BIOSENSE WEBSTER NAVISTAR® THERMOCOOL® Catheter for Radiofrequency Ablation of Symptomatic Paroxysmal Atrial Fibrillation

FDA review of P030031/S11

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Division of Cardiovascular Devices
Office of Device Evaluation
Food and Drug Administration

Circulatory System Devices Panel Meeting
November 20, 2008

FDA Review Team

- Randall Brockman, M.D.
- Laura Thompson, Ph.D.
- Ellen Pinnow, M.S.
- Martin Hamilton
- Benjamin Eloff, Ph.D.

Regulatory History

- **December 10, 2003 –** IDE for the NaviStar ThermoCool catheters for treatment of symptomatic paroxysmal atrial fibrillation (AF).
- **November 5, 2004** – PMA approved for NaviStar and Celsius ThermoCool Catheters for treatment of type I atrial flutter.
- **August 11, 2006** – PMA approved for NaviStar ThermoCool Catheters for treatment of recurrent drug/device refractory sustained monomorphic ventricular tachycardia (VT) due to prior myocardial infarction (MI) in adults.
- **October 10, 2007 –** Sponsor notified FDA that it met interim analysis criteria to close enrollment in the AF IDE application,.
- **August 13, 2008** – Sponsor submitted a Panel-Track PMA supplement (P030031/S011) to add the indication of treatment of drug refractory symptomatic paroxysmal atrial fibrillation to the ThermoCool catheter family .

Proposed Indications for Use for ThermoCool Catheter Family

Existing Indications

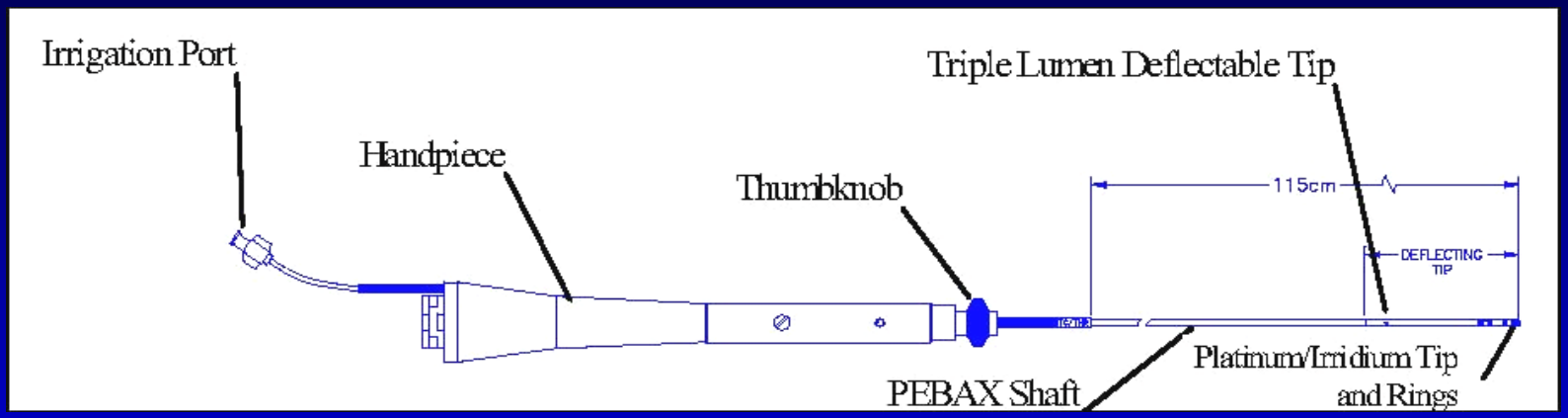
Treatment of:

- Type I atrial flutter in patients age 18 or older.
- Recurrent drug/device refractory sustained monomorphic ventricular tachycardia due to prior myocardial infarction in adults

Proposed new indication

- Drug refractory symptomatic paroxysmal atrial fibrillation

Device Description



- 50 W radiofrequency (RF) energy
- 3.5 mm tip + 3 ring electrodes
- Open-loop Irrigated

ThermoCool Family

Catheter Name	Indications	Location Sensor (CARTO)	Deflection Mechanism	Used in AF study
NaviStar Thermocool	Atrial Flutter VT	Yes	Manual, Unidirectional	Yes
EZ Steer ThermoCool Nav	Atrial Flutter VT	Yes	Manual, Bidirectional	No
NaviStar ThermoCool RMT	Atrial Flutter VT	Yes	Computer-assisted Remote Magnetic	No
Celsius ThermoCool	Atrial Flutter	No	Manual, Unidirectional	No
EZ Steer ThermoCool	Atrial Flutter	No	Manual, Bidirectional	No

Preclinical Review

- Preclinical information (engineering, biocompatibility, sterilization, etc.) accepted previously for prior applications
- Proposed indication for treatment of AF did not raise new preclinical issues
- No catheter design changes
- No outstanding preclinical issues

Study Design Overview

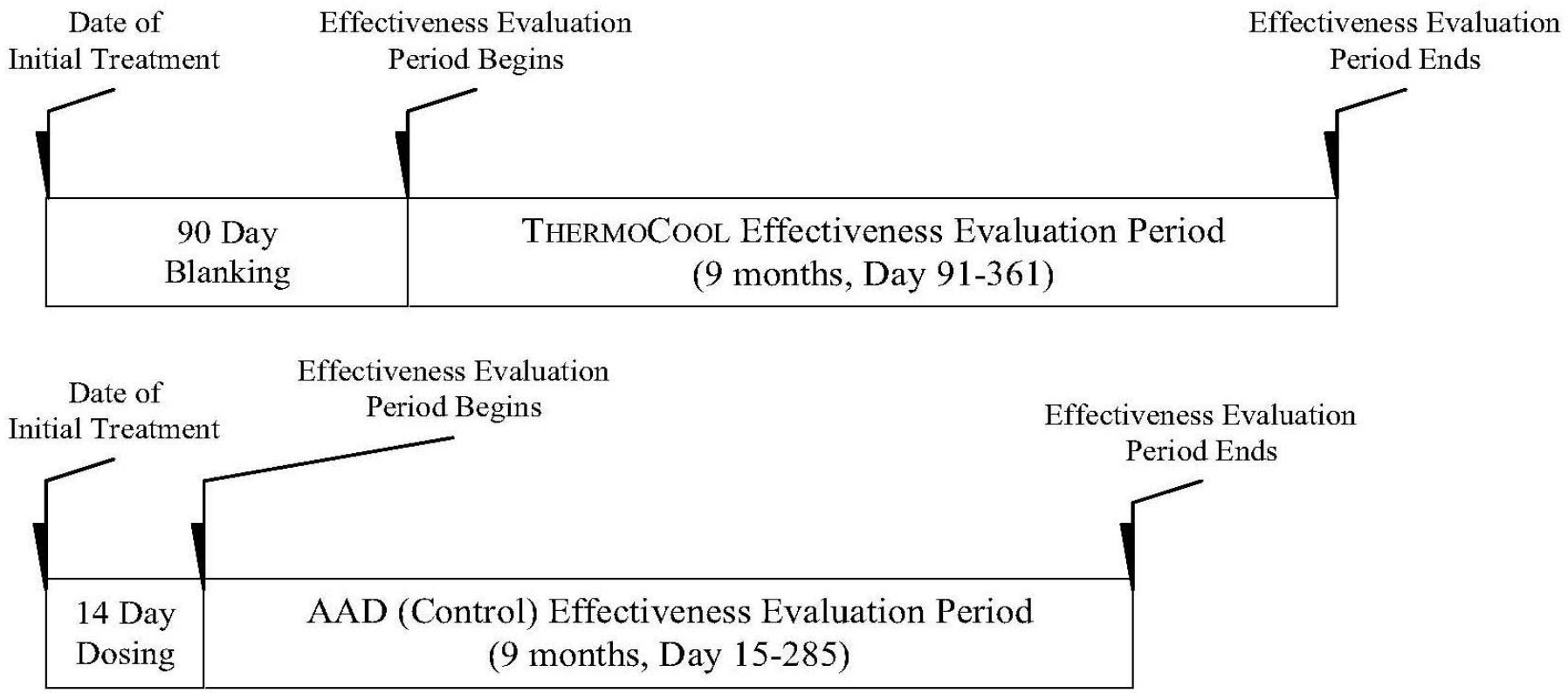
- Treatment group: Ablation with NaviStar ThermoCool
- Control group: AAD not previously prescribed
- Design
  - 2:1 randomization, unblinded
  - 19 centers (4 OUS)
  - 167 subjects, 103 in ablation arm
  - 36 subjects crossed over from control to ablation per protocol
- **Primary effectiveness endpoint**: chronic success for 9 months (superiority)
  - Freedom from documented symptomatic paroxysmal AF episodes and from changes in drug therapy after "blanking" period within each group
- **Primary safety endpoint**: incidence of primary AEs within 7 days (performance goal)

Effectiveness Definitions

- Effectiveness failure for Treatment
  - Documented symptomatic AF
  - Change in AAD regimen after the blanking period
  - Repeat ablation > 80 days
  - Acute Failure
- Effectiveness failure for Control
  - Documented symptomatic AF
  - Change in AAD regimen after the dose-loading period
  - Discontinuation of study AAD

Study Flow

FIGURE 2.2.3.1A Effectiveness Evaluation Windows (270 days)



FDA Presentations

- Laura Thompson, PhD – Statistical
- Randall Brockman, MD – Clinical
- Ellen Pinnow, MS - Epidemiology

BIOSENSE WEBSTER NAVISTAR® THERMOCOOL® Catheter for Radiofrequency Ablation of Symptomatic Paroxysmal Atrial Fibrillation

FDA Statistical Summary

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Division of Biostatistics
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Food and Drug Administration

Circulatory System Devices Panel Meeting
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Outline

- Overview of Bayesian Statistics
- Overview of Study Design
- Primary Endpoint Analyses
- Poolability across sites
- Summary

Discussion Items

- Unblinded Study
  - To what extent did placebo effect occur?
  - Symptoms were self-reported
- Time from randomization to initial treatment varied among subjects.
- The largest-enrolling site performed substantially better than the other sites.

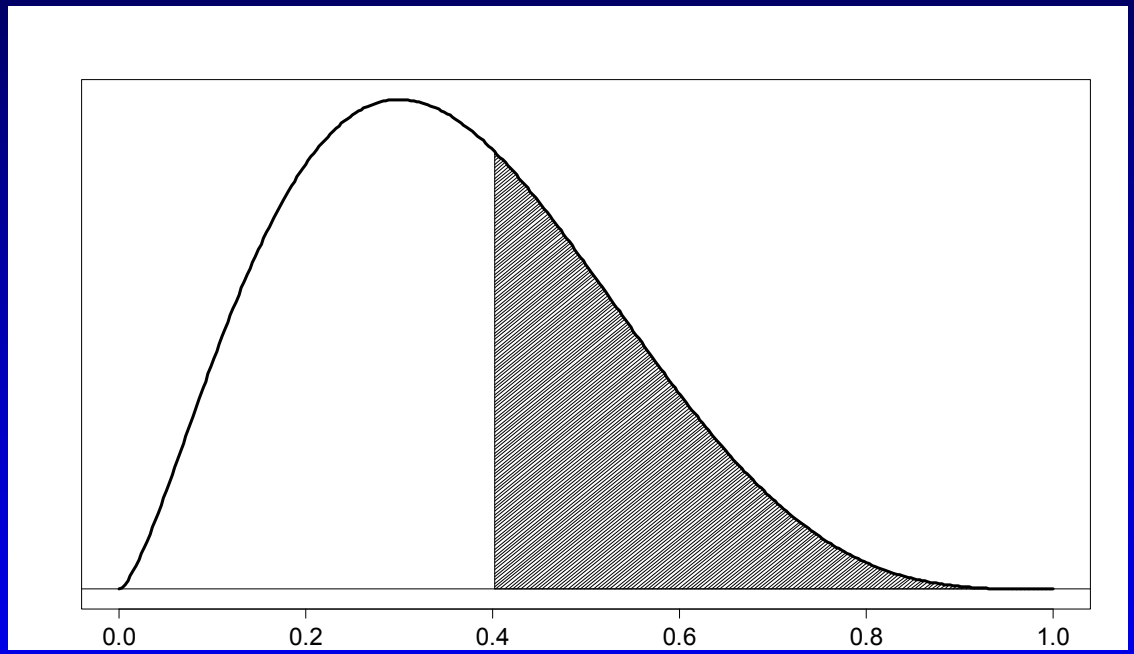
Overview of Bayesian Statistics

Bayesian Statistics Overview

- The Bayesian method is an approach for learning from evidence as it accumulates.
- *Bayes' Theorem* is used to combine prior information with current information on a quantity of interest (e.g., adverse event rate).
- Prior information on quantity of interest comes from:
  - Information from previous comparable studies
  - subjective ideas prior to running the study (discouraged in regulatory setting)
  - "No" prior information: non-informative prior can represent lack of information.

Hypothetical Prior Distribution on an Adverse Event Rate

Prior Mean = 0.35



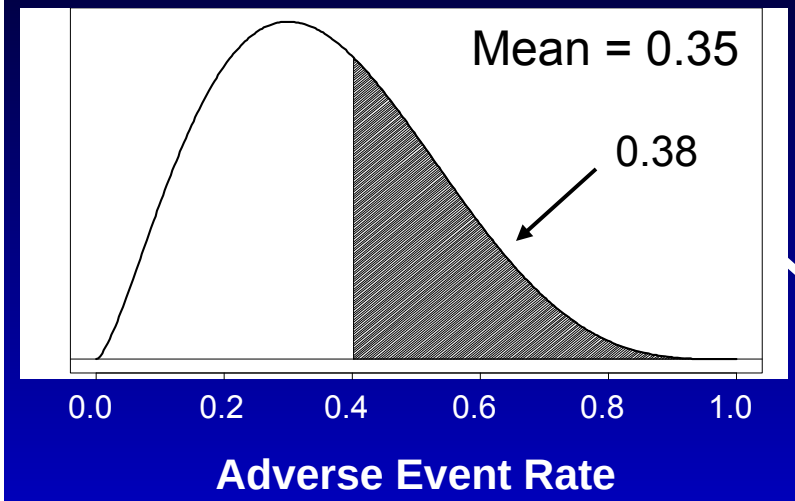
Adverse Event Rate

Hypothetical target = 0.40

Prior Probability that AE > 0.40 = 0.38

Learning from Data

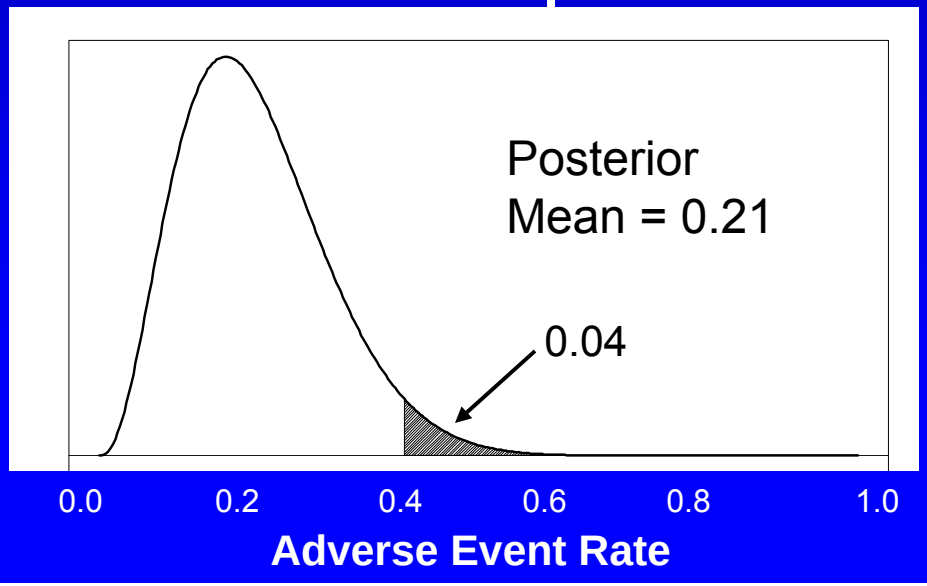
Prior



Study (n=10)

Data: 1 in 10 patients with AEs

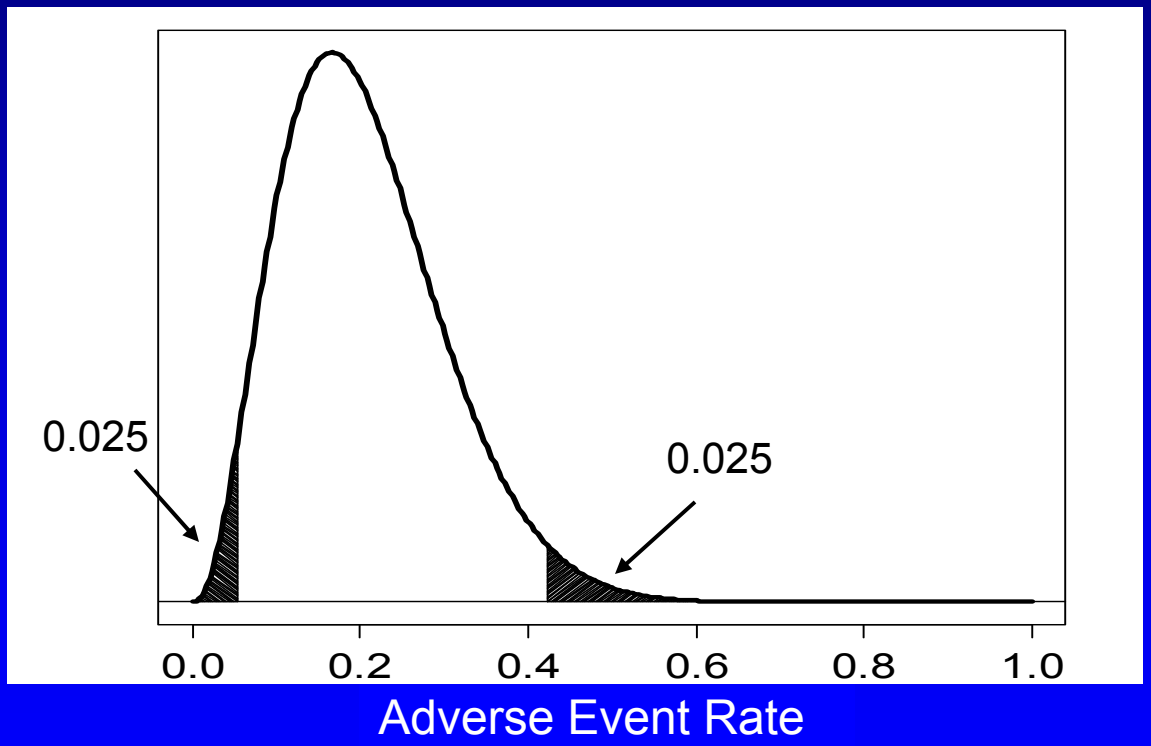
Bayes Theorem



Posterior:
the updated prior distribution after seeing the current data

Bayesian Statistics Overview

- Summary from Posterior Distribution: 95% (posterior) Credible Interval



95% chance that the AE rate falls in [0.06, 0.42]

Bayesian Statistics Overview

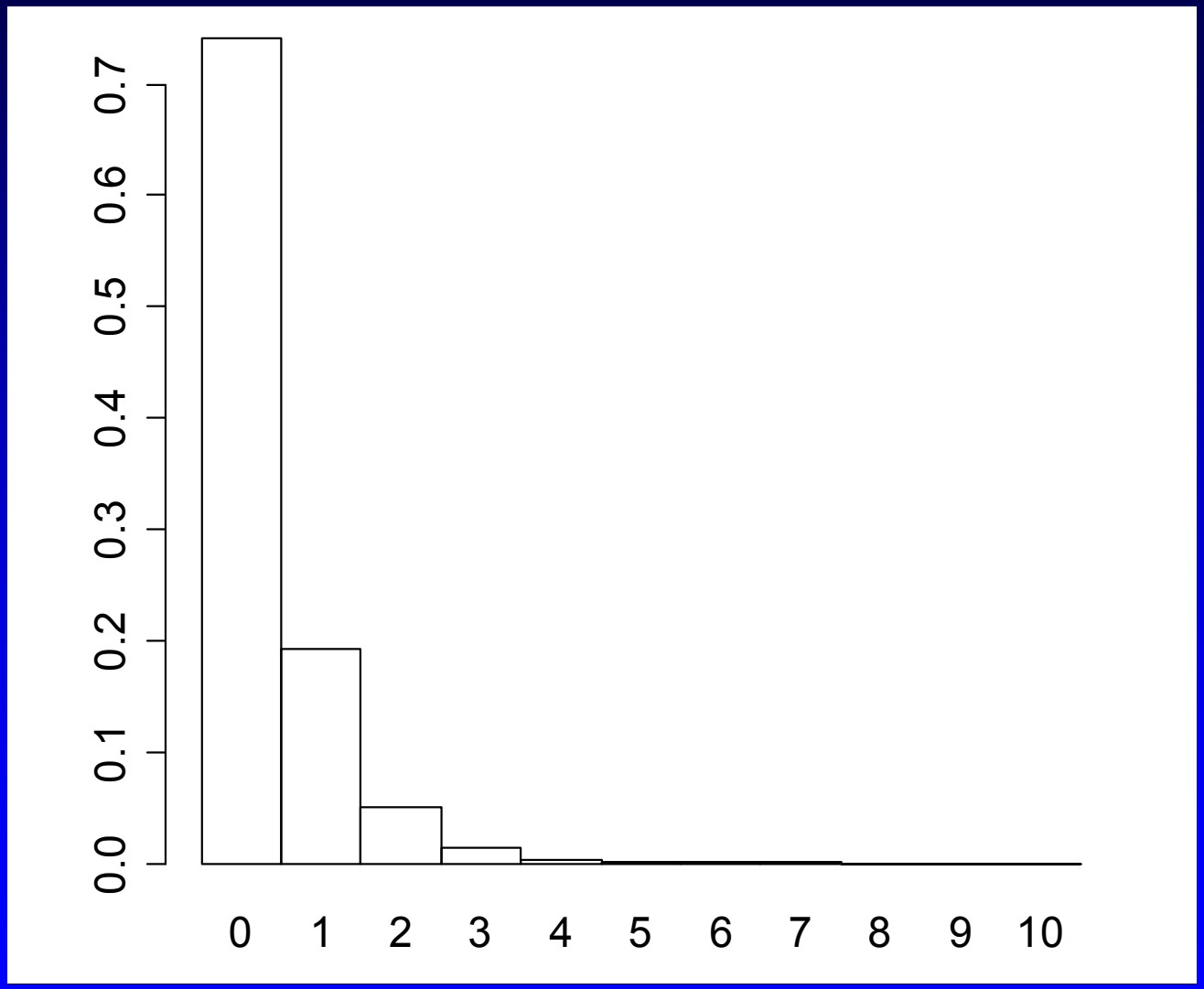
- **Predictive Distribution** - *posterior* distribution of an unknown outcome, but which can potentially be observed in the future.

There was 1 failure among the first 10 patients.

What is the likely result for the next 10 patients?

The predictive distribution for these next 10 patients can help answer this question.

Predictive Distribution for the next 10 patients



Number of Failures

Bayesian Statistics Overview

- Predictive distribution can be used to impute unknown subject outcomes in a trial/study.
  - Impute number of failures for the next 10 subjects.
  - Compute the *posterior* probability that AE rate > 0.40.
  - Compare that posterior probability to a criterion for study success (e.g., 0.025).
  - Determine whether the study is “successful”.

Bayesian Statistics Overview

- We can perform many imputations (e.g., 1,000,000), to get 1,000,000 comparisons to the criterion.
- The proportion of comparisons that beat the criterion is the estimated **predictive probability of a successful study**.
- We obtained this result without collecting the next 10 patients.

Bayesian Statistics Overview

- ***Assumption***: Subjects already in the trial, with known outcomes, are not distinguishable overall from subjects with unknown outcomes, with respect to the primary endpoint.

- This assumption is reasonable for many medical device trials.

Application of Predictive Probability to Adaptive Design

- Deciding when to stop enrollment into a trial
  - If the predictive probability that the trial will eventually be successful once all enrolled patients complete follow-up is sufficiently high, enrollment may be stopped, and follow-up can continue only on patients already enrolled into the trial.
- Deciding when to stop for effectiveness
  - If the predictive probability that the trial will eventually be successful (based on results at an interim point) is sufficiently high, follow-up may be stopped and the trial declared successful before its planned completion.

Sponsor's Application of Predictive Probability

- The sponsor used Bayesian predictive probability to decide whether to stop the trial early, for effectiveness.
- A time-to-event (chronic failure) model was used to model the data and impute unknown outcomes.
- No external prior information was used to obtain the posterior distribution.
- Even though predictive probability was used to stop the trial, posterior results based only on observed data are also in favor of treatment over control.

Bayesian Medical Device Trials

- CDRH supports the use of Bayesian methods for medical device trials.
- Bayesian methods require planning, especially if external prior information is used. Sponsors are encouraged to discuss potential Bayesian methods with FDA prior to planning their trial.
- **"Draft Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials** " issued 5/2006 (finalized Guidance issued soon)

Primary Effectiveness Analysis

Study Design Overview

- Treatment group: Ablation with NaviStar ThermoCool
- Control group: AAD not previously prescribed
- Design
  - 2:1 randomization, unblinded
  - 19 centers (4 OUS)
  - 167 subjects, 103 in ablation arm
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- **Primary effectiveness endpoint**: chronic success for 9 months (superiority)
  - Freedom from documented symptomatic paroxysmal AF episodes and from changes in drug therapy after "blanking" period within each group
- **Primary safety endpoint**: incidence of primary AEs within 7 days (performance goal)

Primary Effectiveness Endpoint Evaluation

- If the posterior probability that treatment chronic success rate P_T exceeds control success rate P_C is greater than 0.98, effectiveness is claimed.

$$P(P_T > P_C \mid data) \geq 0.98$$

- Prior distributions on P_T, P_C are non-informative (uniform).
- Max sample size = 230.
- Two types of interim monitoring:

1. Monitoring for Sample Size

- When accrual reaches sample sizes of 150, 175, and 200 an interim analysis is performed.
- If predictive probability of trial success for all enrolled patients is at least
  - 0.90 at the 150-look
  - 0.80 at the 175, 200-look
- Then, accrual will stop at that sample size

2. Monitoring for Effectiveness

- When accrual stops, an analysis for an early claim of success is done when either:
  - 4.5 months have passed, or
  - at least 50% of enrolled subjects have complete effectiveness outcomes
- If predictive probability of trial success is at least 0.99, effectiveness is claimed.

Sponsor's Predictive Distribution for Yet-to-be-observed Outcomes

- Unknown outcomes must be modeled in order to be predicted, based on follow-up time
- Sponsor assumed time to chronic failure is exponential with rate varying piecewise across time, and different across groups (G):

θ_{1G} : $0 < t \leq ½$ months	θ_{1G}; θ_{2G}; θ_{3G} were given
θ_{2G} : $½ < t \leq 2$	identical prior distributions
θ_{3G} : $2 < t \leq 9$	with prior means of 1

- Assumptions: 1) piecewise failure rate, and 2) prior distribution with mean 1.

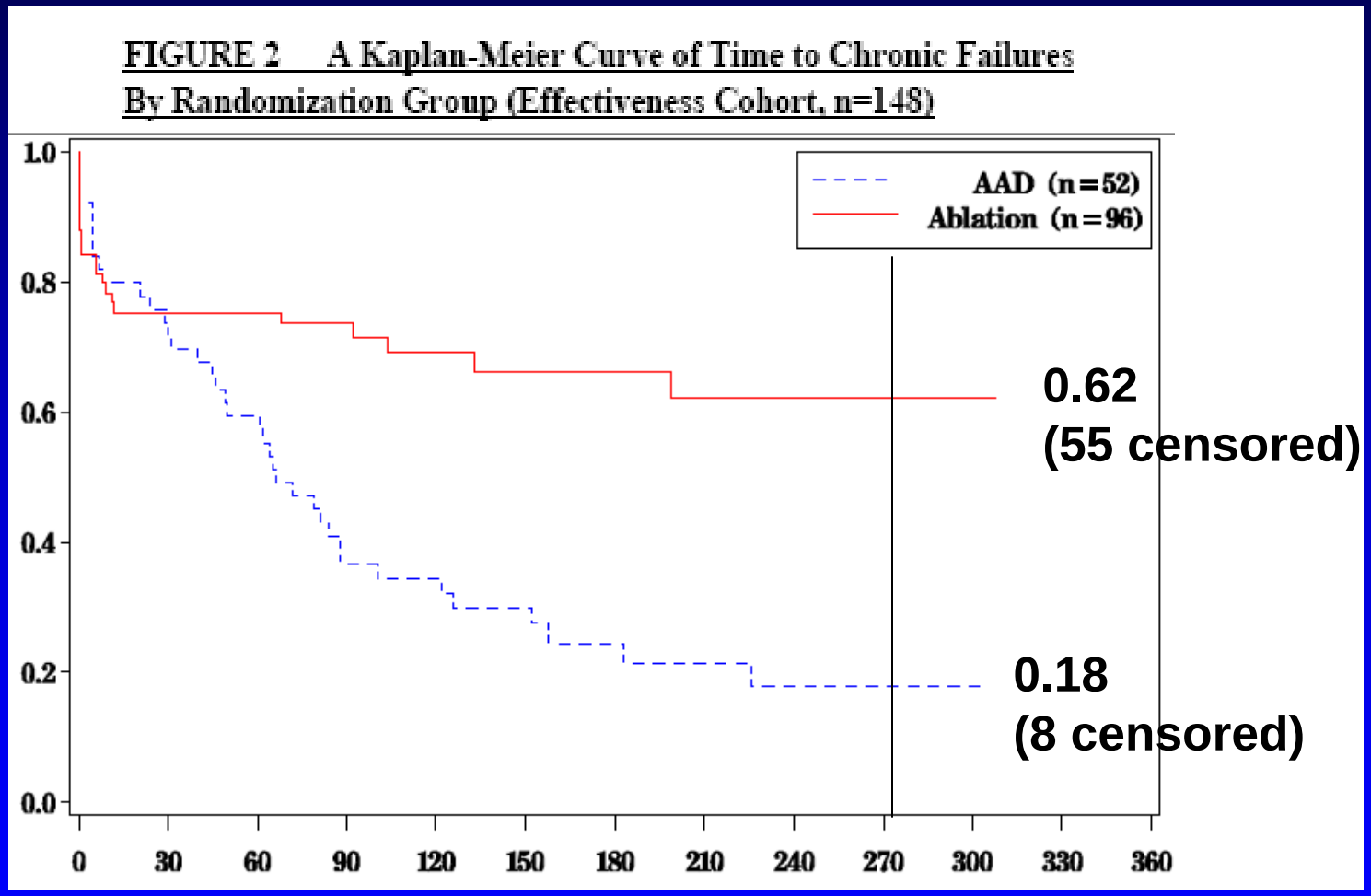
Mid-Course Introduction of Adaptive Design

- Sponsor was having significant enrollment problems in their US sites.
- Proposed to replace a fixed sample size design with an adaptive sample size design, plus interim monitoring for effectiveness.
- 106 patients had been enrolled, with sponsor blind to results at the time.
- Changed the criterion for success to (Bayesian) posterior probability (instead of p-value).

Mid-Course Introduction of Adaptive Design (AD)

- It can be problematic to introduce an AD after the trial has begun.
- Recommendation: Treat the first set of 106 enrolled patients as an interim look, with high threshold for stopping accrual.
- Purpose was to apply a statistical penalty to the change from fixed to adaptive design.
- The penalty resulted in an increased posterior criterion for effectiveness, in order to maintain the (one-sided) type I error rate at 0.025 for reasonable scenarios.

First Interim Point:
160 subjects enrolled, 148 eligible



Probability of Chronic Success

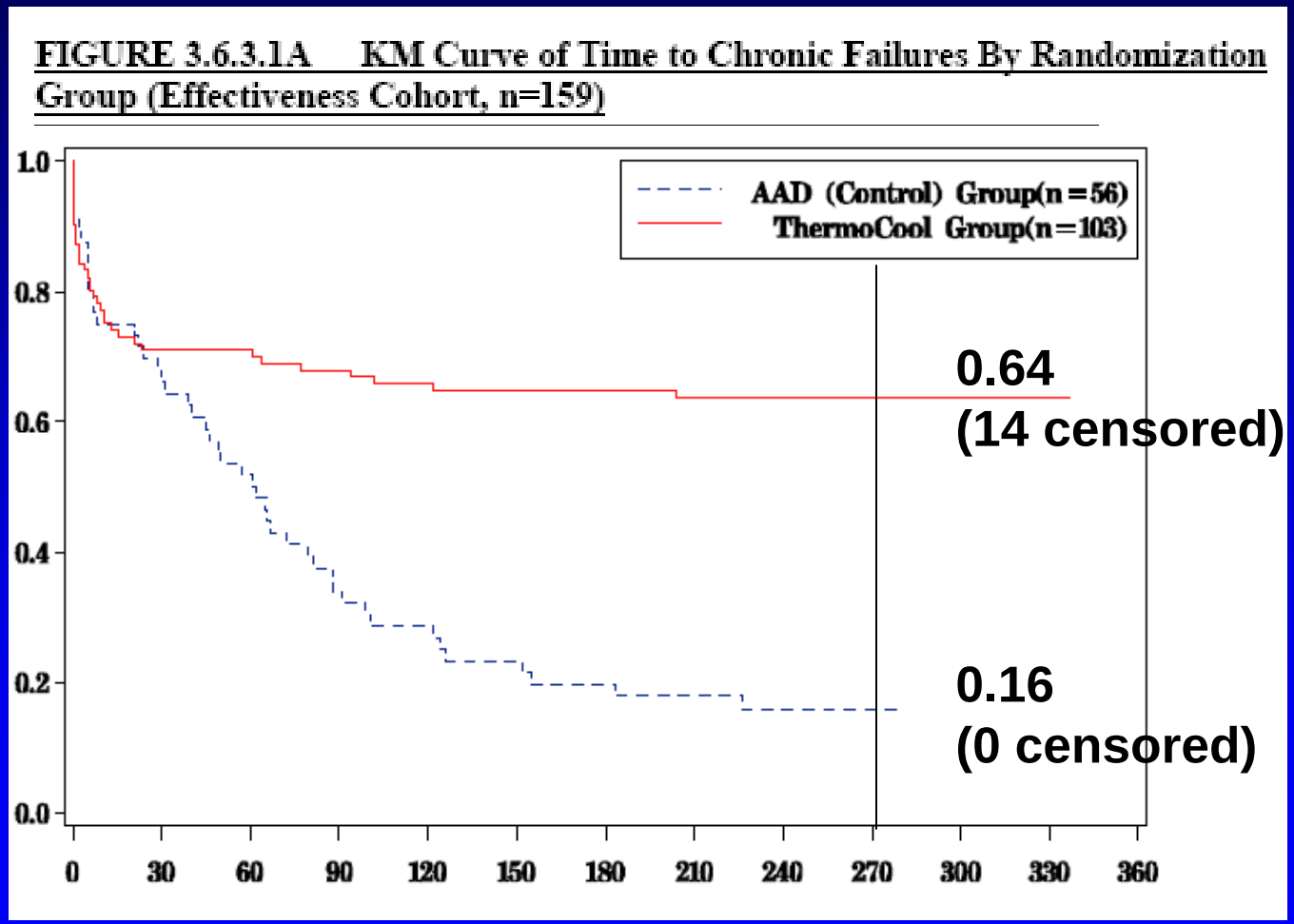
Follow-up Time

First Interim Analysis

- The predictive probability of concluding superiority when all 160 subjects reached an event or 9 months of follow-up was calculated as > 0.999 (exceeding the 0.90 threshold)
  - the sponsor could stop enrollment at 160

- 50% of enrollees had had an effectiveness endpoint determination
  - The sponsor made an early claim of success (because predictive probability exceeded 0.99)

PMA Submission
June 2008, 167 enrolled, 159 eligible



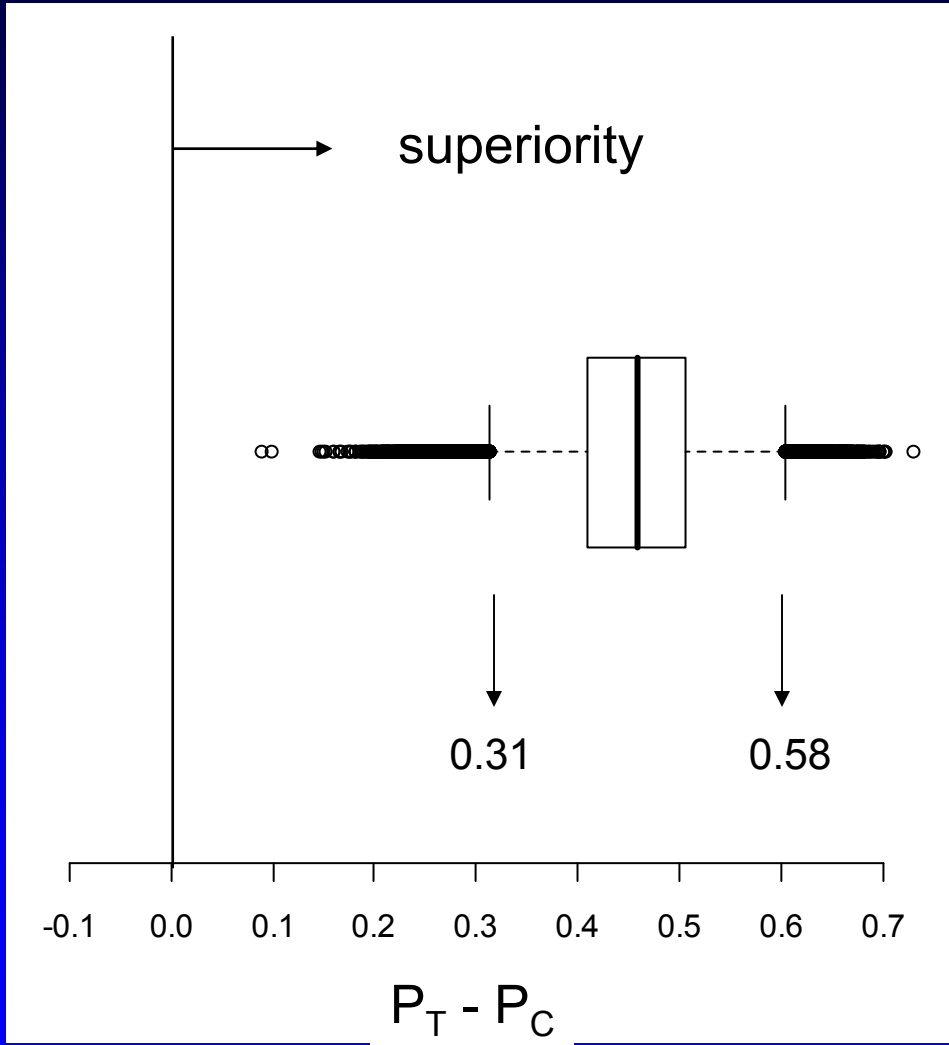
Probability of Chronic Success

Follow-up Time

Final Effectiveness Analysis June 2008

- The posterior probability of superiority at the time of the final analysis was greater than 0.999 (exceeds 0.98).
- Sponsor's 95% posterior credible interval for the difference between the treatment and control probability of success at nine months is (0.31, 0.58), with median of 0.46.
- There is a 95% chance that the actual difference falls within the interval (0.31, 0.58).

Posterior Distribution of P_T - P_C



P_T = probability of chronic success at 9 months (ThermoCool)
P_C = probability of chronic success at 9 months (Control)

FDA's Tipping Point analysis

- Classical Comparison of Proportions
  - Suppose all 14 censored ThermoCool are failures
    - Proportions Test: $p < 0.001$
  - Suppose accrual went to 230 total subjects:
    - 25 Control subjects => 13 are chronic successes
    - 38 ThermoCool subjects => Only need 4 successes to obtain $p = 0.025$

Discussion Items

- Unblinded Study
  - Symptoms were self-reported
  - Placebo Effect?
- Time from randomization to initial treatment varied among subjects.
- The largest-enrolling site performed substantially better than the other sites.

Design Limitations with the Primary Effectiveness Analysis

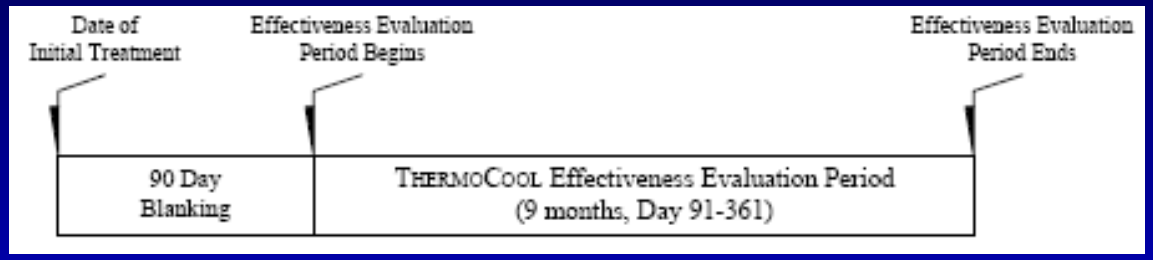
- Trial was unblinded. It is not known to what extent the effectiveness results are due to a placebo effect.
- Subjects' AF symptoms were self-reported.
  - It is unknown whether there was bias in reporting symptoms.
  - Because control subjects were eligible for the newer treatment (cross-over) once they experienced a chronic failure, they might be more inclined to report symptoms.

Discussion Items

- Unblinded Study
  - Symptoms were self-reported
  - Placebo Effect?
- Time from randomization to initial treatment varied among subjects.
- The largest-enrolling site performed substantially better than the other sites.

Timing of Evaluation Periods

Treatment



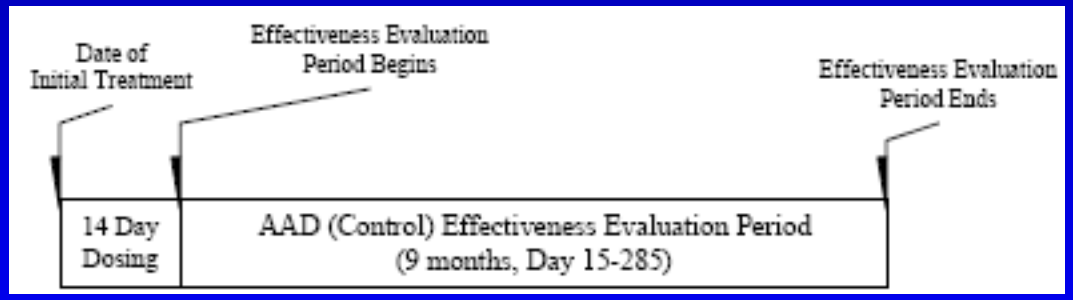
Days from Randomization until Initial treatment

0 28 median 43 mean **max 331**

Randomization

16 mean

0 10 median **max 76**



Control

The beginning times of the blanking and dosing periods after randomization varied from patient to patient, in addition to any "systematic" scheduling delay for the ablation procedure.

Limitations due to Timing of Evaluation Periods

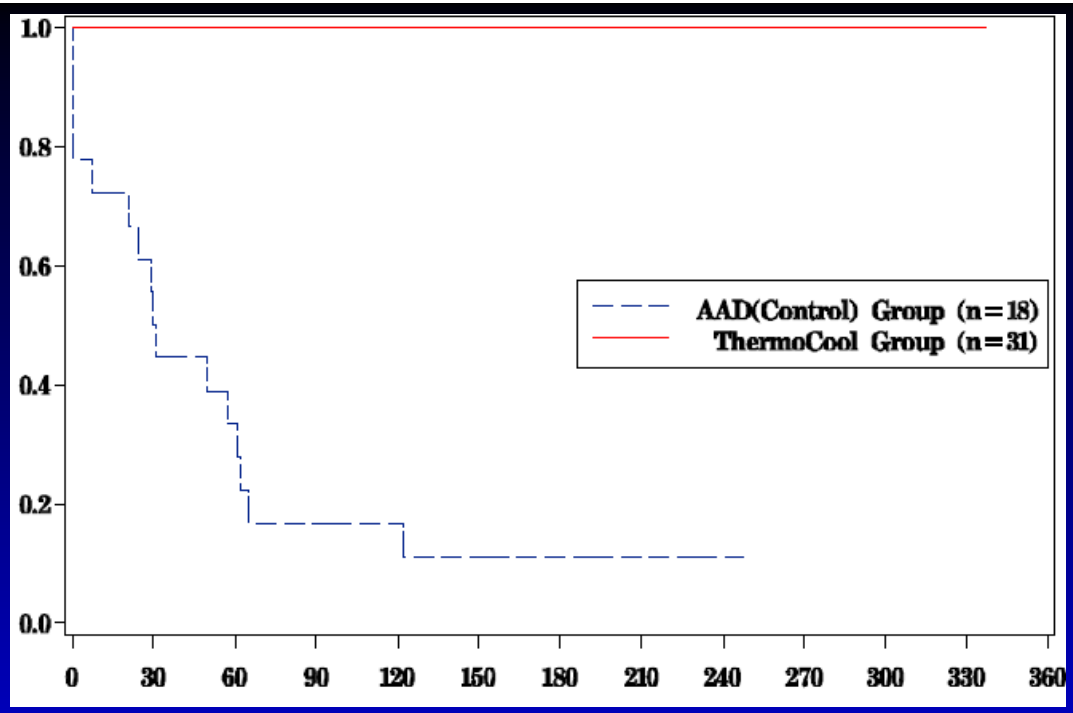
- Although the timing of evaluation periods for this trial was consistent with that of similar trials, the effectiveness results should be interpreted within these limitations.

Discussion Items

- Unblinded Study
  - Symptoms were self-reported
  - Placebo Effect?
- Time from randomization to initial treatment varied among subjects.
- The largest-enrolling site performed substantially better than the other sites.

Poolability across Site Groupings

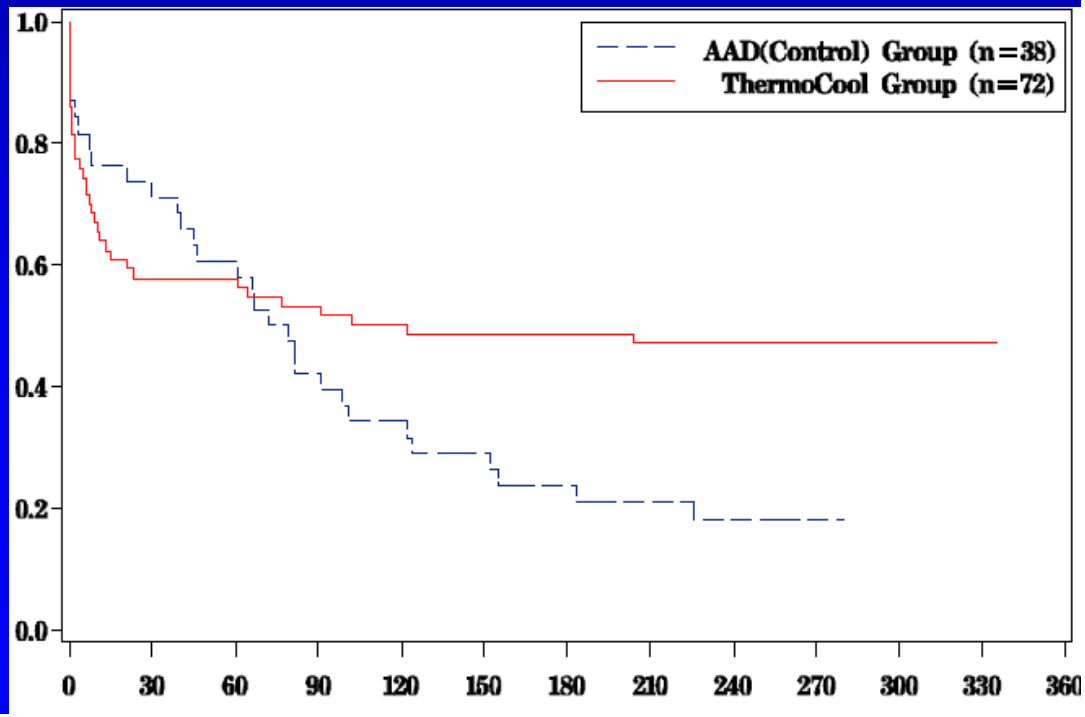
- There was site variation in both effectiveness and safety results.
- OUS sites overall performed better than US sites.
- Primarily due to the better ablation results at highest enrolling site (n = 49).
- Treatment effects across site groupings are all consistent, with ablation performing better than control.



Largest-enrolling Site:

Treatment:
100% chronic success rate

Control:
11% chronic success rate



Other Sites:

Treatment: 47% chronic success rate
Control: 18% chronic success rate

Poolability across Site Groupings

- Posterior probability of positive interaction between largest site/other sites and randomization group on the probability of chronic success is effectively 1.0.
  - likely difference in magnitude of treatment effect at largest site vs. other sites
- Excluding the highest enrolling site, primary effectiveness endpoint is still met.
  - Posterior probability of superiority > 0.999

Primary Safety Results across Site Groupings

- Highest-enrolling site: 2/46 ablation subjects with PAEs
- 4.3% (largest site) vs. 12.9% (other sites)

Limitations about Generalizability

- Given the different magnitudes of observed treatment effects, it is unclear whether the overall results generalize to a solely US population.

Statistical Summary

- The primary effectiveness endpoint was met according to a pre-specified statistical criterion, after a statistical penalty was paid for changing the design from a frequentist fixed sample design to a Bayesian adaptive design.

Statistical Summary

- It is unknown how much of the observed treatment difference is due to placebo effect or bias in reporting symptoms.
- Variability in time from randomization to initial treatment time could be a source of bias.
- Treatment effect in OUS sites might be different than in US sites.

BIOSENSE WEBSTER NAVISTAR® THERMOCOOL® Catheter for Radiofrequency Ablation of Symptomatic Paroxysmal Atrial Fibrillation

FDA Clinical Review

Randall Brockman, M.D.
Division of Cardiovascular Devices
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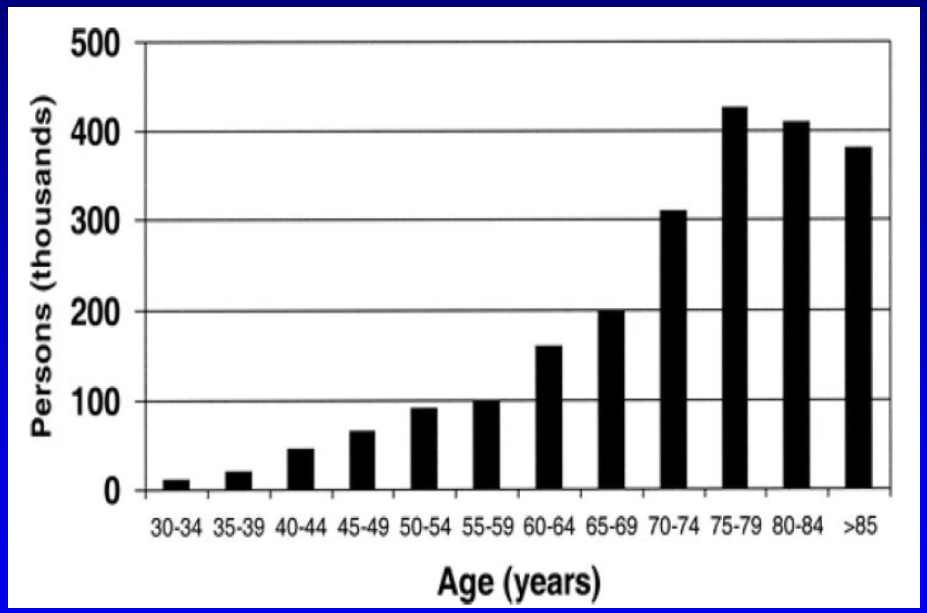
AF Background



Fuster *et al.*
ACC/AHA/ESC Practice Guidelines

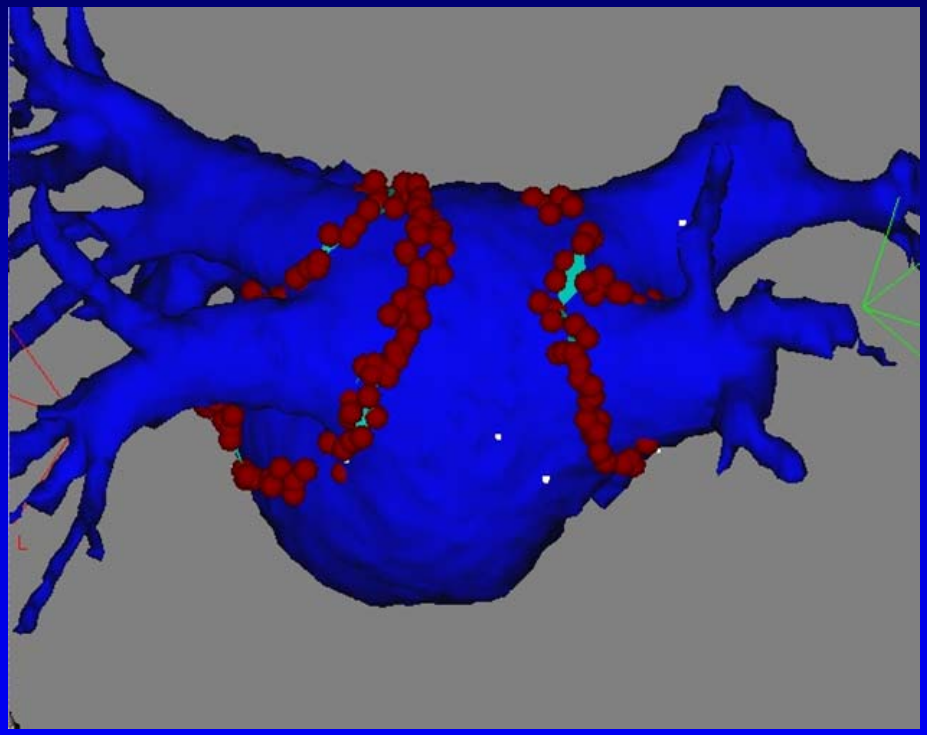
JACC Vol. 48, No. 4, 2006
August 15, 2006:e149–246

- Major public health issue
- Affects broad-spectrum
- Increased risk of stroke, HF, and all-cause mortality
- Principal reason to ablate is to treat symptoms

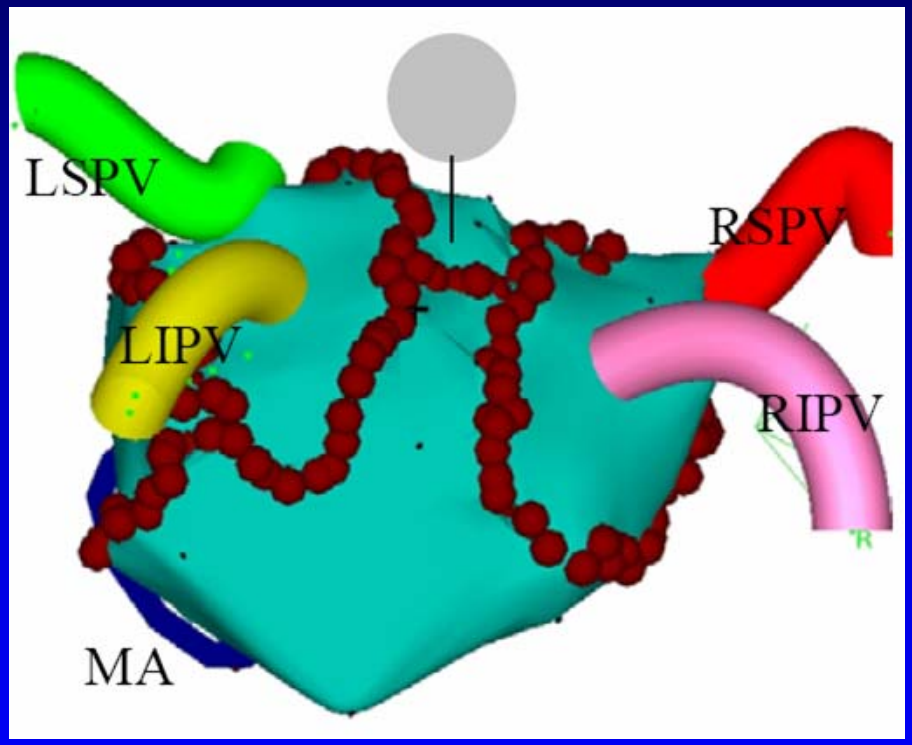
Catheter Ablation of AF

- Differences in technique remain
- Pulmonary vein isolation has been called the “cornerstone”
- Additional elements
  - Linear left atrial lesions
  - complex fractionated electrograms
  - Ganglionated plexi
  - Right atrial/CTI ablation only if atrial flutter is identified

LA Ablation Targets



Dong J, Dickfeld T, Lamiy SZ, Calkins H. Heart Rhythm. 2005;2:1021-2.



Dong J, Calkins H. Nat Clin Pract Cardiovasc Med. 2005;2:159-66.

Pivotal Clinical Trial Design

- Prospective, multi-center, unblinded, controlled trial
- Randomized (2:1) Ablation vs. medical therapy
- Primary Effectiveness compared between arms
- Primary safety compared to a performance goal

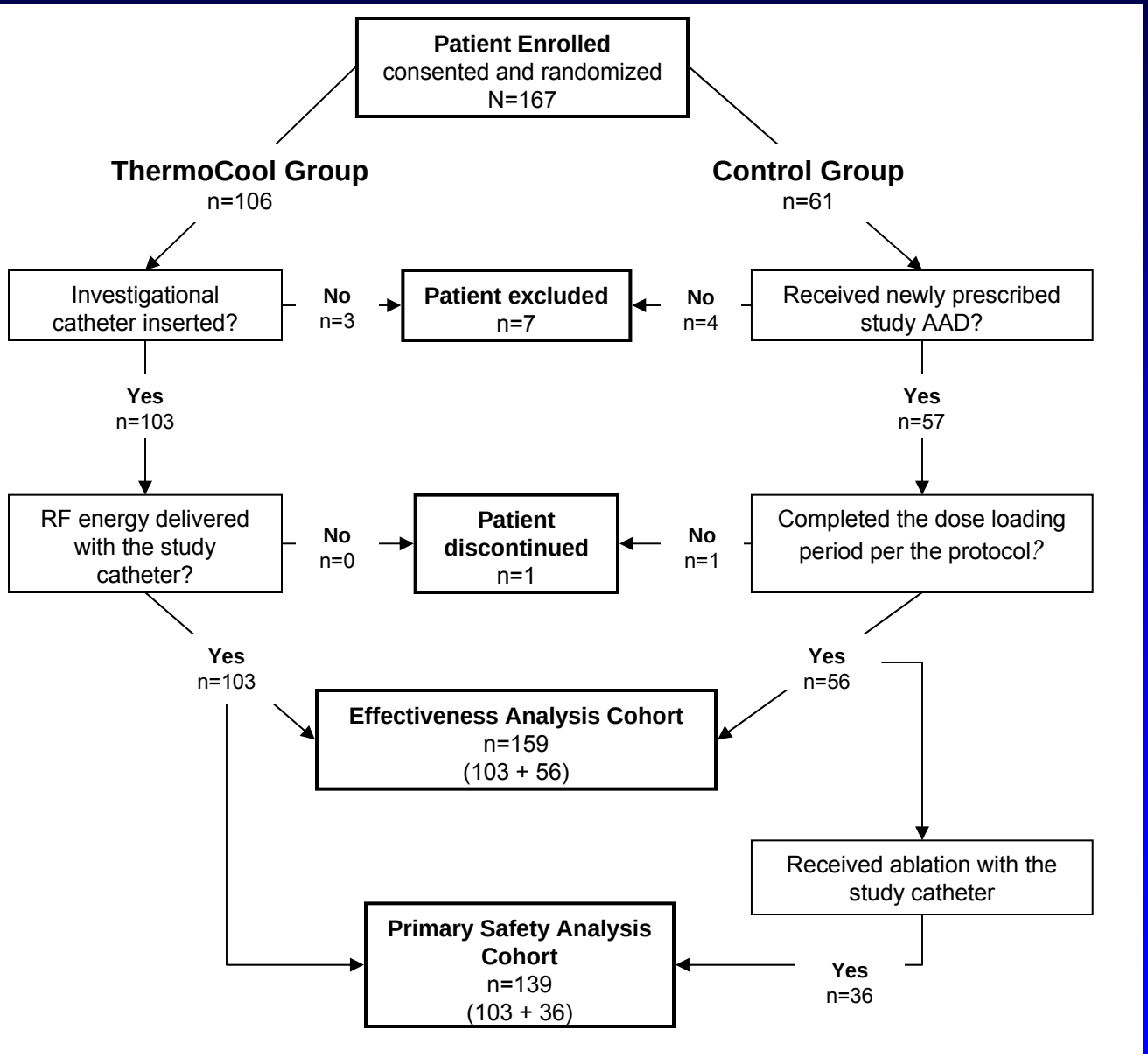
Key Inclusion Criteria

- Symptomatic paroxysmal atrial fibrillation with at least three episodes within 6 months prior to enrollment, only one documented by ECG
- Failure of at least one AAD (class I, II, III or IV)

Key Exclusion Criteria

- AF episodes lasting > 30 days
- Prior AF ablation
- NYHA class III/IV
- LA ≥ 50 mm; LVEF ≤ 40%
- Substantial co-morbidity

Patient Accountability



Baseline Demographics

- Mean age 56 years
- 1/3 women, 2/3 men
- 87% NYHA class I, 13% class II
- Mean LVEF > 60% (only 1 patient < 40%)
- Mean LA diameter 4 cm

Baseline AAD use

- 16% (26/159) of patients in the trial were enrolled due to failure of a rate control drug

Failed AAD at Baseline

	ThermoCool (n=103)	Control (n=56*)	Total (n=159*)
Failed class II/IV only	19	7	26
Failed ≥ 1 class I/III	84	48	132

* One (1) Control group patient was excluded from this analysis pending data query.

Ablation Procedure per Protocol

- Required
  - PV isolation
  - Electroanatomic mapping
- Optional
  - LA roof line and/or mitral isthmus line
  - non-PV foci that initiate atrial fibrillation
  - Linear lesions in the RA for ablation of AFL if AFL is induced during the procedure
  - Isolation of SVC potentials identified during the procedure that trigger atrial fibrillation

Control Medical Therapy

Medication	Class	Minimum recommended daily dose
Dofetilide	III	500 mcg
Flecainide	IC	200 mg
Propafenone	IC	450 mg
Sotalol	III	240 mg
Quinidine	IA	600 mg

Safety Results

Primary Safety Endpoint

- Included all patients that underwent an ablation procedure with the study catheter
- Protocol included a performance goal of ≤16.0% (95% UCB) of patients that could experience a primary safety event
- Protocol defined a list of adverse events that would qualify for this endpoint

Primary Safety Events

- Death
- Myocardial infarction (MI)
- Pulmonary vein (PV) stenosis
- Diaphragmatic paralysis
- Atrio- esophageal fistula
- Transient Ischemic Attack (TIA)
- Stroke
- Thromboembolism
- Pericarditis
- Cardiac Tamponade
- Pericardial effusion
- Pneumothorax
- Atrial perforation
- Vascular Access Complications
- Pulmonary edema
- Hospitalization (initial and prolonged)
- Heart block

Primary Safety Endpoint

- 16 primary adverse events in 15 patients
- Observed proportion 10.8% with 95% UCB 16.1%
- Performance goal was ≤ 16.0%
- Primary safety endpoint was not met

Primary Adverse Events

Description	Number of Patients with Primary AE (%)
Hospitalization	7 (5.0%)
Vascular access complications	5 (3.6%)
Pulmonary edema	1 (0.7%)
Pericarditis	1 (0.7%)
Pericardial effusion	1 (0.7%)
Total	15/139 (10.8%)

Secondary Safety

- Serious Adverse Events that occurred within 7 days
- Serious Adverse Events that occurred within 90 days
- Serious Adverse Events that occurred after 90 days
- Incidence of PV stenosis

Serious Adverse Events within 7 days

- These events were not included in the primary safety endpoint because they were not included in the protocol-specified list
- 7 SAEs reported in 5 patients
- In one patient, intra-procedural evidence of an LA thrombus vs. atrial septal tear resulted in termination of the procedure
- One episode of hemoptysis 48 hours after a procedure was felt to be possibly procedure-related
- Other SAEs (UTI, hematuria, renal neoplasm, recurrent AF) were likely unrelated to device

Serious Adverse Events within 90 days

- Includes all SAEs within 90 days (including those captured in the primary endpoint)
- ThermoCool group: 21 patients (20%)
  - Multiple AF recurrences, dysarthria/vertigo, UTI, renal neoplasm and Stevens-Johnson Syndrome
- Control group: 21 patients (38%)
  - Life-threatening arrhythmias (n=5), multiple AF recurrences

Serious Adverse Events after 90 days

- % of patients that experienced an SAE after 90 days was similar between groups
  - ThermoCool group - one death, HF hospitalization, CP/SOB, syncope, ICD upgrade, PM insertion, coronary angiography, abnormal LFTs, epigastric pain, sinusitis, cholecystectomy, chololithiasis, and dizziness
  - Control group - atrial arrhythmias (7), epigastric pain (2), and one each of pacemaker implant and disorientation with walking

Patient Death

- 71 year old man with CAD, prior MI and CABG, HTN, LVH, diabetes, hyperlipidemia, and symptomatic PAF
- Randomized to ThermoCool group
  - Ablation 5/2007
- Recurrent Symptomatic AF 11/2007
- Chest Pain 3/2008
  - Did not seek medical attention
- Found deceased at home following day

PV Stenosis

- Pulmonary vein stenosis was defined in the study protocol as ≥ 70% reduction in the diameter of the PV from baseline
- No PV stenosis as defined in the protocol was reported.

Degree of PV Narrowing

	None	<50%	50-70%	≥ 70%
3 months (n=82)	5 (6%)	77 (94%)	0	0
12 months (n=29)	1 (3%)	27 (93%)	1 (3%)	0

Effectiveness Results

Acute Effectiveness Endpoint

	ThermoCool (n=103)
Total acute failures	2
PV entrance block not confirmed	0
2nd ablation > 80 days	2
Non-ThermoCool used	0
> 2 repeat ablations	0
Acute effectiveness	101 (98%)

Primary Effectiveness Endpoint

- Chronic success
  - defined as freedom from symptomatic AF based on electrocardiographic data and no changes in the AAD regimen
  - beta blockers (BB), calcium channel blockers (CCB), digitalis, angiotensin receptor blockers or angiotensin converting enzyme (ACE) inhibitors were considered AADs for purposes of determining chronic effectiveness of the ablation or AAD treatment.

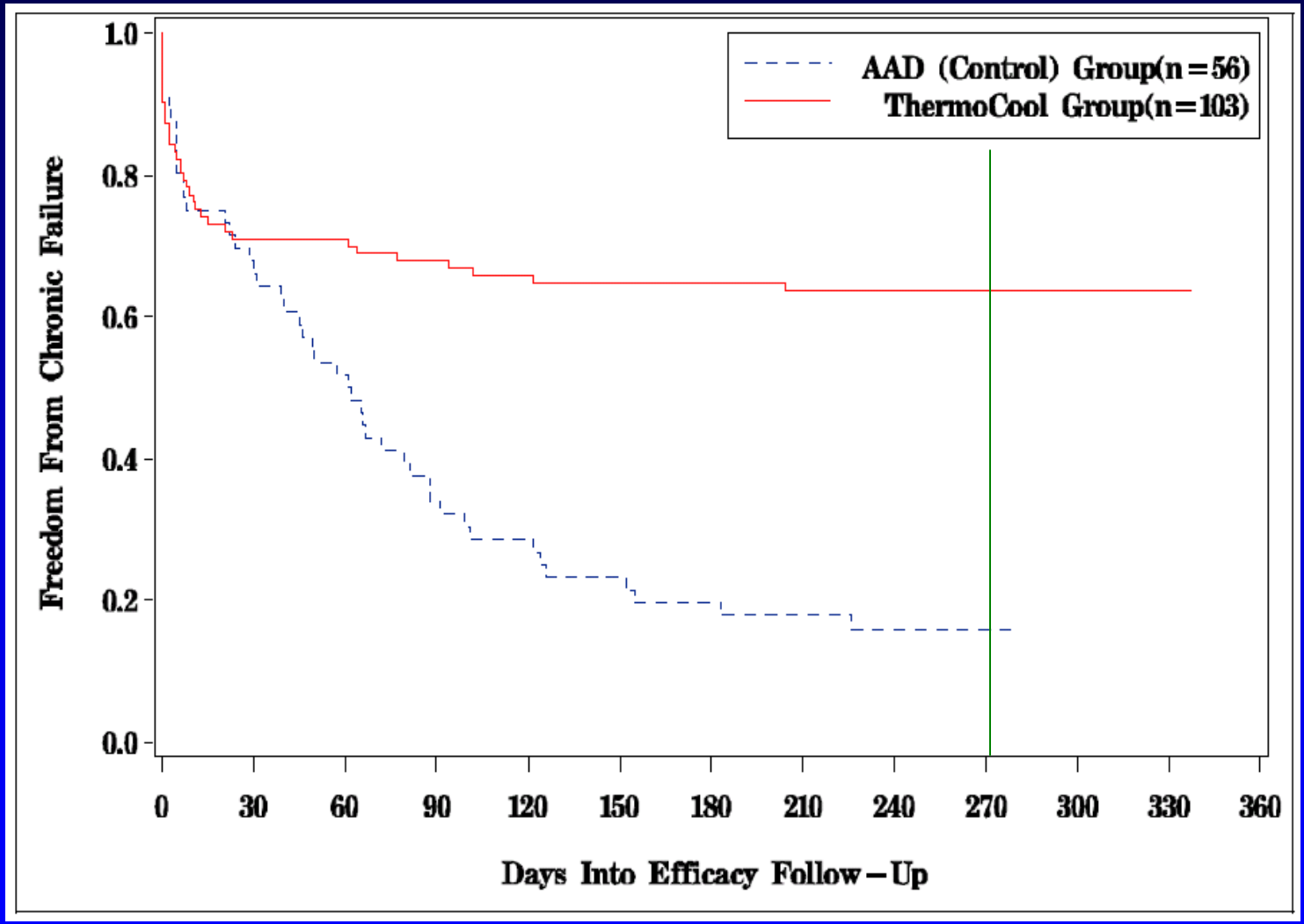
Chronic Effectiveness Monitoring

- Transtelephonic Monitors (TTMs)
  - Transmit tracings on pre-specified schedule
  - Transmit for symptoms
- Additional methods
  - Periodic Holter recordings
  - Periodic 12-lead ECGs
- A Core lab was used for TTMs and Holters

Chronic Effectiveness Results

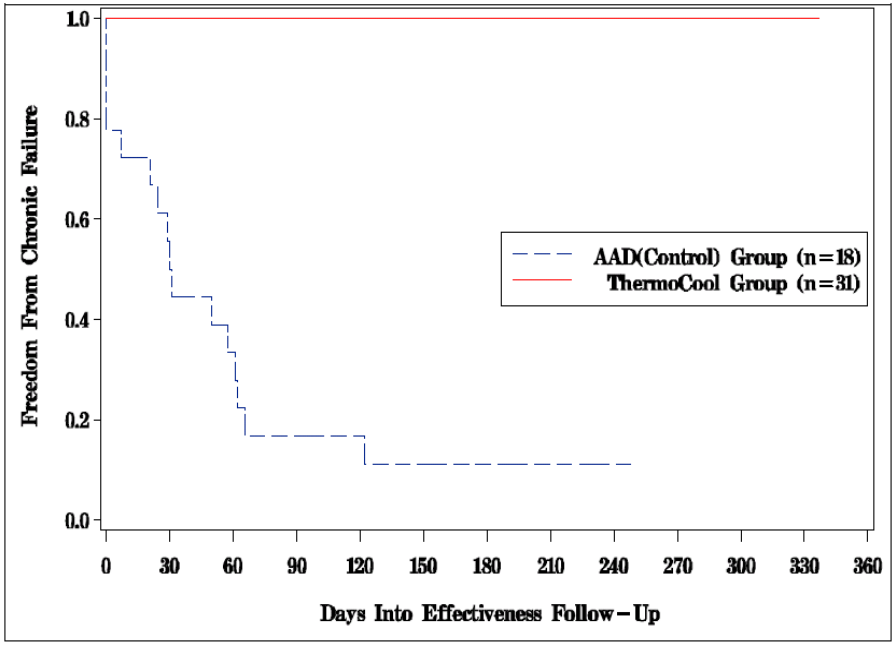
- The ThermoCool group demonstrated a (Bayesian) posterior mean success rate of 62.7 ± 4.8%
- The Control group demonstrated a (Bayesian) posterior mean success rate of 17.2 ± 4.9%
- The primary effectiveness endpoint comparing superiority of Treatment over Control was met with a posterior probability of > 0.999
- Credible interval for Treatment superiority over Control 0.31-0.58 (median 0.46)

Chronic Effectiveness (cont.)

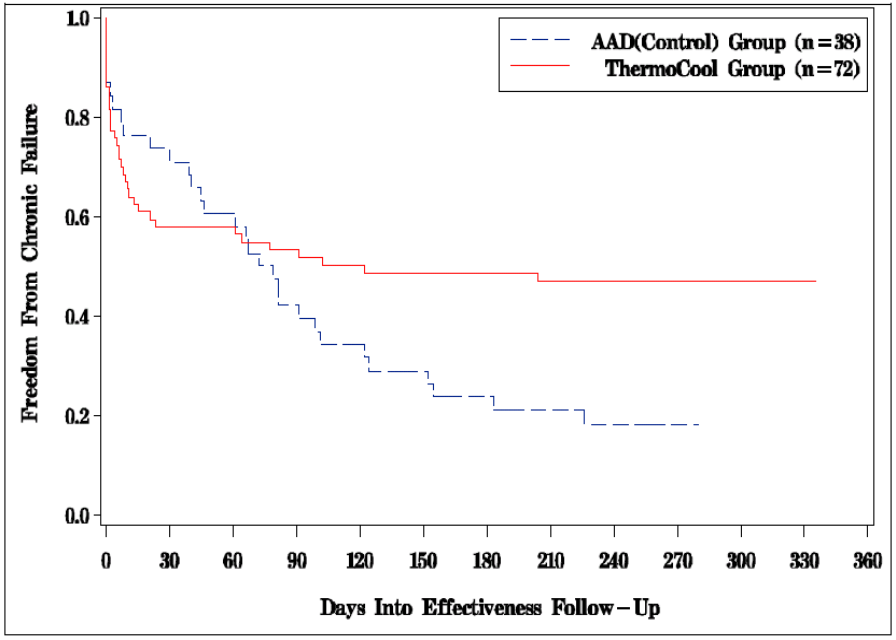


Chronic Effectiveness by Site

Largest Enrolling Site (n=49)



Remaining Sites (n=110)



Proposed Reasons for Site Differences

- Sponsor's reasons:
  - Rigorous conformance to the protocol
  - Protocol-approved medical management
  - Highly experienced investigator
- FDA's possibility
  - Prophylactic right atrial CTI ablation was performed on 23/31 patients at the largest enrolling site site, but on only 1/72 patients at other sites.

Chronic Effectiveness and Control AAD Therapy

- Four (4) Control patients received less than the protocol-recommended minimum AAD dose
- Eleven (11) Control patients received a previously ineffective AAD
- One patient was common to both (total=14)
- A sensitivity analysis was performed to assess the impact of these protocol deviations on chronic effectiveness
- The analysis indicated that the insufficient AAD therapy provided to the 14 Control Group patients did not materially impact the chronic effectiveness result of the study.

Chronic Effectiveness by AAD failed at Baseline

Chronic Outcome	Randomization Group			
	ThermoCool (n=103*)		Control (n=56**)	
	Class I/III (n=76)	Class II/IV (n=13)	Class I/III (n=48)	Class II/IV (n=7)
Success	48 (63%)	5 (39%)	7 (15%)	2 (29%)
Failure	28 (37%)	8 (61%)	41 (85%)	5 (71%)

* 14 patients were still within the effectiveness evaluation period and were not included in this analysis.
** One (1) Control group patient was excluded from this analysis pending data clarification.

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TTM Compliance

- Minimum 15 TTM recordings during 9 month f/u
- One per week for 1st 8 weeks, then one per month
- Compliance calculated as % of total transmissions divided by expected transmissions

	ThermoCool (n=102*)	Control (n=56)	Overall (n=158*)
Compliance (%)	88 ± 16	89 ± 15	88 ± 16

*One patient was lost to follow-up prior to TTM evaluation.

TTM Compliance (cont.)

- U.S. sites 87%
- Non-U.S. sites 90%
- Largest enrolling site 93%
- Relatively stable over time

Protocol Deviations

- 14 Control group patients received AAD therapy that did not adhere to protocol
- 4 patients received amiodarone during follow-up (3 ThermoCool, 1 Control)
  - 3 of the 4 were chronic failures (the chronic success patient received amiodarone for only 2 days)
- "Prophylactic" RA linear lesions performed in 24 ThermoCool patients

Summary

- NaviStar ThermoCool was superior to medical therapy in terms of reducing recurrent symptomatic AF at 9 months
- The largest enrolling site (OUS) had greater effectiveness than other sites
- Primary safety endpoint was not met
- Review of individual safety events did not raise substantial concerns for FDA

BIOSENSE WEBSTER NAVISTAR® THERMOCOOL® Catheter for Radiofrequency Ablation of Symptomatic Paroxysmal Atrial Fibrillation

Post-Approval Study (PAS)

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Epidemiology Branch
Division of Postmarket Surveillance
Office of Surveillance and Biometrics
Food and Drug Administration

Circulatory System Devices Panel Meeting
November 20, 2008

Outline

- General principles
- Rationale for postmarket questions
- Proposed Post-Approval Study (PAS) outline
- Assessment of the PAS outline

Reminder

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.

- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.

- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

General Principles for Post-Approval Studies

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness.
- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

Need for Post-Approval Studies

- Gather postmarket information
  - Longer-term performance
  - Real world community performance
  - Effectiveness of training programs
  - Sub-group performance
  - Rare adverse events
- Account for Panel recommendations

Post-Approval Study Components

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

Important Postmarket Questions for the Navistar Thermocool Catheter

- What will the real world performance of the device be in the more general population of patients and providers?
- What is the long-term durability of effectiveness and the safety profile in patients treated with the device postmarket?
- Is there a difference in the effectiveness outcome in subjects in whom a prophylactic right atrial cavo-tricuspid isthmus (CTI) ablation was performed in addition to the PV isolation?

Center for Devices and Radiological Health CDRH

Overview of Sponsor's PAS Outline

Study Objective	To provide additional corroborative long term safety and effectiveness data for the NaviStar ThermoCool catheter in the treatment of symptomatic paroxysmal atrial fibrillation.
Study Design	Prospective, multi-center cohort, non-inferiority design with historical controls
Population and Sample Size	RFA PAS Group: subjects who will be treated with NaviStar ThermoCool catheter in the PAS (N = 145) Historical Controls: NaviStar ThermoCool catheter subjects in the pivotal study (N = 139)
Follow-up	5-year office visit/phone interview

Overview of Sponsor's PAS Outline (Cont'd)

Safety Endpoints	Primary Safety Objective: Non-inferiority PAS patients with a AE, at 7 days when compared to the IDE study (P030031/S11) Secondary Safety Objective: Descriptive analysis of the long term (5 year) occurrence of AEs (Death, Stroke, MI).
Effectiveness Endpoints	Secondary Objective: Descriptive analysis of the recurrence of symptomatic AF long term (5 years). Secondary Objective: Evaluate the effectiveness outcome in subjects in whom cavo-tricuspid ablation lines are place in addition to the PV isolation.
Hypothesis	The proportion of PAS patients with a AE, at 7 days, is no worse that the RFA treated patients (AE rate=11%) in the pivotal trial with a region of indifference of 9%.

FDA Assessment

Short-term Safety Objective

AE within 7 days

Issues

- N=145
- 10% drop-out rate
- Non-inferiority delta large (11%+9%)

Question: Is the proposed PAS appropriate to assess the procedural safety profile of the device in real world use?

FDA Assessment

Long-term Safety Objectives

Descriptive analysis of the long term (5 year) occurrence of AEs (Death, Stroke, MI)

Issues:

- No hypothesis for long-term safety
- Not powered to evaluate long-term safety
- No control group

Questions: What is an appropriate long-term safety endpoint? What is an appropriate length of follow-up? What is an appropriate control group?

FDA Assessment

Long-term Effectiveness Objective

Descriptive analysis of the recurrence of symptomatic AF long term (5 years)

Issues

- No hypothesis to evaluate durability of effectiveness
- No control group

Questions: What is the appropriate follow-up and appropriate control group needed to evaluate the durability of effectiveness of ablation?

FDA Assessment

Effectiveness Objective

Evaluate the effectiveness outcome in subjects in whom cavo-tricuspid isthmus (CTI) ablation lines are place in addition to the PV isolation

Issues

- Descriptive analysis
- No hypothesis stated
- No estimates of anticipated number of CTI patients
- No comparator population

Questions: Is there need to investigate this difference in effectiveness in the postmarket period? Is it appropriate to randomize patients to prophylactic right atrial ablation?

Questions?

Questions to Panel

1. Design – Comparison to Standard of Care and Generalizability of Results

   Please discuss the impact of excluding amiodarone as a treatment option in the medical control arm. How does this affect the generalizability of the control arm to medical practice in the United States?

Questions to Panel

2. Poolability of US and OUS Sites

Please discuss the impact of differences between OUS and US sites on generalizability of reported results to a solely US population.

Questions to Panel

3. Safety

Please discuss whether the safety results demonstrate that there is a reasonable assurance that the device is safe for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

Questions to Panel

4. Effectiveness Results - General

Please discuss whether the chronic effectiveness results demonstrate that there is a reasonable assurance that the device is effective for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

Questions to Panel

5. Device Labeling

A. Please discuss whether the proposed Indications identify the appropriate patient population for treatment with the device.

B. Please comment on whether the labeling should include a warning that the safety and effectiveness has not been demonstrated in patients with heart failure.

C. Please comment on whether the data collected in the clinical study can be generalized to devices that are not capable of generating electroanatomic maps. If not, please discuss whether the referenced scientific articles provide sufficient information to warrant approval of the requested change in Indications for Use for the non-CARTO equipped catheters.

D. Please discuss whether the trial provides sufficient experience in a population that has failed only rate-control therapy such that the indication statement should include patients that have failed only rate-control medical therapy.

E. Please discuss any additional recommendations you have regarding the device labeling.

Center for Devices and Radiological Health CDRH

Questions to Panel

6. Post-approval Study

A. Please discuss the appropriate trial design for determining the procedural safety profile in a broader patient and provider population. Please comment on what may be an appropriate hypothesis, endpoint, duration of follow-up, and control group.

B. Please discuss the appropriate trial design for evaluating the long-term safety of patients treated with the device. Please comment on what may be an appropriate hypothesis, endpoint, duration of follow-up, and control group.

C. Please discuss the appropriate trial design for evaluating the durability of effectiveness in patients treated with the device. Please comment on what may be an appropriate hypothesis, endpoint, duration of follow-up, and control group.

D. Please discuss the impact of CTI ablation on the premarket effectiveness results and discuss whether this issue should be investigated in the PAS. Please comment on whether it is appropriate to randomize patients to prophylactic CTI ablation.