Medtronic Cardiac Ablation System

FDA Review of P100008

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FDA Presentations

- Linda Ricci
  Introduction
- Dr. Yu Zhao
  Study Statistical Considerations and Conclusions
- Dr. Jun Dong
  Study Clinical Results and Considerations
- Dr. Dale Tavris
  Post-approval Study Considerations
- Linda Ricci
  Conclusions

Introduction Outline

- Proposed Indications for Use
- Key Regulatory Milestones
- Device Background
- Premarket Study Overview
- Discussion Points

Proposed Indications for Use

The Medtronic Cardiac Ablation System is indicated for the treatment of symptomatic, drug refractory, **persistent** atrial fibrillation (AF) or **longstanding persistent** AF of up to four years in duration.

P100008
Key Regulatory Milestones

TTOP-AF Clinical Study

Feasibility Trial

Non-randomized 20 patient study

- February 2007 – received approval
- May 2007 – first patient enrolled

Pivotal Trial

Randomized, multi-center, unblinded, study

- November 2007 – received approval
- November 2007 – first patient enrolled

TTOP-AF Protocol Changes

- After initiation of the pivotal phase of the trial, FDA approved modifications to the TTOP-AF protocol for the following:
  - Inclusion of Interim Analysis
    - Interim analysis could occur once all acute safety data had been collected for entire cohort and 50% of subjects had 6 month effectiveness data
    - Early stopping rules only included effectiveness goals
  - Modification of definition for “failed cardioversion”
    - Changed wording from 30 days to 7 days
- Both of these items were approved after more than half of the patients were enrolled

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Device Background

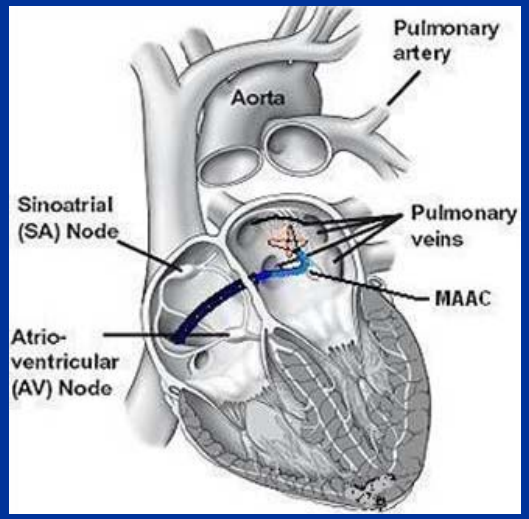
Device Background

The Medtronic Cardiac Ablation System is comprised of the following primary components:

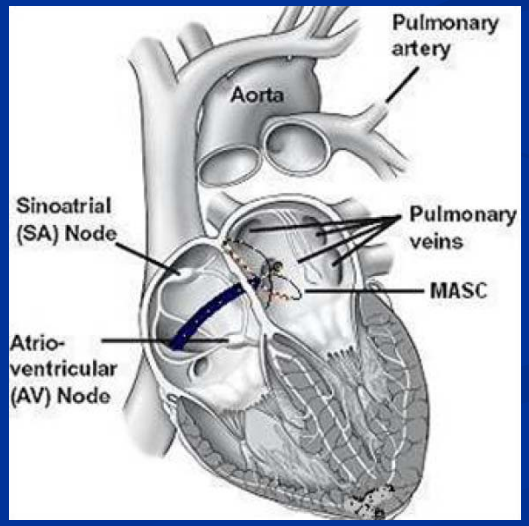
- The Multi-Array Ablation Catheter (MAAC)
- The Multi-Array Septal Catheter (MASC)
- The Pulmonary Vein Ablation Catheter (PVAC)
- The GENius Multi-Channel RF Generator

Catheters

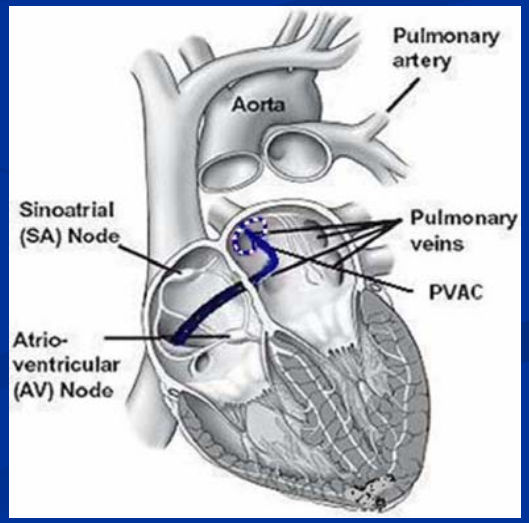
MAAC



MASC



PVAC



Preclinical Testing

- Extensive preclinical testing was performed:
  - Bench testing
  - Animal testing
  - Biocompatibility
  - Sterilization
  - Software Verification and Validation
  - Electrical Safety/Electromagnetic Compatibility

- All issues have been addressed. FDA has no remaining concerns on the preclinical results.

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Pivotal Study Overview

Primary Endpoints

- Chronic effectiveness endpoint definition
  - 90% reduction in clinically significant AF (> 10 minutes) on 48-hour Holter recording.
  - Off all Class I and III AADs at the six month follow-up (AM Arm Only).
  - Acute success of all procedures (AM Arm Only).
- Acute safety endpoint definition
  - Rate of 7-day acute serious procedure and/or device-related adverse events (AM Arm Only)
- Chronic safety endpoint definition
  - Rate of serious procedure and/or device related adverse events (AM Arm Only)
  - Rate of serious adverse events related to management of atrial fibrillation (MM Arm Only)

Quality of Life and Symptom Severity Score

- Secondary Endpoints
- Subjective

- No formal hypothesis was generated

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Primary Discussion Points

Primary Discussion Points

- Overall Adverse Event Rate
- Observed Stroke Rate
- Observed PV Stenosis Rate
- Definition of Ablation Success
- Appropriateness of the Indication
- Long-term Ablation Success
- Post-approval Study Considerations

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FDA's Statistical Review of Medtronic Ablation System

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Center for Devices and Radiological Health
10/27/2011

Outline

- Pivotal Study Design
- Interim Analysis Results
- Analysis Results for All Enrolled Subjects
- Gender Analysis
- Summary

Pivotal Study Design

- Prospective, multi-center, randomized, unmasked, two-arm trial
  - Investigational device arm: Ablation Management
  - Concurrent control arm: Medical Management
- 2:1 Randomization (210 enrolled from 24 sites)
  - Ablation Management: n=138
  - Medical Management: n=72

Pivotal Study Design

- **Primary effectiveness endpoint**
  - **Chronic effectiveness:** $H_0 : P_A^{CE} \leq P_M^{CE}$ **vs.** $H_a : P_A^{CE} > P_M^{CE}$
- **Primary safety endpoints:**
  - **Acute safety:** $H_0 : P_A^{AS} \geq .16$ **vs.** $H_a : P_A^{AS} < .16$
  - **Chronic safety:** $H_0 : P_A^{CS} \geq P_M^{CS} + .06$ **vs.** $H_a : P_A^{CS} < P_M^{CS} + .06$
- **Study Success Rule:**
  - Need to meet both the chronic effectiveness and the acute safety endpoints

Pivotal Study Design

- **One interim analysis for the chronic effectiveness endpoint when**
  - all 210 planned subjects are enrolled; and
  - at least 50% enrolled subjects have reached the chronic effectiveness endpoint; and
  - 100% enrolled subjects have reached their acute safety endpoint
- **The O'Brien-Fleming method was used to preserve the overall one-sided Type I error rate 0.025**
  - Interim analysis: significance level of 0.0015
  - Final analysis: significance level of 0.0245
- **If the chronic effectiveness endpoint is met at the interim analysis, a PMA using the interim results would be filed**

Pivotal Study Design

- **Primary analysis population:**
  The Intent-to-Treat (ITT) population

- **Primary missing data imputation method:**
  All missing endpoints are imputed as failures

Interim Analysis Results

For the chronic effectiveness endpoint:

- The data cutoff date: July 31, 2009
- Analysis population (ITT): n=136
  - 79 Ablation Management subjects
  - 57 Medical Management subjects

	Ablation Management n=79	Medical Management n=57	P-value
Success	44 (56%)	14 (25%)	<0.0001
Failure	26 (33%)	32 (56%)	
Missing	9 (11%)	11 (19%)	

- The chronic effectiveness endpoint was met

Interim Analysis Results

For the acute safety endpoint:

- Analysis population (ITT):

  138 (100%) Ablation Management subjects

	Ablation Management n=138
Number of subjects having one or more acute serious adverse events related to the device or procedure (SADEs) (Failures)	15 (11%)
Missing	0
95% Exact Binomial CI	(6%, 17%)
P-value	0.06

- The acute safety endpoint was not met against PG of 16%

Interim Analysis Results

For the chronic safety endpoint:

- Analysis population (ITT): n=136
  - 79 Ablation Management subjects
  - 57 Medical Management subjects

- Only reported descriptively since the primary acute safety endpoint was not met at the interim analysis

	Ablation Management n=79	Medical Management n=57
Failure	5 (6%)	1 (2%)
Non-Failure	70 (89%)	47 (82%)
Missing	4 (5%)	9 (16%)

Interim Analysis Results

Summary:

- The chronic effectiveness endpoint was met
- The acute safety endpoint was NOT met
- The overall study success was NOT met at the interim analysis
- The sponsor decided to use the interim analysis to support the PMA application

Analysis Results for All Enrolled Subjects

- By FDA's request, the analysis results based on all enrolled subjects were submitted to the agency for review
- The data cutoff date: March 30, 2011
- Analysis population (ITT):
  - 138 Ablation Management subjects
  - 72 Medical Management subjects

Analysis Results for All Enrolled Subjects

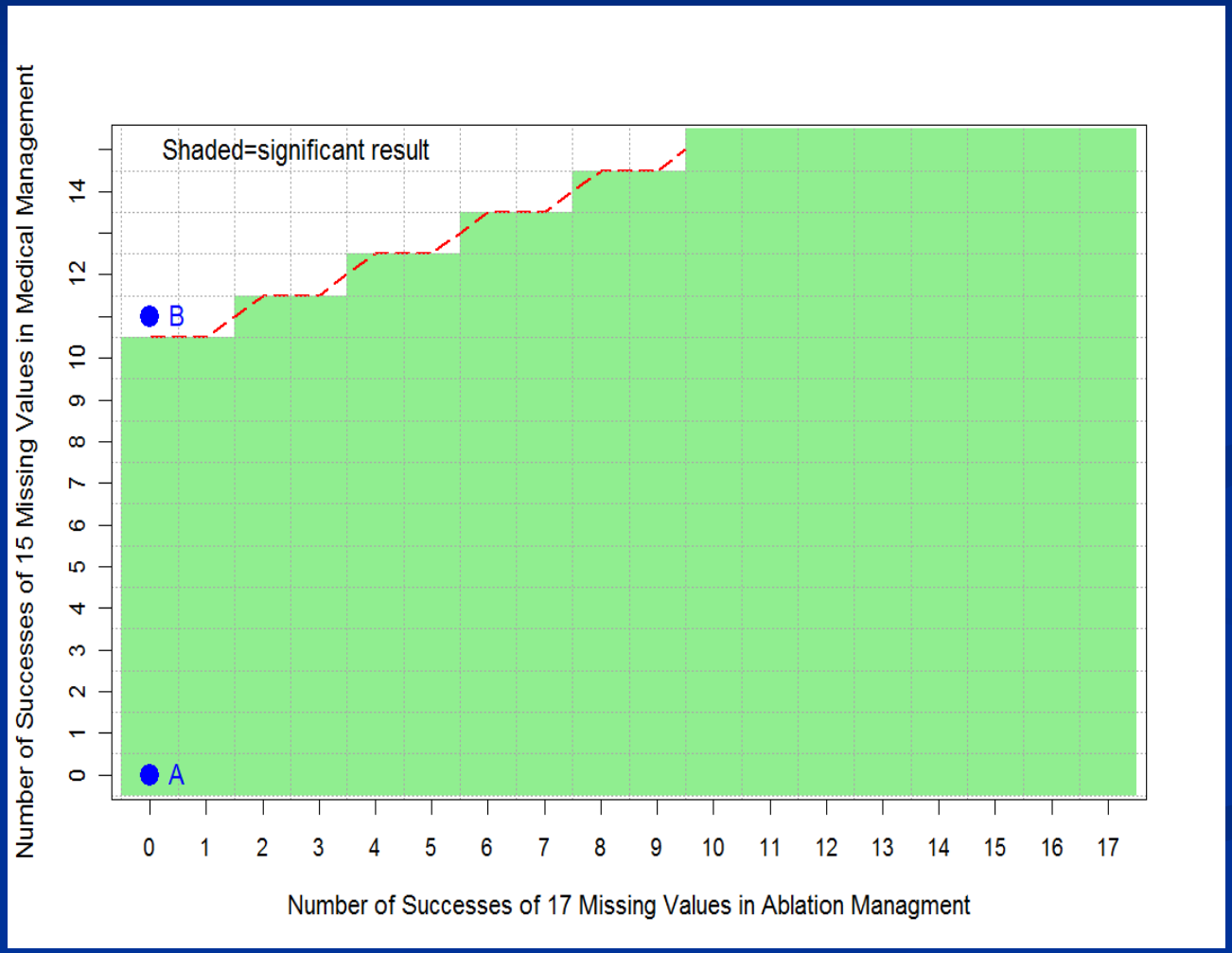
For the chronic effectiveness endpoint:

	Ablation Management n=138	Medical Management n=72	P-value
Success	77 (56%)	19 (26%)	<0.0001
Failure	44 (32%)	38 (53%)	
Missing	17 (12%)	15 (21%)	

- The chronic effectiveness endpoint was met

Analysis Results for All Enrolled Subjects

Tipping point analysis for the chronic effectiveness endpoint:



Analysis Results for All Enrolled Subjects

For the acute safety endpoint:

	Ablation Management n=138
Number of subjects having one or more acute SADEs (Failures)	17 (12%)
Missing	0
95% Exact Binomial CI	(7%, 19%)
P-value	0.14

- The acute safety endpoint was not met against PG of 16%

Analysis Results for All Enrolled Subjects

For the chronic safety endpoint:

- Only reported descriptively since the acute safety endpoint was not met based on all enrolled subjects

	Ablation Management n=138	Medical Management n=72
Failure	9 (7%)	3 (4%)
Non-Failure	123 (89%)	58 (81%)
Missing	6 (4%)	11 (15%)

Analysis Results for All Enrolled Subjects

Summary:

- The chronic effectiveness endpoint was met
- The acute safety endpoint was NOT met
- The overall study success was NOT met based on all enrolled subjects

Gender Analysis

- Males accounted for the majority of enrolled subjects

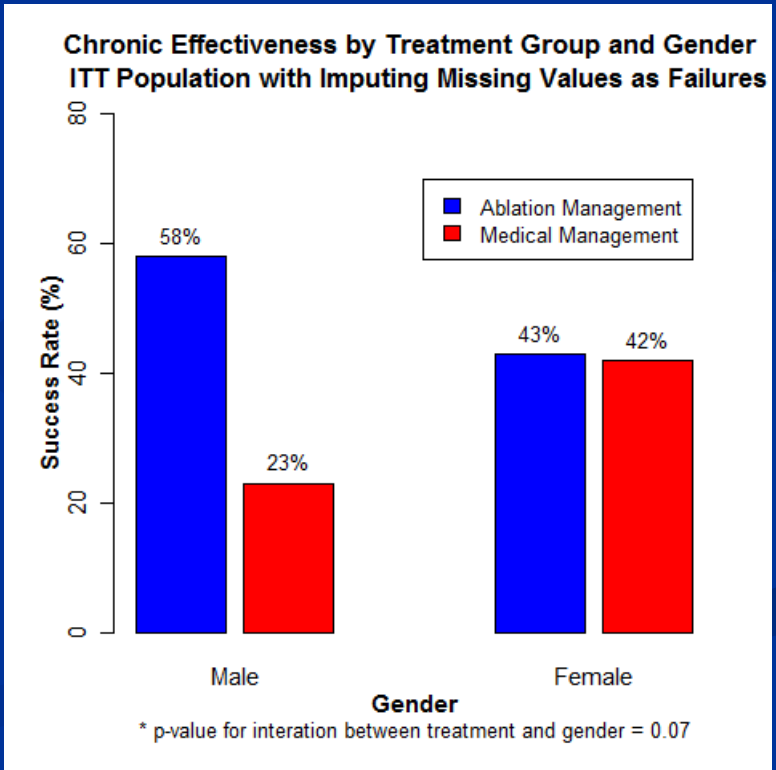
	Ablation Management n=138	Medical Management n=72
Male	115 (83%)	60 (83%)
Female	23 (17%)	12 (17%)

Gender Analysis

For the chronic effectiveness endpoint:

- Males seemed to perform better under the Ablation Management
- Females seemed to perform similar between two arms
- Test of interaction: p-value = 0.07

Success	Ablation Management n=138	Medical Management n=72
Male	58% (67/115)	23% (14/60)
Female	43% (10/23)	42% (5/12)



Gender Analysis

For the acute safety endpoint:

Acute Safety	Ablation Management	
	Male n=115	Female n=23
Number of subjects having one or more acute SADEs (Failures)	12 (10%)	5 (22%)

- Fisher's exact test to compare males and females: p-value=0.16
- No conclusion about the gender difference can be drawn due to limited number of females enrolled

Summary

- At the interim analysis, the chronic effectiveness endpoint was met but not the acute safety endpoint. Therefore, the pre-specified study success rule was not met
- Based on all enrolled subjects, the chronic effectiveness endpoint was met but not the acute safety endpoint. Therefore, the pre-specified study success rule was not met
- Males accounted for the majority of the enrolled subjects
- For males, Ablation Management seemed to be superior in chronic effectiveness compared to Medical Management
- For females, there was no evidence showing that Ablation Management was superior in chronic effectiveness compared to Medical Management

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Medtronic Cardiac Ablation System PMA

FDA Clinical Review

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Division of Cardiovascular Devices
Office of Device Evaluation

October 27, 2011

Atrial Fibrillation Classification

AF Types	2006 ACC/AHA/ESC Guidelines	2007 HRS Expert Consensus Statement
Paroxysmal	self-terminating within 7 days of recognized onset	Recurrent AF (>2 episodes) that terminates spontaneously within 7 days
Persistent	not self-terminating within 7 days, or is terminated electrically or pharmacologically	AF which is sustained beyond 7 days, or lasting less than 7 days but necessitating cardioversion
Longstanding Persistent		Continuous AF of greater than one-year duration
Permanent	AF in which cardioversion has failed or has not been attempted	Patients for whom a decision has been made not to pursue restoration of sinus rhythm by any means

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Permanent	AF in which cardioversion has failed or has not been attempted	Patients where a decision has been made not to pursue restoration of sinus rhythm by any means

AF Ablation Strategies

- Pulmonary vein (PV) isolation for paroxysmal AF
- PV isolation plus substrate modification (e.g. CFAE ablation) for persistent and longstanding persistent AF

AF Ablation with Medtronic Cardiac Ablation System

PVAC

MAAC

MASC

PV Isolation + CFAE Ablation

Pivotal Study Design

- Prospective, multi-center, randomized, unblinded study
- 2:1 Randomization to Ablation Management and Medical Management arms
- Primary effectiveness compared between two arms
- Primary acute safety endpoint compared to a performance goal

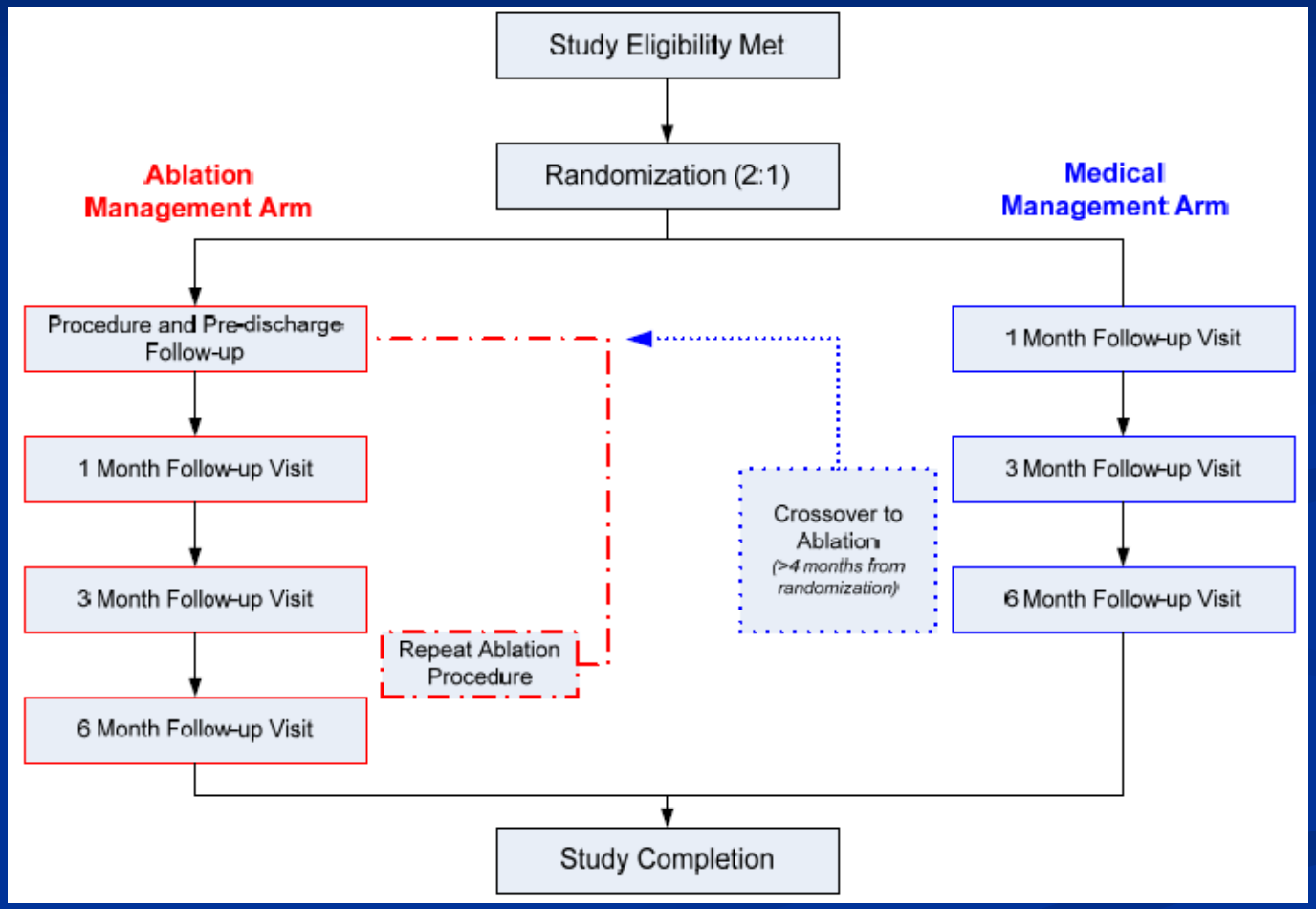
Key Inclusion Criteria

- History of symptomatic permanent AF
  - Continuous AF of 1-4 years duration, OR
  - Non self-terminating AF lasting 7 days to 1 year, with at least one failed DC cardioversion
  - AF symptoms: palpitations, fatigue, exertional dyspnea, and exercise intolerance
- Age between 18-70
- Failure of at least one Class I or III AAD

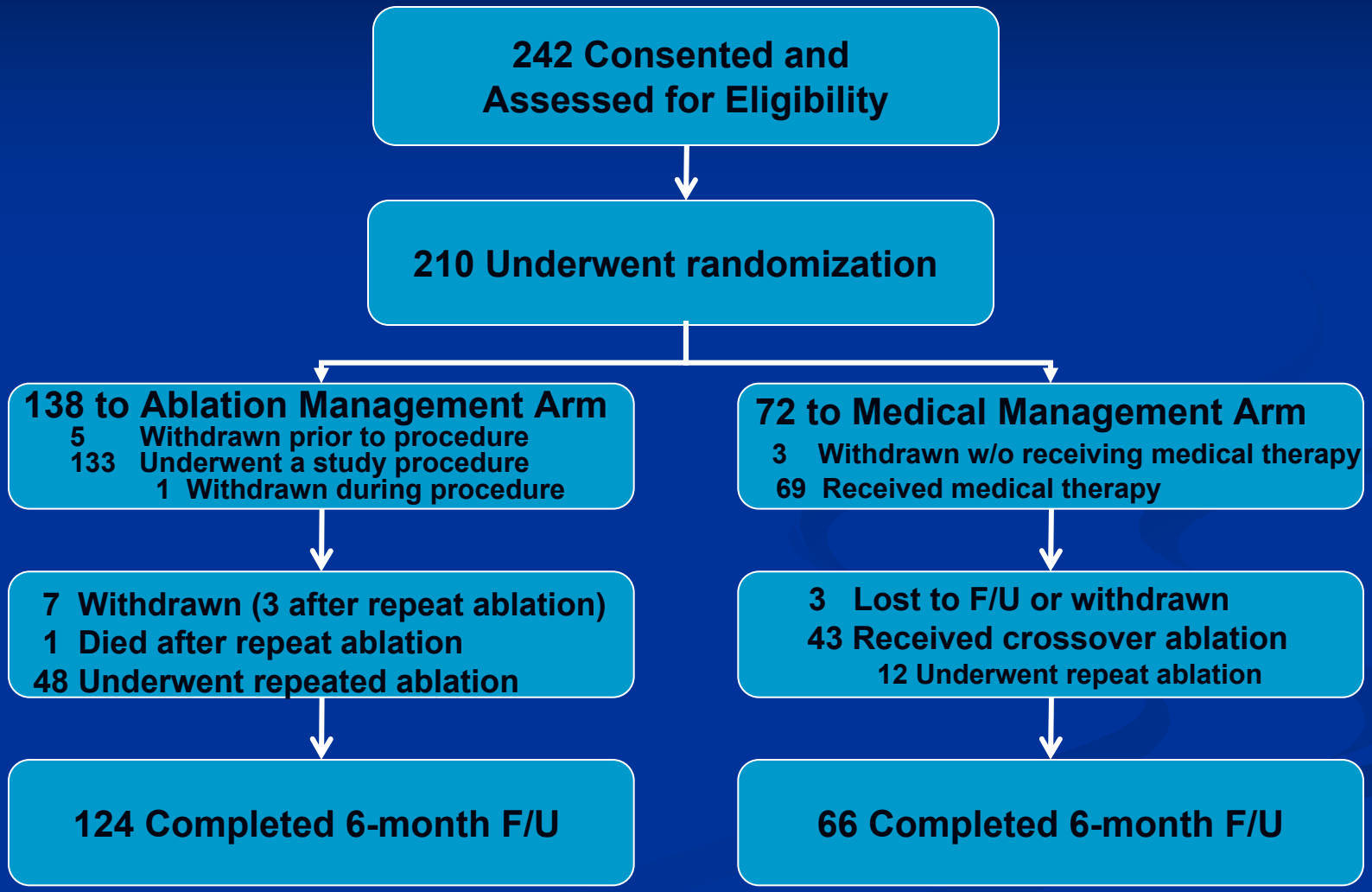
Key Exclusion Criteria

- NYHA Class III or IV
- LVEF < 40%
- LA diameter > 55 mm
- History of stroke or TIA
- Substantial co-morbidity
- Left atrial thrombus

Study Overview



Subject Accountability



Baseline Demographics

- Mean Age: 60 years
- Male: 83%
- Mean LA size: 45 mm
- Mean LVEF: 55%
- History of CAD, cardiomyopathy and valvular disease in 19%, 9%, and 7.1%
- Hypertension: 59%
- Diabetes: 14%
- Average $CHADS_2$ score: 0.8; $CHADS_2$ score ≥2: 16.7%

AF History

- Diagnosis of persistent/permanent AF: 9.9 +/- 10.4 months
- Persistent AF: 73%; longstanding persistent AF: 27%
- Number of failed Class I or III AADs:
  - 1.4 +/- 0.9 for Ablation Management arm
  - 1.1 +/- 0.5 for Medical Management arm
- Number of prior cardioversions: 2.1 +/- 2.3

Ablation Procedure

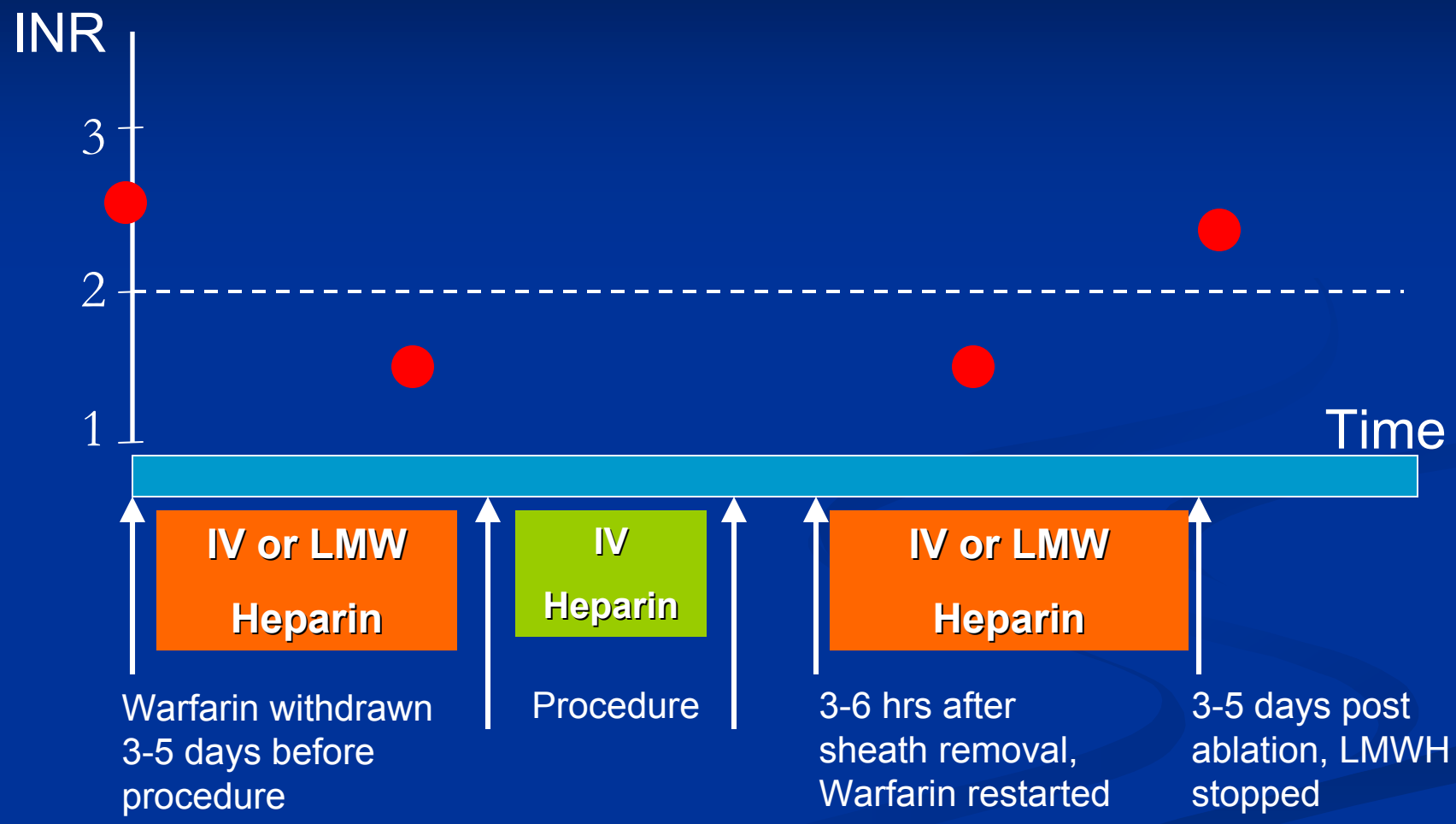
- Required
  - PV isolation with PVAC
  - LA septum CFAE ablation with MASC
  - CFAE ablation at other LA locations with MAAC
  - DC cardioversion if AF continued after ablations above
- Optional
  - SVC ablation using PVAC
  - Other RA ablation including isthmus ablation

Anticoagulation Protocol

- Two peri-procedural anticoagulation strategies*
  - Bridging with intravenous or low molecular weight heparin (LMWH)
  - Continuation of warfarin without bridging
- During the procedure: ACT > 300 seconds
- Oral anticoagulation continued for the whole follow-up period

* Peri-procedural anticoagulation strategy was not a data collection point.

Bridging with IV or LMW Heparin



Treatments for Medical Management Arm

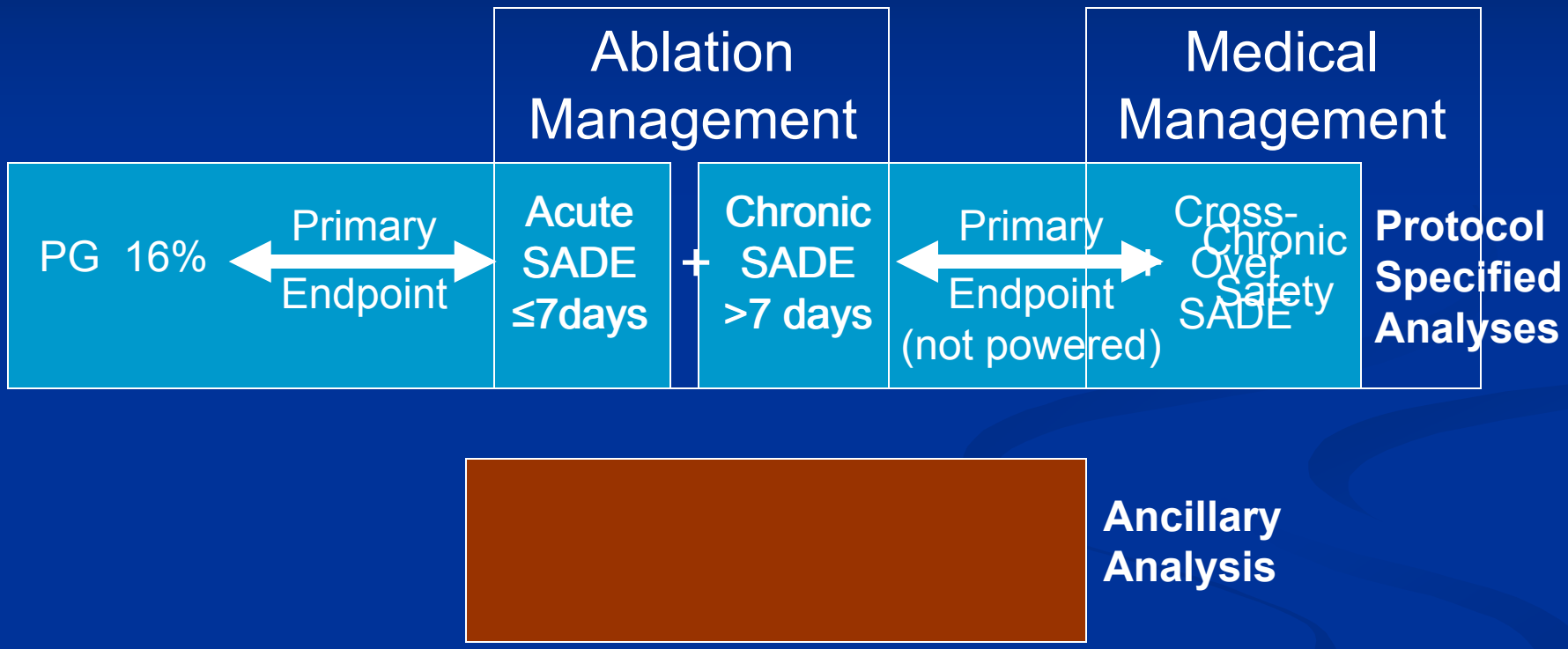
- Initiation of new AADs or titration of existing AAD
- DC cardioversions
  - Separated by at least 30 days
  - ECG 30 days after each cardioversion
  - Two failed DC cardioversions constituted an effectiveness failure

AAD Dose Ranges

Medication	Class	Dose
Amiodarone	III	200 mg/day (Increased to 300mg/day for 30 days if 200 mg/day at baseline)
Dofetilide	III	0.125-0.5 mg BID
Sotalol	III	120-160 mg BID
Flecainide	IC	100-150 mg BID
Propafenone	IC	150-300 mg TID
Rhythmol Extended Release	IC	225-425 mg BID

Safety Results

Safety Analyses



Acute Safety Primary Endpoint

- Definition: Proportion of Ablation Management (AM) subjects with at least one serious procedure and/or device related event (SADE) through 7 days post procedure (acute SADE)
- Included all subjects randomized to the AM arm
- PV stenosis identified on follow-up CT/MRI not considered an acute safety event
- Protocol included a performance goal of 16% (95% UCB) of subjects that could experience an acute SADE

Acute Safety Primary Endpoint

- 21 acute (≤ 7 days) serious adverse device/procedure related events (SADEs) in 17 of 138 AM subjects
- Observed proportion 12.3% with 95% UCB of 19%
- Performance goal was 16.0%
- Acute safety primary endpoint was not met

Acute Safety Events

Description	Number of Patients with Acute SADE (%)
Death	1 (0.7%)
Stroke	4 (2.9%)
Tamponade	2 (1.4%)
Heart failure	1 (0.7%)
Hypotension	2 (1.4%)
Pericarditis	1 (0.7%)
Vascular complications	3 (2.2%)
Pneumonia	1 (0.7%)
Pulmonary infiltrates	1 (0.7%)**
Acute respiratory failure	1 (0.7%)
Hospitalizations	3 (2.2%)
Total	**17/138 (12.3%, UCB 19%)**

** One subject experienced 2 episodes of pulmonary infiltrates

Acute Safety Events + PV Stenosis

Description	Number of Patients with Acute SADE (%)
Death	1 (0.7%)
Stroke	4 (2.9%)
PV stenosis/symptomatic PV narrowing	5 (3.6%)
Tamponade	2 (1.4%)
Heart failure	1 (0.7%)
Hypotension	2 (1.4%)
Pericarditis	1 (0.7%)
Vascular complications	3 (2.2%)
Pneumonia	1 (0.7%)
Pulmonary infiltrates	1 (0.7%)
Acute respiratory failure	1 (0.7%)
Hospitalizations	3 (2.2%)
Total	**22/138 (15.9%, UCB 23.1%)**

Chronic Safety Endpoint

- Definition
  - AM arm: Proportion of subjects with at least one SADE during the 6 month follow-up period (excluding the first 7 days post procedure)
  - MM arm: Proportion of subjects with at least one serious adverse event (SAE) related to AAD therapy or AF during 6 months post randomization

Chronic Safety Events for AM Arm

Description	Number of Patients with Chronic SADE (%)
Stroke	1 (0.7%)
PV stenosis (> 70% diameter reduction)	4 (2.9%)
Symptomatic PV narrowing (50-70% diameter reduction)	1 (0.7%)
Pericardial effusion	1 (0.7%)
Pericarditis/Pleuritis	1 (0.7%)
Persistent ASD	1 (0.7%)
Total	**9/138 (6.5%)**

SAEs Related to AF or AAD Therapy in MM Arm (ITT population)

Description	Number of Patients with SAE (%)
GI bleed secondary to anticoagulation	2 (2.8%)
Hospitalization for AF with RVR	1 (1.4%)
Total	**3/72 (4.2%)**

All SAEs in MM Arm (as treated population)

Description	Number of Patients with SAE (%)
GI bleed secondary to anticoagulation	2 (2.9%)
Hospitalization for AF with RVR	1 (1.4%)
Hyperkalemia	1 (1.4%)
Chest discomfort related to CAD	1 (1.4%)
Total	**4*/69 (5.8%)**

* One patient experienced two events

No death, stroke, TIA, myocardial infarction, or other thromboembolic events.

Acute + Chronic SADEs for subjects with at least one study procedure (133 AM + 43 Crossovers)

Description	Number of Patients with SADE (%)
Death	1 (0.6%)
Stroke	5 (2.8%)
TIA	2 (1.1%)
Tamponade	3 (1.7%)
PV stenosis/symptomatic PV narrowing	7 (4.0%)
Heart failure	1 (0.6%)
Hypotension	3 (1.7%)
Pericarditis	3 (1.7%)
Pericardial effusion	2 (1.1%)
Vascular complications	5 (2.8%)
Pneumonia	1 (0.6%)
Pulmonary infiltrates	1 (0.6%)
Acute respiratory failure	1 (0.6%)
Persistent ASD	1 (0.6%)
Hospitalization	4 (2.3%)
Hyperesthesia in right leg and neuropathy	1 (0.6%)
Total	**38/176 (21.6%, UCB 28.4%)**

Peri-Procedural Stroke

- **5 strokes within one month of a procedure, giving a peri-procedural stroke rate of 2.8% (UCB 6.5%)**
  - 4 strokes occurred within 12 hours post procedure
  - one stroke subject was evaluated for visual field defect on day 31 post procedure but symptoms occurred shortly post ablation
- All stroke subjects received LMWH bridging peri-procedurally
- Not surprisingly, INR < 2 in 4 of 5 stroke subjects at the time of stroke
- Complete resolution of neurological deficits occurred in two stroke subjects by the 6 months follow-up visit
- All 5 strokes were adjudicated as SADEs

Patient Characteristics, Stroke Symptoms and Outcome

Subject ID	Age/ Gender	$CHADS_2$ Score	LA size (cm)	Event Onset	Symptoms/Signs	Outcome
07-315	59/M	1 (HTN)	5.5	< 12 hrs	Dysarthria, right leg weakness, right hand apraxia	Complete recovery by 6 mos
18-305	56/M	1 (HTN)	5.0	12 hrs post ablation	Diplopia, partial gaze palsy, mild dysarthria	Diplopia unresolved by 6 mos
28-304	67/M	2 (HTN, DM)	4.9	< 12 hrs	Anomia, visual filed deficits, right hemiparesis	Anomia unresolved by 6 mos
31-305	49/M	1 (HTN)	4.4	12 hrs post ablation	Left arm weakness, loss of fine motor skills, left facial paresis	Complete recovery by 6 mos
28-305	69/M	3 (DM, HTN, CHF)	4.6	Shortly post ablation	Visual field defect	Unchanged at 6 mos

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28-304	67/M	2 (HTN, DM)	4.9	< 12 hrs	Anomia, visual field deficits, right hemiparesis	Anomia unresolved by 6 mos
31-305	49/M	1 (HTN)	4.4	12 hrs post ablation	Left arm weakness, loss of fine motor skills, left facial paresis	Complete recovery by 6 mos
28-305	69/M	3 (DM, HTN, CHF)	4.6	Shortly post ablation	Visual field defect	Unchanged at 6 mos

Stroke subject 28-305

- 69-year-old male with CAD, DM, HTN and CHF
- Uneventful repeat procedure on 3/6/2009
- On therapeutic anticoagulation post procedure
- Sinus rhythm at 1-month visit (3/23/2009)
- Ophthalmology evaluation on 4/6/2009
  - Complaint: seeing images in right eye periphery that occurred shortly post ablation
  - Exam: right eye temporal visual field defect of 20%
- Ophthalmology evaluation on 5/15/2009
  - Complaint: fixed temporal peripheral vision difficulty in right eye
  - Exam: > 50% inferotemporal visual field defect
  - Impression: occipital stroke
- MRI on 6/8/2009 (3 months post ablation): chronic left occipital infarct

- **Diagnosed as peri-procedural embolic stroke by an independent neurologist after reviewing source documents and MR images**
- **CEC/DSMB re-adjudicated it as device/procedure related stroke**

Incidence of Stroke Between the Two Study Arms

- Ablation Management arm: 6/138 (4.3%)
  - 5 peri-procedural strokes, all device/procedure related by CEC/DSMB
  - One stroke 40 days post ablation, not related to device/procedure, but subtherapeutic anticoagulation.
- Medical Management arm: 0%
  - No stroke
  - 2 TIAs within 7 days post crossover ablation

Peri-procedural Stroke

Authors	Year	Patients (n)	Pts with nonPAF (n)	Pts with Stroke (n)	Overall stroke rate	95% UCB	nonPAF pts with stroke (n)	Stroke rate in nonPAF Pts	95% UCB
TTOP-AF		**176**	**176**	**5**	**2.8%**	**6.5%**	**5**	**2.8%**	**6.5%**
Spragg	2008	517	240	7	1.4%	2.8%	4	1.7%	4.2%
Patel	2010	3060	1209	25	0.8%	1.2%	22*	1.8%	2.7%
Oral	2006	755	265	7**	0.9%	1.9%	1	0.4%	2.1%
Bertaglia	2007	1011	404	4	0.4%	1.0%	0	0	0.7%
Tilz	2010	205	205	2	1%	3.5%	2	1%	3.5%
Oral	2007	100	100	0	0	3%	0	0	3%

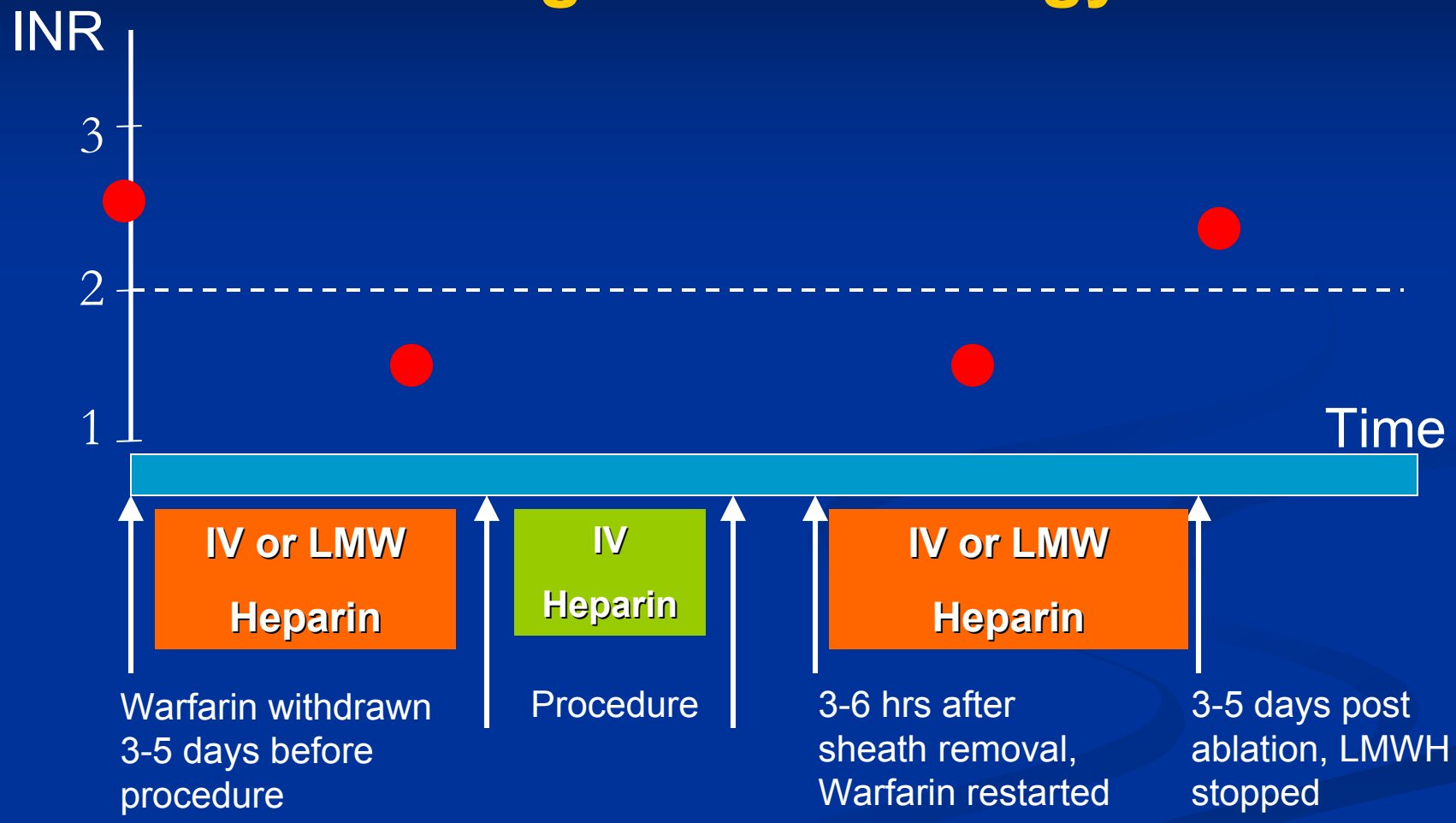
*Might have included one TIA.**Might have included three TIAs.

Peri-procedural Stroke

Authors	Year	Patients (n)	Pts with nonPAF (n)	Pts with Stroke (n)	Overall stroke rate	95% UCB	nonPAF pts with stroke (n)	Stroke rate in nonPAF Pts	95% UCB
TTOP-AF		**176**	**176**	**5**	**2.8%**	**6.5%**	**5**	**2.8%**	**6.5%**
Spragg	2008	517	240	7	1.4%	2.8%	4	1.7%	4.2%
Patel	2010	3060	1209	25	0.8%	1.2%	22*	1.8%	2.7%
Oral	2006	755	265	7**	0.9%	1.9%	1	0.4%	2.1%
Bertaglia	2007	1011	404	4	0.4%	1.0%	0	0	0.7%
Tilz	2010	205	205	2	1%	3.5%	2	1%	3.5%
Oral	2007	100	100	0	0	3%	0	0	3%

*Might have included one TIA.**Might have included three TIAs.

Peri-procedural stroke and anti-coagulation strategy

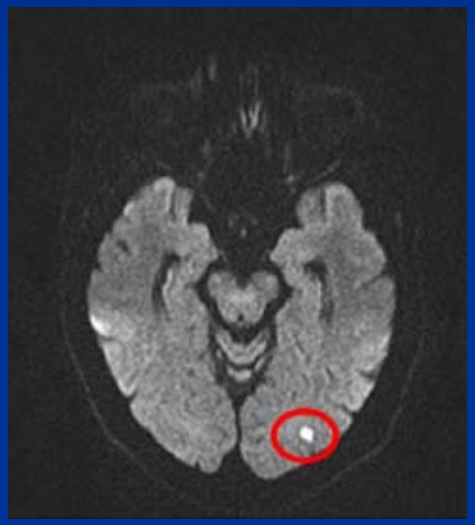


Peri-procedural stroke and anti-coagulation strategy

Authors	Anti-coagulation strategy	Pts (n)	Pts with Stroke (n)	Overall stroke rate	95% UCB	nonPAF pts with stroke (n)	Stroke rate in nonPAF Pts	95% UCB
TTOP-AF	**Bridging or on warfarin**	**176**	**5**	**2.8%**	**6.5%**	**5**	**2.8%**	**6.5%**
Spragg	Bridging	517	7	1.4%	2.8%	4	1.7%	4.2%
Patel	Bridging or on warfarin	3060	25	0.8%	1.2%	22*	1.8%	2.7%
Oral	Bridging	755	7**	0.9%	1.9%	1	0.4%	2.1%
Bertaglia	Bridging	1011	4	0.4%	1.0%	0	0	0.7%
Tilz	Bridging	205	2	1%	3.5%	2	1%	3.5%
Oral	Bridging	100	0	0	3%	0	0	3%

*Might have included one TIA.**Might have included three TIAs

Asymptomatic Cerebral Embolism



Authors	Year	Medtronic Cardiac Ablation System (subject of this PMA)	Irrigated RF	Cryoballoon
Siklody	2011	9/24 (37.5%)	2/27 (7.4%)	1/23 (4.3%)
Gaita	2011	14/36 (38.9%)	3/36 (8.3%)	2/36 (5.6%)
Deneke	2011	30/72 (41.7%)	3/14 (21.4%)	

Siklody C et al.. J Am Coll Cardiol 2011.
Gaita F et al. J Cardiovasc Electrophysiol 2011.
Deneke T et al. Heart Rhythm 2011

Peri-Procedure Stroke Summary

- Observed rate: 2.8%, UCB 6.5%.
- No strokes observed in control group
- Observed rate higher than literature reports
- High stroke rate cannot be definitively attributed to anti-coagulation strategy
- External reports indicate a high incidence of asymptomatic cerebral embolism associated with the subject device

Discussion Item: Peri-Procedure Stroke

- FDA will request panel input on the significance of the high peri-procedural stroke rate observed in this trial

- FDA will request panel input on the emphasis that should be given to external findings of asymptomatic cerebral embolism for assessing the approvability of this application

PV Stenosis

- PV stenosis: > 70% reduction in the diameter of the PV from baseline
- PV narrowing: 50 – 70% reduction in the diameter of PV from baseline

PV Stenosis

	Subjects who underwent at least one study procedure (n = 176)
PV Stenosis	6 (3.4%)
PV Narrowing	12 (6.8%)
Symptomatic PV stenosis	1 (0.6%)
Symptomatic PV narrowing	1 (0.6%)
PV stenosis/Symptomatic PV narrowing	7 (4%, UCB 8%)

PV Stenosis: Comparison to STOP-AF Trial

	TTOP-AF Trial (n = 176)	STOP-AF Trial* (n = 228)
Patients with PV stenosis (> 75% reduction from baseline cross-sectional area)	13 (7.4%)	7 (3.1%)

*Arctic Front Cryoballoon Catheter Instruction for Use

PV Stenosis in Literature

	TTOP-AF Trial (n = 176)	Meta-Analysis* (n = 5831)	ThermoCool AF Trial** (n = 103)
Patients with PV stenosis (> 70% diameter reduction)	6 (3.4%)	91 (1.6%)	0

*Calkins et al. Circ Arrhythm Electrophysiol. 2009.

**Wilber et al. JAMA. 2010.

Discussion Item: PV Stenosis

- FDA is concerned about the high PV stenosis event rate (4%, UCB 8%) observed in this trial
- FDA will request panel input on the significance of the PV stenosis event rate observed in this trial

Effectiveness Results

Effectiveness Analyses

Ablation Management		Medical Management	
90% ⇩ AF @ 6 Months	Primary Endpoint	90% ⇩ AF @ 6 Months	**Protocol Specified Analysis**
HRS AF-Free @ 6 Months		HRS AF-Free @ 6 Months	**Ancillary Analyses**
90% ⇩ AF @ 12 Months		90% ⇩ AF @ 12 Months	

Acute Effectiveness Endpoint

Acute Effectiveness Success Criteria	Ablation Management (n = 138)
Study catheters used to achieve acute success	129
Isolation of all accessible PVs	129
≥ 50% reduction of CFAEs amplitude	131
SR at completion of procedure	128
Acute effectiveness	**128 (92.8%)**

Primary Effectiveness Endpoint

- Chronic effectiveness definition
  - 90% reduction in clinically significant AF (> 10 minutes) on 6-month Holter recording
  - Off all Class I and III AADs at the six month follow-up (Ablation Management arm only)
    - Amiodarone: discontinued 28 days prior to Holter recording
    - Other AADs: discontinued 5 days prior to Holter recording
  - Acute success of all procedures (ablation arm only)

6 Months Chronic Effectiveness Results

	Ablation Management Arm (n = 138)	Medical Management Arm (n = 72)	P value
Subjects meeting all success criteria	77 (55.8%)	19 (26.4%)	<0.0001

The primary effectiveness endpoint was met.

6 months Chronic Effectiveness Stratified by AF Type

	Ablation Management Arm (n = 138)		Medical Management Arm (n = 72)	
	Persistent AF (n = 97)	Longstanding persistent AF (n = 41)	Persistent AF (n = 57)	Longstanding persistent AF (n = 15)
Subjects meeting all success criteria	53 (54.6%)	24 (58.5%)	16 (28.1%)	3 (20.0%)

- The trial was not powered to examine the treatment effect across AF populations
- FDA will ask the panel to comment on whether the study results demonstrated a treatment effect for both the persistent AF population and the longstanding persistent AF population

Ablation Success per HRS Expert Consensus Statement Definition

- Ablation success: Freedom from AF/AFL/AT of ≥ 30 seconds in the absence of Class I and III AAD therapy following a 3 month blanking period

- Failure if any of the followings applies:
  - ECG documented AF/AFL/AT recurrences following 3 month post ablation;
  - DC cardioversion or ablation for AF/AFL/AT following 3 month post ablation;
  - ≥ 30 seconds of continuous AF/AFL/AT on 6-month Holter;
  - On Class I or III AAD following 3 month post ablation

Chronic Effectiveness as Analyzed by HRS Expert Consensus Statement Definition

Ablation Management
n = 138

↓

77 (55.8%)

Chronic successes by protocol definition

↓

66 (47.8%)

No AF/AFL ≥ 30 s on 6-month Holter
No AF/AFL/AT, no CV/ablation after 3 mos

↓

51 (37%)

No AF/AFL ≥ 30 s on 6-month Holter
No AF/AFL/AT, no CV/ablation after 3 mos
off Class I and III AAD after 3 mos

chronic success per HRS definition

Chronic Effectiveness for Medical Management Arm Using 30 Seconds Criterion

Medical Management
n = 72

↓

19 (26.4%)
Chronic successes by protocol definition:
≥ 90% AF burden reduction on 6-month Holter

↓

19 (26.4%)
No AF/AFL ≥ 30 s on 6-month Holter

Discussion Item: Chronic Success

- The prespecified primary effectiveness endpoint was achieved in 55.8% of Ablation Management subjects
- Chronic success rate for the Ablation Management arm drops to 37% when retrospectively applying success definition by the HRS Consensus Statement
- FDA will ask the panel to comment on the chronic success rates observed in the trial using the definition of ablation success from both the approved clinical study protocol and the 2007 HRS Consensus Statement

12 months Holter Request

- At FDA's request, the sponsor made an effort to obtain 12 month follow-up data from as many study subjects as possible
- 12-month follow-up visit with Holter recordings was completed from 106 subjects, accounting for about half of all randomized subjects

Change in AF Burden Reduction at 12 Months

	Subjects with ≥ 90% AF burden reduction on 6-month Holter post ablation		
	Ablation Management (n = 48)	**Crossovers (n = 14)**	**Total (n = 62)**
Subjects with ≥ 90% AF burden reduction on 12-month Holter post ablation	41 (85.4%)	12 (85.7%)	**53 (85.5%)**

Discussion Item: 12 Month Success

- Given the limitations of the long term effectiveness data, FDA requests panel input on the emphasis that should be given to the incomplete 12-month data

Summary

- The primary effectiveness endpoint was met, but the primary safety endpoint was not met
- FDA is particularly concerned about the high incidence of peri-procedural stroke observed in the trial (2.8% with UCB of 6.5%)
- FDA is concerned about the high rate of PV stenosis events (4% with UCB of 8%)
- FDA is also concerned about the high overall procedure/device related serious adverse event rate of 21.6% observed in the trial

Summary (Cont.)

- 6 months chronic success rate decreases from 55.8% to 37% when the HRS Expert Consensus Statement definition of ablation success is applied retrospectively
- Analysis of available 12 month effectiveness data suggests a reduction in chronic success after 6 months post ablation

FDA Presentations

- Linda Ricci
  Introduction
- Dr. Yu Zhao
  Study Statistical Considerations and Conclusions
- Dr. Jun Dong
  Study Clinical Results and Considerations
- **Dr. Dale Tavris**
  Post-approval Study Considerations
- Linda Ricci
  Conclusions

Post-Approval Study (PAS) Considerations

Dale R. Tavris, MD, MPH
Division of Epidemiology
Office of Surveillance and Biometrics

October 27, 2011

Reminder

- The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk/benefit balance

Post-Approval Study Components

- Fundamental study question or hypothesis
- Well specified study population and study design
- Safety endpoints and methods of assessment
- Acute and chronic effectiveness endpoints and methods of assessment
- Duration of follow-up

Important Postmarket Issues

- Long-term performance of the device
  - Chronic effectiveness in the premarket study was assessed only at 6-months
  - Little knowledge of effectiveness beyond that
- Device performance in a representative population of providers and patients
  - Providers in the premarket study may be more skilled in the use of the device than a more representative sample of providers

Sponsor's Proposed Post-Approval Study (PAS): Design and Primary Endpoint

- Prospective multi-site observational study
- Eligibility criteria
  - Symptomatic permanent or long-standing persistent AF
  - Intolerance to or failure of AADs
  - 18 -70 years of age
- 3-year follow-up
- Primary endpoints
  - Chronic treatment success at 3 years
  - Serious procedure- or device-related adverse events at one year

Sponsor's Proposed PAS: Secondary Endpoints

- Major atrial fibrillation events (MAFE)
  - Evaluated at 1, 2, and 3
  - Defined as a non-procedure- or device-related event, including:
    - Cardiovascular death
    - Myocardial infarction
    - All strokes
    - Hospitalization for:
      - AF recurrence or ablation
      - Atrial flutter ablation (excluding Type I)
      - Systemic embolization
      - Congestive heart failure
      - Hemorrhagic event
      - Anti-arrhythmic drug initiation, adjustment or complication

Sponsor's Proposed PAS: Hypotheses

- **Effectiveness hypothesis:**
  3-year treatment success > 20%
  - Cited studies showing approximately 30% success at 20-40 months
  - Cite recurrence rate of 7-9% per year
  - 10% margin
- **Safety hypothesis:**
  Serious procedure- and device-related AE < 19% at 1-year
  - Based on 12.3% rate in premarket study
  - Increase in duration of AE reporting
  - PV stenosis rate of 3.9% at 6 months
  - Margin of 3.1%

FDA Assessment of Sponsor's Proposed PAS

- Effectiveness hypothesis:
  - It is unclear whether the proposed effectiveness success criteria represent clinically acceptable device performance
  - Not clear if treatment success definition is in line with current best practices
- Safety hypothesis
  - It is unclear whether the proposed safety success criteria represent clinically acceptable device performance
- Questions for panel this afternoon will address these issues

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  Conclusions

Conclusions

- The acute safety endpoint was not met
  - Overall Adverse Event Rate
  - Observed Stroke Rate
  - Observed PV Stenosis Rate
- The chronic effectiveness endpoint was met
  - Definition of ablation success
- Appropriateness of the indication
- Long-term outcomes
- Risk/Benefit Profile

Thank you