Acute and long-term efficacy and safety of catheter cryoablation of the cavotricuspid isthmus for treatment of type 1 atrial flutter

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BACKGROUND Atrial flutter (AFL) is commonly treated by radiofrequency catheter ablation. Catheter-based cryoablation may be an effective alternative with potential advantages.

OBJECTIVE The purpose of this study was to study the acute and long-term safety and efficacy of catheter-based cryoablation for treatment of cavotricuspid isthmus–dependent (typical and reverse typical) AFL.

METHODS Catheter-based cryoablation was performed with a 10Fr catheter in 160 patients with cavotricuspid isthmus–dependent AFL (122 men and 38 women; mean age 63.1 ± 9.3 years, mean left ventricular ejection fraction 54.6% ± 10.4%); 94 (58.8%) of these patients also had atrial fibrillation (AF). All patients underwent right atrial (RA) activation mapping and pacing at the cavotricuspid isthmus to demonstrate concealed entrainment and confirm cavotricuspid isthmus dependence of AFL. Catheter-based cryoablation of the cavotricuspid isthmus was performed with multiple freezes (average freeze time 2.3 ± 0.5 minutes) until bidirectional block was demonstrated during pacing from the low lateral RA and coronary sinus, respectively. Patients were evaluated at 1, 3, and 6 months and underwent weekly and symptomatic event monitoring. Acute procedural success was defined as cavotricuspid isthmus block persisting 30 minutes after ablation. Long-term success was defined as absence of AFL during follow-up.

RESULTS Acute success was achieved in 140 (87.5%) of 160 patients. Total procedure time was 200 ± 71 minutes, ablation time (including a 30-minute waiting period after ablation) was 139 ± 62 minutes, and fluoroscopy time was 35 ± 26 minutes. An average of 20.5 ± 11.3 freezes, for a total ablation time of 47.4 ± 24.3 minutes, were required to achieve cavotricuspid isthmus block, with average and nadir temperatures of −81.5°C ± 3.7°C and −85.6° ± 3.6°C, respectively. Four patients (2.5%) had procedure-related adverse events. Of 132 patients with acute efficacy who completed 6-month follow-up, 8 (6%) were lost to follow-up or were noncompliant with event recordings. Using survival analysis, 106 (80.3%) remained free of AFL on strict analysis of event recordings only, and 119 (90.2%) remained clinically free of AFL.

CONCLUSION This large pivotal study demonstrated the acute and long-term efficacy and safety of catheter-based cryoablation for cavotricuspid isthmus–dependent AFL, similar to rates previously reported for radiofrequency catheter ablation.

KEYWORDS Atrial flutter; Cryoablation; Cavotricuspid isthmus

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Introduction

The incidence of cavotricuspid isthmus–dependent atrial flutter (AFL) has been estimated at more than 200,000 in the United States, with a prevalence of 800,000.[1,2] Radiofrequency (RF) catheter ablation is safe and effective treatment of AFL, with cure rates greater than 95%.[3,4] In studies using large-tip RF ablation catheters, acute efficacy ranged from 88% to 93%, long-term 6-month efficacy from 87% to 97%, and complications from 2.7% to 3.6%.[3,4] RF catheter ablation of AFL has been shown to improve quality of life and to reduce recurrence of atrial fibrillation (AF) and frequency of hospitalization compared with medical therapy.[5]

Catheter cryoablation has been used to treat supraventricular arrhythmias, with comparable efficacy and potentially fewer complications compared with RF catheter ablation.[6–11] Unlike RF catheter ablation, catheter-based cryoablation does not cause coagulum formation or endocardial charring.[6–11] It does not cause pain, potentially reducing the amount of sedation required during ablation.[7–10] However, the efficacy of catheter-based cryoablation for treatment of AFL has not been systematically evaluated in a large clinical trial. In this report, the acute and

This study was sponsored by CryoCor, Inc., San Diego, CA. Dr. Feld is a consultant and member of the Scientific Advisory Board for CryoCor, Inc. For a list of the Cryoablation Atrial Flutter Efficacy (CAFÉ) Trial Investigators, see the Appendix. **Address reprint requests and correspondence:** Dr. Gregory K. Feld, Department of Medicine, Division of Cardiology, UCSD School of Medicine, 200 West Arbor Drive, San Diego, California 92103. E-mail address: gfeld@ucsd.edu. (Received January 26, 2008; accepted March 13, 2008.)

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6-month follow-up results in a total of 160 patients treated with catheter-based cryoablation are presented.

Methods

This prospective, multicenter study was designed to evaluate the safety and efficacy of the CryoCor catheter-based cryoablation system (CryoCor, Inc., San Diego, CA.), which has been previously described in detail.[6,7,10–12] In brief, the system consists of a 10Fr, 6.5-mm metal-tip catheter and cryogenerator that produces a nadir temperature of –90°C. The primary end-points of this study were demonstration of acute safety and efficacy, defined by adverse event rates and success in achieving bidirectional cavotricuspid isthmus block. The secondary end-point was demonstration of long-term efficacy defined as the recurrence rate of AFL during 6-month follow-up. Patients were followed after ablation using clinical parameters and symptomatic and random weekly event monitoring to detect recurrences of AFL.

Study inclusion criteria and exclusion criteria

Patients were included in the study if they had symptomatic cavotricuspid isthmus–dependent AFL, were between the ages of 18 and 75 years, had at least one episode of symptomatic AFL documented on ECG in the last 6 months, and had cavotricuspid isthmus–dependent AFL documented in the electrophysiology laboratory just prior to ablation. Patients were excluded if they had undergone cardiac surgery within 6 months of screening, had New York Heart Association class III or IV congestive heart failure and/or ejection fraction $<30\%$, right-sided prosthetic heart valves, myocardial infarction within 3 months of screening, unstable angina or myocardial ischemia, corrected or uncorrected atrial septal defect, congenital heart disease that increased the risk of cryoablation, prior ablation for AFL, ablation other than for AFL within 3 months of screening, AF requiring treatment with an antiarrhythmic drug other than class IC or III, ventricular arrhythmia requiring medical treatment that would confound interpretation of study results, or other medical contraindications.

Preprocedure assessments

Informed consent from was obtained from all patients. Preprocedure information recorded for each patient consisted of demographic data, medical history including treatment of arrhythmias, ECG documentation of symptomatic AFL, and left ventricular ejection fraction within the past 6 months, all cardioactive medications administered within the past 30 days, routine laboratory tests within 72 hours of the procedure, and, if applicable, international normalized ratio and human chorionic gonadotropin. Warfarin was discontinued prior to ablation so that the international normalized ratio was <2.0 at the time of the procedure.

Procedure description

Prior to catheter-based cryoablation, documentation of cavotricuspid isthmus dependence of AFL was required, using standard electrode or three-dimensional activation mapping techniques. If cavotricuspid isthmus–dependent AFL could not be confirmed, the patient was considered a secondary screen failure and was not allowed to proceed with catheter-based cryoablation. If cavotricuspid isthmus–dependent AFL was documented, catheter-based cryoablation of the cavotricuspid isthmus was performed with freezes lasting from 2 to 5 minutes each. Ablation could be performed during sinus rhythm or AFL, but documentation of bidirectional cavotricuspid isthmus conduction block was required using established techniques at least 30 minutes after the last ablation. If cavotricuspid isthmus conduction recovered during this period, further catheter-based cryoablation was allowed, followed again by a 30-minute waiting period before confirmation of cavotricuspid isthmus block. Use of isoproterenol during assessment of cavotricuspid isthmus block was optional.

A catheter-based cryoablation freeze was considered effective if catheter position was stable at the targeted location, a nadir temperature near -90°C was reached during ablation, and the freeze duration was at least 2 minutes. If bidirectional cavotricuspid isthmus block could not be achieved with catheter-based cryoablation, the cavotricuspid isthmus could be ablated with an approved RF catheter ablation device. At this point, the patient was considered a catheter-based cryoablation failure and was discharged from the study.

Intraprocedure parameters collected for each patient included number, temperature, duration, and location of all cryoablations, total fluoroscopy and procedure times (defined as time from femoral cannulation to removal of all catheters), conduction time and/or activation sequence across the cavotricuspid isthmus prior to and immediately following ablation, pacing entrainment methods used to define cavotricuspid isthmus–dependent AFL, time of initial bidirectional cavotricuspid isthmus block, persistence of bidirectional cavotricuspid isthmus block for a minimum of 30 minutes after ablation, and all adverse events.

Follow-up procedure

Following catheter-based cryoablation, subjects were managed according to institutional procedures. After discharge, patients with acute success were evaluated at 1 and 3 months by ECG and assessment of cardioactive medications and adverse events. At 6 months, a telephone interview was conducted for assessment of adverse events and any arrhythmic events. During follow-up, event recordings up to 1 minute in length were obtained weekly and during any symptomatic events thought to be due to arrhythmia. A patient was deemed compliant with event monitoring if at least three recordings per month for at least 5 of the 6 follow-up months, or a total of at least 20 weekly recordings, were available for review.

Patients with clinical evidence of symptomatic recurrent AFL were encouraged to undergo repeat ablation. Treatment of recurrent AFL with catheter-based cryoablation required ECG documentation and demonstration of cavotri-

cuspid isthmus–dependent AFL during repeat electrophysiologic study. Any patient who was re-treated with catheter-based cryoablation for AFL was followed for another 6 months. However, if re-treatment was performed with RF catheter ablation, the patient was followed only through the 6 months remaining after the last catheter-based cryoablation procedure.

A Data Safety Monitoring Board (DSMB) consisting of three independent electrophysiologists met 12 times during the study and provided final adjudication of all serious adverse events. A serious adverse event was defined as any event resulting in death, life-threatening complications, persistent or significant disability/incapacity requiring inpatient hospitalization or prolonged hospitalization, or requiring intervention to prevent permanent impairment of a body function or damage to a body structure. The committee was empowered to recommend corrective actions, including study discontinuation.

A core ECG laboratory (Dr. Melvin Scheinman and colleagues at University of California, San Francisco, CA, USA) analyzed all event monitor recordings for the presence of arrhythmias. These recordings were analyzed sequentially after completion of the study for all patients who completed the entire 6-month follow-up. The core laboratory was not blinded to patient identifiers but had no clinical information on any patients in the study.

Primary and secondary efficacy and safety end-points

The primary end-points were acute safety and efficacy. Acute efficacy was defined as bidirectional cavotricuspid isthmus block a minimum of 30 minutes after the last catheter-based cryoablation. The primary safety outcome was a measurement of all serious adverse events that occurred within 7 days of catheter-based cryoablation. The study sample size was determined based on the primary safety end-point; a minimum of 160 patients was required to demonstrate an incidence of serious adverse events $\leq$7% with a power of 80% and a type 1 error rate of 0.05. All primary analyses were performed using the intention-to-treat method, which included all patients in whom the cryoablation catheter was introduced into the body.

The secondary end-point was chronic efficacy, freedom from recurrent AFL for 6 months, in patients who achieved the primary efficacy end-point of bidirectional cavotricuspid isthmus block. Chronic efficacy was defined using two methods of analysis. The first method used a strict assessment of freedom from recurrent AFL during follow-up, determined solely by event monitor recordings analyzed by the core ECG laboratory. The second method of analysis performed by the sponsor after completion of the study involved both assessment of event monitor recordings analyzed by the core ECG laboratory and clinical evidence of long-term efficacy as determined by each investigator. Because this protocol allowed inclusion of patients with AF, recurrence of AF was not considered a study failure.

Statistical analysis

Once a dataset was compiled, descriptive statistics were performed for demographic summarization. These statistics were in the form of either mean $\pm$ 1 SD or, in the case of count data, a percent derived from binomial proportions. Likewise, estimates provided for safety end-points were calculated, using the binomial proportion, as was an exact 95% confidence interval. For the acute effectiveness end-point, a percent derived from a binomial proportion along with the associated 95% exact confidence interval was calculated.

For long-term efficacy, Kaplan-Meier analysis was used to estimate the proportion of patients who remained free from AFL recurrence at 6 months. An associated conservative Peto 95% lower confidence bound was calculated as well.

Early censoring occurred in survival analysis estimates whenever a subject was found not to be in compliance with event recording requirements or was otherwise lost to follow-up. In such cases, censoring occurred at the last date of event recording compliance or at last known clinic visit, whichever came first. Subjects without recurrence of AFL during 6-month follow-up were censored at either the date of their final event recording or their final clinic visit. No imputation or substitution was performed for missing data.

Results

One hundred sixty patients were enrolled in the study and treated (Table 1). Patients had a mean age of 63.1 $\pm$ 9.3 years and mean left ventricular ejection fraction of 54.6% $\pm$ 10.4%; 122 (76.3%) were male. One hundred four (65%) patients had concomitant arrhythmias, including 94 (58.75%) with AF. The majority had typical AFL (78.75%), most of the remainder had reverse typical AFL (13.8%) or both types of AFL (5.6%), and a small percentage was unreported (1.9%). At the time of ablation, 57 (35.6%) patients were taking antiarrhythmic drugs.

Of the 160 patients treated, 140 (87.50%) achieved acute success with bidirectional cavotricuspid isthmus conduction

Table 1 Clinical characteristics of patients at the time of ablation (N = 160)

	No. (%)
Male/female	122/38 (77% male)
Age (mean $\pm$ SD)	63.03 $\pm$ 9.25 years
Ejection fraction (%)	54.6 $\pm$ 10.4%
Antiarrhythmic drugs	57 (35.6%)
Atrial fibrillation history	94 (59%)
Cardiomyopathy	16 (10%)
Congestive heart failure	27 (17%)
Diabetes	27 (17%)
Hyperlipidemia	84 (53%)
Ischemic heart disease	30 (19%)
Obesity	44 (28%)
Previous myocardial infarction	26 (17%)
Systemic hypertension	98 (62%)
Tobacco abuse	18 (12%)
Ejection fraction $\leq$40	25 (16%)

block. In patients with acute success, the mean total number of freezes was 20.5 ± 11.3, mean number of effective freezes (defined as those in whom there was adequate tissue contact, temperature, and duration) 18.6 ± 9.3, average total freeze duration 47 ± 24 minutes, average freeze time per ablation 2.33 ± 0.50 minutes, average temperature −81.5°C ± 3.7°C, mean nadir temperature −85.6°C ± 3.6°C, average total fluoroscopy time 45 ± 1.5 minutes, and average total procedure time 200 ± 71 minutes.

Of the 140 patients with acute success, eight were excluded from analysis of chronic efficacy because of noncompliance with event recording. Of the remaining 132 patients eligible for analysis at 6-month follow-up, 106 (80.3%) were considered chronic successes and free of AFL on event monitoring as determined by the core ECG laboratory (Figure 1). Of the 26 (20%) patients with at least one event characterized as AFL by the core laboratory during the follow-up period, 5 (13.5%) were reablated with catheter-based cryoablation, 5 (13.5%) were reablated using RF catheter ablation, one underwent electrical cardioversion, and two were treated with amiodarone. The remaining 13 patients were not reablated but were followed by the investigators without changing or, in some cases, discontinuing antiarrhythmic therapy and were considered clinical successes without further recurrence of AFL, resulting in long-term clinical efficacy in 119 (90.2%) patients (Figure 2). Among the 13 patients who were not reablated (the majority of whom the core ECG laboratory diagnosed recurrent AFL on only a single event recording), 10 were reported by the investigator to have experienced nonsustained AF or atrial tachycardia and not AFL, one had a fortuitous overlap of a biphasic T wave and P wave suggesting AFL, and two had only a single apparent episode of AFL without further recurrence during follow-up.

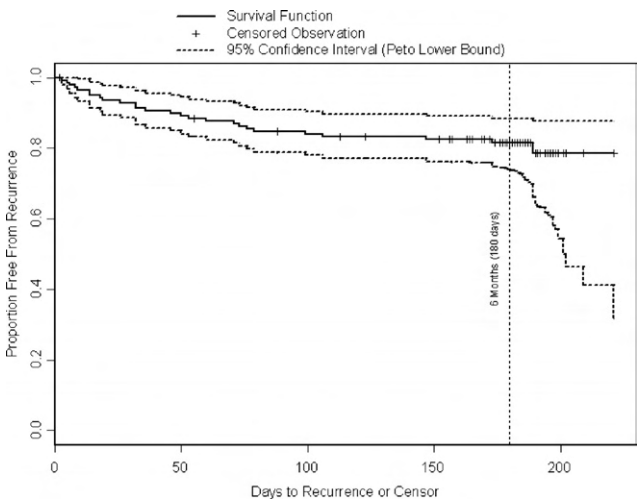

Figure 1 Kaplan-Meier curve showing days to recurrence of atrial flutter by event monitor evidence of atrial flutter recurrence (see Methods for description of analysis). Patients were censored if they were lost to follow-up or were noncompliant with event monitoring. *Solid line* represents survival function, *dashed line* represents 95% confidence interval, and *hash marks* represent points of censor.

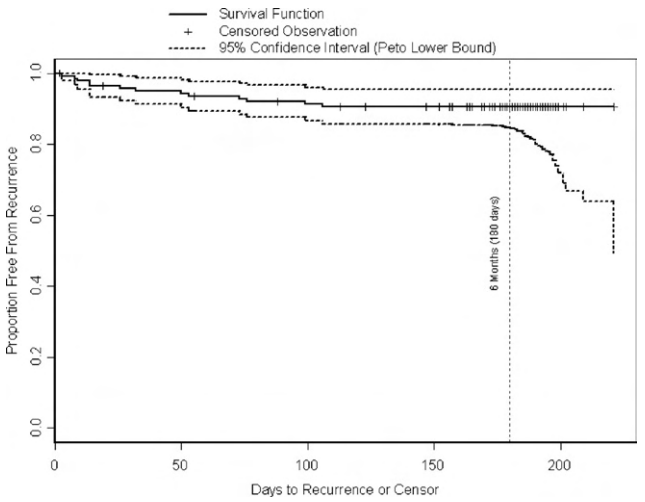

Figure 2 Kaplan-Meier curve showing days to recurrence of atrial flutter by clinical analysis evidence of atrial flutter recurrence (see Methods for description of analysis). Patients were censored if they were lost to follow-up or were noncompliant with event monitoring. *Solid line* represents survival function, *dashed line* represents 95% confidence interval, and *hash marks* represent points of censor.

Of the 160 patients treated, 94 (58.8%) had a history of AF prior to enrollment. Of the 132 patients who had acutely successful ablation and were eligible for analysis at 6-month follow-up, 58 (44%) exhibited AF during follow-up, 48 (36.4%) of whom were controlled with antiarrhythmic drugs. Among the patients with AF, antiarrhythmic drug therapy was changed during follow-up for 15: antiarrhythmic drugs were stopped in 12 and were started for paroxysmal AF in 3 (one patient with AF who was lost to follow-up is not included in these data).

Of the 160 patients treated, 9 (5.6%) had serious adverse events (one per patient) that occurred within 7 days postablation. Serious adverse events included AF (1), groin hematoma (1), cardiac tamponade (1), dizziness (1), acute respiratory failure (1), AFL (1), sick sinus syndrome (2), and complete AV block (1). The DSMB characterized only 4 (2.50%) serious adverse events as device and/or procedure related, specifically groin hematoma (1), cardiac tamponade 6 days postablation (1), acute respiratory failure (1), and complete AV block requiring pacemaker implantation (1). The single instance of AV block resulted from extensive medial (septal) cavotricuspid isthmus ablation and was permanent. All other adverse events, except for the AV block, resolved by the end of the study.

Discussion

Short-term safety and efficacy of cryoablation of AFL

This large 160-patient study confirmed the acute safety and efficacy of catheter-based cryoablation for treatment of cavotricuspid isthmus–dependent AFL. Acute success, defined as bidirectional cavotricuspid isthmus block, was achieved in 87.5% of patients. This is similar to published studies using large-tip RF ablation catheters with high-

power generators, with reported results ranging from 88% to 93%.[3,4] Only 4 (2.5%) patients in this study suffered serious adverse events that were ascribed to the procedure or investigational device, also comparable to the rate described in published studies of RF ablation.[3,4]

Long-term efficacy of cryoablation of AFL

By strict event monitoring, long-term efficacy of catheter-based cryoablation in preventing AFL recurrence was 81.6%. This analysis, by defining any apparent episode of AFL during follow-up as a failure of catheter-based cryoablation, may have been excessively strict compared to previous studies with respect to the clinical relevance of documented arrhythmic events. By considering clinical evidence of AFL recurrence in addition to event recordings of AFL recurrence, the long-term efficacy was 90.5%. This is similar to results from previously published studies of RF catheter ablation using clinical evidence of AFL recurrence, with efficacy ranging from 87% to 97%.[3,4] Thus, determination of long-term success by event recordings alone may have identified episodes of AFL that recurred only once during follow-up and did not lead to a change in therapy, or it may have identified arrhythmic episodes as apparent AFL that were considered by the investigator to represent AF, atrial tachycardia, or another phenomenon mimicking AFL.

Antiarrhythmic drug use

Reduction of antiarrhythmic drug use was observed during follow-up. Twenty-five percent of patients taking antiarrhythmic drugs for suppression of AF actually stopping the drugs because they were no longer required. This is consistent with previous observations suggesting that ablation of the cavotricuspid isthmus for type 1 AFL reduces recurrence of AF in some patients.[13]

Potential safety advantages of catheter-based cryoablation compared with RF catheter ablation

Catheter-based cryoablation may have specific advantages over RF catheter ablation, including greater safety[14] as a result of catheter stability during ablation due to adherence to myocardial tissue, reduced risk of systemic embolization, lower risk of thrombus formation and endothelial disruption,[6–10] and lower risk of myocardial perforation due to preservation of tissue architecture.[9] In addition, catheter-based cryoablation may produce less pain, as shown in small randomized clinical studies in which catheter-based cryoablation was associated with less perceived pain during ablation of the cavotricuspid isthmus for AFL compared with RF catheter ablation.[8,10–11] Nonetheless, two major serious adverse events that occurred during this study, specifically, complete AV block and pericardial effusion with tamponade, were determined by the DSMB to be related to the ablation procedure or the investigational device. In the case of AV block, the operator performed extensive ablation near the septal side of the cavotricuspid isthmus, which is known to increase the risk of AV block with RF catheter ablation as well. No other cases of even transient AV block were noted in this study, suggesting that this serious adverse event likely was due to extensive ablation at an inappropriate location, and that AV block can occur even with catheter-based cryoablation if care is not taken to avoid the septal area. In the case of late pericardial effusion and tamponade, this is a known complication of RF catheter ablation and could be related to some aspect of the ablation procedure, such as right ventricular puncture, and not to the investigational catheter-based cryoablation device. Nonetheless, care should be taken during catheter positioning with this device, especially in view of its larger 10Fr size.

Study limitations

A potential limitation of this study is the lack of randomization between catheter-based cryoablation and RF catheter ablation. A randomized comparative study would have directly compared the safety and efficacy of catheter-based cryoablation with RF catheter ablation. Nevertheless, it is unlikely that such a comparison would have yielded statistically significant differences, as published studies using large-tip ablation catheters and high-power RF generators show generally similar safety and efficacy. Although the follow-up duration in this study was similar to that in published studies of large-tip RF catheter ablation catheters for ablation of AFL,[3,4] it is known that AFL may recur after 6 months and consequently might be missed by this study design, thereby reducing overall success rates.

Conclusion

Catheter cryoablation of AFL in this study was highly effective in short-term and in long-term follow-up over 6 months. The occurrence of serious adverse events appears similar to that observed with RF catheter ablation. Catheter-based cryoablation may have specific safety advantages over RF catheter ablation and may be associated with less perceived pain during ablation.

Appendix CAFÉ trial investigator list

Investigator	Site name and location
Vijendra Swarup, MD	Arizona Arrhythmia Consultants, P.L.C., Phoenix, AZ
James Daubert, MD	University of Rochester Medical Center, Rochester, NY
Gregory Botteron, MD	Metro Heart Group, St. Louis, MO
Roy John, MBBS, PhD	Lahey Clinic, Burlington, MA
Jazbir Sra, MD	Aurora Health Care, Milwaukee, WI
Jack Kron, MD	Oregon Health & Science University, Portland, OR
John Miller, MD	Indiana University, Krannert Institute, Indianapolis, IN
Mark Niebauer, MD	University of Nebraska Medical Center, Omaha, NE
Raul Weiss, MD	Midwest Cardiology Research Foundation, Columbus, OH
Thabet Al-Sheikh, MD	Cardiology Consultants, Pensacola, FL
Robert Hoyt, MD	Iowa Heart Center, Des Moines, IA
David Callans, MD	University of Pennsylvania, Philadelphia, PA

Appendix (continued)

Investigator	Site name and location
Donald Rubenstein, MD, PhD	Arrhythmia Consultants, P.A., Greenville, SC
Gregory K. Feld, MD	University of California Medical Center, San Diego, CA
Charles Athill, MD	San Diego Cardiac Center, San Diego, CA
Eric Johnson, MD	The Stern Cardiovascular Center, Germantown, TN
William Miles, MD	Southwest Florida Heart Group, Ft. Myers, FL
Peter Zimetbaum, MD	Beth Israel-Deaconess Medical Center, Boston, MA
Kalyanam Shivkumar, MD, PhD	University of California, Los Angeles, CA
Andrew Corsello, MD	Maine Medical Center, Portland, ME
Arjun Sharma, MD	Regional Cardiology Associates, Sacramento, CA
Michael Kwasman, MD	Deaconess Medical Center, Spokane, WA
Abraham Kocheril, MD	Carle Heart Center, Urbana, IL
Tariq Salam, MD	Cardiac Study Medical Center, Tacoma, WA

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