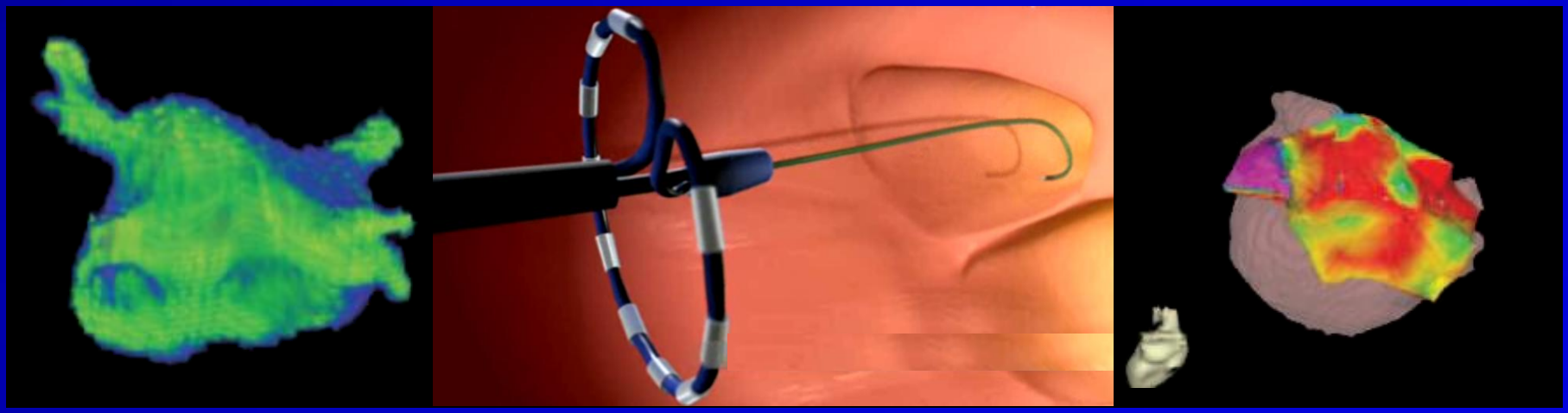


Medtronic Cardiac Ablation System P100008

Circulatory System Devices Advisory Panel

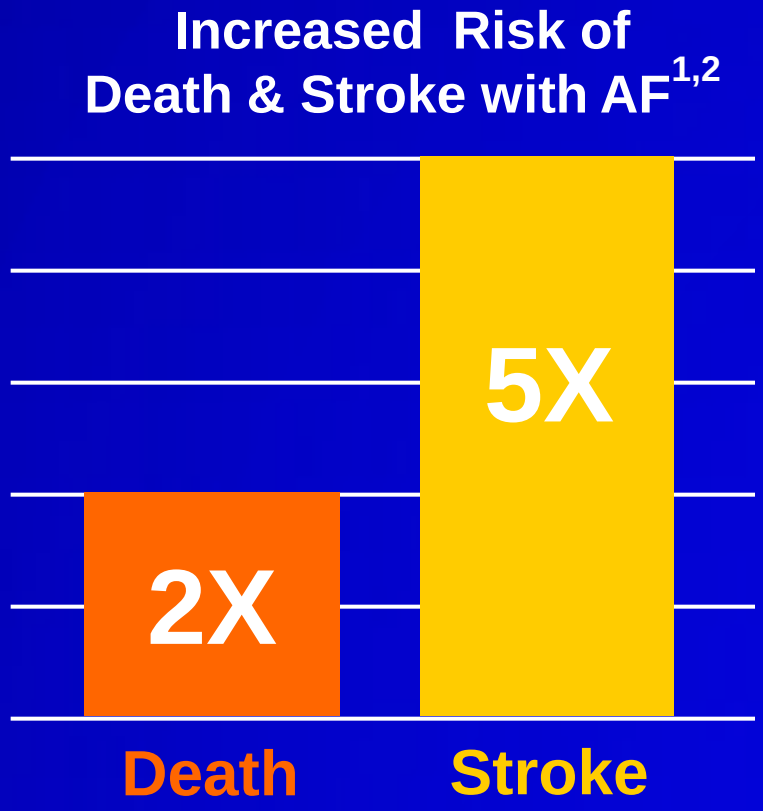
October 27, 2011

David M. Steinhaus, MD

Vice President and Medical Director

Medtronic Cardiac Rhythm Disease Management

Atrial Fibrillation is a Serious Disease



- AF affects ~ 2.7M in US[3]
- Incidence increases with age
- Symptomatic
- Reduced Quality of Life

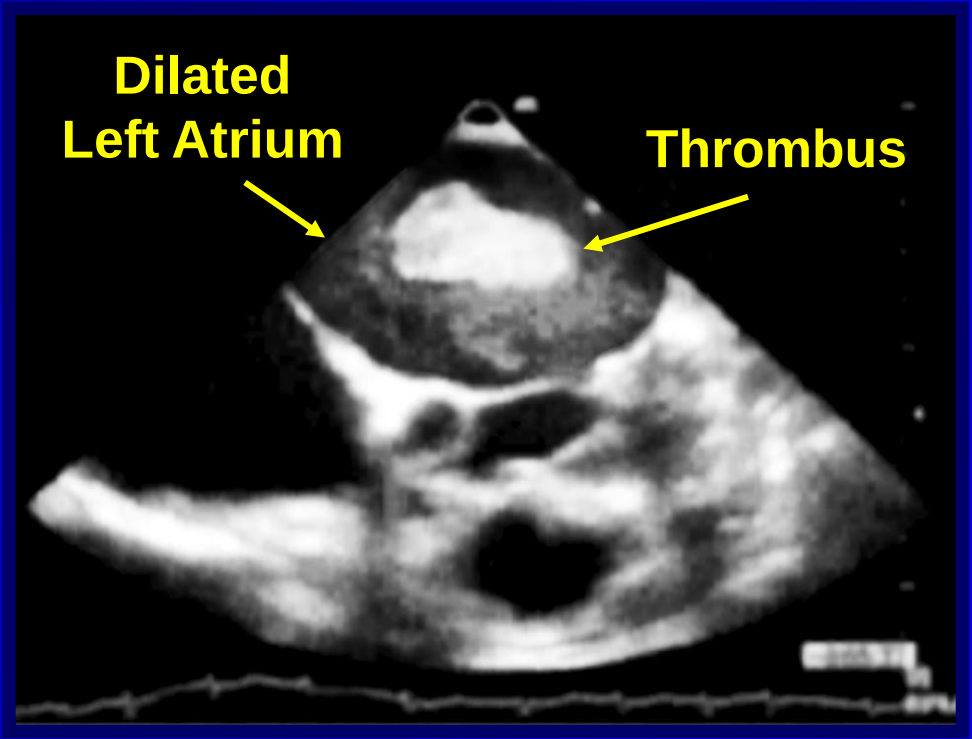
[1]Risk factors for stroke & efficacy of antithrombotic therapy in AF: analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154:1449-1457.

[2]Benjamin, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*.1998;98:946-952.

[3]Go, et al, Prevalence of Diagnosed Atrial Fibrillation in Adults, JAMA, 2001 May 9:285(18): 2370-5

Persistent AF: Complex Population

Functional, Structural and Electrical Changes



- Uncoordinated atrial contractions
- Greater thromboembolic risk
- Reduced cardiac output
- Atrial dilation
- Fibrotic changes
- Electrical remodeling

Persistent AF: Limitations of Current Treatment Options

Anti-Arrhythmic Drugs & Cardioversion	▪ Drug refractory ▪ Cardioversion: temporary resolution
Ablate & Pace	▪ Improves symptoms, AF remains ▪ Pacemaker dependent
Surgical Intervention	▪ Invasive ▪ Concomitant surgical procedure

Medtronic Cardiac Ablation System

- Multi-channel RF Ablation Generator

- Cardiac Ablation Catheters

PVAC

MASC

MAAC

Tailored Treatment of Persistent Atrial Fibrillation (TTOP-AF) Clinical Study

November 2007 – November 2010

Comparing Ablation Therapy to Medical Management in Persistent AF Subjects

- Prospective, multi-center trial
- 210 subjects in 24 centers
- 6-month endpoint
- Safety events independently adjudicated

Indication

For the treatment of:

Symptomatic, drug-refractory persistent or long-standing persistent atrial fibrillation lasting up to 4 years.

Today's Agenda

The Persistent AF Patient and Need for New Technology	**Fred Morady, MD** McKay Professor of Cardiovascular Disease, University of Michigan Health System
TTOP-AF Clinical Study Protocol and Results	**Lucas Boersma, MD, Ph.D.** Head of Cardiology St. Antonius Hospital, The Netherlands
TTOP-AF Results Clinical Perspective	**Hugh Calkins, MD** Nicholas J. Fortuin, M.D. Professor of Cardiology, Johns Hopkins Medical School
Post-Approval Study, Training & Education, Closing Remarks	**David M Steinhaus, MD** Vice President and Medical Director, Medtronic CRDM

Additional Responders

Daryl R. Gress, MD
Associate Professor of Neurology and Neurosurgery
Director, Neurocritical Care, University of Virginia

John Hummel, MD
Director of Clinical Electrophysiology Research
Professor of Medicine, The Ohio State University

Kurt Stromberg, MS
Principal Statistician
Medtronic, Inc.

Persistent AF: Need for New Technology

Fred Morady, MD, FACC
McKay Professor of Cardiovascular Disease
University of Michigan Health System

Identifying a Need

Radiofrequency (RF) Therapy Technology

Focal RF Ablation Catheter

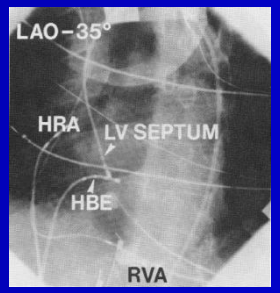
Focal RF Ablation Catheter With Irrigation Cooling

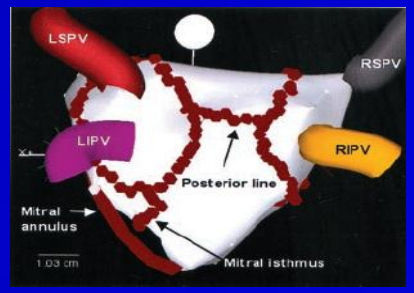
1st Catheter Ablation

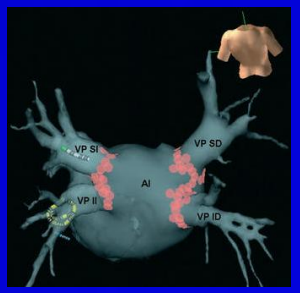
1981 → 1987 → 2011

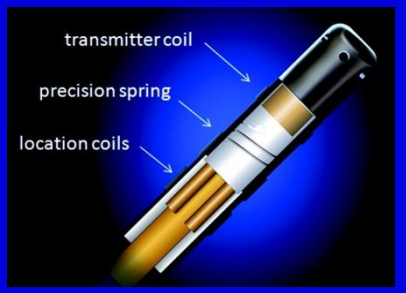
Hardware/Software Technology

Fluoroscopy	3D Mapping	CT/MR Image Integration	Robotic Navigation	Contact Sensing*









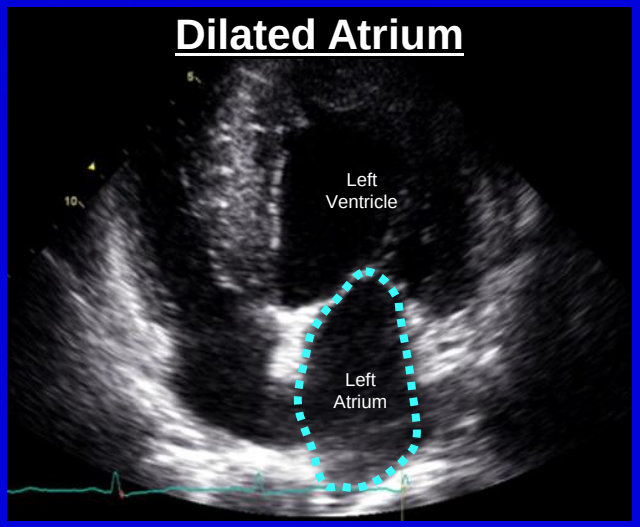
Sousa, et al. Circulation 1991; 84: 567-571 . Scharf C, et al. J Cardiovasc Electrophysiol. 2004;15(5). Merino, et al. Rev Esp Cardiol. 2009;62:314. Ernst S. Heart 2009;95:158-163. Perna F, et. al. Circ Arrhythm Electrophysiol. 2011;4:2 218. * Investigational in the USA.
References not previously provided to FDA

Persistent AF is Different from Paroxysmal AF

- Paroxysmal → minutes to hours
- Persistent AF → continuous until intervention
- AF begets AF
- Left atrium → functional, structural, electrical changes

Left Atrial Functional Changes Reduce Cardiac Output and Increase Stroke Risk

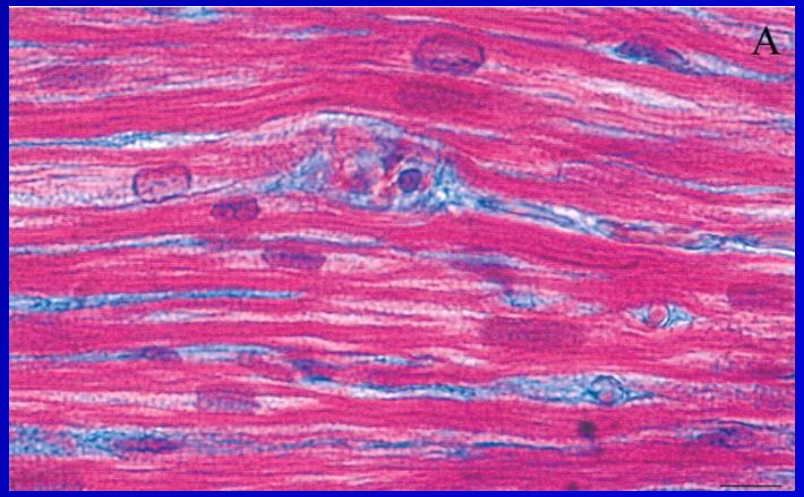
- Loss of coordinated contractions
  - Reduction in cardiac output
  - At risk for stroke
- Leads to left atrial dilitation



Yu CM, et al. *Improvement of atrial function and atrial reverse remodeling after cardiac resynchronization therapy for heart failure*. JACC 2007;50(8)
Reference not previously provided to FDA

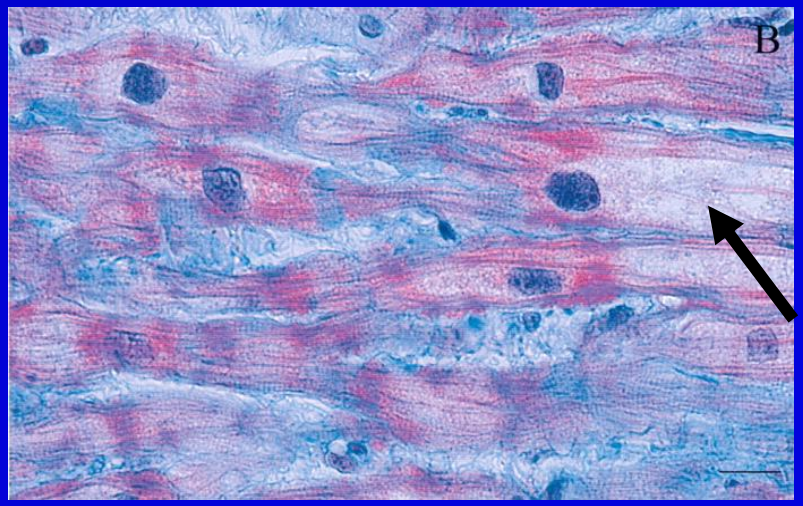
Microscopic Structural Changes Reveal Severe Muscle Degradation and Marked Fibrosis

Normal Atrium



- Healthy cells
- Uniform in size

Fibrillating Atrium

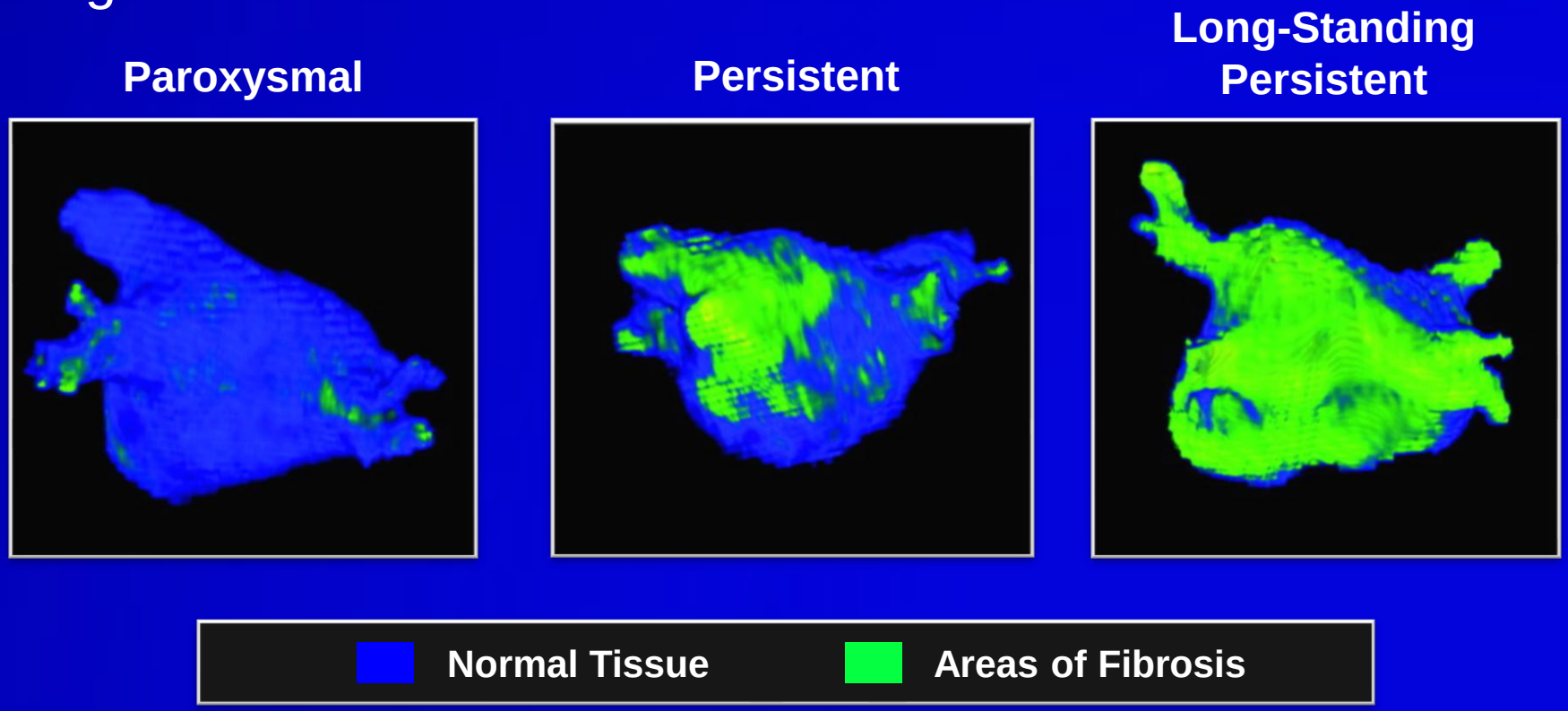


- Enlargement
- Muscle degradation
- Fibrosis

Rücker-Martin C et al. *Differentiation of atrial myocytes during atrial fibrillation: role of fibroblast proliferation in vitro*. Cardiovasc Res 2002;55:38-52

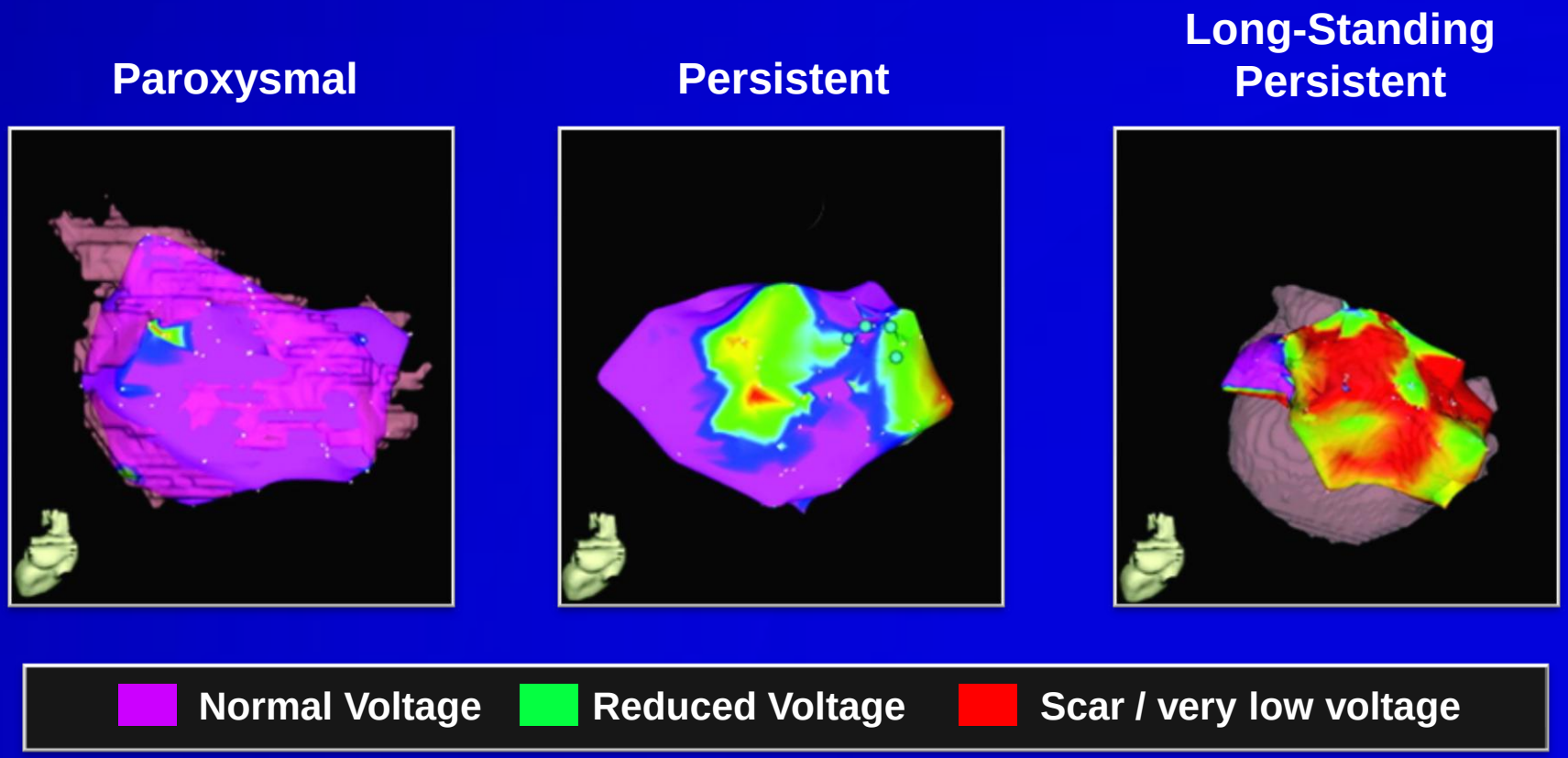
MRI Gadolinium Enhancement Demonstrates Diffuse Left Atrial Fibrosis

Progression of Fibrosis:



Oakes et al. *Detection and quantification of left atrial structural remodeling with delayed enhancement magnetic resonance imaging in patients with atrial fibrillation.* Circulation. 2009;119:1758-67.

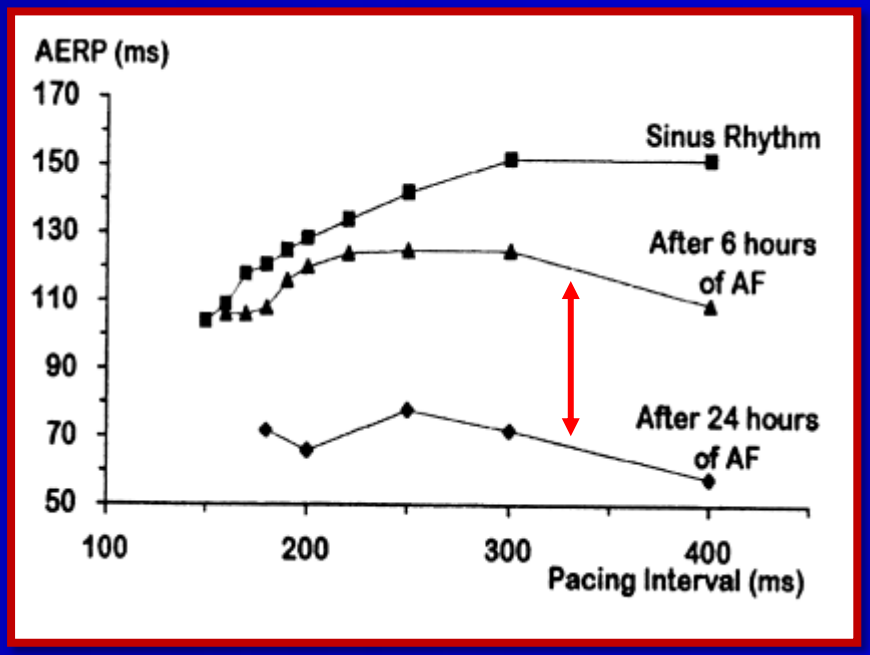
Voltage Mapping Shows Electrical Changes Associated with Areas of Fibrosis



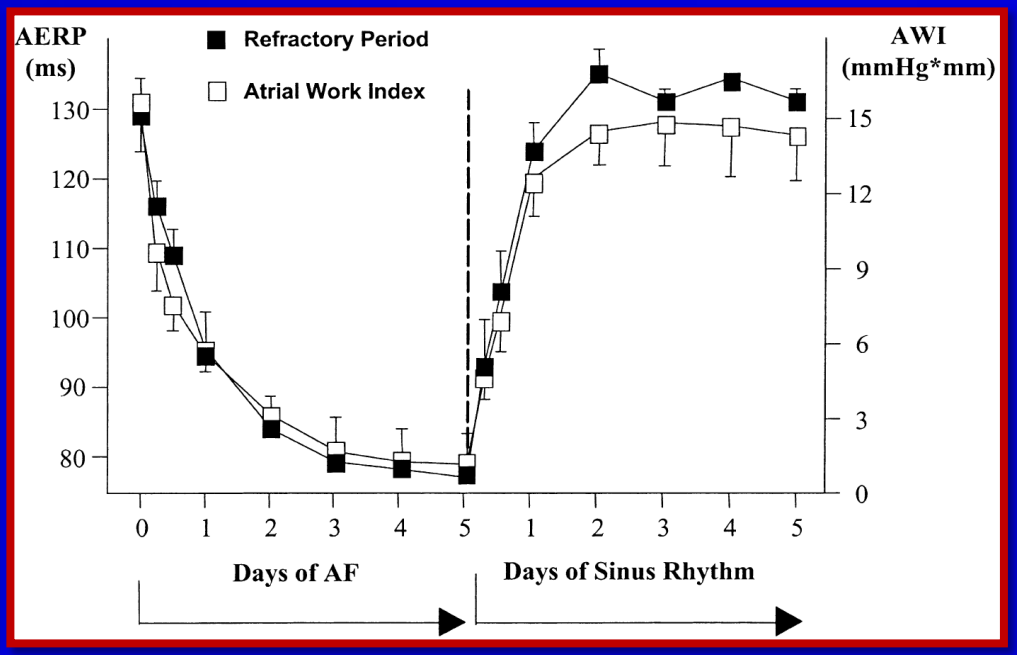
Oakes et al. *Detection and quantification of left atrial structural remodeling with delayed enhancement magnetic resonance imaging in patients with atrial fibrillation*. Circulation. 2009;119:1758-67.

Refractory Period Shortening Promotes AF Maintenance

Atrial Effective Refractory Period (AERP) Changes



AERP Shortens in 24 hours



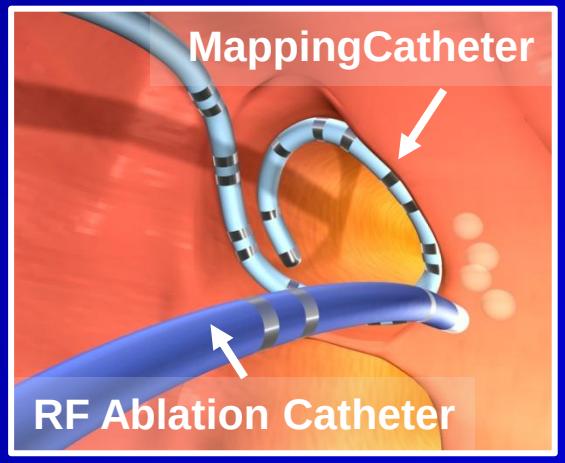
Recovery of AERP within 5 Days of SR restoration

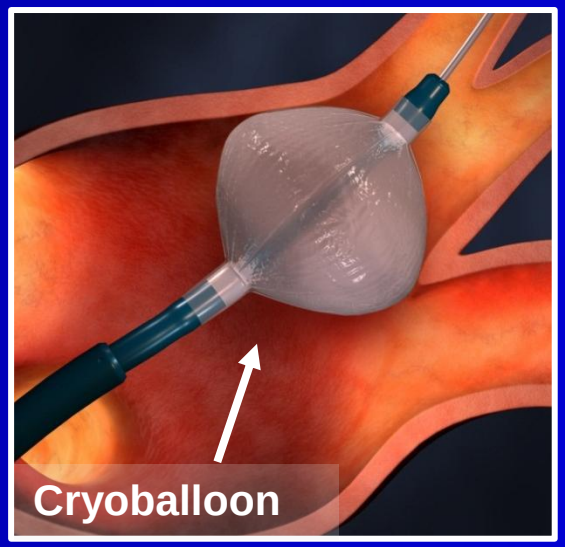
Allessie et al. *Electrical, contractile and structural remodeling during atrial fibrillation.* Cardiovascular Research;2002:54. 230 -246.

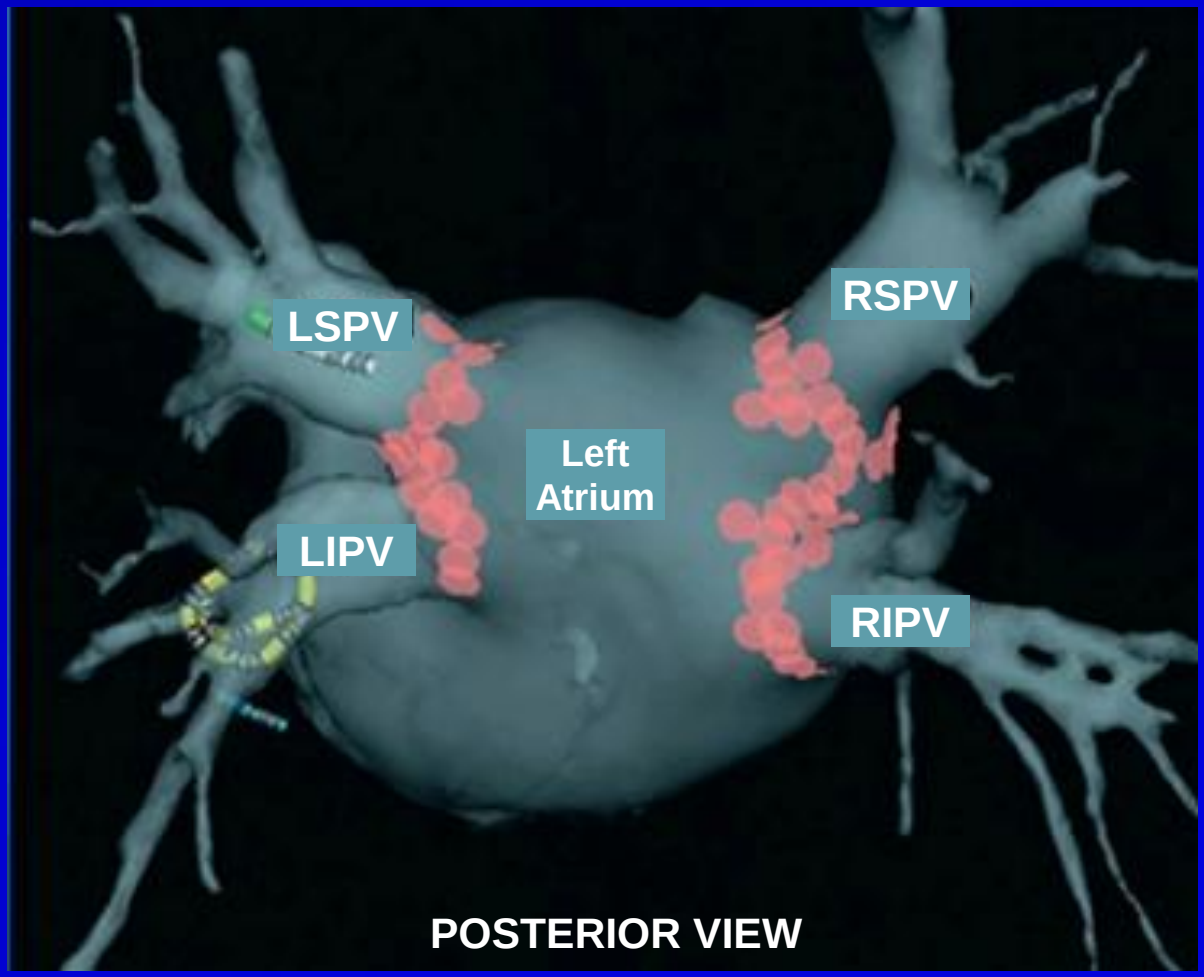
Clinical Consequences of Persistent AF

- Progressively diseased atrium
- Reduced health and quality of life (QoL)
- Symptomatic → fatigue, lack of energy, short of breath, lightheaded, palpitations
- Limited therapy options → fail drugs and cardioversion, AV node ablation unsuitable, surgical MAZE invasive

Catheter Ablation For Paroxysmal AF

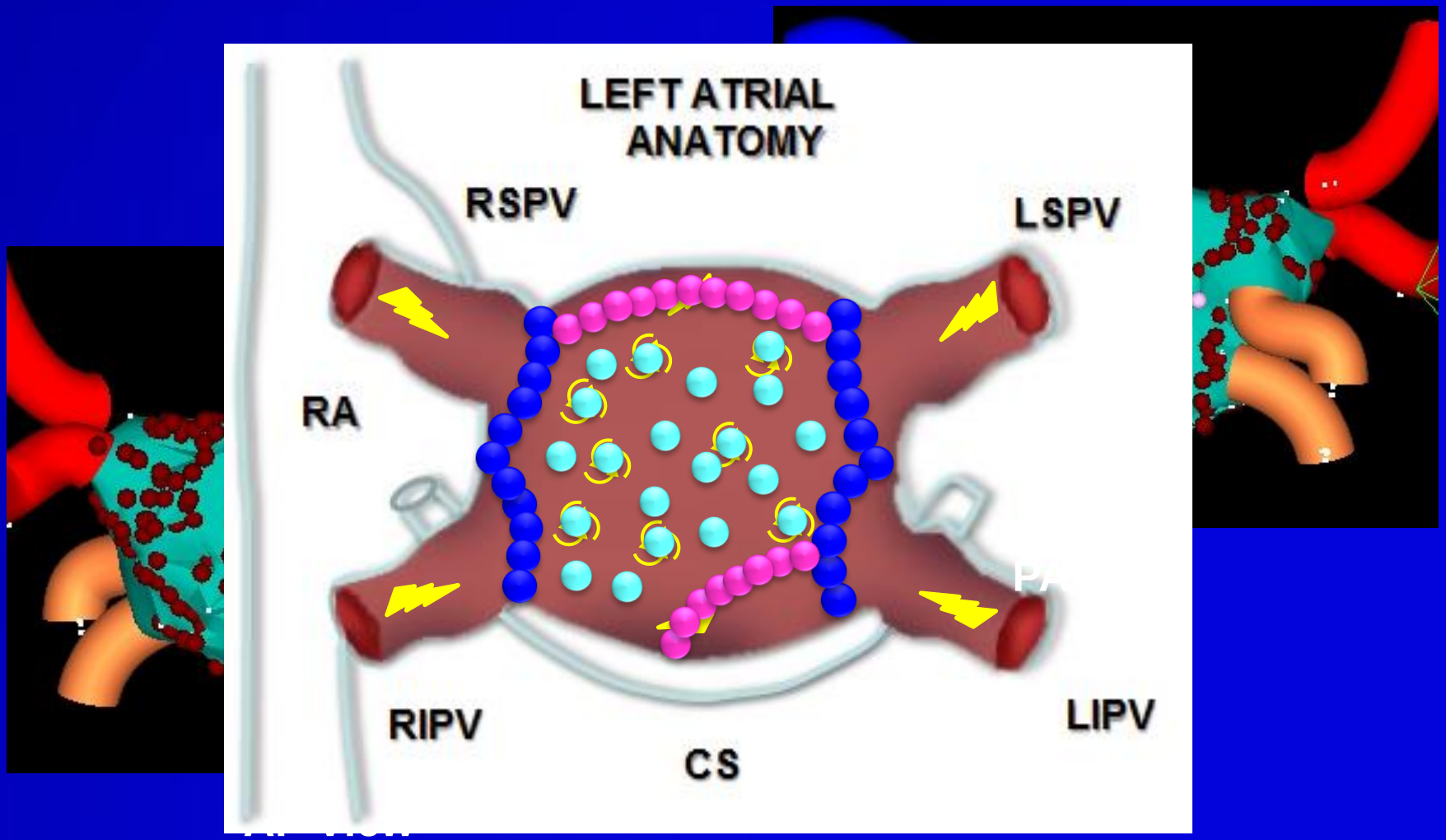






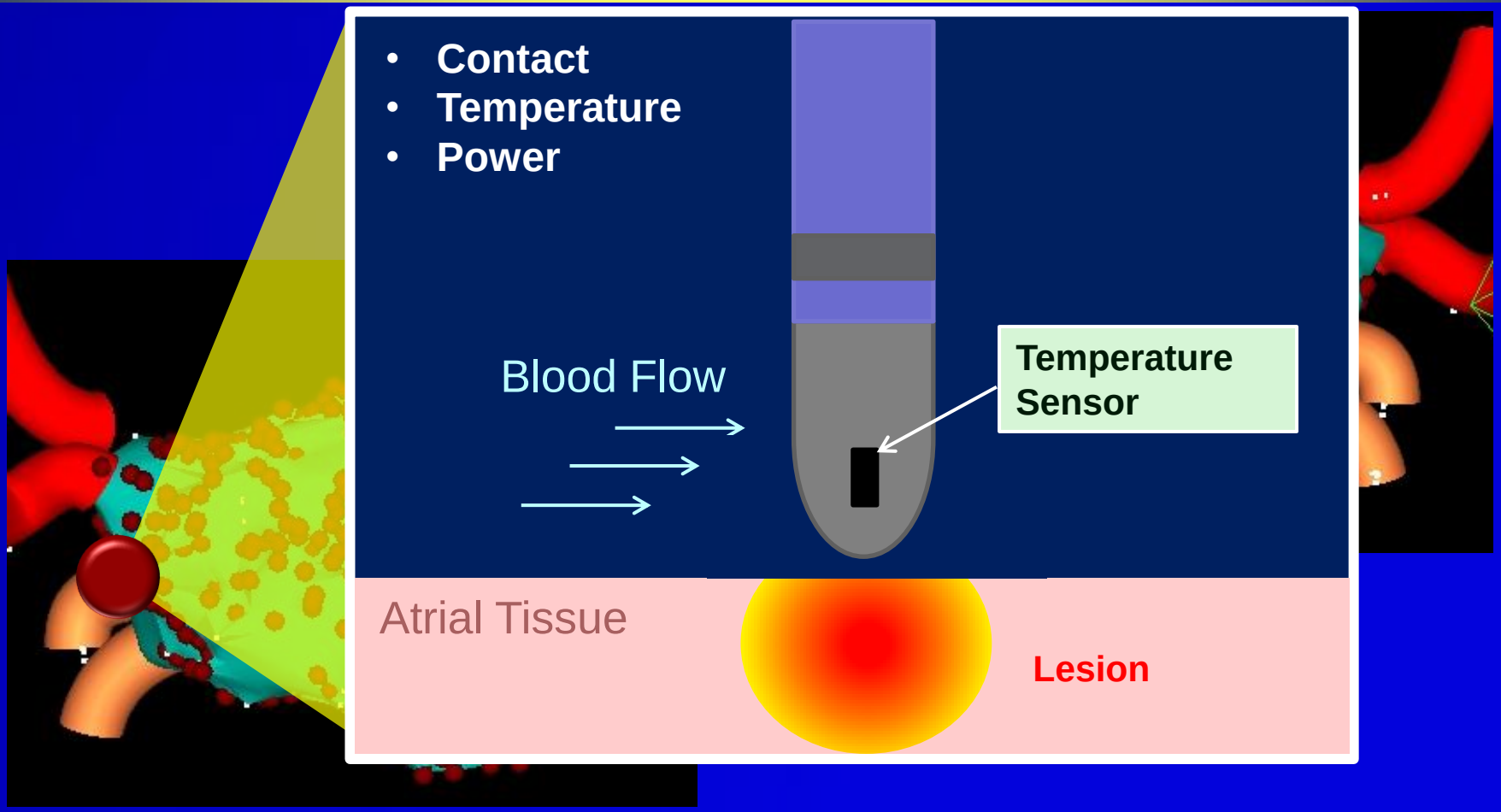
Merino, et al. *Atrial Fibrillation Ablation Guided by Computed Tomography*. Rev Esp Cardiol. 2009;62:314
Reference not previously provided to FDA

Catheter Ablation for Persistent AF



Courtesy of Dr Fred Morady
Image not previously provided to FDA

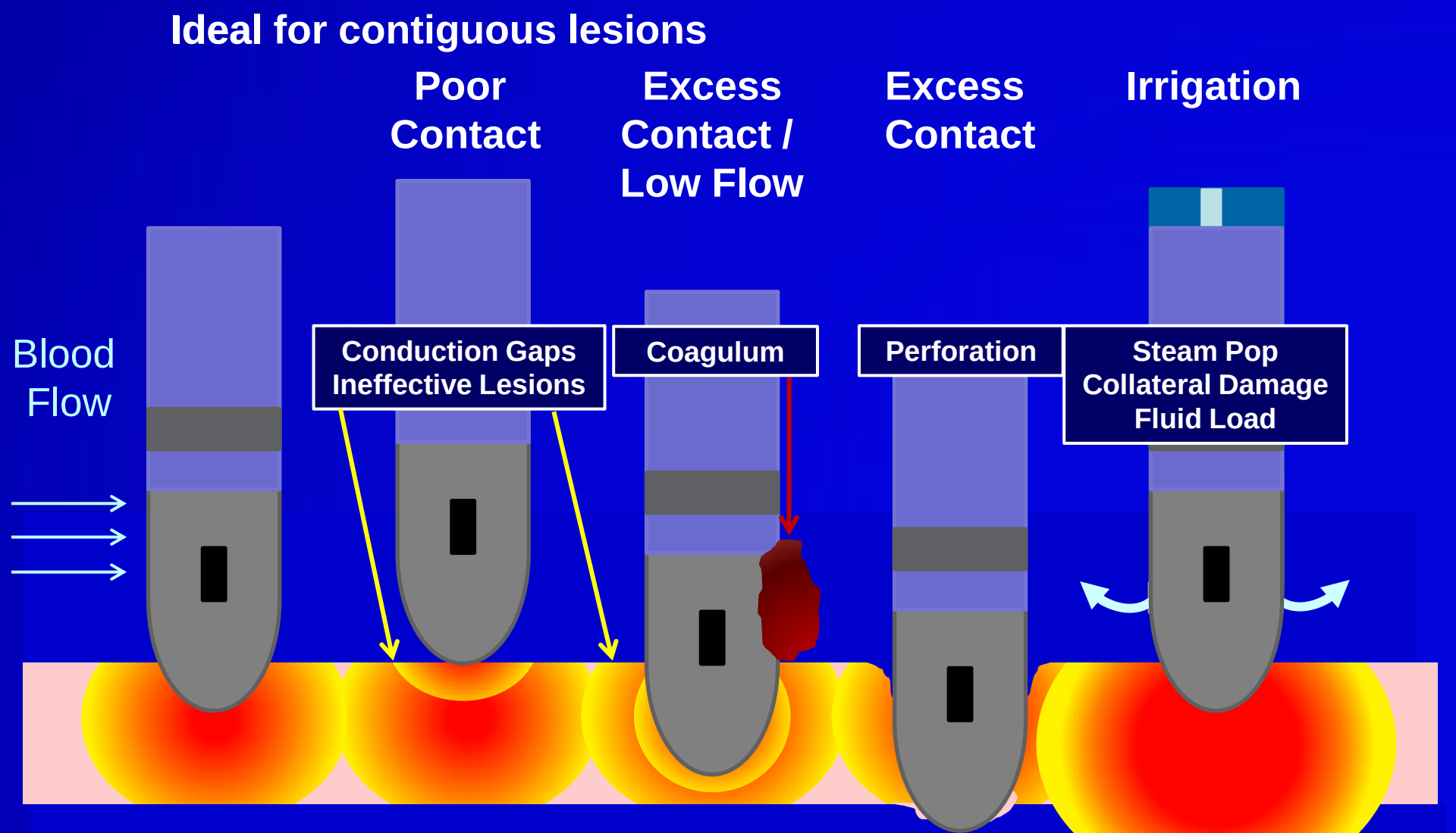
Lesion Creation



AP View

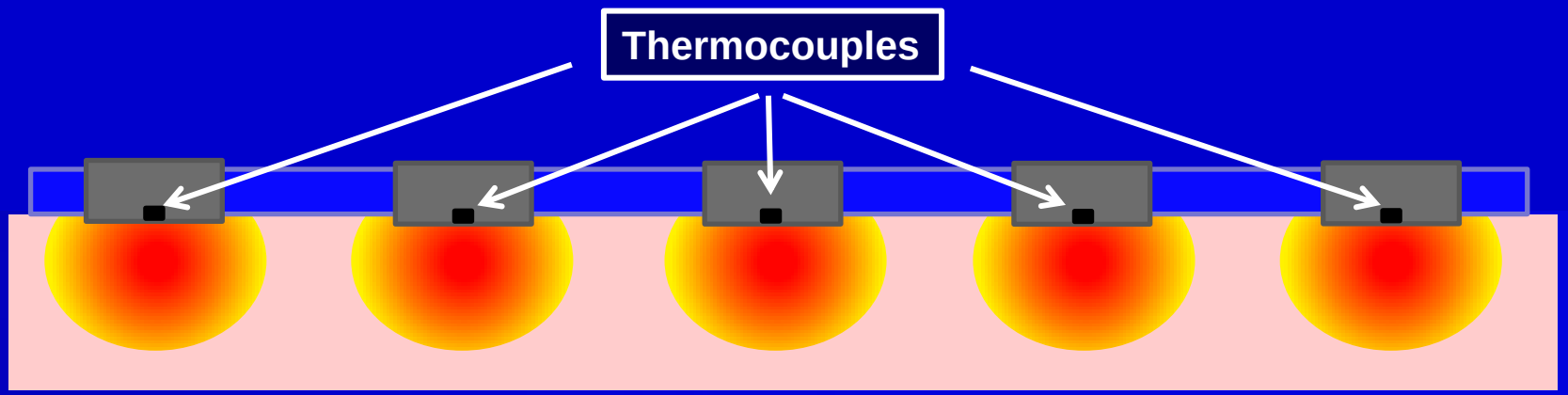
Courtesy of Dr Fred Morady
Image not previously provided to FDA

Conventional RF Challenges

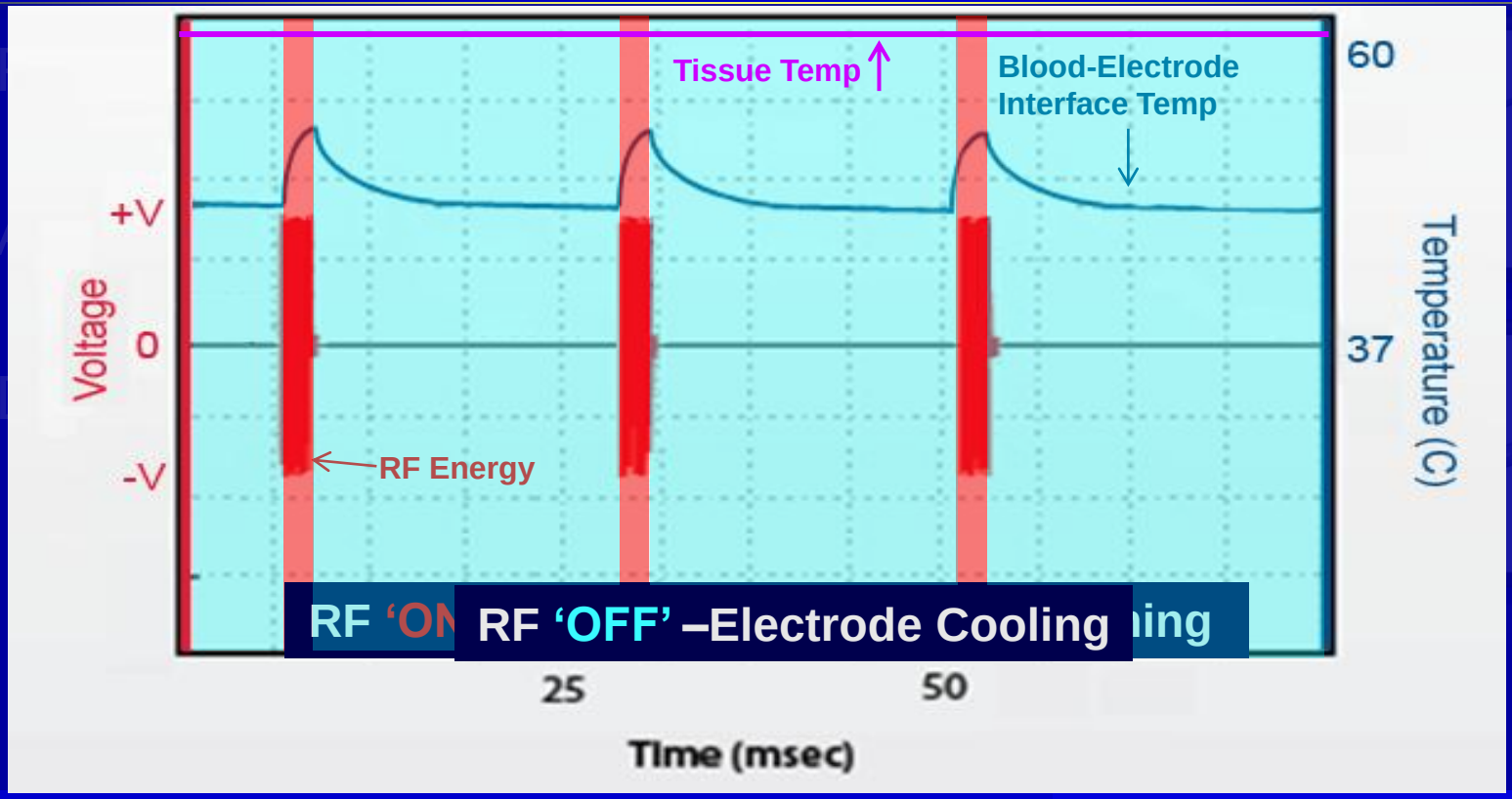


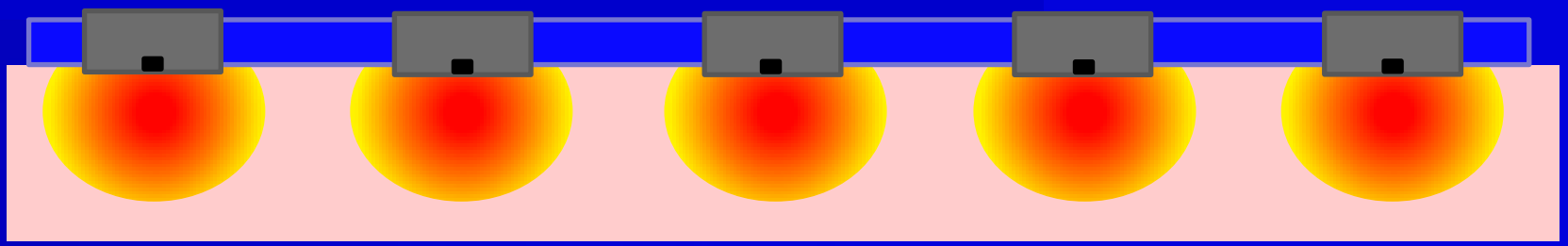
Our Approach

- Flexible multi-electrode array
  - Good contact and stability, reduce perforation
- Accurate temperature control
  - Avoid risks due to irrigation and low power
- Duty cycled RF delivery
  - Enhance cooling, reduce overheating



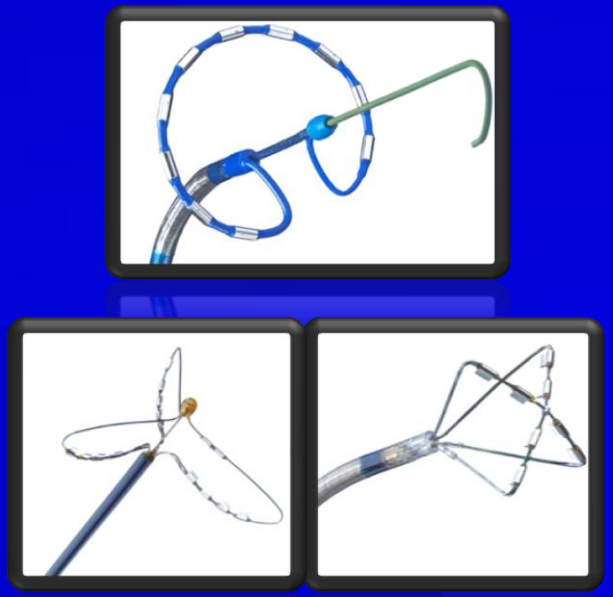
Our Approach

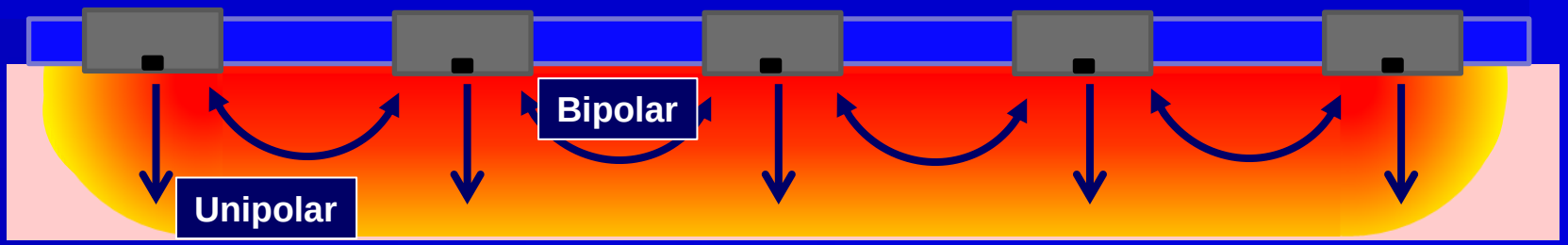




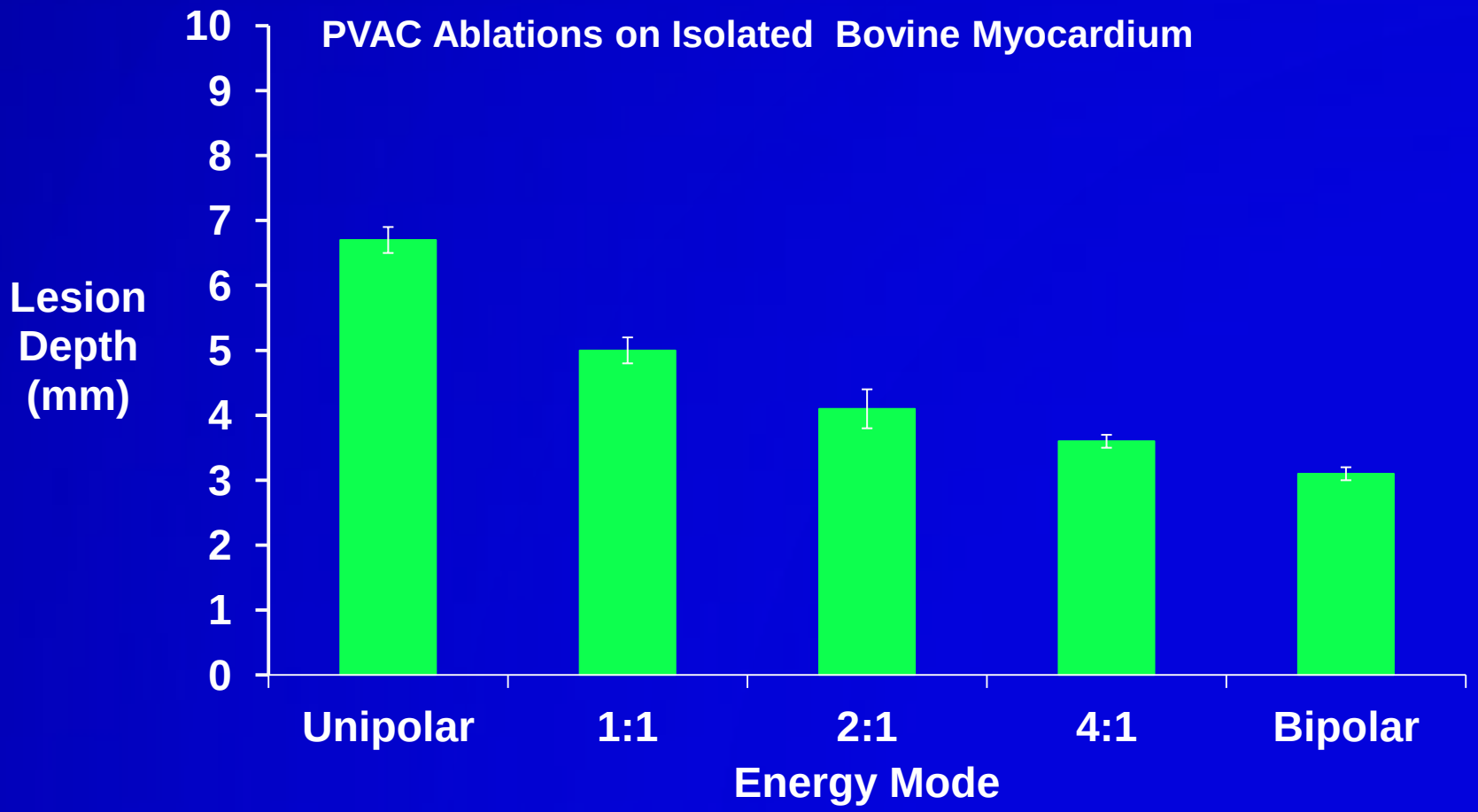
Our Approach

- Flexible multi-electrode array
  - Good contact and stability, reduce perforation
- Accurate temperature control
  - Avoid risks due to irrigation and low power
- Duty cycled RF delivery
  - Enhance cooling, reduce overheating
- Phasing – bipolar:unipolar ratio
  - Lesion depth and contiguity



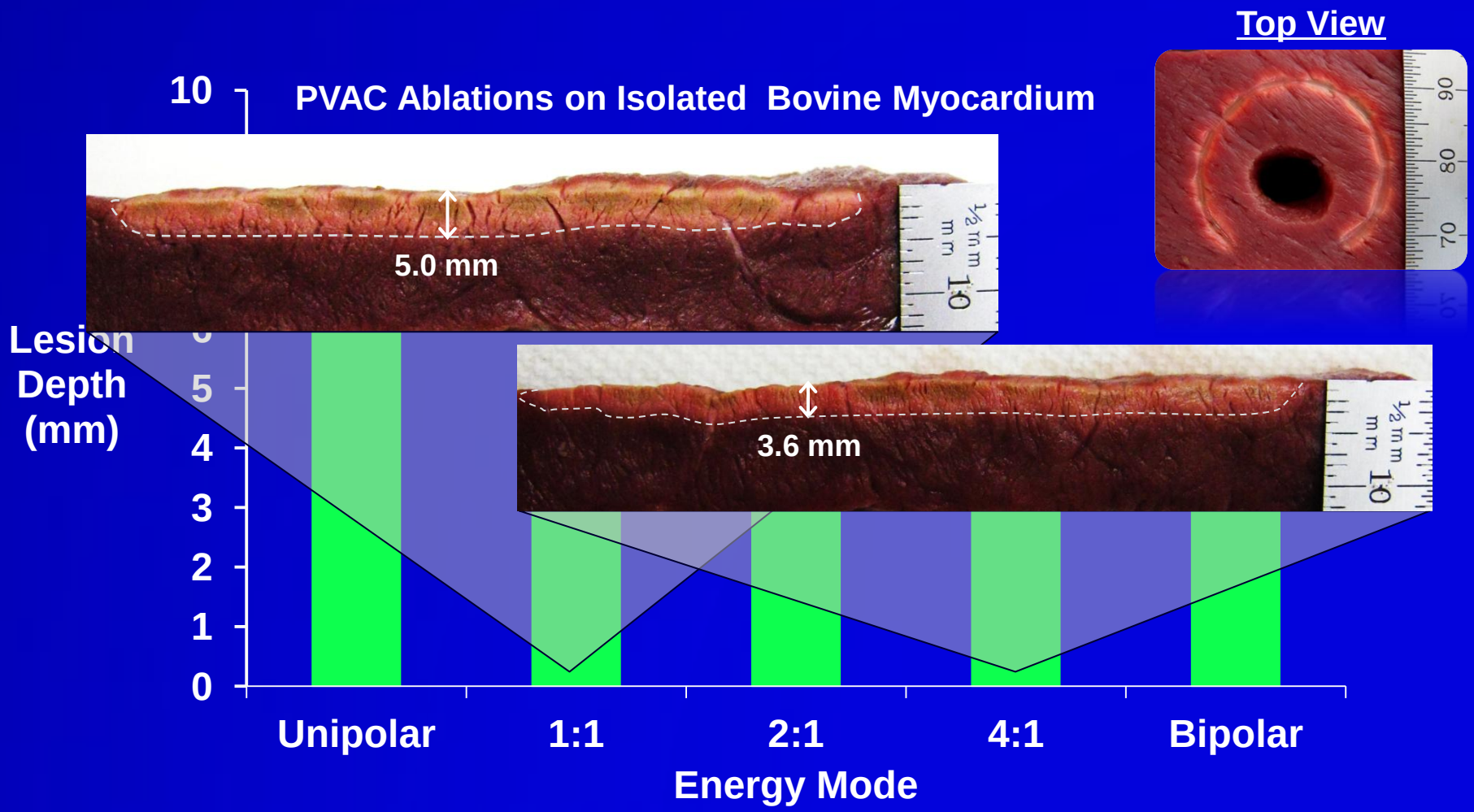


Lesion Depth Control



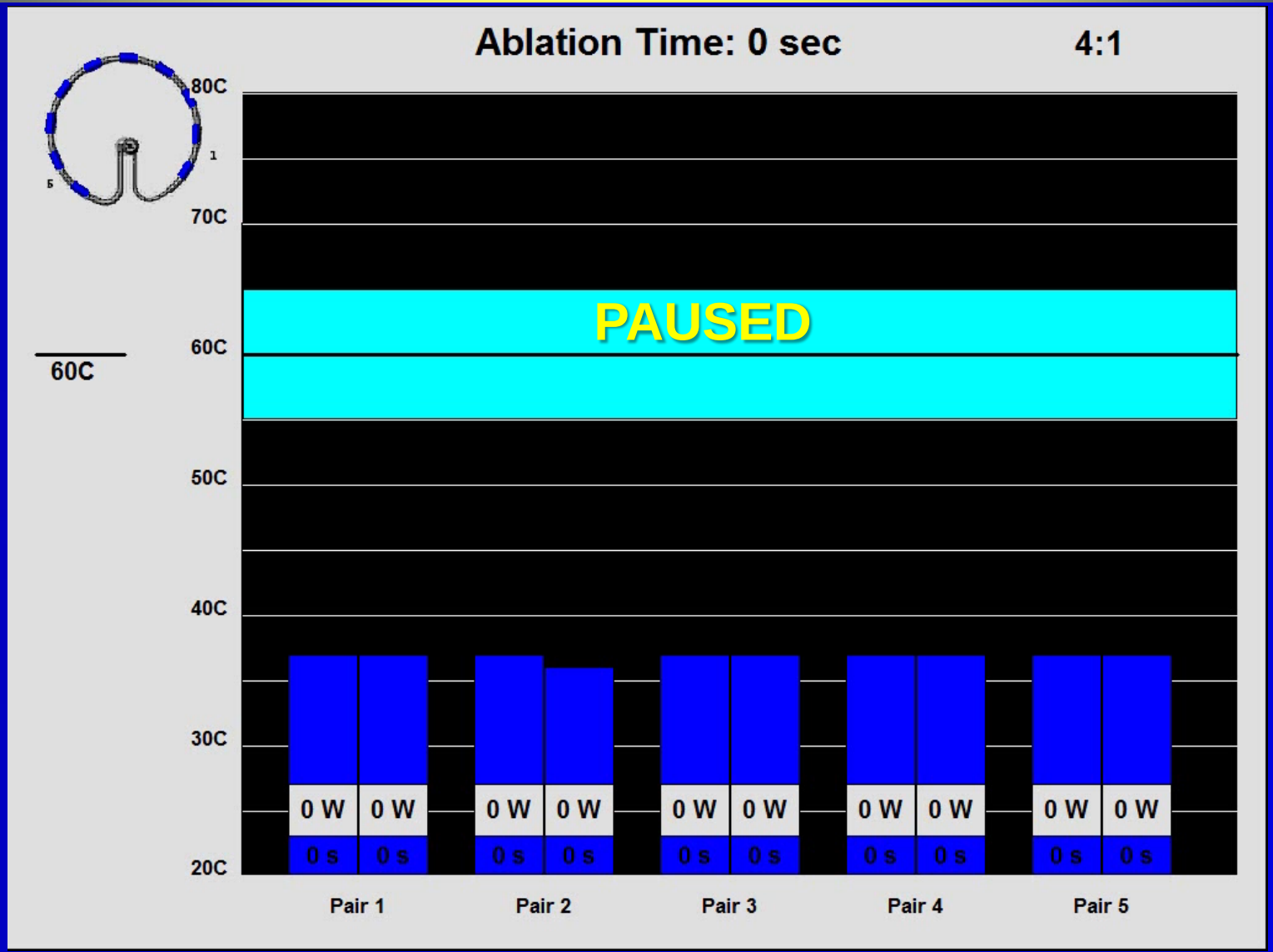
Wijffels, et al. “Characterization of *In Vitro* and *In Vivo* Lesions Made by a Novel Multichannel Ablation Generator and a Circumlinear Decapolar Ablation Catheter.” *J Cardiovasc Electrophysiol, Vol. pp. 1-7.*

Lesion Depth Control

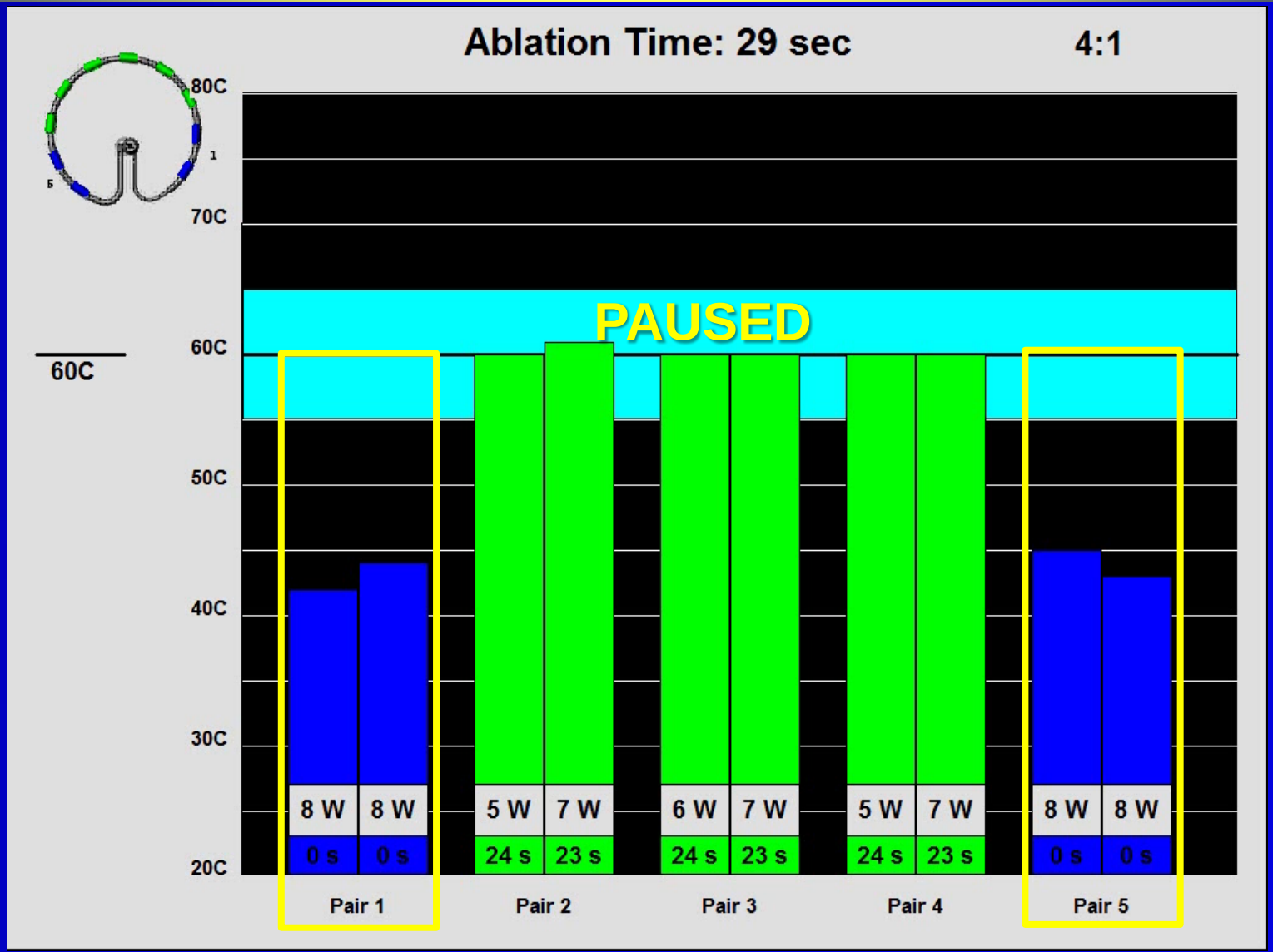


Lesion Images: Training Materials On File; Not previously provided to FDA

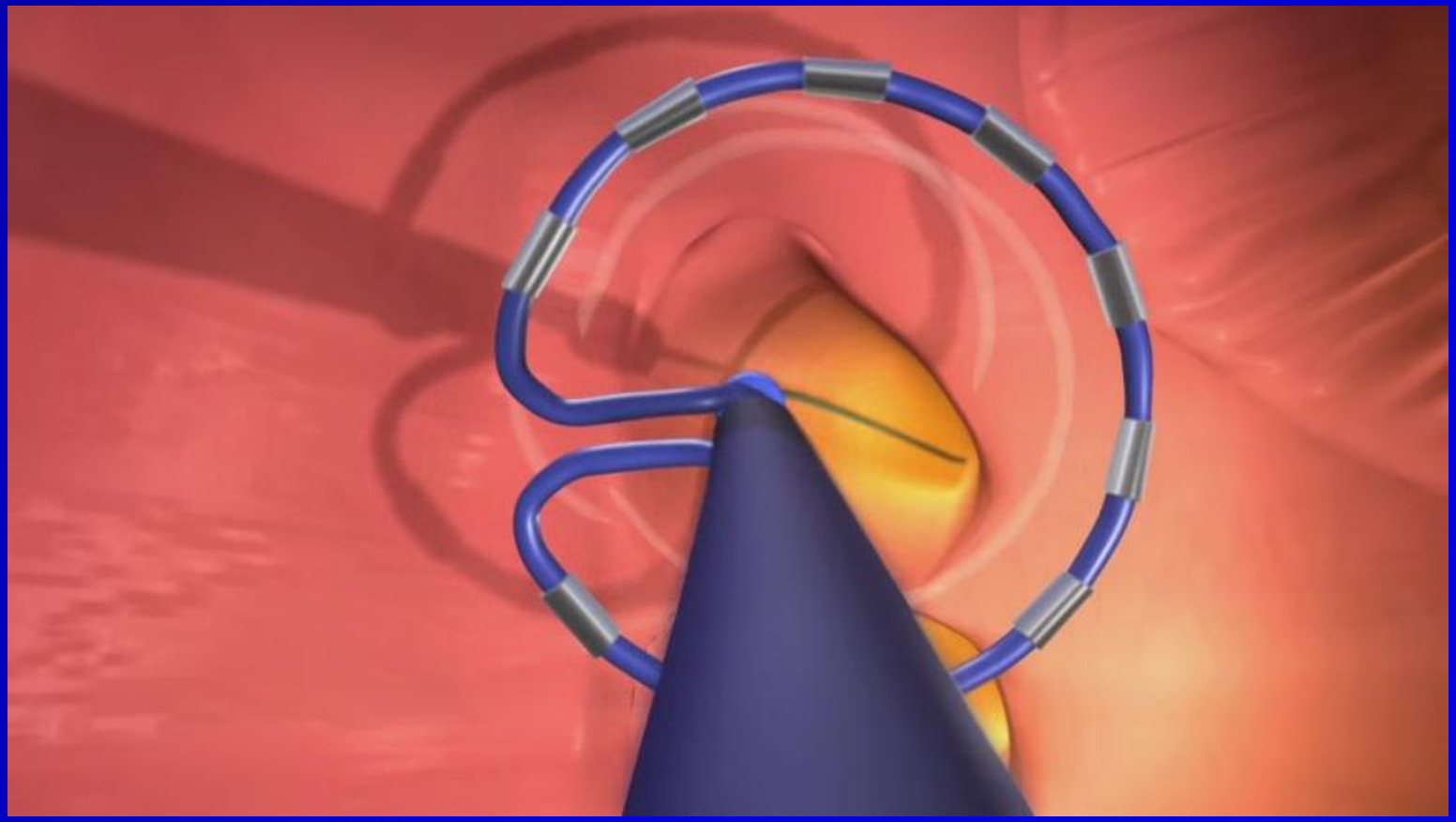
Generator: Intuitive Visual Feedback



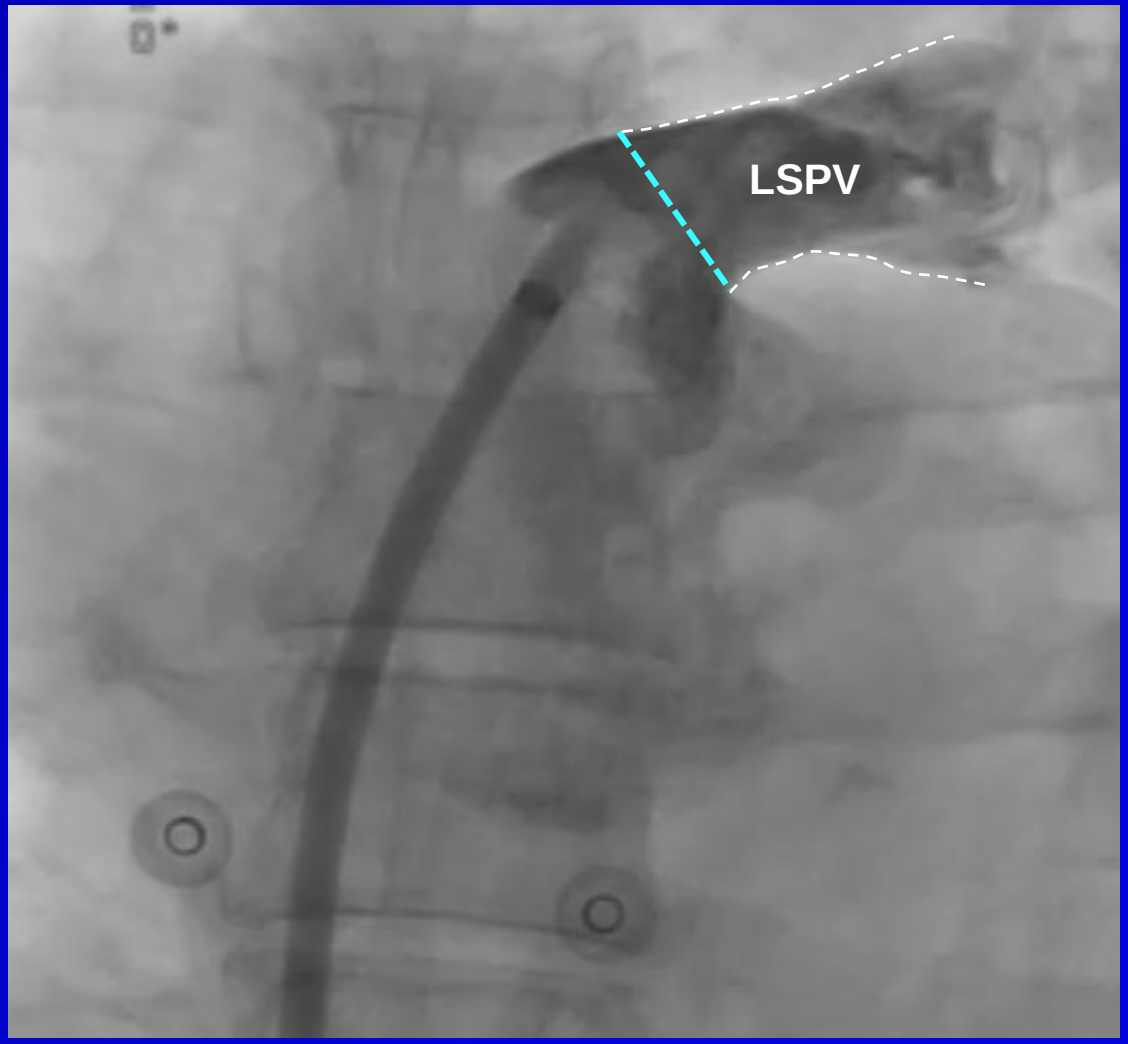
Generator: Intuitive Visual Feedback



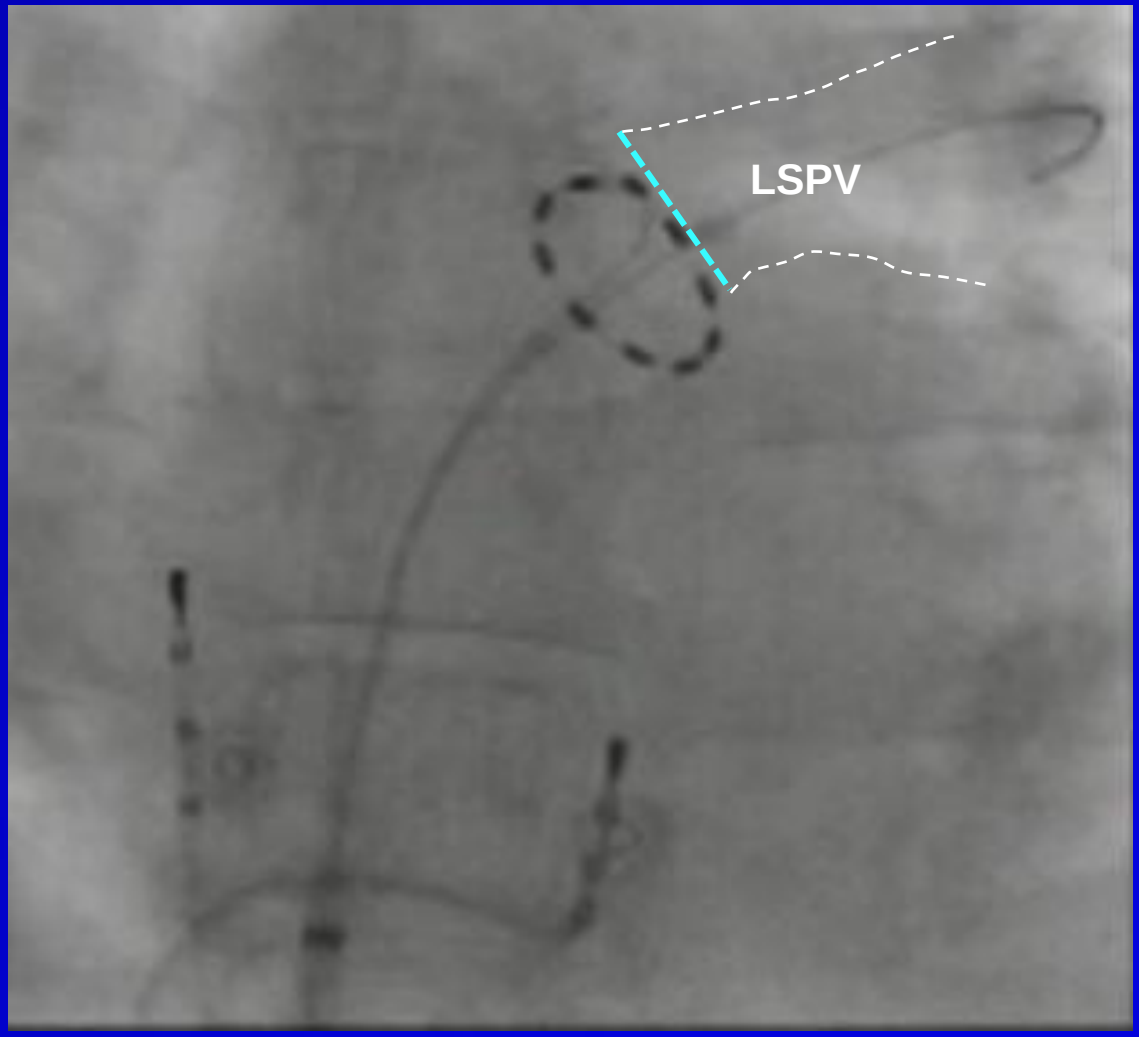
Pulmonary Vein Ablation Catheter (PVAC) in Action



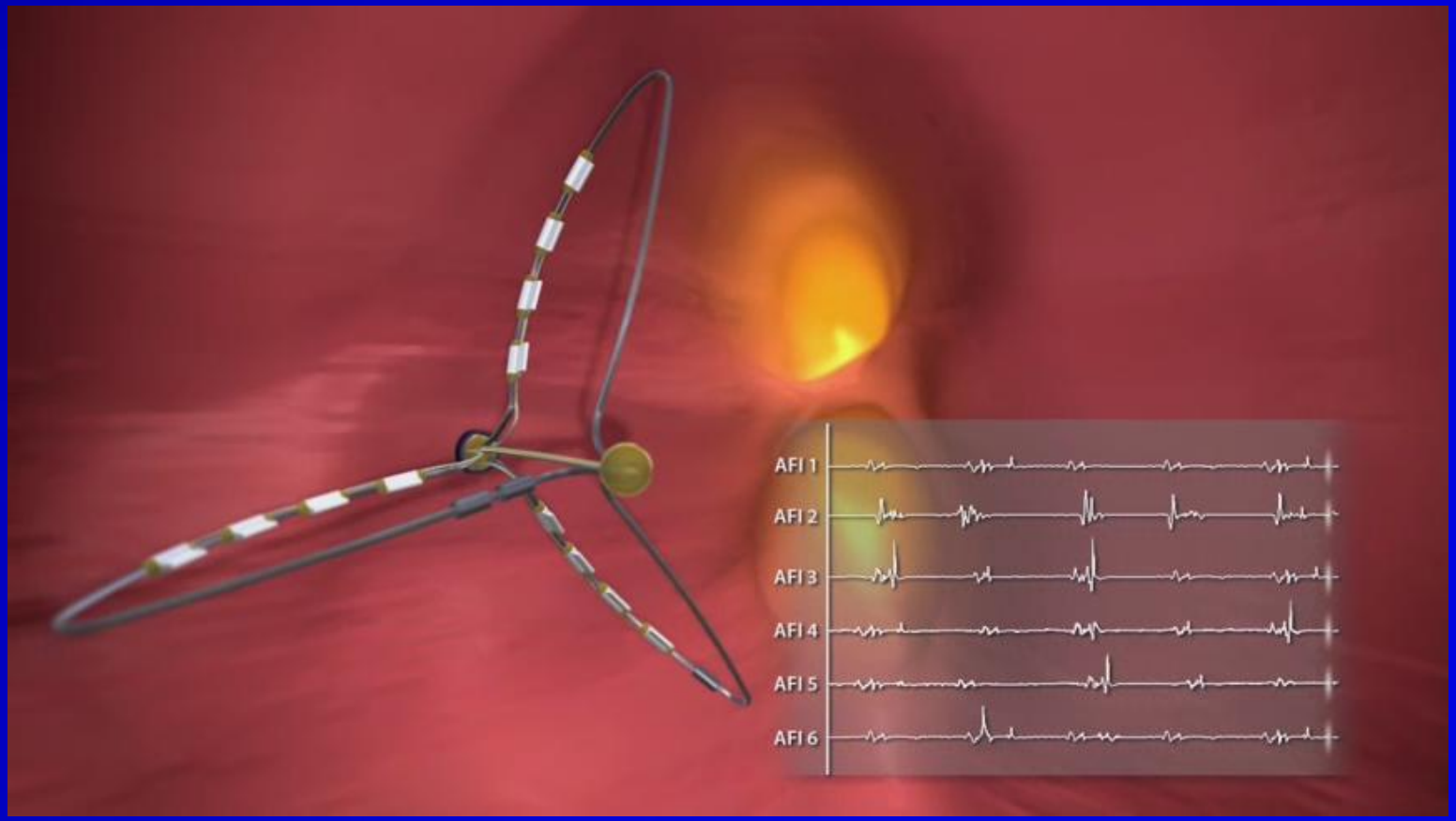
Pulmonary Vein Ablation Catheter (PVAC) in Action



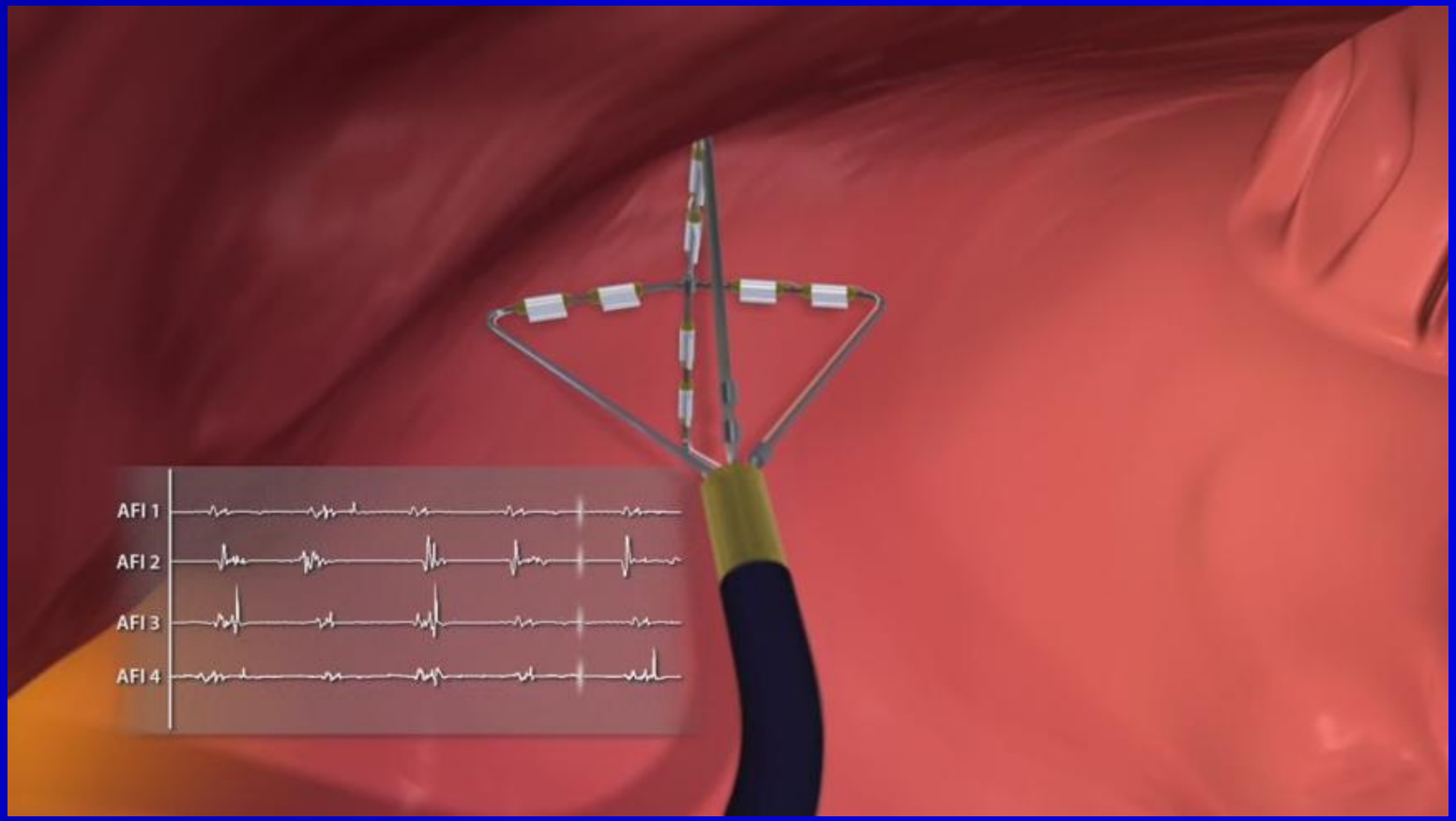
Pulmonary Vein Ablation Catheter (PVAC) in Action



Multi-Array Septal Catheter (MASC) in Action

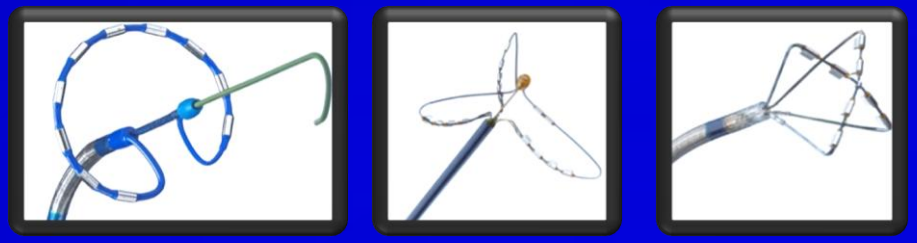


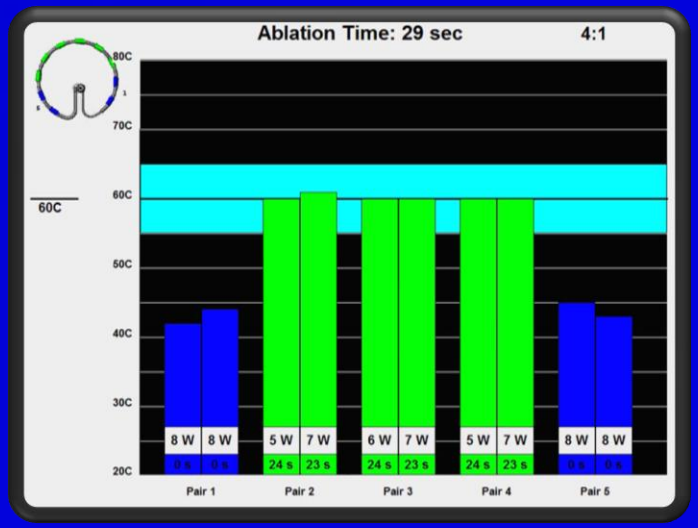
Multi-Array Ablation Catheter (MAAC) in Action



Technology Designed for The Persistent AF Patient

- Advanced technology for a complex disease
  - Flexible arrays
  - Accurate thermal control
  - Duty cycled
  - Phasing
- Overcomes limitations of conventional RF
- Shorter procedure times





Tailored Treatment of Persistent Atrial Fibrillation (TTOP-AF) Clinical Study Results

Lucas Boersma, MD, Ph.D.

St. Antonius Hospital, The Netherlands

TTOP-AF Clinical Investigator

Worldwide Clinical Experience

- CE Mark granted November 2006
- Over 13,000 cases performed, primarily in Europe
- More than 40 peer-reviewed manuscripts

Published Literature

Author(s)	N	Disease	Efficacy Outcome	Follow-Up Method	Fluoro Time (Mins)	Complications	Procedure Time (Mins)
Fredersdorf JCE – 10/09	21	17 PAF 4 CAF	86%	6 months 3d Holter	32 ± 10	0	121 ± 19
Wieczorek JCE – 10/09	88	PAF	79%	12 months 7d Holter	21 ± 13	0	125 ± 28
Boersma Europace 09	210	PAF	76%	12 months 7d Holter	23 ± 16	0	86 ± 28
Beukema Europace-02/10	102	90 PAF 12 CAF	60.8%	12 months 7d Holter	32 ± 11	0	139 ± 38
Deneke Hospital Chronicles – 3/10	152	106 PAF 46 CAF	65% 47%	6 months 7d Holter	20 ± 8	0	100 ± 26
Scharf JACC – 10/09	50	CAF	66%	20 months 7d Holter	55 ± 35	1 TIA, 1 AV fistula, 1 tamponade	155 ± 40
Bulava PACE – 04/10	102	PAF	77%	200 ± 13 days	16 ± 5	0	107 ± 31
Tivig/Scharf Int'l Journal of Card 12/10	143	PAF	82%	8.5 ± 6.5 months	29 ± 13	2 TIA's	128 ± 38
	66	CAF	79%	11.5 ± 8.5 months	46 ± 16		171 ± 39
Choo Arc Card Dis - 07/11	109	73 PAF 36 CAF	68%	6 months 1-2d Holter	39 ± 14	1 per. effusion 1 peri stroke	168 ± 41
Mulder/Boersma Europace – 7/11	89	CAF	56%	12 months 7d Holter	21±10	1 TIA, 1 ST elevation, 1 per. effusion	112 ± 32
Bittner Heart Rhythm - 3/11	80	44 PAF 36 CAF	72%	254 ± 99d 1-4d Holter	26 ± 8	0	171 ± 40

TTOP-AF Investigators

Sean Beinart, MD
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Dan Dan, MD
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Darryl Elmouchi, MD
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Mike Giudici, MD
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John Hummel, MD
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Fred Kusumoto, MD
Moussa Mansour, MD
David Martin, MD
Gregory Michaud, MD
John Miller, MD
Abdi Rasekh, MD
Kalyanam Shivkumar, MD
VJ Swarup, MD
David Tschopp, MD
Ian Woollett, MD

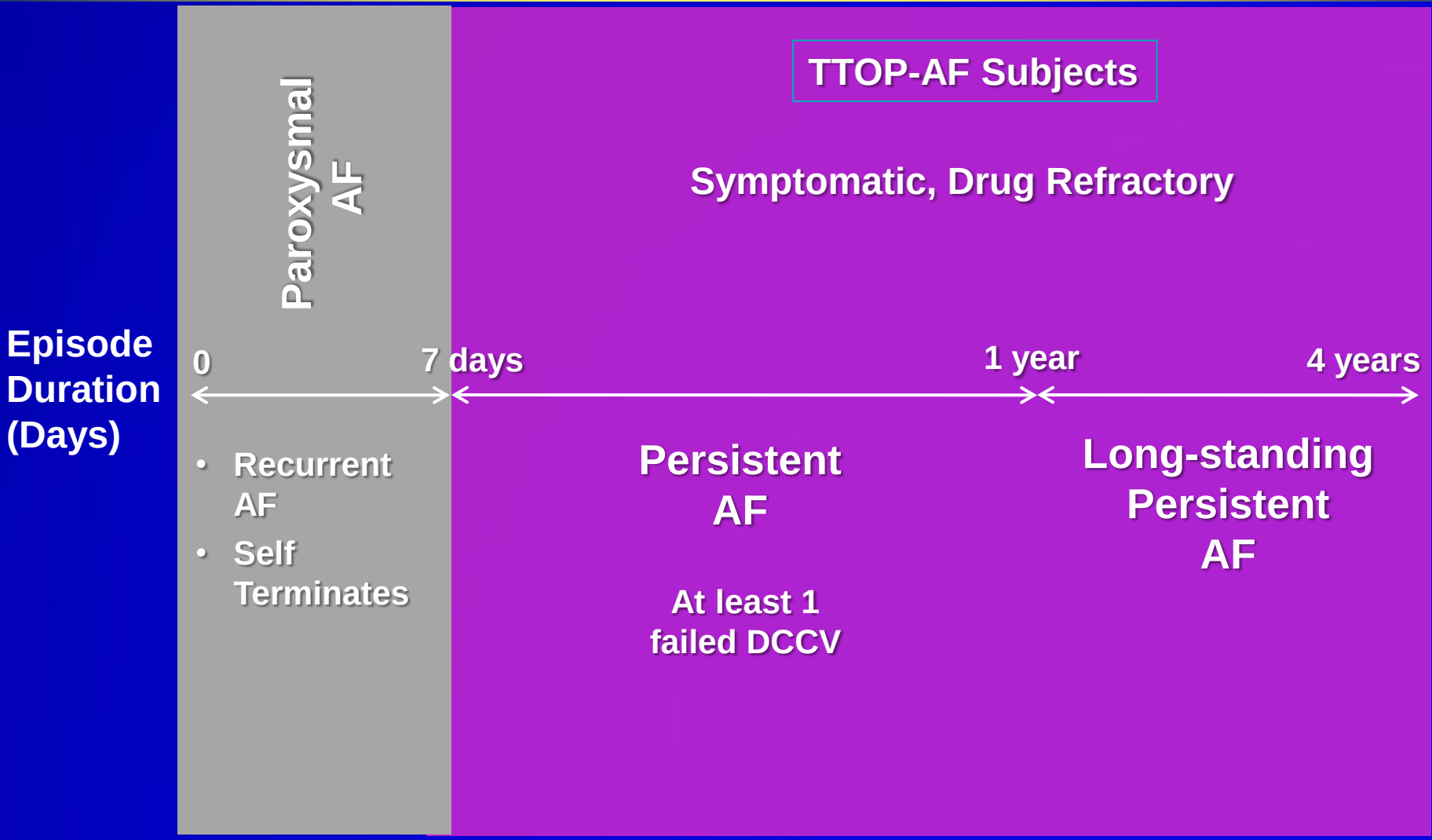
TTOP-AF Study Purpose

- To investigate the safety and effectiveness of the Medtronic Cardiac Ablation System in the treatment of persistent and long-standing persistent atrial fibrillation.

TTOP-AF Study Design

Design	Prospective, randomized, multi-center
Disease State	Symptomatic, drug-refractory, persistent and long-standing persistent AF
Centers	23 US, 1 The Netherlands
Subjects	210 randomized
Study Period	November 2007 – November 2010
Follow-Up Duration	6 months
Data/Events	Independently adjudicated and monitored

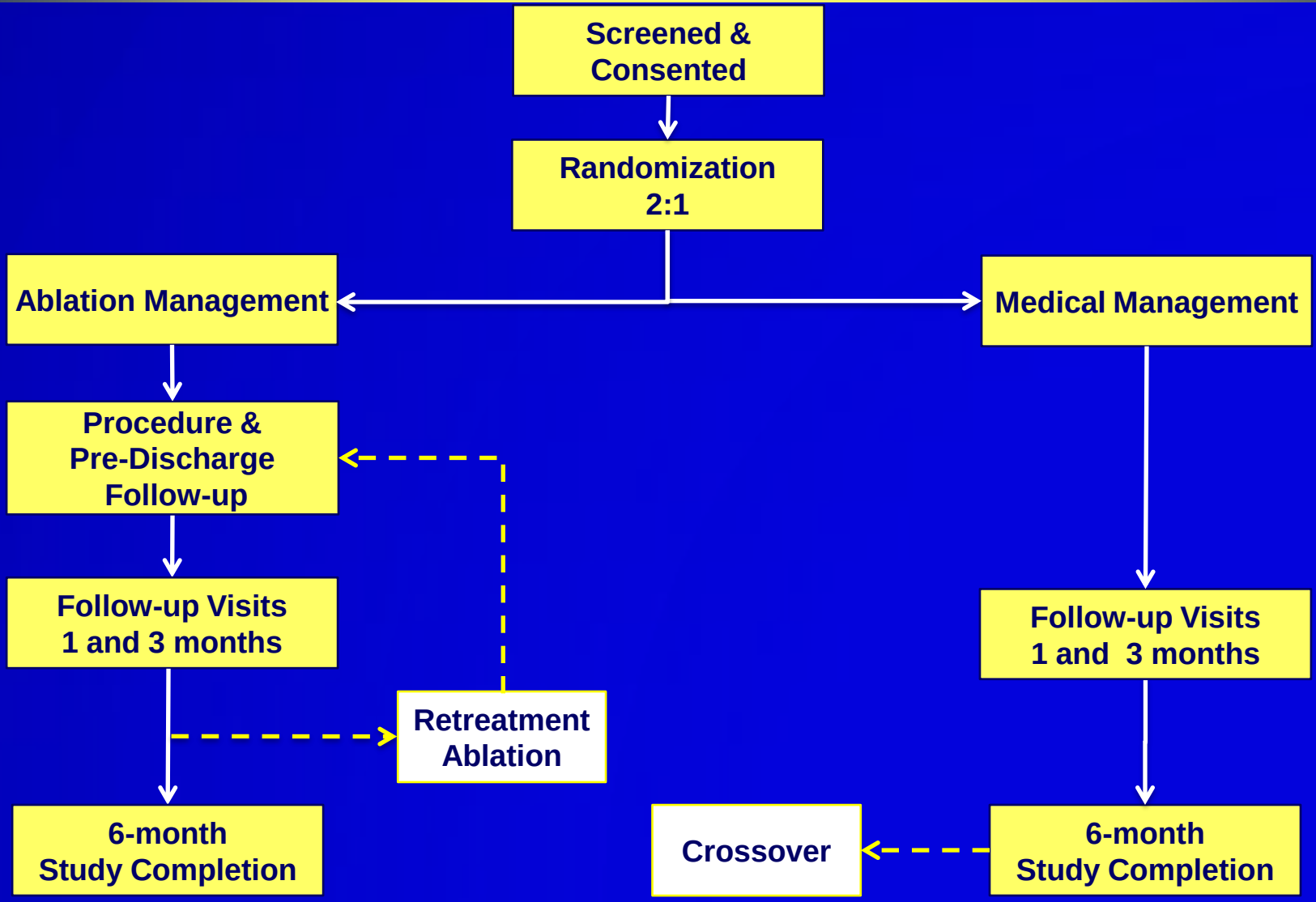
Methods: Major Inclusion Criteria



Exclusion Criteria

- Structural heart disease, including
  - Left Atrial Diameter > 55 mm
  - Symptoms of congestive heart failure
  - LVEF < 40%
  - Hypertrophic cardiomyopathy
- Prior ablation for AF
- History of cerebral vascular disease
- Ventricular tachyarrhythmia currently under treatment
- Left atrial thrombus at the time of ablation

Study Design



Methods: Scheduled Evaluations

	Baseline	1 and 3 Months	6 Months
All Subjects	Medical History ECG AF Symptom Score QoL Survey 48-hour Holter	Medical History ECG AF Symptom Score QoL Survey	Medical History ECG AF Symptom Score QoL Survey 48-hour Holter
Ablation Mgmt Subjects	Transesophageal echocardiogram CT or MRI		CT or MRI

Methods: Ablation Arm Procedures

Procedure

- Anticoagulation per investigator preference
- Left atrial access via single transseptal puncture
- ACT > 300 sec
- PVAC, MASC and MAAC (index procedure)
- DC cardioversion to restore sinus rhythm, as needed

Pre-Hospital Discharge

- 12-lead electrocardiogram
- Physical exam

Method: Medical Management Treatment

- Initiation of new or previously failed antiarrhythmic drugs
- Changes allowed:
  - Dose
  - Drug
  - Drug combinations
- Anticoagulation to maintain INR > 2
- DC cardioversions

Summary of Primary Endpoints

Chronic Efficacy

- Treatment arm comparison at 6 months
- Treatment success:
  - ≥ 90% reduction in clinically significant AF/AFL by 48 -hour Holter
  - Off AAD
  - Acute procedural success
- Intent to Treat (ITT) analysis

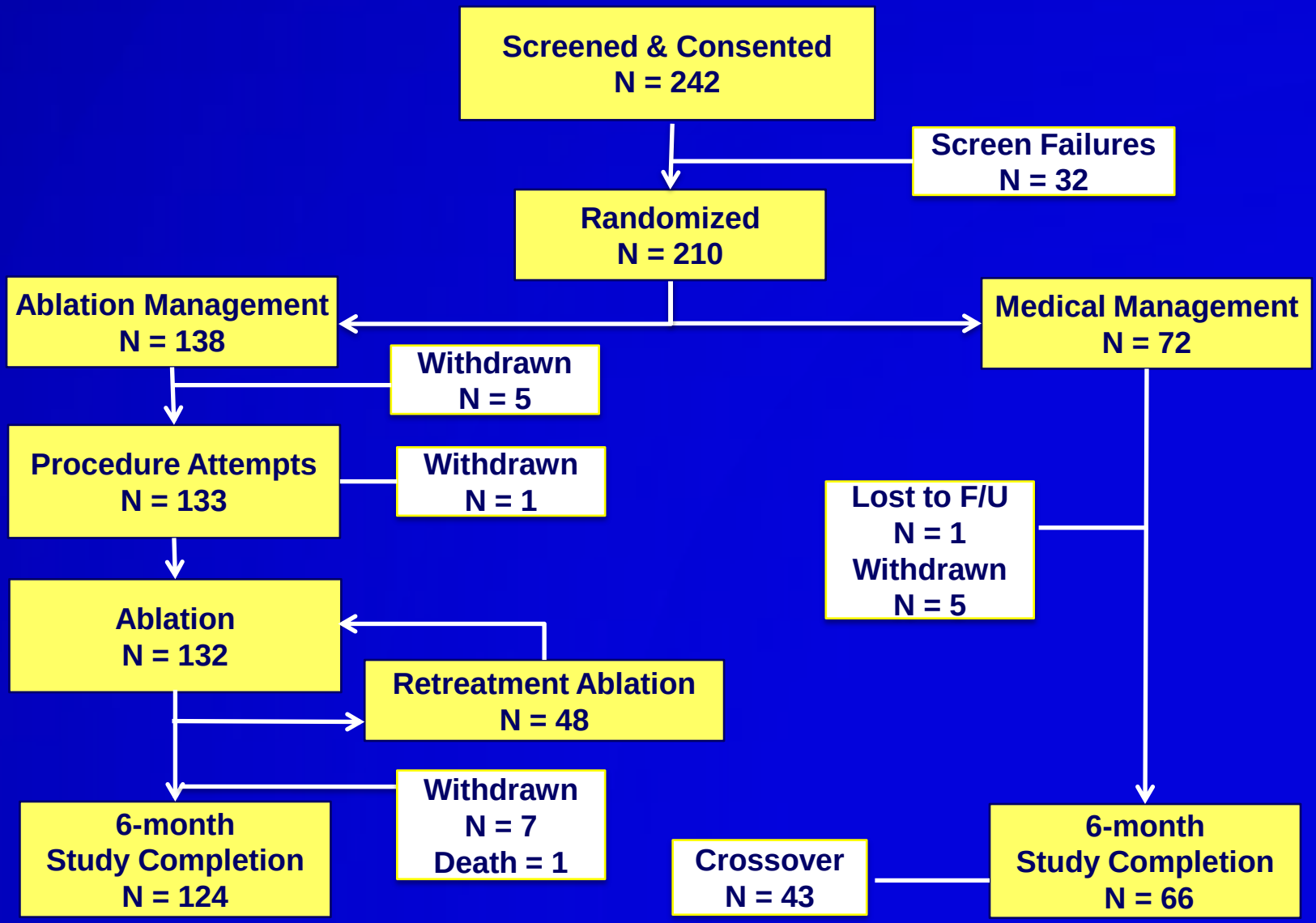
Acute Safety

- Ablation Management arm compared against performance goal.
- Rate of 7-day acute procedural events
- Serious procedure and/or device-related adverse events
- Intent to Treat (ITT) analysis

Chronic Safety

- Treatment arm comparison at 6 months
- Rate of serious events:
  - Ablation Management > 7 days thru 6 months
  - Medical Management from randomization thru 6 months
- Events Included
  - Ablation Management: procedure and/or device-related events
  - Medical Management: events related to AF and its treatment
- Not powered

Subject Accountability



Comparability of Treatment Groups

	Ablation Management n=138	Medical Management n=72
Age (years)	59.6 ± 8.3	60.7 ± 8.9
Gender (% male)	83.3%	83.3%
Hypertension (%)	60.9%	55.6%
$CHADS_2$ Score	0.8 ± 0.8	0.8 ± 0.7
LAD (cm)	4.5 ± 0.5	4.6 ± 0.5
Persistent AF (%)	69.6%	79.2%
Long-Standing AF (%)	30.4%	20.8%
AF/AFL (hours:minutes)	48:25 ± 1:25	48:30 ± 1:04

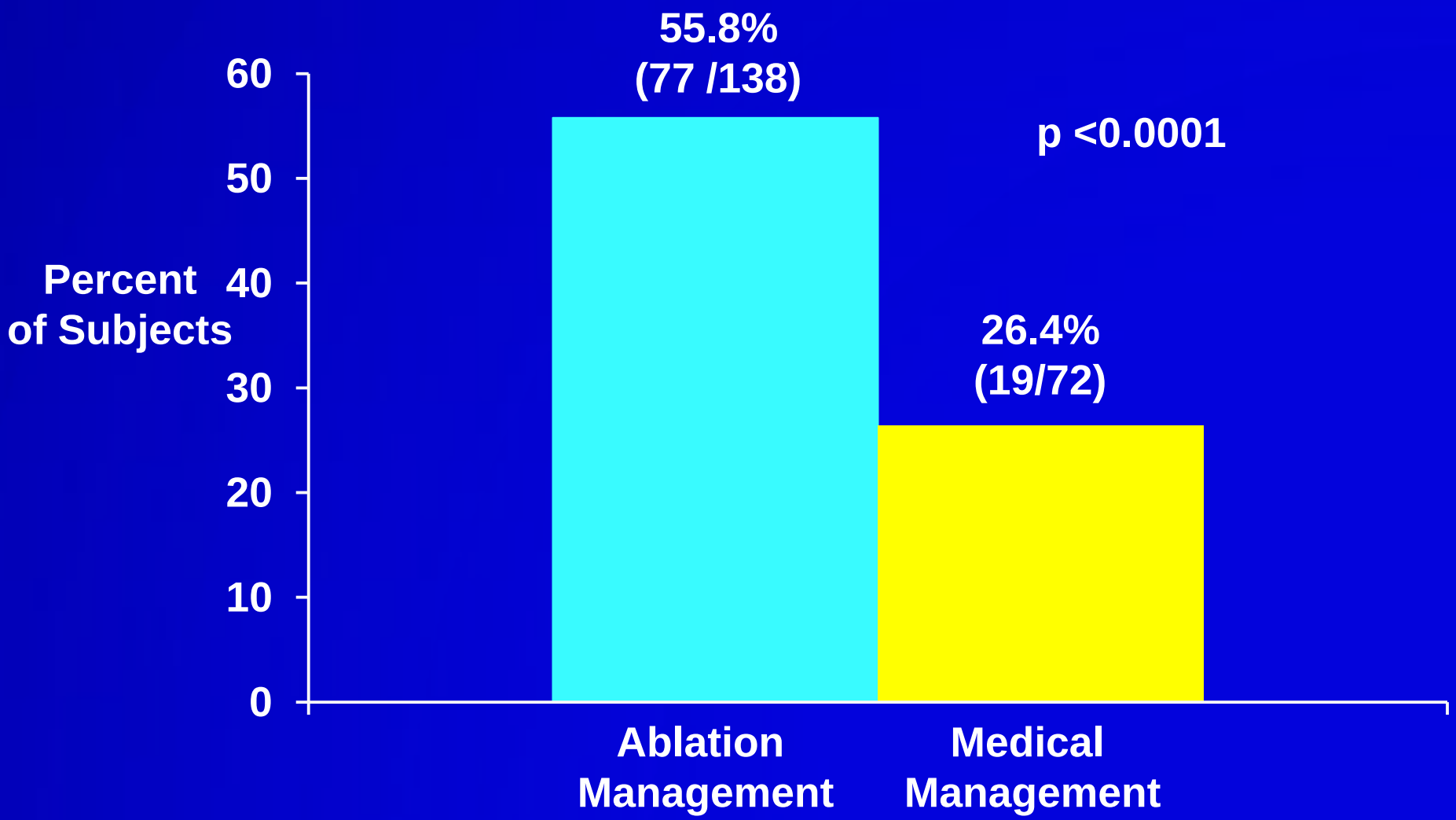
Comparability of Treatment History

	Ablation Management n=138	Medical Management n=72
Number of DCCVs in prior 4 years	2.0 ± 1.1	2.4 ± 3.5
Years since first DCCV	1.3 ± 2.0	1.5 ± 2.3
Years since first AAD prescribed	2.1 ± 3.3	2.5 ± 4.1
Number of failed AADs	1.4 ± 0.9	1.1 ± 0.5

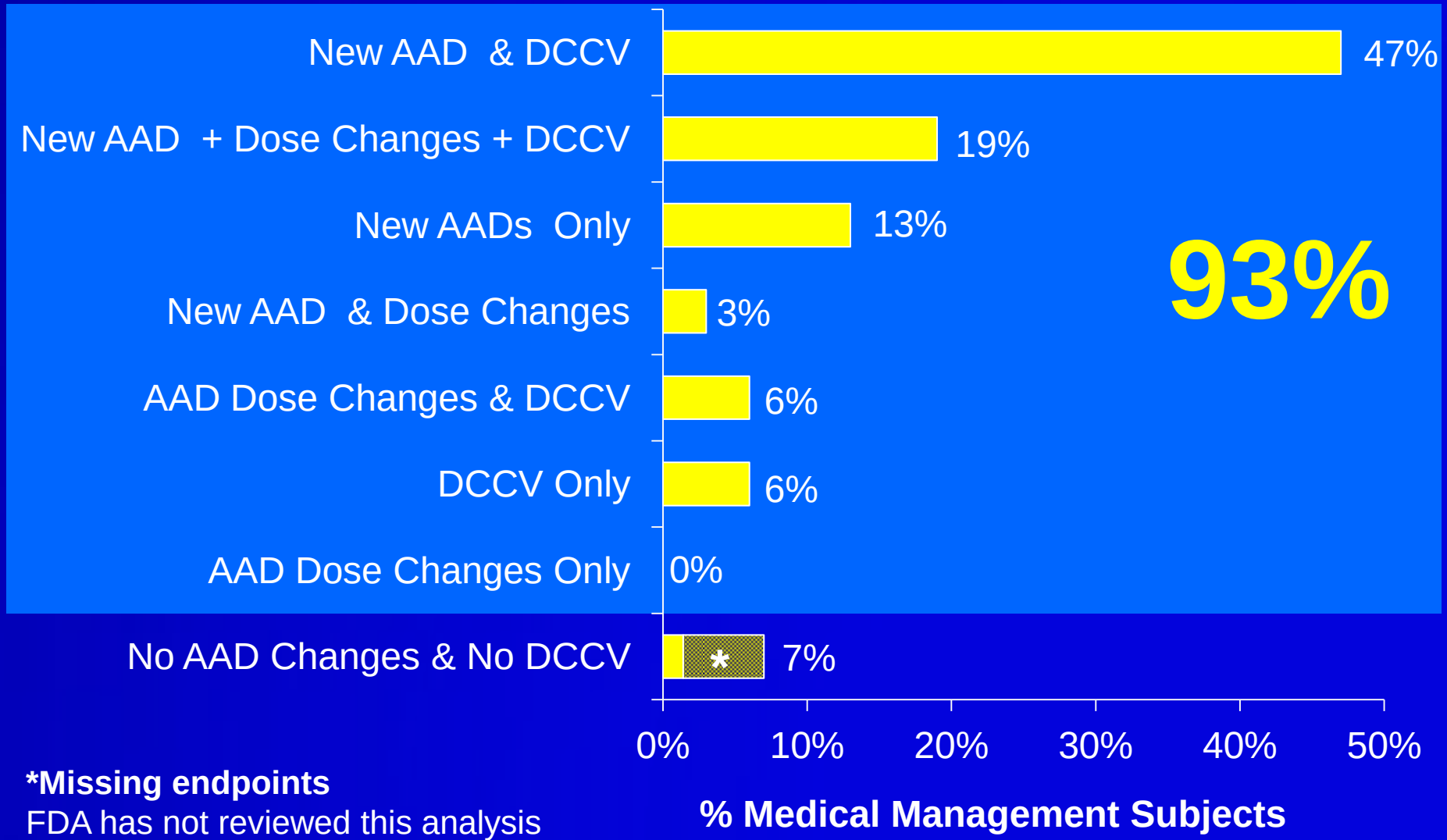
Chronic Effectiveness Success Criteria

Criteria	Ablation Mgmt	Medical Mgmt
All ablation procedures were acute successes • All 3 ablation catheters used (index) • All pulmonary veins isolated • CFAEs mapped & eliminated • Sinus rhythm (± DC cardioversion)	X	
Off all Class I and III AADs	X	
≥ 90% reduction in cumulative time of ≥ 10-minute AF/AFL episodes	X	X

Chronic Effectiveness: ITT Analysis

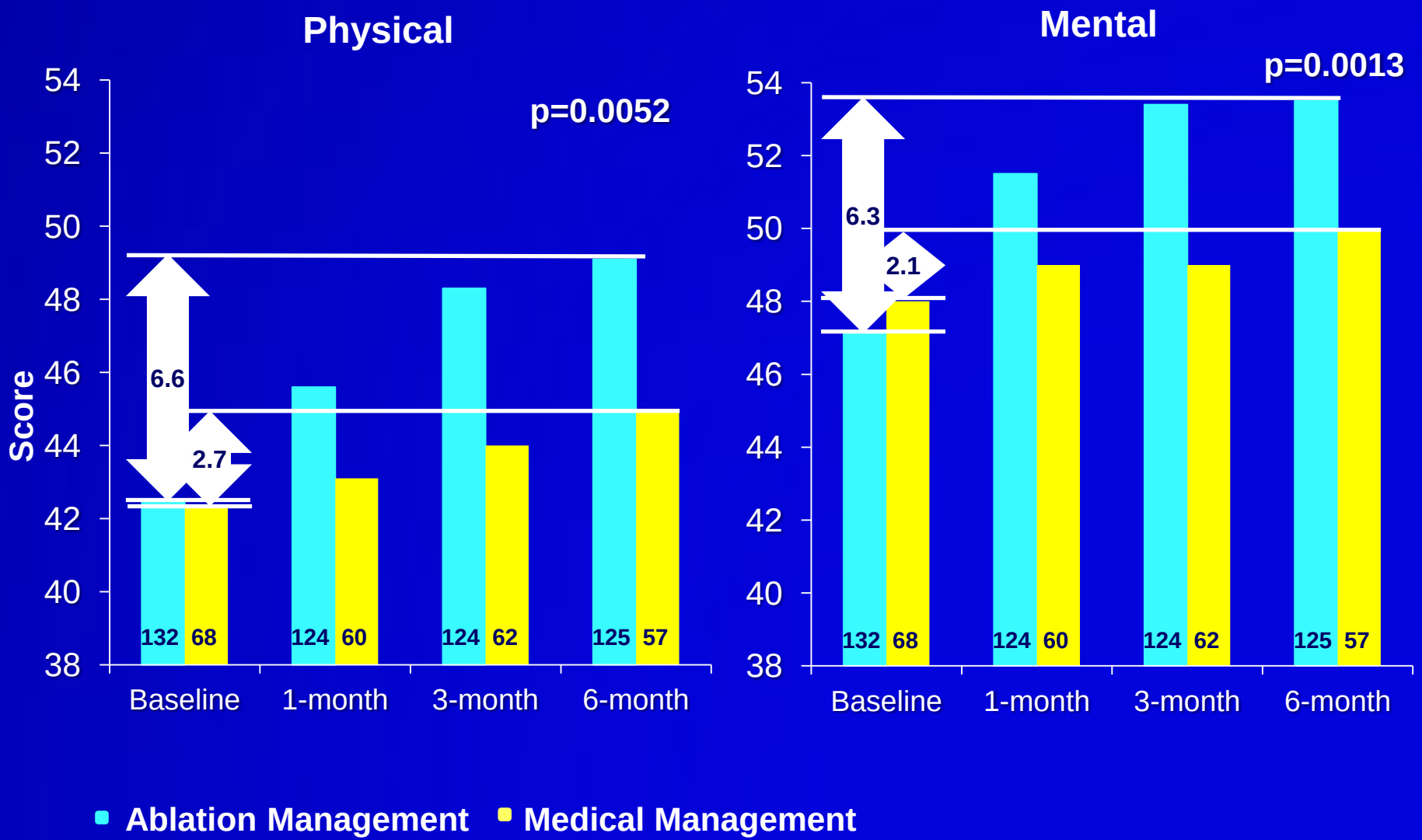


Medical Management Interventions

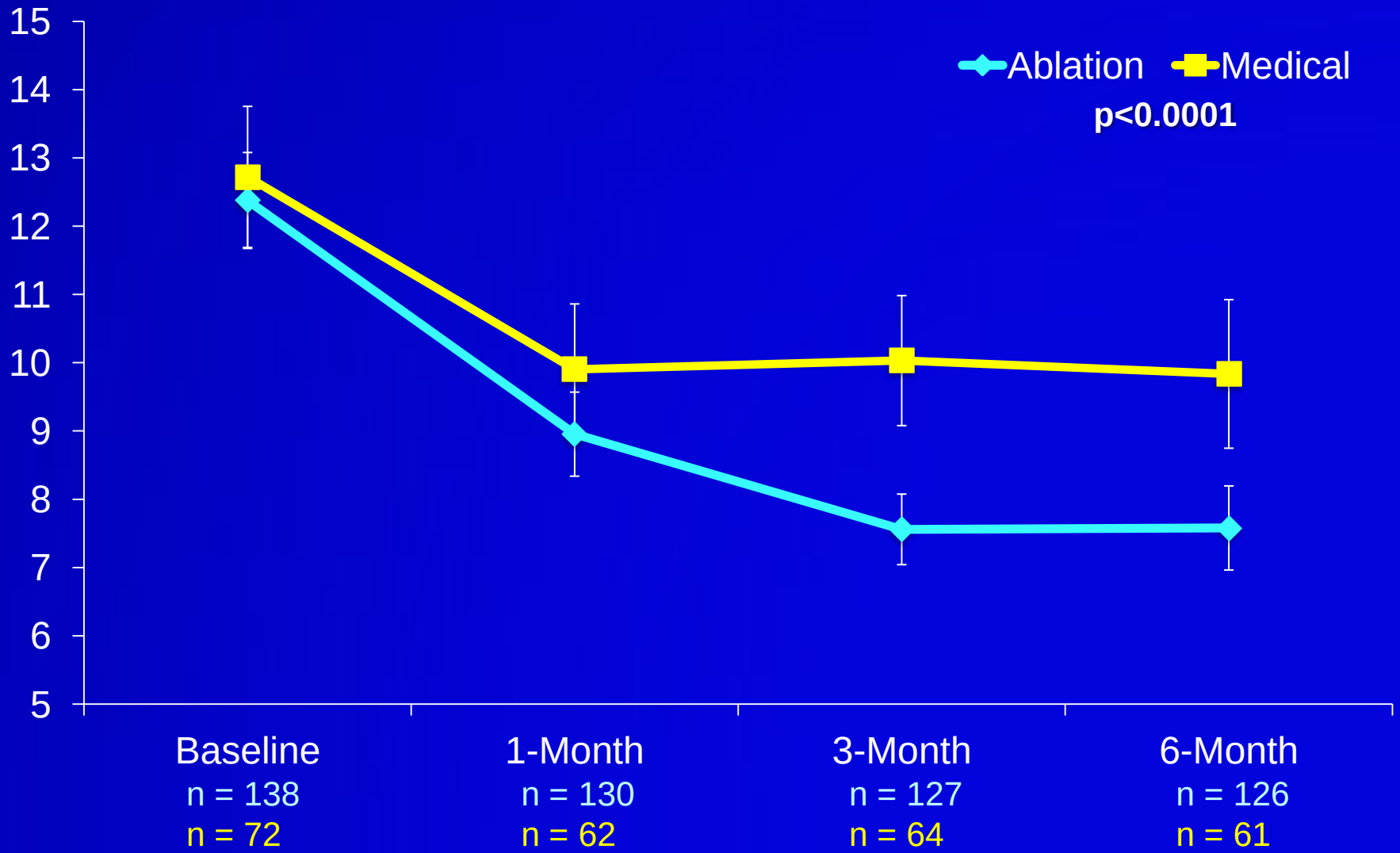


***Missing endpoints**
FDA has not reviewed this analysis

Quality of Life – SF-36 Component Scores



AF Symptom Severity Reduction



Primary Safety Endpoints

Acute Safety – Ablation Management only

- The proportion of subjects free of serious procedure and/or device-related adverse events within 7 days of the index and retreatment ablation procedures

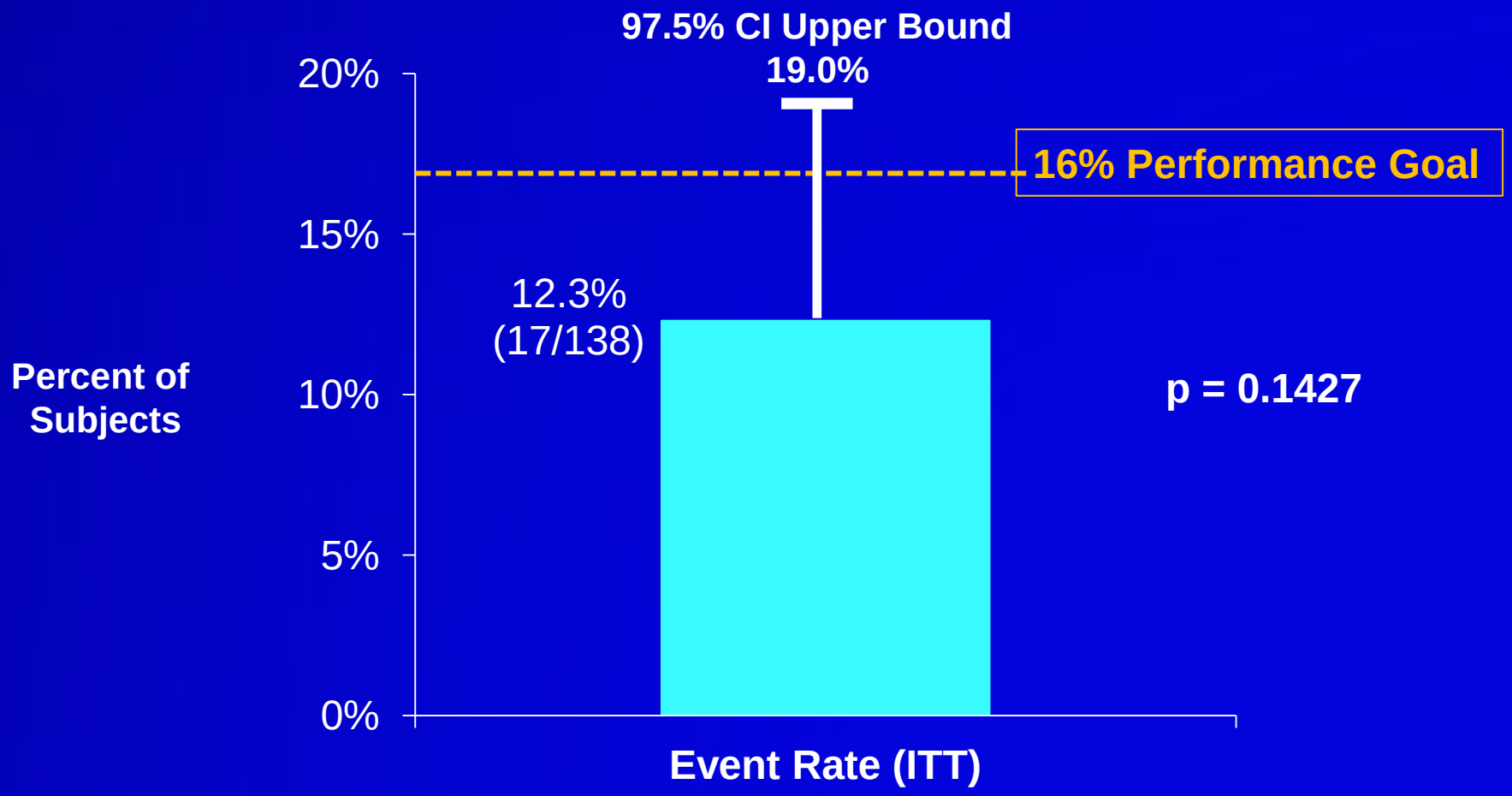
Chronic Safety

- Comparison of Serious Adverse Events (SAEs)
  - SAEs (>7 days through 6 months) for Ablation Management
  - SAEs from time of randomization for Medical Management
- Not prospectively powered

Acute Safety Events: Ablation Management

Event	N=138
Stroke	4 (2.9%)
Cardiac tamponade	2 (1.4%)
Pseudoaneurysm	2 (1.4%)
Heart failure resulting in death	1 (0.7%)
Heart failure	1 (0.7%)
Pulmonary infiltrates with fever (one patient experienced 2 events)	2 (1.4%)
Drop in Hct secondary to ablation	1 (0.7%)
Anesthesia reaction	1 (0.7%)
UTI with prolonged hospitalization	1 (0.7%)
Hypotension secondary to cardiac tamponade	1 (0.7%)
Hypotension/cardiogenic shock	1 (0.7%)
Pneumonia	1 (0.7%)
Acute respiratory failure	1 (0.7%)
Retroperitoneal bleed with right ureter obstruction	1 (0.7%)
Post-procedure pericarditis	1 (0.7%)
Total	21 occurred in 17 subjects

Ablation Management Acute Safety Results



Acute Stroke Outcomes

Subject	Symptom Onset	Presenting Symptoms	Ongoing Symptoms	Rhythm at 6 Months
1	3 - 6 hours	Expressive Aphasia	Minor Difficulties with Word Finding	Sinus Rhythm
2	12 - 18 hours	Diplopia Disconjugate Gaze	Slight Drift and Vision	Sinus Rhythm
3	12 - 18 hours	Left Arm Weakness	Resolved	AF
4	24 - 36 hours	Slurred Speech	Resolved	Sinus Rhythm

Subject Death

- 63-year-old male
- Randomized with LVEF of 45%
- Index Procedure 3 months later
  - Rapid AF with LVEF: 10-15%
  - Acute procedure success
- Retreatment for AF recurrence 5 weeks later
  - LVEF 30-35%, LBBB pattern, NYHA Class III HF
  - Cardiac arrest / HF prior to device deployment
- CEC/DSMB
  - Cause of death: congestive heart failure
  - Definitely related to the procedure, not related to the device

Serious Chronic Safety Events

	Ablation Mgmt n (%) N=138	Medical Mgmt n (%) N=72
Stroke	1 (0.7%)	0
Pulmonary vein stenosis (>70% diameter reduction)	4 (2.9%)	0
Symptomatic PV narrowing (50-70% diameter reduction)	1 (0.7%)	0
Persistent ASD secondary to septal puncture	1 (0.7%)	0
Pericardial effusion	1 (0.7%)	0
Chest pain secondary to pericarditis	1 (0.7%)	0
GI bleed	0	2 (2.8%)
AF with rapid ventricular response	0	1 (1.4%)
Mean Follow-up	9 months	5.8 months
# Chronic SAEs / Subject-Month	.0072	.0071

Conclusion

- Ablation Management is superior to Medical Management at reducing AF burden
- Acute safety rate 97.5% upper bound, exceeded pre-specified performance goal
- Chronic safety event rates similar between Ablation and Medical Management
- Ablation Management confers clinically significant benefit to Quality of Life and reduces AF symptoms

TTOP-AF Results
Clinical Perspective

Hugh Calkins, MD, FHRS

Johns Hopkins Hospital

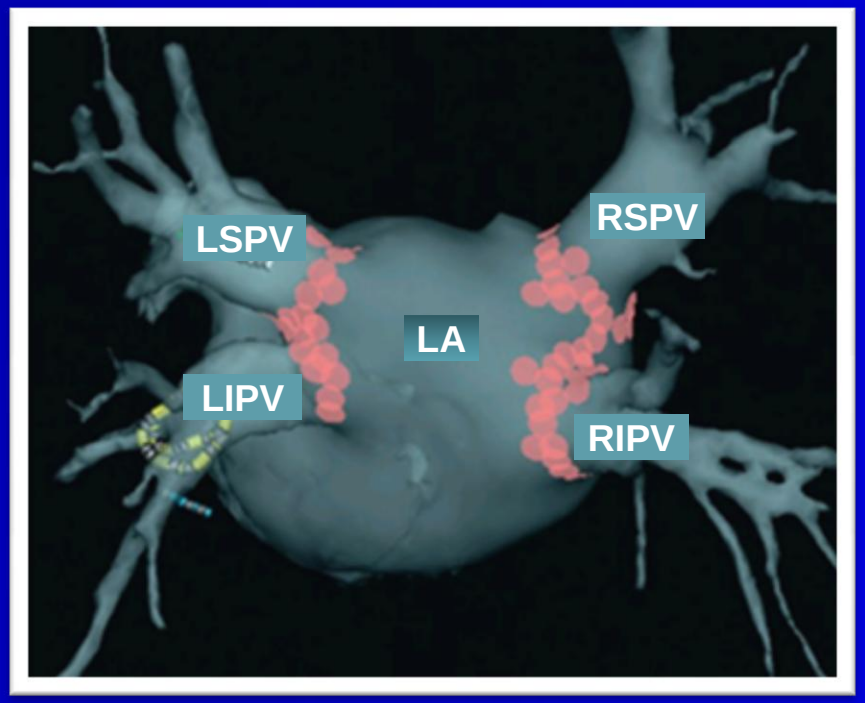
TTOP: Higher Risk Patient Population

	ThermoCool AF Paroxysmal Population[1]	STOP-AF Paroxysmal Population[2]	TTOP-AF Persistent Population
Age (years)	55.5 ± 1.8	56 ± 0.6	59.9 ± 8.5
Gender (% male)	73%	77%	83.3%
Hypertension (%)	48.6%	42.4%	59.0%
Diabetes mellitus	9.5%	7.3%	14.3%
LVEF (%)	62.3% ± 1.9	60.2% ± 5.6	54.7% ± 7.0
LAD (cm)	4.0 ± 0.1	4.0 ± 0.5	4.6 ± 0.5

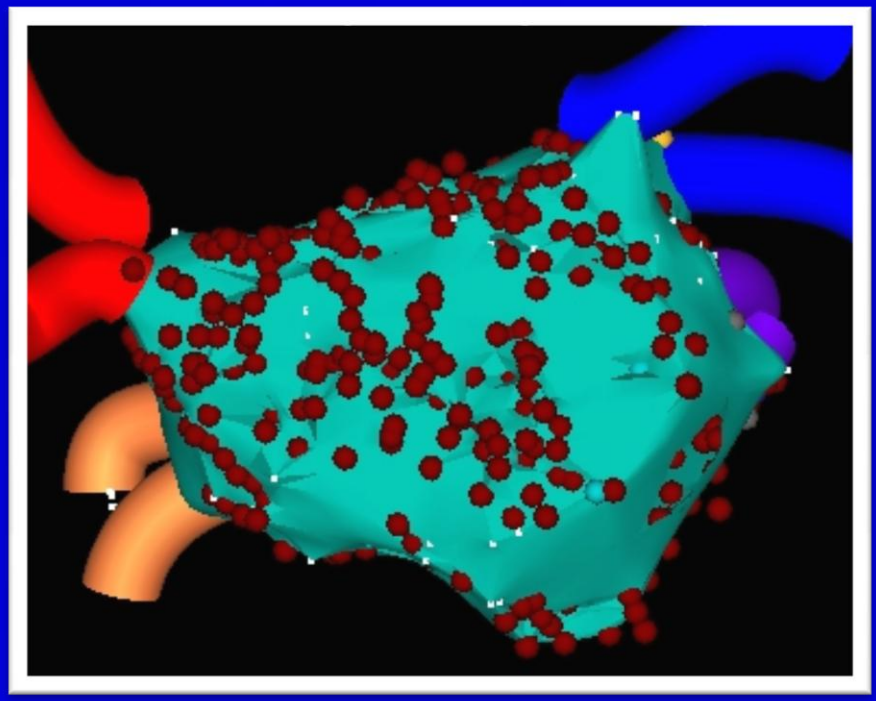
1. Wilber et al., *Comparison of antiarrhythmic drug therapy with radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: A randomized controlled trial.* JAMA 2010.
2. Arctic Front Cryoballoon Catheter Instructions for Use

Different Ablation Procedure

Paroxysmal AF Ablation



Persistent AF Ablation

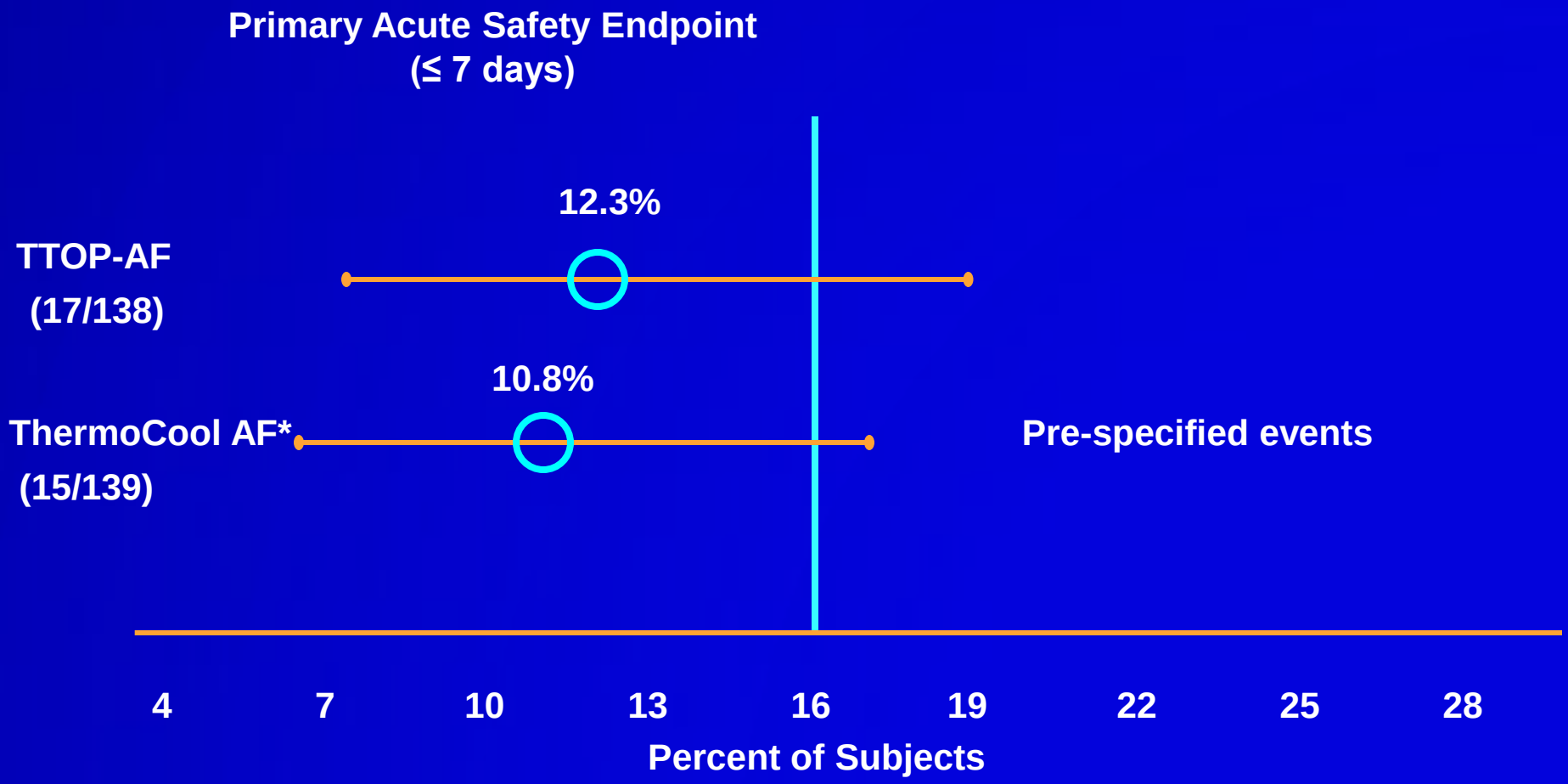


Acute Safety Endpoint

- Upper confidence boundary of 16% based on
  - Right atrial flutter trials[1,2]
  - Non-randomized paroxysmal AF trials[3]
- Persistent AF is a higher risk patient population
- All events versus pre-specified events

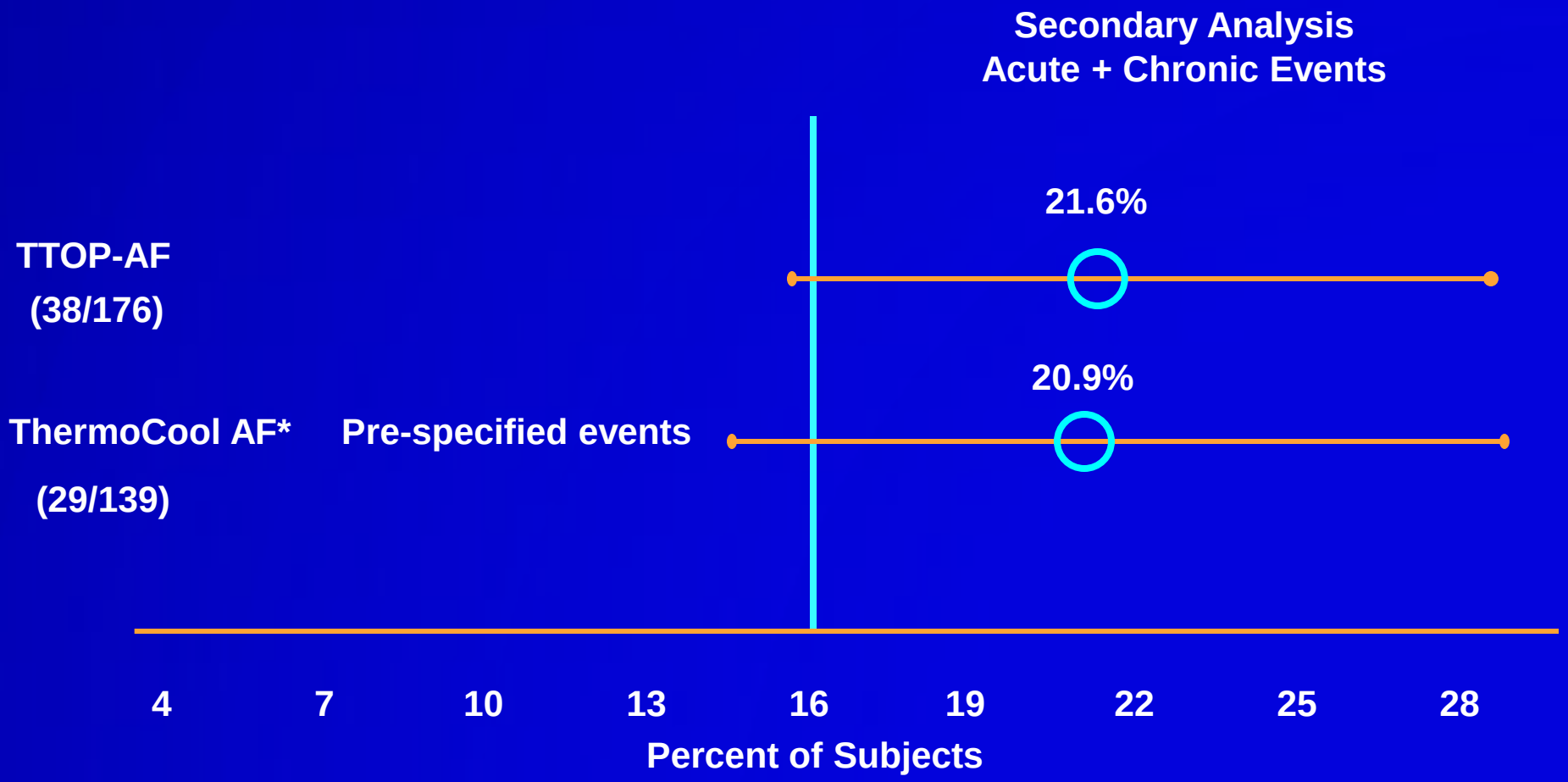
1. PMA P020025 – Summary of Safety and Effectiveness Data: Boston Scientific Corporation Blazer II XP™ Cardiac Ablation Catheter, August 25, 2003.
2. PMA P040042 – Summary of Safety and Effectiveness Data: Irvine Biomedical, Inc. IBI Therapy™ Dual 8™ Ablation Catheter, November 18, 2005.
3. Packer et al. *Progress in nonpharmacologic therapy of atrial fibrillation.* Cardiovaxc Electrophysiol (14). December 2003.

Safety Outcome Comparison



*ThermoCool one-sided upper safety confidence of 16.1% also exceeded the 95% upper safety confidence bound.
Panel Pack Clinical Report (ThermoCool IDE) [redacted], 136 pages plus Appendices, dated October 16, 2008
http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4393b1-01-%20%20Sponsors%20Executive%20Summary.pdf
Analysis not previously provided to FDA

Safety Outcome Comparison



*ThermoCool one-sided upper safety confidence of 16.1% also exceeded the 95% upper safety confidence bound.
Panel Pack Clinical Report (ThermoCool IDE) [redacted], 136 pages plus Appendices, dated October 16, 2008
http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4393b1-01-%20%20Sponsors%20Executive%20Summary.pdf
Analysis not previously provided to FDA

Pulmonary Vein Events

- 7/176 (4%) ablated subjects had a pulmonary vein event
  - 6 subjects had one stenotic PV; One symptomatic
  - 1 subject with symptomatic PV narrowing defined as 50-70% narrowing
- The per subject PV stenosis rate is comparable to the 3.1% per subject rate in the STOP-AF trial*
- No subjects required treatment for PV stenosis

*Arctic Front Cryoballoon Catheter Instructions for Use

Stroke Risk: Patient and Procedural Factors

Patient Factors[1,2,5]

- Persistent AF vs paroxysmal AF
- $CHADS_2$ Score ≥ 2
- Left atrial diameter enlargement

Procedural Factors[3-5]

- Cardioversion
- Extensive ablation
- Peri-procedural anti-coagulation
  - ACT < 300s
  - INR < 2.0 – 3.0

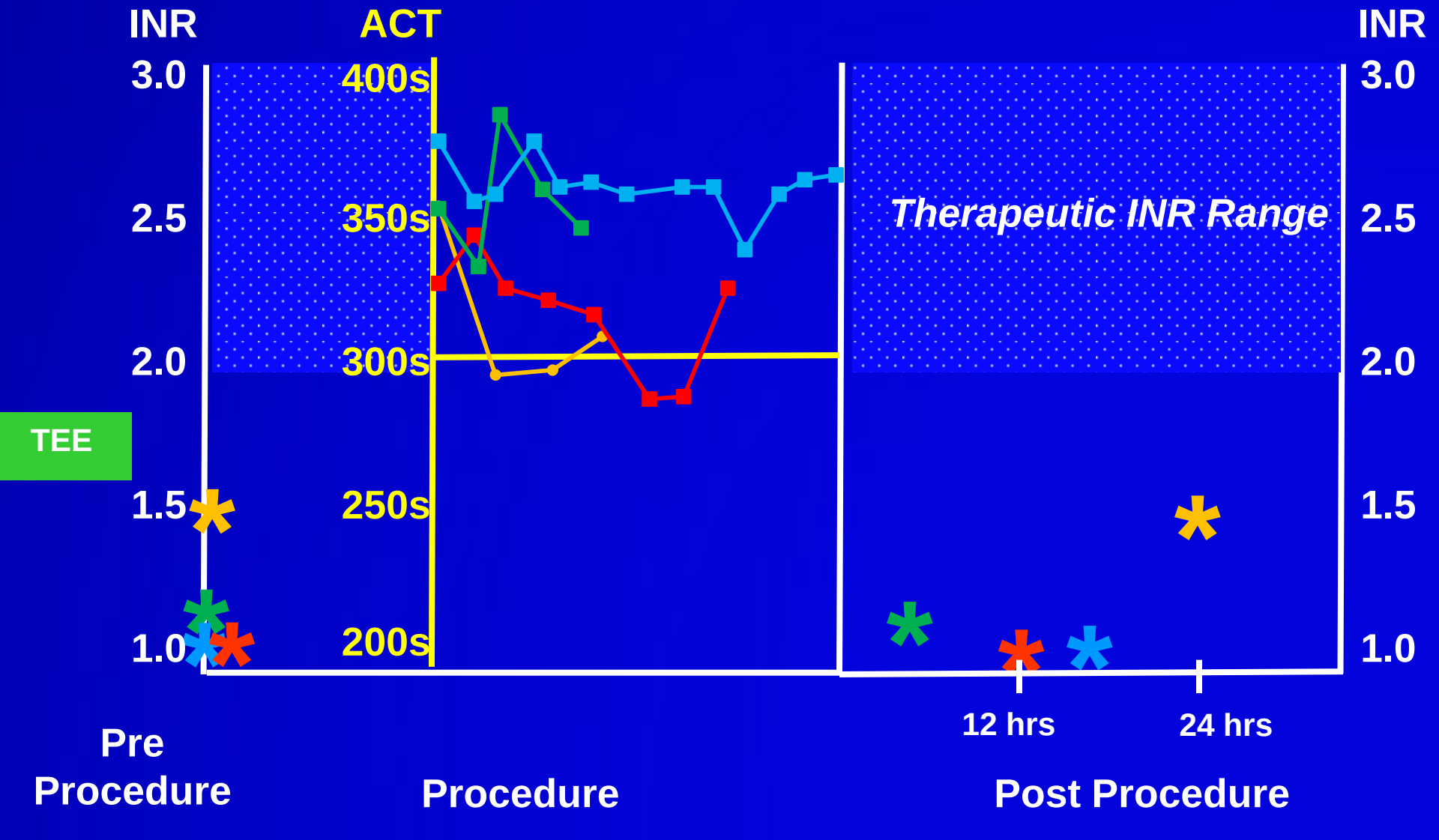
1. Patel et al., *Long-term functional and neurocognitive recovery in patients who had an acute cerebrovascular event secondary to catheter ablation for atrial fibrillation.* J Cardiovasc Electrophysiol. 2010.
2. Scherr et al., *Incidence and predictors of periprocedural cerebrovascular accidents in patients undergoing catheter ablation.* J Cardiovasc Electrophysiol. 2009.
3. Wazni et al., *Embolic events and char formation during pulmonary vein isolation in patients with atrial fibrillation: impact of different anticoagulation regiments and importance of intracardiac echo imaging.* J Cardiovasc Electrophysiol. 2005.
4. DiBiase et al., *Periprocedural stroke and management of major bleeding complications in patients undergoing catheter ablation of atrial fibrillation.* Circulation 2010.
5. Khan IA., *Atrial stunning: Determinants and cellular mechanisms.* Am Heart J 2003.

References 3 and 5 not previously provided to FDA

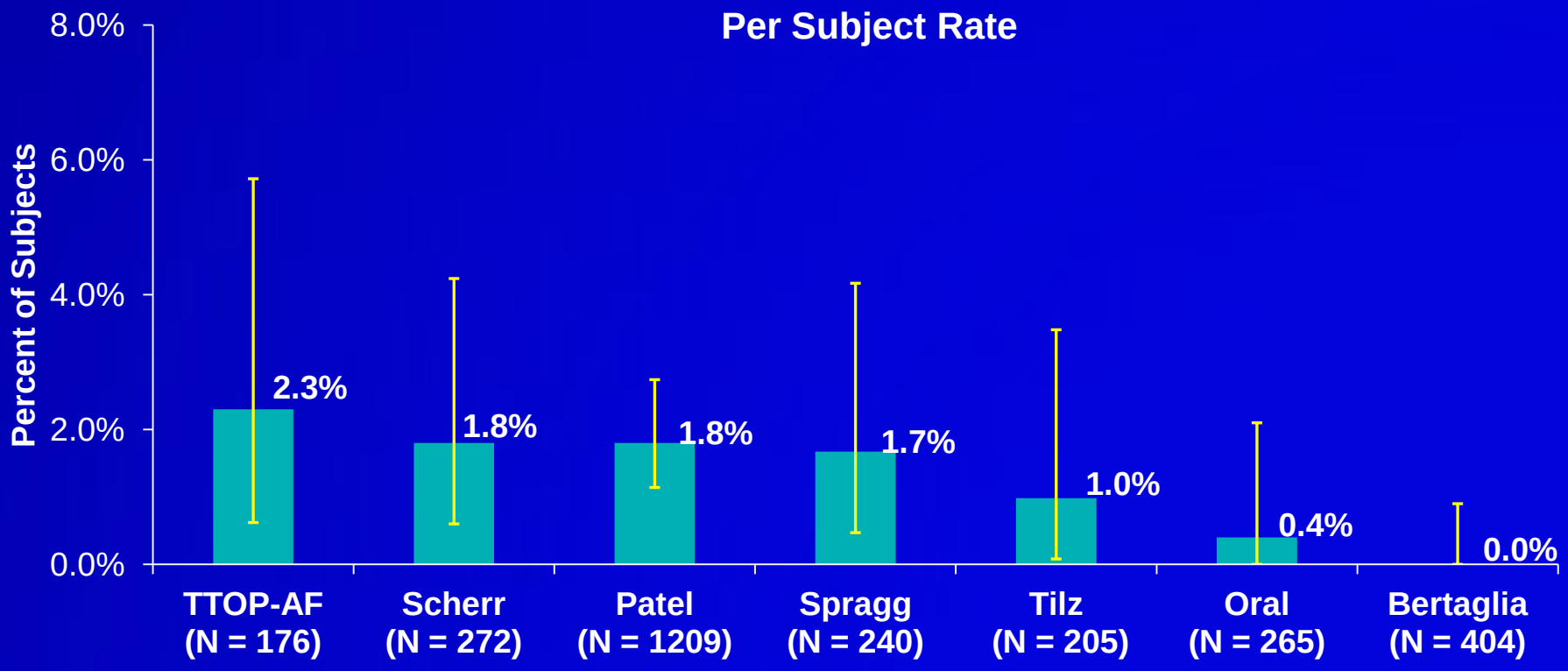
Risk Factors in the TTOP-AF Population

	Subjects with No Acute Stroke (n=172)	Subjects with Acute Stroke (n=4)
Persistent AF	70%	100%
Long-standing persistent AF	30%	0%
$CHADS_2$ score	0.8 ± 0.7	1.3 ± 0.5
LAD (cm)	4.6 ± 0.5	5.0 ± 0.5
Left atrial dwell time (hrs:min)	2:43 ± 0:48	3:46 ± 1:09
Procedure time (hrs:min)	3:16 ± 0:54	4:12 ± 1:12
ACT values during left atrial access (sec)	331.0 ± 35.2	324.9 ± 26.6
Procedural cardioversion rate	86.7%	100%
Procedure INR value	1.6 ± 0.6	1.2 ± 0.2

Anti-Coagulation Details for Acute Stroke Subjects



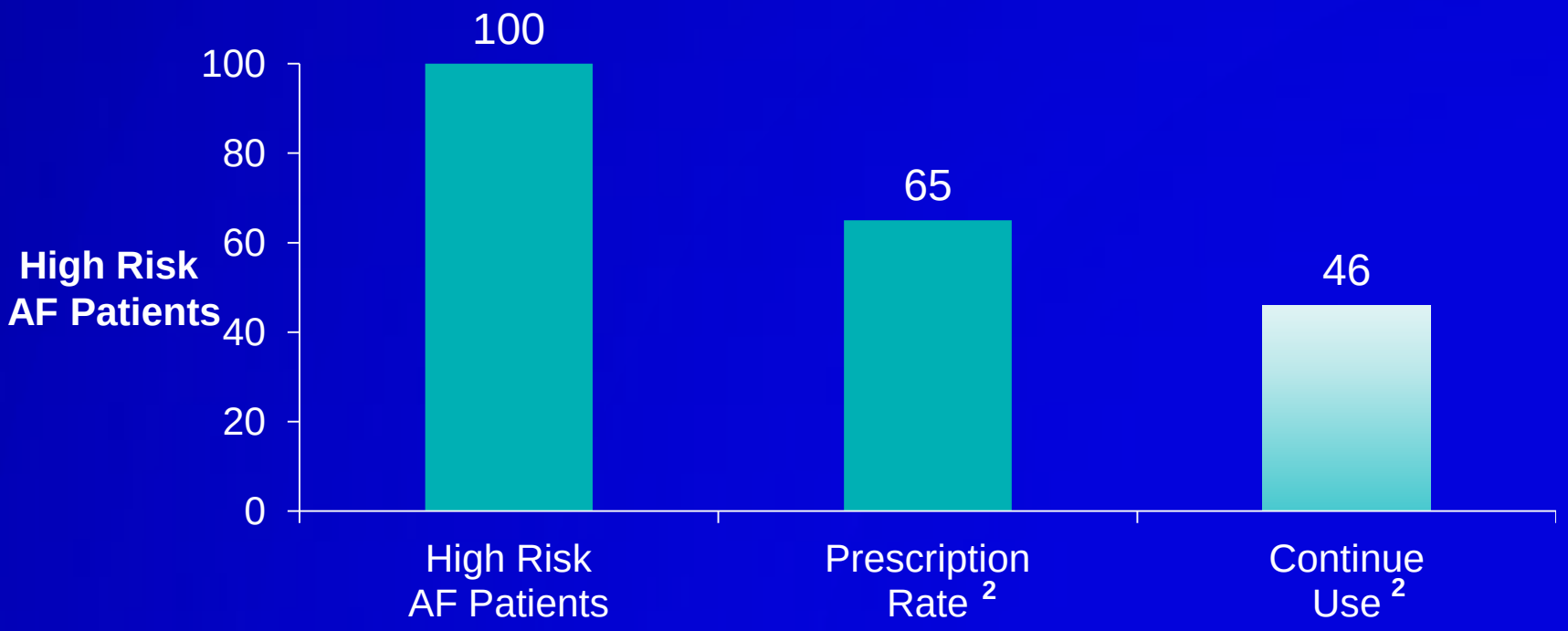
Incidence of Acute Stroke During Ablation of Persistent AF



Scherr et al., *Incidence and predictors of periprocedural cerebrovascular accidents in patients undergoing catheter ablation.* J Cardiovasc Electrophysiol. 2009; Patel et al., *Long-term functional and neurocognitive recovery in patients who had an acute cerebrovascular event secondary to catheter ablation for atrial fibrillation.* J Cardiovasc Electrophysiol. 2010.; Spragg et al., *Complications of catheter ablation for atrial fibrillation: Incidence and predictors.* J Cardiovasc Electrophysiol. 2008; Tilz et al., *Catheter ablation of long-standing persistent atrial fibrillation: A lesson from circumferential pulmonary vein isolation.* J Cardiovasc Electrophysiol. 2010.; Oral et al., *Risk of thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation.* Circulation 2006.; Bertaglia et al., *Early complications of pulmonary vein catheter ablation for atrial fibrillation: A multicenter prospective registry on procedural safety.* Heart Rhythm 2007.

Real World Anti-Coagulation Use

- Stroke rates on warfarin[1]
  - Ischemic stroke: 2.1% with INR > 2.0 and 5.8% with INR < 2. 0



  - Hemorrhagic Stroke: 3.6% INR > 3.0 and 2.6% INR 2-3

1. **Reynolds MW et al.,** ***Warfarin anticoagulation and outcomes in patients with atrial fibrillation: A systematic review and metaanalysis*****. Chest 2004.**
2. **Ogilvie IM et al.,** ***Underuse of oral anticoagulants in atrial fibrillation: A systematic review.*** **Am J Med 2010.**

References not previously provided to FDA

Asymptomatic Cerebral Embolism (ACE) is Not New

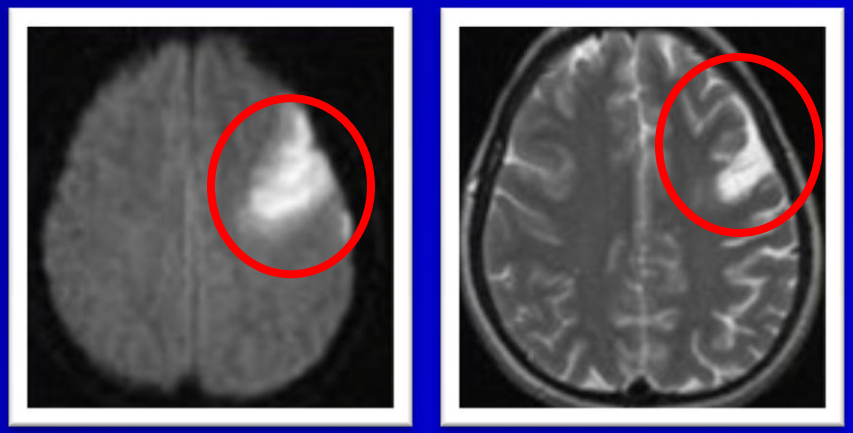
- ACE is not a new finding in invasive cardiology[1]
  - Valve replacement: 47%
  - CABG: 34%
  - Diagnostic coronary angiography: 15%

- Lesion rates in AF ablation vary between technologies[2-5]
  - Cryoballoon: 4.3% - 8.9%
  - Irrigated RF: 6.8 – 38.3%
  - Medtronic Cardiac Ablation System: 37.5 – 41.7%

1. Bendszus M, Stoll G. Silent cerebral ischemia: hidden fingerprints of invasive medical procedures. The Lancet Neurology 2006.
2. Mizukami et al., *Prevalence of risk factors of asymptomatic stroke after pulmonary vein isolation with irrigated tip catheters.* HRJ 2011.
3. Neumann et al., *MEDAFI trial (Microembolization during ablation of atrial fibrillation): Comparison of pulmonary vein isolation using cryoballoon technique vs. radiofrequency energy.* Europace 2011.
4. Herrera Siklody et al., *Incidence of asymptomatic embolic events following pulmonary vein isolation; comparison of different atrial fibrillation ablation technologies in a multicenter center. J Am Coll Cardiol 2011.*
5. Deneke et al., *Post-ablation asymptomatic cerebral lesions: long-term follow-up using magnetic resonance imaging.* HRJ 2011.

ACE Lesions Are Smaller Most Regress

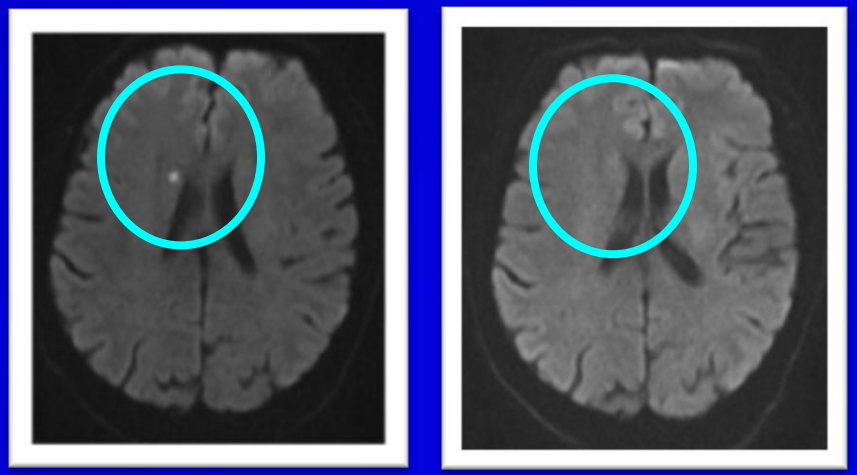
Clinical Stroke Lesion[1-3]



Acute Chronic

13 - 45 cc
(mean values)

Ablation ACE Lesion[4]



Acute Chronic

.004 - 1.0 cc

1. Schaefer PW et al., *Predicting cerebral infarct volume with diffusion and perfusion MR imaging*. Am J Neuroradiol. 23:2002.
2. Kruetzelmann A et al., *Pretreatment diffusion-weighted imaging lesion volume predicts favorable outcome after intravenous thrombolysis with tissue-type plasminogen activator in acute ischemic stroke.* Stroke. 2011; 42:1251-1254.
3. http://www.radiologyassistant.nl/en/483910a4b6f14 (NOT PREVIOUSLY PROVIDED TO FDA)
4. Deneke et al., *Post-ablation asymptomatic cerebral lesions: long-term follow-up using magnetic resonance imaging.* HRJ 2011.

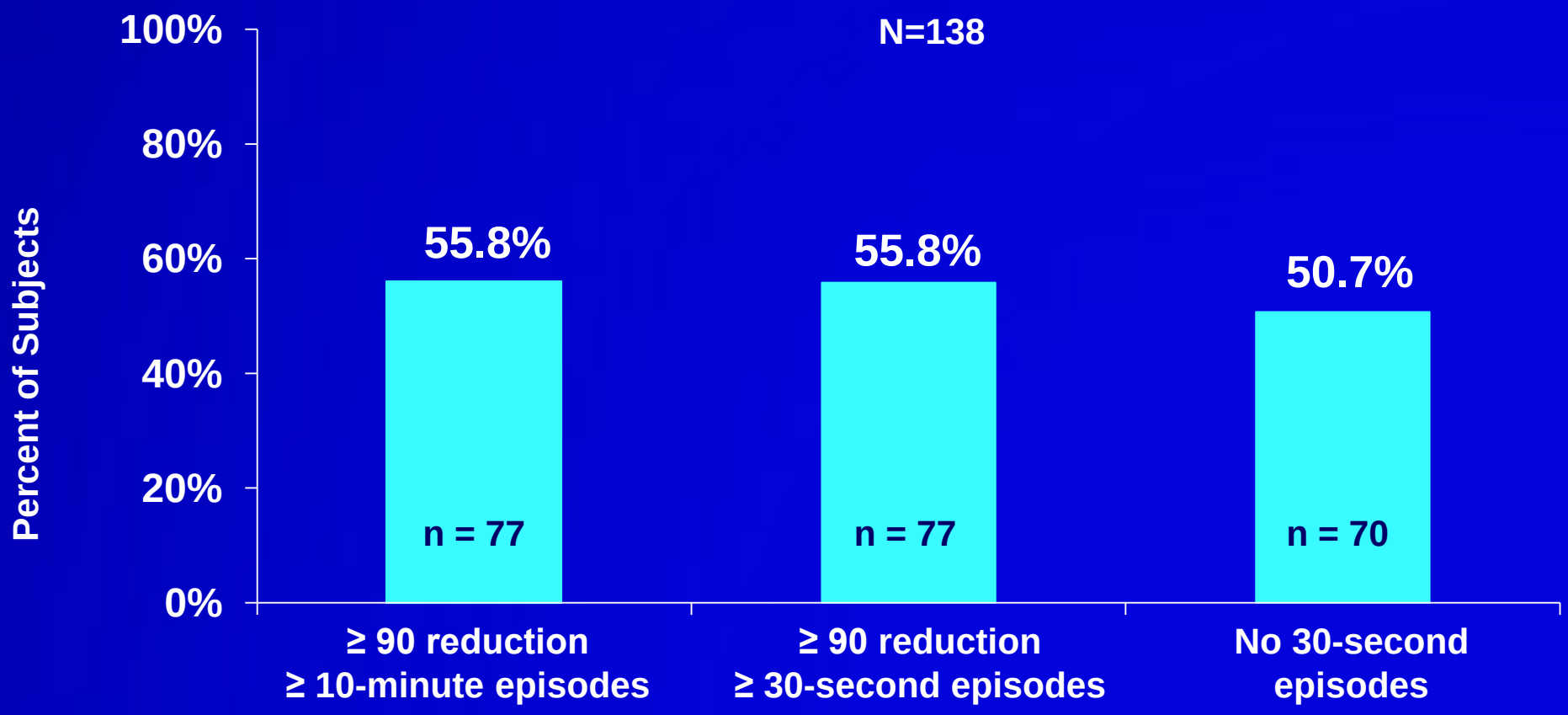
ACE Summary

- Observations of ACE are common following invasive cardiac procedures
- ACE lesions are clinically and biologically distinct from lesions that cause stroke
- ACE lesions are significantly smaller than lesions associated with stroke
- Most ACE lesions regress
- No convincing evidence associating ACE lesions and neurologic deficit

Safety Summary

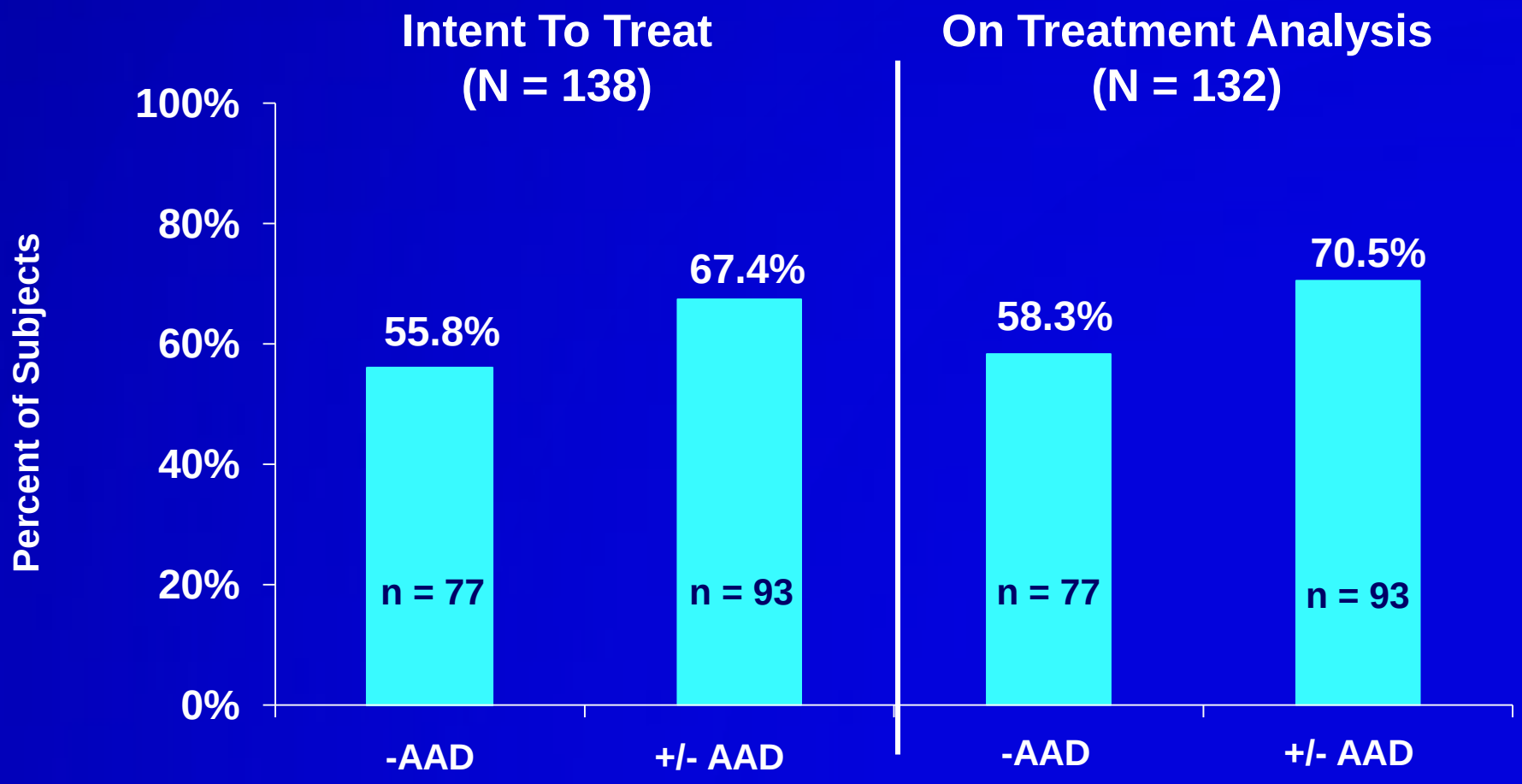
- High risk patient population
- Acute safety endpoint comprehensive
- PV stenosis rates comparable
- Stroke rate in-line with literature

Effectiveness by AF/AFL Episode Definition



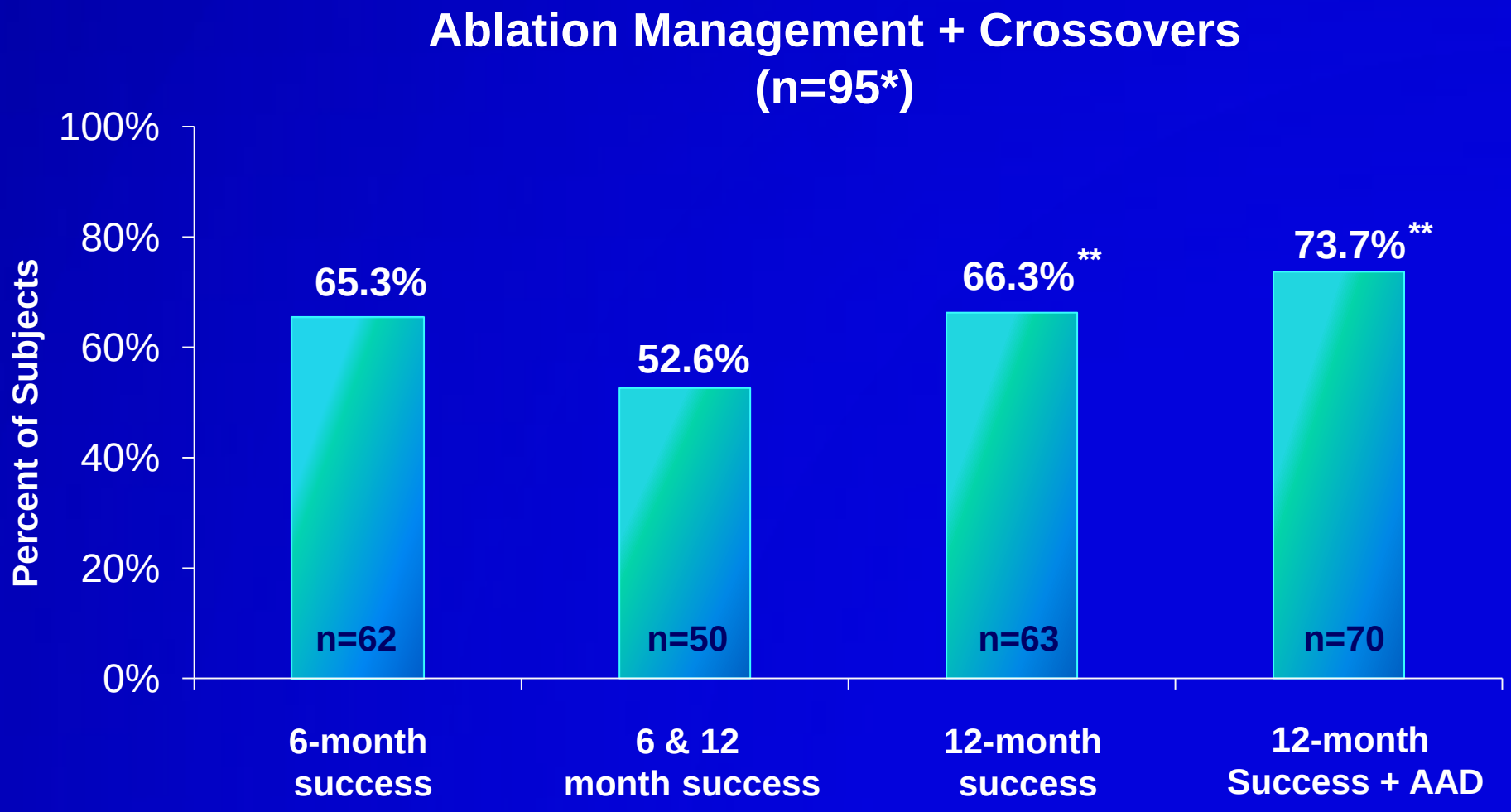
Based on 48-hour Holter data at 6 months

Treatment Success On/Off Anti-Arrhythmic Drugs



≥ 10-minute AF/AFL Episodes
6-month data

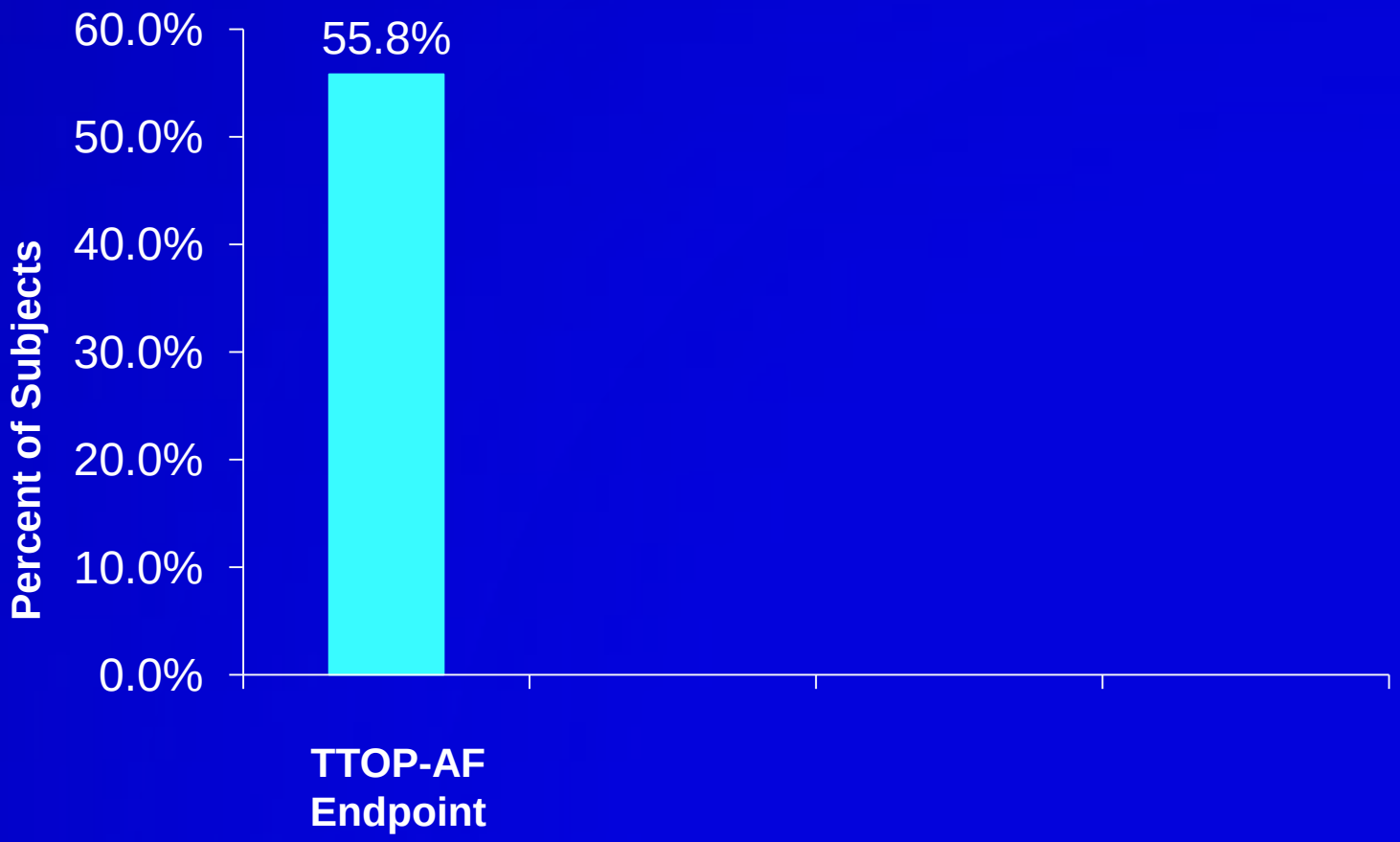
Treatment Effectiveness at 12 Months



*Number of available ablation subjects providing 12-month 48-Holter data

**FDA has not reviewed this analysis

Additional Effectiveness Analysis

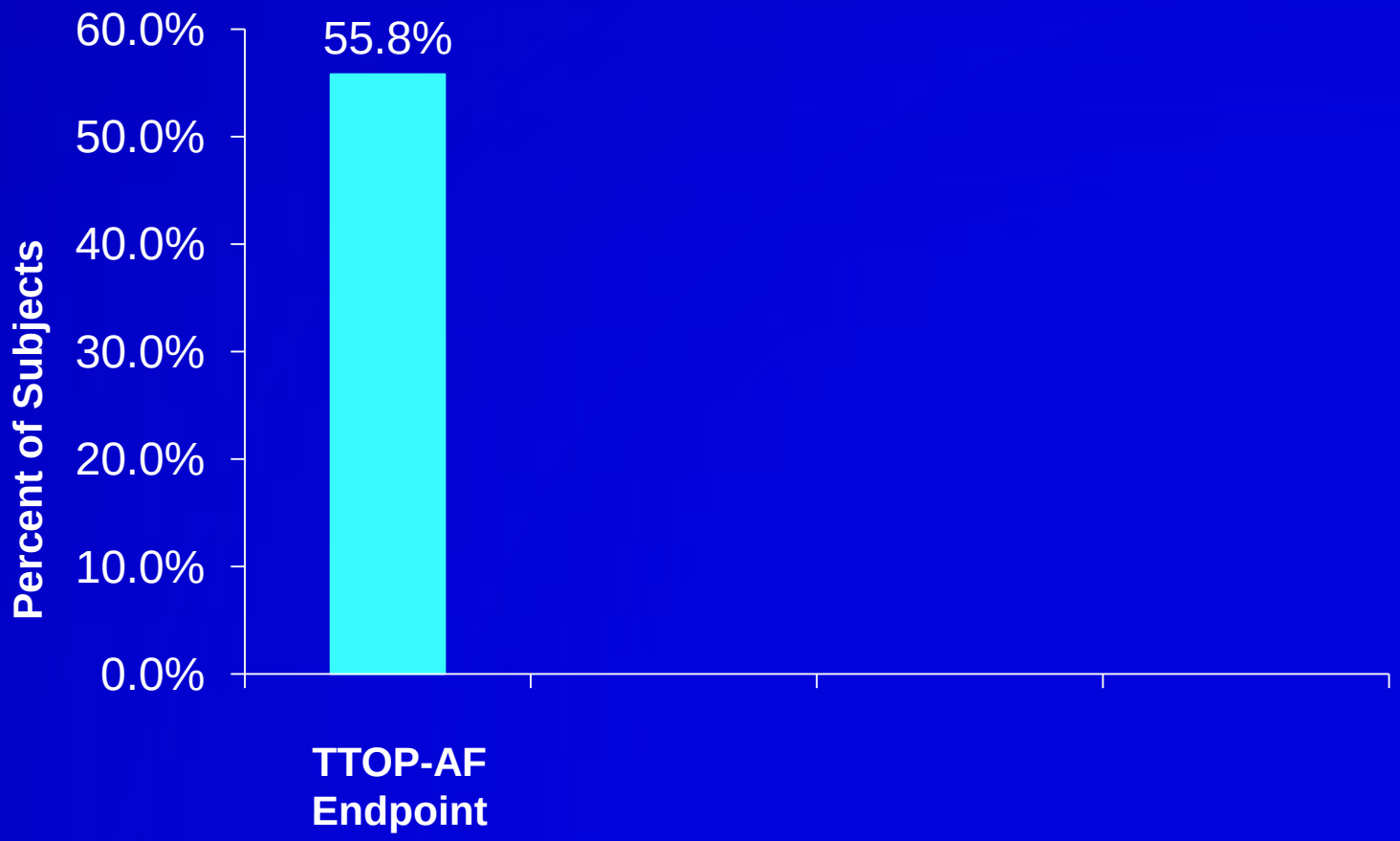


6-month data

Additional Effectiveness Analysis

TTOP AF Success Criteria

1. Acute Success
2. ≥ 90% reduction of AF burden
3. Off AAD at 6 months

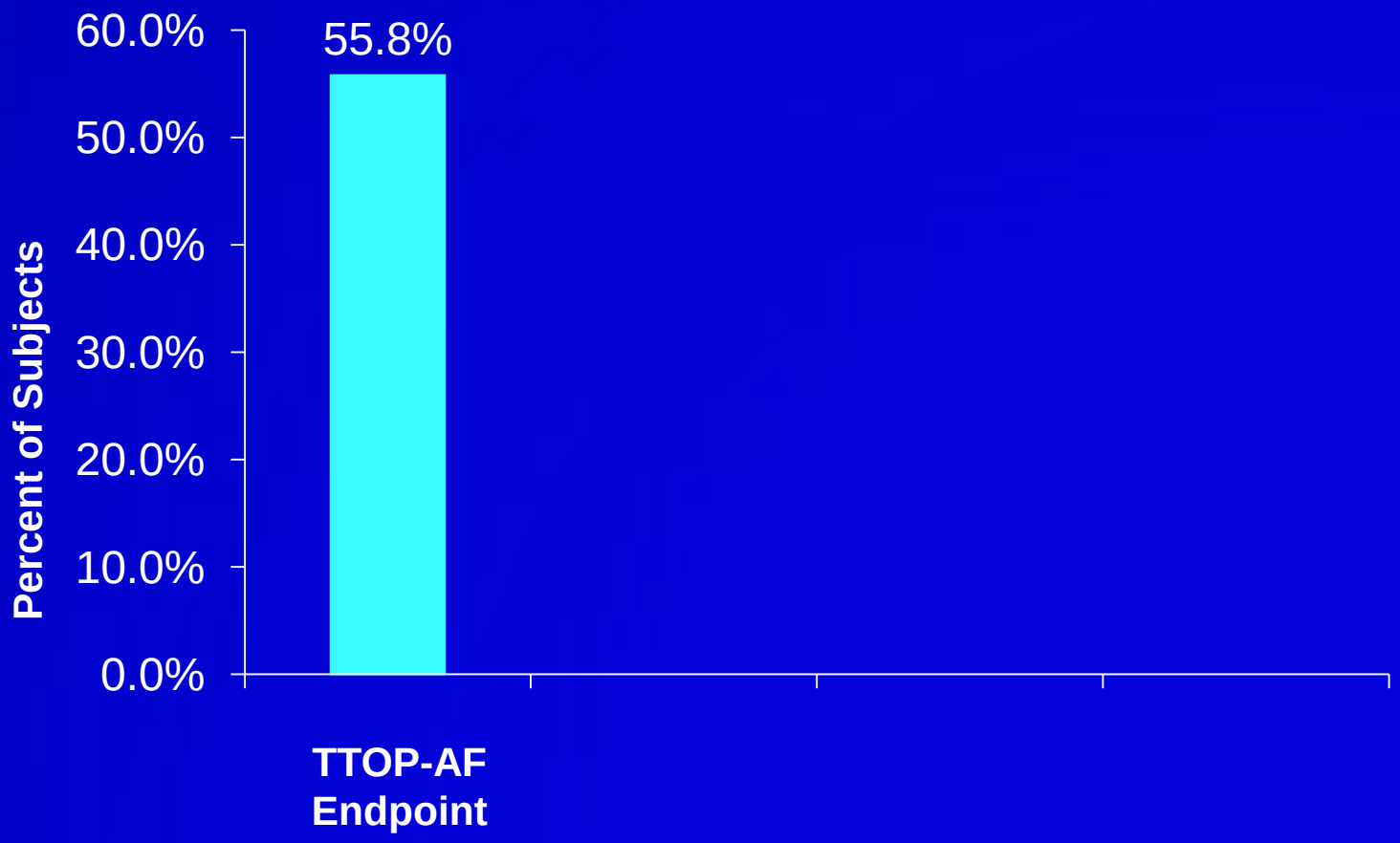


6-month data

Additional Effectiveness Analysis

HRS Success Criteria

1. Acute Success
2. No AF episodes > 30 seconds
3. No recurrence between 3-6 months
4. No DCCV or ablation between 3-6 months
5. Off AAD at 3 months

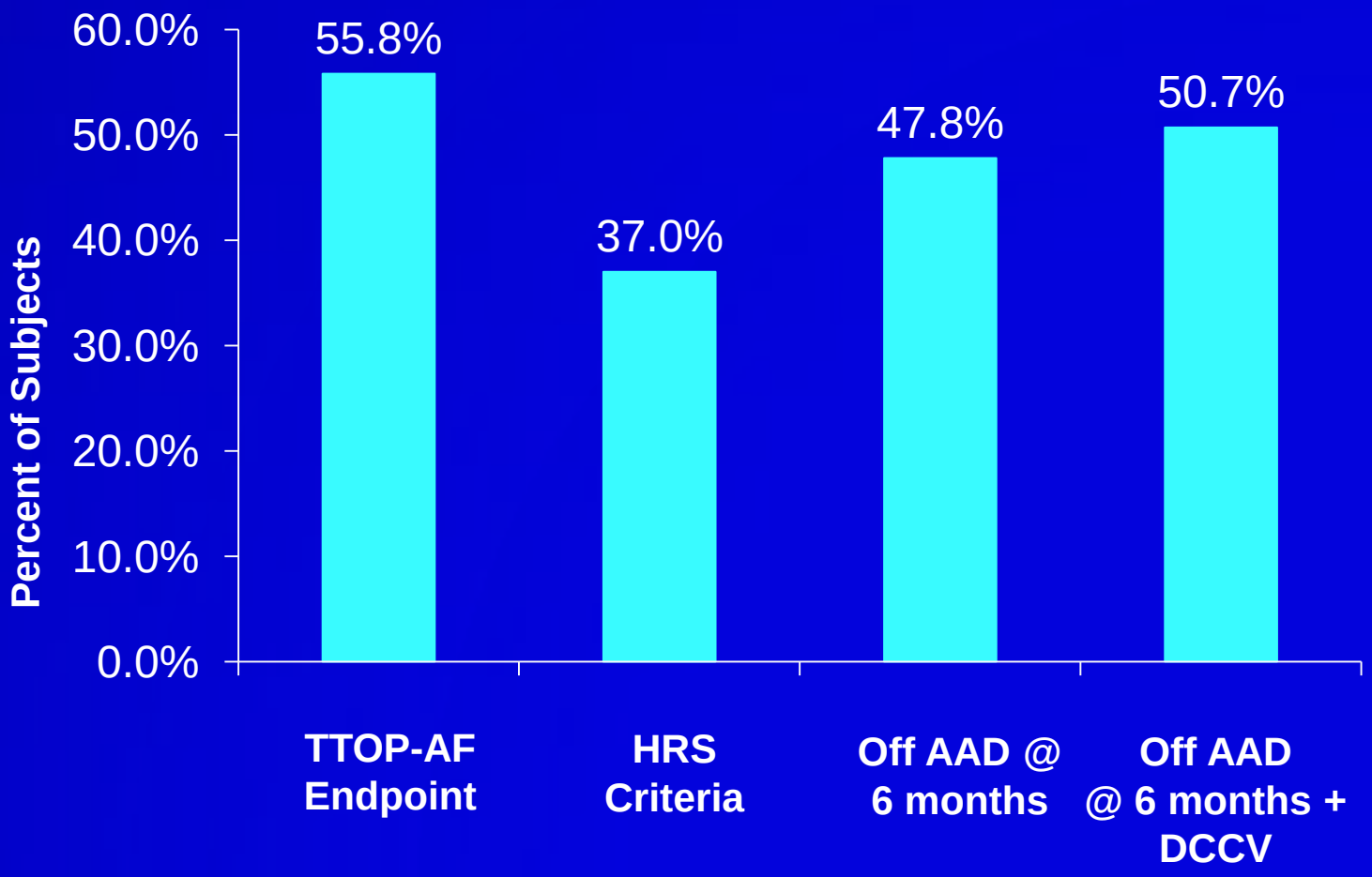


6-month data

Additional Effectiveness Analysis

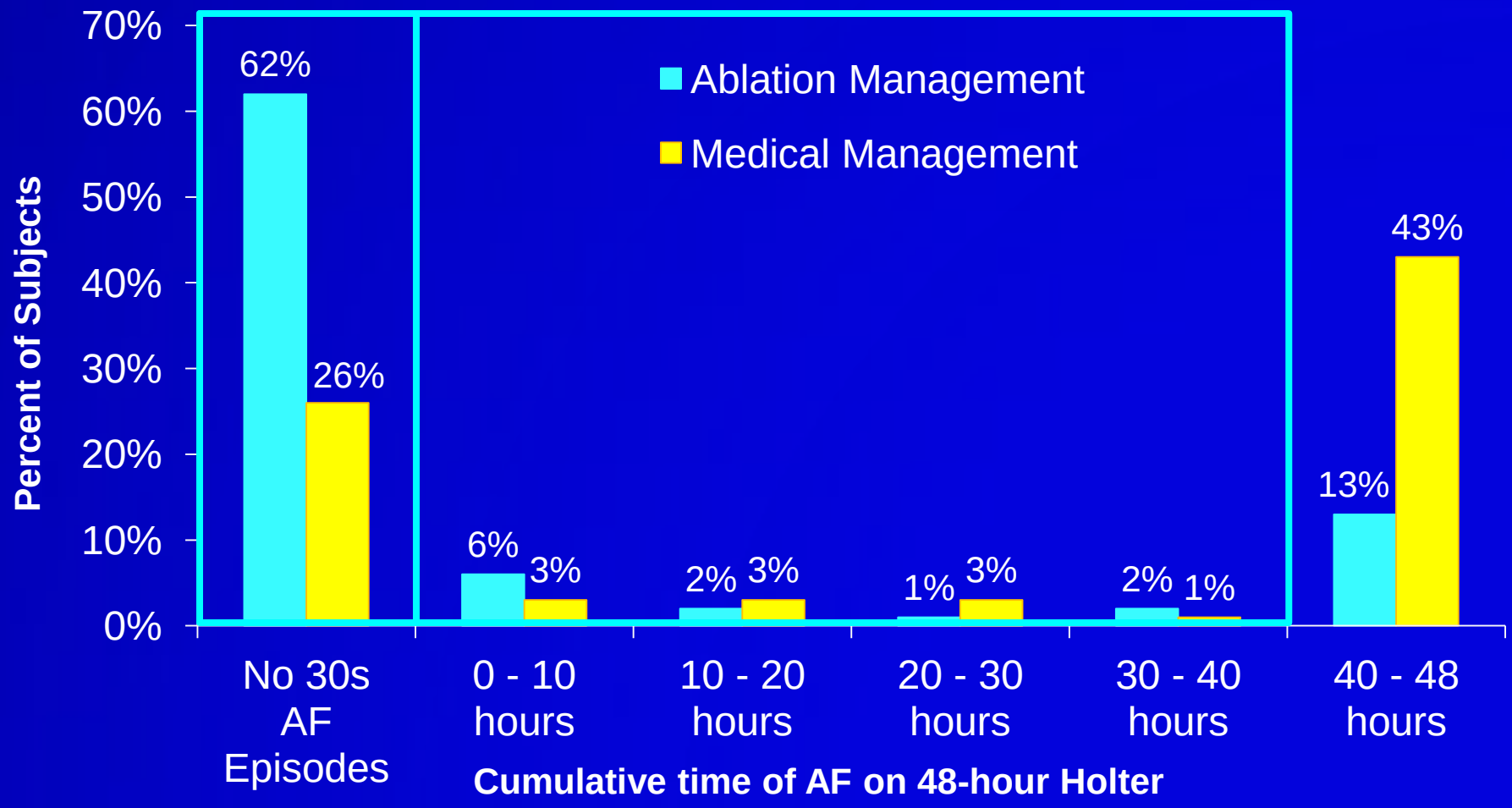
HRS Success Criteria

1. Acute Success
2. No AF episodes > 30 seconds
3. No recurrence between 3-6 months
4. No DCCV or ablation between 3-6 months
5. Off AAD at 3 months



6-month data

Clinical Benefit Achieved



Percentages based on all randomized subjects (N=210)
6-month data
FDA has not reviewed this analysis

Medtronic Cardiac Ablation System Is a Needed Option

	Effectiveness	Stroke	Death	Complications
Rhythm Control Drugs[1-4]	40% - 82.4% Sinus Rhythm	0% - 3.4%	0.8% - 4.8% (1 year)	54% - 80% Hospitalizations
Rate Control Drugs[1-4]	No Burden Reduction	0% - 3.0%	0.8% - 3.3% (1 year)	54% - 57% Hospitalizations
Ablate and Pace[5] (AV Node Ablation)	No Burden Reduction	3.2%	14.7 % (1 year)	9.3%
Surgical[6]	79% to 90% (PAF and Permanent AF)	0.5 -1.6%	2.1% - 4.2% (30 days)	4.4% - 5.8%
Medtronic Cardiac Ablation System	67.4% w/AAD 55.8% off AAD	2.3%	0.6%	12.3%

1. Hohnloser, et al. Lancet 2000; 356:1789-94.
2. Van Gelder et al. NEJM 2002; 347:1834-40.
3. AFFIRM Investigators. NEJM 2002; 347:1825-33.
4. Carlsson, et al. J. Am. Cardiol 2003; 41:1690-96.
5. Kay GN et al. JICE 1998:2:121-135.
6. Herzschr Elektrophys 18:68–76 (2007)

Conclusion

- Effective therapy
- Reasonable risk/benefit profile
- Physicians and patients should have access to this therapy

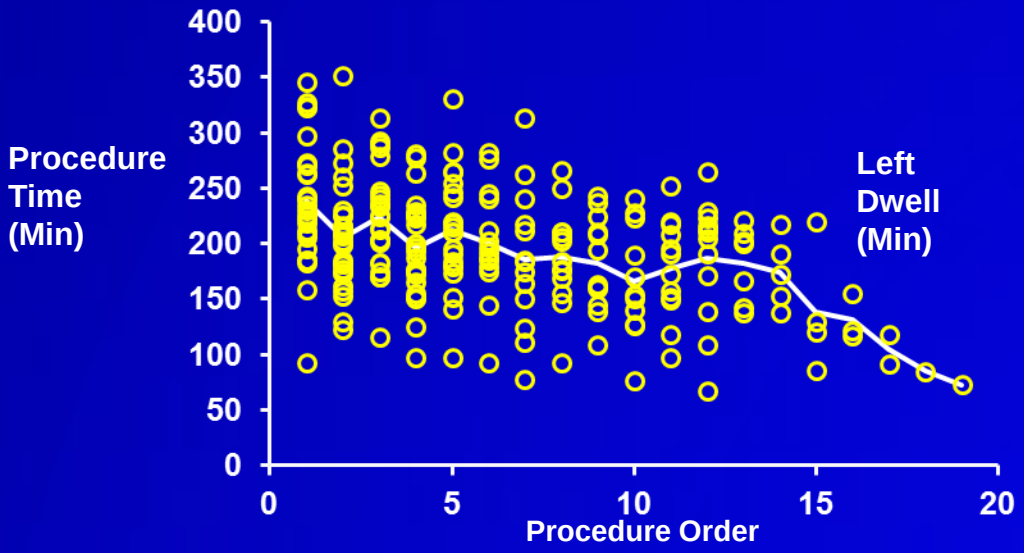
Post-Approval Study Training and Education

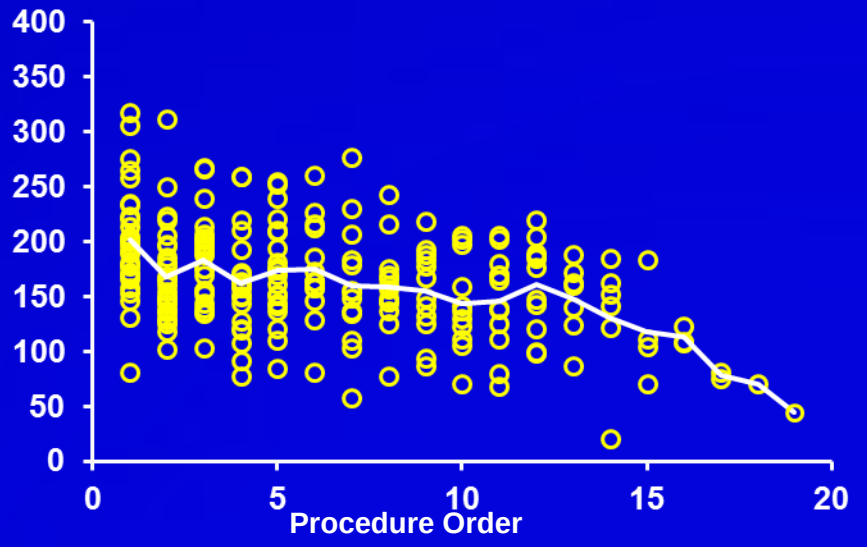
David M. Steinhaus, MD
Vice President and Medical Director
Medtronic Cardiac Rhythm Disease Management

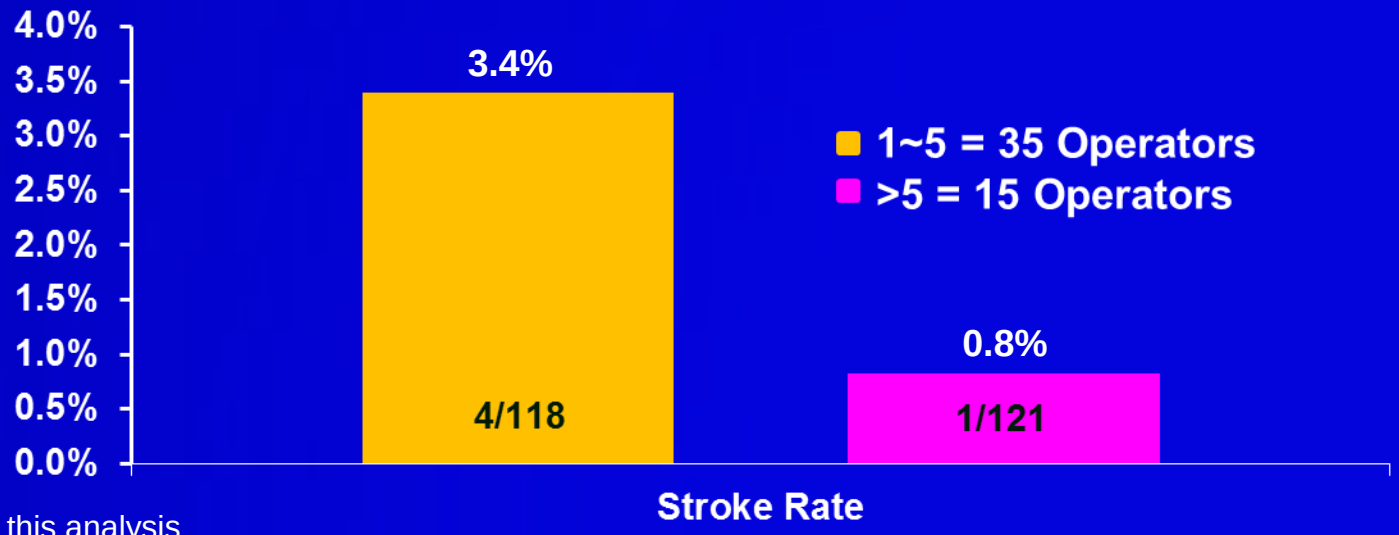
Medtronic Proposed Post Approval Study

- Study Design
  - Prospective, multi-center, global, non-randomized clinical evaluation
  - Sample Size: 400
  - Duration: 36 months
- Primary Study Objectives
  - Subjects with >90% AF burden reduction at 3 years
  - Proportion of acute safety failures < 13%
- Secondary Study Objectives
  - Chronic treatment success at 12, 24, and 36 months
  - Rate of MAFE at 12, 24 and 36 months

May Suggest Learning Curve Effect







FDA has not reviewed this analysis

Proposed Training Curriculum

- Technology-specific practices:
  - Improved Procedure Efficiency
  - Catheter & electrode position
- Generally-accepted practices:
  - Transseptal sheath management
  - Peri-procedural anti-coagulation

Training, Education, & Support

- Physicians
  - Training program taught by physicians experienced with Medtronic system
- Allied Health Professionals
  - In-serviced by the Medtronic Representatives
- Trained Medtronic Support
  - On-site support during initial procedures & ongoing
- Live Technical Support & Website

Closing Remarks

- Persistent AF is different from Paroxysmal AF
- No FDA approved treatment options
- Significant symptoms and sequelae
- Medtronic Catheter Ablation System demonstrated safe and effective

- AF is a serious disease
- Persistent AF: unique population
- Need for new treatment options

Summary

- Unique, advanced ablation system
- Effective treatment for persistent AF
- Reasonable risk/benefit ratio
- Physicians should have the option to offer this new ablation therapy