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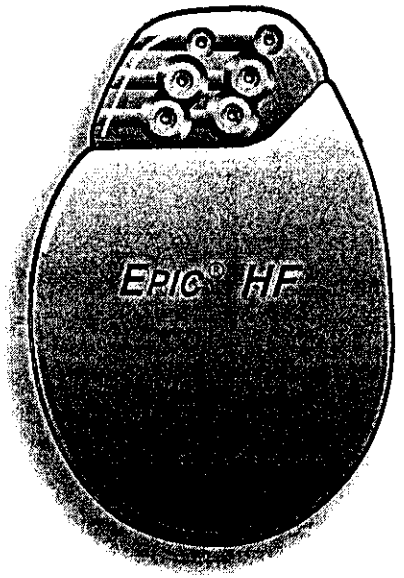

Epic® HF
Models V-337, V-338

Cardiac Resynchronization Therapy Defibrillator

User's Manual

USER'S MANUAL

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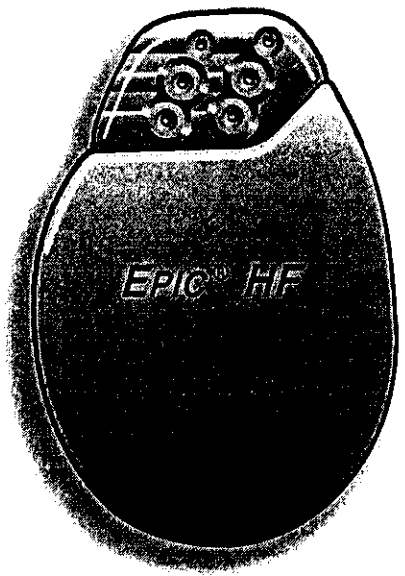

Epic® HF
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Cardiac Resynchronizatin Therapy Defibrillator

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

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PREFACE

This booklet describes the St. Jude Medical® Epic® HF (Model V-337, V-338) cardiac resynchronization therapy defibrillator (also referred to as the "Epic HF pulse generator") along with implantation instructions. For information on programming the pulse generator, refer to the appropriate reference manual.

Typographic Conventions

This manual uses different formats to distinguish tasks, notes, cautions, and warnings.

1. Numbered paragraphs contain instructions.

   Paragraphs like this one provide explanations of the paragraph above it as well as additional information that might be useful at that point in the procedure.

Note

Notes provide useful or important information.

Caution

Precautions flag conditions that may damage the pulse generator or that may prevent its safe and effective use.

WARNING

Warnings call attention to potential safety hazards and situations that may cause personal injury.

Device Description

The St. Jude Medical® Epic® HF cardiac resynchronization therapy defibrillators (CRT-D), Model V-337 and Model V-338, monitor and regulate a patient's heart rate by providing ventricular tachyarrhythmia therapy and dual-chamber bradycardia pacing with ventricular resynchronization therapy.

The pulse generator, along with compatible, commercially available leads, constitutes the implantable portion of the CRT-D system. The lead systems are implanted using either transvenous or transthoracic techniques. The St. Jude Medical Model 3510 Programmer, the software 3307 version 3.2m[1] (or greater), and a telemetry wand constitute the external portion of the CRT-D system.

Indications and Usage

The St. Jude Medical (SJM) Epic HF system is intended to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias. In patients indicated for an ICD, the Epic HF system is also intended:

- to provide a reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy (as defined in the clinical trials section) and have a left ventricular ejection fraction less than or equal to 35% and a prolonged QRS duration
- to maintain synchrony of the left and right ventricles in patients who have undergone an AV nodal ablation for chronic (permanent) atrial fibrillation and have NYHA Class II or III heart failure.

Contraindications

Contraindications for use of the pulse generator system include ventricular tachyarrhythmias resulting from

1. For devices with serial numbers ≥13000, software Model 3307 version 4.5m (or greater).

transient or correctable factors such as drug toxicity, electrolyte imbalance, or acute myocardial infarction.

Warnings and Precautions

Resuscitation Availability. Do not perform device testing unless an external defibrillator and medical personnel skilled in cardiopulmonary resuscitation (CPR) are readily available.

Lead system. Do not use another manufacturer's lead system without demonstrated compatibility as undersensing cardiac activity and failure to deliver necessary therapy may result.

Avoiding shock during handling. Program the device to Defib Off mode during surgical implant and explant or post-mortem procedures as well as when disconnecting leads as the device can deliver a serious shock if you touch the defibrillation terminals while the device is charged.

Additional pacemaker implanted. This device provides dual-chamber bradycardia pacing with ventricular resynchronization therapy. If another pacemaker is used, it should have a bipolar pacing reset mode and be programmed for bipolar pacing to minimize the possibility of the output pulses being detected by the device.

Sterilization, Storage and Handling

Resterilization. Do not resterilize and re-implant explanted pulse generators.

Use before date. Do not implant the device after the "use before" date because the battery may have reduced longevity.

If package is damaged. Do not use the device or accessories if the packaging is wet, punctured, opened or damaged because the integrity of the sterile packaging may be compromised. Return the device to St. Jude Medical.

Device storage. Store the device in a clean area, away from magnets, kits containing magnets, and sources of electromagnetic interference (See *Environmental and Medical Therapy Hazards* on page 4.) to avoid device damage. Store the device between 10° and 45° C (50°

to 113° F) because temperatures outside this range may damage the device.

Temperature Equilibration. After cold storage, allow the device to reach room temperature before charging the capacitors, programming, or implanting the device because cold temperature may affect initial device function.

Implantation and Device Programming

Do not position a magnet over the device as that suspends detection and treatment (unless the device has been programmed to ignore the magnet).

Replace the device when the battery voltage reaches 2.45 V. From ERI to EOL (2.45 to 2.35 V) the device will continue to operate according to specifications, except for a change in the pacing amplitude (see *Operating Parameters Tolerances* on page 73) and high-voltage charge time.

Program device parameters as specified in the reference manual.

Follow-up Testing

Ensure that an external defibrillator and medical personnel skilled in cardiopulmonary resuscitation (CPR) are present during post-implant device testing should the patient require external rescue.

Be aware that the changes in the patient's condition, drug regimen, and other factors may change the defibrillation threshold (DFT), which may result in non-conversion of the arrhythmia. Successful conversion of ventricular fibrillation or ventricular tachycardia during arrhythmia conversion testing is no assurance that conversion will occur post-operatively.

Pulse Generator Explant and Disposal

Interrogate the device and program the pulse generator to Defib Off and Pacer Off before explanting, cleaning or shipping the device to prevent unwanted shocks.

Return all explanted pulse generators and leads to St. Jude Medical.

Never incinerate the device because of the potential for explosion. The device must be explanted before cremation.

Environmental and Medical Therapy Hazards

Patients should be directed to avoid devices which generate a strong electric or magnetic interference (EMI). EMI could cause device malfunction or damage, resulting in non-detection or delivery of unneeded therapy. Moving away from the source or turning it off will usually allow the pulse generator to return to its normal mode of operation.

Hospital and Medical Environments

Electrosurgical cautery. Electrosurgical cautery could induce ventricular arrhythmias and/or fibrillation, or may cause device malfunction or damage. If electrocautery is necessary, keep the current path and groundplate as far away from the pulse generator and leads as possible.

External defibrillation. External defibrillation may damage the pulse generator or may result in temporary and/or permanent myocardial damage at the electrode-tissue interface as well as temporarily or permanently elevated pacing capture thresholds. Minimize current flowing through the pulse generator and lead system by following these precautions when using external defibrillation on a patient with a pulse generator:

- Position defibrillation paddles as far from the pulse generator as possible (minimum of 5 inches [13 cm])
- Use the lowest clinically appropriate energy output
- Confirm pulse generator function following any external defibrillation.

High radiation sources. Do not direct high radiation sources such as cobalt 60 or gamma radiation at the pulse generator. If a patient requires radiation therapy in the vicinity of the pulse generator, place lead shielding over the device to prevent radiation damage and confirm its function after treatment.

Lithotripsy. Lithotripsy may permanently damage the pulse generator. Avoid it unless the therapy site is not near the pulse generator and leads.

Diathermy. Avoid diathermy, even if the device is programmed off, as it may damage tissue around the implanted electrodes or may permanently damage the pulse generator.

Magnetic resonance imaging (MRI). MRI may cause device malfunction or damage. If MRI must be used, patients should be closely monitored and programmed parameters should be verified upon cessation of MRI.

Ultrasound therapy. Diagnostic and therapeutic ultrasound treatment is not known to affect the function of the pulse generator.

Transcutaneous Electrical Nerve Stimulation (TENS). TENS may interfere with device function. To reduce interference, place the TENS electrodes close to one another and as far from the device/lead system as possible. Monitor cardiac activity during TENS use.

Radiofrequency ablation. Radiofrequency (RF) ablation in a patient with a pulse generator may cause device malfunction or damage.

Minimize RF ablation risks by:

- Programming the device to Defib Off and Pacer Off
- Avoiding direct contact between the ablation catheter and the implanted lead or pulse generator
- Positioning the groundplate so that the current pathway does not pass near the pulse generator system, i.e., place the groundplate under the patient's buttocks or legs
- Having external defibrillation equipment available.

Home and Occupational Environments

High-voltage power transmission lines. High-voltage power transmission lines may generate enough EMI to interfere with pulse generator operation if approached too closely.

Communication equipment. Communication equipment such as microwave transmitters or high-power amateur transmitters may generate enough EMI to interfere with pulse generator operation if approached too closely.

Home appliances. Home appliances in good working order and properly grounded do not usually produce enough EMI to interfere with pulse generator operation. There are reports of pulse generator disturbances caused by electric hand tools or electric razors used directly over the pulse generator implant site.

Industrial equipment. A variety of industrial equipment produce EMI of sufficient field strength and

modulation characteristics to interfere with proper operation of the pulse generator. These include, but are not limited to: arc welders; induction furnaces; very large or defective electric motors; and internal combustion engines with poorly shielded ignition systems.

Electronic Article Surveillance (EAS)

Advise patients that the Electronic Article Surveillance/Anti-theft (EAS) systems such as those at the point of sale and entrances/exits of stores, libraries, banks, etc., emit signals that may interact with the device. It is very unlikely that these systems will interact with their device significantly. However, to minimize the possibility of interaction, advise patients to simply walk through these areas at a normal pace and avoid lingering near or leaning on these systems.

Metal Detectors

Advise patients that metal detector security systems such as those found in airports and government buildings emit signals that may interact with the device. It is very unlikely that these systems will interact with their device significantly. To minimize the possibility of interaction, advise patients to simply walk through these areas at a normal pace and avoid lingering. Even so, the CRT-D system contains metal that may set off the airport security system alarm. If the alarm does sound, the patient should present security personnel with their patient identification card. If security personnel perform a search with a handheld wand, the patient should ask that they perform the search quickly, stressing that they should avoid holding the wand over the device for a prolonged period.

Cellular Phones

The pulse generator has been tested for compatibility with handheld wireless transmitters in accordance with the requirements of AAMI PC69. This testing covered the operating frequencies (450 MHz - 3 GHz) and pulsed modulation techniques of all of the digital cellular phone technologies in worldwide use today. Based on the results of this testing, the pulse generator should not be affected by the normal operation of cellular phones.

Adverse Events

The reported adverse events in the following section (pages 7 through 15) summarize the adverse events in the Resynchronization for HemodYnamic Treatment for Heart Failure Management (RHYTHM ICD) trial. A description of the RHYTHM ICD study begins on page 22.

The reported adverse events on pages 15 through 21 summarize the adverse events in the Post-AV Node Ablation Evaluation (PAVE) study. A description of the PAVE study begins on page 43.

Reported Adverse Events for the RHYTHM ICD Study

Per the investigational plan, an *adverse event* was defined as any unfavorable clinical event which impacts, or has the potential to impact the health or safety of a Clinical Study participant caused by or associated with a study device or intervention. Adverse events were classified as complications or observations based on the following definitions:

- *Complications* were defined as adverse events that require invasive intervention (e.g. lead dislodgment requiring repositioning).
- *Observations* were defined as adverse events that can be managed without invasive intervention (e.g., oversensing or loss of pacing capture, which was then remedied by reprogramming of the pulse generator).
- *Other Reported Event* was defined as any other clinical event that was reported by the investigator, which was not an Adverse Event as defined above.

Table 1 lists the observations and complications reported during the RHYTHM ICD clinical trial (see *Summary Of RHYTHM ICD Study* on page 22). A total of 107 adverse events have been reported in 73 patients, of which 31 are complications and 76 are observations.

Event Description	# of Patients with AEs* (n= 205)	% of Patients with AEs	# AEs	AE/pt-years (n=231.95 yrs)
Complications (total)	**22**	**10.7%**	**31**	**0.134**
Coronary Sinus Perforation/Dissection	2	1.0%	2	0.009
Diaphragmatic/Phrenic Nerve Stimulation	3	1.5%	3	0.013
Lead Dislodgment or Migration	9	4.4%	10	0.043
Bleeding/Hematoma†	6	2.9%	6	0.026
Blood Clot/Thrombosis	1	0.5%	1	0.004
High Defibrillation/Cardioversion Requirements	2	1.0%	2	0.009
Infection	2	1.0%	2	0.009
Noise on EGM Post Shock (Non-SJM RV lead)	1	0.5%	1	0.004
Pneumothorax	2	1.0%	2	0.009
Retained Foreign Body (surgical sponge)	1	0.5%	1	0.004
Elevated Pacing Threshold – LV Lead	1	0.5%	1	0.004

Table 1. RHYTHM ICD Adverse Events

Event Description	# of Patients with AEs* (n=205)	% of Patients with AEs*	# AEs	AE/pt-years (n=231.95 yrs)
Observations (total)	**59**	**28.8%**	**76**	**0.328**
Asystolic Episode during LV Lead Placement	1	0.5%	1	0.004
Bleeding/Hematoma†	10	4.9%	10	0.043
Blood Clot/ Thrombosis	2	1.0%	2	0.009
Coronary Sinus Perforation/Dissection	6	2.9%	6	0.026
Diaphragmatic/Phrenic Nerve Stimulation – LV Lead	14	6.8%	14	0.060
Diaphragmatic/Phrenic Nerve Stimulation – RV Lead	2	1.0%	2	0.009
Elevated Pacing Thresholds – LV Lead	12	5.9%	12	0.052
Elevated Pacing Thresholds – RV Lead	2	1.0%	2	0.009
Heart Block at Implant	2	1.0%	2	0.009
High Defibrillation/Cardioversion Requirements	1	0.5%	1	0.004
Hypotension Requiring Ventilatory Support	1	0.5%	1	0.004
Inappropriate Therapy for SVT	11	5.4%	14	0.060
Infection	4	2.0%	4	0.017

Table 1. RHYTHM ICD Adverse Events (continued)

Event Description	# of Patients with AEs* (n= 205)	% of Patients with AEs	# AEs	AE/pt-years (n=231.95 yrs)
Possible Pulmonary Embolism	1	0.5%	1	0.004
T-Wave Sensing	2	1.0%	3	0.013
Lead Insulation Damage - RA Lead	1	0.5%	1	0.004

Table 1. RHYTHM ICD Adverse Events (continued)

* Some patients experienced more than one observation and/or complication and therefore the # of patients is less than the # of events.

† Fifteen (15) of the 16 patients with bleeding/hematoma related adverse events were on active anticoagulation therapy.

Event Description	# of Patients	# of Events	Comments
Atrial arrhythmias observed	7	8	Atrial arrhythmias noted on electrograms that did not result in therapy delivery.
Bacteremia	2	2	Chronically diagnosed Gram positive bacteremia, unrelated to implant procedure, treated with antibiotics.
Cardiopulmonary/respiratory arrest	1	1	Syncopal episode leading to brief respiratory arrest probably due to vagal response while retching with spontaneous resolution following re-hydration.

Table 2. RHYTHM ICD Other Reported Events

Event Description	# of Patients	# of Events	Comments
Chest pain/tightness	3	3	ER visit for chest pain associated with pleurisy (1 pt.); Chest pain associated with leaking thoracic aneurysm (1 pt.); Chest pain managed medically (1 pt.).
CNS related disorders	4	4	Seizure in 2 pt. with history of seizure disorder; changes in mental status (2 pts.): secondary to dementia in 1 pt. and wife withheld medication for 1 pt.
Fatigue/Shortness of breath	1	1	Shortness of breath/fatigue reported on a clinic visit possibly secondary to resolving pneumonia.
Hemoptysis	1	1	Blood noted in sputum; lung biopsy performed; no further events reported.
Inflammatory response/ swelling/elevated WBCs	3	3	General clinical symptoms evaluated and treated medically; no further sequelae reported.
Elective surgery	4	4	Left hydrocelectomy; cholecystectomy; hernia repair; percutaneous transluminal coronary angioplasty.
Inappropriate mode switches	9	12	Ten events were resolved with device re-programming.
Nausea/Vomiting/Diarrhea/ Abdominal pain or bloating	6	6	GI symptoms treated medically with no further sequelae.

Table 2. RHYTHM ICD Other Reported Events (continued)

Event Description	# of Patients	# of Events	Comments
Nose bleed	1	1	Resulted from elevated INR while on coumadin therapy; dose adjustment and no further sequelae.
Occasional crosstalk noted on electrogram	1	1	Resolved with device reprogramming.
Occasional Far-R sensing noted on electrogram	2	2	Did not result in mode switching or other inappropriate device behavior; devices re-programmed.
Pacing sensation	3	4	Symptoms possibly associated with pacing felt in chest. 1 pt. required re-programming.
Pain not related to procedure	2	2	Pain not associated with the device implant procedure: 1 pt. was R/O ischemia and discharged and 1 pt. diagnosed with gangrene of leg.
Pericardial effusion/Pericarditis	2	2	Treated medically with NSAIDs; no further sequelae.
Placement of LV epicardial leads	1	1	During LV lead revision, endocardial lead removed and not able to recannulate. Epicardial leads placed with no further sequelae.
Post-operative pain at incision site	2	3	Post surgical incisional pain treated with analgesics; no further sequelae reported.
PVC resulting in shortened AV delay	1	1	Device reprogrammed

Table 2. RHYTHM ICD Other Reported Events (continued)

Event Description	# of Patients	# of Events	Comments
Renal insufficiency/Elevated BUN and creatinine	1	1	Acute renal failure secondary to bilateral renal artery stenosis; treated medically with no further sequelae reported.
Respiratory related events	8	11	Reports of pneumonia, cough, bronchitis, cold, or wheezing treated medically; no further sequelae.
Shocks delivered for SVT/Afib in ventricular fibrillation zone	6	7	Therapy delivery appropriate: device performed as programmed (SVT discrimination not available to be programmed in Fib zone).
Shocks for MTD/MTF during SVT episode	2	2	Therapy delivery appropriate: device and features performed as Programmed. 1 pt. was re-programmed and 1 pt. prescribed amiodarone therapy.
Sinus bradycardia observed	4	4	2 pts. resolved by device reprogramming pacing rate; 2 pts. did not require re-programming.
Stroke/TIA	2	2	TIA in setting of continuous AF at 3 mos. post-op in 1 pt.; Mid-cerebral artery CVA in 1 pt.
Syncope/Pre-syncope/Dizziness/ Vasovagal/Hypotension	5	5	General clinical symptoms treated medically with IV fluids post-op (2 pts.) and rest (3 pts.); no further sequelae reported.
Replacement of RA lead during initial implant procedure	1	1	Replacement of RA lead due to helix extension mechanism failure during initial implant procedure.

Table 2. RHYTHM ICD Other Reported Events (continued)

Event Description	# of Patients	# of Events	Comments
VT below rate cut-off of device	1	1	Cardioversion performed and device re-programmed.
VF episode requiring multiple external shocks prior to Epic HF system implant	1	1	Ventricular fibrillation episode that occurred in the EP lab during initial implant procedure and reported as possibly associated with hypokalemia.
Occasional noise/EMI noted on electrogram	2	3	Noise observed on atrial channel of stored electrogram was not reproduced in clinic; device re-programming was not required.
TOTAL	68*	100	

Table 2. RHYTHM ICD Other Reported Events (continued)

* Some patients experienced more than one event, and therefore the number of patients is less than the number of events.

Twenty-two (22) patients enrolled in the RHYTHM ICD clinical investigation were withdrawn from the study due to death. Three (3) of the deaths occurred in patients with an unsuccessful implant, 2 deaths occurred between the implant and the Baseline visit, 8 deaths occurred between Baseline and the 6-month visit and 9 deaths occurred after the 6-month visit. Five (5) of the twenty-two deaths were considered to be *peri-operative mortalities* (occurred ≤ 30 days post-implant). There were no deaths classified as related to the pulse generator or lead system. The 3 deaths in patients with an unsuccessful Epic HF system implantation were not attributed to the attempted implantations.

A summary of the Events Committee death classifications are shown in Table 3.

Primary Cause	CRT OFF	CRT ON	N/A*	Total
Cardiac-Arrhythmic	0	0	0	0
Cardiac-Nonarrhythmic	1	2	4	7
Cardiac-Unknown	0	1	0	1
Non-Cardiac	3	8	1	12
Unknown	0	2	0	2
Total	**4**	**13**	**5**	**22**

Table 3. RHYTHM ICD Events Committee Classification of Patient Deaths

* Death occurred in patients who did not have a successful Epic HF system implant (unrelated to the implant procedure) or death occurred before their Baseline visit and randomization.

Reported Adverse Events for the PAVE Study

Per the investigational plan, an adverse event was defined as any unfavorable clinical event which impacts, or has the potential to impact the health or safety of a Clinical Study participant caused by or associated with a study device or intervention. Adverse events were classified as complications or observations based on the following definitions:

- *Complications* were defined as any adverse event resulting in an injury or an invasive intervention (e.g. lead repositioning after lead dislodgement) which would not have occurred in the absence of the implanted device and/or system components.
- *Observations* were defined as any adverse event that is not associated with injury to the patient or an invasive intervention, but which was associated with the system under investigation, or the programming thereof.
- *Other Reported Events* were defined as any other clinical event that was reported by the investigator, which was not caused by, or associated with the study device.

Table 4 lists the observations and complications reported from the PAVE study (see *Summary of the PAVE Study* on page 43). A total of 169 adverse events were reported, of which 56 were complications and 113 were observations.

Events	BV, LV, and Roll-in (N=259)*			
	# of AEs	# of Patients with AEs	% of Patients with AEs	AE/ device-month†
Complications (total)	56	48	18.5	0.0094
Acute LV Lead Dislodgement	11	11	4.2	0.0019
Acute RV Lead Dislodgement	3	2	0.8	0.0005
Arrhythmia – VT at Implant	1	1	0.4	0.0002
Cardiac Tamponade at Implant	1	1	0.4	0.0002
CS Dissection at Implant	7	7	2.7	0.0012
CS Perforation at Implant	3	3	1.2	0.0005
Diaphragmatic Stimulation	6	6	2.3	0.0010
High LV Pacing Threshold at Implant, Later System Revised	9	8	3.1	0.0015
LV Lead Dislodgment during Ablation Procedure	1	1	0.4	0.0002
LV Lead Loss of Capture	4	4	1.5	0.0007
Oversensing	1	1	0.4	0.0002

Table 4. PAVE Adverse Events‡

Events	BV, LV, and Roll-in (N=259)*			
	# of AEs	# of Patients with AEs	% of Patients with AEs	AE/ device-month†
Pectoral Stimulation	1	1	0.4	0.0002
Pneumothorax at Implant	3	3	1.2	0.0005
Pulmonary Edema post Ablation	1	1	0.4	0.0002
RV Insulation Failure	2	2	0.8	0.0003
RV Lead Fracture	1	1	0.4	0.0002
RV Perforation	1	1	0.4	0.0002
Observations (total)	**113**	**83**	**32.0**	**0.0191**
Acute LV Lead Dislodgment (minor)	2	2	0.8	0.0003
Arrhythmia – Torsades	1	1	0.4	0.0002
CS Dissection at Implant	3	3	1.2	0.0005
Device Site Discomfort	1	1	0.4	0.0002
Diaphragmatic Stimulation	22	20	7.7	0.0037
Discomfort - Chest	1	1	0.4	0.0002

Table 4. PAVE Adverse Events‡ (continued)

Events	BV, LV, and Roll-in (N=259)*			
	# of AEs	# of Patients with AEs	% of Patients with AEs	AE/ device-month†
Dyspnea on Exertion	2	2	0.8	0.0003
Fatigue	7	7	2.7	0.0012
Hematoma at Implant	8	8	3.1	0.0013
High LV Threshold at Implant	7	7	2.7	0.0012
High LV Pacing Threshold	15	15	5.8	0.0025
Hypotension	1	1	0.4	0.0002
Infection	5	5	1.9	0.0008
LV Loss of Capture	3	3	1.2	0.0005
LV Lead Undersensing	1	1	0.4	0.0002
Noise on IEGM	1	1	0.4	0.0002
Oversensing	3	3	1.2	0.0005
Palpitation	1	1	0.4	0.0002
Pectoral Stimulation	17	15	5.8	0.0029

Table 4. PAVE Adverse Events‡ (continued)

Events	BV, LV, and Roll-in (N=259)*			
	# of AEs	# of Patients with AEs	% of Patients with AEs	AE/ device-month†
Pneumothorax	1	1	0.4	0.0002
RV Back-up Pacing due to PVCs	1	1	0.4	0.0002
RV Loss of Capture	1	1	0.4	0.0002
Stuck Stylet	1	1	0.4	0.0002
Syncope	1	1	0.4	0.0002
Telemetry Error	3	2	0.8	0.0005
Thrombosis	2	2	0.8	0.0003
Transient Ischemic Attack	1	1	0.4	0.0002
VVI Backup	1	1	0.4	0.0002

Table 4. PAVE Adverse Events‡ (continued)

* System-related complications and observations based on total number of attempted implants (N = 259), Procedure-related complications based on total number of procedures (N = 260).

† Events per Device-Month calculated as number of events divided by the total device cumulative duration in months in BV, LV and Roll-in groups. The cumulative duration in months in these groups was 5,927 (5,928 for procedure related complication calculation).

‡ Each patient may have more than one complication or observation in more than one category.

Table 5 lists the other reported events. Events categorized here were a result of the underlying conditions of the patient, and were either resolved spontaneously or through adjustments in medication or other medical intervention unrelated to the device, the device therapy, or the study procedure.

Event Description	BV (N=151)	LV (N=53)	Roll-in (N=56)
Arrhythmia – NSVT	0	3	0
Cardiovascular – Non-Study	25	3	9
Dyspnea	3	1	3
Fatigue	2	0	0
Lead Dislodgment during CABG Procedure	0	1	0
Lead Dislodgement during Valve Surgery	0	1	0
Non-cardiovascular	66	19	17
Palpitations	1	0	1
Pre-Syncope	10	0	2
Pulmonary Diseases	7	2	1
Renal Insufficiency	1	0	0
Surgery – Unrelated	0	0	1
Syncope	8	0	2
Thromboembolic Events	4	0	2
Ventricular Arrhythmia	5	3	0
Worsening Heart Failure	34	17	10
Total Events	**166**	**50**	**48**
Total Patients	**73**	**30**	**23**

Table 5. PAVE Other Reported Events

Table 5. PAVE Other Reported Events (continued)

Forty-seven (47) deaths occurred throughout the PAVE study in the BV, LV, and Roll-in groups. A summary of the Events Committee death classifications are shown in Table 6.

Primary Cause	BV (N=109)	LV (N=151)	Roll-in (N=56)	Total
Cardiac-Arrhythmic	1	2	0	3
Cardiac-Other	6	3	2	11
Cardiac-Unknown	2	0	0	2
Non-Cardiac	5	6	5	16
Unknown	7	4	3	14
Total	**21**	**15**	**10**	**46***

Table 6. PAVE Events Committee Classification of Patient Deaths

* One additional patient was consented, but died prior to any study-related procedures.

Potential Adverse Events

Possible adverse events (in alphabetical order) associated with the system, include, but are not limited to the following:

- Acceleration of arrhythmias (caused by device)
- Air embolism
- Allergic reaction
- Bleeding
- Cardiac tamponade
- Chronic nerve damage
- Death
- Erosion
- Exacerbation of heart failure
- Excessive fibrotic tissue growth
- Extracardiac stimulation (phrenic nerve, diaphragm, chest wall)
- Extrusion
- Fluid accumulation
- Formation of hematomas or cysts

- Inappropriate shocks
- Infection
- Keloid formation
- Lead abrasion and discontinuity
- Lead migration/ dislodgment
- Myocardial damage
- Pneumothorax
- Shunting current or insulating myocardium during defibrillation with internal or external paddles
- Potential mortality due to inability to defibrillate or pace
- Thromboemboli
- Venous occlusion
- Venous or cardiac perforation.

Patients susceptible to frequent shocks despite antiarrhythmic medical management may develop psychological intolerance to a CRT-D system that may include the following:

- Dependency
- Depression
- Fear of premature battery depletion
- Fear of shocking while conscious
- Fear that shocking capability may be lost
- Imagined shocking (phantom shock).

CLINICAL STUDIES

Summary Of RHYTHM ICD Study

The St. Jude Medical, Inc. Resynchronization for Hemo-dYnamic Treatment for Heart Failure Management (RHYTHM) ICD study was conducted under an IDE (investigational device exemption).

The purpose of the clinical study was to assess the safety and effectiveness of the Epic HF CRT-D system in patients who were indicated for standard implantable cardioverter defibrillation therapy with New York Heart Association Classification of III or IV and a prolonged QRS duration.

Study Design

The RHYTHM ICD study was a prospective, multicenter, randomized, double-blind, controlled clinical investigation designed to assess the safety and effectiveness of the Epic HF CRT-D system in patients who were indicated for standard implantable cardioverter defibrillation therapy with New York Heart Association Classification of III or IV and a prolonged QRS duration. The products being evaluated were the Epic HF V-338[2] CRT-D and the Aescula and QuickSite LV leads.

Figure 1 depicts the RHYTHM ICD study design.

2. The Epic HF Model V-338 devices included in the RHYTHM ICD study did not include the AutoIntrinsic Conduction Search or the Rate-Responsive PVARP programmable parameters, or device-based battery management. For information on these features, refer to the reference manual.

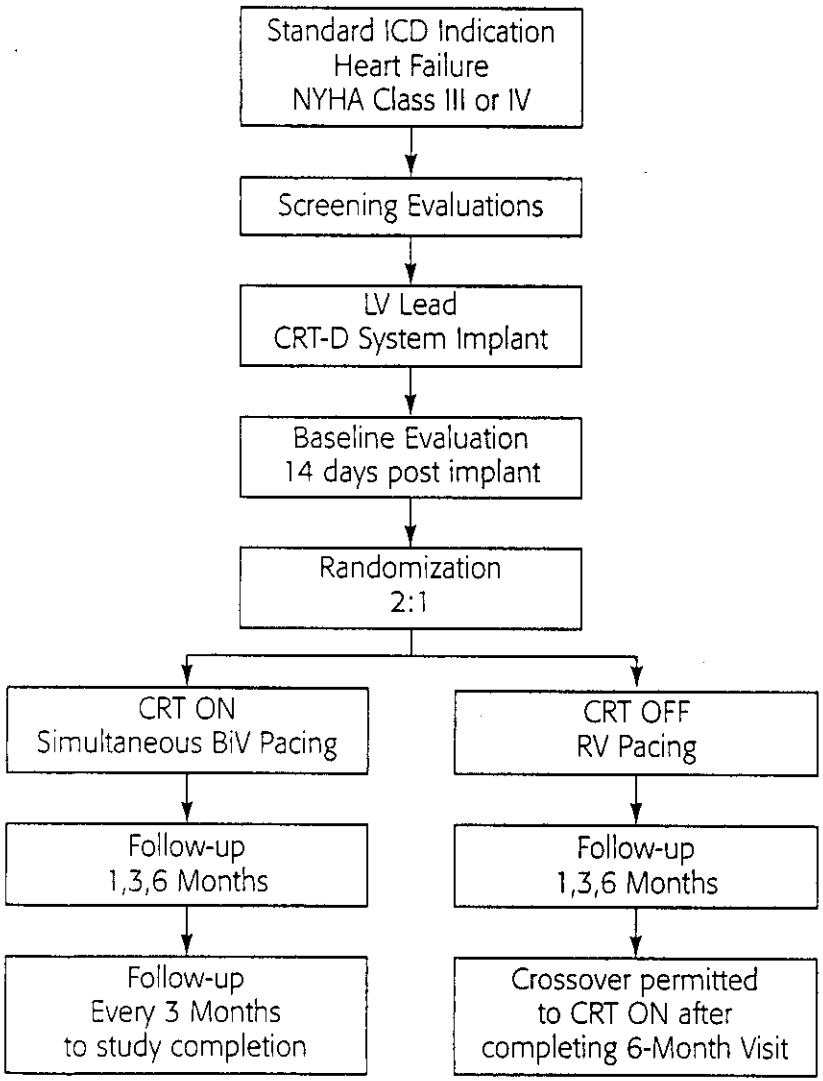


Figure 1. RHYTHM ICD Study Design

Study Objectives

The objective of this clinical study was to verify the safety and effectiveness of the Epic HF CRT-D (Model V-338) system in a standard ICD indicated patient population with advanced heart failure (NYHA Classification III or IV) and prolonged QRS duration.

Primary Objectives

The following are the primary safety and effectiveness objectives defined for this study.

- Safety of the Epic HF CRT-D system evaluated in terms of survival from LV lead and system related complications.
- Defibrillation system effectiveness determined in terms of detection/redetection times and compared to those observed in the St. Jude Medical Photon DR clinical investigation.
- Resynchronization effectiveness evaluated in terms of exercise capacity, as measured by cardiopulmonary exercise testing.

Secondary Objectives

The secondary objectives are listed below.

- NYHA Classification
- Quality of Life Questionnaire
- 6-Minute Hall Walk Test
- Implant success rate for the Aescula Model 1055K LV pacing lead
- Aescula Model 1055K LV lead electrical performance

Patient Selection Criteria

Inclusion Criteria

Patients eligible for enrollment had:

- An approved indication for implantation of a standard ICD for treatment of a life-threatening ventricular tachyarrhythmia(s).
- Symptomatic, advanced heart failure (ischemic or non-ischemic) not due to reversible causes, diagnosed for at least 6 months.
- A New York Heart Association (NYHA) Classification of III or IV, despite receiving a minimum of 90 days of appropriate pharmacological therapy.
- Received optimal pharmacological therapy for CHF (including angiotensin converting enzyme inhibitor and beta blocker, as tolerated) which has been stable during the 30 days prior to enrollment.
- A left ventricular ejection fraction (LVEF) ≤ 35%.
- A ventricular conduction delay manifested as a QRS duration ≥ 150 ms.
- The ability to complete cardiopulmonary exercise stress testing and 6-minute hall walk test, with the only limiting factor(s) being fatigue and/or shortness of breath.
- The ability to independently comprehend and complete a quality of life questionnaire.
- The ability to provide informed consent for study participation and be willing and able to comply with the prescribed follow-up tests and schedule of evaluations.

Exclusion Criteria

Eligible patients did not/were not:

- Have a standard bradycardic indication for pacing.
- Have a history of chronic atrial fibrillation (continuous AF lasting > 1 Month) within 1 year prior to enrollment or have undergone cardioversion for AF in the past month.
- Have the ability to walk > 450 meters during the 6-minute walk test.
- Have a NYHA Classification of I or II.
- Have a contraindication for an emergency thoracotomy.
- Have a classification of Status 1 for cardiac transplantation or consideration for transplantation over the next 6 months.
- Have a recent myocardial infarction, unstable angina or cardiac revascularization (PTCA or CABG) within 1 month of enrollment.
- Have a recent CVA or TIA - within 3 months of enrollment.
- Have severe musculoskeletal disorder(s).
- Pregnant or a planning for pregnancy in the next 6 months.
- Currently participating in, or had participated in any clinical investigation within the last 30 days. (The only exception being that of a registry trial.)
- Have a life expectancy of less than 6 months.
- Less than 18 years of age.

Clinical Study Results

Patient Population

Two-hundred five (205) patients were enrolled at 50 clinical sites in the RHYTHM ICD clinical investigation. The first Epic HF V-338 and Aescula 1055K left ventricular lead system was implanted on July 8, 2002. The first QuickSite 1056K lead was implanted on March 26, 2003.

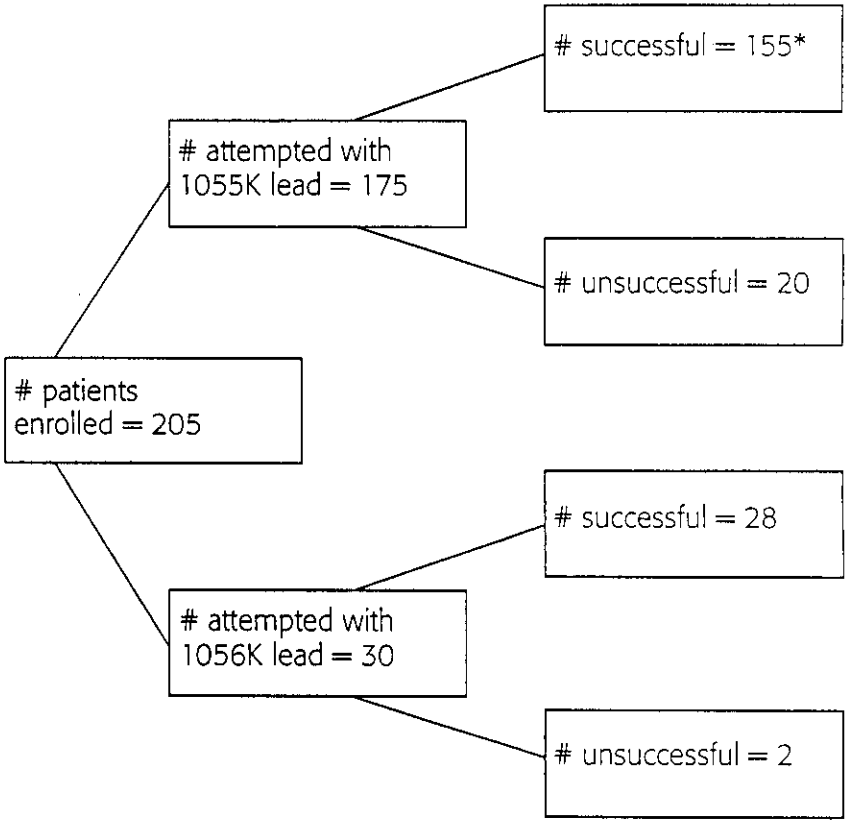
Of the 205 patients enrolled in the RHYTHM ICD study, one hundred and eighty-three (183) lead implant attempts were successful (180 successful on the first attempt and 3 successful on the second attempt). One additional patient had a successful left ventricular lead implant, but had high defibrillation thresholds. This

patient was withdrawn from the study and received a heart transplant, leaving a total of 182 successful system implants. Table 7 has a breakdown of the reasons for the 23 unsuccessful implants.

Reason	# Patients
LV Lead Related:	
Unable to Cannulate the CS	7
Unable to Obtain Distal Placement	6
Unable to Obtain Stable Lead Position	3
High Pacing Thresholds	3
CS Dissection	3
Other:	
High Defibrillation Threshold	1
TOTAL	**23**

Table 7. Unsuccessful Implants (N = 23)

Figure 2 displays the leads used and the number of successful system implants for each category of leads.



* Includes one patient with a successful lead implant, but an unsuccessful system implant due to high defibrillation thresholds

Figure 2. Number of Patients Attempted and Implanted with Model 1055K and 1056K Leads

The total time of follow-up from the time of successful implant was 2755 patient-months. The average time of follow-up was 15.1 ± 4.1 (range 0.3 to 23.8) patient-months.

Baseline Demographic Data

Patients who were successfully implanted with the Epic HF CRT-D system had a Baseline visit approximately two weeks after implant, during which the following tests/assessments were performed: Electrical measurements on RA, RV and LV leads, cardiopulmonary exercise (CPET) test, echocardiogram, NYHA class assessment, 6-minute walk test, and Minnesota Living with Heart Failure (MLWHF) questionnaire. Of the182 patients with successful implants, two patients expired and one patient withdrew from the study before the Baseline visit and therefore, 179 patients had a Baseline visit. One additional patient who had a Baseline follow-up visit refused randomization and all the Baseline evaluations except device interrogation and electrical measurements, but remained in the study. Therefore, a total of 178 patients completed the requirements of the Baseline visit.

Table 8 summarizes all the reported data on the 178 patients available for analysis at the Baseline visit, as well as broken down by randomization group.

Demographic variable	Overall Group (n = 178)*	CRT OFF (N = 59)	CRT ON (N = 119)	p-value (CRT ON vs. CRT OFF)
NYHA Class, n (%):				0.61
I	3 (1.7%)	2 (3.4%)	1 (0.8%)	
II	10 (5.6%)	4 (6.8%)	6 (5.0%)	
III	154 (86.5%)	50 (84.7%)	104 (87.4%)	
IV	11 (6.2%)	3 (5.1%)	8 (6.7%)	

Table 8. Summary of Baseline Variables and Comparisons Between CRT OFF and CRT ON groups

Demographic variable	Overall Group (n = 178)*	CRT OFF (N = 59)	CRT ON (N = 119)	p-value (CRT ON vs. CRT OFF)
LV Ejection Fraction (%) - ECHO: Mean ± SD Range	24.8 ± 7.7 (9, 48)	23.3 ± 6.4 (11, 43)	25.6 ± 8.3 (9, 48)	0.07
QRS Duration (ms): Mean ± SD Range	168 ± 15 (120, 210)	167 ± 15 (130, 200)	169 ± 16 (120, 210)	0.40
LVEDD (mm): Mean ± SD Range	66.2 ± 8.8 (47.7, 85.9)	66.0 ± 9.4 (50.1, 84.2)	66.2 ± 8.5 (47.7, 85.9)	0.88
LVESD (mm): Mean ± SD Range	57.0 ± 9.87 (37.1, 78.2)	56.9 ± 10.5 (37.9, 78.2)	57.1 ± 9.4 (37.1, 76.2)	0.93
Quality of Life Score: Mean ± SD Range	48 ± 24 (0, 103)	46 ± 24 (4, 100)	48 ± 24 (0, 103)	0.53
Six-Minute Walk (meters): Mean ± SD Range	280 ± 99 (31, 561)	291 ± 89 (31, 480)	275 ± 103 (37, 561)	0.30

Table 8. Summary of Baseline Variables and Comparisons Between CRT OFF and CRT ON groups (continued)

Demographic variable	Overall Group (n = 178)*	CRT OFF (N = 59)	CRT ON (N = 119)	p-value (CRT ON vs. CRT OFF)
CPET Test:				
Peak VO_2 (ml/kg/min):				
Mean ± SD	11.3 ± 3.3	12.3 ± 3.5	10.8 ± 3.0	0.006
Range	(4.3, 26.9)	(6.0, 23.1)	(4.3, 26.9)	
Exercise Time (minutes):				
Mean ± SD	8.3 ± 3.3	8.9 ± 3.6	8.0 ± 3.2	0.08
Range	(0.7, 19.8)	(2.3, 19.8)	(0.7, 16.5)	
Baseline Medications, n (%):				
ACE Inhibitors/Substitutes	129 (72.5%)	44 (74.6%)	85 (71.4%)	0.79
Beta Blockers	147 (82.6%)	52 (88.1%)	95 (79.8%)	0.24
Angiotensin Receptor Blockers	34 (19.1%)	10 (16.9%)	24 (20.2%)	0.76
Diuretics	157 (88.2%)	54 (91.5%)	103 (86.6%)	0.47
Positive Inotropics/Glycoside	112 (62.9%)	39 (66.1%)	73 (61.3%)	0.65
Nitrates	62 (34.8%)	23 (39.0%)	39 (32.8%)	0.51
Anti-Coagulants and Anti-Platelets	150 (84.3%)	48 (81.4%)	102 (85.7%)	0.59
Calcium Channel Blockers	20 (11.2%)	9 (15.3%)	11 (9.2%)	0.35
Anti-Arrhythmics	42 (23.6%)	13 (22.0%)	29 (24.4%)	0.87

Table 8. Summary of Baseline Variables and Comparisons Between CRT OFF and CRT ON groups (continued)

* Of the 182 patients that had successful system implants, two patients expired and one patient withdrew from the study before their Baseline visit; one additional patient refused randomization and all Baseline evaluations, except device interrogation and electrical measurements, and therefore, is not included.

Primary Safety Endpoint Results

LV Lead-Related Complications (at 6 Months)

Table 9 summarizes the LV Lead Related Complications at 6 months. One hundred and fifty-five (155) patients who had a successful 1055K LV lead implant were analyzed for this endpoint. A total of 11 patients experienced 13 1055K LV lead related complications.

The survival from 1055K lead related complications at 6-months was calculated as 92.8% with a 95% lower confidence bound of 89.4%, which is greater than the objective performance criteria of 75%.

Description of Complication	Number of Events	Number of Patients
Diaphragmatic Stimulation	3	3
Lead Dislodgment/Migration	9	8
Elevated Pacing Threshold	1	1
TOTAL	13	11*

Table 9. Aescula 1055K LV Lead Related Complications

* One patient experienced both a lead dislodgment/migration and diaphragmatic stimulation, and one patient experienced two lead dislodgments/migrations.

Epic HF System-Related Complications (at 6 Months)

Table 10 summarizes the System Related Complications at 6 months. One hundred and eighty-two (182) patients who had a successful Epic HF system implant with either the Aescula or QuickSite LV lead were analyzed for this endpoint. A total of 14 patients experienced 18 Epic HF system-related complications.

The survival from system-related complications at 6-months was calculated as 92.8% with a 95% lower confidence bound of 89.7%, which is greater than the objective performance criteria of 70%.

Description of Complication	Number of Events	Number of Patients
Diaphragmatic Stimulation	3	3
High Defibrillation/Cardioversion Requirements	2	2
Infection	2	2
Lead Dislodgment/Migration	9	8
Elevated Pacing Threshold	2	2
TOTAL	18	14*

Table 10. Epic HF System-Related Complications

* One patient experienced both a lead dislodgment/migration and diaphragmatic stimulation, one patient experienced two lead dislodgments/migrations, one patient had high defibrillation threshold and lead dislodgment/migration, and one patient had an elevated pacing threshold and an infection.

Survival from All Complications (at 6 months)

In addition to the protocol-specified LV-lead related and system-related complication endpoints, survival from all complications at 6 months, including procedural complications and patients with unsuccessful implants, was analyzed following a review of the clinical results.

Two hundred and five (205) patients who were attempted with the Epic HF system were included in this analysis. Table 11 lists all complications experienced by each patient. A total of 22 patients experienced 31 complications.

The survival from all complications at 6-months was calculated as 89.6% with a 95% lower confidence bound of 85.9%.

Description of Complication	Number of Events	Number of Patients
Bleeding/Hematoma	6	6
Blood Clot/Thrombosis	1	1
CS Dissection	2	2

Table 11. All Complications

Description of Complication	Number of Events	Number of Patients
Diaphragmatic/Phrenic Nerve Stimulation	3	3
High Defibrillation/Cardioversion Requirements	2	2
Infection	2	2
Noise on EGM Post Shock (non-SJM RV lead)	1	1
Lead Dislodgment/Migration	9	8
Retained Foreign Body	1	1
Pneumothorax	2	2
Elevated Pacing Threshold	2	2
TOTAL	31	22*

Table 11. All Complications (continued)

* Five patients each experienced 2 complications and one patient experienced 4 complications.

Primary Effectiveness Endpoint Results

Defibrillation System Effectiveness: VF Detection/Redetection Times

The defibrillation system effectiveness of the Epic HF CRT-D system was evaluated by comparing the time to detect or redetect an episode of ventricular fibrillation to performance criteria established in the protocol based on historical data from the Photon DR study (P910023/S47). A total of 440 episodes in 172 patients were analyzed for detection times, and 90 episodes in 55 patients were analyzed for redetection times.

Table 12 displays a summary of the detection and redetection times for VF episodes. The mean detection and redetection times were within the objective performance criteria of 3.4 seconds and 1.9 seconds, respectively. The p-values for the detection and redetection time hypotheses were less than 0.0004. The 95% upper confidence bound was 3.11 seconds for the mean detection time and 1.61 seconds for the redetection time.

Summary	Detection Time	Redetection Time
n (episodes)	440	90
N (patients)	172	55
Mean ± SD	3.1 ± 0.66	1.6 ± 0.35
Range	(1.5, 6.8)	(0.8, 2.8)

Table 12. Summary of VF Detection and Redetection Times

Primary Cardiac Resynchronization Therapy Effectiveness Endpoint

The resynchronization effectiveness of the Epic HF CRT-D system was evaluated by comparing the CRT ON group to the CRT OFF group for peak VO_2, an indicator of a patient's maximal exercise capacity. Patients completed a CPET at the baseline visit approximately two weeks after their CRT-D implant, and again at the 6-month visit. The sample size required to satisfy this endpoint was 126 patients.

In the intention-to-treat analysis, patients who crossed over from the CRT OFF group to the CRT ON group during the study were analyzed according to the original treatment group they belonged to.

Table 13 contains a summary of the improvement in peak VO_2 values in the two treatment groups for this analysis. The average improvement in the CRT ON group over the CRT OFF group was approximately 1.9 ml/kg/min. The p-value was 0.001.

	CRT OFF Mean ± SD (N = 43)	CRT ON Mean ± SD (N = 83)
Baseline	12.8 ± 3.7	11.2 ± 3.0
6-months	11.4 ± 5.6	11.7 ± 3.2
Change	-1.41 ± 4.6	0.52 ± 2.5
Overall improvement in CRT ON vs. CRT OFF = 1.9 ml/kg/min		

Table 13. Improvement in Peak VO_2 Values (ml/kg/min) Intention-To-Treat Analysis (N = 126)

Analysis of Exercise Time

The improvement in exercise time between the Baseline and 6-month visits was analyzed. Patients who were not able to perform the CPET at 6-months due to documented heart failure were assigned exercise times of 0. Table 14 shows that the CRT ON group had an improvement in exercise time over the CRT OFF group of approximately 109 seconds. The p-value was 0.002.

	CRT OFF Mean ± SD (N = 43)	CRT ON Mean ± SD (N = 83)
Baseline	558 ± 216	498 ± 192
6-months	510 ± 270	558 ± 210
Change	-50.4 ± 252	58.2 ± 132
Overall improvement in CRT ON vs. CRT OFF = 09 seconds		

Table 14. Change in Exercise Time (seconds) (N = 126)

Secondary Endpoint Results

Resynchronization Effectiveness

Secondary endpoints for resynchronization effectiveness were NYHA class, Quality of Life, and the 6-Minute Hall Walk Test. These endpoints were evaluated on the same patient group that was analyzed for the Peak VO_2 endpoint.

New York Heart Association Classification

Table 15 shows the average change in NYHA Class from Baseline to 6 months for each group. Overall the improvement in the CRT ON group was greater than the improvement in the CRT OFF group by approximately 0.2 functional classes.

	CRT OFF Mean ± SD (N = 43)	CRT ON Mean ± SD (N = 83)
Baseline	2.86 ± 0.52	3.01 ± 0.33
6-months	2.58 ± 0.73	2.53 ± 0.69
Change	-0.28 ± 0.63	-0.48 ± 0.65
Overall change in CRT ON vs. CRT OFF = 0.2 functional classes		

Table 15. Average Improvement in NYHA Class (N = 126)

Quality of Life

Patient quality of life was assessed with the MLWHF questionnaire. A lower score indicates an improvement in quality of life.

Table 16 contains a summary of the improvement in quality of life in the two treatment groups. The average improvement in the CRT ON group over the CRT OFF group was approximately 11 points.

	CRT OFF Mean ± SD (N = 43)	CRT ON Mean ± SD (N = 83)
Baseline	42.0 ± 23	48.3 ± 24
6-months	45.4 ± 31	40.4 ± 22
Change	3.4 ± 31	-7.8 ± 22
Overall improvement in CRT ON vs. CRT OFF = 11 points		

Table 16. Improvement in Quality of Life Score (N = 126)

6-Minute Hall Walk Test

Table 17 contains a summary of the improvement in 6-minute walk distance in the two treatment groups for this analysis. The average improvement in the CRT ON group over the CRT OFF group was approximately 28 meters.

	CRT OFF Mean ± SD (N = 43)	CRT ON Mean ± SD (N = 83)
Baseline	298 ± 94	284 ± 105
6-months	283 ± 150	297 ± 122
Change	-15 ± 142	13 ± 74
Overall improvement in CRT ON vs. CRT OFF = 28 meters		

Table 17. Improvement in 6-minute Walk Distance (meters) (N = 126)

Additional Data

Echocardiographic Data

Echocardiographic analysis was performed at the Baseline and 6-month follow-up visits. The following parameters were evaluated from the echocardiographic analysis: LVEDD, LVESD, LVEF, MR, E/A Wave Point Ratio, and Sphericity Index. Cardiac dyssynchrony (including Pre-Ejection Delay Time and Intraventricular Mechanical Delay) was also evaluated at Baseline and 6-Months. Table 18 displays summaries of the improvement in these parameters between Baseline and 6-months.

Parameter	CRT OFF Mean ± SD (N = 40)	CRT ON Mean ± SD (N = 82)
LVEDD (mm)	-2.4 ± 6.5	-4.3 ± 5.4
LVESD (mm)	-3.0 ± 6.4	-4.6 ± 7.0
LVEDV (ml)	-37 ± 53	-43 ± 69
LVESV (ml)	-36 ± 47	-43 ± 58
LVEF (%)	2.9 ± 6.2	4.3 ± 9.9
MR (grade)	0.10 ± 0.50	-0.06 ± 0.74
E/A Wave Point Ratio	-0.02 ± 1.2	-0.08 ± 0.8
Sphericity Index	0.02 ± 0.1	-0.02 ± 0.1
Pre-Ejection time (ms)	7.3 ± 33	-1.5 ± 52

Table 18. Improvement in Echocardiography Parameters

Parameter	CRT OFF Mean ± SD (N = 40)	CRT ON Mean ± SD (N = 82)
IVMD (ms)	-6.4 ± 48	-14.5 ± 52
Tei Index	-0.05 ± 0.5	-0.4 ± 0.8
Contraction Interval (ms)	-55 ± 103	-94 ± 124

Table 18. Improvement in Echocardiography Parameters (continued)

Biventricular Pacing at 6-months

The average percentage of biventricular pacing at the 6-month visit in the 83 patients who were in the CRT ON group among the 126 patients in the primary resynchronization cohort was 95% ± 6%, with a range of 70 to 100%.

Patient Discontinuation/Withdrawals

A total of 47 patients participating in the RHYTHM ICD study were withdrawn from the study. Twenty (20) patients (including the 19 patients with unsuccessful LV lead implants and the one patient with an unsuccessful system implant due to high defibrillation thresholds) were withdrawn approximately one month after unsuccessful system implants in accordance with the protocol. Twenty-two (22) patients died and were also withdrawn from the study. Three of the 22 deaths occurred in patients who had previously unsuccessful implants. In addition to these 20 unsuccessful implants and 22 deaths, 5 additional patients were withdrawn from the study. Table 19 summarizes the reason for these 5 patient withdrawals.

Reason for Withdrawal	CRT Group	Days after Implant
System Explant	N/A*	1
Heart Transplant	ON	75
Patient Request	ON	28
Patient Request	ON	397
Patient's Family Request	ON	293

Table 19. Patient Discontinuations/Withdrawals (Excludes Withdrawals for Deaths and after Unsuccessful Implants)

* Patient was withdrawn before the Baseline visit and randomization.

Conclusions Drawn From The RHYTHM ICD Study

In NYHA Class III and IV heart failure patients with LV dyssynchrony and a standard ICD indication, this study demonstrated that cardiac resynchronization is safe and improves functional status.

Summary of the V-V Optimization Phase of the RHYTHM ICD Study

The objective of the V-V Optimization Phase of the RHYTHM ICD study was to demonstrate that optimizing the interventricular timing of biventricular pacing therapy yields an improvement in exercise capacity (Peak VO_2) or in left ventricular performance as measured by echocardiography using the left ventricular end systolic diameter (LVESD), that is similar to simultaneous biventricular pacing in a standard ICD indicated patient population with advanced heart failure (NYHA Classification III or IV) and prolonged QRS duration. Included in the study were the Epic HF Models V-337 and V-338[3] devices and the Atlas+ HF Model V-343 device.

The primary endpoint was stated as follows (where p is defined as the percentage of patients improved):

H_0: p (Optimized V-V) ≤ p (Simultaneous) - 0.25
H_1: p (Optimized V-V) > p (Simultaneous) - 0.25.

3. The Epic HF Model V-338 device had the Interventricular Pace Delay enabled by the programmer.

Patients completed a cardiopulmonary exercise test (CPET) and an echocardiography test at the Baseline and 6-month visits. The sample size required to satisfy the endpoint was 120 patients (72 in the Simultaneous group and 48 in the Optimized group).

The total time of follow-up from the time of successful implant was 3328.7 patient months. The average time of follow-up was 15.2 ± 4.3 (range 0.7 to 26.7) patient months.

Summary of V-V Optimization

At the time of the Baseline visit, all patients underwent echo guided optimization of their AV delay. Patients who were randomized to the Optimized group also underwent echo guided optimization of the interventricular pace delay (V-V delay). Optimization of the V-V delay was determined using the procedure defined in the protocol, which evaluated multiple V-V delays ranging from 20-80 ms with either the LV or RV chamber selected as the first chamber paced. This testing sequence was randomized to minimize any bias in performing this evaluation. The final programmed value for the V-V delay was determined based on the maximum left ventricular velocity time integral (VTI), which was assessed by pulse wave Doppler interrogation of the left ventricular outflow tract.

Table 20 displays the distribution of the optimized V-V delay settings among the 48 patients in the Optimized group. The optimized V-V settings were approximately evenly distributed among the patients. Only 5 patients (10.4%) were optimized to the simultaneous setting.

First Chamber Paced: V-V Delay	Number of Patients (N = 48)
LV First: 80 ms	6 (12.5%)
LV First: 40 ms	8 (16.7%)
LV First: 20 ms	9 (18.8%)
Simultaneous	5 (10.4%)
RV First: 20 ms	7 (14.6%)
RV First: 40 ms	6 (12.5%)
RV First: 80 ms	7 (14.6%)

Table 20. Distribution of Optimized V-V delay among Optimized group

Clinical Study Results

Three patients in the V-V Optimization Phase of the RHYTHM ICD study were not able to complete all the testing requirements at six months due to worsening heart failure. One patient was withdrawn prior to the 6-month visit when he received a heart transplant. This patient did not complete a 6-month CPET or echocardiographic evaluation. The other two patients completed a 6-month echocardiographic evaluation, but were not able to complete a 6-month CPET due to worsening heart failure.

Table 21 and Table 22 contain summaries of the Peak VO_2 and LVESD values at Baseline and 6-months, as well as the improvement from Baseline in the two treatment groups.

	Simultaneous Mean ± SD (N = 72)	Optimized Mean ± SD (N = 45)
Baseline	11.3 ± 3.1	11.5 ± 3.5
6-months	11.9 ± 3.3	12.4 ± 3.4
Change	0.57 ± 2.6	0.93 ± 3.2

Table 21. Baseline and 6-month Peak VO_2 (ml/kg/min)

	Simultaneous Mean ± SD (N = 72)	Optimized Mean ± SD (N = 45)
Baseline	57.0 ± 9.8	54.1 ± 12.1
6-months	52.2 ± 9.8	50.7 ± 11.9
Change	-4.7 ± 7.2	-3.4 ± 5.8

Table 22. Baseline and 6-month and LVESD (mm)

An analysis of the observed difference between the Optimized and Simultaneous groups was performed. A significant p-value ($p < 0.05$) meant that optimized pacing was not inferior to simultaneous pacing. The analysis compared patients that showed improvement in both Peak VO_2 *and* LVESD. Table 23 contains a summary of this analysis. The observed difference in proportion improved between the Simultaneous and Optimized groups (i.e., $p_{sim} - p_{opt}$) is 0.6% and the 95% Blackwelder confidence interval for the difference is (-100%, 14.5%). The p-value was 0.0004. The null hypothesis was rejected, and therefore optimized V-V pacing is not inferior to simultaneous pacing. Overall, improvement in Peak VO_2 and improvement in LVESD did not trend in the same direction. Simultaneous patients showed a greater improvement in LVESD and Optimized patients showed a greater improvement in Peak VO_2.

	Simultaneous (N = 72)		Optimized (N = 45)	
	Peak VO_2	LVESD	Peak VO_2	LVESD
% Improved*	37.5%	47.2%	45.8%	43.8%
% No Change	38.9%	44.4%	27.1%	45.8%
% Worsened	23.6%	8.3%	27.1%	10.4%
% Improved* in Peak VO_2 *and* LVESD	19.4%		18.8%	

Table 23. Percent of Improvement in Peak VO_2 (ml/kg/min) and LVESD (mm)

* Improvement in Peak VO_2 was defined as an increase of at least 1.1 ml/kg/min and improvement in LVESD was defined as a decrease of at least 5 mm

Conclusions Drawn From the V-V Optimization Phase of the RHYTHM ICD Study

Cardiac resynchronization therapy (CRT) with optimization of V-V delay was shown to be similar to CRT with

simultaneous pacing in terms of the percentage of patients that were found to be responders.

Summary of the PAVE Study

The Post-AV Node Ablation Evaluation (PAVE) study was a prospective, randomized, controlled, multi-center clinical trial conducted at 49 participating sites (44 in the US, 5 in Canada) comparing the safety and effectiveness results for patients receiving the Frontier™ Model 5508 CRT-P and the Aescula™ 1055K Left Heart Lead to those receiving legally marketed right ventricular pulse generators and standard leads following an AV nodal ablation for chronic atrial fibrillation. Chronic AF is defined as persisting without interruption for at least one month.

Patients with chronic (permanent) atrial fibrillation may also be indicated for and receive an ICD under FDA approved standard ICD indication language. The standard ICD indication includes patients who have experienced an episode of ventricular tachycardia or ventricular fibrillation (secondary prevention) or meet the criteria for prophylactic ICD therapy (primary prevention). Likewise, patients who have atrial fibrillation may receive a biventricular pacemaker if they have undergone AV nodal ablation for chronic (permanent) atrial fibrillation and have NYHA Class II or III heart failure. The prospective, randomized, controlled PAVE study was completed and successfully demonstrated that biventricular pacing is safe and effective in post-AV nodal ablation patients with NYHA Class II or III heart failure. The addition of ICD back-up therapy will not affect the biventricular pacing performance of the device and ICD therapy is the standard of care in patients with an ICD indication and chronic (permanent) atrial fibrillation. In addition, St. Jude Medical CRT-D devices have previously been proven to be safe and effective (RHYTHM ICD Study) in patients with an ICD indication and NYHA Class III or IV heart failure with prolonged QRS durations and LVEF £ 35%. Since the Epic HF CRT-D provides biventricular pacing similar to the Frontier II CRT-P[4], no additional clinical evaluation was performed.

4. The Frontier II CRT-P has the same functionality as the Frontier CRT-P with the addition of independently programmable ventricular outputs.

The study's cumulative implant duration for all enrolled patients was 8,979 months with a mean of 24.33 ± 15.22 months (range of 0.13 to 55.95 months). Two hundred and ten patients underwent successful LV lead placement. The cumulative duration for all investigational patients (BV, LV and Roll-in groups only) was 5,928 months.

For this randomized study, the key inclusion criteria were:

- Patients who will undergo complete AV nodal ablation for chronic atrial fibrillation (defined as persisting without interruption for at least one month) resulting in complete AV block
- Patients who are on a stable medical therapy regimen, and
- Patients who are able to complete the six-minute walk with the only limiting factor(s) being fatigue and/or shortness of breath.

Key study exclusion criteria were:

- Patients who are classified as NYHA Class IV
- Patients who can walk > 450 meters in six-minute walk test
- Patients who have an implanted ICD or being considered for implant of an ICD
- Patients with prosthetic valve replacements
- Patients with severe musculoskeletal disorder(s). and
- Patients who cannot independently comprehend and complete the quality of life questionnaire.

The overall study population included 369 patients. One hundred and fifty-one were randomized to BV, and 109 were randomized to RV. In addition, 53 were randomized to LV pacing under a previous revision of the investigational plan. Fifty-six were "Roll-in" patients (nonrandomized) and received the biventricular pacing system (Frontier CRT-P and Aescula lead system). All patients had permanent pacemaker implant indication following an elective AV nodal ablation for chronic atrial fibrillation. The mean age was 69.3 ± 9.93 years; 34.4% were female and 65.6% were male. Fourteen percent of the patients had no diagnosis of heart failure or were NYHA Class I, 49% were NYHA Class II, and 37% were NYHA Class III prior to implant.

Primary Effectiveness Objective and Result

Exercise capacity as measured by distanced walked in six-minute walk test

Objective: To determine if the treatment group (BV) shows a statistically significant improvement over the control group (RV) at the six months follow-up time.

Results: The treatment group (BV) showed statistically significant improvement over the control group (RV) in distance walked from pre-implant to six months ($p = 0.03$). The BV group also had a greater percentage of patients showing improvements than the RV group ($p = 0.035$). Figure 3 illustrates the improvement in the six-minute walk between BV and RV groups. Table 24 outlines the improvement distribution in the six-minute walk between BV and RV groups.

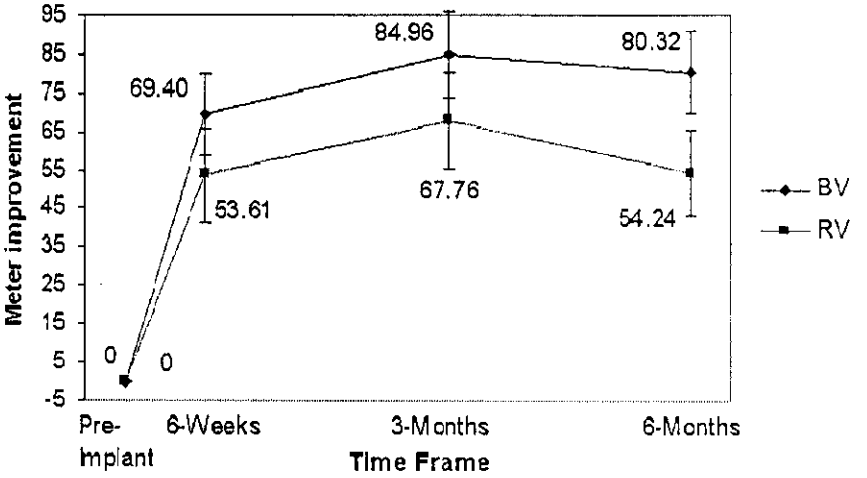


Figure 3. Improvements in Six-Minute Walk Distance in BV and RV Groups ($p = 0.03$)

	RV (N = 66)	BV (N = 84)
Improved (> 5 m)	46 (69.70%)	69 (82.14%)
No Change (–5 to 5 m)	4 (6.06%)	4 (4.76%)
Worsened (< –5 m)	16 (24.24%)	11 (13.10%)

Table 24. Distribution of Improvement in BV and RV Group in Six-Minute Walk (p = 0.035)

Secondary Effectiveness Objectives and Results

Quality of life as measured by SF-36 score

Objective: To determine if the BV group shows improvement over the RV group at the six-month follow-up in the health-related quality of life as measured by the SF-36 score.

Results: Using the SF-36 Quality-of-Life questionnaire, a standardized measurement of quality of life, the study found that for the six-week to six-month visit time period, the improvement in SF-36 scales was not different between groups.

Functional capacity as measured by peak VO_2

Objective: To determine if the BV group shows improvement in functional capacity, as measured by peak VO_2, from the six-week follow-up to the six-month follow-up.

Results: The BV group showed an improvement of 0.86 ml/kg/min in peak VO_2 from six weeks to six months measured during CPX testing. The BV group also had a greater percentage of patients showing improvement in peak VO_2. Figure 4 illustrates the improvement in peak VO_2 in BV and RV groups. Table 25 outlines the distribution of improvement in peak VO_2 between BV and RV groups.

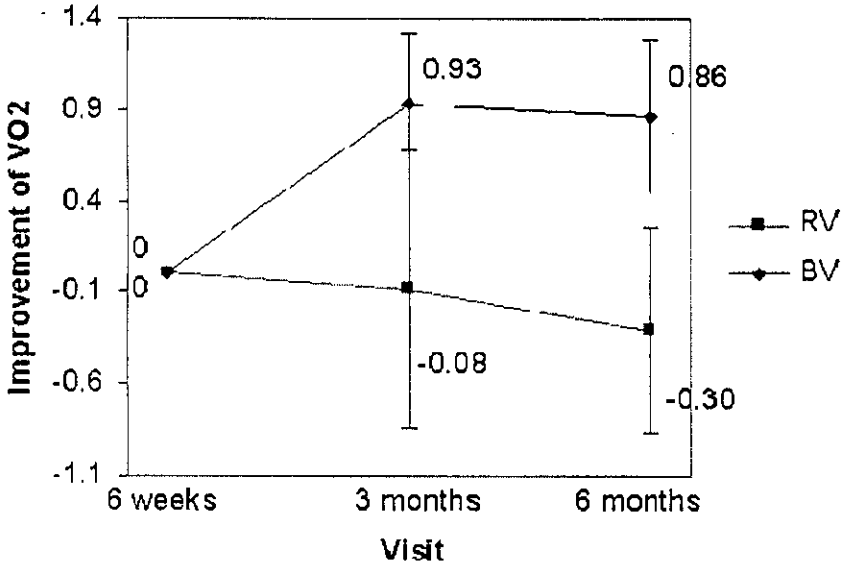


Figure 4. Improvements in Peak VO_2 in BV and RV Groups

Change in Peak VO_2 (ml/kg/min)	RV (N = 10)	BV (N = 35)
Improved (> 0.5)	4 (40%)	21 (60.0%)
No Change (–0.5 to 0.5)	0 (0%)	4 (11.4%)
Worsened (< –0.5)	6 (60%)	10 (28.6%)

Table 25. Distribution of Improvements in VO_2 in BV and RV groups

Patient Selection and Treatment

Pectoral or abdominal implant site. Evaluate the prospective patient's size and activity level to determine whether a pectoral or abdominal implant is suitable.

Exercise stress testing. If the patient's condition permits, use exercise stress testing to:

- Determine the maximum rate of the patient's normal rhythm
- Identify any supraventricular tachyarrhythmias
- Identify exercise-induced tachyarrhythmias.