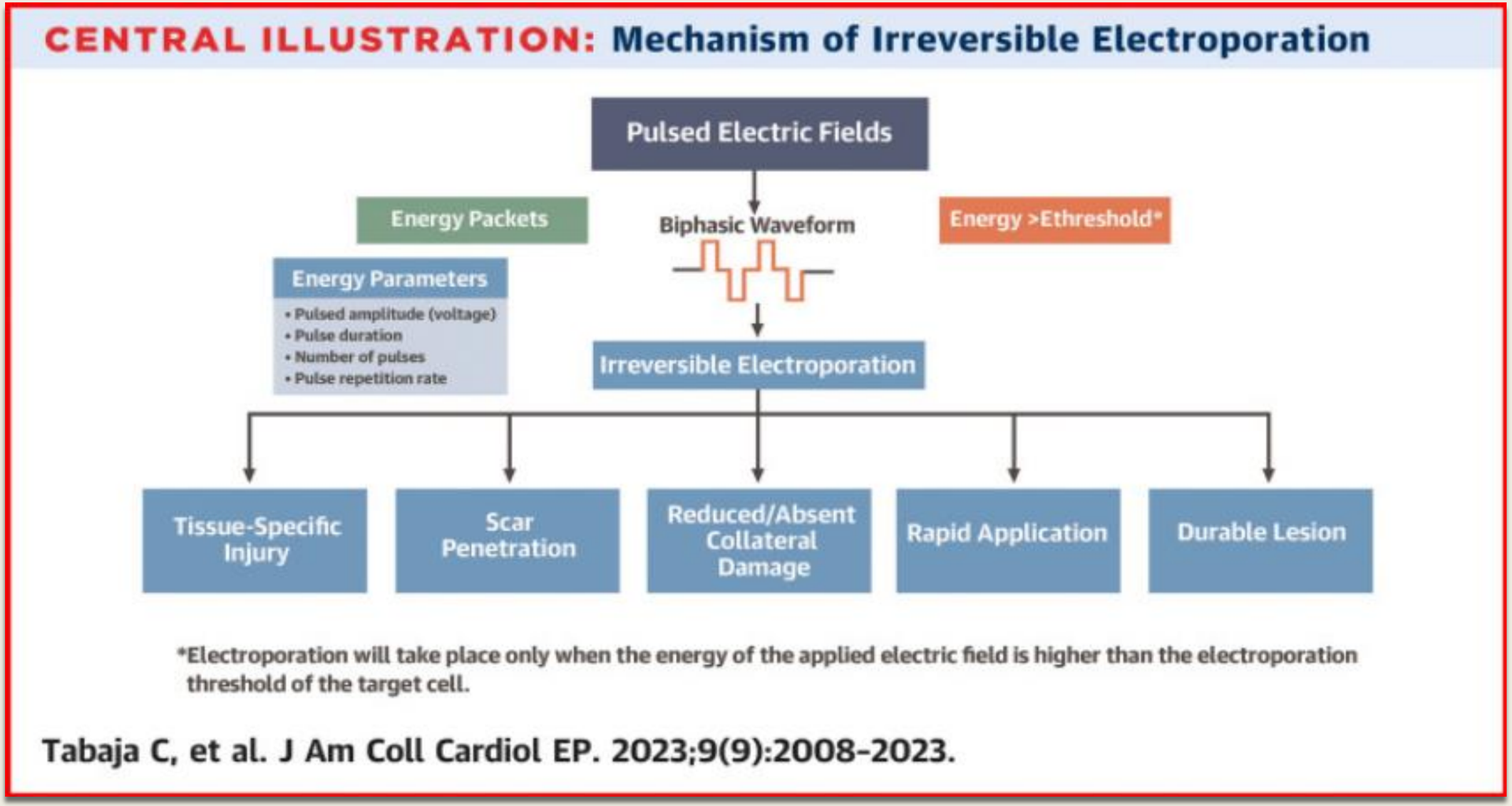
Pulsed-field ablation (PFA)

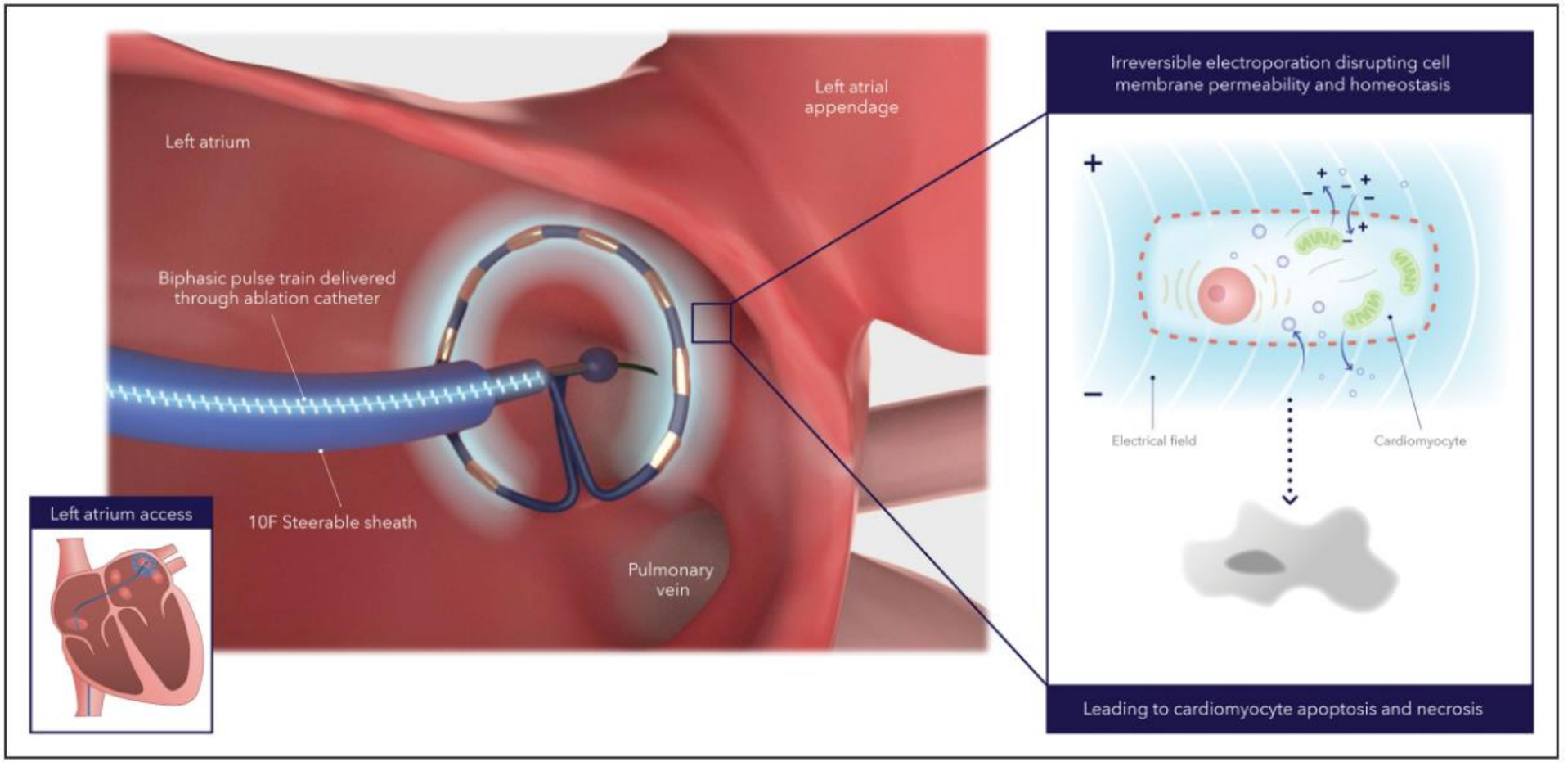
- PFA is a nonthermal method of tissue ablation technology that utilizes high-amplitude pulsed electrical fields to create irreversible electroporation (IRE) in tissues.

- PFA creates nanopores in cell membranes due to transient, high-voltage exposure that disrupts cell wall integrity, which leads to cell death.

- PFA potentially creates full transmural lesions in the atrial myocardium while avoiding damage to adjacent tissues and structures, making it a promising alternative to traditional thermal ablation methods.

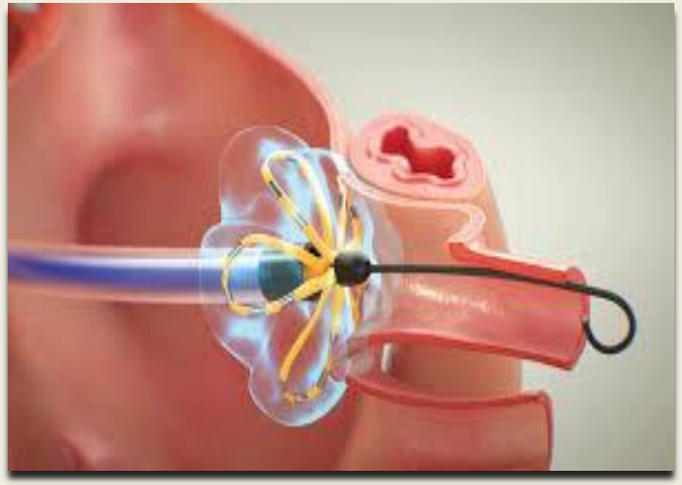
Mechanism of Irreversible Electroporation





Catheter ablation method with pulsed field ablation system. Alternating positive and negative electrodes sustains a bipolar electrical field around the catheter that extends into the tissue. The electrical field increases cell membrane permeabilization, which then leads to cell function disruption and eventually to cell death (ie, apoptosis and necrosis).

Pulsed-field ablation



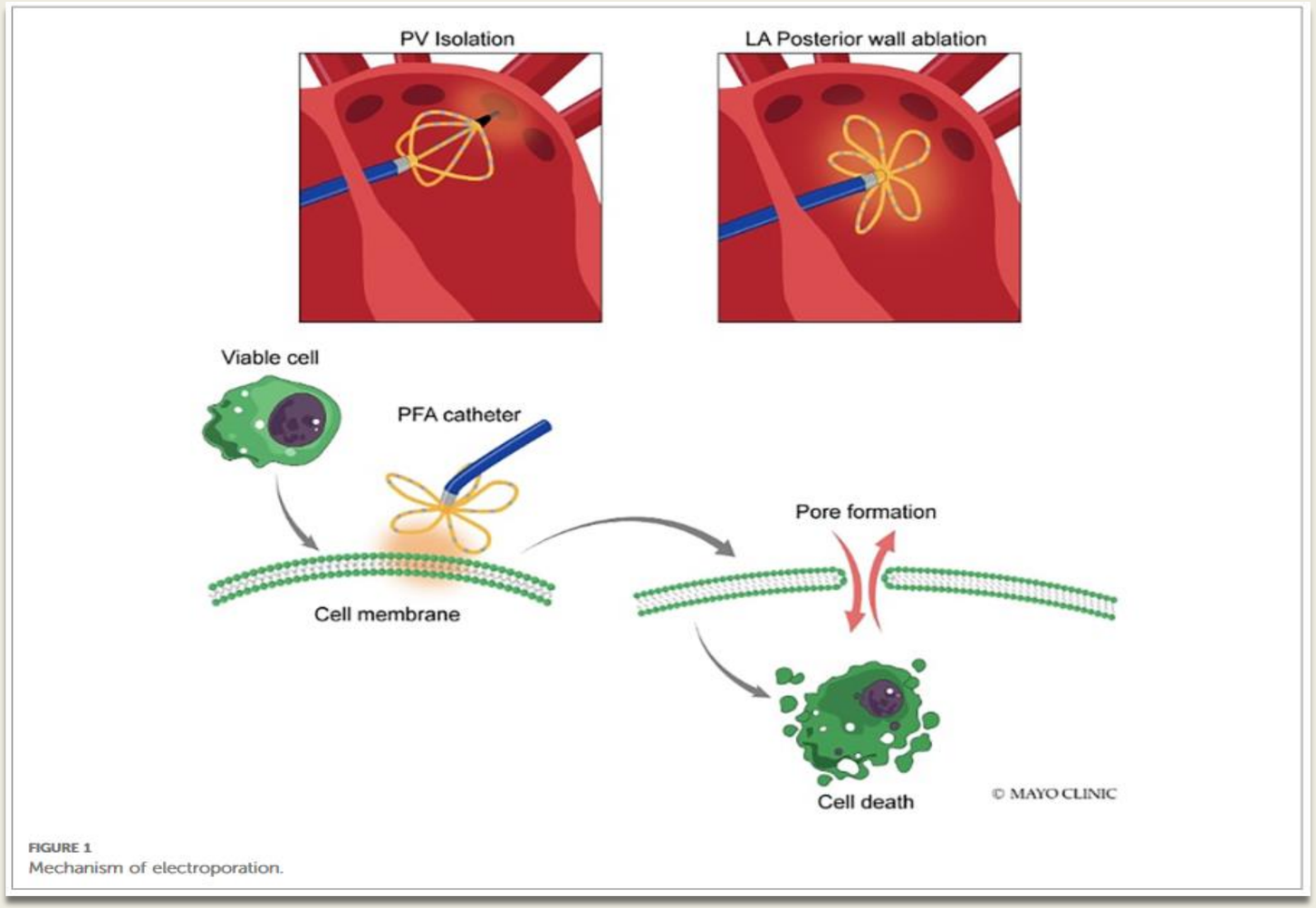


FIGURE 1
Mechanism of electroporation.

Circulation
Volume 147, Issue 19, 9 May 2023; Pages 1422-1432
https://doi.org/10.1161/CIRCULATIONAHA.123.063988

ORIGINAL RESEARCH ARTICLE

Pulsed Field Ablation for the Treatment of Atrial Fibrillation: PULSED AF Pivotal Trial

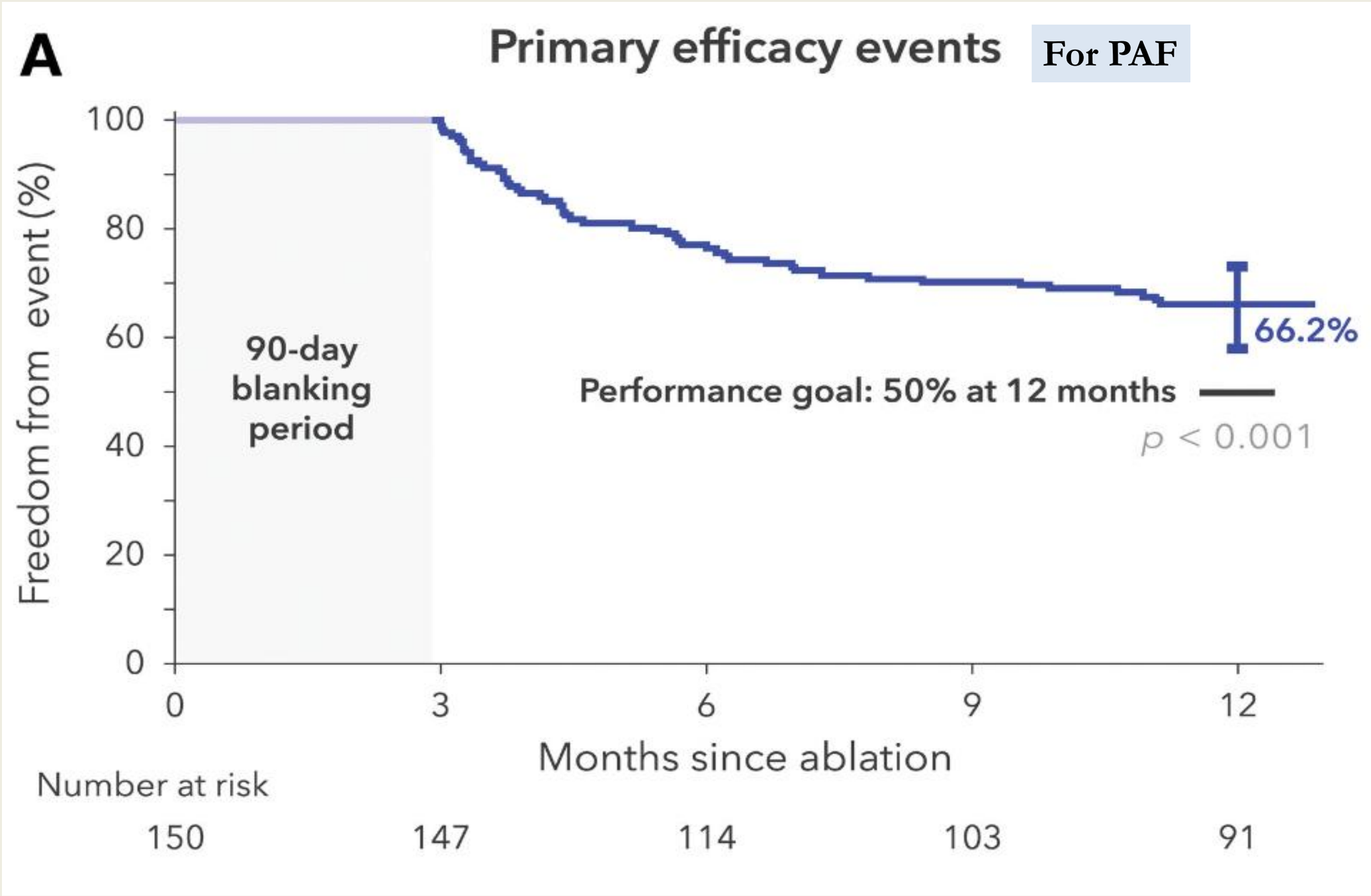
Editorial, see p 1433

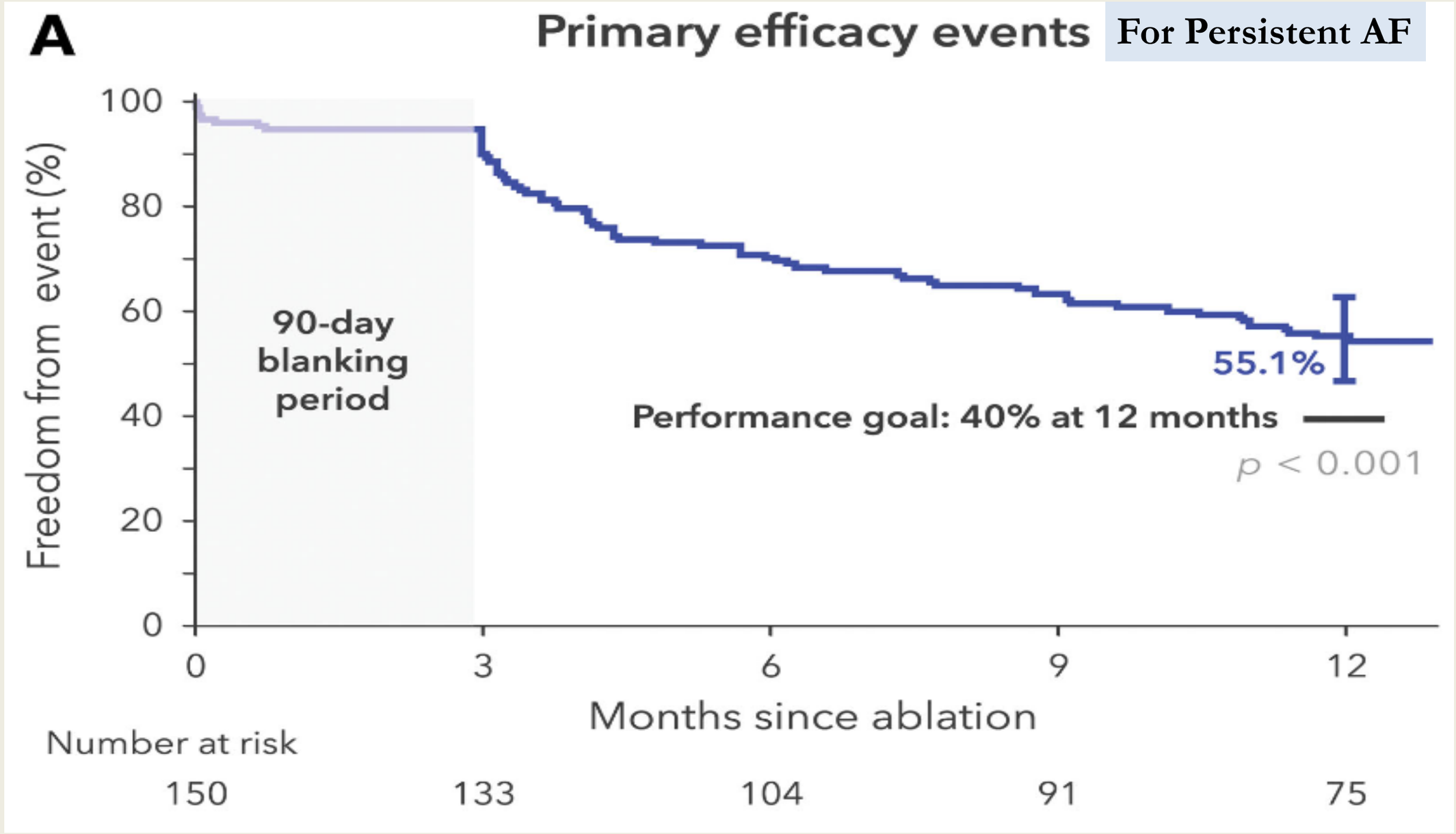
Atul Verma, MD, David E. Haines, MD, Lucas V. Boersma, MD, Nitesh Sood, MD, Andrea Natale, MD, Francis E. Marchlinski, MD, Hugh Calkins, MD, Prashanthan Sanders, MBBS, Douglas L. Packer, MD, Karl-Heinz Kuck, MD, Gerhard Hindricks, MD, Birce Onal, PhD, Jeffrey Cerkvenik, MS, Hiroshi Tada, MD, David B. DeLurgio, MD, and on behalf of the PULSED AF Investigators

https://images.app.goo.gl/FC54VLQ2zziJdWCf6

Pulsed Field Abaltion for the Treatment of AF: PULSED AF Pivotal Trial

- Prospective, multicenter, nonrandomized
- Symptomatic PAF (150)/ Persistent AF (150), 1 yr follow-up
- Primary effectiveness end point was freedom from a composite of acute procedural failure, arrhythmia recurrence or antiarrhythmic escalation
- Primary safety end point was freedom from a composite of serious procedure & device related adverse events


A
Primary efficacy events
For PAF
100
80
60
40
20
0
Freedom from event (%)
90-day blanking period
66.2%
Performance goal: 50% at 12 months
p < 0.001
0
3
6
9
12
Months since ablation
Number at risk
150
147
114
103
91


A
Primary efficacy events
For Persistent AF
100
80
60
40
20
0
Freedom from event (%)
90-day blanking period
55.1%
Performance goal: 40% at 12 months
p < 0.001
0
3
6
9
12
Months since ablation
Number at risk
150
133
104
91
75

Summary of PULSED AF Pivotal

- The primary safety end point occurred in 1 patient in both paroxysmal & persistent AF

- Conclusions: PULSED AF demonstrated a low rate of primary safety adverse events and provided effectiveness consistent with established ablation technologies using a novel irreversible electroporation energy

Circulation

ORIGINAL RESEARCH ARTICLE

Safety and Effectiveness of Pulsed Field Ablation to Treat Atrial Fibrillation: One-Year Outcomes From the MANIFEST-PF Registry

AMERICAN COLLEGE of CARDIOLOGY

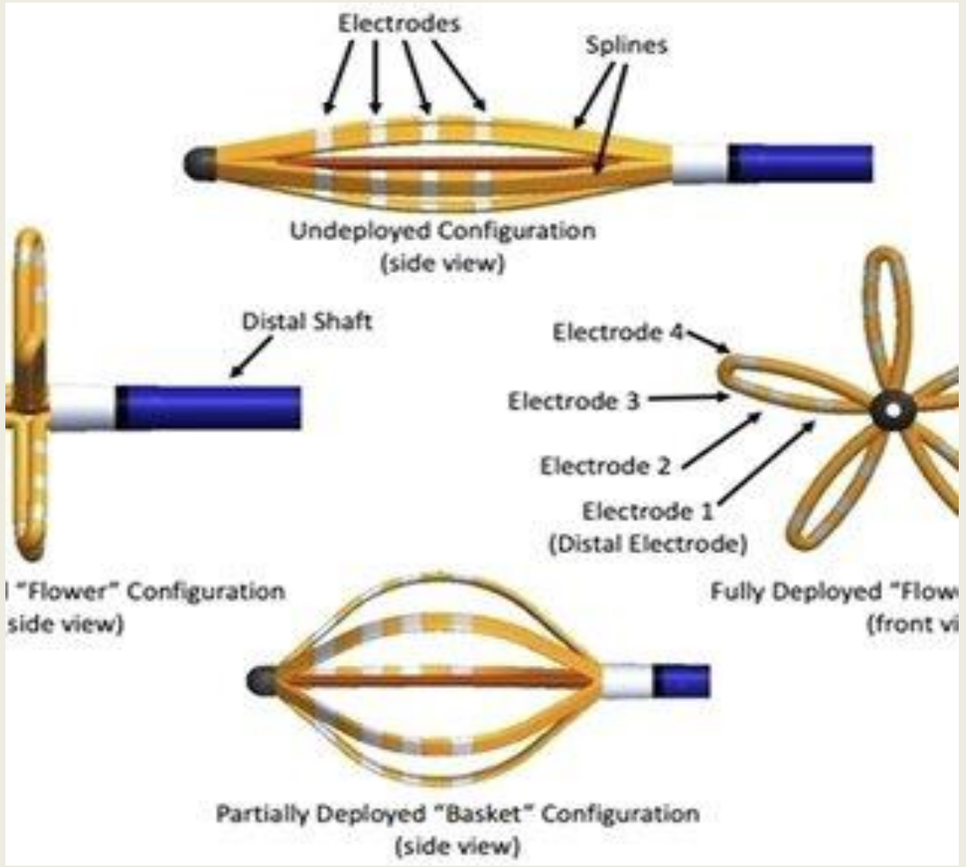
Findings of the MANIFEST PF Survey: Real World Experience With Pulsed Field Ablation

Jan 09, 2023 | Daniel Musikantow, MD; Jacob Koruth, MD

Expert Analysis

MANIFEST-PF study

- The MANIFEST-PF study across 24 centers (retrosepctive Multi-National Survey), 77 operators
- Used a special catheter (pentaspline PFA)
- 1,568 atrial fibrillation patients(PAF/ persistent: 65%/ 32%)
- PVI was achieved in 99.2%, freedom for atrial arrhythmia 78.1% (PAF 81.6% > Persistent 71.5%, P=0.001)
- Acute major adverse events occurred in 1.9%



MANIFEST-PF study : Complications

Major Complications	N (%)
Pericardial Tamponade	17 (0.97)
Stroke	7 (0.39)
Vascular Complications Requiring Surgery	4 (0.23)
Coronary Spasm	1 (0.06)
Death	1 (0.06)

Minor Complications	N (%)
Transient Ischemic Attack (TIA)	2 (0.11)
Transient Phrenic Nerve Injury	8 (0.46)
Vascular Complications Not Requiring Surgery	56 (3.28)
Other	2 (0.11)

Summary of MANIFEST - PF

- Survey aims to assess whether PFA delivers on safety & efficacy when employed in commercial use
- Acute procedural success involving isolation of the pulmonary veins was almost universally achieved
- Complications were rare & not associated directly with PFA.
- Larger studies will be needed to assess rare complications specific to PFA

ADVENT

PIVOTAL TRIAL

ADVENT Pivotal Trial

- A randomized clinical trial: directly compared FARAPULSE™ PFA to standard of care thermal ablation (force-sensing RFA or Cryo ablation) for the treatment of PAF.

- A multi-center, prospective, non-inferiority clinical trial with 1:1 randomization of PFA to thermal ablation evaluating single-procedure, off-drug study endpoints, including:
  - Primary Safety
  - Primary Effectiveness
  - Procedural Characteristics

The most rigorous PFA clinical trial (ADVENT)

- Patients randomized to PFA or thermal ablation (RFA or CBA)
- Re-ablations not allowed in 90-day blanking period
- Freedom from Class I/III anti-arrhythmic drug (AAD) after the 90-day blanking period (amiodarone was not allowed at any time)
- Stringent monitoring with 72-hour Holters
- Largest PFA trial with 305 patients treated with PFA

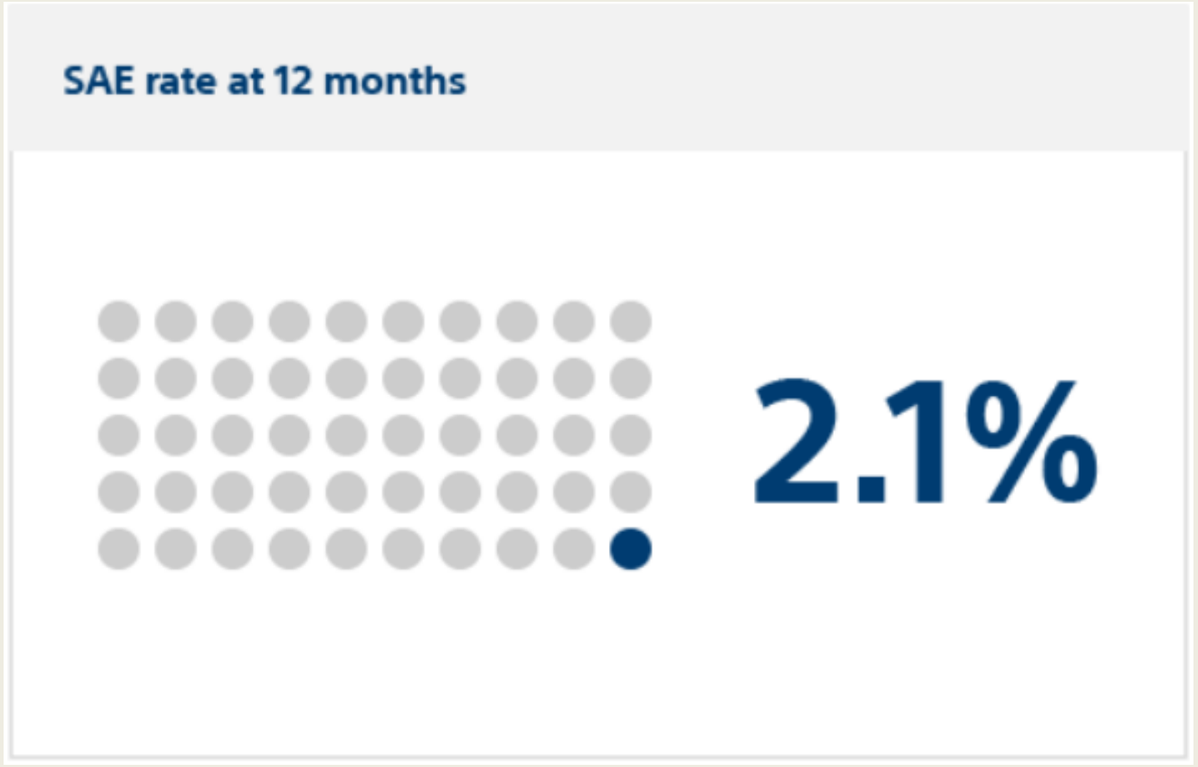
Results of ADVENT

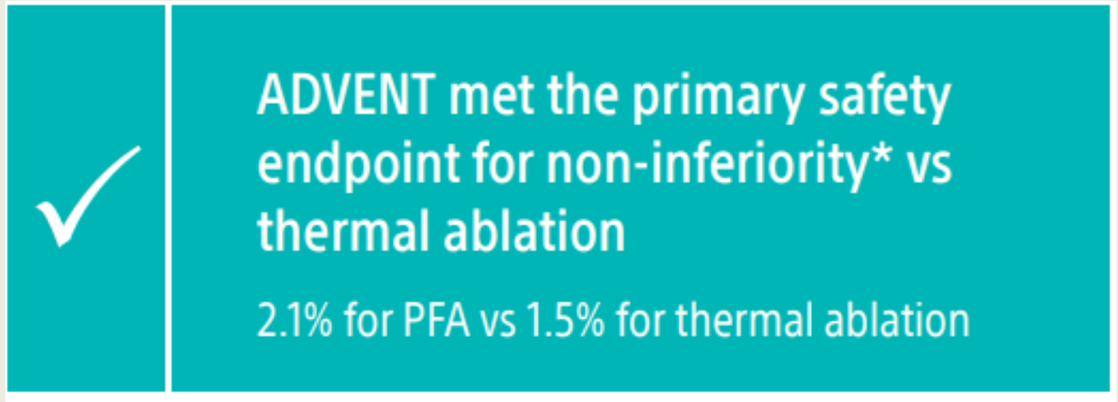
- The randomized ADVENT achieved non-inferiority in the primary safety & efficacy endpoints when comparing the FARAPULSE PFA system against thermal ablation modalities

  (Posterior probability > 0.999)

Primary safety endpoint: Severe adverse events (SAEs) (ADVENT)

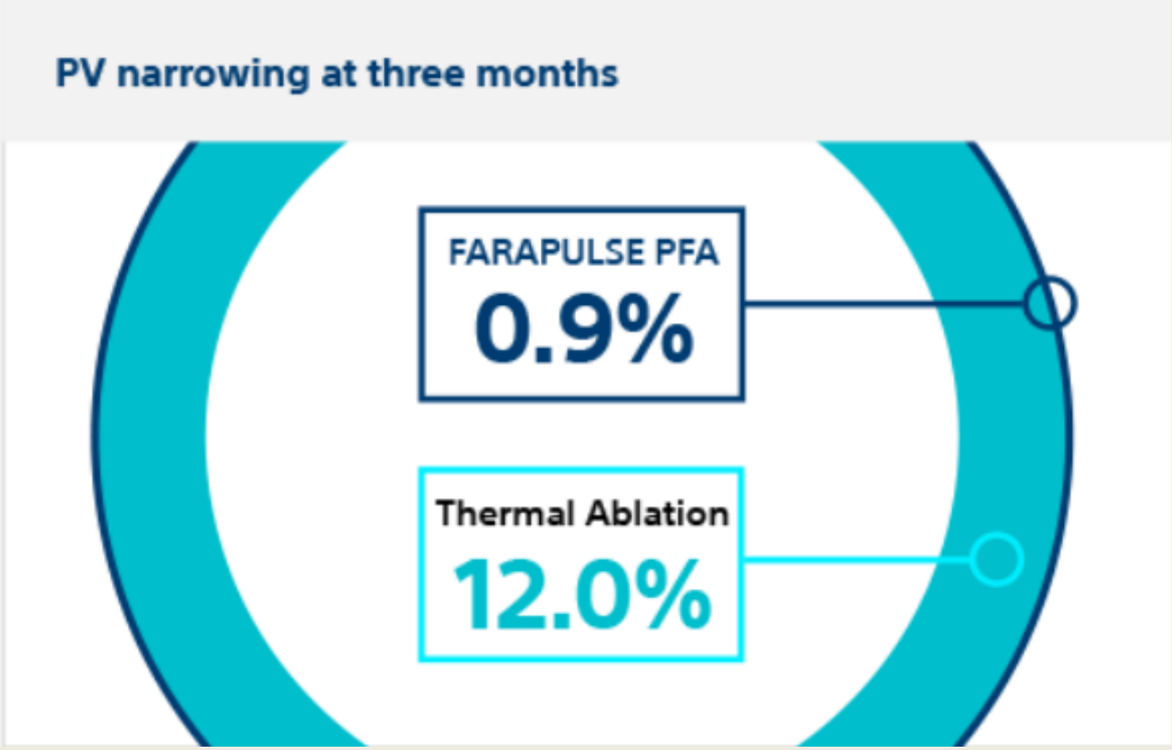
- SAEs occurred in six FARAPULSE PFA patients (estimated incidence: 2.1%) vs. four thermal patients (1.5%), meeting the criterion for non-inferiority (posterior probability >0.999).

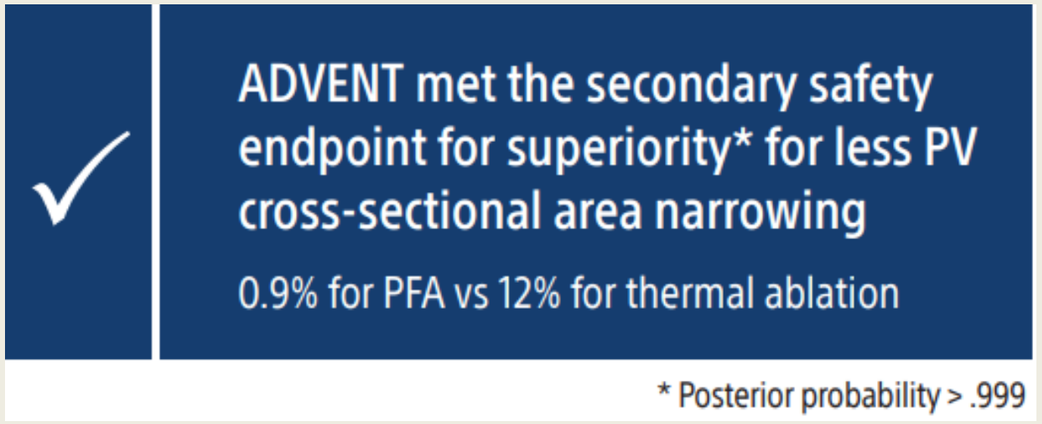




Secondary safety endpoint: Pulmonary vein narrowing (ADVENT)

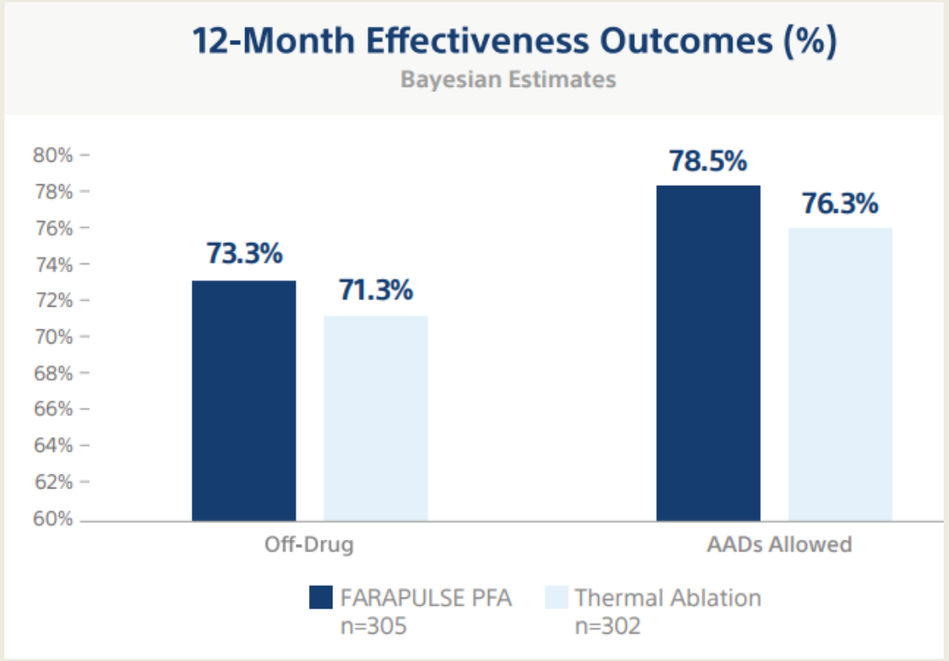
- Significantly less pulmonary vein cross-sectional narrowing (CT/MRI) in FARAPULSE PFA patients (0.9%) vs thermal ablation patients (12.0%), meeting the criterion for superiority (posterior probability >0.999)

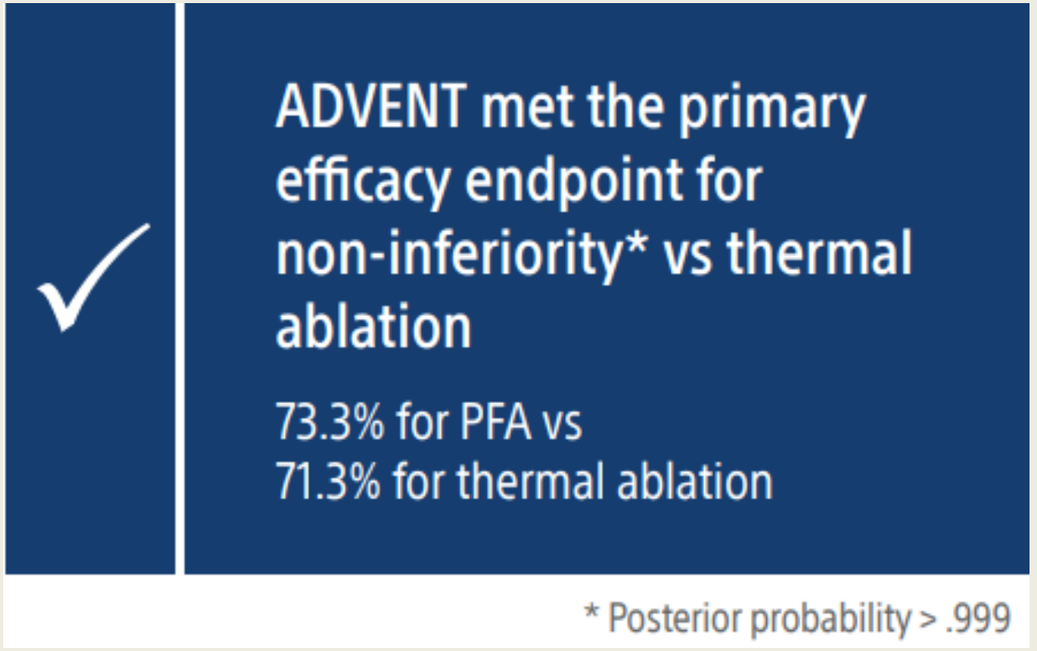




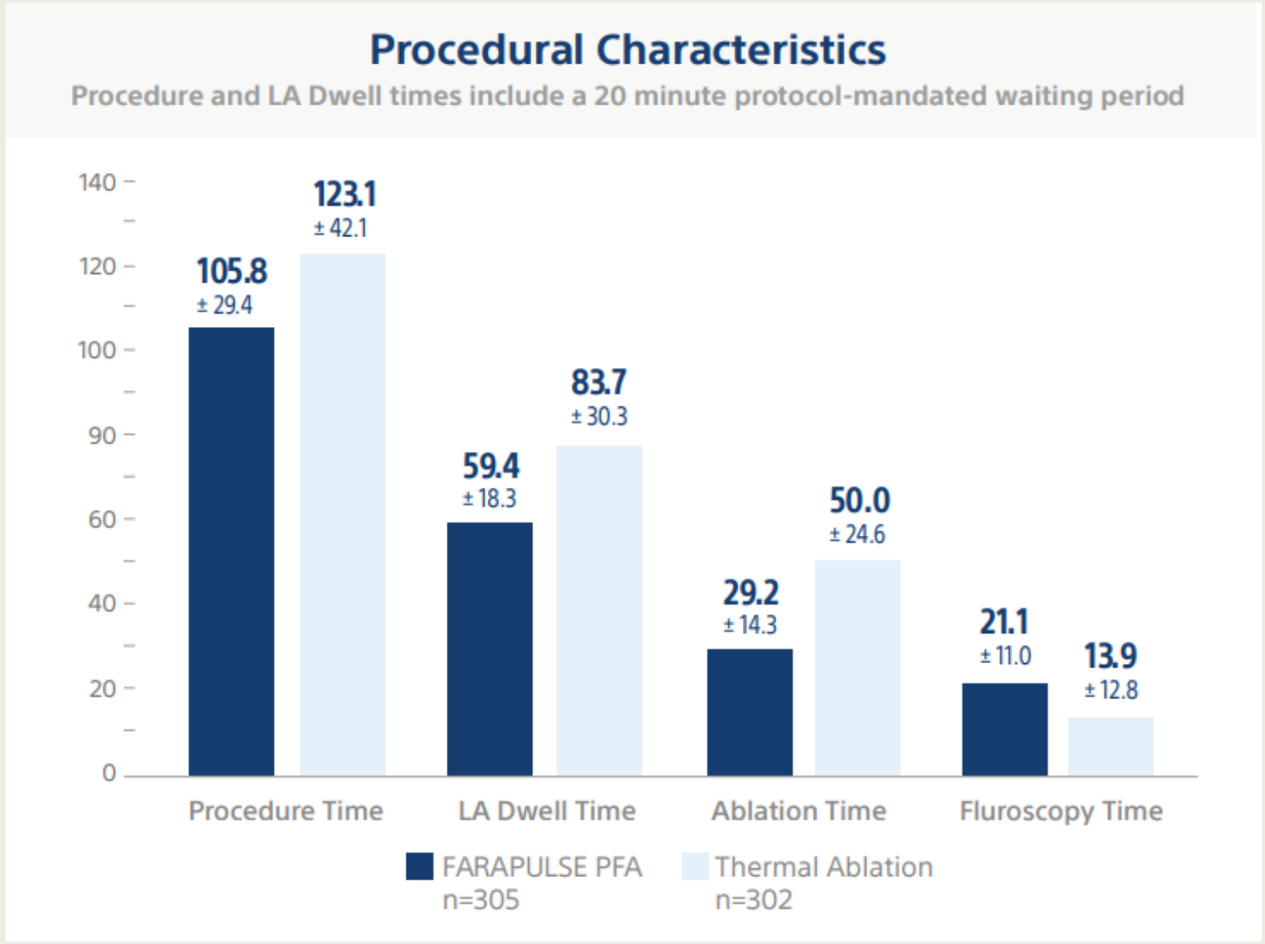
Effectiveness outcomes (ADVENT)

- The primary effectiveness endpoint required both acute procedural success (PVI) & chronic success, which included freedom from Class I/III AADs, repeat ablation, cardio-version, and documented AF, AFL, or AT through 12 months.
- The acute PVI rates were 99.6% for FARAPULSE and 99.8% for thermal ablation.





Procedural Characteristics (ADVENT)

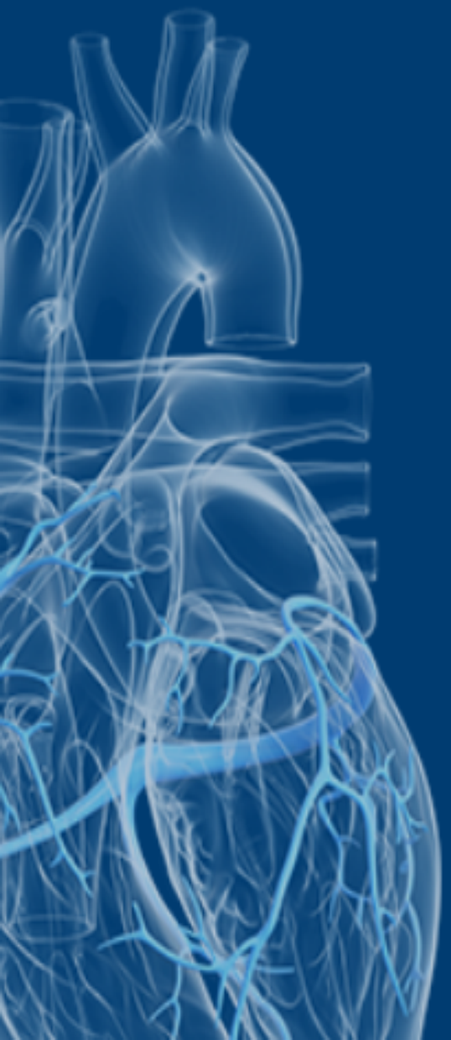


FARAPULSE PFA procedure times were significantly* shorter with less variability than thermal ablation.

105.8 ± 29.4 min for PFA vs
123.1 ± 42.1 min for thermal ablation

* BCI does not contain zero

Summary of ADVENT Pivotal Trial



In the ADVENT Pivotal Trial, FARAPULSE demonstrated:

- Non-inferiority for both the primary safety and effectiveness outcomes compared to thermal technology.*
- Significantly less pulmonary vein cross-sectional narrowing compared to thermal ablation.*
- Significantly shorter procedure times, reduced LA dwell time and total ablation time versus thermal ablation. Lower standard deviations across these characteristics also indicate less variability within the PFA procedures.

* posterior probability >0.999

ORIGINAL ARTICLE

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

Mattias Duytschaever, MD, PhD; Tom De Potter, MD; Massimo Grimaldi, MD, PhD; Ante Anic, MD; Johan Vijgen, MD; Petr Neuzil, MD, PhD; Hugo Van Herendael, MD; Atul Verma, MD; Allan Skanes, MD; Daniel Scherr, MD; Helmut Pürerfellner, MD; Gediminas Rackauskas, MD; Pierre Jaïs, MD; Vivek Y. Reddy, MD; on behalf of the inspIRE Trial Investigators*

FULLY INTEGRATED BIPHASIC PULSED FIELD ABLATION SYSTEM WITH VARIABLE LOOP CIRCULAR CATHETER FOR PAROXYSMAL ATRIAL FIBRILLATION ABLATION

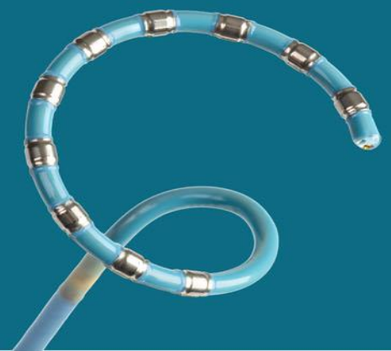
STUDY DESIGN

13
EUROPE & CANADA
CENTERS

226
PATIENTS
WAVE I: 40; WAVE II: 186

WITH DRUG-REFRACTORY SYMPTOMATIC PAROXYSMAL ATRIAL FIBRILLATION

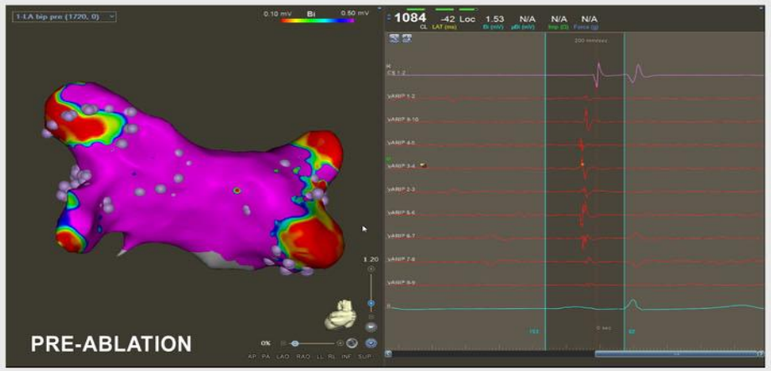
58.4-59.4 years old; 57.5-70.4% male; 1.3-1.8 CHA_2DS_2-VASc
38.0-39.4 mm LA diameter; 57.9-60.8% LVEF

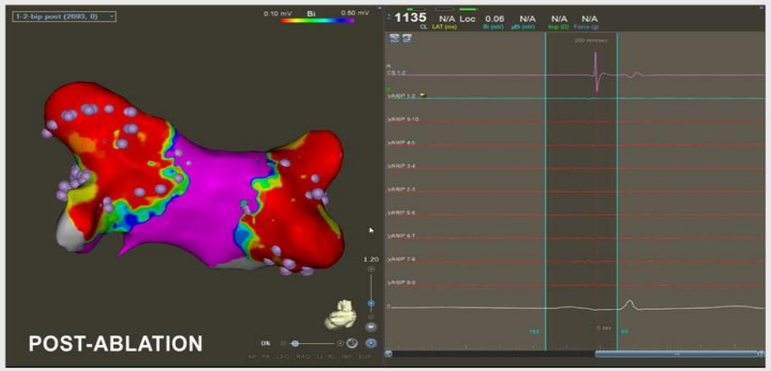


PROCEDURAL DATA

CHARACTERISTICS	WAVE I (N=40)	WAVE II (N=186)
Procedure time, min	82.4	70.1
LA dwell time, min	46.2	44.7
Fluoroscopy time, min	9.8	7.8

PRE- VS. POST-ABLATION VOLTAGE MAP SHOWING LEVEL OF ISOLATION
(SHOWN IN RED)



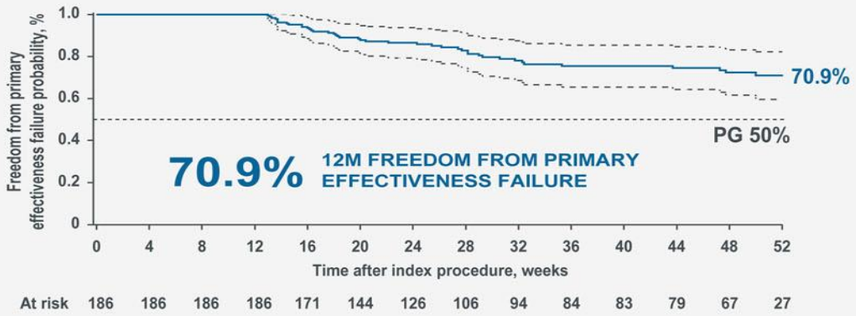


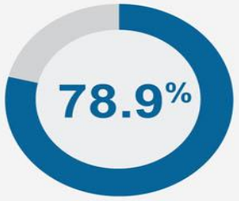
CLINICAL OUTCOMES

PRIMARY ADVERSE EVENTS (WAVE I & II)

0% NO PV STENOSIS, ESOPHAGEAL THERMAL LESIONS, AE FISTULA, THROMBOEMBOLISM, TIA, OR MYOCARDIAL INFARCTION

12-MONTH EFFECTIVENESS (WAVE II)





CLINICAL SUCCESS

FREEDOM FROM REPEAT ABLATION

Conclusions of inspIRE

- **The inspIRE trial confirmed the safety and effectiveness of the novel mapping-integrated PFA system.**

ESC European Society of Cardiology

Europace (2023) **25**, 1–11
https://doi.org/10.1093/europace/euad185

CLINICAL RESEARCH

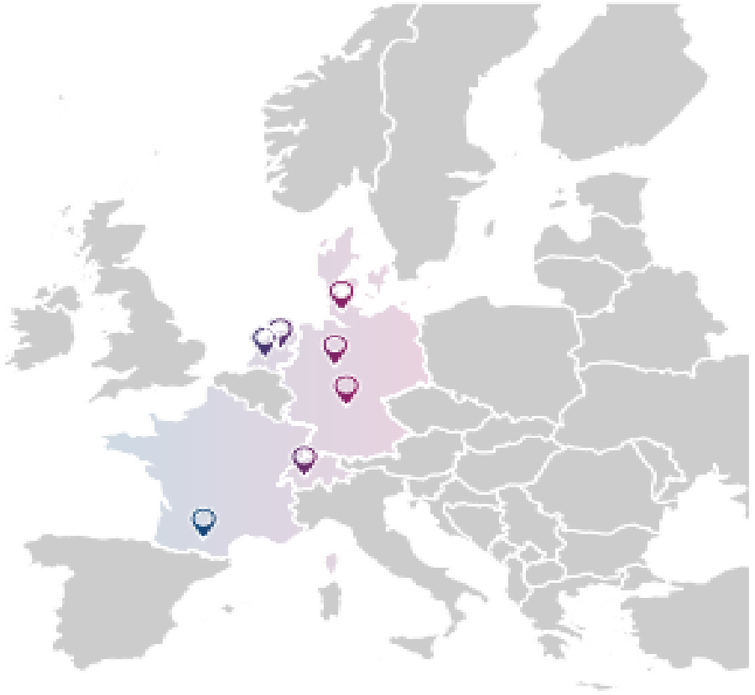
EUropean real-world outcomes with Pulsed field ablatiOn in patients with symptomatic atRIAl fibrillation: lessons from the multi-centre EU-PORIA registry

Boris Schmidt [1,2]*, Stefano Bordignon [1], Kars Neven [3,4], Tobias Reichlin [5], Yuri Blaauw[6], Jim Hansen [7], Raquel Adelino [8], Alexandre Ouss [9], Anna Füting [3,4], Laurent Roten [5], Bart A. Mulder [6], Martin H. Ruwald [7], Roberto Mené [8], Pepijn van der Voort [9], Nico Reinsch [3,4], Thomas Kueffer [5], Serge Boveda [8], Elizabeth M. Albrecht[10], Christopher W. Schneider [10], and Kyoung Ryul Julian Chun [1]

[1]Cardioangiologisches Centrum Bethanien, Wilhelm-Epstein Str. 4, 60431 Frankfurt, Germany; [2]Universitätsklinikum Frankfurt, Medizinische Klinik 3- Klinik für Kardiologie, Theodor-Stern-Kai 7, Frankfurt, Germany; [3]Department of Electrophysiology, Alfried Krupp Hospital, Essen, Germany; [4]Department of Medicine, Witten/Herdecke University, Witten, Germany; [5]Inselspital—Bern University Hospital, University of Bern, Bern, Switzerland; [6]Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [7]Arrhythmia Unit, Department of Cardiology, Gentofte Hospital, Copenhagen, Denmark; [8]Heart Rhythm Department, Clinique Pasteur, Toulouse, France; [9]Heart Center Catharina Hospital, Eindhoven, The Netherlands; and [10]Boston Scientific Corporation, St. Paul, MN, USA

Received 6 May 2023; accepted after revision 23 May 2023; online publish-ahead-of-print 28 June 2023

Graphical Abstract



7 European centers

42 operators

1233 AF patients treated with PFA

EUPORIA

Acute efficacy

99.96% PVI
58 min procedure time

Acute safety

1.7% major complications

(1.1% pericardial tamponade, 0.41% stroke, 0.16% TIA)

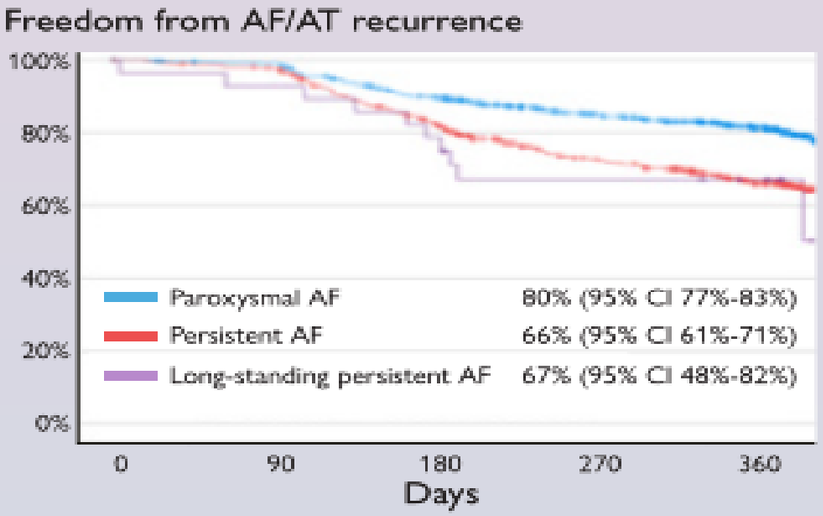
Chronic efficacy

AF/AT-free survival at 365 days median follow up

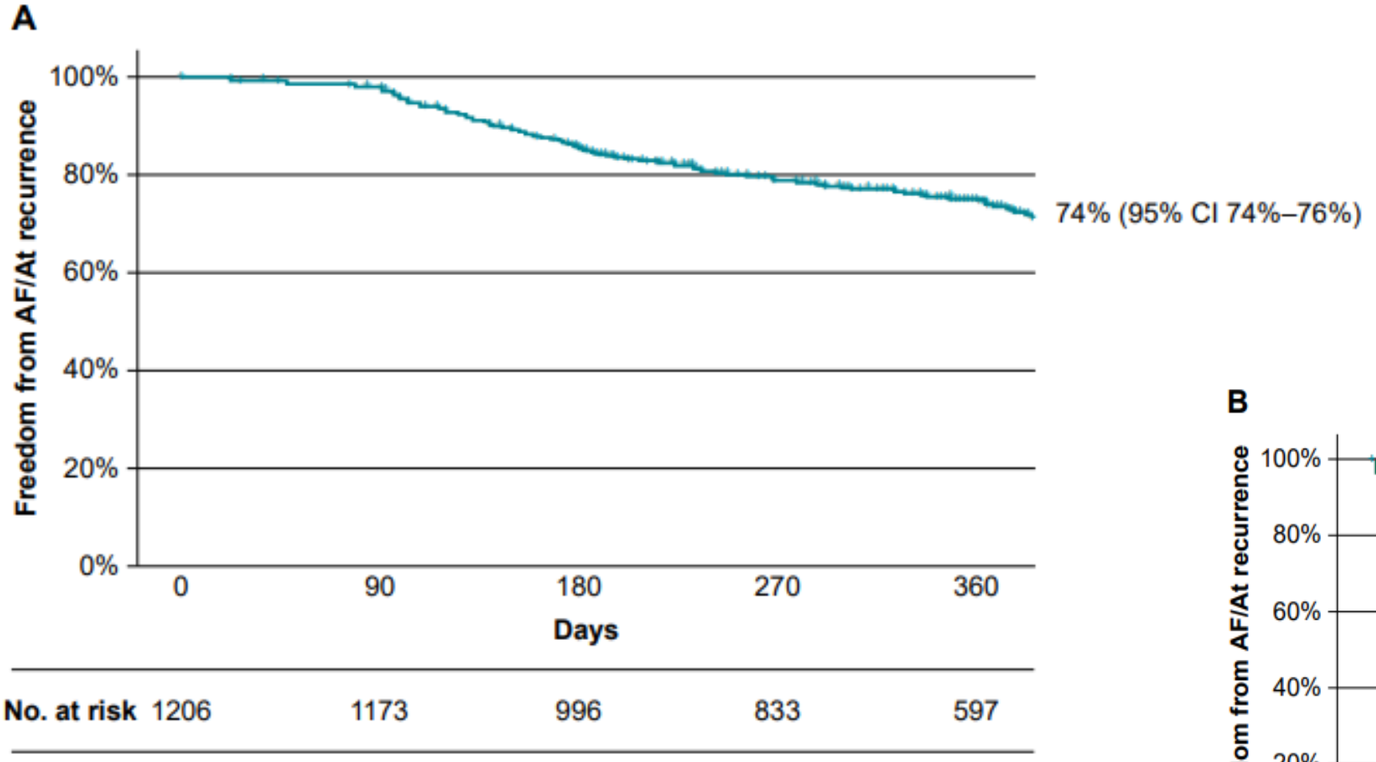
80% in paroxysmal AF
66% in persistent AF

Reproducible results among centers irrespective of operator experience

Freedom from AF/AT recurrence by AF indication (PFA index procedures)



Keywords Ablation • Atrial fibrillation • Pulsed field ablation • Electroporation



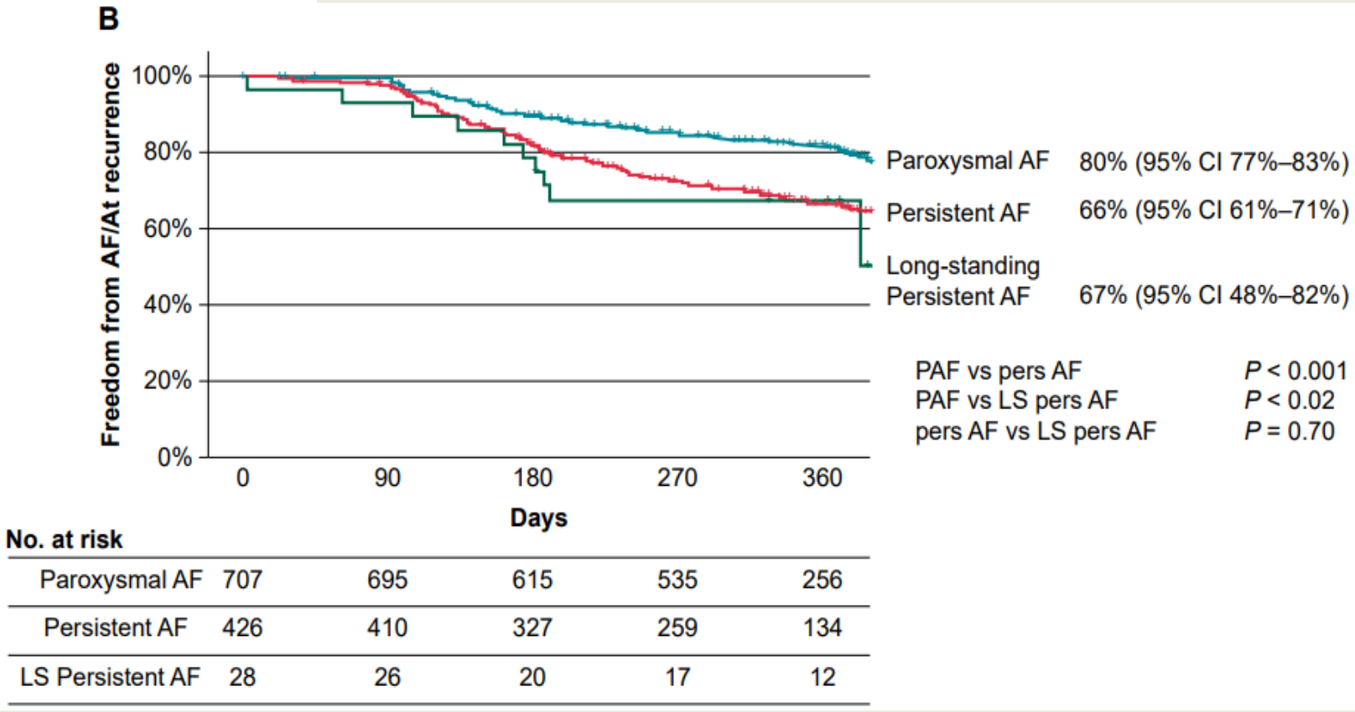


Figure 2 Kaplan–Meier curve of atrial fibrillation (AF)/atrial tachycardia (AT)-free survival for (*A*) all patients and (*B*) patients who underwent an index pulsed field ablation (PFA) procedure.

Conclusions of EU-PORIA registry

- **EU-PORIA registry demonstrated a high single-procedure success rate with an excellent safety profile and short procedure times in real-world, all-comer AF patient population**

i1198 Europace 2023 Volume 25 Supplement 1

9.4.4 - Catheter Ablation of Arrhythmias

Pulsed-field- vs. cryo- vs. radiofrequency ablation: one-year recurrence rates after pulmonary vein isolation in patients with persistent atrial fibrillation

Mr Kueffer T; Doctor Madaffari A; Ms Muehl A; Doctor Maurhofer J; Ms Stefenova A; Doctor Seiler J; Doctor Thalmann G; Doctor Kozhuharov NA; Doctor Servatius H; Professor Tanner H; Associate Professor Haeberlin A; Doctor Baldinger SH; Doctor Noti F; Professor Roten L; Professor Reichlin T.

Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Aim- To compare procedural & one-yr recurrence data of patients with persistent AF undergoing first PVI using PFA, Cryo, or RFA (N 177)

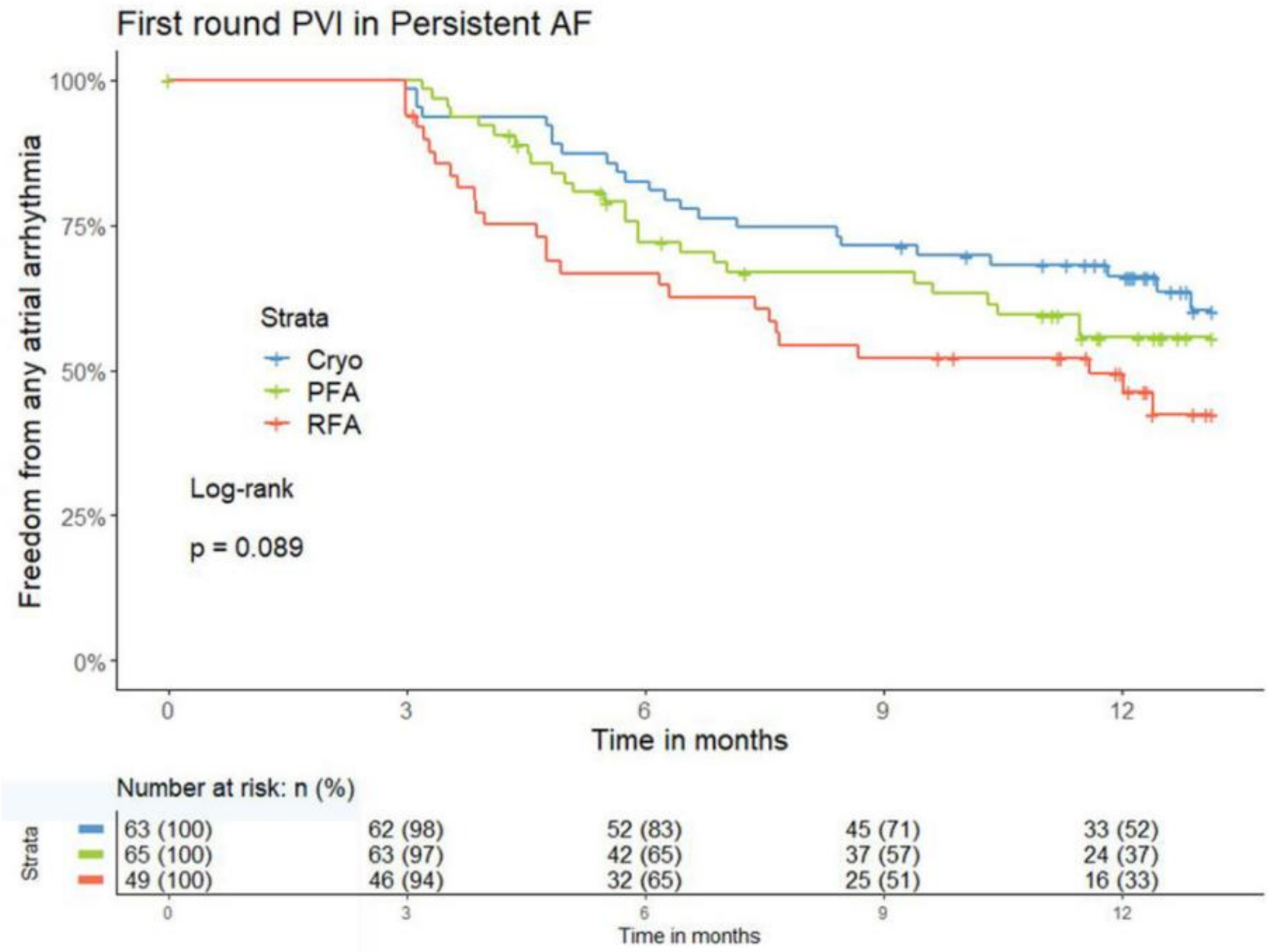


Figure: Freedom from any atrial arrhythmia after first pulmonary vein isolation using different technologies in persistent atrial fibrillation patients

Recurrence of atrial arrhythmias in the KM- analysis after 12 months was not different all 3

Ongoing Clinical Trial

- AVANT GUARD Clinical Trial to evaluate FARAPULSE PFA system as first-line treatment for Persistent AF
- Randomized trial comparing PFA with anti-arrhythmic drug therapy for first-line treatment of Persistent AF
- ADVANTAGE AF Study: to establish the safety & effectiveness of FARAPULSE PFA system for treatment of drug resistant, symptomatic persistent AF
- A prospective single arm open label study with persistent AF

Evidence from clinical trails of PFA (overall)

- Excellent efficacy, with PVI achieved in almost all patients
- Low rate of major complications, mostly due to pericardial tamponade, stroke & coronary spasm
- Significantly faster procedure time than Cryo or RFA ablation
- Good overall freedom from AF after one year for paroxysmal or persistent AF with excellent durability in some cohorts

Pearls and Pitfalls of PFA

Irreversible electroporation

- tissue-sensitive, preserved tissue compliance

Efficacy and safety

- deep, transmural, durable lesions
- sparing adjunctive tissue
  - no PV stenosis
  - no esophageal lesions
  - no tissue coagulation
  - minimal effects on phrenic nerve
  - low safety risk of overtreatment

Workflow

- standardized and time-efficient, short learning curve using single shot device
- single-tip similar to RF-ablation

Current literature

-excellent limited data mainly from observational studies for PVI

Irreversible electroporation

- cellular mechanisms, necrosis Vs apoptotic pathway not entirely understood

Efficacy and safety

- dose dependent, optimal dose unclear
- distinct IRE programming crucial to avoid collateral damage
- vasospasm during PFA adjacent to coronaries
- PFA ≠ PFA
  - validation for each system and indication
  - results not transferable

Workflow

- only 2 ablation systems approved with limited experience

Current literature

- no long-term data available
- no randomized controlled trials available

Challenges & Advancements

- Lack of standardized protocols for various target tissue & clinical indications: includes energy delivery parameters (energy intensity, pulse duration & frequency, biphasic vs monophasic pulse delivery), different electrode configurations, variations of diverse device design

- Difficult to compare results across studies & hinders the adoption of PFA

- Coronary artery spasm, pulmonary artery hemorrhage, dose-dependent phrenic stunning observed as complications in clinical trial

- Further research is needed to optimize treatment parameters of PFA

Challenges & Advancements

- For difficult structures; hard to access or have complex anatomies, improved imaging techniques (MRI & CT) & real time guidance system (ICE) can help to overcome

- Miniaturization of PFA catheters, which enables their use in smaller and more complex anatomical structures, allowing for more targeted and precise ablation.

- Although PFA is a novel procedure, it is difficult to be adopted by all institutions because of the equipment cost and the need for specialized training

- Furthermore, long-term data on the safety & efficacy is still limited, and large-scale studies with longer follow up periods are needed to evaluate the long-term benefits and risks

Conclusion

- PFA provides a nonthermal approach to inducing cell death, which can lead to faster and safer cardiac ablation, ultimately improving its efficiency and effectiveness

- PFA may have effectiveness comparable to traditional catheter ablation while preventing thermally mediated complications.

- PFA shows promise in CTI, posterior wall isolation, and VT ablation.

THANK YOU