Medtronic

MAXIMO® II CRT-D D264TRM

Digital implantable cardioverter defibrillator with cardiac resynchronization therapy (VVE-DDDR)

ATP During Charging™ Feature, TherapyGuide™ Feature, and Conexus® Wireless Telemetry

Clinician Manual

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

MAXIMO® II CRT-D D264TRM

Clinician Manual

A guide to the operation and programming of the Model D264TRM Maximo II CRT-D digital implantable cardioverter defibrillator with cardiac resynchronization therapy (VVE-DDDR)

Contents

1 System overview

1.1 Introduction

1.1.1 About this manual

This manual describes the operation and intended use of the Maximo II CRT-D Model D264TRM system.

1.1.1.1 Manual conventions

Throughout this manual, the word “device” refers to the implanted Maximo II CRT-D device.

The symbol ◈ in parameter tables indicates the Medtronic nominal value for that parameter.

The programmer screen image examples in this manual were produced using a Medtronic CareLink Model 2090 Programmer. These screen images are provided for reference only and may not match the final software.

The names of on-screen buttons are shown within brackets: [Button Name].

Programming instructions in this manual are often represented by a programming block, which describes the path through the application software to specific screens or parameters. The following conventions are used in programming blocks:

- The “⇒” symbol precedes the screen text you can select to navigate to a new screen.
- The “▷” symbol precedes the name of a parameter you can program for a feature.
- When a navigation step refers to a field on the screen that is labeled with both a row title and a column title, the “ | ” character is used to divide the separate titles. Parameter values, however, do not use this convention.
- When a particular value for a parameter must be selected to make the remaining parameters or navigation possible, that value appears within <brackets>.

Here is an example of a programming block using these conventions:

Select Params icon
- ⇒ Screen text to select…
  - ⇒ Screen field Row Title | Column Title…
    - ▷ Parameter Name <Required Value>
    - ▷ Parameter Name
    - ▷ Parameter Name

1.1.1.2 Nomenclature for product battery life terms

This manual uses a nomenclature for certain terms related to product battery life as defined in CENELEC pacemaker standard EN 45502-2-1:2003. This standard applies to Active Implantable Medical Devices (AIMD) intended to treat bradyarrhythmias. This standard was approved and published in December 2003.

Medtronic has adopted this nomenclature to comply with the CENELEC standard and in anticipation of the nomenclature becoming an international standard. The nomenclature defined in EN 45502-2-1:2003 replaces previously used terms related to product battery life.

The nomenclature defined in EN 45502-2-1:2003, and the terms this nomenclature replaces, are presented in the following table:

Nomenclature in EN 45502-2-1: 2003		**Previously used nomenclature**	
BOS	Beginning of Service	BOL	Beginning of Life
EOS	End of Service	EOL	End of Life
RRT	Recommended Replacement Time	ERI	Elective Replacement Indicator
PSP	Prolonged Service Period	Post-ERI conditions	
Projected service life		Longevity projections	

1.1.2 Product literature

Before implanting the device, it is strongly recommended that you take the following actions:

- Read the product literature provided for information about prescribing, implanting, and using the device, and for conducting a patient follow-up session.
- Thoroughly read the technical manuals for the leads used with the device. Also read the technical manuals for other system components.
- Discuss the device and implant procedure with the patient and any other interested parties, and provide them with any patient information materials packaged with the device.

1.1.3 Technical support

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products.

In addition, Medtronic maintains a professional staff of consultants to provide technical consultation to product users.

For more information, contact your local Medtronic representative, or call or write Medtronic at the appropriate address or telephone number listed on the back cover.

1.1.4 Customer education

Medtronic invites physicians to attend an educational seminar on the device. The course describes indications for use, system functions, implant procedures, and patient management.

1.1.5 References

The primary reference for background information is Zacouto FI, Guize LJ. Fundamentals of Orthorhythmic Pacing. In: Luderitz B, Ed. *Cardiac Pacing Diagnostic and Therapeutic Tools.* New York: Springer-Verlag; 1976: 212-218.

See these additional references for more background information:

- Estes M, Manolis AS, Wang P, Eds. *Implantable Cardioverter-Defibrillators*. New York, NY: Marcel Dekker, Inc. 1994.
- Kroll MW, Lehmann MH, Eds. *Implantable Cardioverter-Defibrillator Therapy: The Engineering-Clinical Interface*. Norwell, MA: Kluwer Academic Publishers 1996.
- Singer I, Ed. *Implantable Cardioverter-Defibrillator*. Armonk, NY: Futura Publishing Co. 1994.
- Singer I, Barold SS, Camm AJ, Eds. *Nonpharmacological Therapy of Arrhythmias for the 21st Century: The State of the Art*. Armonk, NY: Futura Publishing Co. 1998.
- Stadler RW, Gunderson BD, Gillberg JM. An Adaptive Interval-Based Algorithm for Withholding ICD Therapy During Sinus Tachycardia. *Pace*. 2003; 26:1189–1201.

1.1.6 FCC Compliance information

FCC ID:LF5MICSIMPLANT2 – This device complies with Part 15 of the FCC rules respectively. Operation is subject to the following two conditions: (1) this device may not cause harmful interference, and (2) this device must accept any interference received, including interference that may cause undesired operation. The user is cautioned that changes or modifications not expressly approved by the party responsible for compliance could void the user's authority to operate the equipment.

This transmitter is authorized by rule under the Medical Device Radio Communications Service (47 C.F.R. Part 95) and must not cause harmful interference to stations operating in the 400.150 - 406.000 MHz band in the Meteorological Aids (i.e., transmitters and receivers used to communicate weather data), the Meteorological Satellite, or the Earth Exploration Satellite Services and must accept interference that may be caused by such aids, including interference that may cause undesired operation.

This transmitter shall be used only in accordance with the FCC Rules governing the Medical Device Radio Communications Service. Analog and digital voice communications are

prohibited. Although this transmitter has been approved by the Federal Communications Commission, there is no guarantee that it will not receive interference or that any particular transmission from this transmitter will be free from interference.

1.1.7 Explanation of symbols

The following list of symbols applies to various products. Refer to the package labels to see which symbols apply to this product.

Table 1. Explanation of symbols on package labeling

Symbol	Explanation
CE 0123	Conformité Européenne (European Conformity). This symbol means that the device fully complies with AIMD Directive 90/385/EEC (NB 0123) and R&TTE Directive 1999/5/EC.
N13571 Z813	This symbol means that the device fully complies with the Australian Communications and Media Authority (ACMA) and the New Zealand Ministry of Economic Development Radio Spectrum Management standards for radio communications products.
www.medtronic.com/radio	Radio compliance. This symbol means that telecommunications and radio communications regulations in your country may apply to this product. Please go to www.medtronic.com/radio for specific compliance information related to telecommunications and radio standards for this product in your country.
MR	MR Conditional. The SureScan pacing system is safe for use in the MRI environment when used according to the instructions in the SureScan technical manual. **Note:** Not all devices are MR Conditional.
!	Caution
	Open here
	Do not use if package is damaged
2	Do not reuse
STERILE EO	Sterilized using ethylene oxide
i	Consult instructions for use

Table 1. Explanation of symbols on package labeling (continued)

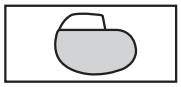
Symbol	Explanation
! USA	For US audiences only
	Date of manufacture
	Manufacturer
EC REP	Authorized representative in the European community
	Use by
LOT	Lot number
REF	Reorder number
SN	Serial number
	Temperature limitation
	Adaptive
	Package contents
	IPG device
	Coated (IPG device)

Table 1. Explanation of symbols on package labeling (continued)

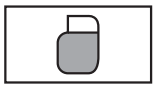
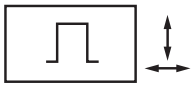
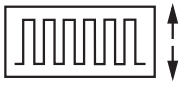
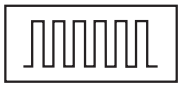
Symbol	Explanation
	ICD device
	Coated (ICD device)
	Cardiac resynchronization therapy (CRT) device
	Coated (CRT device)
	Product documentation
	Torque wrench
	Accessories
	Amplitude/pulse width
	Atrial amplitude/pulse width
	RV amplitude/pulse width
	LV amplitude/pulse width
	Upper tracking rate/lower rate
	Rate

Table 1. Explanation of symbols on package labeling (continued)

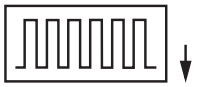
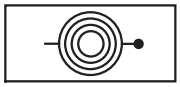
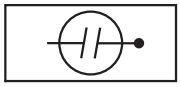
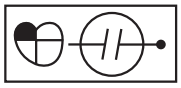
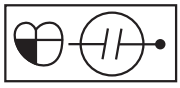
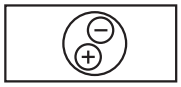
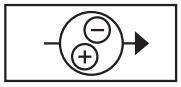
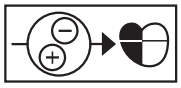
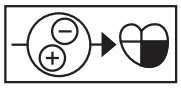
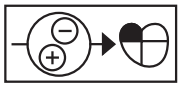
Symbol	Explanation
	Lower rate
	Sensitivity
	Sensed A-V interval
	A-V interval (paced/sensed)
	Refractory period
	Atrial refractory period
	Ventricular refractory period
	(PVARP) Post Ventricular Atrial Refractory Period
	Polarity
	Pacing polarity (single chamber)
	Pacing polarity (dual chamber)
	LV Pace polarity
	Atrial Pace polarity

Table 1. Explanation of symbols on package labeling (continued)

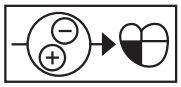
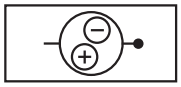
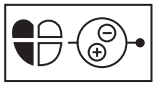
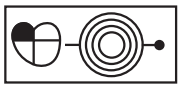
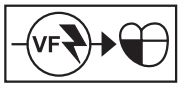
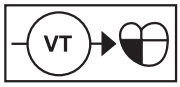
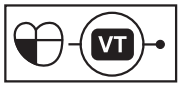
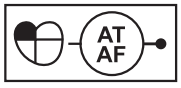
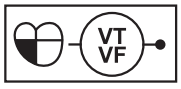
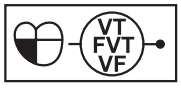
Symbol	Explanation
	RV Pace polarity
	Sensing polarity (single chamber)
	Sensing polarity (dual chamber)
	Atrial sensitivity
	Ventricular sensitivity
	VF therapies (del/sto)
	VT therapies
	V pacing/V-V pace delay
	VT monitor
	AT/AF detection
	VT, VF detection
	VT, FVT, VF detection
	AT/AF therapies

Table 1. Explanation of symbols on package labeling (continued)

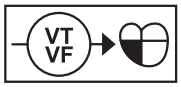
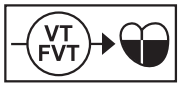
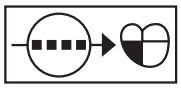
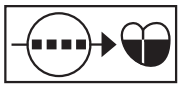
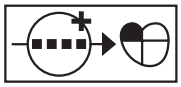
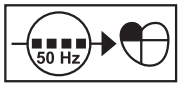
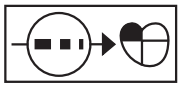
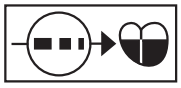
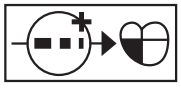
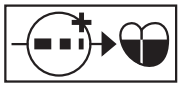
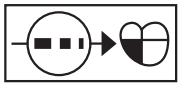
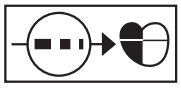
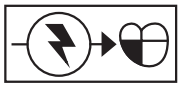
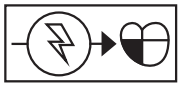
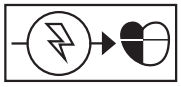
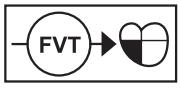
Symbol	Explanation
	VT, VF therapies
	VT, FVT therapies (CRT)
	AT/AF intervention
	Burst
	Burst (CRT)
	Burst+
	50 Hz Burst
	A ramp
	Ramp (CRT)
	Ramp+
	Ramp+ (CRT)
	V ramp
	AV ramp

Table 1. Explanation of symbols on package labeling (continued)

Symbol	Explanation
	Defibrillation
	V cardioversion
	AV cardioversion
	FVT therapies
	Mode Switch
	Magnet Rate
	Dangerous voltage
	Active Can

1.1.8 Notice

The Patient Information feature of the programmer software application is provided as an informational tool for the end user. The user is responsible for accurate input of patient information into the software. Medtronic makes no representation as to the accuracy or completeness of the patient information that end users supply for use with the Patient Information feature. Medtronic SHALL NOT BE LIABLE FOR ANY DIRECT, INDIRECT, INCIDENTAL, OR CONSEQUENTIAL DAMAGES TO ANY THIRD PARTY WHICH RESULT FROM THE USE OF THE PATIENT INFORMATION SUPPLIED BY END USERS TO THE SOFTWARE.

For more information about the Patient Information feature, see Section 4.10.

1.2 System description

The Medtronic Model D264TRM Maximo II CRT-D dual chamber implantable cardioverter defibrillator with cardiac resynchronization therapy (CRT-D) is a multiprogrammable cardiac device that monitors and regulates the patient's heart rate by providing single or dual chamber rate-responsive bradycardia pacing, sequential biventricular pacing, and ventricular tachyarrhythmia therapies.

The device senses the electrical activity of the patient's heart using the electrodes of the implanted atrial and right ventricular leads. It then analyzes the heart rhythm based on selectable detection parameters.

The device can automatically detect ventricular tachyarrhythmias (VT/VF) and provide treatment with defibrillation, cardioversion, and antitachycardia pacing therapies. The device can also automatically detect atrial tachyarrhythmias (AT/AF). Simultaneous or sequential biventricular pacing is used to provide patients with cardiac resynchronization therapy. The device responds to bradyarrhythmias by providing bradycardia pacing therapies.

The device also provides diagnostic and monitoring information that assists with system evaluation and patient care.

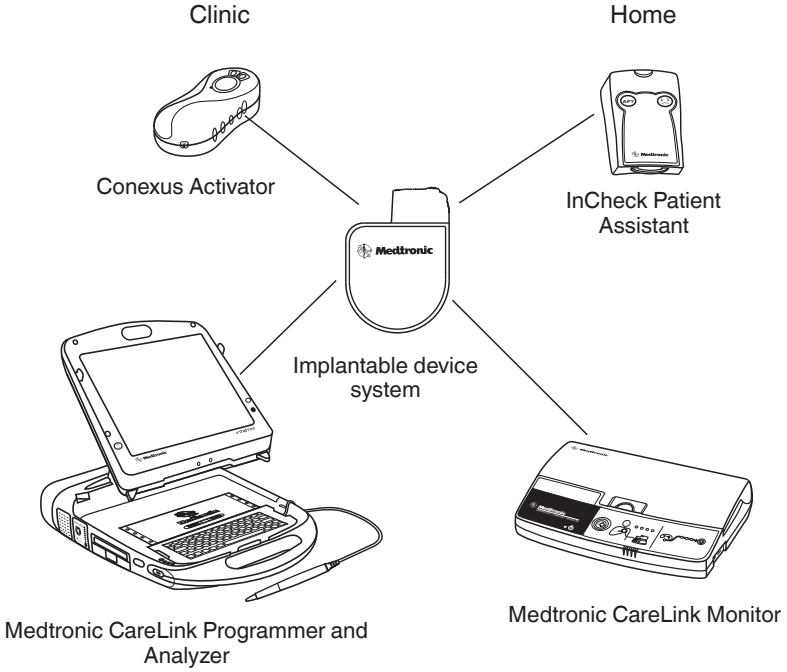
The device has the DF4 inline connector, which facilitates the connection of a DF4-LLHH or DF4-LLHO lead during the implant. DF4-LLHH and DF4-LLHO refer to the international standard ISO 27186:2010, where the lead connector contacts are defined as low voltage (L), high voltage (H), or open (O).

Leads – The lead system used with this device must provide pacing to the left ventricle (LV); sensing, pacing, and cardioversion and defibrillation therapies to the right ventricle (RV); and sensing and pacing to the atrium (A). Do not use any lead with this device without first verifying lead and connector compatibility.

For information about selecting and implanting leads for this device, refer to Section 5.2, "Selecting and implanting the leads", page 99.

Implantable device system – The Model D264TRM Maximo II CRT-D along with pacing leads and defibrillation leads constitute the implantable portion of the device system. The following figure shows the major components that communicate with the implantable device system.

Figure 1. System components



Programmers and software – The Medtronic CareLink Model 2090 Programmer and software are used to program this device. The Medtronic CareLink Model 2090 Programmer with Conexus wireless telemetry is designed to provide clinicians and patients with an easy and efficient implant, follow-up, and monitoring experience. Conexus wireless telemetry eliminates the need to have a programming head placed over the implanted device for the duration of a programming or monitoring session. The system uses radio frequency (RF) telemetry for wireless communication between the implanted device and programmer in the hospital or clinic. Conexus telemetry operates within the Medical Implant Communications Service (MICS) Band, which is the only band designated for implantable medical devices. Using the MICS Band prevents interference with home electronics such as microwaves, cell phones, and baby monitors.

To turn on Conexus telemetry in an implanted device, you must use the Conexus Activator or the programming head. If you do not use the Conexus Activator or if you are using a programmer with nonwireless telemetry, you will need to use the programming head to both initiate and conduct communications with the device in the clinic.

During a wireless telemetry session, all other programmers are prevented from communicating or initiating a session with the patient's implanted device, maintaining patient safety and privacy. Similarly, other patients with implanted devices are not affected by any communication or programming occurring during the patient's session.

Programmers from other manufacturers are not compatible with Medtronic devices but will not damage Medtronic devices.

Model 27901 Conexus Activator – The Medtronic Model 27901 Conexus Activator allows you to turn on Conexus wireless telemetry for implanted devices that support wireless telemetry. The Conexus Activator is used in conjunction with the Medtronic CareLink Model 2090 Programmer with Conexus telemetry in the hospital or clinic.

Model 2290 Analyzer – The system supports the use of the Medtronic CareLink Model 2290 Analyzer, an accessory of the Medtronic CareLink programmer. The system allows you to have a device session and an analyzer session running at the same time, to quickly switch from one to the other without having to end or restart sessions, and to send data from the analyzer to the programmer.

Remote View – The system supports Remote View, which allows you to use your personal computer to view the screen displays from a Medtronic CareLink programmer that may be in a clinic, hospital or other location. You need to install and configure the Remote View software on your personal computer before you are able to view a programming session. Installation and configuration instructions are provided with the software. Refer to the programmer reference guide for information about using Remote View.

Model 2490C Medtronic CareLink Monitor – Patients use the Model 2490C monitor to automatically gather information from their implanted device and communicate the information to their physician. The monitor communicates wirelessly with the patient's device and transmits the information over a home telephone line at times scheduled by the clinic. Typically, these transmissions are scheduled while the patient is asleep. The monitor can also send device alerts to the clinic outside of the scheduled transmission times, if the device has been programmed to do so. The patient does not need to interact with the monitor other than performing the initial setup procedure. Refer to the monitor literature for connection and usage information.

Model 2696 InCheck Patient Assistant – Patients can use the Model 2696 InCheck Patient Assistant to perform the following tasks:

- Initiate recording of cardiac event data in the device memory.
- Verify whether the implanted device has detected a suspected atrial tachyarrhythmia.

Contents of sterile package – The package contains one implantable cardioverter defibrillator and one torque wrench.

1.3 Indications and usage

The Maximo II CRT-D system is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias and for providing cardiac resynchronization therapy in heart failure patients on stable, optimal heart failure medical therapy if indicated, and meet any of the following classifications:

- New York Heart Association (NYHA) Functional Class III or IV and who have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration.
- Left bundle branch block (LBBB) with a QRS duration ≥ 130 ms, left ventricular ejection fraction ≤ 30%, and NYHA Functional Class II.
- NYHA Functional Class I, II, or III and who have left ventricular ejection fraction ≤50% and atrioventricular block (AV block) that are expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize right ventricular pacing. Optimization of heart failure medical therapy that is limited due to AV block or the urgent need for pacing should be done post implant.

1.4 Contraindications

The Maximo II CRT-D system is contraindicated for patients experiencing tachyarrhythmias with transient or reversible causes including, but not limited to, the following: acute myocardial infarction, drug intoxication, drowning, electric shock, electrolyte imbalance, hypoxia, or sepsis.

The device is contraindicated for patients who have a unipolar pacemaker implanted.

The device is contraindicated for patients with incessant VT or VF.

2 Warnings, precautions, and potential adverse events

2.1 General warnings and precautions

Avoiding shock during handling – Disable tachyarrhythmia detection during implant, explant, or postmortem procedures. The device can deliver a high-voltage shock if the defibrillation terminals are touched.

Electrical isolation during implant – Do not allow the patient to have contact with grounded electrical equipment that might produce electrical current leakage during implant. Electrical current leakage may induce tachyarrhythmias that may result in the patient's death.

External defibrillation equipment – Keep external defibrillation equipment nearby for immediate use whenever tachyarrhythmias are possible or intentionally induced during device testing, implant procedures, or post-implant testing.

Lead compatibility – Do not use another manufacturer's leads without demonstrated compatibility with Medtronic devices. If a lead is not compatible with a Medtronic device, the result may be undersensing of cardiac activity, failure to deliver necessary therapy, or a leaking or intermittent electrical connection.

2.2 Explant and disposal

Consider the following information related to device explant and disposal:

- Interrogate the device and disable tachyarrhythmia detection before explanting, cleaning, or shipping the device. This prevents the device from delivering unwanted shocks.
- Explant the implantable device postmortem. In some countries, explanting battery-operated implantable devices is mandatory because of environmental concerns; please check the local regulations. In addition, if subjected to incineration or cremation temperatures, the device may explode.
- Medtronic implantable devices are intended for single use only. Do not resterilize and reimplant explanted devices.
- Please use the Tachyarrhythmia Product Information Report to return explanted devices to Medtronic for analysis and disposal.

2.3 Handling and storage instructions

Carefully observe these guidelines when handling or storing the device.

2.3.1 Device handling

Checking and opening the package – Before opening the sterile package tray, visually check for any signs of damage that might invalidate the sterility of the package contents.

If the package is damaged – The device packaging consists of an outer tray and inner tray. Do not use the device or accessories if the outer packaging tray is wet, punctured, opened, or damaged. Return the device to Medtronic because the integrity of the sterile packaging or the device functionality may be compromised. This device is not intended to be resterilized.

Sterilization – Medtronic has sterilized the package contents with ethylene oxide before shipment. This device is for single use only and is not intended to be resterilized.

Device temperature – Allow the device to reach room temperature before it is programmed or implanted. Device temperature above or below room temperature may affect initial device function.

Dropped device – Do not implant the device if it has been dropped on a hard surface from a height of 30 cm (12 in) or more after it is removed from its packaging.

“Use by” date – Do not implant the device after the “Use by” date because the battery longevity could be reduced.

For single use only – Do not resterilize and reimplant an explanted device.

2.3.2 Device storage

Avoid magnets – To avoid damaging the device, store the device in a clean area away from magnets, kits containing magnets, and any sources of electromagnetic interference.

Temperature limits – Store and transport the package between –18 °C and +55 °C (0 °F and 131 °F). Electrical reset may occur at temperatures below –18 °C (0 °F). Device longevity may decrease and performance may be affected at temperatures above +55 °C (131 °F).

2.4 Lead evaluation and lead connection

Refer to the lead technical manuals for specific instructions and precautions about lead handling.

Hex wrench – Use only the torque wrench supplied with the device. The torque wrench is designed to prevent damage to the device from overtightening a setscrew. Other torque

wrenches, (for example a blue-handled or right-angled hex wrench) have torque capabilities greater than the lead connector can tolerate.

Lead connection – Consider the following information when connecting the lead and the device:

- Cap abandoned leads to avoid transmitting electrical signals.
- Plug any unused lead ports to protect the device.
- Verify lead connections. Loose lead connections may result in inappropriate sensing and failure to deliver arrhythmia therapy.

Lead Impedance – Consider the following information about lead impedance when evaluating the lead system:

- Ensure that the defibrillation lead impedance is greater than 20 Ω. An impedance of less than 20 Ω may damage the device or prevent delivery of high-voltage therapy.
- Before taking electrical or defibrillation efficacy measurements, move objects made from conductive materials, such as guide wires, away from all electrodes. Metal objects, such as guide wires, can short circuit a device and lead, causing electrical current to bypass the heart and possibly damage the device and lead.
- If the LV pacing impedance for pacing LVtip to RVcoil is greater than 3000 Ω and the V. Defib (HVB) impedance is greater than 200 Ω, then use LV EGM (LVtip to Can) to assess the integrity of the LV lead.

Patch leads – Do not fold, alter, or remove any portion of a patch lead. Doing so may compromise electrode function or longevity.

2.5 Device operation

Accessories – Use this device only with accessories, parts subject to wear, and disposable items that have been tested to technical standards and found safe by an approved testing agency.

Battery depletion – Carefully monitor battery longevity. Battery depletion eventually causes the device to stop functioning. Cardioversion and defibrillation are high-energy therapies that shorten battery longevity. An excessive number of charging cycles also shortens battery longevity.

Charge Circuit Timeout or Charge Circuit Inactive – Contact a Medtronic representative and replace the device immediately if the programmer displays a Charge Circuit Timeout or Charge Circuit Inactive message. If this message is displayed, high-voltage therapies are not available for the patient.

Concurrent pacemaker use – If a separate pacemaker is used concurrently with the ICD, verify that the ICD does not sense the pacemaker output pulses because this can affect the detection of tachyarrhythmias by the ICD. Program the pacemaker to deliver pacing pulses at intervals longer than the ICD tachyarrhythmia detection intervals.

Device status indicators – If any of the device status indicators (for example, Electrical Reset) are displayed on the programmer after interrogating the device, inform a Medtronic representative immediately. If these device status indicators are displayed, therapies may not be available to the patient.

Electrical reset – Electrical reset can be caused by exposure to temperatures below –18 °C (0 °F) or strong electromagnetic fields. Advise patients to avoid strong electromagnetic fields. Observe temperature storage limits to avoid exposure of the device to cold temperatures. If a partial reset occurs, pacing resumes in the programmed mode with many of the programmed settings retained. If a full reset occurs, the device operates in VVI mode at 65 bpm. Electrical reset is indicated by a programmer warning message that is displayed immediately upon interrogation. To restore the device to its previous operation, it must be reprogrammed. Inform a Medtronic representative if your patient's device has reset.

End of Service (EOS) indicator – Replace the device immediately if the programmer displays an EOS indicator. The device may soon lose the ability to pace, sense, and deliver therapy adequately.

Follow-up testing – Consider the following information when performing follow-up testing of the device:

- Keep external defibrillation equipment nearby for immediate use. Potentially harmful spontaneous or induced tachyarrhythmias may occur during device testing.
- Changes in the patient's condition, drug regimen, and other factors may change the defibrillation threshold (DFT), preventing the device from terminating the patient's tachyarrhythmias postoperatively. Successful termination of ventricular fibrillation or ventricular tachycardia during the implant procedure is no assurance that tachyarrhythmias can be terminated postoperatively.

Higher than programmed energy – The device may deliver a therapy of higher than programmed energy if it was previously charged to a higher energy and that charge remains on the capacitors.

Magnets – Positioning a magnet over the device suspends tachyarrhythmia detection, but does not alter bradycardia therapy. If you place a programming head over the device during a wireless telemetry session, the magnet in the programming head always suspends tachyarrhythmia detection. If you place a programming head over the device and establish a nonwireless telemetry session, tachyarrhythmia detection is not suspended.

Pacemaker-mediated tachycardia (PMT) intervention – Even with the PMT Intervention feature programmed on, PMTs may still require clinical intervention such as device reprogramming, drug therapy, or lead evaluation.

Pacing and sensing safety margins – Lead maturation may cause sensing amplitudes to decrease and pacing thresholds to increase, which can cause undersensing or a loss of capture. Provide an adequate safety margin when selecting values for pacing amplitude, pacing pulse width, and sensitivity parameters.

Patient safety during a wireless telemetry session – Make sure that you have selected the appropriate patient before proceeding with a wireless patient session. Maintain visual contact with the patient for the duration of the session. If you select the wrong patient and continue with the session, you may inadvertently program the patient's device to the wrong settings.

Phrenic nerve stimulation – Phrenic nerve stimulation may occur as a result of left ventricular pacing at higher amplitudes. Although this is not life threatening, it is recommended that you test for phrenic nerve stimulation at various pacing amplitude settings with the patient in various positions. If phrenic nerve stimulation occurs with the patient, determine the minimum pacing threshold for phrenic nerve stimulation and program the pacing amplitude to a value that minimizes stimulation but provides an adequate pacing safety margin. Carefully consider the relative risks of phrenic nerve stimulation versus loss of capture before programming lower pacing amplitudes for the patient.

Programmers – Use only Medtronic programmers and application software to communicate with the device. Programmers and software from other manufacturers are not compatible with Medtronic devices.

Rate-responsive modes – Do not program rate-responsive modes for patients who cannot tolerate rates above the programmed Lower Rate. Rate-responsive modes may cause discomfort for those patients.

Shipping values – Do not use shipping values or nominal values for pacing amplitude and sensitivity without verifying that the values provide adequate safety margins for the patient.

Single chamber atrial modes – Do not program single chamber atrial modes for patients with impaired AV nodal conduction. Ventricular pacing does not occur in these modes.

Slow retrograde conduction and PMT – Slow retrograde conduction may induce pacemaker-mediated tachycardia (PMT) when the VA conduction time is greater than 400 ms. Programming PMT Intervention can only help prevent PMT when the VA conduction time is less than 400 ms.

Testing for cross-stimulation – At implant, and regularly when atrial ATP therapy is enabled, conduct testing at the programmed atrial ATP output settings to ensure that ventricular capture does not occur. This is particularly important when the lead is placed in the inferior atrium.

Twiddler's syndrome – Twiddler's syndrome, the tendency of some patients to manipulate their device after implant, may cause the pacing rate to increase temporarily if the device is programmed to a rate-responsive mode.

2.5.1 Pacemaker-dependent patients

Ventricular Safety Pacing – Always program Ventricular Safety Pacing (VSP) to On for pacemaker-dependent patients. Ventricular Safety Pacing prevents ventricular asystole due to inappropriate inhibition of ventricular pacing caused by oversensing in the ventricle.

ODO pacing mode – Pacing is disabled under ODO pacing mode. Do not program the ODO mode for pacemaker-dependent patients. Instead, use the Underlying Rhythm Test to provide a brief period without pacing support.

Underlying Rhythm Test – Use caution when using the Underlying Rhythm Test to inhibit pacing. The patient is without pacing support when pacing is inhibited.

2.6 Medical therapy hazards

Computed tomographic x-ray (CT scan) – If the patient undergoes a CT scan procedure and the device is not directly in the CT scan beam, the device is not affected.

If the device is directly in the CT scan beam, oversensing may occur for the duration of time the device is in the beam. If the device will be in the beam for more than 4 s, take the following precautions to minimize complications:

- Suspend tachyarrhythmia detection using a magnet, or disable tachyarrhythmia detection using the programmer. After the CT scan is complete, remove the magnet or use the programmer to enable tachyarrhythmia detection.
- If appropriate for the patient, program the pacing mode to minimize the effects of oversensing on pacing (for example, false inhibition). For pacemaker-dependent patients, program the device to an asynchronous pacing mode. After the CT scan is complete, program the pacing mode to its original setting.

Diathermy – People with metal implants such as pacemakers, implantable cardioverter defibrillators (ICDs), and accompanying leads should not receive diathermy treatment. The interaction between the implant and diathermy can cause tissue damage, fibrillation, or damage to the device components, which could result in serious injury, loss of therapy, and/or the need to reprogram or replace the device.

Electrosurgical cautery – Electrosurgical cautery may induce ventricular tachyarrhythmias and fibrillation or may cause device malfunction. If electrosurgical cautery cannot be avoided, take the following precautions to minimize complications:

- Keep temporary pacing and defibrillation equipment available.

- For pacemaker-dependent patients, program the device to an asynchronous pacing mode. After the electrosurgical cautery procedure is complete, program the pacing mode to its original setting.
- Suspend tachyarrhythmia detection using a magnet, or disable tachyarrhythmia detection using the programmer. After the electrosurgical cautery procedure is complete, remove the magnet or use the programmer to enable tachyarrhythmia detection.
- Use a bipolar electrocautery system if possible. If unipolar cautery is used, position the ground plate so the current pathway does not pass through or near the device and lead system. The current pathway should be a minimum of 15 cm (6 in) away from the device and lead system.
- Avoid direct contact of the cautery equipment with the implanted device or leads. Direct contact may damage the device or leads.
- Use short, intermittent, and irregular bursts at the lowest clinically appropriate energy levels.

External defibrillation – External defibrillation may damage the implanted device. External defibrillation may also temporarily or permanently elevate pacing thresholds or temporarily or permanently damage the myocardium at the electrode tissue interface. Current flow through the device and lead may be minimized by taking the following precautions:

- Use the lowest clinically appropriate defibrillation energy.
- Position the defibrillation patches or paddles a minimum of 15 cm (6 in) away from the device.
- Position the defibrillation patches or paddles perpendicular to the device and lead system.

If an external defibrillation is delivered within 15 cm (6 in) of the device, contact a Medtronic representative.

Lithotripsy – Lithotripsy may permanently damage the device if the device is at the focal point of the lithotripter beam. If lithotripsy must be performed, take the following precautions:

- Disable tachyarrhythmia detection using the programmer. After the lithotripsy procedure is complete, enable tachyarrhythmia detection.
- For pacemaker-dependent patients, program the device to an asynchronous pacing mode. After the lithotripsy procedure is complete, program the pacing mode to its original setting.
- Keep the focal point of the lithotripter beam a minimum of 2.5 cm (1 in) away from the implanted device.

Magnetic resonance imaging (MRI) – Do not use magnetic resonance imaging (MRI) on patients who have this device implanted. MRI can induce currents on implanted leads, potentially causing tissue damage and the induction of tachyarrhythmias. MRI may also cause damage to the device.

Medical treatment influencing device operation – The electrophysiological characteristics of a patient's heart can change over time, especially if the patient's medications have changed. As a result of the changes, programmed therapies may become ineffective and possibly dangerous to the patient. Conduct regular follow-up appointments to monitor the appropriateness of programmed therapies.

Radio frequency (RF) ablation – An RF ablation procedure may cause device malfunction or damage. Radio frequency ablation risks may be minimized by taking the following precautions:

- Keep temporary pacing and defibrillation equipment available.
- Program the pacing mode to minimize the effects of oversensing on pacing (for example, false tracking or false inhibition). For pacemaker-dependent patients, program the device to an asynchronous pacing mode. For patients who are not pacemaker-dependent, program the device to a nonpacing mode. After the ablation procedure is complete, program the pacing mode to its original setting.
- Suspend tachyarrhythmia detection using a magnet, or disable tachyarrhythmia detection using the programmer. After the ablation procedure is complete, remove the magnet or use the programmer to enable tachyarrhythmia detection.
- Avoid direct contact between the ablation catheter and the implanted system.
- Position the ground plate so the current pathway does not pass through or near the device and lead system. The current pathway should be a minimum of 15 cm (6 in) away from the device and lead system.

Radiotherapy and oversensing – If the patient undergoes radiotherapy, the device may inappropriately sense direct or scattered radiation as cardiac activity for the duration of the procedure. Take the following precautions to minimize complications:

- Suspend tachyarrhythmia detection using a magnet, or disable tachyarrhythmia detection using the programmer. After the radiotherapy procedure is complete, remove the magnet or use the programmer to enable tachyarrhythmia detection.
- For pacemaker-dependent patients, program the device to an asynchronous pacing mode. After the radiotherapy procedure is complete, program the pacing mode to its original setting.

Radiotherapy and device damage – Do not expose the device to high doses of direct or scattered radiation. An accumulated dose of radiation to the device circuits above 5 Gy may damage the device; however, the damage may not be immediately apparent. Damage may

present in various ways including increased current drain leading to shortened device life or a shift in sensing performance.

If a patient requires radiation therapy, from any source, do not expose the device to radiation exceeding an accumulated dose of 5 Gy. Use appropriate shielding or other measures to limit device exposure. The accumulated dose from diagnostic x-ray, CT scan, or fluoroscopic equipment is normally not sufficient to cause damage to the device. Consider the accumulated dose to the device from previous exposures for patients undergoing multiple radiation treatments.

Radiotherapy and device operational errors – Exposing the device to direct or scattered neutrons may cause electrical reset of the device, errors in device functionality, errors in diagnostic data, or loss of diagnostic data. To help reduce the chance of electrical reset due to neutron exposure, deliver radiotherapy treatment using photon beam energies less than or equal to 10 MV. The use of conventional x-ray shielding during radiotherapy does not protect the device from the effects of the neutrons. If photon beam energies exceed 10 MV, Medtronic recommends interrogating the device immediately after radiotherapy treatment. An electrical reset requires reprogramming of device parameters. Electron beam treatments do not cause electrical reset of the device.

Therapeutic ultrasound – Do not expose the device to therapeutic ultrasound. Therapeutic ultrasound may permanently damage the device.

2.7 Home and occupational environments

Cellular telephones – This device contains a filter that prevents most cellular telephone transmissions from interacting with device operation. To further minimize the possibility of interaction, instruct patients to:

- Maintain a minimum separation of 15 cm (6 in) between the device and the cellular telephone, even if the cellular telephone is not on.
- Maintain a minimum separation of 30 cm (12 in) between the device and any antenna transmitting above 3 W.
- Hold the cellular telephone to the ear farthest from the device.

This device has been tested using the EN 45502–2–2:2008 and ANSI/AAMI PC-69:2007 standards to ensure compatibility with cellular telephones and other hand-held transmitters with similar power. These transmission technologies represent the majority of cellular telephones used worldwide. The circuitry of this device, when operating under nominal conditions, has been designed to eliminate any significant effects from cellular telephones.

Electromagnetic interference (EMI) – Instruct patients to avoid devices that generate strong EMI. Electromagnetic interference may result in delivery of unneeded therapy. Electromagnetic interference may also cause device malfunction or damage. The patient

should move away from the EMI source or turn off the source because this usually allows the device to return to its normal mode of operation. EMI may be emitted from the following sources:

- high-voltage power lines
- communication equipment such as microwave transmitters, linear power amplifiers, or high-powered amateur transmitters
- commercial electrical equipment such as arc welders, induction furnaces, or resistance welders

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

Carefully evaluate the possibility of increased susceptibility to EMI and oversensing before changing the sensitivity to its minimum (most sensitive) setting of 0.15 mV.

Electronic article surveillance (EAS) – Electronic article surveillance equipment, such as retail theft prevention systems, may interact with devices and result in inappropriate therapy delivery. Advise patients to walk directly through an EAS system and not remain near an EAS system longer than necessary.

Static magnetic fields – Patients should avoid equipment or situations where they would be exposed to static magnetic fields greater than 10 gauss or 1 mT. Static magnetic fields may suspend tachyarrhythmia detection. Sources of static magnetic fields include, but are not limited to, stereo speakers, bingo wands, extractor wands, magnetic badges, or magnetic therapy products.

2.8 Potential adverse events

The potential adverse events associated with the use of transvenous leads and pacing systems include, but are not limited to, the following events (listed in alphabetical order):

- acceleration of tachyarrhythmias (caused by device)
- air embolism
- bleeding
- body rejection phenomena, including local tissue reaction
- cardiac dissection
- cardiac perforation
- cardiac tamponade

- chronic nerve damage
- constrictive pericarditis
- death
- device migration
- endocarditis
- erosion
- excessive fibrotic tissue growth
- extrusion
- fibrillation or other arrhythmias
- fluid accumulation
- formation of hematomas/seromas or cysts
- heart block
- heart wall or vein wall rupture
- hemothorax
- infection
- keloid formation
- lead abrasion and discontinuity
- lead migration/dislodgement
- mortality due to inability to deliver therapy
- muscle and/or nerve stimulation
- myocardial damage
- myocardial irritability
- myopotential sensing
- pericardial effusion
- pericardial rub
- pneumothorax
- poor connection of the lead to the device, which may lead to oversensing, undersensing, or a loss of therapy
- threshold elevation
- thrombotic embolism

- thrombosis
- tissue necrosis
- valve damage (particularly in fragile hearts)
- venous occlusion
- venous perforation

An additional potential adverse event associated with the use of transvenous left ventricular pacing leads is coronary sinus dissection.

Additional potential adverse events associated with the use of ICD systems include, but are not limited to, the following events:

- inappropriate shocks
- potential mortality due to inability to defibrillate
- shunting current or insulating myocardium during defibrillation

Patients susceptible to frequent shocks despite medical management could develop psychological intolerance to an ICD system that might include the following conditions:

- dependency
- depression
- fear of premature battery depletion
- fear of shocking while conscious
- fear that shocking capability may be lost
- imagined shocking (phantom shock)

3 Clinical data

3.1 Adverse events and clinical trial data

Information regarding clinical studies and adverse events related to this device is available at www.medtronic.com/manuals.

The following clinical studies are related to this device:

BLOCK HF clinical study – The Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block Clinical Study investigated the safety and efficacy of biventricular pacing compared to right ventricular pacing. This study provides support for biventricular pacing in Maximo II CRT-D Model D264TRM devices.

EnTrust clinical study – This clinical study, which evaluated the safety and clinical performance of the EnTrust ICD system, provides support for the Maximo II CRT-D Model D264TRM devices.

EnTrust tachyarrhythmia detection performance vs. GEM DR tachyarrhythmia detection performance – This retrospective evaluation of the EnTrust detection algorithm was performed on spontaneous rhythms recorded in patients implanted with the GEM DR ICD. It provided support for the modifications made to the PR Logic Sinus Tachycardia criterion in the EnTrust devices. These modifications also apply to the Maximo II CRT-D Model D264TRM devices.

GEM DR clinical studies – This clinical study, which evaluated the appropriateness of dual chamber sensing and tachyarrhythmia detection during induced and simulated cardiac arrhythmias in GEM DR devices, provides support for the Maximo II CRT-D Model D264TRM devices.

InSync ICD clinical study – This clinical study, which evaluated the safety and efficacy of cardiac resynchronization therapy (CRT) in patients who are indicated for an ICD, provides support for CRT pacing in Maximo II CRT-D Model D264TRM devices.

InSync Marquis clinical study – This clinical study assessed the safety of the InSync Marquis dual chamber, rate responsive ICD with CRT Therapy, and confirmed appropriate VT/VF detection and bivetricular capture over the range of heart rates achieved during exercise. It provides support for the Maximo II CRT-D Model D264TRM devices.

InSync III Marquis clinical study – This clinical study, which evaluated the safety and efficacy of sequential biventricular CRT pacing and the Conducted AF Response feature in the InSync III Marquis devices, provides support for CRT pacing and Conducted AF Response in Maximo II CRT-D Model D264TRM devices.

Kappa 700 implant study – This study, which evaluated the safety and clinical performance of the Kappa 700 pacemakers, provides support for bradycardia pacing features.

Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) and Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT) – These clinical studies, which evaluated cardiac resynchronization therapy in mildly (REVERSE and RAFT) symptomatic and moderately symptomatic (RAFT) heart failure patients, provide support for Maximo II CRT-D Model D264TRM devices in these patients.

Medtronic

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BLOCK HF CLINICAL STUDY

Summary of clinical results

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Summary of Clinical Results

The “Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block clinical study investigated the safety and efficacy of biventricular pacing compared to right ventricular pacing for subjects with:

- Mild to moderate heart failure (New York Heart Association (NYHA) functional class I, II and III)
- Some degree of left ventricular dysfunction (left ventricular ejection fraction (LVEF) $\leq$ 50%)
- Atrioventricular (AV) block
- Standard pacing indications and/or indications for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias

The study compared results from subjects randomized to biventricular pacing to those of subjects randomized to right ventricular pacing. This study is also referred to as the BLOCK HF Study in the medical literature.

1 Study Purpose

The purpose of the BLOCK HF clinical study was to demonstrate the benefit of biventricular pacing compared to right ventricular pacing as evidenced by a composite endpoint of mortality, morbidity, and changes in cardiac volume as measured by echocardiography.

2 Study Scope, Design, and Methods

BLOCK HF was a prospective, multi-site, randomized, double-blinded, parallel-controlled Investigational Device Exemption (IDE) clinical study. Subjects were randomized in a 1:1 ratio to biventricular pacing or right ventricular pacing.

Randomization occurred 30-60 days after a successful implant procedure which allowed for initial pharmacological therapy to be managed. A successful implant was defined as implantation of market-released right ventricular (RV) and left ventricular (LV) leads, and a Medtronic Cardiac Resynchronization Therapy (CRT-P) or a CRT with defibrillation capabilites (CRT-D) device. Implantation of a right atrial lead was up to the discretion of the physician.

Clinical data were collected at baseline, implant, post-implant baseline/randomization and follow-up visits occurring at 3, 6, 9, 12, 15, 18, 21 and 24 months post-randomization, with further follow-up visits required every three months thereafter until sufficient data were collected for evaluation of the primary objective.

Data were also collected upon system modification, notification of adverse events and hospitalizations, (including adverse event-related emergency department and urgent care visits), interim follow-up visits, study exits, crossovers, deviations, and deaths. Data collected included case report forms to capture demographics, medical history, device interrogations, echocardiograms (echo), assessment of clinical and functional status, as well as quality of life. Device data files and echocardiographic recordings were used as electronic data.

The primary objective was to demonstrate the time until the first event of all-cause mortality, heart-failure-related urgent care, or a significant increase in left ventricular end systolic volume (LVESVI) for subjects programmed to biventricular pacing is superior to that of subjects programmed to right ventricular pacing.

Heart failure-related urgent care was defined as experiencing one of the following:

- A heart failure-related hospitalization requiring intravenous heart failure therapy or,
- An emergency department visit for heart failure requiring intravenous heart failure therapy or,
- A visit in which the subject presents with signs or symptoms consistent with heart failure or heart failure exacerbation, and intravenous therapy is required

A significant increase in LVESVI was defined as a 15% or more increase in the normalized left ventricular end systolic volume from post-implant baseline/randomization to the time point of interest where the normalized systolic volume is systolic volume divided by body surface area.[1]

3 Subject Inclusion and Exclusion Criteria

Subjects who satisfied all inclusion and no exclusion criteria were eligible to participate in the study.

Inclusion Criteria

- Subject had a standard Class I or Class IIa indication for pacemaker in accordance with current ACC/AHA/HRS guidelines at time of the implant
- Subject had been diagnosed with at least one of the following:
    - Third degree AV block
    - Symptomatic or asymptomatic second degree AV block
    - First degree AV block with symptoms similar to pacemaker syndrome
    - Documented Wenckebach or PR interval ≥ 300ms when paced at 100 ppm
- Subject is receiving a first-time device implant
- Subject is indicated for ICD implantation for the automated treatment of life-threatening arrhythmias *(required only if the subject was to receive a CRT-D device)*
- Subject has been classified as NYHA functional class I, II or III within 30 days prior to study enrollment
- Subject's most recent documented left ventricular ejection fraction (by any methodology) was less than or equal to 50% and documented within 90 days prior to enrollment
- Subject was at least 18 years old at the time of consent
- Subject or authorized legal guardian or representative had signed and dated the Subject Informed Consent
- Subject could receive a pectoral implant
- Subject was expected to remain available for follow-up visits at the trained study center
- Subject was willing and able to comply with the protocol

[1] Yu C, Fung W, Lin H, et al. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. Am J. Cardiol. 2002;91:684-688.

Exclusion Criteria

- Subject had ever had a previous or existing pacemaker, ICD or CRT device
- Subject had unstable angina, acute myocardial infarction (MI), coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within 30 days prior to study enrollment
- Subject had a valve replacement or repair within six months (180 days) prior to study enrollment
- Subject had valvular disease and was indicated for a valve repair or replacement
- Subject had a mechanical right heart valve
- Subject was indicated for a biventricular pacing device (CRT-P or CRT-D)
- Subject was enrolled in a concurrent study that may have confounded the results of BLOCK HF
- Subject was pregnant, or a childbearing potential and not on a reliable form of birth control
- Subject was status post heart transplant
- Subject was classified as NYHA functional class IV within 90 days prior to study enrollment
- Subject, legal guardian or authorized representative was unable or unwilling to cooperate or give written informed consent

4 Study Objectives

Primary Objective

The primary objective of the BLOCK HF clinical study was designed to demonstrate the time until the first event of all-cause mortality, heart-failure-related urgent care, or a significant increase in left ventricular end systolic volume (LVESVI) for subjects programmed to biventricular pacing is superior to that of subjects programmed to right ventricular pacing.

Key Secondary Objectives

Secondary objectives were intended to provide additional information on subject response, system performance and corroborate the results of the primary objective. The following were pre-specified for evaluation; however, since the statistical plan did not control for Type I error for any secondary objectives, all results are considered observational and hypothesis generating.

- Hazard rate for time to all-cause mortality
- Hazard rate for time to all-cause mortality or first heart failure-related hospitalization
- Hazard rate for time to all-cause mortality or significant increase (>15%) in LVESVI
- Hazard rate for time to first heart failure hospitalization; number of days hospitalized for heart failure per month
- Changes in NYHA functional classification
- Changes in heart failure stage
- Change in the use of cardiovascular medications over time
- Assess the frequency of occurrence of all trial reportable adverse events

- Assess the frequency of occurrence of cardiovascular health care utilizations
- Changes in quality of life scores as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ)
- Changes in cardiac structure and function per echocardiography (LVEF, LVESVI, Left Ventricular End Diastolic Volume Index (LVEDVI), LV dimension in diastole, LV dimension in systole, LV mass, mitral regurgitation, cardiac index, interventricular mechanical delay, and E-wave/A-wave ratio)
- Changes in the Heart Failure Clinical Composite scores
- Proportion of subjects with a successful implant of a biventricular pacing system (CRT-P/CRT-D)
- For subjects implanted with a CRT-D: Compare the hazard rate for time to first VT/VF episodes

5 Statistical Analysis

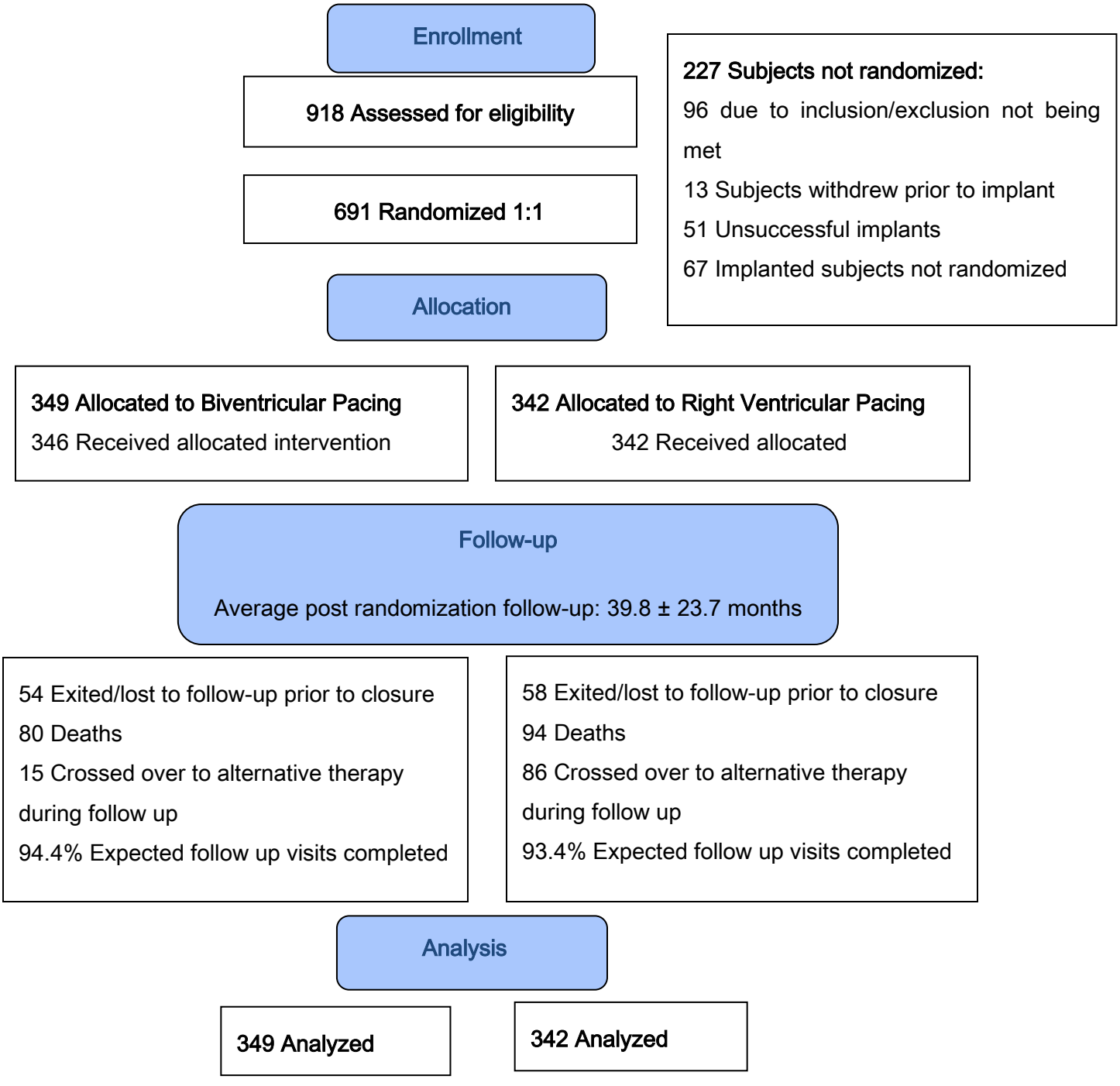
The prespecified statistical approach for the primary objective and stopping rules for data collection and trial completion was an adaptive Bayesian statistical design. Posterior probabilities and 95% credible intervals were the metrics generated in lieu of Frequentist statistical measures such as p-values and confidence intervals. A posterior probability that a parameter (e.g. BiV to RV hazard ratio for mortality) falls within a given range is a number between 0 and 1 that represents the likelihood, based on pre-trial assumptions and accumulated trial data, that the parameter falls in that range. The objective was met if the probability that the parameter fell within the rejection region exceeded the pre-specified threshold. The primary objective was met if the posterior probability (PP) that the combined hazard ratio was less than 1 exceeded 0.9775. A 95% credible interval is a range of values a parameter falls within with a posterior probability of 0.95. An intention-to-treat analysis served as the primary analysis for each objective. Similar models were used to assess several of the secondary objectives. However, Type I error was not controlled for the analysis of secondary objectives, so their results should be interpreted with caution.

6 Results

Accountability of PMA Cohort

A total of 918 subjects were enrolled at 58 sites in the United States and two sites in Canada. Of the 918 subjects enrolled, 691 were randomized. There were 531 CRT-P and 227 CRT-D devices successfully implanted during the initial implant procedure, with 484 subjects randomized in the CRT-P group and 207 subjects randomized in the CRT-D group. **Figure 1** shows the number of subjects included in the analysis of the primary objective.

Figure 1: CONSORT Flow Diagram of Subjects Analyzed for Primary Objective



Study Population Demographics and Baseline Parameters

Table 3 summarizes the baseline demographics for all 691 randomized subjects. Mean and standard deviation are presented for continuous variables.

Table 1: Baseline Demographics of All Randomized Subjects

Subject Characteristic	CRT-P (N= 484)		CRT-D (N=207)		Total (N=691)
	BiV Arm (N=243)	RV Arm (N=241)	BiV Arm (N=106)	RV Arm (N=101)	
Gender (N, %)					
Male	181 (74.5%)	168 (69.7%)	87 (82.1%)	81 (80.2%)	517 (74.8%)
Female	62 (25.5%)	73 (30.3%)	19 (17.9%)	20 (19.8%)	174 (25.2%)
Ethnic Origin (N, %)					
Subject did not offer ethnicity	6 (2.5%)	5 (2.1%)	4 (3.8%)	3 (3%)	18 (2.6%)
African American	8 (3.3%)	10 (4.1%)	4 (3.8%)	4 (4%)	26 (3.8%)
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Caucasian	225 (92.6%)	224 (92.9%)	96 (90.6%)	90 (89.1%)	635 (91.9%)
Hispanic	3 (1.2%)	1 (0.4%)	2 (1.9%)	2 (2%)	8 (1.2%)
Native American	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.1%)
Other	1 (0.4%)	0 (0%)	0 (0%)	2 (2%)	3 (0.4%)
Age (years)					
Mean ± Standard Deviation	74.4 ± 10.2	73.8 ± 10.8	72 ± 9.3	71 ± 10	73.3 ± 10.3
Minimum - Maximum	43.8 - 92.4	25.9 - 93.2	40.2 - 88.4	40.6 - 89.5	25.9-93.2
LVEF Measurement (%)					
Mean ± Standard Deviation	43.4 ± 6.5	42.5 ± 6.6	33 ± 7.8	32.9 ± 8	40.0 ± 8.3
Median	45	45	35	32	40
25^{th} Percentile - 75^{th} Percentile	40 - 49	40 - 47	29 - 38	29 - 35	35 - 45
NYHA Classification (N, %)					
Class I	35 (14.4%)	47 (19.5%)	11 (10.4%)	16 (15.8%)	109 (15.8%)
Class II	141 (58%)	126 (52.3%)	67 (63.2%)	58 (57.4%)	392 (56.7%)
Class III	66 (27.2%)	68 (28.2%)	28 (26.4%)	27 (26.7%)	189 (27.4%)
Class IV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not Available	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Heart Failure Stage Classification (N, %)					
Stage A	1 (0.4%)	3 (1.2%)	0 (0%)	0 (0%)	4 (0.6%)
Stage B	34 (14%)	40 (16.6%)	9 (8.5%)	14 (13.9%)	97 (14.0%)
Stage C	207 (85.2%)	198 (82.2%)	97 (91.5%)	87 (86.1%)	589 (85.2%)
Stage D	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not Available	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)

The percent ventricular pacing was high, over 90% among at least 75% of subjects consistently across different intervals of follow-up, and consistently among both device and treatment arms. The overall median percent RV pacing for the study was over 98%. This supported the trial enrollment goal that subjects must have AV block that requires pacing. Of note, BLOCK HF enrolled very few ethnic minorities with more than 90% of enrollees having Caucasian ethnicity.

Safety and Effectiveness Results

A. Primary Objective

The primary objective was a composite endpoint that demonstrated the time to the first event of all-cause mortality, heart failure-related urgent care visit, or a ≥15% increase in LVESVI for subjects with BiV pacing is superior to that of subjects with RV pacing.

The primary endpoint was met in 186 of 349 (53%) subjects in the BiV pacing arm, compared to 219 of 342 (64%) subjects in the RV pacing arm. Subjects with missing LVESVI measures at the required timepoints of post-implant baseline, 6, 12, 18 and 24 months were censored at the last visit with a readable LVESVI measure prior to the visit with missing data, even if an endpoint was later met. Thus, some primary endpoint events did not contribute to the analysis of the primary objective. After accounting for censoring, 160 (45.8%) of subjects in the BiV pacing arm and 191 (55.8%) of subjects in the RV pacing arm experienced primary endpoints that were included in the primary objective analysis. See **Table 4** and **Figure 2**.

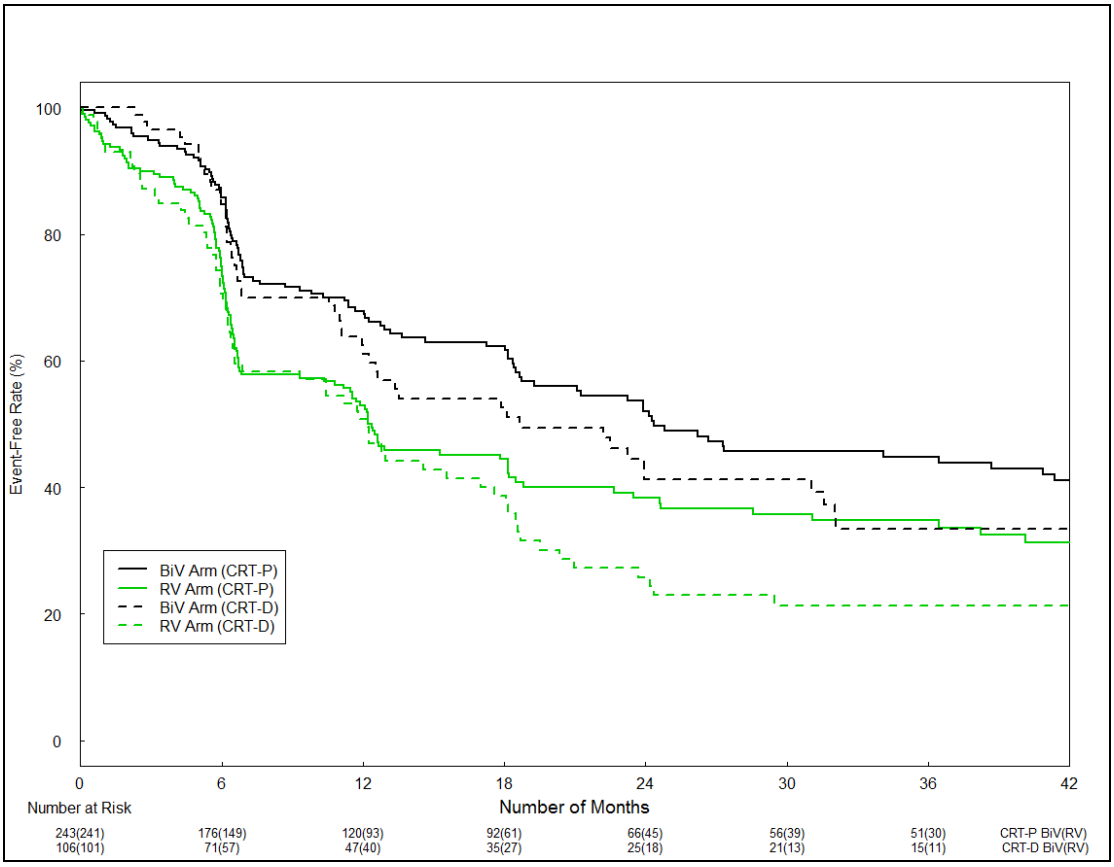
Table 2: Primary Endpoint Events for Analysis of Primary Objective

	Number of Subjects (% of Subjects)				
	CRT-P (N=484)		CRT-D (N=207)		Total Randomized Subjects (N=691)
	BiV Arm (N=243)	RV Arm (N=241)	BiV Arm (N=106)	RV Arm (N=101)	
Primary Endpoint Events	**109 (44.9%)**	**128 (53.1%)**	**51 (48.1%)**	**63 (62.4%)**	**351 (50.8%)**
LVESVI Events	55 (22.6%)	78 (32.4%)	30 (28.3%)	36 (35.6%)	199 (28.8%)
HF Urgent Care	40 (16.5%)	39 (16.2%)	16 (15.1%)	23 (22.8%)	118 (17.1%)
Deaths	14 (5.8%)	11 (4.6%)	5 (4.7%)	4 (4.0%)	34 (4.9%)

Among events that counted towards the primary objective analysis, the most common event type was an increase in LVESVI (28.8% of randomized subjects), followed by a heart failure-related urgent care visit (17.1% of randomized subjects), and death (4.9% of randomized subjects).

Among the LVESVI endpoints, LVESVI increased on average 33.5%.

Figure 2: Time to Mortality, HF Urgent Care Visit, or ≥ 15% Increase in LVESVI



Biventricular pacing resulted in an overall 27% reduction in the primary endpoint achieving Bayesian statistical significance (Posterior Probability = 0.999) of the Hazard Ratio (HR) < 1. Sensitivity analyses including censored data yielded similar findings and the observed relative benefit of biventricular pacing was comparable across device groups . **Table 5** provides the results of the Bayesian primary objective for CRT-P and CRT-D devices and for all subjects.

Table 3: Statistical Analysis of Primary Objective

Subject Group	Hazard Ratio (95% CI)
CRT-P (N=484)	0.72 (0.57, 0.90)
CRT-D (N=207)	0.74 (0.56, 1.00)
All Subjects (N=691)	0.73 (0.59, 0.89)

B. Secondary Objectives

The results of all secondary objectives are provided below in **Table 6**. Since the statistical plan did not control for Type I error for any secondary objectives, all results below are considered observational and hypothesis generating.

Table 4: Analysis of Secondary Objectives

Secondary Objective	Results
Mortality	A mortality endpoint occurred in 80 (23%) of 349 subjects in the BiV group compared with 94 (27%) of 342 subjects in the RV pacing group.
Time to Mortality/HF-related Hospitalization	A mortality/first HF hospitalization endpoint occurred in 121(35%) of 349 subjects in the BiV group compared with 135 (39%) of 342 subjects in the RV pacing group.
Mortality/Change in LVESVI	A mortality/ ≥15% increase in LVESVI occurred in 158 (45.3%) of BiV subjects and 201 (58.8%) of RV subjects.
Change in Heart Failure-related Hospitalizations	There were 147 HF hospitalizations among 79 (22.6%) of 349 subjects in the BiV arm compared to 157 HF hospitalizations among 92 (26.9%) of 342 RV arm subjects. BiV arm subjects were observed to have overall lower mean rates of days hospitalized for HF per year than RV arm subjects.
Change in NYHA Functional Classification	The analyses comparing the observed mean change in NYHA from Post-implant baseline/randomization to 6, 12, 18, and 24 months post randomization showed similar results between arms.
Change in Heart Failure Stage	The analyses comparing the observed mean change in HF Stage from Post-implant baseline/randomization to 6, 12, 18, and 24 months post-randomization showed similar results between arms: most subjects were Stage C at randomization and remained at Stage C at the other time points of study

Change in Cardiovascular Medications	The targets for medical therapy recommended in the trial were consistent with AHA/ACC Guidelines for Heart Failure. The observed, administered doses of heart failure medications were lower than the recommended targets. In spite of the lower EF in the CRT-D group, the ACE Inhibitor doses were low, but similar across groups. In addition, in spite of lower EF in the CRT-D group, 85% were on beta blockers with doses at approximately 35% of recommended by the study. After 6 months of pacing, however, beta blocker doses had changed only minimally to 38% of recommended doses.
Frequency of Adverse Events	There were 3064 adverse events (1669 complications, 1395 observations) experienced by 655 subjects. Observed rates of heart-failure related adverse events were observed to be lower in the BiV arm, while rates of inappropriate device stimulation of tissue were observed to be higher in the BiV arm. Among CRT-D subjects more generator-related complications were observed in the BiV arm. Most of these complications were device changeouts due to the device reaching end of life. The time frame for many of these events was four to five years post implant, corresponding to observed battery longevity.
Cardiovascular Health Care Utilizations	There were 2345 post-randomization CV healthcare utilizations among 527 randomized subjects. Observed rates of heart failure-related hospitalizations were lower in the BiV arm among CRT-P subjects and comparable between arms among CRT-D subjects. Observed CV-related urgent care/clinic visits were lower in the BiV arm across device groups, while rates of observed CV related hospitalizations for reasons other than HF (e.g. lead dislodgement, device changeouts) were higher in the BiV arm.
Change in Quality of Life	Change in Quality of Life score from randomization was compared between arms at 6, 12, 18, and 24 months post randomization. Subjects in the BiV arm were observed to have an average improvement in quality of life at 6 and 12 months, but saw less improvement at 18 and 24 months. Subjects randomized to RV pacing averaged little observed difference in their quality of life through 24 months.

Change in Cardiovascular Structure and Function per Echocardiography	Changes in cardiovascular structure and function were assessed at 6, 12, 18, and 24 months post randomization. Subjects who received BiV pacing were observed to have better outcomes as measured by change in LVEF, LVESVI, LVEDVI, LV diastolic dimension, LV mass, and Interventricular Mechanical Delay compared to subjects with RV pacing through 24 months. No differences were observed between randomization groups for change in the following parameters between randomization and any subsequent time points: Cardiac Index, Mitral Regurgitation, LV systolic dimension, and E-Wave/A-Wave Ratio.
Change in Heart Failure Clinical Composite Score	Subjects who received BiV pacing were observed to achieve a better clinical composite score than subjects with RV pacing through 24 months of receiving the therapy.
CRT-P and CRT-D System Implant Success Rate	A CRT system (with or without an RA lead) was successfully implanted in 93.7% of the subjects who received an implant attempt. CRT-D system implant was successful in 227 (91.5%) of 248 attempts. An initial implant attempt of a CRT-P system was made in 561 subjects, and was successful in 531 (94.7%) of those subjects. In all 51 of the unsuccessful cases, the LV lead could not be successfully implanted.
Incidence of VT/VF	More subjects in the BiV arm experienced post-randomization VT/VF (37%) and non-VT/VF (55%) than subjects in the RV arm (31% experienced VT/VF and 47% experienced non-VT/VF).

7 Adverse Events Summary

In this study, all cardiovascular-related, pulmonary-related, renal-related, system-related, procedure-related, and any events in which the subject presents with symptoms compatible with fluid retention and/or decreased exercise tolerance were reported. Adverse events were classified for Seriousness, Complications/Observations, and Relatedness. A complication was defined as an adverse event that results in death, involves any termination of significant device function, or requires invasive intervention. An observation was defined as any adverse event that is not a complication. System relatedness was assessed with respect to device and the leads. The Adverse Event Adjudication Committee (AEAC) adjudicated relatedness for all adverse events.

Out of the 809 subjects in whom implants were attempted, 143 subjects (17.7%) experienced a serious adverse event within 30 days of the initial procedure and 207 subjects (25.6%) experienced a procedure, generator or LV lead related complication. The **Table 7** below summarizes the serious adverse events and complications observed by type.

Table 5: Adverse Events in BLOCK HF Study

Event Type	# Subjects (%)				
	CRT-P (N=484)		CRT-D (N=207)		Others with Implant Attempt (N=118)
	BiV (N=243)	RV (N=241)	BiV (N=106)	RV (N=101)	
Serious Adverse Event ≤ 30 days	41 (16.9%)	28 (11.6%)	18 (17.0%)	15 (14.9%)	41 (34.7%)
Procedure-related complication	42 (17.3%)	26 (10.8%)	21 (19.8%)	16 (15.8%)	34 (28.8%)
Generator-related complication	11 (4.5%)	10 (4.1%)	34 (32.0%)	18 (17.8%)	8 (6.8%)
LV lead-related complication	14 (5.8%)	12 (5.0%)	6 (5.7%)	9 (8.9%)	10 (8.5%)

LV Lead-Related Safety

Given that the LV lead was required to function adequately only in the subjects assigned to BiV pacing, the LV lead related complication rate in the BiV arm of 5.7% was used for evaluation of the additional LV lead-related risks of a CRT device over an RV pacemaker. This rate is comparable with recent CRT trials, including RAFT (7.4% LV lead related complications at 12 months post implant) and REVERSE (9.1% LV lead related complications at 12 months post implant). The main causes of the lead related complications in the BiV arm are shown in **Table 8** below.

Table 6: LV Lead Related Complications in BiV Arm (N=349)

	# Subjects (%)
All complications	20 (5.7%)
Diaphragmatic stimulation	12 (3.4%)
Lead dislodgement	4 (1.1%)
Failure to capture	1 (0.3%)

An additional consideration for safety is the ability to implant an LV lead. In 51 (6.3%) of the 809 subjects in which implants were attempted, an LV lead implant was not possible. Although increased surgical time is required for attempted, but unsuccessful LV lead implants, not all result in complications. No epicardial leads were used in this study.

8 Death Summary

Of the 691 subjects randomized, 25.2% died during their follow-up. The majority of deaths were non cardiac related (88/174 = 50.6%). The overall mortality rate was similar in study groups, trending lower for the BiV-randomized arm. No deaths were adjudicated to be procedure-related; one death was found to be system-related. The following table categorizes the deaths observed in the study.

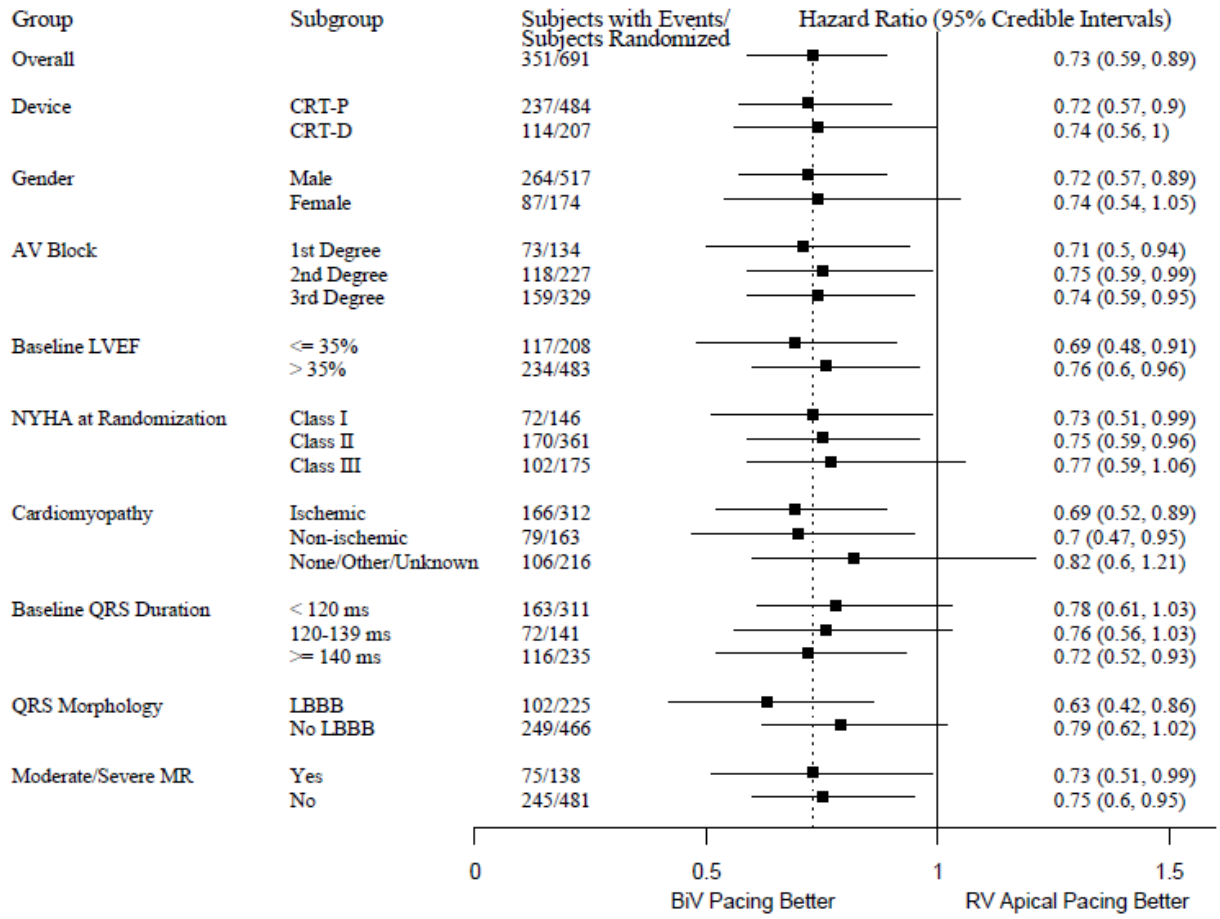
Table 7: Deaths by Device Type and Treatment Arm

AEAC Classification	Number of Subjects (% of Subjects)				
	CRT-P (N=484)		CRT-D (N=207)		Total Randomized Subjects (N=691)
	BiV Arm (N=243)	RV Arm (N=241)	BiV Arm (N=106)	RV Arm (N=101)	
Sudden Cardiac	9 (3.7%)	11 (4.6%)	2 (1.9%)	2 (2.0%)	24 (3.5%)
Non-sudden cardiac	18 (7.4%)	12 (5.0%)	5 (4.7%)	10 (9.9%)	45 (6.5%)
Non-cardiac	25 (10.3%)	34 (14.1%)	14 (13.2%)	15 (14.9%)	88 (12.7%)
Unknown	5 (2.1%)	9 (3.7%)	2 (1.9%)	1 (1.0%)	17 (2.5%)
Heart Failure Related	16 (6.6%)	14 (5.8%)	5 (4.7%)	11 (10.9%)	46 (6.7%)
Total	**57 (23.5%)**	**66 (27.4%)**	**23 (21.7%)**	**28 (27.7%)**	**174 (25.2%)**

9 Subgroup Analysis

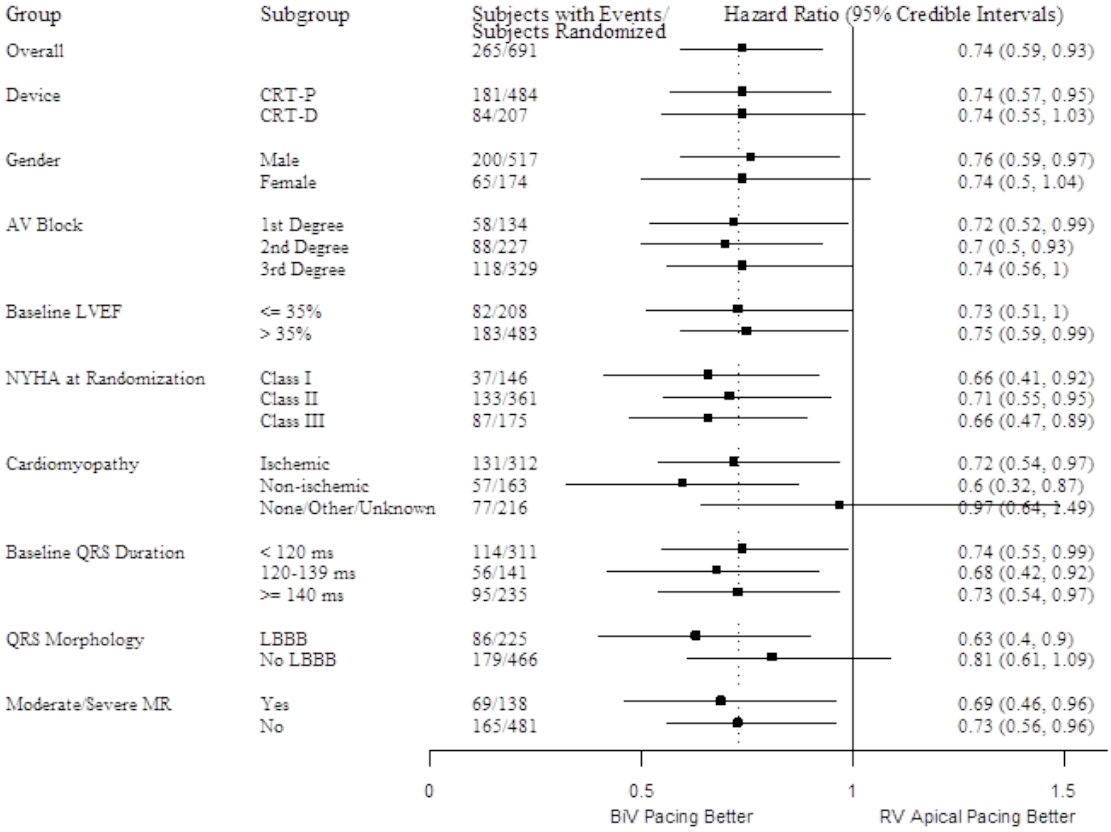
The treatment effect for key clinical subgroups was examined by calculating the hazard ratio in each group as shown in **Figure 3**.

Figure 3: Subgroup Analysis Forest Plot for Primary Objective



The treatment effect when LVESVI is excluded was also examined. See **Figure 4**.

Figure 4: Subgroup Analysis Forest Plot for Death of HF-Related Urgent Care Visit



The treatment effect was consistent across subgroups, noting that some subgroups had higher enrollment than others.

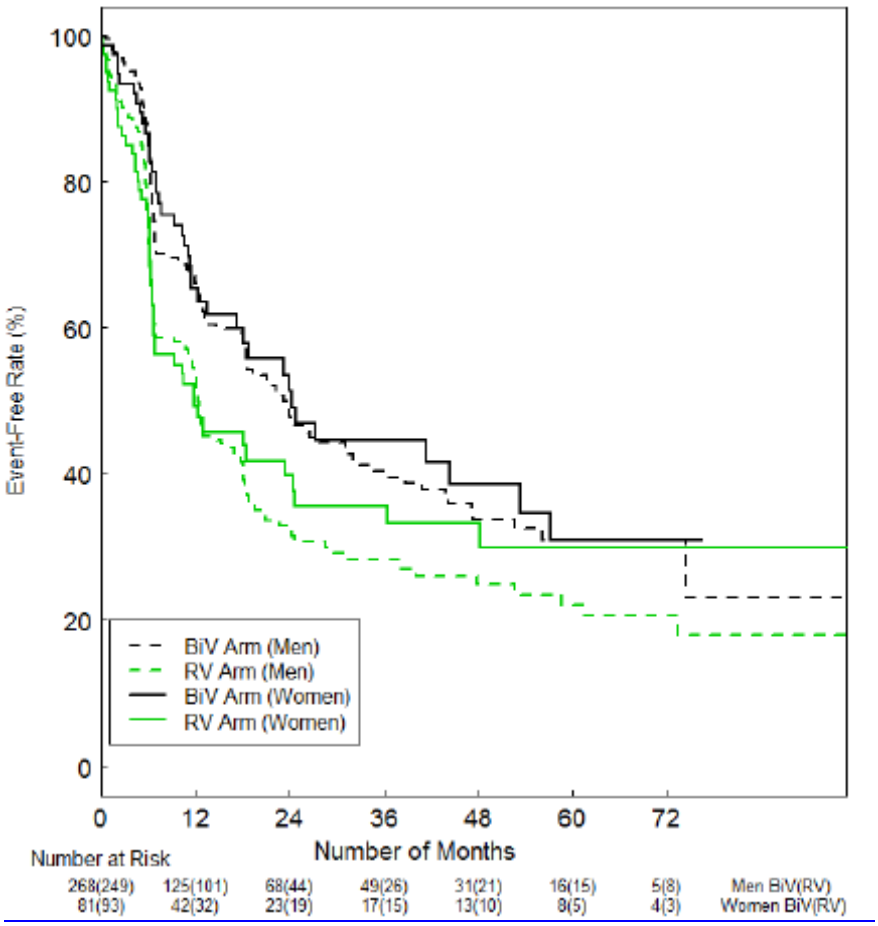
10 Gender Analysis

Additional subgroup analyses were performed by gender. The interpretability of these analyses is limited given the low enrollment of women in the BLOCK HF study, 174/691 (25.2%). Both men and women demonstrated similar improvement trends with BiV pacing compared to RV pacing which is discussed further below.

The proportion of female subjects enrolled in the BLOCK HF study is lower than the gender-specific incidence or prevalence of heart failure in this patient population. Of the 5.3 million Americans affected by heart failure, nearly 50% are women[1]. However, the proportion of women enrolled in BLOCK HF is similar to that observed in other trials of CRT and to that observed of AV block subjects with an ICD or pacemaker in the Medtronic Product Surveillance database.

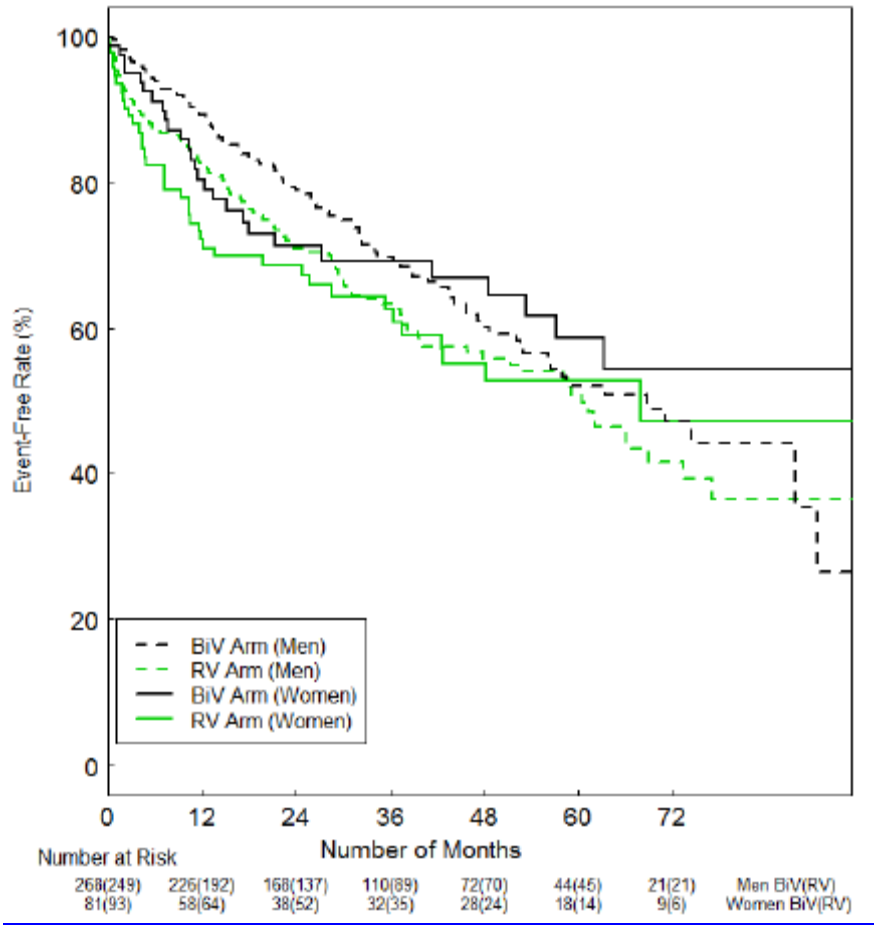
To examine the results of the primary objective by gender, a hierarchical model similar to that used in the main analysis was used to generate the hazard ratios and corresponding 95% two sided credible intervals. In women, biventricular pacing results in an overall 26% reduction in the primary endpoint, while in men the reduction was more (28%). See **Figure 5**. It is important to note that the BLOCK HF study was not designed with a statistically powered sample size for this analysis and that the number of women enrolled in the study was quite low, so interpretation of the results shown in the figure below is limited.

Figure 5: Time to Mortality, HF Urgent Care Visit, or ≥ 15% Increase in LVESVI



An analysis was also done excluding LVESVI. See **Figure 6**. Results still trended toward benefit in both men and women (hazard ratio of 0.80 and 0.76, respectively) when a Frequentist approach is used to analyze the data. A Frequentist approach was used given that no Bayesian analysis was pre-specified for this particular analysis and the priors selected may not have been appropriate for this analysis. It is important to note that the number of women enrolled in the study was quite low, so interpretation of the results shown in the figure below is limited.

Figure 6: Time to Mortality or HF Urgent Care Visit



Baseline demographics are provided by gender in **Table 10**. While the overall sample size for women was low, this analysis provides support that women in BLOCK HF had generally similar demographics as men. Women did, however, have more advanced symptoms than men as evidenced by a higher percentage of Class III enrollments. Women were also less likely to meet the criteria for defibrillation coming in to the trial.

Table 8: Baseline Demographics of All Randomized Subjects

Subject Characteristic	Men (517, 74.8%)	Women (174, 25.2%)	p-value
Ethnic Origin (N, %)			0.05
Subject did not offer ethnicity	15 (3%)	3 (2%)	
African American	16 (3%)	10 (6%)	
Asian	--	--	
Caucasian	479 (93%)	156 (90%)	
Hispanic	4 (1%)	4 (2%)	
Native American	0 (0%)	1 (1%)	
Other	3 (1%)	0 (0%)	
Age (years)			0.946
Mean ± Standard Deviation	73 ±10	73 ±11	

Minimum - Maximum	26 -93	40 -89	
LVEF Measurement (%)			0.374
Mean ± Standard Deviation	40 ± 8	40 ± 9	
Median	40	45	
25th Percentile - 75th Percentile	35 -45	35 -46	
NYHA Classification (N, %)			0.0008
Class I	81 (16%)	28 (16%)	
Class II	312 (60%)	80 (46%)	
Class III	123 (24%)	66 (38%)	
Class IV	--	--	
Not Available	1 (0%)	0 (0%)	
Heart Failure Stage Classification (N, %)			0.958
Stage A	3 (1%)	1 (1%)	
Stage B	72 (14%)	25 (14%)	
Stage C	441 (85%)	148 (85%)	
Stage D	--	--	
Not Available	1 (0%)	0 (0%)	
Device Type (N, %)			0.012
CRT-P	349 (68%)	135 (78%)	
CRT-D	168 (32%)	39 (22%)	

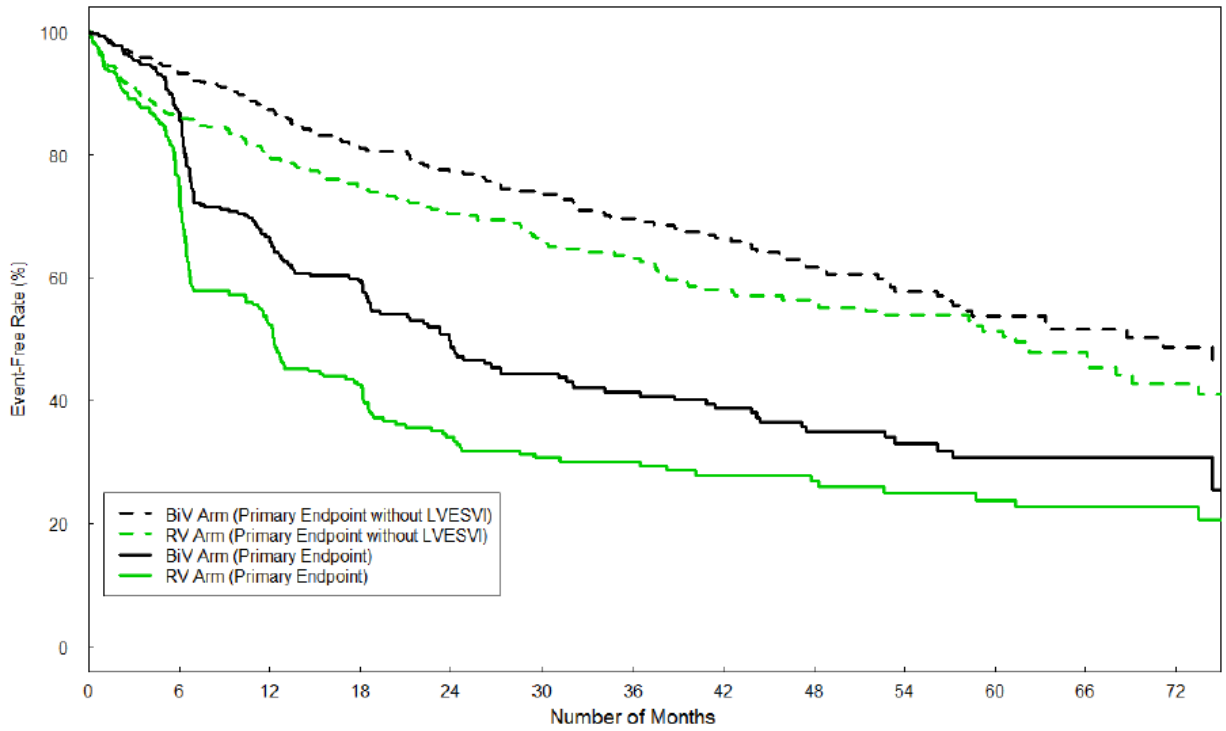
11 Additional Analysis to Understand the Impact of LVESVI

Given the large contribution of events contributing to the primary objective that were increases in LVESVI (53.1% in the BiV arm and 59.7% in the RV arm), the below analyses were conducted.

Time to First Event without LVESVI

The exploratory Kaplan Meier analysis in **Figure 7** shows time to primary endpoint events including mortality or heart failure-related urgent care, but excluding LVESVI events. Superimposed on the graph are the results for the primary objective (when LVESVI is included). By excluding LVESVI events this analysis has fewer than half the events of the analysis of the primary objective. Results still trend towards benefit (hazard ratio of 0.80) when a Frequentist approach is used to analyze the data. For comparison, the hazard ratio when LVESVI is included is 0.68. A Frequentist approach was used given that no Bayesian analysis was pre-specified and the priors selected may not have been appropriate for this analysis.

Figure 7: Time to 1st Event With (solid lines) and Without (dotted lines) LVESVI by Randomization Arm



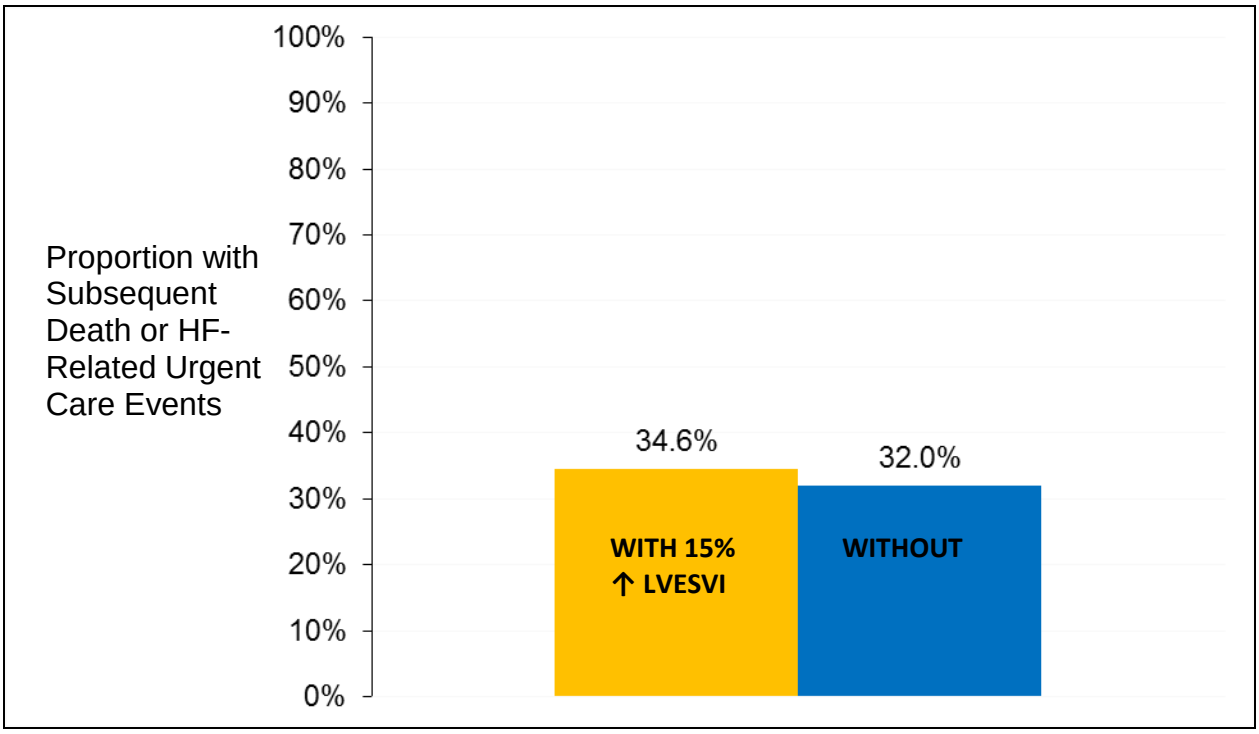
Predictive Value of LVESVI

LVESVI events counted equally as death and heart failure events toward the composite primary objective. LVESVI events also occurred more often than death or heart failure events combined. For this reason, the value of LVESVI events was examined further, including whether LVESVI events predicted (i.e. preceded, in this study) future clinically meaningful death or heart failure-related urgent care events. The predictive value of an LVESVI event was examined using two methods.

A. Proportion of Subjects with Future Death or Heart Failure-Related Urgent Care Events

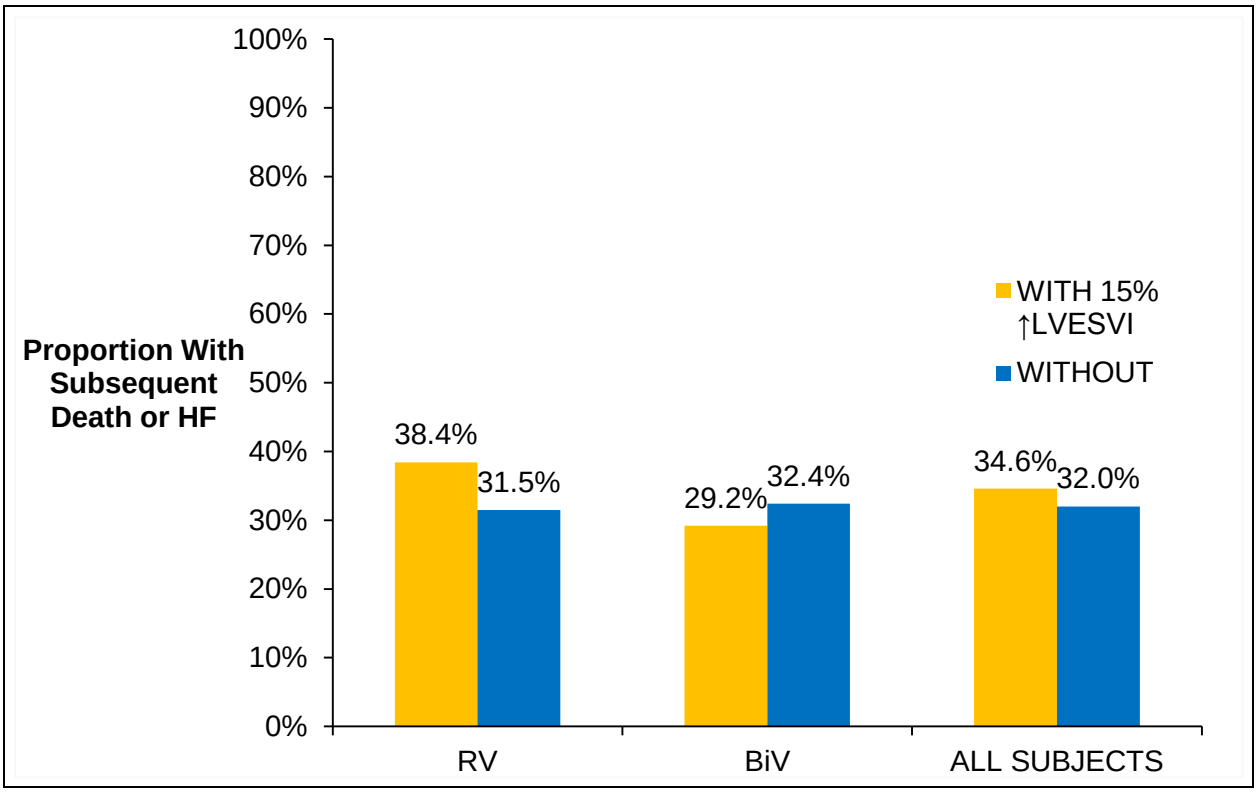
Subjects whose first primary endpoint event was a significant increase in LVESVI were examined for the occurrence of subsequent death or heart failure-related urgent care to assess whether LVESVI changes predicted future death or HF-related urgent care events. This proportion was compared to the proportion of death or HF-related urgent care events among subjects who did not have a primary endpoint LVESVI event. Increased proportion of death or HF-related urgent care events for those with LVESVI events first versus those without LVESVI events was considered evidence that LVESVI changes predicted clinically meaningful outcomes.

Figure 8: Proportion of Subjects with 1st Event of LVESVI Increase and Future Event of Death or Heart Failure-Related Urgent Care



This same analysis was conducted for BiV vs RV arms and for the entire randomized cohort.

Figure 9: Proportion of Subjects with 1st Event of Increase in LVESVI that have Later Event of Death or Heart Failure-Related Urgent Care



The results indicated that LVESVI is of limited value in predicting future death or heart failure-related urgent care.

B. Cox Regression Analysis

The question of predictive value was also examined through a Cox Regression Analysis. In this analysis, values greater than one suggests that having a 15% or more increase in LVESVI predicts future death or heart failure-related urgent care. A hazard ratio of one suggests no predictive value.

Table 9: Cox Regression Analysis for Predictive Value of 1st Event being LVESVI for Future Death or Heart Failure-Related Urgent Care

Category	Hazard Ratio	95% Confidence Interval
All Subjects	1.35	(1.00, 1.82)
RV Arm	1.74	(1.15, 2.65)
BiV Arm	1.00	(0.63, 1.59)

The results indicated that there is no consistent predictive value of LVESVI events for future death or heart failure-related urgent care. However, the trial was not prospectively designed nor powered to determine the predictive nature of LVESVI events with regard to mortality/morbidity; this represented a post-hoc analysis, and so the results should be considered with caution.

Annualized Rates for Death and Heart Failure-Related Urgent Care

To further understand the results of the study without LVESVI, the absolute benefit seen in annualized rate for mortality (**Figure 10**) and heart failure-related urgent care (**Figure 11**) was examined.

Figure 10: Annualized Mortality Rate by Randomization Arm

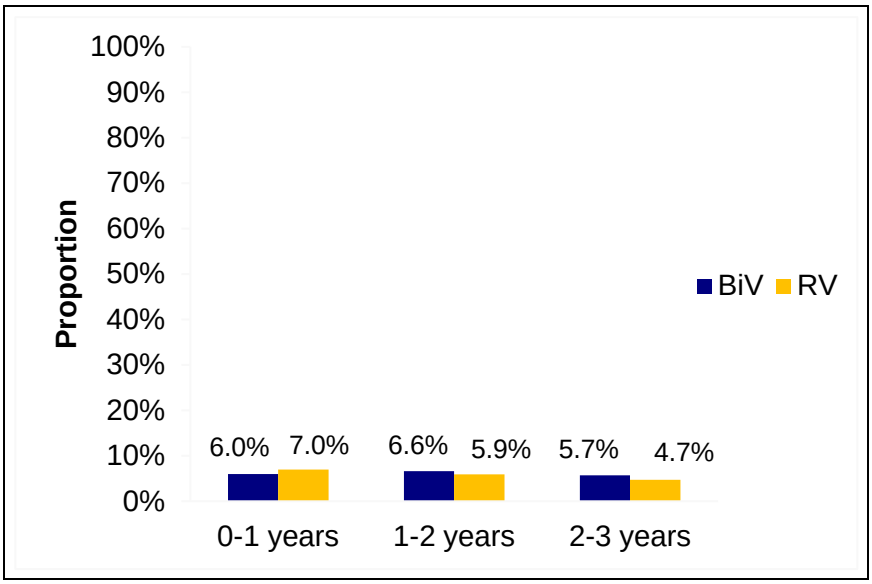
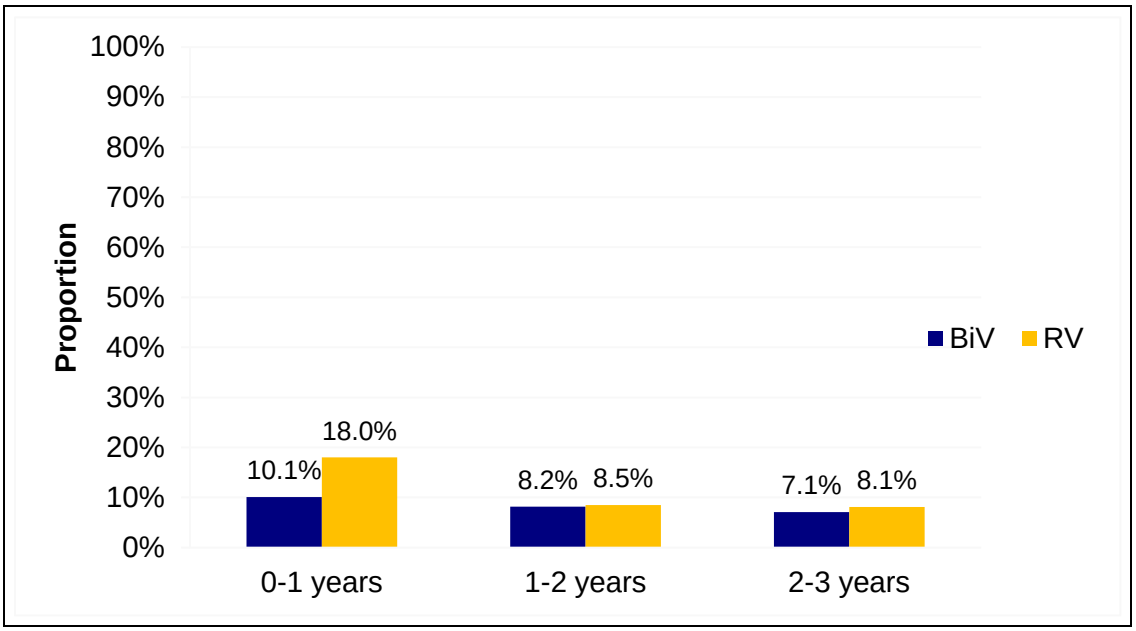


Figure 11: Annualized Heart Failure-Related Urgent Care by Randomization Arm



The suggested clinical benefit is a reduction in the occurrence of heart failure related urgent care of 7.9% in year one. No consistent mortality benefit was observed.

12 Clinical Study Conclusion

The BLOCK HF Trial compared BiV pacing to RV pacing in subjects with NYHA Class I, II or III, and LVEF $\leq$ 50% and AV block using a composite primary endpoint of mortality, morbidity and cardiac function. The trial demonstrated that BiV pacing results in a 27% reduction in the risk of the composite primary endpoint.

Safety Conclusions

In 51 subjects (6.3%), implantation of an LV lead was not possible. In those subjects in whom an LV lead was implanted and BiV pacing was used, 20 (5.7%) had an LV lead related complication. The definition of a complication in the BLOCK HF study is an adverse event that resulted in death, involved any termination of significant device function, or required invasive intervention. The LV lead complications most commonly did not result in death, but required a second surgery to revise the lead or involved loss of LV lead function. During deliberations, the Panel also indicated that the need for an additional surgery due to more frequent battery usage, and therefore, quicker battery depletion, when BiV pacing is used instead of RV pacing should be considered as a potential risk. The Panel and FDA acknowledged that the infrequent risks associated with LV lead use were different in kind and severity than the infrequent occurrence of heart failure and death attributable to RV pacing instead of BiV pacing.

Effectiveness Conclusions

The primary objective of the BLOCK HF study examined the effectiveness of BiV pacing over RV pacing at reducing risk of occurrence of death, heart failure-related urgent care, or a ≥15% increase in LVESVI. The study met is its primary objective, demonstrating a 27% relative reduction in the risk of developing one of the three primary endpoint events. However, given the lack of clarity regarding the clinical meaning of an increase in LVESVI, the annualized rates were examined individually for death and heart failure-related urgent care to understand the results when LVESVI is excluded. The absolute benefit seen in clinically meaningful events is a reduction in heart failure-related urgent care of 7.9%; no consistent reduction in mortality was seen. Time to event analyses were also conducted, which indicated treatment effect still trends towards benefit when LVESVI is removed. These analyses in total suggested a modest benefit from BiV vs RV pacing predominantly in reduced heart failure events within the first year after implant.

It should be noted that the potential for pharmacological therapy in combination with BiV or RV pacing to impact the occurrence of primary objective events was not thoroughly evaluated since the cardiovascular medication doses prescribed (particularly those for beta blockers) were lower than those recommended by the study protocol and the AHA/ACC Guidelines for Heart Failure.

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