

INTERVENE
INDIAN TRIAL OF ENDOCARDIAL VENTRICULAR SUBSTRATE ABLATION
TO PREVENT RECURRENT VT EVENTS

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NCT02301390

Document Date: April 22, 2014

INTERVENE

INDIAN TRIAL OF ENDOCARDIAL VENTRICULAR SUBSTRATE ABLATION TO PREVENT RECURRENT VT EVENTS

**A prospective, multi-center, unblinded,
randomized trial**

PROTOCOL SIGNATURE PAGE

Indian Trial of Endocardial Ventricular Substrate Ablation to PreEvent RecurreNt VT Events (INTERVENE)

A prospective, multi-center, unblinded, randomized study to evaluate the safety and effectiveness of adjuvant catheter ablation in post-MI patients who have survived a VT/VF arrest, but cannot afford ICD implantation.

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational device and the conduct of the study according to 21 CFR parts 50, 54, 56 and 812, to GCP as described in ICH guideline E6 and to hospital IRB/ethics committee requirements.

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Clinical Site

Principal Investigator Signature

Date

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Printed Name**

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PROTOCOL SUMMARY

Title: **Indian Trial of Endocardial Ventricular Substrate Ablation to Prevent Recurrent VT Events (INTERVENE)**

Objective: The objective of the INTERVENE trial is to determine the role of catheter-based VT ablation in the prevention of recurrent VT in post-MI patients who survive a life-threatening VT/VF event (that is, AVID / CASH / CIDS criteria) but cannot afford an implantable defibrillator. Patients will be randomized to either Amiodarone (usual therapy) or Amiodarone plus catheter ablation.

Design: This study is a prospective, multi-center, unblinded, randomized (1:1) clinical trial that will compare two treatment strategies. Subjects will be randomized to either an Amiodarone control group or an Amiodarone + catheter ablation study group. Subjects will only be eligible for this study if they: i) have had a prior ventricular arrhythmic event (VT/VF), ii) have a history of a myocardial infarction, and iii) cannot afford the cost of an ICD. Once randomized, the ablation group will undergo a strategy of catheter-based VT substrate modification. Follow-up will be conducted in regular intervals over a 24 month period.

Enrollment: 136 subjects (68 control group, 68 study group).

Clinical Sites: 5-12 sites in India

Time Course: Initial enrollment: Q4 2008
Last enrollment: Q2 2015
Last 24-month follow-up: Q2 2017

Subject Description: Eligible subjects include those who have sustained a previous MI (at least 1 month prior) *and* have survived a VT/VF event that would mandate the placement of an ICD. However, eligible patients cannot afford an ICD, and would instead be treated solely with chronic Amiodarone therapy.

Study Group: The subjects in this group will receive treatment with oral Amiodarone treatment as per usual medical therapy. Additionally, this group will undergo electroanatomic mapping to delineate the endocardial infarct margins (CARTO, Biosense Webster, Inc). Substrate modification will be performed using one or more of a

number of acceptable substrate mapping strategies (e.g., targeting the exit sites of induced VTs, targeting late potentials within the scar, etc.) using a saline-irrigated radiofrequency mapping/ablation catheter (NaviStar™ ThermoCool® catheter, Biosense Webster, Inc).

Control Group: Subjects in the control group will receive treatment with oral Amiodarone treatment as per usual medical therapy (outlined in the protocol).

Primary Endpoint: All-cause mortality + Cardiac Arrest + Sustained VT

Secondary Endpoints:

1. Proportion of subjects that die within a) 30 days, or b) by the end of the study (~24 months).
2. Total number of ventricular arrhythmic events, compared between the 2 treatment arms.
3. Differences in LV ejection fraction between paired measurements recorded at baseline and 3 months for each patient will be used to test for significant differences between the two treatment arms.

Primary Analytical Analysis: Intent to treat analysis

Secondary Analytical Analysis: Per protocol analysis

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Study Sponsor: Vivek Reddy, MD, Icahn School of Medicine at Mount Sinai

Study Funding Agency: Biosense Webster Inc.

TABLE 1. SCHEDULE OF TREATMENTS AND TESTS

	Baseline	Ablation Procedure*	Discharge	3, 6, 9, 12, 18, 24Months
Type of visit	Office	Hospital		Office
Informed Consent	X			
Brief History & Physical	X		X	X
12-lead ECG	X		X	X
Randomization	X			
Hospital Admission		X		
EP Mapping & Ablation		X*		
Warfarin		X 4-6 weeks		
Transthoracic echocardiogram	X		X	3, 24 month visit
Medications	X	X	X	X
Adverse Events		X	X	X

* The ablation procedure must be performed during the 2-month “blinking” period of Amiodarone loading. Multiple ablations may be performed within the initial hospitalization, without constituting treatment failure. Ablation procedures will be done only at principal investigators and not in satellite sites.

INTRODUCTION

2.1 Background

Sudden cardiac death (SCD) accounts for approximately 50% of all cardiac death, representing an estimated annual incidence ranging from 250,000 to 350,000 cases in the United States.ⁱ The pathophysiologic mechanism for sudden death in the majority of these patients is thought to be ventricular tachycardia (VT) related to coronary artery disease (CAD), which can then degenerate to ventricular fibrillation (VF). Patients who survive an initial episode of VT/VF are prone to an extremely high incidence of recurrent life-threatening events (~25% at one year).ⁱⁱ Even in patients without a history of VT/VF, the presence of CAD and left ventricular (LV) dysfunction confers a two-year mortality rate of 22%.ⁱⁱⁱ If VT is inducible at electrophysiological testing, the two-year mortality is ~30%.^{iv, v}

The pathogenesis of VT in the setting of CAD is reentry in the area of the scarred myocardium.^{vi, vii} After an MI, the tissue can be broadly divided into three zones: the dense scar, the surrounding live myocardial tissue, and the intervening border zone. After a myocardial infarction (MI), the “border zone” between dense scar and live tissue contains electrically-active live myocardial fibrils interspersed in areas of infarcted, fibrotic tissue—setting the stage for local reentrant circuits that result in VT (**Figure 1**).

The use of antiarrhythmic medications (AADs) to suppress the occurrence/recurrence of VT/VF in these high-risk patients has been mostly disappointing. In large clinical trials, most AADs have not only proved to be inefficacious, but to actually increase mortality.^{viii, ix, x, xi, xii, xiii, xiv, xv} The one potential exception appears to be Amiodarone: one study suggests some mortality benefit (GESICA), while others suggest that Amiodarone provides significant antiarrhythmic benefits without a change in mortality (EMIAT, CAMIAT, SCD-HeFT). However, even the use of Amiodarone is plagued with multiple organ toxicities, ranging from pulmonary fibrosis to hepatitis, and thyroid dysfunction.^{xvi}

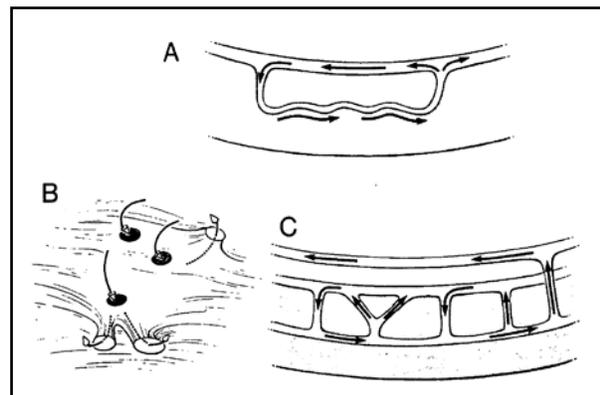
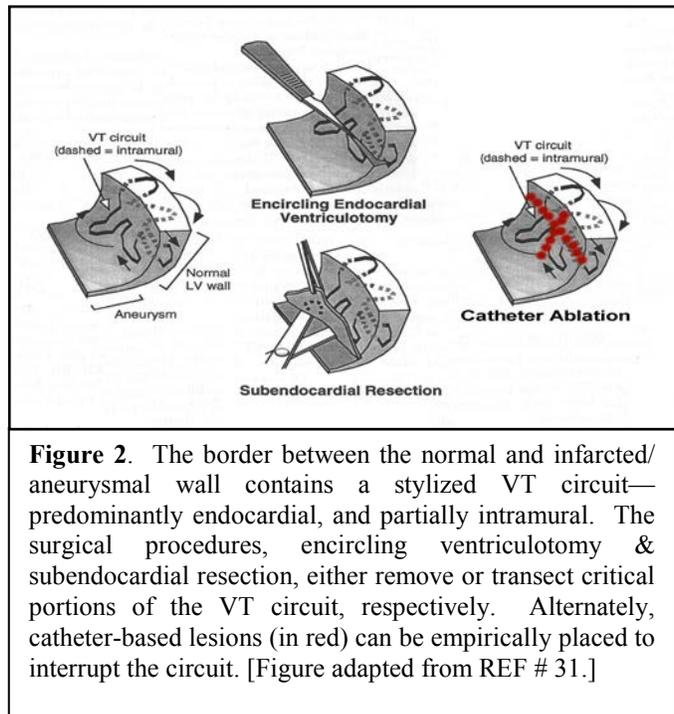


Figure 1 Instead of a single bundle of myocardium forming the tachycardia circuit (A), there is an extensive sheet of surviving myocardial fibers linked in the subendocardium through multiple entrance and exit points (B & C).²⁶ This accounts for multiple reentrant paths (that is, different VT morphologies) at different times all originating from the same mass of infarcted tissue. [Figure adapted from REF # 26.]

An important alternative to such questionably efficacious antiarrhythmics is the implantable cardio-defibrillator (ICD), which can accurately and effectively detect and terminate VT/VF, resulting in a significant mortality benefit in both the primary^{iii,iv,v} and secondary^{ii,xvii} prevention of sudden cardiac death. Yet, despite these beneficial results, ICD implantation cannot be considered a cure for VT. In addition, it is common for patients to experience painful high-voltage shocks secondary to recurrent ventricular arrhythmias, or to lose consciousness prior to the delivery of therapy. Moreover, the considerable cost of ICDs severely limits their availability in the developing world—where public and/or private health insurance systems are rudimentary at best, and where the incidence of coronary artery disease is four times higher than that of the developed world—highlighting the urgency of establishing an alternative therapy for post-MI patients with ventricular arrhythmias that is both accessibly and effective.

One such option may be catheter ablation of ventricular arrhythmias. It has been well described that for hemodynamically-stable VT circuits, careful ventricular mapping to identify sites critical to the maintenance of a given circuit, followed by discrete applications of catheter-based radiofrequency (RF) energy, can effectively eliminate VT.

This strategy mocks surgical approaches that have been used extensively since the late 1970s for modification of the arrhythmogenic substrate in patients with chronic myocardial infarction. Since the location of the reentrant circuit is most often located at the junction of the normal and scarred myocardium, two effective general strategies were developed over time: a) subendocardial resection—involving surgical removal of the subendocardial layer containing the arrhythmogenic substrate in this border zone,^{xviii, xix, xx} and b) encircling endocardial ventriculotomy—consisting of the placement of a circumferential surgical lesion through the border zone and, presumably, interrupting potential VT circuits (**Figure 2**).^{xxi, xxii} When performed at experienced centers, the long-term freedom from malignant VT/VF after surgery is >90%. However, the significant mortality (3-14%) and morbidity associated with this invasive procedure has curtailed its use in general practice.



The less invasive, catheter approach to substrate modification relies on electroanatomical mapping systems that create a high fidelity representation of the endocardium, allowing

for the reconstruction and electronic manipulation of an endocardial cast of the ventricular chamber that carefully delineates the normal and abnormal tissues. This is based on the observation that during normal sinus rhythm, there are distinguishing characteristics of the endocardial electrogram (EGM) of normal and abnormal tissue: abnormal tissue manifests a lower voltage amplitude, prolonged EGM duration, and the presence of late and fractionated potentials.^{xxiii,xxiv,xxv} Marchlinski and colleagues reported in a seminal study that by using a substrate-mapping strategy, catheter-based RF ablation lesions directed in a linear fashion were effective in controlling scar-related drug-refractory unstable VT.^{xxvi} Furthermore, using this high-density electroanatomical mapping 1) this strategy can be utilized to localize the arrhythmogenic substrate in the majority of patients with a history of myocardial infarction and sustained ventricular tachyarrhythmias, and 2) RF ablation using an irrigated-tip ablation catheter can be effectively and safely used to modify the arrhythmogenic substrate to render VT non-inducible even in the presence of multiple VT morphologies.^{xxvii}

The favorable results in these non-randomized reports prompted the initiation of SMASH-VT (Substrate Mapping & Ablation in Sinus Rhythm to Halt Ventricular Tachycardia Trial), a prospective randomized clinical trial to objectively assess the clinical utility of substrate ablation of scar-related VT. This trial was a randomized-controlled trial examining the role of substrate mapping and RF ablation in the primary prevention of ICD shocks in patients presenting with clinically life-threatening VT/VF. That is, patients with a history of MI, and who survive an episode of VT/VF are at high-risk for recurrent VT and thus treated with ICDs (in essence, these patients meet AVID/CIDS/CASH criteria). In normal clinical practice, these patients are not routinely treated with adjuvant medications because of their proarrhythmic potential and side effects. In addition to an ICD and routine clinical care, these patients were additionally randomized in SMASH-VT to substrate-based catheter ablation. This catheter ablation group underwent electroanatomic mapping to delineate the endocardial infarct margins (CARTO, Biosense-Webster, Inc). Substrate modification was then performed targeting the exit sites of induced VTs and/or late potentials within the scar using standard or irrigated radiofrequency ablation catheters.

As published in late 2007,^{xxxvi} the 30-day post-ablation mortality was zero, and there was no significant change in ventricular function or functional class during follow up. During an average follow-up of 22.5±5.5 months, appropriate defibrillator therapy (anti-tachycardia pacing and shocks) occurred in 21 control (33%) and 8 ablation (12%) patients (p=0.007 by the log rank test). Of these, appropriate defibrillator shocks alone occurred in 20 control (31%) and 6 ablation (9%) patients (p=0.003). Mortality was not increased in the ablation arm (control 17%, ablation 9%; p=0.29); indeed, there was a trend to decreased mortality in the ablation arm. Thus, the SMASH-VT study revealed several important points: 1) adjuvant substrate based catheter ablation is feasible in this patient population, 2) use of a saline-irrigated RF ablation catheter for this ablation strategy is safe, and 3) this strategy decreases subsequent ICD therapies in post-myocardial infarction patients receiving defibrillators for the secondary prevention of sudden death.

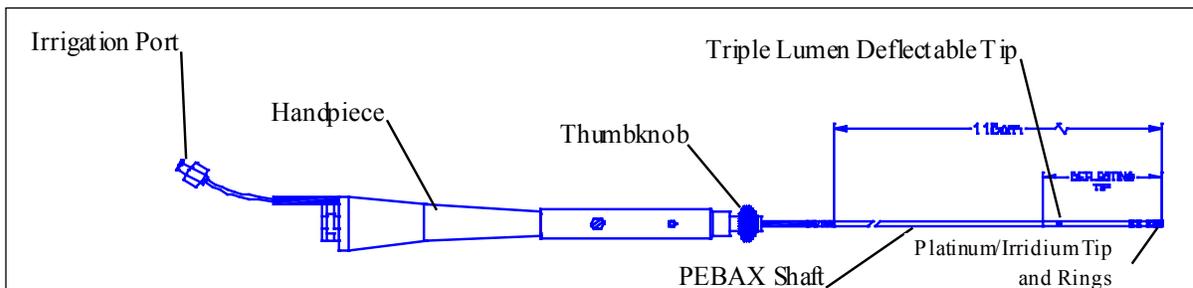
The favorable results of SMASH-VT, combined with considerable technical and scientific improvements in catheter ablation of scar-related VT, also raise the possibility that the

therapeutic benefit of ablation may be extrapolated to similar patients in the developing world, who have had an MI and have survived a ventricular arrhythmic event, but are unable to afford an ICD. This is of particular importance because such patients are typically treated with chronic Amiodarone therapy—a strategy with an unestablished mortality benefit and significant side effects.

We therefore propose a randomized clinical trial, in which India—a nation with a population of 1.2 billion—will serve as a representative model for the developing world. The study will evaluate the safety and efficacy of adjunctive catheter ablation in post-myocardial infarction patients who have additionally survived a ventricular arrhythmic event, and would be initiated on chronic Amiodarone therapy because of an inability to afford ICD therapy. Patients will therefore be randomized in an even proportion to either a) **the control group**, receiving chronic Amiodarone therapy, or **the study group**, undergoing catheter ablation of VT in addition to chronic Amiodarone therapy.

2.2 Description of Device

The NAVISTAR® THERMOCOOL® Catheter



The NAVISTAR® THERMOCOOL® catheter is a luminal, electrophysiology electrode catheter with a 3.5-mm tip electrode, three ring electrodes, a location sensor and a temperature sensor incorporated into the 7.5 F deflectable tip (see Figure 3). The 3.5-mm tip electrode serves to deliver RF current from the RF generator to the desired ablation site, and incorporates several small holes through which normal saline is passed for irrigation and cooling. A temperature sensor is embedded in the tip electrode and is mainly used to verify that the irrigation flow rate is adequate.

The tip electrode and ring electrodes are made from platinum-iridium; the spacing of the ring electrodes is 2-5-2. The deflectable tip is extruded from biocompatible polyurethane and is comprised of three lumens: one lumen (.022”) contains a coil spring and a puller-wire; the second lumen (expanded to .033”) is used for irrigation; and the third lumen (.036”) contains the location sensor and lead wires.

The catheter body is single lumen high-torque 7.5 F shaft extruded from biocompatible PEBAX with handpiece at the proximal end. A pullwire is anchored in the tip electrode and runs through

the catheter shaft to a piston in the handpiece. A saline tube also extends from the tip, through the shaft to an irrigation port on the handpiece. The irrigation port terminates in a standard Luer-lock fitting to permit the injection of normal saline to irrigate the tip electrode.

The irrigation is typically performed using the COOLFLOW™ Irrigation Pump. This is a peristaltic pump designed for the delivery of sterile saline irrigation solution. The pump has a dual rate feature for one-touch irrigation rate change between a low flow rate (1-5 ml/min) and a high flow rate (5-60 ml/min). A large LED display indicates the flow rate selected. An optional foot pedal can be used to initiate high flow irrigation.

The catheter tip is deflected via the pullwire. The piston in the handpiece is attached to the pullwire and is operated by a thumbknob. When the thumbknob is pushed forward, the tip is deflected (curved). When the thumbknob is pulled back, the tip straightens. The shape of the curve depends on the deflectable tip length (2"-3"). The high-torque shaft allows the plane of the curved tip to be rotated to facilitate accurate positioning of the catheter tip at the desired site, while the deflectable tip feature allows physicians to maneuver the catheter to perform both the prerequisite mapping and placement of the electrode tip for ablation. A compression coil translates the force of deflection onto the piston without buckling the catheter shaft.

The usable length of the NAVI STAR® THERMO COOL® catheter is 115 cm. The catheter is provided sterile.

The NAVI STAR® THERMO COOL® catheter is designed to work with the CARTO™ Cardiac Electrophysiological Mapping System (CARTO™ system) to provide the user with real-time anatomical and electrophysiological information. The CARTO™ system consists of a location positioning sensor embedded in the tip of the NAVI STAR® THERMO COOL® catheter, an external reference device (REF STAR™), an external magnetic field generator located underneath the subject (locator pad), a post-processing graphical display unit (CARTO™), and a junction box which serves to connect the catheters to the processing unit and to the RF generator.

The locator pad is placed beneath the operating table and includes three coils that generate ultralow magnetic fields. When the catheter is moved within this magnetic field, the currents generated within the positioning sensor represent movement in three dimensions. The spatial and temporal characteristics of the sensed magnetic fields contain the information necessary to determine the location (x, y, and z) and orientation (roll, yaw, and pitch) of the catheter. The resolution of the location capabilities of the system has been shown to be < 1mm in both *in vitro* and *in vivo* studies.

This information enables tracking of the tip of the mapping catheter within the heart, enabling navigation of the catheter independent of the use of fluoroscopy. Signals generated within the location sensor are transmitted through a printed circuit board (PCB) in the catheter handpiece to the main processing unit, via the junction box. The 3D geometry of the chamber is reconstructed in real time and the color-coded electrophysiological information obtained by the sensing electrode can be superimposed on the anatomical map.

3. STUDY OBJECTIVE, ENDPOINTS, AND DESIGN

3.1 Objective

The objective of this study is to compare Amiodarone plus substrate-based VT ablation to Amiodarone (usual therapy) for all-cause mortality, including cardiac arrest and sustained VT, in patients with recurrent VT post-MI who have survived a life-threatening VT/VF event (that is, AVID / CASH / CIDS criteria) but cannot afford an implantable defibrillator.

3.2 Endpoints

3.2.1 Primary Endpoint

The primary endpoint of this study is freedom from all-cause mortality, sustained VT and cardiac arrest, at 24 months.

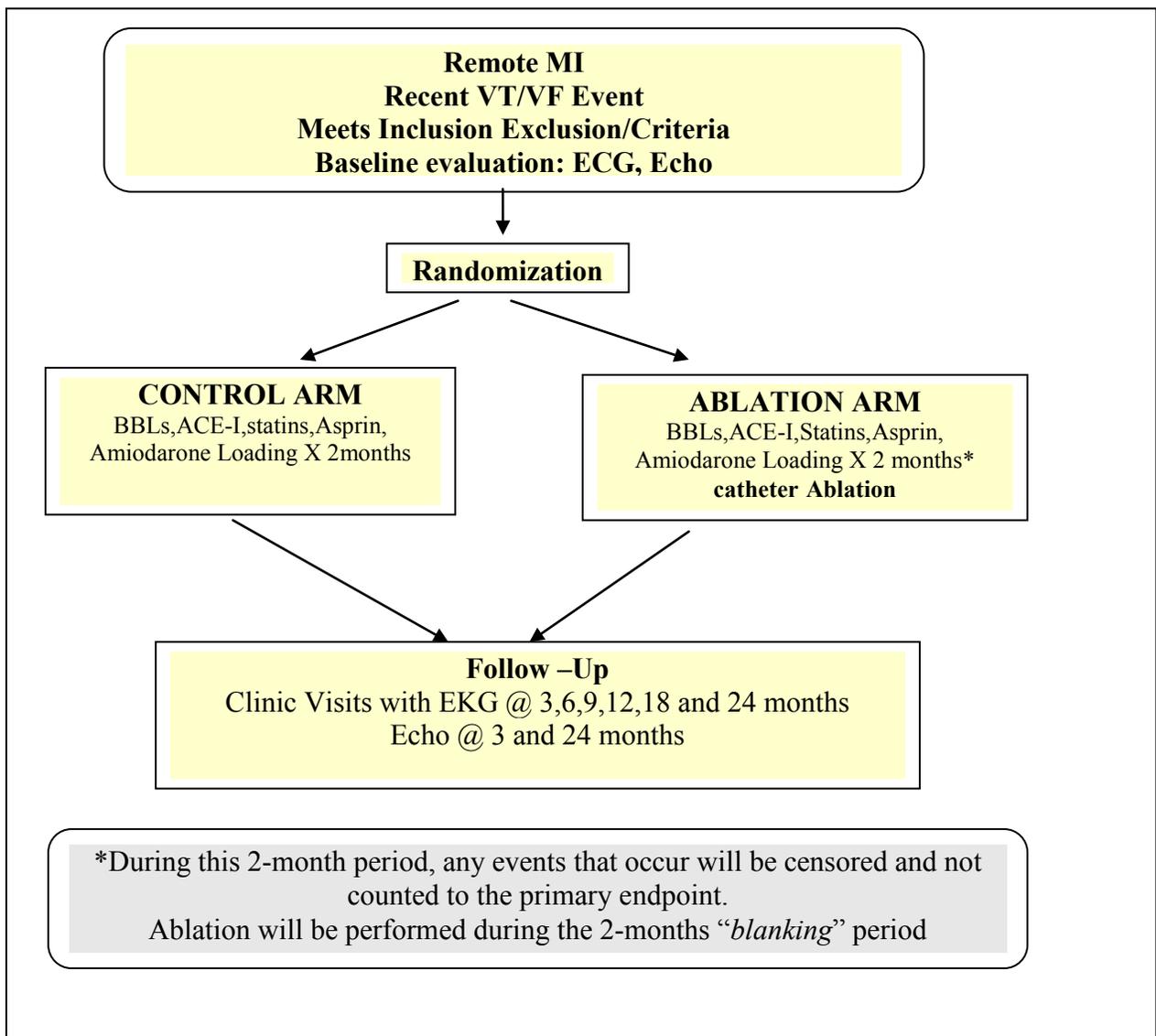
3.2.2 Secondary Endpoints

The secondary endpoints in this study are:

1. Proportion of subjects that die within 30 days or die by 24 months.
2. Total number of ventricular arrhythmic events, compared between the 2 treatment arms.
3. Differences in LV ejection fraction between paired measurements recorded at baseline and 24 months, for each patient will be used to test for significant differences between the two treatment arms.

3.3 Study Design

This is a prospective, multi-center, unblinded, randomized, trial which will randomize (1:1) 136 post-MI subjects who have survived a recent VT/VF episode, thereby mandating ICD implantation. However, these patients are unable to afford an ICD and thus would receive medical therapy with chronic Amiodarone therapy. This study will take place at 5-15 Indian sites, and will compare chronic Amiodarone therapy alone (control group) and catheter ablation + chronic Amiodarone therapy (study group). Additionally, the study group will undergo a strategy of substrate modification or VT ablation with a saline-irrigated radiofrequency ablation catheter. Follow-up will be conducted in regular intervals over a 24 month period. All physicians participating in this study are expected to have previous experience using NaviStar™ ThermoCool® catheter.



3.4 Analysis Population

The primary and all secondary endpoints will be analyzed on an intent-to-treat basis for all enrolled patients. Patients who qualify for the study by medical history and who provide consent will be included in the primary analysis population, regardless of the actual sequence of treatments.

4.0 PROTOCOL

4.1 Inclusion Criteria

Candidates will be included in the study if **all** of the following conditions apply.

1. ≥ 18 and ≤ 85 years of age
2. History of a remote MI (≥ 1 month)
3. Survival of a ventricular arrhythmic event (VT/VF) that would mandate placement of an implantable cardioverter-defibrillator (ICD)
 - [Clarification] Patients who experience a ventricular arrhythmic event (VT/VF) while already being treated with Amiodarone (100-200 mg/day) are not excluded from the study. This is permitted provided that the patient had been treated with Amiodarone for at least 2 months prior to experiencing the index VT/VF event. These patients are randomized to either a higher dose of Amiodarone (e.g., 100mg/day \rightarrow 200mg/day or 200mg/day \rightarrow 400mg/day) or a higher dose of Amiodarone plus catheter ablation.
4. Patient cannot afford an ICD and thus has been planned for treatment with Amiodarone (or an increased dose of Amiodarone)
5. Ability to understand the requirements of the study
6. Willingness to adhere to study restrictions and comply with all post-procedural follow-up requirements

4.2 Exclusion Criteria

Candidates will be excluded from the study if **any** of the following conditions apply.

1. Patients with NYHA class IV congestive heart failure
2. Prior ablation for a ventricular arrhythmia
3. Presence of an LV thrombus
4. Contraindication to anticoagulation
5. Inability to access the endocardium because of mechanical mitral and aortic valve
6. Life expectancy < 1 year for any medical condition

4.3 Patient Enrollment

4.3.1 Screening Procedure

The investigator or designated member of the research team will approach the patient to obtain written informed consent. The background of the proposed study and the potential benefits and risks of the study will be explained to the patient. The patient must sign the consent form prior to enrollment. This form must have prior approval of the study site's Investigational Review

Board (IRB) or Ethics Committee (EC) prior to obtaining patient consent. Failure to obtain informed consent renders the patient ineligible for the study.

4.3.2 Informed Consent

The investigator or designated member of the research team will approach the patient to obtain written informed consent. The background of the proposed study and the potential benefits and risks of the study will be explained to the patient. The patient must sign the consent form prior to enrollment. This form must have prior approval of the study site's Investigational Review Board (IRB) or Ethics Committee (EC) prior to obtaining patient consent. Failure to obtain informed consent renders the patient ineligible for the study.

4.3.3 Randomization Procedure

Randomization will be done using treatment allocation list provided by the sponsor. The sequence of allocation is at random. The allocation list will be in possession with a designated person in the National central site.

4.4 Study Procedures

4.4.1. Pre-randomization Procedures

After the patient provides written informed consent, the following data will be collected and examinations and tests performed (if required data has not been previously collected within the specified window):

- Relevant history and medical exam
- 12-lead ECG
- Baseline Echocardiogram (performed within 3 months prior to randomization)

Once the above information has been obtained and the inclusion and exclusion criteria have confirmed the patient's continued eligibility, randomization will then be performed. The patient will be randomized into one of the two groups:

1. Control Group: Amiodarone loading will be initiated in these subjects. No further treatment is required as a part of the study. Further follow-up will be as detailed in this protocol. Any VT/VF events that occur in the 2-month blanking period designated for Amiodarone loading will not be included in the analysis.
 - Patients who experience a ventricular arrhythmic event (VT/VF) while already being treated with Amiodarone (100-200 mg/day) for at least 2 months will receive a higher dose of Amiodarone (e.g., 100mg/day → 200mg/day or 200mg/day → 400mg/day). Again a 2-month blanking period will be used.
2. Study Group: Amiodarone loading will also be initiated in these subjects. In addition, this group will undergo electrophysiology study with subsequent radiofrequency ablation of their arrhythmogenic substrate, within 2 months of Amiodarone initiation. Any VT/VF events that occur in the 2-month blanking period designated for Amiodarone loading will not be included in the analysis.

4.4.2. Recruiting sites: Patients for the study would be recruited at principal and satellite sites. Principal sites are the sites that have CARTO™ facility. Satellite sites are sites without CARTO™ and would refer patients for ablation procedures randomized to ablation arm to geographically proximate principal sites for procedures. All other study related procedures including follow up would be done at the respective satellite centers as for patients in control arm.

Sites identified for enrollment of the patients are the following:

Principal sites

1. CARE Hospitals, Hyderabad, Nagpur and Bhubaneswar.
2. CARE Institute of Medical Sciences, Ahmedabad, Gujarat
3. KEM hospital, Mumbai, Maharashtra
4. Jawaharlal Institute for Postgraduate Medical Education and Research, Puducherry, Tamil Nadu
5. Amrita Institute of Medical Sciences, Cochin, Kerala

Satellite Sites

1. Baroda Heart Institute, Vadodara
2. Poona Hospital and Research Centre, Pune, Maharashtra
3. Avanti Institute of Cardiology Pvt.Ltd., Nagpur, Maharashtra
4. Sri Ramachandra Medial Centre, Porur, Chennai, Tamil Nadu
5. Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh
6. Calicut Medical College, Calicut, Kerala

4.4.3 Ablation Procedure (study group only)

- Patient anesthesia will be administered according to standard EP lab protocol.
- Arterial and venous access will be achieved through cannulation of the right and/or left femoral arteries and veins as determined by the treating electrophysiologist.
- Electrophysiology study will be performed using up to triple ventricular extrastimuli from the right or left ventricle in standard fashion. Before VT is deemed non-inducible, the following stimulation attempts must be performed: i) stimulation at ≥ 2 ventricular sites (e.g. RV apex + RV outflow tract, or RV apex + LV), ii) stimulation at ≥ 2 drive cycle lengths, and iii) triple extrastimuli. Of course, if VT is inducible early in the stimulation protocol, the remaining protocol does not need to be completed if deemed inappropriate from a safety perspective by the physician.
- Twelve lead electrocardiograms will be obtained for all inducible ventricular arrhythmias. An inducible sustained VT is defined as a monomorphic VT lasting >15 seconds or requiring termination with pacing or cardioversion.

- In order to minimize the chance of post-procedural pulmonary edema, the fluid status (I/O, left atrial pressure if a transseptal sheath is employed, etc.) must be carefully monitored. Also, a Foley urinary catheter is strongly recommended for patients with an LVEF < 25% or a clinical history of Class III congestive heart failure. Hemodynamic support and type of sedation are at the investigator's discretion.
- a. **Electroanatomic mapping**
 - Catheter access to the LV includes retrograde aortic and transseptal approaches. Either or both approaches are acceptable. The RV might also require mapping in certain patients: e.g., interventricular septal wall involvement.
 - All patients will undergo electroanatomic mapping using CARTO (Biosense Webster, Inc) and a saline irrigated mapping/ablation catheter (NaviStar™ ThermoCool® catheter, Biosense Webster, Inc). Other Navistar catheters may be employed during the mapping procedures, but only the ThermoCool catheter may be used for ablation.
 - CARTO is a system that uses a low intensity magnetic field to localize the mapping catheter in space. The accuracy of the system has been estimated at 0.8 mm and 5 degrees. Bipolar electrograms are recorded at multiple locations in the LV endocardium using the mapping/ablation catheter in sinus or paced rhythm. Using the measured electrograms, the CARTO system will create a color electroanatomic map of the LV endocardium based on activation time (in comparison to a designated surface electrocardiographic lead) or voltage amplitude. Normal myocardium will be defined as having a voltage amplitude >1.5 mV.
 - The NaviStar™ ThermoCool® RF catheter has a 3.5mm electrode tip with a saline-irrigation cooling system. In addition to measuring bipolar electrograms, the catheter maintains low electrode-tissue interface temperatures during RF application at high powers without an impedance rise. This allows larger, deeper lesions and reduces the time and the risk of tip charring that can lead to coagulum formation and thromboembolic events.
 - During electroanatomic mapping, heparin will be given intravenously as a bolus followed by continuous intravenous infusion. Activated clotting times (ACT) will be monitored every 30-60 minutes with a target ACT value >250 seconds.
- b. **Ablation**
 - After a detailed ventricular endocardial voltage electroanatomic map is created, radiofrequency ablation will then be performed using the NaviStar™ ThermoCool® catheter.
 - While a number of ablation strategies have been reported for substrate-based VT ablation, there is one important fundamental thematic basis to this approach – namely that a firm understanding of the location/extent of the infarcted tissue facilitates one's ability

to identify critical portions of various VT circuits to target for ablation. While there is considerable overlap, these ablation strategies can be sub-divided into two general groups: i) identifying percolations of myocardial activity within the infarcted tissue that represent putative physiologic components of the circuit, and ii) identifying and targeting putative areas of exit of the VT circuits from the infarcted tissue. These strategies can be further expanded as follows:

1. Targeting percolations of myocardial activity:

- a. Entrainment mapping: For VTs that are hemodynamically tolerable for at least a short period of time (with or without hemodynamic support), entrainment (or resetting) can be performed during the VT to identify regions of the scar that participate in the circuit. RF lesions can be delivered to these regions.
- b. Identification of diastolic potentials: For VTs that are hemodynamically tolerable for at least a short period of time (with or without hemodynamic support), diastolic potentials can be identified in the area of the scar during the VT and targeted for RF ablation.
- c. Pace-mapping can be performed to identify regions of dense scar based upon the inability of pacing stimuli to capture any myocardium at a particular site (using pulses of 2-ms duration, 10-mA amplitude, unipolar stimuli).^{xxviii} These areas of “electrically unexcitable scar” may delineate isthmuses for VT circuits that can be transected with ablation lesions connecting these various dense scar regions to each other and to fixed anatomical barriers (such as the mitral valve). Alternatively, it is possible to target channels of high voltage surrounded by lower voltage in regions of confluent low voltage < 1.0mV.
- d. Ablation of late potentials: Another strategy involves targeting of split/late potentials based on the observation that the late and long-duration electrograms, despite a low specificity, were highly sensitive for identifying VT circuits.^{xxix} This criterion requires recording high-frequency EGMs with multiple components separated by an isoelectric line. It is certainly true that targeting these EGMs would invariably result in ablation of bystander sites that may not be operative in any VTs (e.g. a “dead-end” pathway); but, this approach has the advantage of placing ablation lesions at regions far from the normal tissue. Of note, fractionated and late EGMs are infrequently identified during sinus rhythm. One potential reason is that overlapping of EGMs or a particular orientation of a line of block with respect to the activation wavefront may preclude the identification of multiple components during sinus rhythm. The sensitivity of identifying these components during catheter mapping may be increased by changing the propagation wavefront during catheter mapping by RV pacing or LV pacing (for example, from within a ventricular branch of the coronary sinus).^{xxx} From a practical perspective, this can be accomplished by pacing whenever the EGM at the site being mapped is suggestive for, but does not conclusively identify a late potential site.

- e. Ablation of sites of Latency: The alternative, “inverse”, strategy to identification of late potentials is to stimulate directly within the infarcted tissue at target sites of questionable significance (that is, sites at which it is difficult to determine if a late potential is present). Because of the limited myocardial tissue depolarized, activation of the isthmus contributes negligibly to the surface electrocardiogram until the wavefront of activation exits to the normal myocardium – thereby producing the observed QRS complex. Therefore, pace-mapping from a site more proximally-located within the isthmus should produce a QRS complex similar to the VT QRS morphology, albeit with a longer stimulus-to-QRS interval. Accordingly, the duration of the stimulus-to-QRS interval can serve as a surrogate to late potentials and can be targeted for catheter ablation to empirically eliminate VT circuits.^{xxxi}

2. Targeting putative VT exit sites:

- a. Pace-mapping: For hemodynamically unstable VTs, pace mapping will be performed in the area of the scar to identify the exit sites of the VT. Once the substrate map is constructed, pace-mapping during sinus or paced rhythm can be performed to localize the exit site of each inducible monomorphic VT. When a site is found at which the paced QRS matches the QRS during VT in 12 leads, this exit site will be marked on the CARTO map. Linear ablation lesions that bisect this site can be made: one from the center of the substrate through the exit site, and the second, perpendicular to the first line at the location of the exit site. Each line will be made up of multiple sequential lesions placed 5-10 mm apart. Of note, while at least one of these lines (parallel or perpendicular to the scar border) should be placed when employing this strategy, the physician may elect to omit one or the other line if deemed unnecessary. Also, in patients with LVEF < 25% and/or severe CHF, particular care will be taken to minimize the number of lesions placed at the borders of the scar in order to minimize any potential adverse effect on left ventricular function. Especially in these patients, targets deep within the scar such as late potentials can be targeted for ablation (these lesions are less likely to have any significant adverse effect on LV function).
 - b. Encircling ablation procedure: The placement of catheter-based ablation lesions completely around the scar (mimicking the surgical partial encircling endocardial ventriculotomy procedure) may be employed – particularly in the setting of a smaller identifiable scar with poor pacemap sites and no late potentials.
- Which ablation targets/strategy should be used? The relative efficacy of these various criteria to guide identification and targeting of the “arrhythmogenic” portion of the scar is unknown. However, certain general principles can be stated. Trying to minimize the number of ablation lesions placed at the border zone would be advantageous in minimize adverse effect on left ventricular function. Indeed, a strategy targeting late potentials is particularly attractive in patients with depressed ventricular function or congestive heart

failure. Conversely, in patients with preserved ventricular function and small or patchy scars it not necessarily possible to identify channels of activity, and ablation lesions based in large part on pace-mapping or attempts to make a series of ablation lesions to “encircle” the scar (to empirically transect circuits at the scar borders) would be appropriate.

- In order to minimize adversely affecting LV function, in general ablation lesions should be confined to areas with abnormal (<1.5 mV or fractionated) electrograms.
- During ablation, power titration should be performed as per the physician’s usual practice to avoid thromboembolic complications. One reasonable strategy includes careful power titration to achieve an impedance drop not exceeding 10%.
 1. Under no circumstances should the tip temperature exceed 45°C, preferably should stay below 42°C.
- Standard saline irrigation parameters should be used:
 1. During mapping, the flow rate should be 2 ml/min.
 2. During ablation, the flow rate should be 17-30 ml/min when using <30 Watts, and at least 30 ml/min when using ≥ 30 Watts of energy.
- As previously discussed, in order to minimize the chance of post-procedural pulmonary edema:
 1. The fluid status (I/O, left atrial pressure if a transseptal sheath is employed, etc.) must be carefully monitored
 2. A Foley urinary catheter is strongly recommended for patients with an LVEF < 25% or a clinical history of Class III congestive heart failure.
 3. IV diuresis should be considered after the infusion of 1 liter of saline through the ablation catheter.
 4. Additional hemodynamic/inotropic support may be used at the investigator’s discretion.
- Regardless of the ablation strategy used, the overall length of the procedure should not exceed a maximum time limit of 8 hours.
- Percutaneous pericardial mapping and ablation is not to be employed in this study.
- During the ablation, an intravenous heparin infusion will be maintained for a target ACT >250 seconds. ACTs will be monitored every 30-60 minutes.
- Following completion of the ablation, the heparin infusion will be discontinued. The arterial and venous sheaths will be removed and hemostasis achieved with either (or both):
 1. Manual pressure once ACT <200 sec (protamine may be used to facilitate this).

2. Percutaneous vascular closure devices may also be employed as per the institution's practice.

4.4.4. Post-procedure Hospitalization

- Post-ablation patients will be admitted overnight to a telemetry unit for monitoring. The following medication regimen will be observed:
 1. Intravenous heparin will be administered overnight. Weight-adjusted low molecular weight heparin may be given subcutaneously until the INR ≥ 2.0 .
 2. Warfarin will be initiated within the hospital and continued for at least 4-6 weeks following ablation (target INR 2-3). Alternatively, if the number of ablation lesions is minimal, aspirin treatment alone (325 mg QD) may be prescribed as per the physician's judgment.

4.5 Follow-up

Routine follow-up will be at 3, 6, 9, 12, 18 and 24 months. Each visit will consist of the following as detailed in the case report forms (see attached):

1. Review of hospitalization and ER/OFFICE visits for VF/prolonged VT
2. Documentation of medication changes
3. Documentation of interim adverse events
4. Transthoracic echocardiogram (at 3 and 24 month visits only).
5. ECG at Every Visit

5.0 STATISTICAL RATIONALE AND ANALYSIS PLAN

5.1 General Considerations

The primary objective of this study is to investigate whether catheter ablation treatment can be effective and safe in prolonging survival free from recurrent VT/VF events in post-MI patients who have survived a recent VT/VF event, and have been planned for Amiodarone therapy because of an inability to afford an ICD. The study is designed as a prospective, multi-center, unblinded, randomized (1:1) clinical trial with the goal of comparing two treatment arms: an Amiodarone control and Amiodarone + catheter study group.

The null hypothesis of principal interest is that there will be no difference at 24 months between the two treatment arms in patient survival that is free from all-cause mortality, cardiac arrest, and sustained VT after a 2-month blanking period. As secondary objectives, the study will compare the following additional measures of efficacy between the catheter-ablation treated and the non-treated groups: I) the proportion of subjects that die within a) 30 days, or b) by the end of the study (~24 months); II) the total number of ventricular arrhythmic events; III) differences in LV

ejection fraction between paired measurements recorded at baseline, 3 months and 24 months for each patient.

The primary efficacy measure will be analyzed using Kaplan-Meier methods.^{xxxii} The log-rank test will be used to test for difference in event-free survival between the two treatment groups. Treatment group differences between survival curves will be further assessed using the stratified log-rank test (stratified by primary versus secondary prevention category). Because this study involves many centers with relatively small enrollment size per center, data from all centers will be pooled for analyses. The Cox proportional hazards model will be used to further explore relationships between event-free survival in the two treatment groups and covariates of interest.

5.2 Analyses Datasets

5.2.1 *Intent-to-Treat (ITT) Analysis Set.* The ITT population will consist of all enrolled patients who have provided consent and have qualified on the basis of inclusion/exclusion criteria. All patients in the ITT population will be randomized and included in the analysis of all primary and secondary endpoints. A list of major protocol violations will be identified in the Statistical Analysis Plan (SAP). Protocol violations will be summarized by treatment and clinically-relevant demographic and baseline characteristic groups.

5.2.2 *Safety Analysis Set.* The ITT population will also be considered as the safety population. All randomized patients will be included in the analysis of safety, demographic, and baseline characteristic data.

5.3 Sample Size and Statistical Power

Sample size calculation is based on the primary hypothesis that there will be a difference in survival curves between the ICD control and the ICD + catheter ablation groups. Fifty percent of patients are expected to meet the primary endpoint in the control arm, and a 50% reduction in the primary endpoint is expected in study group patients undergoing adjuvant catheter ablation. The sample size was calculated using the log-rank test with a significance level of $\alpha=0.05$ and 80% statistical power^{xxxiii} (nQuery Advisor Version 6.0). This study is powered (at 80%) to detect at least a 30% decrease in the primary endpoint based upon the results of the SMASH-VT study^{xxxvi} and another study.^{xxxix} The required sample size is 68 patients per treatment arm, or a total sample size of 136.

Plan for Sample Size Re-estimation

A single interim analysis will be performed after one-half of patients reach a study endpoint. The group sequential approach of Lan and Demets will be used, with an O'Brien-Fleming type spending function. The critical value will be 2.96 for the interim analysis and 1.97 for the interim analysis.

As part of the group sequential monitoring plan for this trial, we will consider re-estimating the sample size at the proposed interim analysis based on the trial's conditional power at the interim

analysis. Sample size might be re-estimated if event rates were different from expected or if the effect size were different than expected. Our approach for maintaining the trial's Type I error rate should the sample size be re-estimated will be based on that described by Wassmer, which is based on pooling the p-values obtained from each of the trial's two stages through the inverse normal method. This method, which maintains the Type I error of the trial employs weights (w_1, w_2) based on the information fraction at which the single interim analysis will be performed, i.e., $w_1 = \sqrt{n_1/n}$ and $w_2 = \sqrt{(n - n_1)/n}$ (where n is the pre-determined total sample size and n_1 is the number randomized at the time of the first interim analyses (more generally, these weights would be based on the information fractions at the time of the one (or more) interim analysis). The terminal critical value will be determined by

$$\pi(p_1, p_2) = w_1 \Phi^{-1}(1 - p_1) + w_2 \Phi^{-1}(1 - p_2)$$

where p_1 and p_2 are the p-values associated with the statistical test of the primary endpoint performed using data collected during each stage (i.e., prior and subsequent to the interim analysis), $w_1^2 + w_2^2 = 1$, and $\Phi^{-1}(\cdot)$ represent the inverse-normal cumulative distribution function. The analysis informing the sample size re-estimation will be performed by an independent statistician.

5.4 Randomization

Study subjects will be randomly assigned to one of the 2 treatment arms. This will be done with pre-numbered Treatment Allocation List (random assignment of numbers) which will be in possession with the National central site. Each set will contain equal numbers of Control and Study group randomization results, in random order.

5.5 Treatment Group Comparability at Baseline

The comparability among treatment groups will be evaluated with respect to all clinically relevant demographic and baseline characteristic variables. All randomized patients will be included in the analysis of demographic and baseline characteristics.

5.6 Safety Analyses

All randomized patients will be included in the safety analyses. Descriptive statistics and listings will be generated for all safety parameters in the study. Adverse events information will be collected throughout the study and listed by patient. Summary statistics will be presented for treatment-emergent adverse events (AE) under 4 categories (as defined in section 5.0): (i) death, (ii) serious adverse event (SAE), and (iii) anticipated adverse event (ADE). Each monitored adverse event will be described in detail in the SAP and will include specification of each variable with its operational unit of measurement.

5.7 Interim and Futility Analyses

Interim and futility analyses will be performed at one year. The study will be terminated if the study demonstrates a significant mortality benefit from ablation, or conversely, significant increase in mortality with ablation.

6.0 ADVERSE EVENT HANDLING

6.1 Adverse Events

An adverse event is any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring in a subject that could be associated with the investigational product(s) that appears or worsens during a clinical study. Significant device failure may constitute an adverse event if an undesirable experience occurs.

Adverse events information will be collected throughout the study. Adverse events will be recorded on the case report forms by the investigator or designee. Event, date of onset, severity, duration, and relationship to device will be recorded on the appropriate case report form. Adverse events will be followed until they are adequately resolved, stabilized or explained. A list of adverse events, which may result from this procedure, is located in Section 6.4.

6.2 Serious Adverse Events and Death

The investigator must decide whether each event meets the definition of a “serious” adverse event. The regulatory definition of a serious adverse event is an event that is fatal or life threatening, results in persistent or significant disability, requires intervention to prevent permanent impairment/damage, or an event that results in congenital anomaly, malignancy, hospital admission or prolongation of hospitalization.

Any serious adverse event or subject death occurring during the follow-up period, regardless of cause, must be reported to the Study Principal Investigator and HCRI within one working day after the investigator first learns of the event.

6.3 Unanticipated Adverse Device Effects

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death that is caused by or associated with an investigational device. The effect must have not been previously identified in nature, severity or degree of incidence in the investigational plan. Other serious problems associated with the device that effect the rights or welfare of study subjects may also be considered UADEs.

A list of expected adverse events is provided in Section 6.4. The occurrence of expected adverse events should be reported using the appropriate CRF.

UADEs must be reported to the Study Principal Investigator, the Institutional Review Board (IRB)/Ethics Committee (EC) and the Mount Sinai Coordinating Center within one working day after the Investigator first learns of the effect.

6.4 Anticipated Adverse Events

The following ANTICIPATED EVENTS have been identified as possible complications of the electrophysiology study and VT ablation procedure with a saline-irrigated ablation catheter.

- Allergic reactions can occur to the local anesthetic, sedatives, x-ray dye, heparin, protamine, or other agents administered during the procedure.
- Arterial or venous injury including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels (risk <1%). This may result in hemorrhage, hematoma or ischemic injury to an extremity or major organ.
- Hemorrhage as a result of anticoagulation (risk <0.5%) that may require transfusion.
- Infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%). This risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.
- Radiofrequency current may cause occlusion of a coronary artery, either by direct thermal damage, spasm, or thrombosis (risk <0.5%). The risk of this complication may be higher when epicardial ablation is performed. Coronary arterial occlusion could produce myocardial infarction, angina or death. Should occlusion of a coronary artery occur for any reason, the physician will attempt to restore coronary blood flow through pharmacological, catheter and/or surgical intervention as medically indicated.
- The application of radiofrequency current close to the AV node or His bundle could damage or destroy the normal AV conduction system, producing complete heart block. Patients will be protected due to the presence of back-up pacing from the ICD. However, if this complication does occur, patients may need an addition of an atrial lead (if not already present) and upgrade of the ICD to a dual chamber device.
- A thrombus may form on the ablation electrode during the application of radiofrequency current, usually indicated by an impedance rise. The thrombus might become dislodged and embolize to produce a stroke, myocardial infarction, or other ischemic injury. The risk of an embolus is reduced by quickly terminating the application of current after an impedance rise, which limits the size of the coagulum on the electrode.
- The placement of linear lines of ablation may require a large number of RF lesions to be delivered to the left ventricle. The risk of stroke due to embolization of thrombus is approximately 1%. To minimize this risk, patients will be heparinized to an activated clotting time of greater than 250 seconds during the procedure.
- Thrombus formation on the endocardium following ablation may produce an arterial or pulmonary embolus. This risk may be reduced by the use of aspirin or other anticoagulant therapy, at the discretion of the investigator.
- Cardiac perforation may result from catheter manipulation or application of radiofrequency current (risk is <1%). This may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. Significant hemodynamic compromise can result in neurological injury or death. An increased risk of cardiac perforation may be associated with the use of saline-irrigated electrode catheter due to its creation of a larger, deeper RF lesion.
- Injury to a cardiac valve may result from catheter manipulation or the application of radiofrequency current (risk <1%). This may produce valvular insufficiency and possibly require surgical valve replacement.

- Radiation exposure during the fluoroscopic imaging of the catheters may result in an increase in the lifetime risk of developing a fatal malignancy (0.1%) or a genetic defect in offspring (0.002%).
- The risk associated with use of the saline-irrigated electrode catheter rather than the standard electrode catheter is expected to be small. The larger RF lesion size produced with this catheter could theoretically increase pain associated with RF applications and may increase the risk of cardiac rupture (in practicality, this has not been observed in clinical studies). Increased pain, however, can be managed with intravenous analgesics. Additionally, use of the cooled electrode tip catheter may reduce procedural time, fluoroscopy time and increase procedural success by increasing lesion depth and by minimizing coagulum formation that necessitates removal and re-deployment of the catheter. The risk of cardiac rupture is minimized by having experienced, thoroughly trained electrophysiologists with experience in VT ablation perform the procedures. Pulmonary edema secondary to the volume load from the saline-irrigated catheter is possible; certainly, some amount of a saline load is expected. For example, a procedure lasting 5 hours with a total of 30 minutes of RF ablation delivered would result in the delivery of 1.5 liters of fluid from the ablation catheter irrigation alone. Diuretics will be given to minimize this possibility.
- Rales, pulmonary edema, ARDS and asthmatic attack can be sequelae of aspiration pneumonia and nosocomial pneumonia. Aspiration of gastric contents can occur when subjects are intubated, and nosocomial pneumonia is well documented as the second most common nosocomial infection. It is now more common in surgical subjects than surgical-site or wound infection. Although it is not a direct comparison, in various cardiac surgical procedures, the incidence of aspiration pneumonia and nosocomial pneumonia range from 2% to 6.5%.
- Phrenic nerve can be a sequela of epicardial radiofrequency ablation.
- The electromagnetic field required to use the CARTO mapping system is extremely weak and not known to be associated with any side effects. It has been safely used with ICDs and has no known adverse effects.
- Proarrhythmia, another hypothetical risk, has not been reported with VT ablation. All patients involved in the study will be protected against potential life threatening arrhythmias with ICDs.
- Ablation could potentially worsen left ventricular function. However, the tissue being ablated in these patients will be scar tissue as identified by substrate mapping. Ablation in this scar region should cause minimal, if any, impairment of left ventricular function. Furthermore, as stated above in the Description of Treatments section, every effort will be made to place lesions within the scar, and to minimize the number of lesions placed in normal myocardial tissue.

7.0 RISK ANALYSIS

7.1 Risks

7.1.1. Electrophysiology study and ablation

- Electrophysiology study and VT ablation are associated with risks including:

1. Bleeding
 2. Vascular injury
 3. Arrhythmia
 4. Cardiac perforation
 5. Heart block
 6. Thromboembolism including stroke. Ablation in the left ventricle has an associated 0.5-1% risk of stroke (a risk that is further minimized by use of the saline irrigated ablation catheter).
- The electromagnetic field required to use the CARTO mapping system is extremely weak and not known to be associated with any side effects.
 - The placement of linear lines of ablation may require a large number of RF lesions to be delivered to the left ventricle--this may increase the risk of stroke to approximately 1%. To minimize this risk, patients will be heparinized to an activated clotting time of greater than 250 seconds during the procedure.
 - Proarrhythmia, another hypothetical risk, has not been reported with VT ablation.
 - Ablation could potentially worsen left ventricular function. However, the tissue being ablated in these patients will be scar tissue as identified by substrate mapping, and its exclusion should cause minimal, if any, impairment of left ventricular function. Furthermore, as stated above in the Description of Treatments section, every effort will be made to minimize the placement of ablation lesions in normal ventricular tissue.

7.2 Benefits

- The major potential benefit of undergoing substrate modification is the possibility of providing an alternative to ICD therapy in patient populations unable to afford it.
- Data from the preliminary study, SMASH-VT (described in part in the Introduction-Background section above), revealed a decrease in the overall mortality of patients enrolled in the ablation+ICD vs. ICD alone arms (8.3% vs. 14.12%, respectively; $p = 0.12$; unpublished observations: V.Y. Reddy, P. Neuzil & M.E. Josephson). While these data are preliminary, are not statistically significant and include patients post-ICD implantation, they do at least raise the potential for a mortality benefit from adjunctive substrate modification.

8.0 STUDY ORGANIZATION AND STUDY COMMITTEES

8.1 Principal Investigators

The Principal Investigator for this trial is Vivek Y. Reddy, MD. The National (India) lead investigator is Dr. C. Narasimhan, MD, DM.

8.2 Executive Committee

The Executive Committee will approve the final trial design and protocol issued to the Data and Safety Monitoring Board (DSMB) and the clinical sites. This committee by majority vote will also be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications by members of the Steering

Committee. The Executive Committee will also have sole discretion for stopping or otherwise modifying the trial based on the recommendations of the DSMB.

The Executive Committee includes:

Vivek Y. Reddy, MD	Principal Investigators
Andre d'Avila, MD	Associate Principal Investigators
Srinivas Dukkipati, MD	
Calambur Narasimhan, MD	

8.3 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is an independent safety oversight board. They are responsible for review of the data for safety and for making recommendations to the Operations Committee regarding endpoint analysis and any potential problems. An initial DSMB meeting will occur shortly after beginning the trial to establish a charter and set trial guidelines. Planned meetings will occur during patient enrollment per the committee's discretion, and more often as required by observed events. If the DSMB determines the trial should be stopped early either because of efficacy or safety concerns, or otherwise modified, the DSMB will prepare formal written recommendations to the Executive Committee to consider final action. Moreover, any safety concerns that the DSMB identifies will be verbally communicated to both the Executive Committee as soon as possible, prior to written documentation.

The DSMB will consist of at least one Statistician and several Cardiologists with expertise in electrophysiology. Members will not have any affiliation with the manufacturers of the ablation catheter used in the study, be participating as a study investigator or be the Study Principal Investigator of the trial.

The tentative members of the DSMB are (note that this may change with circumstances):

- Jonathan Halperin MD, Mount Sinai (Chair)
- Jacob Koruth MD, Mount Sinai
- K.K. Narayanan Namboodri MD, SCT Trivandrum
- Michael K. Parides (Statistician)
- O. Sai Satish MD, Nizam's Institute of Medical Sciences

8.4 Clinical Events Committee

The Clinical Events Committee (CEC) will be responsible for adjudicating all clinical events associated with the primary and secondary endpoints and significant device related complications reported during the study. The CEC membership consists of invasive cardiologists and non-invasive cardiologists, some of whom will have a specialty in

electrophysiology and arrhythmia management, who are not participating in the study and do not sit on other similarly related study committees.

9.0 ETHICAL AND REGULATORY CONSIDERATIONS

9.1. Role of the Coordinating Center

As principal investigator and study sponsor of this clinical study, Vivek Y. Reddy, MD assumes the overall responsibility for the conduct of the study, including assurance that the study meets national and institutional guidelines for study conduct. In this study, Vivek Y. Reddy, MD will have certain direct responsibilities and will delegate other responsibilities to his staff at the Data Coordinating Center at Icahn School of Medicine at Mount Sinai. Together, the coordinating center will: 1) ensure adherence to the national and institutional regulations and the sponsor general duties; 2) develop and distribute protocols and case report forms; 3) coordinate data organization; 4) forward adverse event reporting to the DSMB; 5) perform statistical analyses.

9.2. Maintaining Records

The Data Coordinating Center will maintain copies of correspondence, data, adverse device effects and other records related to the clinical trial.

9.3. Site Record Retention Policy

All clinical sites will maintain study records for two years after research termination.

9.4. Informed Consent and Institutional Review Board (IRB) / Ethics Committee (EC)

All patients must provide written informed consent in accordance with the local clinical site's IRB/EC. A copy of the consent form from each center must be forwarded to HCRI for review and approval. The principal investigator at each site must provide HCRI with a copy of the clinical site's IRB/EC approval for the protocol. Yearly approvals for the continuation of the trial at each clinical site must also be forwarded to HCRI. The IRB/EC of the principal sites will have the dual responsibility for overseeing the activities of both the principal site and the respective satellite site (s) attached to them.

9.5. Patient Confidentiality

Patient confidentiality will be maintained throughout the clinical study in a way that assures that data can always be tracked back to the source data. For this purpose, a unique subject identification code (ID number and patient name code) will be used that allows identification of all data reported for each subject.

Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidential and that the patient's privacy is guaranteed.

10.0 STUDY MANAGEMENT

Central Site in India: CARE Hospital, Banjara Hills, Hyderabad will be the National Central Site. The Central Site will be responsible for the coordination of study activities of the various sites in India.

10.1. Study Data Collection and Processing

The Case Report Form (CRF) is an integral part of the study and subsequent reports. The CRF must be used to capture all study data recorded in the patient's medical record. The CRF must be kept current to reflect patient status during the course of the study. Only a patient identification number and patient initials will be used to identify the patient. The investigator must keep a separate log of patient names and medical record numbers (or other personal identifiers) for their own reference.

The PI is responsible for ensuring the following at his/her site: 1) adherence to the protocol; 2) verifying adherence to local regulations on the conduct of clinical research; and 3) ensuring completeness, accuracy, and consistency of the data entered in the CRF.

Final CRFs in human readable format must be reviewed and verified for accuracy by the study site Principal Investigator and signed-off. A copy of the final CRF will remain at the investigator's site at the completion of the study. All completed CRFs will be sent to central site where data screening will be done. Data queries will be generated at the central site and disseminated to respective sites for query resolution. Data entry done at the central site will be shared with the coordinating center.

10.2 Institutional Review Board (IRB) / Ethics Committee (EC) Information

This protocol and the informed consent must be reviewed and approved by the appropriate IRB/EC where the trial is to be conducted before enrollment of patients. Changes to the protocol that may increase the risk or present new risks to the patient, or may adversely affect the validity of the trial, must be approved in writing by the IRB/EC before the change is made.

The study site Principal Investigator(s) is responsible for submitting and obtaining initial and continuing review (at intervals not greater than once a year) of the trial by their IRB/EC.

10.3 Deviations from Protocol

The investigator will not deviate from the protocol except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the trial. In medical emergencies, prior approval for protocol deviations will not be required, but the IRB/EC must be notified within five days of the incident.

Appendix A: References

- ⁱ Zipes DP, Wellens HJJ. Sudden cardiac death. *Circulation*. 1998; 98:2334-51.
- ⁱⁱ The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med*. 1997; 337:1576-83.
- ⁱⁱⁱ Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877-883.
- ^{iv} Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implantable defibrillator in patients with coronary disease at high risk for ventricular arrhythmia (MADIT). *N Engl J Med*. 1996; 335(26):1933-40.
- ^v Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease (MUSTT). *N Engl J Med*. 1999; 341(25):1882-90.
- ^{vi} Josephson ME, Horowitz LN, Farshidi A, Kastor JA. Recurrent sustained ventricular tachycardia. 1. Mechanisms. *Circulation*. 1978; 57:431-40.
- ^{vii} Downar E, Harris L, Michleborough LL, Shaikh N, Parson ID. Endocardial mapping of ventricular tachycardia in the intact human heart: Evidence for reentrant mechanisms. *J Am Coll Cardiol*. 1988; 11:783-91.
- ^{viii} The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary Report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med*. 1989; 321:406-12.
- ^{ix} The Cardiac Arrhythmia Suppression Trial II (CAST II) Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med*. 1992; 327:227-33.
- ^x Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, Pitt B, Pratt CM, Schwartz PJ, Veltri EP. Effect of *d*-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction (SWORD). *Lancet*. 1996; 348:7-12.
- ^{xi} Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: A meta-analysis of randomized control trials. *Circulation*. 1990; 82:1106-16.
- ^{xii} Moosvi AR, Goldstein S, Medendorp SV, Landis JR, Wolfe RA, Leighton R, Ritter G, Vasu

CM, Acheson A. Effect of empiric antiarrhythmic therapy in resuscitated with out-of-hospital cardiac arrest victims with coronary artery disease. *Am J Cardiol.* 1990; 65:1192-7.

^{xiii} Stanton MS, Prystowsky EN, Fineberg NS, Miles WM, Zipes DP, Heger JJ. Arrhythmogenic effects of antiarrhythmic drugs: A study of 506 patients treated for ventricular tachycardia or fibrillation. *J Am Coll Cardiol.* 1989; 14(1):209-15.

^{xiv} IMPACT Research Group. International mexiletine and placebo antiarrhythmic coronary trial: Report on arrhythmia and other findings. *J Am Coll Cardiol.* 1984; 4:1148-63.

^{xv} Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from randomized controlled trials [see coments]. *JAMA.* 1993; 270:1589-95.

^{xvi} Jafari-Fesharaki M, Scheinman MM. Adverse effects of amiodarone. *PACE.* 1998; 21[Pt.1]:108-120.

^{xvii} Hohnloser SH. Implantable devices versus antiarrhythmic drug therapy in recurrent ventricular tachycardia and ventricular fibrillation. *Am J Cardiol.* 1999; 84:56R-62R.

^{xviii} Miller JM, Kienzle MG, Harken AH, Josephson ME. Subendocardial resection for ventricular tachycardia: Predictors for surgical success. *Circulation.* 1984; 70:624-31.

^{xix} Garan H, Nguyen K, McGovern B, Buckley M, Ruskin JN. Perioperative and long-term results after electrophysiologically directed ventricular surgery for recurrent ventricular tachycardia. *J Am Coll Cardiol.* 1986; 8(1):201-9.

^{xx} Haines DE, Lerman BB, Kron IL, DiMarco JP. Surgical ablation of ventricular tachycardia with sequential map-guided subendocardial resection: Electrophysiologic assessment and long-term follow-up. *Circulation.* 1988; 77:131-41.

^{xxi} Ostermeyer J, Breithardt G, Borggrefe M, Godehardt E, Seipel L, Bircks W. Surgical treatment of ventricular tachycardias: Complete versus partial encircling endocardial ventriculotomy. *J Thorac Cardiovasc Surg.* 1984; 87:517-25.

^{xxii} Miller J, Rothman SA, Addonizio VP. Surgical techniques for ventricular tachycardia ablation. In: Singer I, ed: *Interventional Electrophysiology.* Baltimore: Williams & Wilkins, 1997:641-684.

^{xxiii} Cassidy DM, Vassallo JA, Marchlinski FE, Buxton AE, Untereker WJ and Josephson ME. Endocardial mapping in humans in sinus rhythm with normal left ventricles: activation patterns and characteristics of electrograms. *Circulation.* 1984; 70:37-42.

^{xxiv} Callans DJ, Ran J-F, Michele J, Marchlinski FE, Dillon SM. Electroanatomic left ventricular

mapping in the porcine model of healed anterior myocardial infarction: Correlation with intracardiac echocardiography and pathological analysis. *Circulation*. 1999; 100:1744-50.

^{xxv} Wroblewski D, Houghtaling C, Josephson ME, Ruskin JN, Reddy VY. Use of Electrogram Characteristics During Sinus Rhythm to Delineate the Endocardial Scar in a Porcine Model of Healed Myocardial Infarction. *J Cardiovasc Electrophysiol* 2003;14(5):524-529.

^{xxvi} Marchlinski FE, Callans DJ, Gottlieb CD, Zado E. Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy. *Circulation*. 2000;101:1288-96.

^{xxvii} Reddy VY, Neuzil P, Taborsky M, Ruskin J. Substrate-mapping and radiofrequency ablation of ischemic ventricular tachycardia using an irrigated-tip ablation catheter. *J Am Coll Cardiol* 2003; 41:2228-36.

^{xxviii} Soejima K, Stevenson WG, Maisel WH, Sapp JL, Epstein LM: Electrically unexcitable scar mapping based on pacing threshold for identification of the reentry circuit isthmus: Feasibility for guiding ventricular tachycardia ablation. *Circulation* 2002; 106:1678-1683.

^{xxix} Arenal A, Glez-Torrecilla E, Ortiz M, et al: Ablation of electrograms with an isolated, delayed component as treatment of unmappable monomorphic ventricular tachycardias in patients with structural heart disease. *J Am Coll Cardiol* 2003; 41:81-92.

^{xxx} Brunckhorst CB, Stevenson WG, Jackman WM, et al: Ventricular mapping during atrial and ventricular pacing: Relationship of multipotential electrograms to ventricular tachycardia reentry circuits after myocardial infarction. *Eur Heart J* 2002; 23:1131-1138.

^{xxxi} Brunckhorst CB, Delacretaz E, Soejima K, Maisel WH, Friedman PL, Stevenson WG: Identification of the ventricular tachycardia isthmus after infarction by pace mapping. *Circulation* 2004; 110:652-659.

^{xxxii} Allison, P.D. 1995. Survival Analysis Using the SAS System. A Practical Guide. SAS Institute, Inc., Cary, North Carolina.

^{xxxiii} Elashoff, J.D. 2005. nQuery Advisor, Version 6.0 User's Guide, Los Angeles, California.

^{xxxiv} Fleiss, J.L., Levin, B. and Paik, M.C. 2003. Statistical Methods for Rates and Proportions. 3rd Edition, Wiley Series in Probability and Statistics, Wiley-Interscience, Hoboken, New Jersey.

^{xxxv} Karl-Heinz, L. et al., 2003. Exaggerated Electrodermal Startle Responses after Intracardiac Shock Discharges in Patients with Implanted Cardioverter Defibrillators. *Psychosomatic Medicine* **65**:222-228.

^{xxxvi} Reddy, V.Y., Neuzil, P., Richardson, A.W., Kralovec, S., Jongnarangsi, K., Reynolds, M.R.,

Taborsky, M., Sediva, L., Ruskin, J.N. and Josephen, M.E. Prevention of implantable defibrillator therapy by catheter ablation: results of the Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH VT) Trial. *New England Journal of Medicine* 2007 Dec 27;357(26):2657-65.

^{xxxvii} Wei, L.J., Lin, D.Y. and Weissfeld, L. 1989. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *Journal of the American Statistical Association* **84**:1065-1073.

^{xxxviii} Woodward, M. 1999. Epidemiology Study Design and Analysis. Texts in Statistical Science, Chapman & Hall/CRC, Boca Raton, Florida.

^{xxxix} Daubert, J.P., Zareba, W., Hall, W.J., Schuger, C., Corsello, A., Leon, A., Andrews, M.L., McNitt, S., Huang, D.T., and Moss, A.J. Predictive Value of Ventricular Arrhythmia Inducibility for Subsequent Ventricular Tachycardia or Ventricular Fibrillation in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II Patients. *Journal of the American College of Cardiology* 47 (1): 98-107.