Randomized Controlled Trial for Pulsed Field Ablation versus Standard of Care Thermal Ablation for Paroxysmal Atrial Fibrillation

Primary Results of the *ADVENT* Trial

27 August 2023

Vivek Y. Reddy MD,[1] Edward P. Gerstenfeld MD,[2] Andrea Natale MD,[3] William Whang MD,[1] Frank A. Cuoco MD,[4] Chinmay Patel MD,[5] Stavros E. Mountantonakis MD,[6] Douglas N. Gibson MD,[7] John D. Harding MD,[8] Christopher R. Ellis MD,[9] Kenneth A. Ellenbogen MD,[10] David B. DeLurgio MD,[11] Jose Osorio MD,[12] Anitha B. Achyutha MTech MSE,[13] Christopher W. Schneider BSE MEng,[13] Andrew S. Mugglin PhD,[14] Elizabeth M. Albrecht PhD,[15] Kenneth M. Stein MD,[15] John W. Lehmann MD MPH,[16] and Moussa Mansour MD[17]

On behalf of the *ADVENT* Investigators.

[1]Helmsley Electrophysiology Center, Icahn School of Medicine at Mount Sinai, New York, NY; [2]University of California San Francisco, San Francisco, CA; [3]Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, TX & Case Western Reserve University, Cleveland, OH; [4]Trident Medical Center, Charleston, SC; [5]UPMC Pinnacle, Harrisburg, PA; [6]Lenox Hill Hospital, Northwell Health, New York City, NY; [7]Scripps Clinic and Prebys Cardiovascular Institute, San Diego, CA; [8]Doylestown Hospital, Doylestown, PA; [9]Vanderbilt University Medical Center, Nashville, TN; [10]Virginia Commonwealth University, Richmond, VA; [11]Emory University Hospital, Atlanta, GA; [12]Grandview Medical Center, Birmingham, AL; [13]Boston Scientific Corporation, Menlo Park, CA; [14]Paradigm Biostatistics LLC, Anoka, MN; [15]Boston Scientific Corporation St. Paul, MN; [16]Lehmann Consulting, Naples, FL; [17]Massachusetts General Hospital, Boston MA.

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The Pulsed Field Ablation system studied in this trial (Farawave) does have CE Mark approval, but **does not have US FDA approval** (and should thus be **considered investigational** in the US).

Principal Investigators, DSMB & CEC

Principal Investigators	Investigational Site
William Whang	Mt. Sinai Hospital
David DeLurgio	Emory University Hospital
Jose Osorio **Anil Rajendra**	Grandview Medical Center
Benjamin D'Souza	Penn Presbyterian Medical Center
Frank Cuoco	Trident Health System
Marcos Daccarett	St. Luke's Regional Medical Center
John Harding	Doylestown Hospital
Robert Pickett	St. Thomas Heart at Baptist Hospital
Andrea Natale	Texas Cardiac Arrhythmia Research Foundation
Sanjaya Gupta	Saint Luke's Hospital of Kansas City
Moussa Mansour	Massachusetts General Hospital
Jeffrey Winterfield	Medical University of South Carolina
Tom McElderry	University of Alabama at Birmingham
Larry Chinitz	New York University Langone Medical Center
Hugh Calkins	Johns Hopkins Hospital
Zayd Eldadah	MedStar Washington Hospital Center

Principal Investigators	Investigational Site
Michael Mangrum	University of Virginia Medical Center
Douglas Gibson	Scripps Clinic
Christopher Woods	California Pacific Medical Center
Christopher Ellis	Vanderbilt University Medical Center
Edward Gerstenfeld	University of California, San Francisco
Stavros Mountantonakis	Northwell Health
Wilber Su	Banner University Medical Center – Phoenix
Pasquale Santangeli **David Lin**	Hospital of the University of Pennsylvania
Jamie Kim	Catholic Medical Center - Manchester
Matthew Latacha	Nebraska Methodist Hospital
Chinmay Patel	Pinnacle Health Cardiovascular Institute Inc.
Kenneth Ellenbogen	Virginia Commonwealth University Health System
Blair Halperin	Providence St. Vincent Medical Center
Andre D'Avila	Beth Israel Deaconess Medical Center

Data Safety Monitoring Board
Jason T. Connor, PhD
John D. Day, MD
George Neal Kay, MD (Chair)
Eric N. Prystowsky, MD

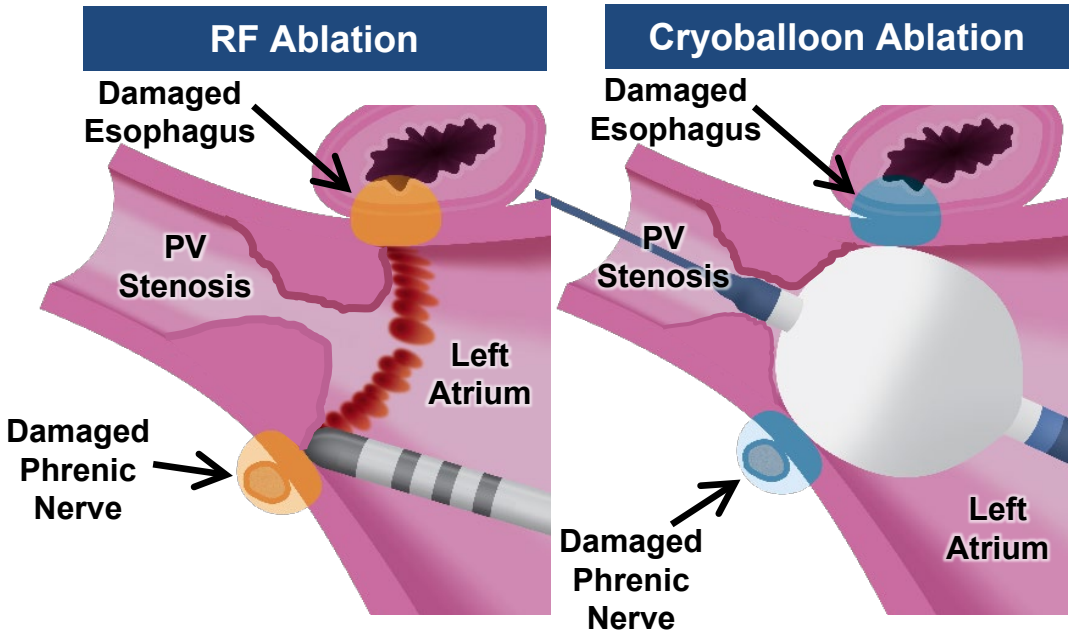
Clinical Events Committee
Henry Hsia, MD
Daniel Lustgarten, MD, PhD (Chair)
Peter Zimetbaum, MD

Background – Conventional Thermal Ablation (RF & Cryo)

Thermal Ablation (RF / Cryo) – Highly effective in treating Paroxysmal AF

Thermal energies propagate indiscriminately, spreading into surrounding tissue

- Physicians take precautions to minimize damage to these adjacent structures
- But serious complications can nonetheless rarely occur



VY.Reddy, P.Neuzil, J.Koruth, et al, *JACC* 74:315–26 (2019)

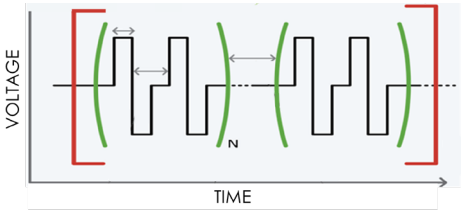
Thermal Complication	HRS Consensus 2017	Recent Study
AE Fistula	**0.02-0.1%**	0.038% RFA; 0.0015% Cryo **65.8% Mortality** *(POTTER-AF 2023)*
PV Stenosis	**Up to 0.4%**	0% severe 20.8% mild/moderate *(ADVICE 2020)*
Phrenic Nerve Palsy	**< 1%**	3% lasting >12mo 0.06% symptomatic and permanent *(YETI Registry 2022)*

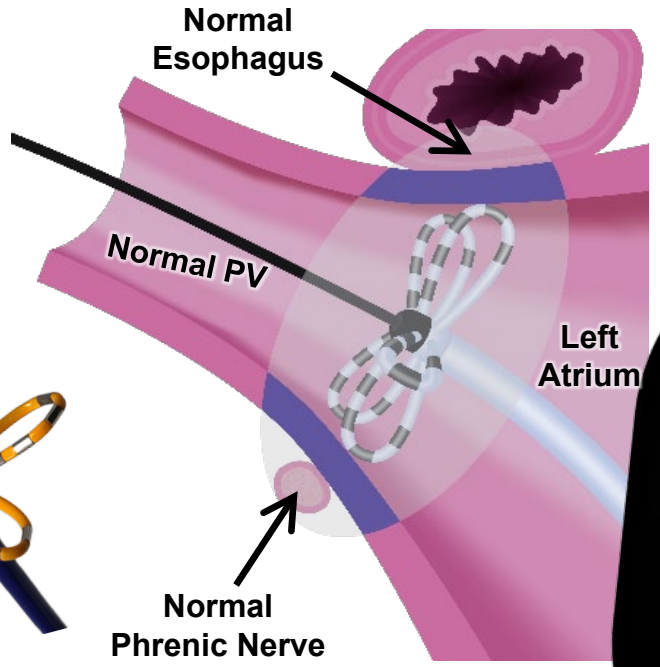
Background – Pulsed Field Ablation (PFA)

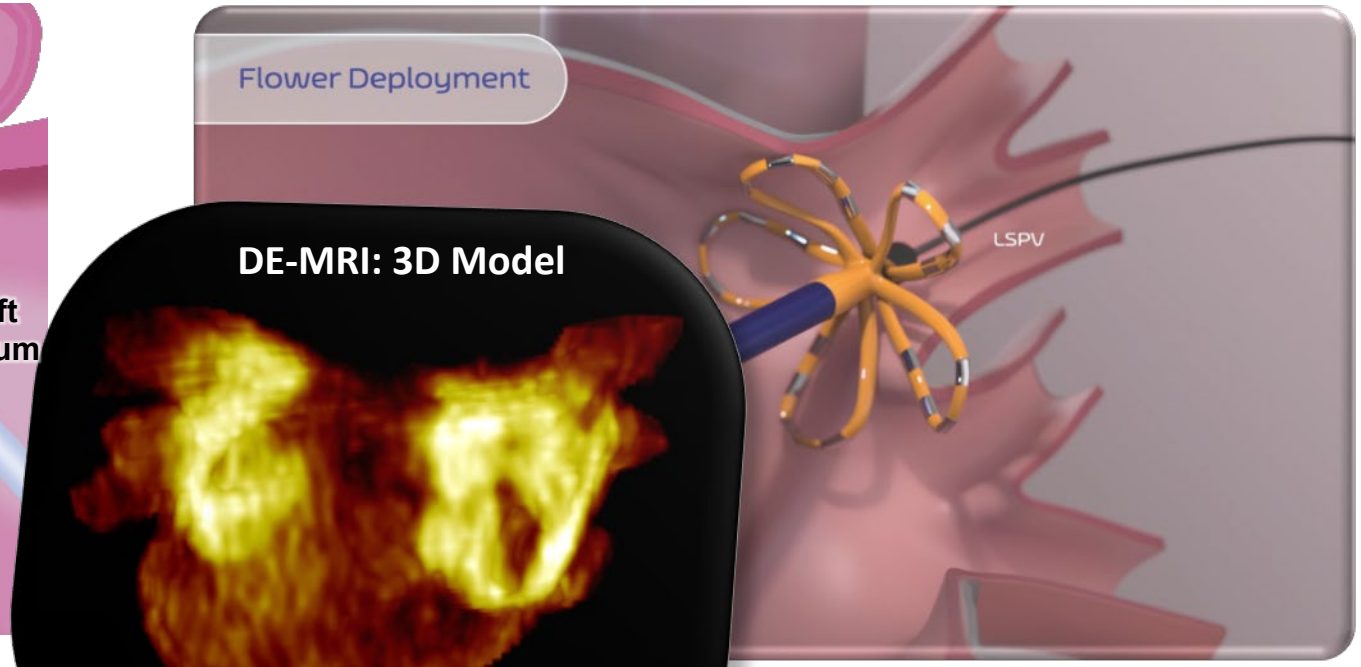
PFA ➔ employs **high energy electrical pulses** for microsecond durations

➔ exhibits **sufficient ablative specificity –** myocardial tissue can be largely preferentially ablated with limited effect on adjacent tissues

➔ Despite no safety precautions being taken (eg, Eso temp monitoring, phrenic pacing)

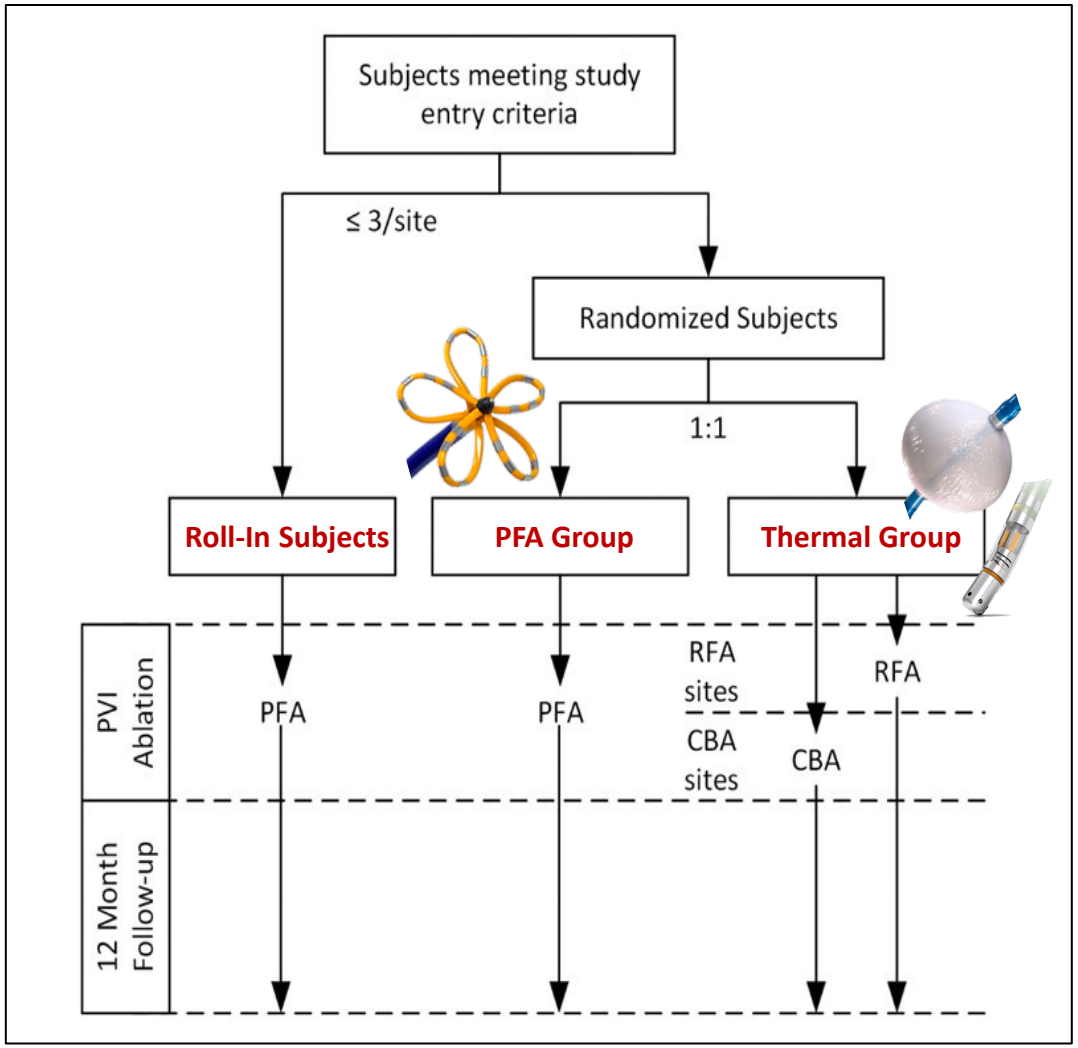






ADVENT: Study Design

- Multicenter, prospective, **single-blind, non-inferiority,** randomized controlled trial
- **Objective:** Compare the effectiveness and safety of **PFA** to standard-of-care, **thermal ablation** using either force-sensing RF or cryoballoon ablation
- **Indication:** Drug-refractory (Class I-IV) paroxysmal AF
  - **Randomized 1:1 PFA to thermal**
  - Each center was assigned to either RF or Cryo as their control
- **Follow-up Duration: 12 months**
- **Follow-up Efficacy Assessments:**
  - 72-hr Holter at 6 and 12 months
  - Trans-telephonic ECG monitoring: Weekly & for Symptoms

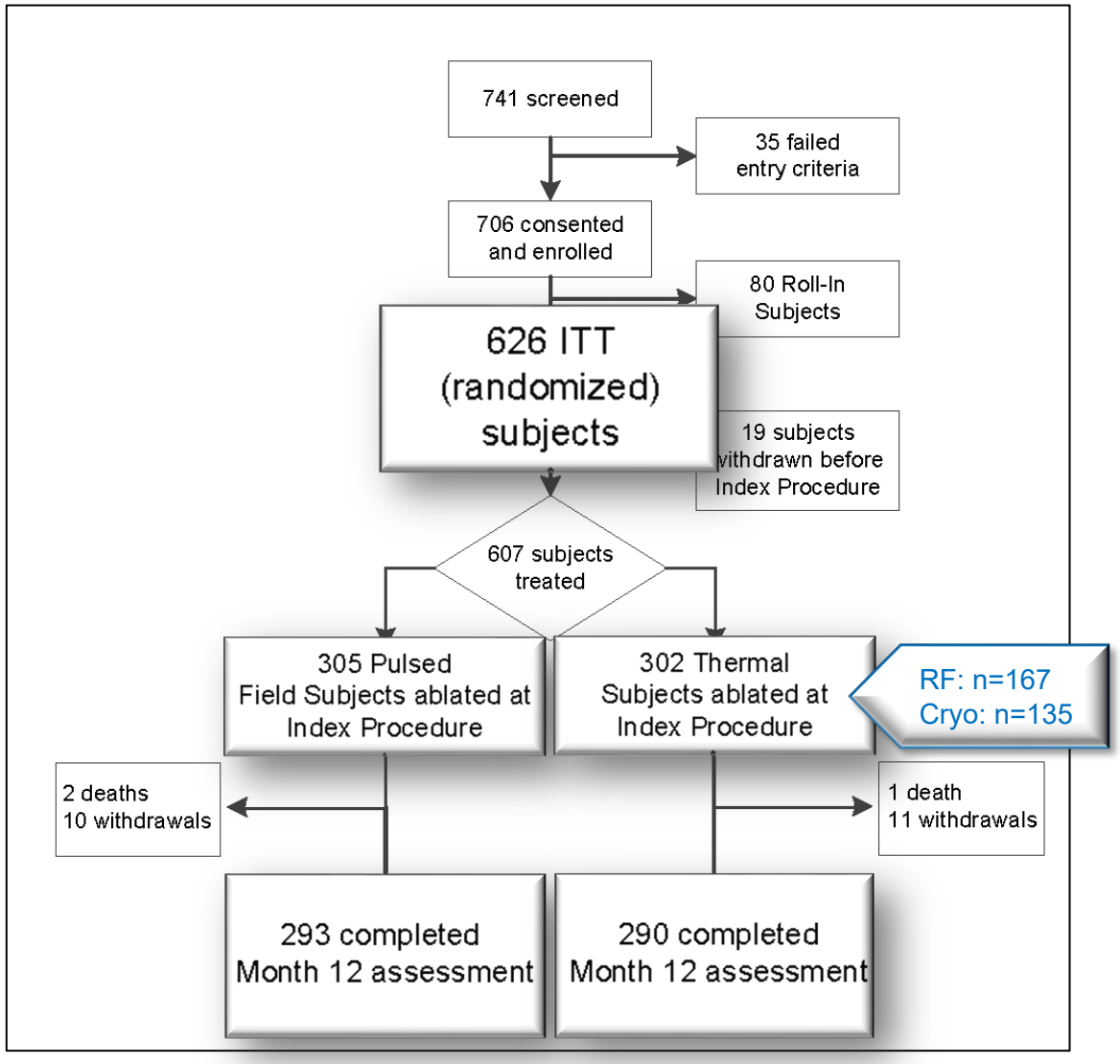


Study Design - Endpoints

Effectiveness	Safety
Primary Endpoint Treatment success required both **acute procedural** and **chronic success** which includes: ○ Freedom from documented **AF, AFL, or AT ≥30s** ○ Freedom from **repeat ablation** for AF, AFL, or AT at any time ○ Freedom from **cardioversion** for AF, AFL, or AT ○ Freedom from use of **Class I or III AAD** after the blanking period ***or*** amiodarone at any time Tested for **non-inferiority** to thermal ablation	**Primary Endpoint** Composite of defined device- or procedure-related serious adverse events **(SAEs) occurring within 7 days** of the primary procedure and SAEs **(PV stenosis and atrio-esophageal fistula) out to 12 months** Tested for **non-inferiority** to thermal ablation
Secondary Endpoint Same as primary but tested for **superiority** to thermal ablation	**Secondary Endpoint** Change in aggregate **PV cross-sectional area** between baseline and 3 months compared between randomization groups Tested for **superiority** of PFA to thermal ablation

Study Design

- **Bayesian statistical methods, with noninformative prior distributions**
- **Sample size determined adaptively**
  - Interim analysis at 350, 450, **550**, 650, 750 to assess predictive probability that noninferiority would be demonstrated
  - **95% power** to assess for non-inferiority (assumed **efficacy of 65%** & assumed **safety event rate of 8%**)
- **Both primary endpoints were tested for non-inferiority of PFA to thermal ablation**
  - Absolute margin for safety: 8%
  - Absolute margin for effectiveness: 15%
- **All endpoints were analyzed in the modified intention-to-treat population**
  - Randomized patients in whom **ablative energy was delivered** with the assigned catheter



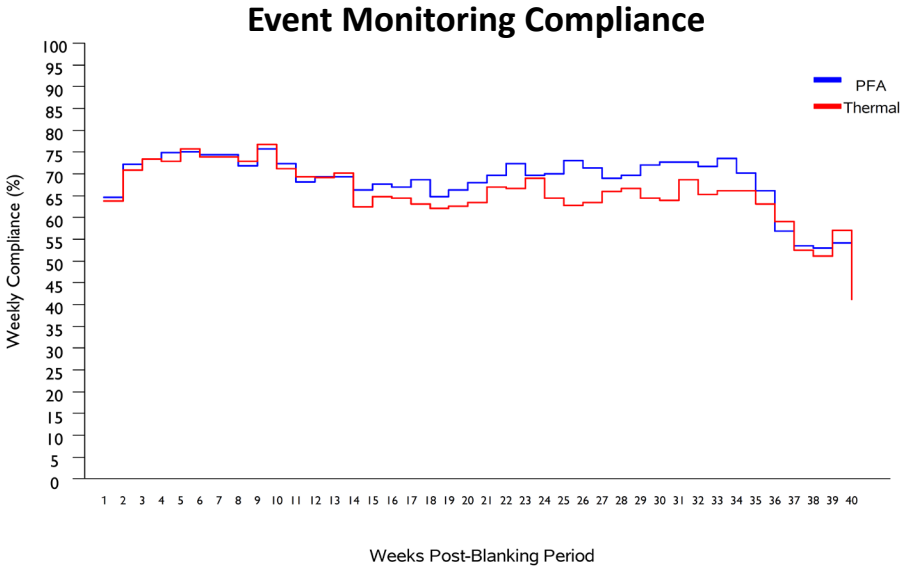
Patient Demographics

	Pulsed Field Group (n=305)	Thermal Group (n=302)
Age, years	62.4 ± 8.7	62.5 ± 8.5
Sex - Female, no. (%)	103 (33.8)	107 (35.4)
Body mass index, kg/m^2	28.3 ± 4.6	29.0 ± 4.8
CHA_2DS_2-VASc Score, mean	1.7 ± 1.2	1.7 ± 1.2
Years since first PAF diagnosis	3.8 ± 6.2	3.3 ± 4.5
Typical atrial flutter history, no. (%)	83 (27.2)	100 (33.1)
Left atrial diameter, mm	38.8 ± 5.7	39.6 ± 5.8
Concomitant clinical conditions, no (%)		
Coronary artery disease	32 (10.5)	51 (16.9)
CHF: NYHA Class I or II	59 (19.3)	59 (19.5)
Diabetes	33 (10.8)	32 (10.6)
Dyslipidemia	133 (43.6)	141 (46.7)
Hypertension	174 (57.0)	159 (52.6)
Sleep apnea	81 (26.6)	88 (29.1)
Prior stroke / TIA	12 (3.9)	15 (5.0)
AADs at baseline, no. (%)		
Any AAD	301 (98.7)	300 (99.3)
Class I	115 (37.7)	101 (33.4)
Class II	174 (57.0)	201 (66.6)
Class III	70 (23.0)	72 (23.8)
Class IV	79 (25.9)	66 (21.9)

Patient Compliance & Blinding

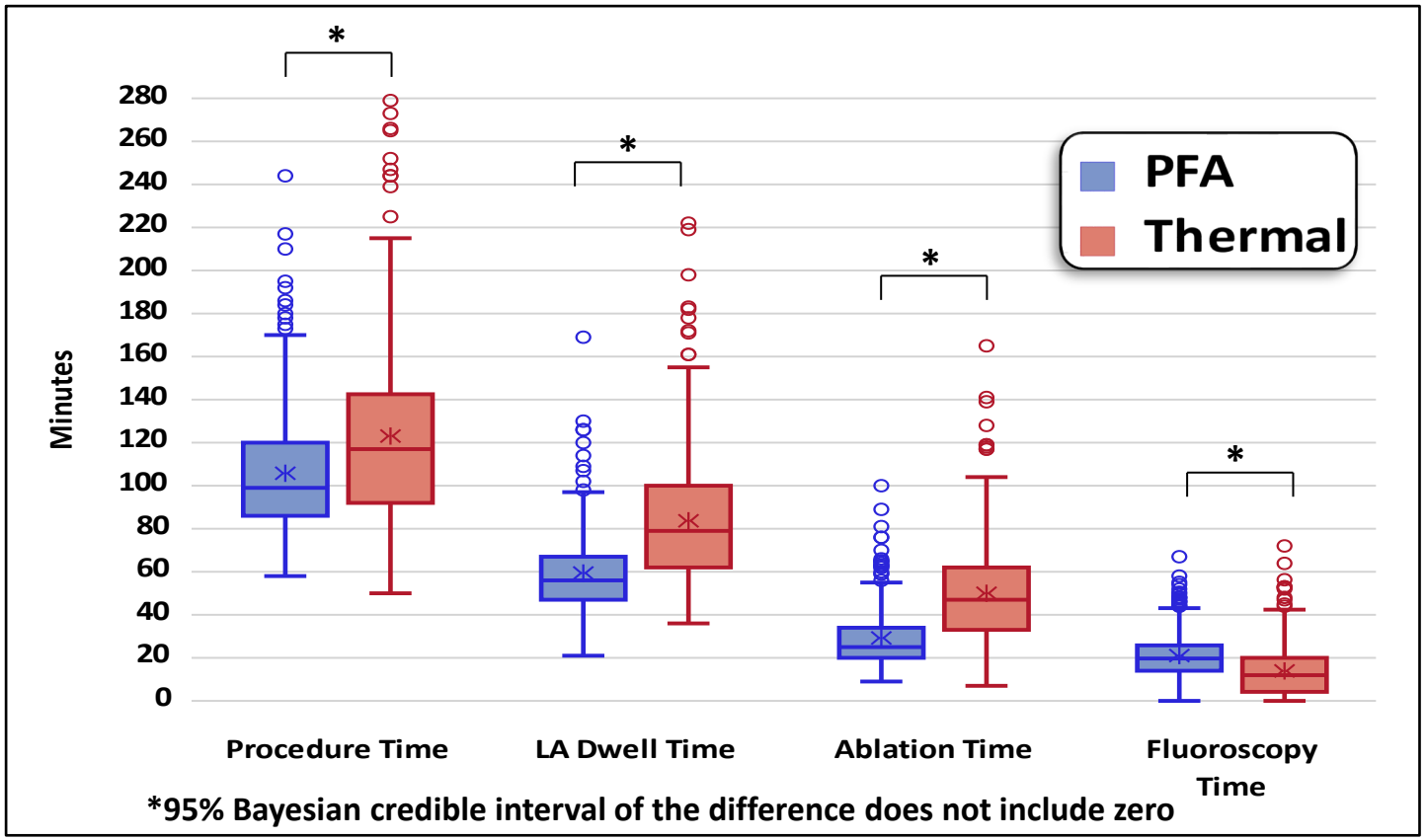
Rhythm Monitoring Compliance	Pulsed Field Subjects no. / total no. (%)	Thermal Subjects no. / total no. (%)
Clinical follow-up visits	1800/1813 (99.3)	1786/1799 (99.3)
Weekly event monitoring	8,101/11,765 (68.9)	7,655/11,572 (66.2)
12-Lead Electrocardiograms	540/601 (89.9)	526/593 (88.7)
Holter monitoring (72-hour)	508/600 (84.7)	464/593 (78.2)

Blinding Assessment		Pre-Discharge no. / total no. (%)	Month 12 no. / total no. (%)
Subjects with Blinding Data			
Pulsed Field Subjects		287/305 (94.1)	290/305 (95.1)
Thermal Subjects		283/302 (93.7)	289/302 (95.7)
Subject-Asserted Treatment Status			
Pulsed Field	Guess PFA	44/287 (15.3)	96/290 (33.1)
	Guess Thermal	6/287 (2.1)	8/290 (2.8)
	Don't Know	**237/287 (82.6)**	**186/290 (64.1)**
Thermal	Guess PFA	31/283 (11.0)	45/289 (15.6)
	Guess Thermal	16/283 (5.7)	44/289 (15.2)
	Don't Know	**236/283 (83.4)**	**200/289 (69.2)**



Procedural Characteristics

- Acute success of PV isolation: PFA - **99.6%** & Thermal - **99.8%**
- Procedure time, LA dwell, and ablation time were **significantly shorter for PFA**
- Fluoroscopy time was longer with PFA (but by only ~7 min)

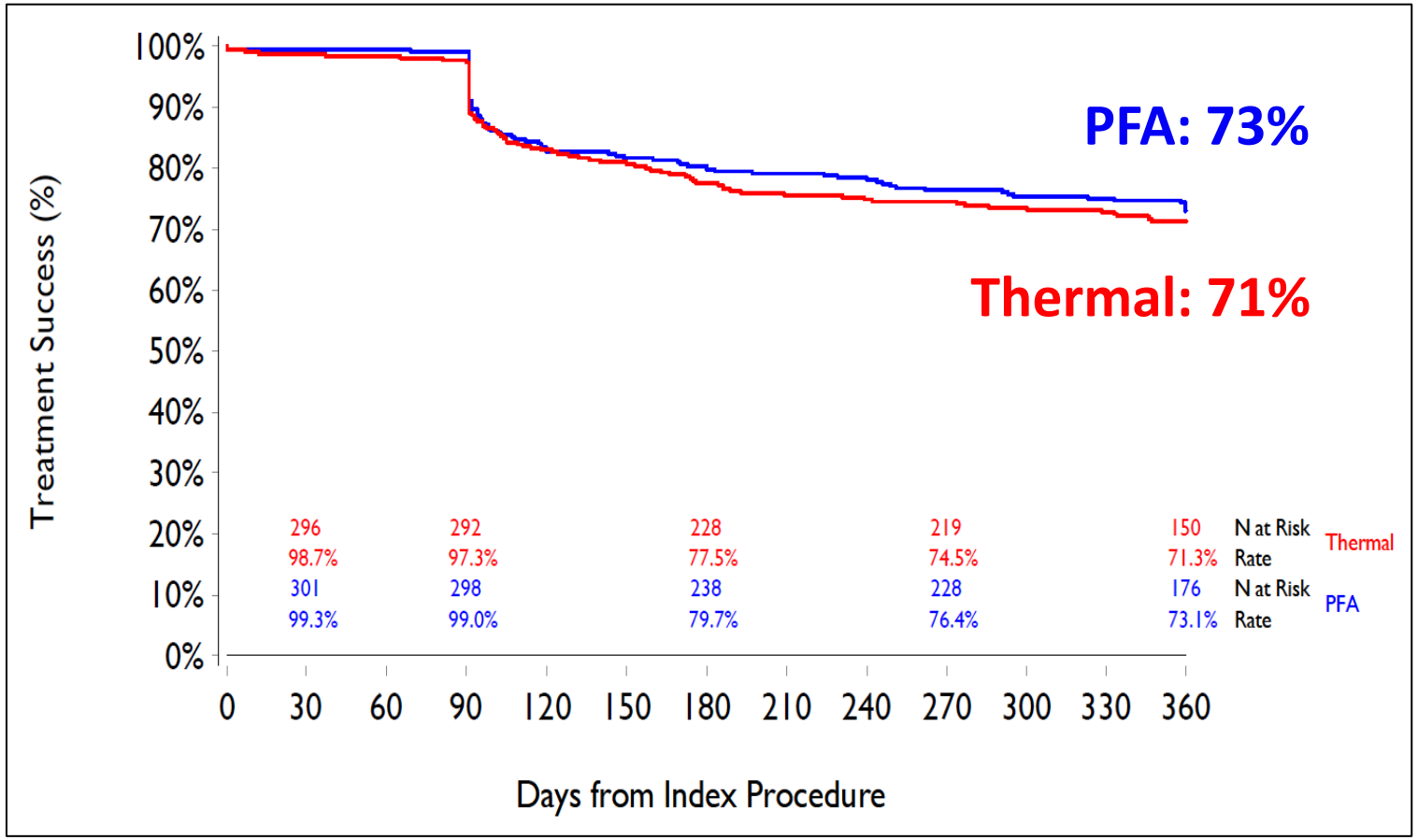


Definitions:

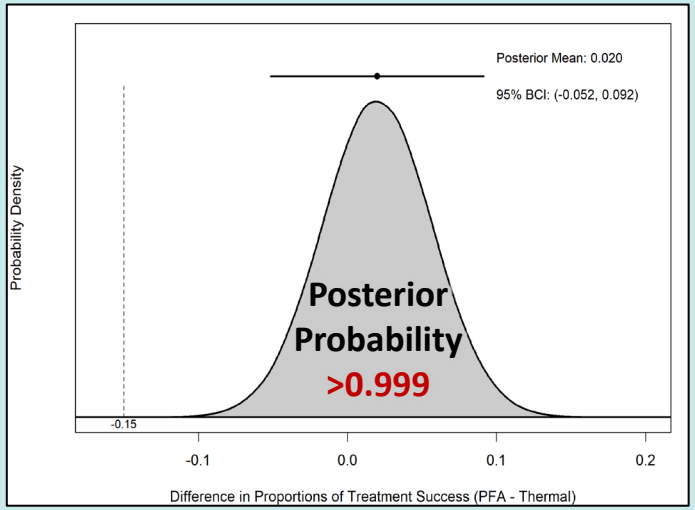
- **Procedure time:** venous access to access closure including a 20-minute post-ablation waiting period and CTI, if performed (23% PFA, 28.5% Thermal subjects)
- **LA Dwell time:** total time in minutes that an ablation catheter is in the LA
- **Ablation time:** elapsed time from first to last ablation
- **Rem**: Most operators* had never used this PFA catheter (***vs*** most had performed thousands of thermal ablation procedures)

** Only 1 center had prior clinical experience with this PFA catheter*

Primary Effectiveness Endpoint

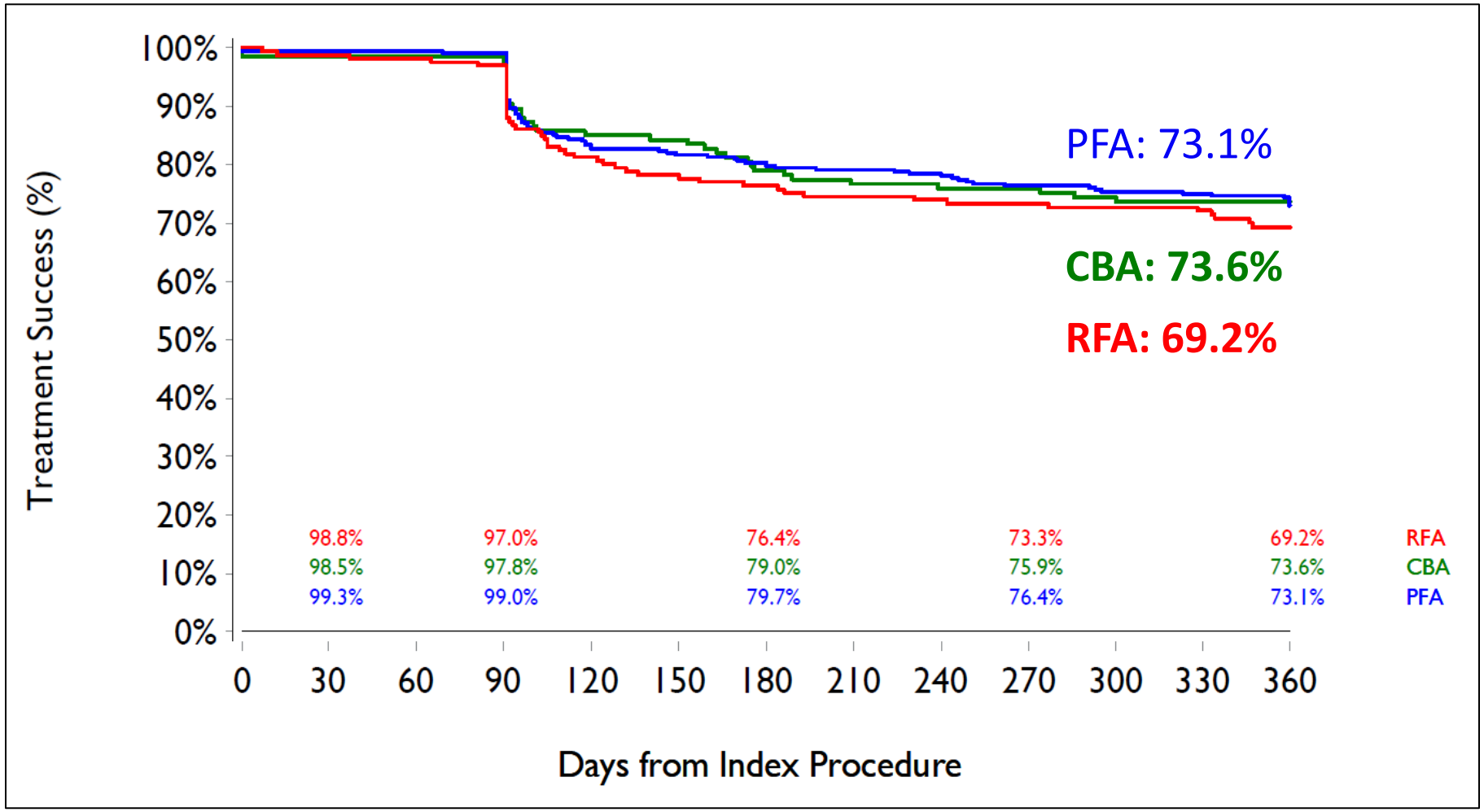


Single-procedure, off-drug treatment success between PFA and thermal ablation met the criterion for **non-inferiority**



➢ **Did not meet the criteria for Superiority (of PFA)**

1-Year Effectiveness by Ablation Modality



Additional Effectiveness Endpoints

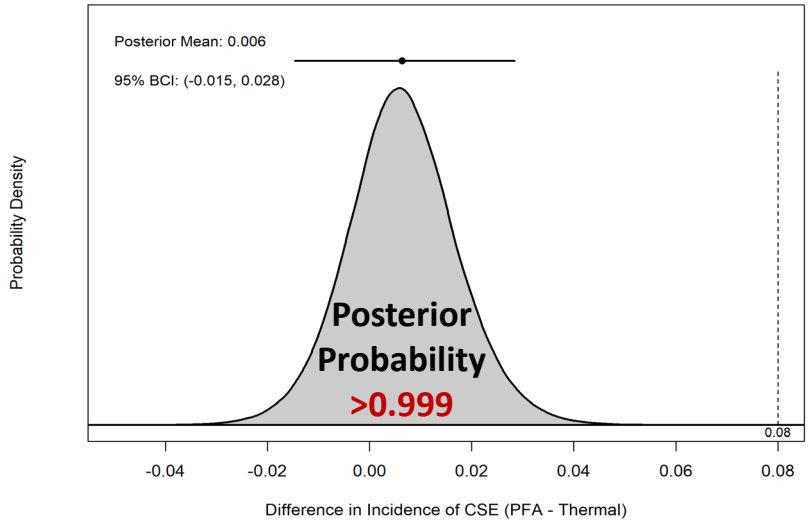
	Pulsed Field Group (n=305)	Thermal Group (n=302)	Difference (95% BCI)
Mode of first failure of the primary efficacy endpoint, no. (%)			
Acute procedural failure	2 (0.8)	2 (0.8)	0 (-1.5, 1.5)
Recurrent atrial arrhythmia (AF / AFL / AT), ≥ 30 seconds	51 (17.2)	48 (16.4)	0.7 (-5.2, 6.7)
Cardioversion after the 3-month blanking period	1 (0.5)	0 (0.2)	0.3 (-0.6, 1.5)
Use of Class I/III AADs after the 3-month blanking period	24 (8.1)	27 (9.2)	-1.1 (-5.6, 3.4)
Amiodarone use at any time	1 (0.5)	7 (2.5)	-2.0 (-4.2, -0.2)
Repeat catheter ablation at any time	1 (0.5)	1 (0.5)	0 (-1.2, 1.2)
Other Prespecified Efficacy Endpoints			
Treatment success allowing re-ablation	204 (73.3)	194 (71.3)	2.0 (-5.2, 9.2)
Treatment success allowing Class I/III AADs	219 (78.5)	208 (76.3)	2.3 (-4.4, 9.0)
Quality of Life – Change from baseline to 1-year			
AFEQT score	30.1 (27.7, 32.5)	27.7 (25.2, 30.3)	2.3 (-1.19, 5.88)
EQ-5D score	0.05 (0.03, 0.06)	0.04 (0.03, 0.06)	0.01 (-0.02, 0.03)
EQ-VAS score	7.9 (6.5, 9.4)	6.8 (5.1, 8.4)	1.2 (-1.03, 3.36)

Primary Safety Endpoint

	Serious Composite Safety Events	
	Pulsed Field Group, N = 305 n (%)	Thermal Group, N = 302 n (%)
Any Composite Safety Event	**6 (2.0) †**	**4 (1.3)**
Death	1 (0.3)	0
Myocardial infarction	0	0
Persistent phrenic nerve palsy	0	0
Stroke	0	1 (0.3)
Transient ischemic attack	1 (0.3)	0
Systemic thromboembolism	0	0
Cardiac tamponade or perforation	2 (0.7)	0
Pericarditis	1 (0.3)	0
Pulmonary edema	1 (0.3)	1 (0.3)
Vascular access complication	1 (0.3)	2 (0.7)
Heart block	0	0
Gastric motility/ pyloric spasm	0	0
Pulmonary vein stenosis	0	0
Atrio-esophageal fistula	0	0

† One patient who sustained a cardiac tamponade subsequently died; accordingly, the individual components add to more than the composite total.

The primary safety endpoint occurred in 6 PFA and 4 thermal subjects with an estimated incidence of 2.1% versus 1.5% (posterior means), meeting the criteria for **non-inferiority**



Primary Safety Endpoint

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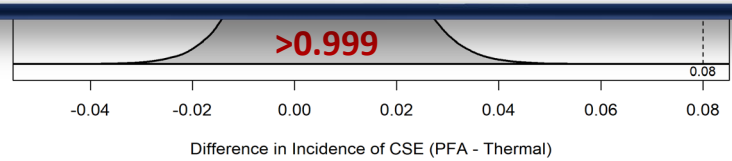
Death	1 (0.3)	0
Myocardial infarction	0	0
Persistent phrenic nerve palsy	0	0
Stroke	0	1 (0.3)
Transient ischemic attack	1 (0.3)	0
Systemic thromboembolism	0	0
Cardiac tamponade or perforation	2 (0.7)	0
Pericarditis	1 (0.3)	0
Pulmonary edema	1 (0.3)	1 (0.3)
Vascular access complication	1 (0.3)	2 (0.7)
Heart block	0	0
Gastric motility/ pyloric spasm	0	0
Pulmonary vein stenosis	0	0
Atrio-esophageal fistula	0	0

† One patient who sustained a cardiac tamponade subsequently died; accordingly, the individual components add to more than the composite total.

Is this death spurious or specific to PFA?

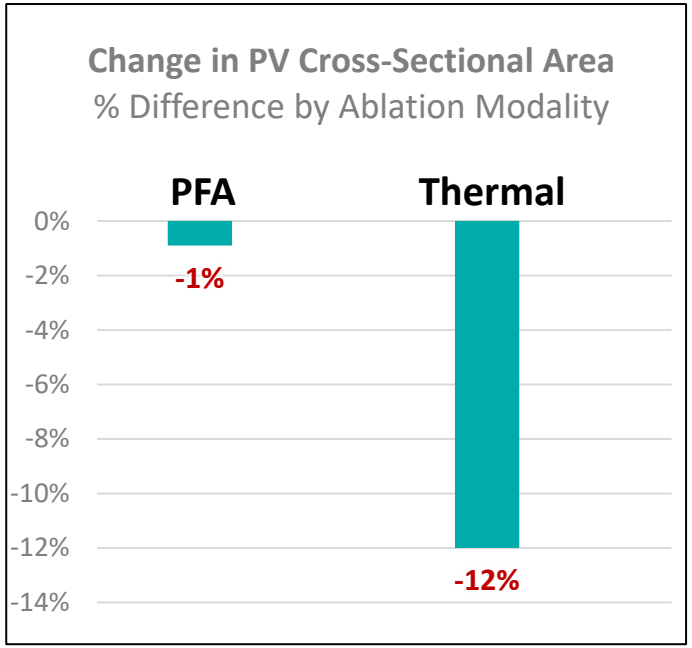
- The pentaspline PFA catheter received CE-Mark Approval in March 2021
- Registry of all sites performing PFA
  - **24 EU centers / 77 operators**
  - **1,568 patients**
- Mortality:
  - **1 in 1,568 → 0.06%**

M.Turagam, P.Neuzil, B.Schmidt…VY.Reddy, *Circulation* 148:35–46 (2023)



Secondary Safety Endpoint

- *Is there any evidence of tissue specificity to PFA?*
- Assess for any **changes in post-ablation PV diameter**
  → Differentially favorable healing with PFA??
- Greater reduction in PV cross-sectional area in the thermal (-1.18 cm^2; **12.0%**) *versus* PFA (-0.18 cm^2; **0.9%**) group
- **Met the prespecified criterion for superiority of PFA**



Change in PV cross-sectional area	Pulsed Field Group (n=305)	Thermal Group (n=302)	Difference (95% Credible Interval)	Posterior Probabilities – Superiority
Absolute difference, cm^2, mean (95% BCI)	-0.18 (-0.37, 0.00)	-1.18 (-1.39, -0.97)	1.00 (0.72, 1.28)	**>0.999**
Percent difference, mean (95% BCI)	-0.9% (-3.0, 1.1)	-12.0% (-14.2, -9.7)	11.0% (8.0, 14.1)	

Additional Safety Endpoint – Serious & Non-Serious CSE

	Serious Composite Safety Events		Serious & Non-Serious Composite Safety Events	
	Pulsed Field Group, N = 305 n (%)	Thermal Group, N = 302 n (%)	Pulsed Field Group, N = 305 n (%)	Thermal Group, N = 302 n (%)
Any Composite Safety Event	**6 (2.0) †**	**4 (1.3)**	**7 (2.3) †**	**6 (2.0)**
Death	1 (0.3)	0	1 (0.3)	0
Myocardial infarction	0	0	0	0
Persistent phrenic nerve palsy	0	0	0	2 (0.7)
Stroke	0	1 (0.3)	0	1 (0.3)
Transient ischemic attack	1 (0.3)	0	1 (0.3)	0
Systemic thromboembolism	0	0	0	0
Cardiac tamponade or perforation	2 (0.7)	0	2 (0.7)	0
Pericarditis	1 (0.3)	0	2 (0.7)	0
Pulmonary edema	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Vascular access complication	1 (0.3)	2 (0.7)	1 (0.3)	2 (0.7)
Heart block	0	0	0	0
Gastric motility/ pyloric spasm	0	0	0	0
Pulmonary vein stenosis	0	0	0	0
Atrio-esophageal fistula	0	0	0	0

† One patient who sustained a cardiac tamponade subsequently died; accordingly, the individual components add to more than the composite total.

Both thermal subjects treated with cryoballoon ablation

Additional Safety Endpoints

	Pulsed Field Subjects no. / total no. (%)	Thermal Subjects no. / total no. (%)
Phrenic Nerve Injury (PNI)		
Intraprocedural PNI *Resolved during ablation procedure*	1/305 (0.3)	4/302 (1.3)
Resolved PNI *With documented resolution*	3/305 (1.0)	1/302 (0.3)
Persistent PNI *Without documented resolution*	0/305 (0)	2/302 (0.7)
Total with any PNI	4/305 (1.3)	7/302 (2.3)
Brain MRI Sub-Study: Silent Cerebral Lesions / Events (MRI within 48 hours)		
Center Adjudicated	6/34 (17.6)	4/37 (10.8)
Core Lab Adjudicated	3/33 (9.1)	0/37 (0)

Limitations

- Trial was not powered for superiority
- Implantable loop recorders not employed → Cannot rule out undetected asymptomatic recurrences of AF/AFL
- These safety and efficacy data may not be applicable for other PFA technologies

Conclusions

- The *ADVENT* RCT demonstrated that in performing PVI for the treatment of Paroxysmal AF, the **safety and effectiveness of PFA was non-inferior to thermal ablation (either RFA or CBA)**
  - By operating physicians who were highly-experienced with thermal ablation, but not PFA
- With all ablation technologies, ablation safety and success were better than anticipated
  - One-year results across all modalities were similar
- Significantly more efficient procedure times with PFA
- PV narrowing not observed with PFA (unlike with thermal ablation)
- Data consistent with initial post-approval EU clinical experience *

* M.Turagam, P.Neuzil, B.Schmidt … VY.Reddy, *MANIFEST-PF* Registry *Circulation* 148:35–46 (2023)

Thank You

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ORIGINAL ARTICLE

Pulsed Field or Conventional Thermal Ablation for Paroxysmal Atrial Fibrillation

Vivek Y. Reddy, M.D., Edward P. Gerstenfeld, M.D., Andrea Natale, M.D., William Whang, M.D., Frank A. Cuoco, M.D., Chinmay Patel, M.D., Stavros E. Mountantonakis, M.D., Douglas N. Gibson, M.D., John D. Harding, M.D., Christopher R. Ellis, M.D., Kenneth A. Ellenbogen, M.D., David B. DeLurgio, M.D., Jose Osorio, M.D., Anitha B. Achyutha, M.Tech., M.S.E., Christopher W. Schneider, M.Eng., Andrew S. Mugglin, Ph.D., Elizabeth M. Albrecht, Ph.D., Kenneth M. Stein, M.D., John W. Lehmann, M.D., M.P.H., and Moussa Mansour, M.D., for the ADVENT Investigators*