NAVISTAR THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

SINGLE USE ONLY. DO NOT RESTERILIZE.

I. Indications and Usage

The NAVISTAR THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter and related accessory devices, when used with the STOCKERT 70 Radiofrequency (RF) Generator, are indicated for the treatment of recurrent drug/device refractory sustained monomorphic ventricular tachycardia (VT) due to prior myocardial infarction (MI) in adults.

The NAVISTAR THERMOCOOL catheter provides location information when used with the CARTO EP / XP Navigation System, and can be used for catheter-based cardiac electrophysiological mapping (stimulation and recording).

II. Device Description

The Biosense Webster NAVISTAR THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter is a 7.5 F luminal catheter with a deflectable tip designed to facilitate electrophysiological mapping of the heart and to transmit radiofrequency current to the catheter tip electrode for ablation purposes. For ablation, the catheter is used in conjunction with a radiofrequency generator and a dispersive pad (reference electrode).

The catheter has a high-torque shaft with a deflectable tip section containing an array of platinum electrodes. All of the electrodes may be used for recording and stimulation purposes. The tip electrode serves to deliver radiofrequency current from the radiofrequency generator to the desired ablation site. The tip electrode and ring electrodes are made from platinum-iridium. The catheter incorporates either a thermocouple or thermistor temperature sensor that is embedded in the 3.5 mm tip electrode.

Tip deflection is controlled at the proximal end by a handpiece in which a piston slides: a thumbknob on the piston controls piston travel. 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"). Five curve types designated "B", "C", "D", "F" and "J" are available. The "J" curve type is only available with the thermocouple and not with the thermistor temperature sensor. The high torque shaft also allows the plane of the curved tip to be rotated to facilitate accurate positioning of the catheter tip at the desired site.

At the proximal end of the catheter, a saline port with a standard luer fitting terminates from the open lumen. This saline port serves to permit the injection of normal saline to irrigate the tip electrode. During ablation, normal heparinized saline is passed through the .027" diameter lumen of the catheter and through the tip electrode, to irrigate and cool the ablation site. The CoolFlow™ Irrigation pump is approved for use to control the saline irrigation.

A feature of this catheter is that it has a magnetic location sensor embedded in the tip electrode that transmits location information to the CARTO EP /XP Navigation System.

The catheter interfaces with standard recording equipment and the STOCKERT 70 RF Generator via accessory extension cables with the appropriate connectors.

For further description of the operation of the CARTO EP/XP Navigation System, STOCKERT 70 RF Generator, refer to the operating instructions for these instruments.

III. Contraindications

Do not use the NAVISTAR THERMOCOOL catheter:

- If the patient has had a ventriculotomy or atriotomy within the preceding eight weeks because the recent surgery may increase the risk of perforation
- In patients with prosthetic valves as the catheter may damage the prosthesis
- In the coronary vasculature due to risk of damage to the coronary arteries
- In patients with an active systemic infection because this may increase the risk of cardiac infection
- In the patient with a myxoma or an intracardiac thrombus as the catheter could precipitate an embolus
- Via the transseptal approach in a patient with an interatrial baffle or patch because the opening could persist and produce an iatrogenic atrial shunt

IV. Warnings and Precautions

- Do not use the temperature sensor to monitor tissue temperature. The temperature sensor located within the electrode does not reflect either electrode-tissue interface or tissue temperature due to the cooling effects of the saline irrigation of the electrode. The temperature displayed on the generator is the temperature of the cooled electrode. not tissue temperature. The temperature sensor is used to monitor the catheter tip temperature, which is an indication of the adequacy of the irrigation flow rate. Before initiating the application of radiofrequency current, a decrease in electrode temperature confirms the onset of saline irrigation of the ablation electrode. Monitoring the temperature from the electrode during the application of radiofrequency current indicates that the irrigation flow rate is being maintained.
- Monitor the patient's fluid balance throughout the procedure to avoid fluid overload.
- Purge catheter and irrigation tubing.
- The device may not be safe at electrode temperatures > 50° C.

- Follow the power titration procedure as specified in the directions for use. Too rapid an increase in power during ablation may lead to perforation caused by steam pop.
- Have temporary external sources of pacing and defibrillation available during ablation and temporarily reprogram the pacing system to minimum output or OFF mode to minimize the risk of inappropriate pacing, as implantable pacemakers and implantable cardioverter defibrillators (ICDs) may be adversely affected by radiofrequency current. Exercise extreme caution during ablation when in close proximity to atrial or ventricular permanent leads; program the ICD to the OFF mode during the ablation procedure; and perform complete implantable device analysis on all patients after ablation.
- Use adequate fluoroscopic visualization during the trans-aortic approach. This is necessary to avoid placement of the catheter in the coronary vasculature. Intracoronary placement of the ablation catheter, radiofrequency energy application, or both have been associated with MI.
- Minimize X-ray exposure during the procedure. Catheter ablation procedures present the potential for significant x-ray exposure, which can result in acute radiation injury as well as increased risk for somatic and genetic effects to both patients and laboratory staff due to the x-ray beam intensity and duration of the fluoroscopic imaging. Catheter ablation should only be performed after adequate attention has been given to the potential radiation exposure associated with the procedure, and steps have been taken to minimize this exposure. Careful consideration must therefore be given to the use of the device in pregnant women.
- Do not attempt to operate the Biosense Webster NAVISTAR THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter or the STOCKERT 70 RF generator prior to completely reading and understanding the applicable instructions for use.
- Cardiac ablation procedures should be performed by appropriately trained personnel in a fully equipped electrophysiology laboratory. Appropriate clinical instruction in use of the NAVISTAR THERMOCOOL catheters should also be completed.
- The long-term risks of protracted fluoroscopy and creation of RF induced lesions have not been established. Careful consideration must therefore be given for the use of the device in prepubescent children. Furthermore, the risk/benefit in asymptomatic patients has not been studied.
- Use intravenous heparin to avoid thromboemboli, when entering the heart during ablation. Many physicians also prescribe aspirin, less often warfarin, for about 3 months afterward. No consensus yet exists about the need for short-term anticoagulation after ablation.
- Perform catheter advancement under fluoroscopic guidance. Do not use excessive force to advance or withdraw the catheter when resistance is encountered. The firmness of the braided tip dictates that care be taken to prevent perforation of the heart. When using the Biosense Webster NAVISTAR THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter with conventional systems (using fluoroscopy to determine catheter tip location), or with the CARTO EP / XP Navigation System, careful catheter manipulation must be performed in order to avoid cardiac damage, perforation, or tamponade.
- Always pull the thumbknob back to straighten the catheter tip before insertion or withdrawal of the catheter.

- Always maintain a constant heparinized saline infusion to prevent coagulation within the lumen of the catheter.
- The catheter should be removed, and the tip cleaned of coagulum (if present) when radiofrequency current is interrupted for either a temperature or an impedance rise (when the set limit is exceeded),. When cleaning the tip electrode, be careful not to twist the tip electrode with respect to the catheter shaft; as twisting may damage the tip electrode bond and loosen the tip electrode. Make sure the irrigation holes are not plugged prior to re-insertion.
- Apparent low power output, high impedance reading or failure of the equipment to function correctly at normal settings may indicate faulty application of the dispersive electrode(s) or failure of an electrical lead. Do not increase power before checking for obvious defects or for proper application of the dispersive electrode.
- Read and follow the dispersive electrode manufacturer's instructions for use; the use of dispersive electrodes that meet or exceed ANSI/AAMI requirements (HF18) is recommended, eg, the 3M Model 1149F or Valley Lab Model 7505.
- The Biosense Webster NAVISTAR THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter is indicated for use only with the STOCKERT 70 RF Generator, Biosense Webster cables, and other appropriate interface cables and connectors.
- The Biosense Webster NAVISTAR THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter has been shown to create larger lesions than standard radiofrequency ablation catheters. Care should be taken when ablating near structures such as the sino-atrial and atrioventricular nodes.
- Inspect the sterile packaging and catheter prior to use. Do not use if the packaging or catheter appears damaged.
- The catheters are sterilized with ethylene oxide gas and should be used by the "Use By" date on the device package. Do not use the device if past the "Use By" date.
- The Biosense Webster NAVISTAR THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter is intended for single patient use only.
- Do not resterilize and reuse.
- Do not expose the catheter to organic solvents such as alcohol.
- Do not autoclave the catheter.
- Do not immerse proximal handle in fluids; electrical performance could be affected.
- Do not scrub or twist the distal tip electrode during cleaning.
- Inspect irrigation saline for air bubbles prior to its use in the procedure. Air bubbles in the irrigation saline may cause emboli.
- Do not use near MRI equipment since movement or heating of the catheter may occur and the image on the STOCKERT 70 display may become distorted.
- Use both fluoroscopy and electrogram data to monitor catheter advancement and reduce risk of tissue injury.
- The Biosense Webster NAVISTAR THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter used in conjunction with the STOCKERT 70 Generator is capable of delivering significant electrical power. Patient or operator injury can result from improper handling of the catheter and dispersive electrode, particularly when operating the device. During energy delivery, the patient should not be allowed to come in contact with grounded metal surfaces. If during ablation, temperature does not rise, discontinue ablation immediately and remove the catheter.

- The risk of igniting flammable gases or other materials is inherent in electrosurgery. Precautions must be taken to restrict flammable materials from the electrosurgical suite.
- Electromagnetic interference (EMI) produced by the Biosense Webster NAVISTAR THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter when used in conjunction with the STOCKERT 70 RF Generator during normal operation may adversely affect the performance of other equipment.
- Electrodes and probes used for monitoring and stimulating devices can provide paths for high frequency current. The risk of burns can be reduced but not eliminated by placing the electrodes and probes as far away as possible from the ablation site and the dispersive electrode. Protective impedance may reduce the risk of burns, and permit continuous monitoring of the electrocardiogram during energy delivery.
- The temperature sensor measures electrode tip temperature, not tissue temperature. The temperature displayed on the generator is for the cooled electrode only and does not represent tissue temperature. If the generator does not display temperature, verify that the appropriate cable is plugged into the generator. If temperature is still not displayed, there may be a malfunction in the temperature sensing system that must be corrected prior to applying radiofrequency current.
- Before use, check to ensure that irrigation ports are patent by infusion of normal heparinized saline through the catheter.
- Regularly inspect and test re-useable cables and accessories.
- Do not use the catheter if the small vent hole at the connector end of the handpiece is occluded as evidenced by difficulty in deflecting the catheter tip and the inability of the catheter to hold a curve.
- Do not exceed impedance cut-off settings of 200 Ohms or temperature cut-off settings $< 100^{\circ}C$.

V. Adverse Events

Of the 233 subjects in the Safety Analysis Cohort, 53 major adverse events (AEs) were reported in 42 subjects. See Section VI, "Summary of Clinical Studies", below for a complete description of the AEs encountered during the study.

VI. Summary of Clinical Studies

The clinical testing described below was performed with the NAVISTAR THERMOCOOL catheter.

A. Objective

The objective of the study was to evaluate the safety and effectiveness of the NAVISTAR THERMOCOOL catheter used in conjunction with CARTO EP/XP Navigation System and the STOCKERT 70 RF Generator and related accessories for ablation of recurrent drug/device refractory sustained monomorphic VT due to prior MI in adults.

B. Study Design

The study was a single-arm, prospective, non-randomized, unblinded, multi-center study conducted at 18 investigational sites located in the United States.

B.1 Study Endpoints

The endpoints for the study were as follows:

Acute procedural success for VT was defined as the termination and non-inducibility of all clinically relevant VTs upon hospital discharge. A clinically relevant VT was defined as any spontaneous VT or any induced VT, with cycle lengths equal to (± 20 msec) or greater than that of the spontaneous clinical VT.

Acute procedural success in subjects with incessant VT was defined as termination of the incessant VT and no recurrence prior to hospital discharge. Incessant VT was defined as those VTs which continue despite attempted electrical or pharmacological cardioversion such that the VT is present more than 50% of the time for a period of > 12 hours. Subjects with incessant VT were considered acute failures if incessant VT recurred prior to hospital discharge.

Chronic success for VT was defined at 6 months following the RF ablation procedure as no recurrence of clinically relevant monomorphic VT(s) that were targeted at ablation. In order to qualify for chronic success, a patient must have already met the acute procedural success endpoint. Chronic success was the primary effectiveness endpoint for the study. VT recurrences were to be documented by ICD telemetry for subjects who had an implanted defibrillator, or by transtelephonic monitoring (TTM), ECG recordings from paramedics or emergency room visits in the event of recurrence of sustained VT in subjects who did not have an ICD implant. Chronic success for incessant VTs was also defined as no recurrence of incessant VTs during the 6-month follow-up period.

Note: Acute procedural success and chronic success were determined from the last study ablation procedure prior to hospital discharge. Subjects who underwent an ablation procedure during the 6-month follow-up period (after hospital discharge) were deemed chronic failures.

Procedural safety was determined by the number of subjects who experienced acute or sub-chronic major complications associated with the use of the investigational device within seven days of the ablation procedure.

B.2 Protocol Endpoints

The protocol endpoints were prospectively established. The protocol endpoint for the safety endpoint was based on selected medical literature. The success criteria are defined below:

- **Safety**: major adverse events (AEs) within 7 days of the procedure occur at a rate of **22%** or less with a **30%** one-sided 95% upper confidence bound;
- **Acute procedural success**: **75%** with a **65%** one-sided 95% lower confidence bound.
- **Chronic success**: **50%** with a **40%** one-sided 95% lower confidence bound.

The trial design and endpoints of this study were based on historical controls. Limitations of the historical controls used for this study included the following:

- Available literature included incomplete recording of safety results.
- Literature patient populations were not necessarily comparable to current study population in disease severity, treatment of ischemic heart disease, duration of follow up, type of ablation treatment, ablation treatment not standardized, percent of patients with implanted defibrillators, and percent of patients treated with amiodarone.
- Available literature included some non-randomized descriptions of patient care.

B.3 Patient Accountability

Table 1 documents the accountability and disposition of enrolled subjects.

TABLE 1. Subject Enrollment and Accountability

Subject Disposition	
Total Number of Subjects Enrolled	**240**
Subjects Excluded (prior to ablation)	7
Safety Analysis Cohort	**233**
Discontinued Subjects (prior to ablation)	7
Effectiveness Analysis Cohort	**226**
Subjects who underwent ablation with **only** NAVISTAR THERMOCOOL catheter	205
Subjects who underwent ablation with NAVISTAR THERMOCOOL catheter **and** non-investigational catheter*	21

* This category involved enrolled subjects that were treated with the investigational catheter at the beginning of the procedure and the investigator then switched to a non-protocol catheter to complete the treatment of VT. Furthermore, subjects who could not be treated due to investigational device failure are included in this category. These subjects were considered acute procedural and chronic failures.

The following definitions were used to classify subjects:

Enrolled Subjects (n = 240) are subjects who signed informed consent.

Excluded Subjects (n = 7) are subjects that were enrolled but never underwent insertion of the investigational catheter.

Discontinued Subjects (n = 7) are subjects that had the investigational catheter inserted but did not undergo an ablation procedure with the investigational device, (ie. no RF energy was applied).

Effectiveness Analysis Cohort (n = 226) included the 226 subjects that underwent an ablation procedure with the investigational device.

Safety Analysis Cohort (n = 233) included the 226 subjects in the Effectiveness Analysis Cohort plus the 7 discontinued subjects.

The Safety Analysis Cohort (n = 233) and Effectiveness Analysis Cohort (n = 226) include 205 subjects who underwent ablation with the investigational device and 21 subjects who underwent ablation with the investigational device and a non-investigational device due to investigator preference, procedural complications, suspected catheter malfunction, perceived lack of effectiveness, subject anatomy, fluid management, or non-investigational device malfunction (and were deemed an effectiveness failure under the protocol).

The results of this study were evaluated as point estimates and qualitatively compared to existing literature and the current state of clinical practice for this patient group and indication.

B.4 Subject Demographics

Table 2 summarizes the demographic information of all enrolled subjects in the study.

TABLE 2. Summary Demographics (Enrolled Subjects with Data, n = 240)

Description	Enrolled	
	n	%
Gender		
Female	25	10.4
Male	215	89.6
Total	240	100.0
Age (years)		
Mean	65.1	
Standard Deviation	10.8	
Minimum	31	
Maximum	87	

Of the 240 enrolled subjects, 232 (96.7%) had a preexisting history of myocardial infarction (MI). Additionally, 225 (93.8%) subjects were confirmed to have an ICD implanted prior to study enrollment. Spontaneous monomorphic VT characteristics were reported in 199 of the 240 subjects with data enrolled in the study. Three hundred and ten (310) spontaneous VTs were reported in 199 subjects. The predominant VT QRS morphology of those reported was right bundle branch block superior axis (24.2%, 75/310), followed by left bundle branch block superior axis (9.4%, 29/310) and right bundle branch block inferior axis (8.1%, 25/310). The average cycle length of the VTs was 397.4 ms, with a median at 400 ms.

A total of 889 VTs were induced in 224 subjects, an average of approximately 3.97 VTs per subject. (VTs were not induced in two subjects who underwent ablation with the

investigational device). The majority of the subjects (171/226; 75.7%) had induction of at least one unmappable VT during the procedure. Thirty point five percent of subjects (30.5%; 69/226) exhibited only unmappable induced VTs.

C. Results

C.1 Intraprocedural Data

Tables 3 and 4 present the procedural data.

TABLE 3. Summary of RF Applications, Saline Infused, Power, Temperature and Impedance Data (Effectiveness Analysis Cohort, n = 226[1])

Description	Mean ± Standard Deviation
Number of RF Applications (n = 256 procedures)	26.4 ± 16.5
Total Saline Infused (ml) by NAVISTAR THERMOCOOL Catheter (n = 233 procedures)	1483.8 ± 838.4
Maximum Power (W)/application (n = 6509 RF applications)	42.5 ± 13.1
Maximum Temperature (°C)/application (n = 6506 RF applications)	39.3 ± 7.8
Maximum Impedance (ohms)/application (n = 6531 RF applications)	103.0 ± 58.2

[1] Complete procedural data were not reported for all subjects.

Note: Above table includes all ablation procedures including repeat procedures.

TABLE 4. Summary of Overall Fluoroscopy and Procedure Time (Effectiveness Analysis Cohort, n = 226)

Description	Mean ± Standard Deviation
Total fluoroscopy time (hrs)/procedure (n = 244 procedures)	1.0 ± 1.8
Total procedure time (hrs)/procedure[1] (n = 258 procedures)	5.6 ± 2.2

[1] Time from first cannula placed into vein/artery of subject to time when all catheters were removed from subject.

Note: Above table includes all ablation procedures including repeat procedures.

The overall fluoroscopy and procedure times reported include both the investigational (NAVISTAR THERMOCOOL) procedure time and all other procedures performed during the subject's stay in the EP lab. Therefore, the data do not solely reflect the actual use of the NAVISTAR THERMOCOOL catheter.

C.2 Acute Procedural Success

Acute procedural success results are presented in Table 5.

TABLE 5. Summary of Acute Procedural Success (Effectiveness Analysis Cohort, n = 226)

Subset Description	n	Acute Success	Percent (%)	95% C.I.[1]
Effectiveness Analysis Cohort[2,3]	226	171	75.7	71
Protocol Endpoint			75	65

[1] Exact binomial confidence bound.

[2] Data includes non-protocol catheter procedures considered *a priori* acute failures.

[3] Data includes subjects with incessant VT.

The results from the acute outcome analysis based on termination of all clinical relevant VT upon hospital discharge demonstrate that the percentage of subjects achieving acute success (75.7%; 95% lower confidence bound of 71%) met the protocol endpoint for acute procedural success.

C.3 Chronic Success - Freedom from VT Recurrence at Six-Month Follow-Up

Chronic success results are described in Table 6.

TABLE 6. Summary of Chronic Success (Effectiveness Analysis Cohort, n = 226)

Subset Description	n	Chronic Success	Percent (%)	95% C.I.[1]
Effectiveness Analysis Cohort[2,3]	226	107	47.3	41.7
Protocol Endpoint			50	40

[1] Exact binomial confidence bound.

[2] Data includes non-protocol catheter procedures considered a priori acute failures.

[3] Data includes subjects with incessant VT.

The results demonstrate that the percentage of subjects achieving chronic success (47.3%, 95% lower confidence bound of 41.7%) met the protocol endpoint for chronic success. This is due to the fact that although the point estimate for chronic success was lower than the protocol endpoint, the 95% lower confidence bound of the estimate was higher than the protocol endpoint.

Kaplan-Meier Analysis

A Kaplan-Meier analysis was performed to estimate the time to VT recurrence. Standard errors were computed by the Peto method. The one hundred and seventy-one (171) subjects who achieved acute successwere included in this analysis. Table 7 provides the number of subjects at risk (number of subjects entering the follow-up interval with acute success), number of subjects censored (number of subjects for whom the last follow-up exhibited freedom from recurrence of VT, at the time-point), number of events (subjects who experienced recurrence of VT), and the point and one-sided 95% C.I. estimation of VT recurrence-free probability. These numbers are defined at the exact time-point indicated, and do not necessarily correspond to the number of subjects followed with the follow-up windows. **Figure 1** provides the freedom from VT recurrence curve.

Freedom from VT recurrence following acute success was 67.5% at 6 months.

TABLE 7 Kaplan-Meier Data Including the Nominal Interval, Number of Subjects at Risk, Number of Subjects Censored, and Number of Events, Point and One-sided 95% Confidence Interval Estimation of Recurrence-Free Probability Using Peto Method (Acute Success Subjects, n = 171)

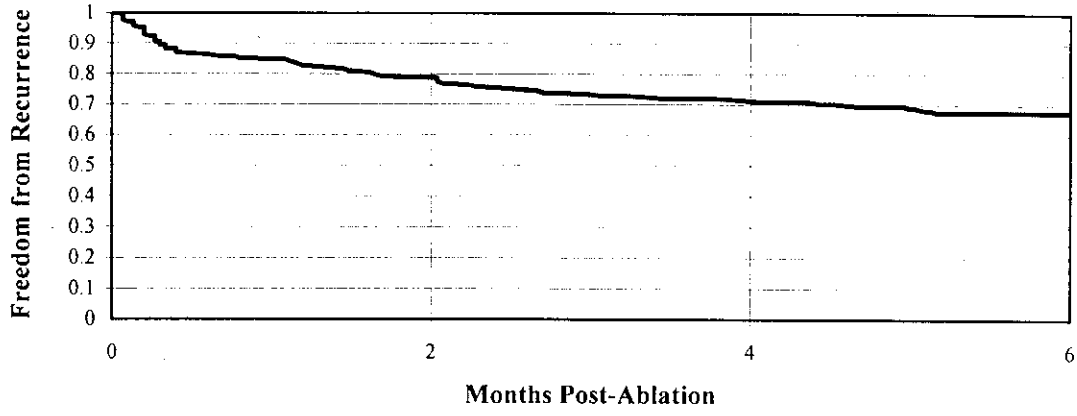
Nominal Interval	No. of Subjects at Risk[1]	Cumulative		Recurrence-Free Probability		
		No. of Subjects Censored	No. of Subjects with Events	Point Estimate	Peto Standard Error	One-sided 95% Lower Confidence Limit (Peto)
Day 0	171	0	0	1.0000	0.0000	1.0000
Discharge[2]	164	0	8	0.9529	0.0162	0.9262
3-weeks[3]	145	2	24	0.8586	0.0268	0.8145
1-month	143	3	25	0.8526	0.0274	0.8076
2-months	132	3	36	0.7870	0.0316	0.7350
3-months	124	3	45	0.7332	0.0343	0.6768
4-months	115	8	48	0.7148	0.0356	0.6563
5-months	107	14	52	0.6890	0.0379	0.6267
6-months	54	64	54	0.6754	0.0534	0.5876

[1] The number of subjects at risk is the number who did not have events or censoring before the time-point. If there are no events at a time-point, the total number of subjects in the analysis (171) equals the number at risk + the cumulative number censored + the cumulative number of events. This equation holds except at discharge, 3-months, 5-months, and 6-months. There are an event exactly at discharge, an event at 3-months, an event and a censoring at 5-months, and a censoring at 6-months.

[2] Subjects were discharged within 5 days from ablation. For the purpose of computation, discharge was defined as 5 days.

[3] For purposes of this table, 3 weeks = 21 days, 1 month = 30 days, 2 months = 61 days, 3 months = 91 days, 4 months = 122 days, 5 months = 152 days, and 6 months = 183 days.

FIGURE 1 Freedom from VT Recurrence
(Acute Procedural Success Subjects, n = 171)



Post hoc analysis of the treatment of Unmappable VT

Acute procedural success in subjects with only mappable induced VTs and in subjects with only unmappable induced VTs was 73.6% and 75.4%, respectively. Acute outcome for subjects with both mappable and unmappable VTs induced during the ablation procedure was 77.5%. Additionally, 67.3% of the 205 subjects who underwent an electrical stimulation protocol at the end of the procedure had no inducible VTs.
In addition, chronic success rates did not significantly differ among subjects with only mappable, only unmappable, or both mappable and unmappable VTs. Chronic success in subjects with only induced mappable VTs was 52.8% while in subjects with induced unmappable VT only, the success rate was 52.2%. Chronic success outcome for subjects with both mappable and unmappable VTs induced during the ablation procedure was 41.2%. Although the success rate was slightly lower for the combined mappable and unmappable group, this is not unexpected considering that multiple different VTs in a single subject have previously been associated with lower success outcomes.

Reduction in Post-ablation ICD therapies analyzed in selected subset of the study population

Data were available to calculate the reduction in ICD therapies after the ablation procedure for 130 subjects in the effectiveness analysis cohort. While not an endpoint for the study, a reduction in the number of VT therapies is also considered clinically relevant and has been used in literature to define "clinical success". The significant proportion of subjects with ICDs allowed for a comparison of the frequency of VT episodes before and after ablation (utilizing subjects as their own control). Of the effectiveness analysis cohort, 130 subjects were available for analysis through 6 months follow-up. There were a total of 79.2% (103/130) subjects with evidence of reduction in the rate of VT episodes post-ablation, while in 20.8% (27/130), there was an increase in the rate of VT episodes

post-ablation. In this study, all sustained VTs detected by ICD were considered, not just VTs that met the predefined endpoint as significant, thus representing a conservative evaluation of the endpoint. The absolute magnitude of the reduction in rate of ICD therapies was substantial for more than two thirds of this group. Approximately 70% (70.0%; 91/130) of the subjects had a documented reduction of more than 75% in ICD therapies during the follow-up period. For chronic failure subjects with available data, 55.4% (31/56) demonstrated a reduction in ICD therapies during the follow-up period.

C.4 Adverse Events

The protocol defined a major AE as any clinical event within seven days of the procedure that resulted in death, a life-threatening complication, or a persistent or significant disability/incapacity that requires inpatient hospitalization or prolongs hospitalization or requires intervention to prevent a permanent impairment of a body function or damage to a body structure. A minor AE was defined as any AE resulting in minimal transient impairment of a body function or damage to a body structure, or which does not require any intervention other than monitoring or events occurring more than 7 days after the procedure.

The study was not designed nor statistically powered to measure the long-term impact of ablation with the NaviStar ThermoCool catheter on cardiac function and mortality.

Major AEs

Of the 233 subjects in the safety analysis cohort, 53 major AEs were reported for 42 subjects. The overall percentage of subjects who experienced a major AE was 18%. Table 8 summarizes the major AEs.

Table 8. Major AEs observed within 7 Days Post-Ablation (Safety Analysis Cohort, n = 233)

Description	No. of Subjects	
Cardiovascular	**21**	**9.01%**
Incessant VT – Death	4	1.72%
Hypotension	2	< 1%
VT Storm – Death	2	< 1%
Recurrent VT	1	< 1%
Acute MI – Death	1	< 1%
Congestive Heart Failure	1	< 1%
Cardiogenic Shock - Death	1	< 1%
Atrial ICD Lead Malfunction	1	< 1%
VF Refractory to Monophasic Defibrillation	1	< 1%
Mitral Valve Regurgitation	1	< 1%
Mild Pericarditis	1	< 1%
Recurrent Atrial Flutter	1	< 1%
Mild Congestive Heart Failure	1	< 1%
Cardiac Ischemia	1	< 1%

Table 8. Major AEs observed within 7 Days Post-Ablation (Safety Analysis Cohort, n = 233)

Incessant VT	1	< 1%
Multiple VT	1	< 1%
Recurrent ICD Shocks	1	< 1%
Pulmonary	**8**	**3.43%**
Pulmonary Edema	4	1.72%
Transient Respiratory Insufficiency (no intubation required)	1	< 1%
Hypoxia - Volume Overload	1	< 1%
Respiratory Distress (required intubation)	1	< 1%
Pleural Effusion	1	< 1%
Peripheral Vascular	**13**	**5.58%**
Hematoma	4	1.72%
Pseudoaneurysm	3	1.29%
Groin Bleeding	2	< 1%
Hematoma/Hypotension	1	< 1%
Hematoma and Pseudoaneurysm	1	< 1%
Hematoma Post-cardiac Catheterization	1	< 1%
Bilateral Cephalic Vein Thrombosis	1	< 1%
Genitourinary	**3**	**1.29%**
Bleeding - Traumatic Foley Insertion	1	< 1%
Hematuria, Urinary Retention	1	< 1%
Hypergastric Pain Related to Urinary Retention	1	< 1%
Hematologic	**3**	**1.29%**
Anemia	1	< 1%
Heparin-Induced Thrombocytopenia and Disseminated Intravascular Coagulation	1	< 1%
Epistaxis secondary to over anticoagulation	1	< 1%
Systemic Infection	**1**	**< 1%**
Methicillin Resistant *S. aureus* Infection	1	< 1%
Neurovascular	**1**	**< 1%**
CVA	1	< 1%
Gastrointestinal	**1**	**< 1%**
Diverticulosis	1	< 1%
Musculoskeletal	**1**	**< 1%**
Atypical chest pain	1	< 1%

Note: 1. Fifty-three major AEs were reported for 42 subjects. 2. Some subjects are listed more than once in above table

Preexisting Conditions as a Predictor of Major AEs

So that one may determine if a sub-population of subjects is at differential risk, preexisting cardiac function (LVEF) data were analyzed as a potential predictor of major AEs. Table 9 lists the LVEF measurements stratified by the presence or absence of major AEs. Survival status stratified by LVEF (%) is presented in Table 10.

Data showed that the subjects who had LVEF measurements ≤ 30% had a significantly higher major AE rate than the subjects with LVEF measurements > 30% (22.6% vs 10.0%, p = 0.0258, Fisher's Exact test). Of note, 62.7% (146/233) of the Safety Analysis Cohort had LVEF ≤ 30% and would therefore be considered at higher risk of morbidity than study subjects who had higher LVEF. A cut off of 30% LVEF was used to dichotomize the analysis.

TABLE 9. Major AEs by LVEF (%) (Safety Analysis Cohort, n = 233)

LVEF (%)	Total Number of Subjects	With Major AE* n (%)	Without Major AE n (%)
≤ 30	146	33 (22.6)	113 (77.4)
> 30	70	7 (10.0)	63 (90.0)
Not Reported	17	2 (11.8)	15 (88.2)

* p = 0.0258

The subjects who had LVEF measurements ≤ 30% had a significantly higher death rate than the subjects with LVEF measurements > 30% (24.7% vs 8.6%, p = 0.0055 Fisher's Exact test). This reflects a study population at high risk of mortality at study entrance secondary to their baseline cardiovascular condition. In the Safety Analysis Cohort, a total of 45 (45/233, 19.3%) deaths occurred.

TABLE 10. Survival Status by LVEF (%) (Safety Analysis Cohort, n = 233)

LVEF (%)	Total Number of Subjects	Deceased Subjects* n (%)	Subjects Alive n (%)
≤ 30	146	36 (24.7)	110 (75.3)
> 30	70	6 (8.6)	64 (91.4)
Not Reported	17	3 (17.6)	14 (82.4)

* p = 0.0055

The overall percentage of subjects who experienced a major AE was 18% (42/233) (one-sided upper confidence bound (UCB) of 23%). The safety protocol endpoints specified in the protocol was 22% (UCB of 30%). Therefore, this study population met the protocol safety endpoint for this clinical trial (see Table 11).

TABLE 11. **Comparison of Safety Endpoint between NAVISTAR THERMOCOOL Study and Protocol Endpoint (Safety Analysis Cohort, n = 233)**

Endpoint	Protocol Established Endpoints[1]		NAVISTAR THERMOCOOL Study	
	%	One-sided 95% Confidence Bound[2]	% (n)	One-sided 95% Confidence Bound[2]
Major Complications	22	30	18.0 (42/233)	23 (Upper Bound)

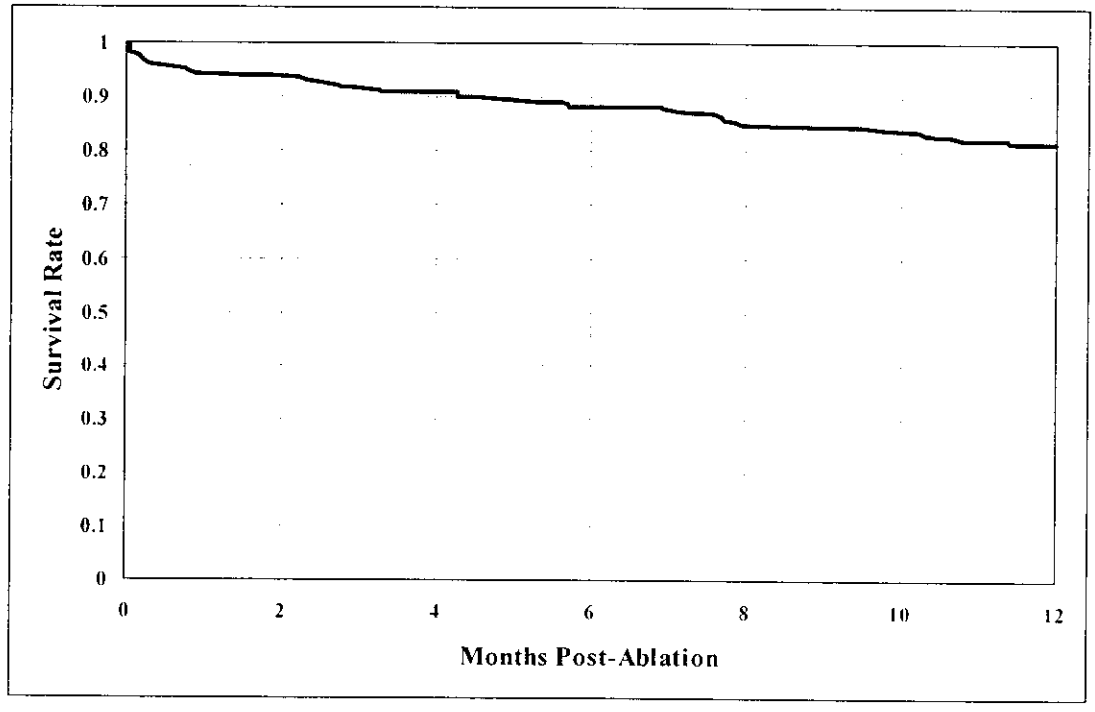
[1] Safety endpoint based on literature search.

[2] Exact binomial using a commercially-available software package.

A total of 45 deaths (45/233, 19.3%) occurred during the study. Eight subjects (8/233; 3.4%) expired within seven days of the ablation procedure, while an additional 37 (37/233; 15.9%) subjects expired more than 7 days post-procedure.

A Kaplan-Meier Analysis was performed to estimate survival rate after first ablation procedure. Standard errors were computed by the Peto method. Two hundred and thirty-three subjects were included in this analysis. The survival rate was 82 % at 12-months. **Figure 2** provides the survival curve over 12-months after first ablation procedure.

Figure 2. Survival Rate by Time Post-Ablation (Safety Analysis Cohort, n=233)



C.5 Analysis of study results compared to protocol endpoints

Table 12 summarizes the results of the open label single arm observational trial when compared to the protocol established for safety and effectiveness endpoints.

TABLE 12. Comparison of Endpoints Between NAVISTAR THERMOCOOL Study and Protocol Endpoint

Endpoint	Protocol Established Endpoints[1]		NAVISTAR THERMOCOOL Study	
	%	One-sided 95% Confidence Bound[2]	% (n)	One-sided 95% Confidence Bound[2]
Acute Procedural Success	75	65	75.7	71(Lower bound)
Chronic Success	50	40	47.3	41.7(Lower bound)
Procedural Safety	22	30	18.0 (42/233)	23 (Upper bound)

[1] Effectiveness endpoints established in the protocol are based on protocol endpoint; Safety endpoint based on literature search

[2] Exact binomial using a commercially-available software package.

In conclusion, the results demonstrate that the NAVISTAR THERMOCOOL catheter met the protocol endpoints for all safety and effectiveness endpoints.

VII. How Supplied

- The NAVISTAR THERMOCOOL Diagnostic/Ablation Catheter is supplied STERILE (EtO).
- The catheter is supplied with a choice of five curve types: B, C, D, F and J.
- The STOCKERT 70 RF Generator with appropriate interface cables is supplied separately.
- The CoolFlow™ Irrigation Pump and tubing sets are supplied separately.
- A grounding (dispersive) pad is supplied separately.
- The CARTO EP / XP Navigation System is supplied separately.
- The REFSTAR™ with QWIKPATCH™ Reference Patch is provided separately.

A. Packaging

The NAVISTAR THERMOCOOL Diagnostic/Ablation Catheter is provided in sterile packaging. The catheter is secured to a mounting card placed in a sealed film/Tyvek® pouch and packaged inside a cardboard box. Both the pouch and the shipping container are labeled sterile.

B. Storage

The NAVISTAR THERMOCOOL Diagnostic/Ablation Catheter must be stored in a cool, dry place. Storage temperature should be between 5°C and 25°C (41°F and 77°F).

C. Shelf-Life

The NAVISTAR THERMOCOOL Diagnostic/Ablation Catheter has a shelf-life of three (3) year.

VIII. Directions for Use

Please refer to both these instructions for use and the CARTO System User Manual when using the NAVISTAR THERMOCOOL Diagnostic/Ablation Catheter in conjunction with the CARTO System.

1. Remove catheter from package and place in a sterile work area.
2. Create a vascular access in a large central vessel using aseptic techniques.
3. To verify compatibility between sheath and catheter, advance catheter through sheath prior to insertion. May be used with an 8 Fr introducer sheath.
4. Connect the catheter to the junction box via the appropriate Biosense Webster cable with 25-pin Hypertronics interlocking connectors on both ends. Connect the junction box to the STOCKERT 70 RF Generator via the Biosense Webster cable with 10-pin Redel connectors on both ends. Connect the junction box to appropriate recording and mapping systems, including the CARTO EP / XP Navigation System, with appropriate interface cables. Use only Biosense Webster interface cables. If electrogram recording equipment is used, the catheter tip electrode must be switched from the electrogram equipment (via the generator controls or an external switch) to the RF generator power output for ablation. To complete the electrical circuit, connect a dispersive pad to the reference electrode input on the generator.
5. Turn the CATHETER SELECTION KNOB on the STOCKERT 70 RF Generator to the "Biosense Webster" option.
6. Purge catheter and tubing per standard technique.
7. Connect the CoolFlow™ Pump irrigation output to the irrigation input of the catheter. The CoolFlow™ Pump is preset with a low flow rate of 2ml/min and a high flow rate of 30 ml/min. Use the 2 ml/min. infusion to check that the irrigation holes are patent.
8. Set the temperature cutoff limit to 50°C. Press MENU and select the TEMPERATURE menu, select 'cutoff' and adjust the cutoff temperature to 50°C using the SELECTOR KNOB.
9. Set the RF generator to *power control mode* by pressing the MANUAL button. Set the initial power level to 31 watts.
10. Start continuous irrigation with room temperature, heparinized saline (1 U heparin/ml) at a flow rate of 2 ml/min.
11. Increase the irrigation flow rate to 30 ml/min up to 5 seconds before the onset of RF energy delivery and maintain this higher flow rate until 5 seconds after termination of the energy application. Note: RF energy can be applied to a maximum power level of 50W for a duration of 120 seconds while maintaining a saline flow rate of 30ml/min for all RF applications. The RF application must be terminated immediately if the tip temperature exceeds 45°C to 50°C.
12. The application of RF energy must not be initiated until the increase in irrigation flow rate is confirmed by a 3°C-5°C decrease in tip electrode temperature.

13. If the temperature increases to 50°C during RF application, power delivery will be interrupted by the temperature cutoff. The irrigation system must be rechecked prior to restarting RF.
14. Insert the catheter via the entrance site, using an introducer sheath.
15. Advance the catheter to the area under investigation. Use both fluoroscopy and electrograms to aid in proper positioning.
16. The catheter tip can be deflected to facilitate positioning by using the thumbknob to very tip curvature. Pushing the thumbknob forward causes the catheter tip to deflect; when the thumbknob is pulled back, the tip straightens.
17. When the ablation site is identified, adjust the CoolFlow™ Irrigation Pump to deliver a flow rate of 30ml/min and stand by while the voltage and power application time of the radiofrequency generator are set.
18. Watch the electrode tip temperature decrease.
19. When it has been determined that the tip electrode is in stable contact with the intended ablation site, the catheter tip electrode connection must be switched from the recording equipment to the radiofrequency generator in preparation for delivery of radiofrequency current. Verify that the CATHETER SELECTION KNOB on the STOCKERT 70 RF Generator is on the "Biosense Webster" option. Circuit impedance should be approximately 100 ohms upon initiation of radiofrequency current.
20. Monitor the temperature throughout the procedure. The peak temperature should be not exceed 45°C - 50°C during RF energy delivery. Note: The displayed temperature represents the temperature of the electrode only, not the temperature of the tissue.
21. Start a procedure at 31 W. If needed, increase power in 5 W increments (to maximum 50 W, see below for specific criteria), until a transmural lesion is achieved. The duration of each RF application will not exceed 120 seconds. Dragging the catheter to the next site is permissible during the 120-second energy application.
22. After radiofrequency current is discontinued, decrease irrigation to 2 ml/min on the irrigation pump.
23. Radiofrequency current may be re-applied to the same or alternate sites using the same catheter. However, in the event of a generator cutoff (impedance or temperature), the catheter must be withdrawn and the tip electrode cleaned of coagulum before radiofrequency current is re-applied. A sterile gauze pad dampened with sterile saline may be used to gently wipe the tip section clean; do not scrub or twist the tip electrode as damage to the tip electrode bond may occur and loosen the tip electrode. Prior to reinsertion, ensure that the irrigation holes are not plugged. If irrigation hole occlusion occurs:
    a) Remove the catheter from the patient.
    b) Fill a 1 or 2 ml syringe with sterile saline and attach to the sidearm.
    c) Carefully inject the saline from the syringe into the catheter. A stream of fluid should be visible from all six (6) holes.
    d) Repeat steps b and c, if necessary.
    e) If the holes are cleared, the catheter can be reintroduced into the patient.

    WARNING: Do not continue use of the catheter if still occluded or it is not functioning properly.

24. If the RF generator does not display temperature, verify that the appropriate cable is plugged into the generator. If the generator still does not display temperature, there may be a malfunction in the temperature sensing system. Correct this malfunction prior to reapplying RF energy.
25. If preset temperature or impedance levels are exceeded during operation, design safety features of the RF generator cause the RF energy to stop. A likely cause of this may be accumulated coagulum on the tip electrode. Withdraw the catheter and examine the tip electrode. If coagulum accumulation is present, clean the tip electrode by gently wiping with a sterile gauze pad dampened with sterile saline. Use caution to not twist the tip electrode relative to the catheter shaft during cleaning because this may damage the tip electrode bond and loosen the tip electrode.

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The NAVISTAR THERMOCOOL Diagnostic/Ablation Catheter and accessories are protected under one or more of the following U.S. Patent Nos.: 5,827,278; 5,6,171,277, and other patents pending in the U.S. and other countries.