Medtronic

CONSULTA® CRT-P C4TR01

Digital pacemaker with cardiac resynchronization therapy (OAE-DDDR)

Complete Capture Management® Diagnostic (ACM, RVCM, LVCM) with Detailed EGM™ Viewer, OptiVol® Fluid Status Monitoring, Vision 3D Quick Look™ II, AT/AF Suite Diagnostics and Therapies, and Medtronic CareLink® Network compatible

Clinician Manual

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

CONSULTA® CRT-P C4TR01

Clinician Manual

A guide to the operation and programming of the Consulta CRT-P Model C4TR01 digital pacemaker with cardiac resynchronization therapy (OAE-DDDR)

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1 System overview

1.1 Introduction

1.1.1 About this manual

This manual describes the operation and intended use of the Consulta CRT-P Model C4TR01 system.

1.1.1.1 Manual conventions

Throughout this manual, the word “device” refers to the implanted Consulta CRT-P 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
```

1.1.2 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 Explanation of symbols

The following list of symbols and abbreviations applies to various products. Refer to the package labels to see which of these 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.
	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 Medtronic 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
! USA	For US audiences only
	Date of manufacture
	Manufacturer

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

Symbol	Explanation
EC REP	Authorized representative in the European community
	Use by
LOT	Lot number
REF	Reorder number
SN	Serial number
+ XX °C + XXX °F – XX °C – XX °F	Temperature limitation
	Adaptive
	Package contents
	Implantable device
	IPG device
	Coated (IPG device)
	ICD device
	Coated (ICD device)

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

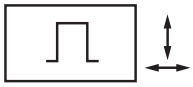
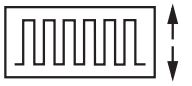
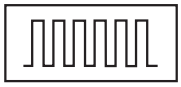
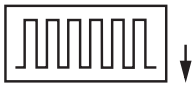
Symbol	Explanation
	Cardiac resynchronization therapy (CRT) device
	Coated (CRT device)
	Dual chamber IPG with cardiac resynchronization therapy (CRT-P)
	Product documentation
	Torque wrench
	Accessories
	Amplitude/pulse width
	Atrial amplitude/pulse width
	RV amplitude/pulse width
	LV amplitude/pulse width
	Upper tracking rate/lower rate
	Rate
	Lower rate

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

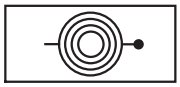
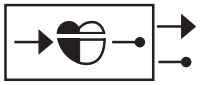
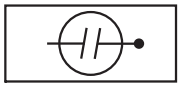
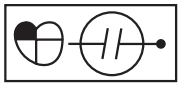
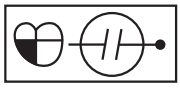
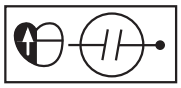
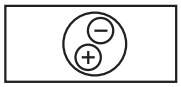
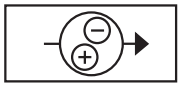
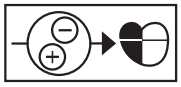
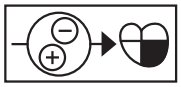
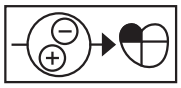
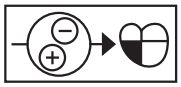
Symbol	Explanation
	Sensitivity
	Sensed A-V interval
	A-V interval (paced/sensed)
	Refractory period
	Atrial refractory period
	Ventricular refractory period
	(PVARP) Post Ventricular Atrial Refractory Period
	Polarity
	Pacing polarity (single chamber)
	Pacing polarity (dual chamber)
	LV Pace polarity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

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

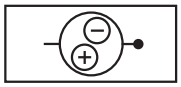
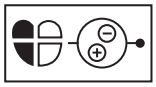
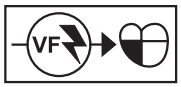
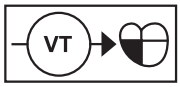
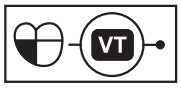
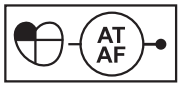
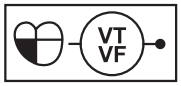
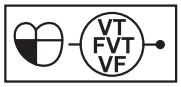
Symbol	Explanation
	Sensing polarity (single chamber)
	Sensing polarity (dual chamber)
	Atrial sensitivity
	Ventricular sensitivity
	VF therapies (delivered/stored)
	VT therapies
	V pacing/V-V pace delay
	VT monitor
	AT/AF detection
	VT, VF detection
	VT, FVT, VF detection
	AT/AF therapies
	VT, VF therapies

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

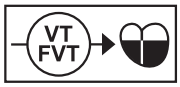
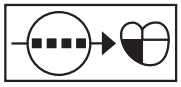
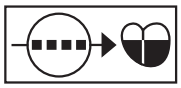
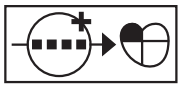
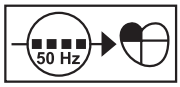
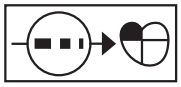
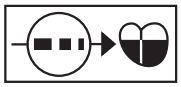
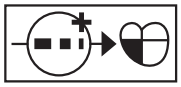
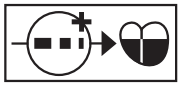
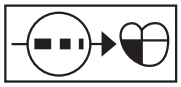
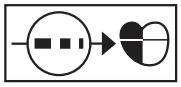
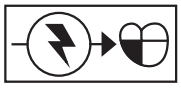
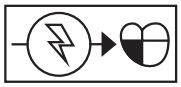
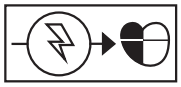
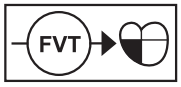
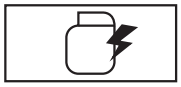
Symbol	Explanation
	VT, FVT therapies (CRT)
	AT/AF intervention
	Burst
	Burst (CRT)
	Burst+
	50 Hz Burst
	A ramp
	Ramp (CRT)
	Ramp+
	Ramp+ (CRT)
	V ramp
	AV ramp
	Defibrillation

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

Symbol	Explanation
	V cardioversion
	AV cardioversion
	FVT therapies
	Mode Switch
	Magnet Rate
	Dangerous voltage
	Active Can
TR	Triple chamber rate responsive pacemaker
DR	Dual chamber rate responsive pacemaker
D	Dual chamber pacemaker
SR	Single chamber rate responsive pacemaker
S	Single chamber pacemaker

1.1.6 Notice

The Patient Information screen 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 enter into the Patient Information screen. 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 screen, see Section 4.9.

1.2 System description

The Medtronic Consulta CRT-P Model C4TR01 dual chamber implantable pacemaker with cardiac resynchronization therapy (CRT-P) 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 atrial 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 automatically detects atrial tachyarrhythmias (AT/AF) and provides treatment with antitachycardia pacing therapies. The device monitors the heart rhythm for ventricular tachyarrhythmias and uses detection criteria to distinguish between true ventricular arrhythmias and rapidly conducted supraventricular tachycardia (SVT). The device responds to bradyarrhythmias by providing bradycardia pacing therapy. Simultaneous or sequential biventricular pacing is used to provide patients with cardiac resynchronization therapy.

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

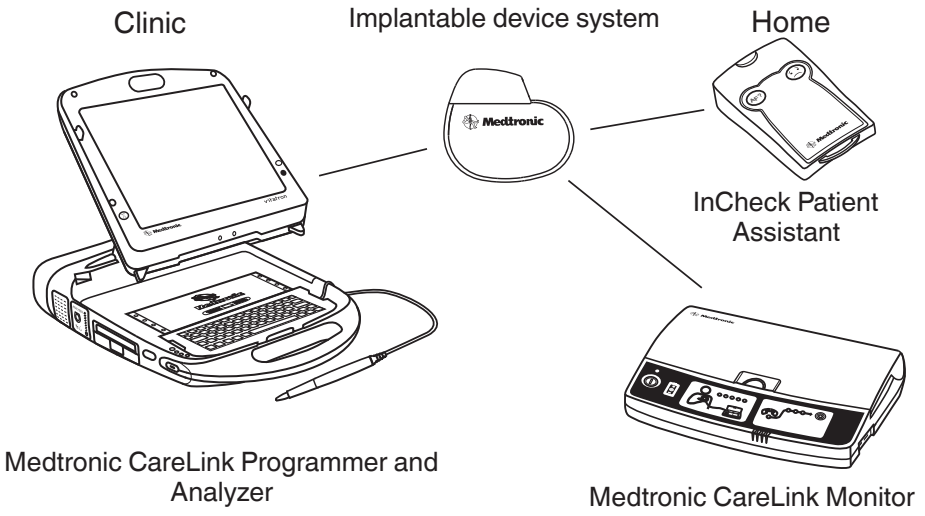
Rate response – Rate response is controlled through an activity-based sensor.

Leads – The lead system used with this device must provide pacing to the left ventricle (LV), sensing and pacing 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 92.

Implantable device system – The Consulta CRT-P Model C4TR01 device and the pacing 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



Programmer and software – The Medtronic CareLink Model 2090 Programmer and software are used to program this device. You will need to use the programming head for communications with this device. Programmers from other manufacturers are not compatible with Medtronic devices but will not damage Medtronic devices.

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.

Model 2490G Medtronic CareLink Monitor – Patients use the Model 2490G monitor and a home telephone line to transmit information from their implanted device to their physician. Patients collect information from the device by placing a telemetry head over the device. The monitor then transmits the information over the home telephone line to the CareLink Network, where it can be viewed by the clinic. Refer to the monitor literature for connection and usage information.

Transtelephonic monitor – Patients may use a transtelephonic monitor to transmit ECG information from their implanted device to their physician over a home telephone line. During a transtelephonic session, the patient places a magnet over their device to initiate magnet mode operation, which temporarily provides asynchronous pacing at a fixed rate. At the end

of the session, the patient removes the magnet to restore operation of the pacemaker to its permanent status. 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. Cardiac event data can be viewed either on the programmer or using CareLink. In addition, when the InCheck Patient Assistant is activated, the EGM signals of the programmed EGM sources and markers are stored in the device and are available for review using CareLink. The CareLink monitor transmits the EGM data and markers from the patient's device to the CareLink Network. You can identify patients who have new, not previously viewed patient-activated episodes and then proceed to view their EGM data using the Detailed EGM Viewer on CareLink.
- Verify whether the implanted device has detected a suspected atrial tachyarrhythmia.

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

1.3 Indications and usage

The Consulta CRT-P system is indicated for:

- NYHA Functional Class III and IV patients who remain symptomatic despite stable, optimal medical therapy and have LVEF ≤ 35% and a prolonged QRS duration.
- NYHA Functional Class I, II, or III patients who have LVEF ≤ 50%, are on stable, optimal heart failure medical therapy if indicated and have 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.

Rate adaptive pacing is provided for those patients developing a bradycardia indication who might benefit from increased pacing rates concurrent with increases in activity.

Dual chamber and atrial tracking modes are indicated for patients who may benefit from maintenance of AV synchrony.

Antitachycardia pacing (ATP) is indicated for termination of atrial tachyarrhythmia in patients with one or more of the above pacing indications.

1.4 Contraindications

The Consulta CRT-P system is contraindicated for:

- Concomitant implant with another bradycardia device
- Concomitant implant with an implantable cardioverter defibrillator

There are no known contraindications for the use of pacing as a therapeutic modality to control heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implant procedure used by the physician.

- Rate-responsive modes may be contraindicated in those patients who cannot tolerate pacing rates above the programmed Lower Rate.
- Dual chamber sequential pacing is contraindicated in patients with chronic or persistent supraventricular tachycardias, including atrial fibrillation or flutter.
- Asynchronous pacing is contraindicated in the presence (or likelihood) of competition between paced and intrinsic rhythms.
- Single chamber atrial pacing is contraindicated in patients with an AV conduction disturbance.
- ATP therapy is contraindicated in patients with an accessory antegrade pathway.

2 Warnings, precautions, and potential adverse events

2.1 General warnings and precautions

Anti-coagulation – Use of the device should not change the application of established anti-coagulation protocols.

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:

- 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 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.

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.

Atrial Capture Management – Atrial Capture Management does not adjust atrial outputs to values greater than 5.0 V or 1.0 ms. If the patient needs atrial pacing output greater than 5.0 V or 1.0 ms, manually program the atrial amplitude and pulse width. If a lead dislodges partially or completely, Atrial Capture Management may not prevent loss of capture.

Atrial lead maturation – Do not program AT/AF detection to On or enable automatic atrial ATP therapies until the atrial lead has matured (approximately one month after implant). If the atrial lead dislodges and migrates to the ventricle, the device could inappropriately detect AT/AF, deliver atrial ATP to the ventricle, and possibly induce a life-threatening ventricular tachyarrhythmia.

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.

Effects of myopotential sensing in unipolar pacing configurations – In unipolar sensing configurations, the device may not distinguish myopotentials from cardiac signals. This may result in a loss of pacing due to inhibition. Also, unipolar atrial sensing in atrial tracking modes can result in elevated ventricular pacing rates. To address these situations, the device may be programmed to be less sensitive (using higher sensitivity values), but the sensitivity level must be balanced against the potential to undersense true cardiac signals. Typically, this balance is easily attained for ventricular sensing using sensitivity values around 2.8 mV, but it may be difficult to attain for atrial sensing because of the smaller P-wave amplitudes.

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.

Extended Upper Tracking Rate – When programming Upper Tracking Rates of 190, 200, or 210 bpm, be careful to ensure that these rates are appropriate for the patient.

False bipolar pathway with unipolar lead – When implanting a unipolar lead, ensure that the tip setscrew is properly engaged and that all electrical contacts are sealed to prevent electrical leakage. Electrical leakage may cause the device to inappropriately identify a unipolar lead as bipolar, resulting in loss of output.

Magnets – Placing a magnet over the device suspends tachyarrhythmia detection and initiates asynchronous, fixed-rate bradycardia pacing. The programming head contains a magnet that can cause magnet operation to occur. However, magnet operation does not occur if telemetry between the device and programmer is established.

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

Pacing and sensing safety margins – Lead maturation (at least one month after implant) 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.

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. If LV Capture Management is used, set the LV Maximum Adapted Amplitude to a value that minimizes phrenic nerve 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 control – Decisions regarding rate controls should not be based on the ability of the device to prevent atrial arrhythmias.

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.

RV Capture Management – RV Capture Management does not program right ventricular outputs to values greater than 5.0 V or 1.0 ms. If the patient needs right ventricular pacing output greater than 5.0 V or 1.0 ms, manually program right ventricular amplitude and pulse width. If a lead dislodges partially or completely, RV Capture Management may not prevent loss of capture.

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.

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.

Polarity override – Do not override the polarity verification prompt with bipolar polarity when a unipolar lead is connected. Overriding the polarity verification prompt results in no pacing output.

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 Warnings, precautions, and guidance for clinicians performing medical procedures on cardiac device patients

This section is intended for physicians and other health care professionals who perform medical procedures on patients with Medtronic implanted cardiac device systems and who consult with the patients' cardiologists. This section provides warnings, precautions, and guidance related to medical therapies and diagnostic procedures that may cause serious injury to a patient, interfere with a Medtronic implanted cardiac device system, or permanently damage the system.

Note: Some common medical procedures that pose no risk are also listed in this section.

For additional guidance on medical procedures not addressed in this section, customers can contact the following resources:

- Customers in the United States can contact either of the following telephone numbers: for pacemakers, contact Medtronic Technical Services at +1 800 505 4636; for ICDs, contact Medtronic Technical Services at +1 800 723 4636. You may also submit questions to tshelp@Medtronic.com or your Medtronic representative.
- Customers outside of the United States can contact a Medtronic representative.

Ablation (RF ablation or microwave ablation) – Ablation is a surgical technique in which radio frequency (RF) or microwave energy is used to destroy cells by creating heat. Ablation used in cardiac device patients may result in, but is not limited to, induced ventricular tachyarrhythmias, oversensing, unintended tissue damage, device damage, or device malfunction.

Pulse-modulated ablation systems may pose higher risk for induced ventricular tachyarrhythmias. Medtronic cardiac devices are designed to withstand exposure to ablation energy. To mitigate risks, observe the following precautions:

- Ensure that temporary pacing and defibrillation equipment is available.
- Avoid direct contact between the ablation catheter and the implanted system.
- Position the return electrode patch so that the electrical current pathway does not pass through or near the device and leads.
- Always monitor the patient during ablation with at least two separate methods, such as arterial pressure display, ECG, manual monitoring of the patient's rhythm (taking pulse) or monitor by some other means such as ear or finger pulse oximetry, or Doppler pulse detection.

To avoid or mitigate the effects of oversensing, if appropriate for the patient, initiate asynchronous pacing by implementing one of the following precautions;

- Initiate the magnet mode (asynchronous pacing) by placing a magnet over the device.
- Program the device to an asynchronous pacing mode (for example, DOO).

After the ablation procedure, remove the magnet or restore device parameters.

Capsule endoscopy, pH capsule procedures – Capsule endoscopy is a procedure in which a capsule containing a tiny camera is swallowed by the patient to take pictures of the patient's digestive tract. Capsule endoscopy and pH capsule procedures should pose no risk of electromagnetic interference.

Dental procedures – Dental equipment, such as ultrasonic scalers, drills, and pulp testers, poses no risk of electromagnetic interference. Keep a cardiac device at least 15 cm (6 in) away from magnets, such as magnets found in dental office pillow headrests.

Diagnostic radiology (CT scans, fluoroscopy, mammograms, x-rays) – Diagnostic radiology refers to the following medical procedures:

- Computed axial tomography (CT or CAT scan)
- Fluoroscopy (an x-ray procedure that makes it possible to see internal organs in motion by producing a video image)
- Mammograms
- X-rays (radiography, such as chest x-rays)

Normally, the accumulated dose from diagnostic radiology is not sufficient to damage the device. If the device is not directly exposed to the radiation beam, no risk of interference with device operation occurs. However, if the device is directly in a CT scan beam, see the following precautions in "CT scan". Similar interference may be observed for some forms of high-intensity fluoroscopy.

CT scan – A CT scan is a computerized process in which two-dimensional x-ray images are used to create a three-dimensional x-ray image. If 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 longer than 4 s, to avoid or mitigate the effects of oversensing, if appropriate for the patient, initiate asynchronous pacing by implementing one of the following precautions:

- Initiate the magnet mode (asynchronous pacing) by placing a magnet over the device.
- Program the device to an asynchronous pacing mode (for example, DOO).

After completing the CT scan, remove the magnet or restore device parameters.

Diagnostic ultrasound – Diagnostic ultrasound is an imaging technique that is used to visualize muscles and internal organs, their size, structures, and motion as well as any

pathological lesions. It also is used for fetal monitoring and to detect and measure blood flow. Diagnostic ultrasound, such as echocardiogram, poses no risk of electromagnetic interference. For precautions about therapeutic ultrasound, see “Diathermy treatment (including therapeutic ultrasound)”.

Diathermy treatment (including therapeutic ultrasound) – Diathermy is a treatment that involves the therapeutic heating of body tissues. Diathermy treatments include high frequency, short wave, microwave, and therapeutic ultrasound. Except for therapeutic ultrasound, do not use diathermy treatments on cardiac device patients. Diathermy treatments may result in serious injury or damage to an implanted device and leads. Therapeutic ultrasound is the use of ultrasound at higher energies than diagnostic ultrasound to bring heat or agitation into the body. Therapeutic ultrasound is acceptable if treatment is performed with a minimum separation distance of 15 cm (6 in) between the applicator and the implanted device and leads.

Electrolysis – Electrolysis is the permanent removal of hair by using an electrified needle (AC or DC) that is inserted into the hair follicle. Electrolysis introduces electrical current into the body, which may cause oversensing. Evaluate any possible risks associated with oversensing with the patient’s medical condition. To avoid or mitigate the effects of oversensing, if appropriate for the patient, initiate asynchronous pacing by implementing one of the following precautions:

- Initiate the magnet mode (asynchronous pacing) by placing a magnet over the device.
- Program the device to an asynchronous pacing mode (for example, DOO).

After completing electrolysis, remove the magnet or restore device parameters.

Electrosurgery – Electrosurgery (including electrocautery, electrosurgical cautery, and Medtronic Advanced Energy surgical incision technology) is a process in which an electric probe is used to control bleeding, to cut tissue, or to remove unwanted tissue. Electrosurgery used on cardiac device patients may result in, but is not limited to, oversensing, unintended tissue damage, tachyarrhythmias, device damage, or device malfunction. If electrosurgery cannot be avoided, consider the following precautions:

- Ensure that temporary pacing and defibrillation equipment is available.
- Use a bipolar electrosurgery system or Medtronic Advanced Energy surgical incision technology, if possible. If a unipolar electrosurgery system is used, position the return electrode patch so that the electrical current pathway does not pass through or within 15 cm (6 in) of the device and leads.
- Do not apply unipolar electrosurgery within 15 cm (6 in) of the device and leads.
- Use short, intermittent, and irregular bursts at the lowest clinically appropriate energy levels.

- Always monitor the patient during electrosurgery. If the ECG tracing is not clear due to interference, manually monitor the patient's rhythm (take pulse); alternatively, monitor by some other means such as ear or finger pulse oximetry, Doppler pulse detection, or arterial pressure display.

To avoid or mitigate the effects of oversensing, if appropriate for the patient, initiate asynchronous pacing by implementing one of the following precautions:

- Initiate magnet mode (asynchronous pacing) by placing a magnet over the device.
- Program the device to an asynchronous pacing mode (for example DOO).

After completing electrosurgery, remove the magnet or restore device parameters.

External defibrillation and cardioversion – External defibrillation and cardioversion are therapies that deliver an electrical shock to the heart to convert an abnormal heart rhythm to a normal rhythm.

Medtronic cardiac devices are designed to withstand exposure to external defibrillation and cardioversion. While damage to an implanted system from an external shock is rare, the probability increases with increased energy levels. These procedures may also temporarily or permanently elevate pacing thresholds or temporarily or permanently damage the myocardium. If external defibrillation or cardioversion are required, consider the following precautions:

- Use the lowest clinically appropriate energy.
- Position the patches or paddles a minimum of 15 cm (6 in) away from the device.
- Position the patches or paddles perpendicular to the device and leads.
- If an external defibrillation or cardioversion is delivered within 15 cm (6 in) of the device, use a Medtronic programmer to evaluate the device and lead system.

Hyperbaric therapy (including hyperbaric oxygen therapy, or HBOT) – Hyperbaric therapy is the medical use of air or 100% oxygen at a higher pressure than atmospheric pressure. Hyperbaric therapies with pressures exceeding 2.5 ATA (approximately 15 m (50 ft) of seawater) may affect device function or cause device damage. To avoid or mitigate risks, do not expose implanted devices to pressures exceeding 2.5 ATA.

Lithotripsy – Lithotripsy is a medical procedure that uses mechanical shock waves to break up kidney or gallbladder stones. If the device is at the focal point of the lithotripter beam, lithotripsy may permanently damage the device. If lithotripsy is required, keep the focal point of the lithotripter beam a minimum of 2.5 cm (1 in) away from the device. To avoid or mitigate the effects of oversensing, if appropriate for the patient, initiate asynchronous pacing by implementing one of the following precautions:

- Initiate the magnet mode (asynchronous pacing) by placing a magnet over the device.
- Program the device to an asynchronous pacing mode (for example, DOO).

After completing the lithotripsy treatment, remove the magnet or restore device parameters.

Magnetic resonance imaging (MRI) – An MRI is a type of medical imaging that uses magnetic fields to create an internal view of the body. Do not conduct MRI scans on patients who have this device or lead implanted. MRI scans may result in serious injury, induction of tachyarrhythmias, or implanted system malfunction or damage.

Radiotherapy – Radiotherapy is a cancer treatment that uses radiation to control cell growth. When performing radiotherapy, take precautions to avoid oversensing, device damage, and device operational errors, as described in the following sections:

- Oversensing – If the patient undergoes radiotherapy treatment and the average dose rate at the device exceeds 1 cGy/min, the device may inappropriately sense direct or scattered radiation as cardiac activity for the duration of the procedure. To avoid or mitigate the effects of oversensing, if appropriate for the patient, initiate asynchronous pacing by implementing one of the following precautions:
  - Initiate the magnet mode (asynchronous pacing) by placing a magnet over the device. After completing radiotherapy treatment, remove the magnet.
  - Program the device to an asynchronous pacing mode (for example, DOO). After completing radiotherapy treatment, restore device parameters.
- Device damage – Exposing the device to high doses of direct or scattered radiation from any source that results in an accumulated dose greater than 500 cGy may damage the device. Damage may not be immediately apparent. If a patient requires radiation therapy from any source, do not expose the device to radiation that exceeds an accumulated dose of 500 cGy. To limit device exposure, use appropriate shielding or other measures. For patients who are undergoing multiple radiation treatments, consider the accumulated dose to the device from previous exposures.

  Note: Normally, the accumulated dose from diagnostic radiology is not sufficient to damage the device. See “Diagnostic radiology” for precautions.
- Device operational errors – Exposing the device to 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 by 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 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 that do not produce neutrons do not cause electrical reset of the device.

Stereotaxis – Stereotaxis is a catheter navigation platform that allows clinicians to steer catheter-based diagnostic and therapeutic devices throughout the body by using magnetic

navigation. During a stereotaxis procedure, the magnetic field may activate the magnet detection sensor in the implanted device, which suspends tachyarrhythmia detection. The device resumes normal programmed operation after the procedure.

Transcutaneous electrical nerve stimulation (TENS) – TENS (including neuromuscular electrical stimulation or NMES) is a pain control technique that uses electrical impulses passed through the skin to stimulate nerves. A TENS device is not recommended for in-home use by cardiac device patients due to a potential for oversensing, inappropriate therapy, or inhibition of pacing. If a TENS device is determined to be medically necessary, contact a Medtronic representative for more information.

Transurethral needle ablation (Medtronic TUNA therapy) – Transurethral needle ablation is a surgical procedure used for benign prostatic hyperplasia (BPH) in which precisely focused, conducted radio frequency energy is used to ablate prostate tissue. Patients with implanted cardiac devices may conditionally undergo procedures that use the Medtronic TUNA system. To avoid affecting cardiac device function when performing the TUNA procedure, position the return electrode on the lower back or lower extremity at least 15 cm (6 in) away from the implanted device and leads.

2.7 Warnings, precautions, and guidance related to electromagnetic interference (EMI) for cardiac device patients

Many cardiac device patients resume their normal daily activities after full recovery from surgery. However, there may be certain situations that patients need to avoid. Because a cardiac device is designed to sense the electrical activity of the heart, the device may sense a strong electromagnetic energy field outside of the body and deliver a therapy that is not needed or withhold a therapy that is needed. The following sections provide important information to share with patients about electrical equipment or environments that may cause interference with their implanted cardiac device.

For additional guidance about EMI, customers can contact the following resources:

- Customers in the United States can contact either of the following telephone numbers: for pacemakers, contact Medtronic Technical Services at +1 800 505 4636; for ICDs, contact Medtronic Technical Services at +1 800 723 4636. You may also submit questions to tshelp@Medtronic.com or your Medtronic representative.
- Customers outside of the United States can contact a Medtronic representative.

General EMI guidelines for patients – Patients should observe the following general guidelines regarding EMI:

- Area restrictions – Before entering an area where signs are posted prohibiting persons with an implanted cardiac device, such as a pacemaker or ICD, consult with your doctor.

- Symptoms of EMI – If you become dizzy or feel rapid or irregular heartbeats while using an electrical item, release whatever you are touching or move away from the item. The cardiac device should immediately return to normal operation. If symptoms do not improve when you move away from the item, consult with your doctor. If you have an ICD and you receive a therapy shock while using an electrical item, release the item or move away from it, then consult with your doctor.
- Proper grounding of electrical items – To avoid interference from electrical current that may leak from improperly grounded electrical items and pass through the body, observe the following precautions:
  - Make sure that all electrical items are properly wired and grounded.
  - Make sure that electrical supply lines for swimming pools and hot tubs are properly installed and grounded according to local and national electrical code requirements.

Wireless communication devices – Wireless communication devices include transmitters that can affect cardiac devices. When using wireless communication devices, keep them at least 15 cm (6 in) away from your cardiac device. The following items are examples of such devices:

- Hand-held cellular, mobile, or cordless telephones (wireless telephones); two-way pagers; personal digital assistants (PDAs); smartphones; and mobile email devices
- Wireless-enabled devices such as laptop, notebook, or tablet computers; network routers; MP3 players; e-readers; gaming consoles; televisions; DVD players; and headsets
- Remote keyless entry and remote car starter devices

Household and hobby items with motors or magnets and other items that cause EMI – Household and hobby items that have motors or magnets or that generate electromagnetic energy fields could interfere with a cardiac device. Keep a cardiac device at least 15 cm (6 in) away from the following items:

- Hand-held kitchen appliances, such as electric mixers
- Sewing machines and sergers
- Personal care items, such as corded hand-held hair dryers, corded electric shavers, electric or ultrasonic toothbrushes (base charger), or back massagers
- Items that contain magnets, such as bingo wands, mechanic's extractor wands, magnetic bracelets, magnetic clasps, magnetic chair pads, or stereo speakers
- Remote controller of radio-controlled toys
- Two-way walkie-talkies (less than 3 W)

The following household and hobby items require special precautions:

- Boat motors – Keep a cardiac device at least 30 cm (12 in) away from electric trolling motors or gasoline-powered boat motors.
- Electronic body fat scale – Using this type of scale is not recommended for cardiac device patients because it passes electricity through the body and can interfere with the device.
- Electronic pet fences or invisible fences – Keep a cardiac device at least 30 cm (12 in) away from the buried wire and the indoor antenna of electronic pet fences or invisible fences.
- Home-use electric kilns – Keep a cardiac device at least 60 cm (24 in) away from home-use electric kilns.
- Induction cook tops – An induction cook top uses an alternating magnetic field to generate heat. Keep a cardiac device at least 60 cm (24 in) away from the heating zone when the induction cook top is turned on.
- Magnetic mattress pads or pillows – Items containing magnets can interfere with the normal operation of a cardiac device if they are within 15 cm (6 in) of the device. Avoid using magnetic mattress pads or pillows because they cannot easily be kept away from the device.
- Portable electric generators up to 20 kW – Keep a cardiac device at least 30 cm (12 in) away from portable electric generators.
- UPS (uninterruptible power source) up to 200 A – Keep a cardiac device at least 30 cm (12 in) away from a UPS. If the UPS is operating by battery source, keep a cardiac device at least 45 cm (18 in) away.

Home power tools – Most home power tools should not affect cardiac devices. Consider the following common-sense guidelines:

- Keep all equipment in good working order to avoid electrical shock.
- Be certain that plug-in tools are properly grounded (or double insulated). Using a ground fault interrupter outlet is a good safety measure (this inexpensive device prevents a sustained electrical shock).

Some home power tools could affect cardiac device operation. Consider the following guidelines to reduce the possibility of interference:

- Electric yard and hand-held power tools (plug-in and cordless) – Keep a cardiac device at least 15 cm (6 in) away from such tools.
- Soldering guns and demagnetizers – Keep a cardiac device at least 30 cm (12 in) away from these tools.

- Gasoline-powered tools and gasoline-powered yard equipment – Keep a cardiac device at least 30 cm (12 in) away from components of the ignition system. Turn off the motor before making adjustments.
- Car engine repair – Turn off car engines before making any adjustments. When the engine is running, keep a cardiac device at least 30 cm (12 in) away from components of the ignition system.

Industrial equipment – After recovering from implant surgery, you likely will be able to return to work, school, or daily routine. However, if you will be using or working near high-voltage equipment, sources of high electrical current, magnetic fields, or other EMI sources that may affect device operation, consult with your doctor. You may need to avoid using, or working near, the following types of industrial equipment:

- Electric furnaces used in the manufacturing of steel
- Induction heating equipment and induction furnaces, such as kilns
- Industrial magnets or large magnets, such as those used in surface grinding and electromagnetic cranes
- Dielectric heaters used in industry to heat plastic and dry glue in furniture manufacturing
- Electric arc and resistance welding equipment
- Broadcasting antennas of AM, FM, shortwave radio, and TV stations
- Microwave transmitters. Note that microwave ovens are unlikely to affect cardiac devices.
- Power plants, large generators, and transmission lines. Note that lower voltage distribution lines for homes and businesses are unlikely to affect cardiac devices.

Radio transmitters – Determining a safe distance between the antenna of a radio transmitter and a cardiac device depends on many factors such as transmitter power, frequency, and the antenna type. If the transmitter power is high or if the antenna cannot be directed away from a cardiac device, you may need to stay farther away from the antenna. Refer to the following guidelines for different types of radio transmitters:

- Two-way radio transmitter (less than 3 W) – Keep a cardiac device at least 15 cm (6 in) away from the antenna.
- Portable transmitter (3 to 15 W) – Keep a cardiac device at least 30 cm (12 in) away from the antenna.
- Commercial and government vehicle-mounted transmitters (15 to 30 W) – Keep a cardiac device at least 60 cm (24 in) away from the antenna.
- Other transmitters (125 to 250 W) – Keep a cardiac device at least 2.75 m (9 ft) away from the antenna.

For transmission power levels higher than 250 W, contact a Medtronic representative for more information.

Security systems – When passing through security systems, follow these precautions:

- Electronic antitheft systems, such as in a store or library, and point-of-entry control systems, such as gates or readers that include radio frequency identification equipment – These systems should not affect a cardiac device, but as a precaution, do not linger near or lean against such systems. Simply walk through these systems at a normal pace. If you are near an electronic antitheft or entry control system and experience symptoms, promptly move away from the equipment. After you move away from the equipment, the cardiac device resumes its previous state of operation.
- Airport, courthouse, and jail security systems – Given the short duration of security screening, it is unlikely that metal detectors (walk-through archways and hand-held wands) and full body imaging scanners (also called millimeter wave scanners and three-dimensional imaging scanners) in airports, courthouses, and jails will affect a cardiac device. When encountering these security systems, follow these guidelines:
  - Always carry your cardiac device ID card. If a cardiac device sets off a metal detector or security system, show your ID card to the security operator.
  - Minimize the risk of temporary interference with your cardiac device while going through the security screening process by not touching metal surfaces around any screening equipment.
  - Do not stop or linger in a walk-through archway; simply walk through the archway at a normal pace.
  - If a hand-held wand is used, ask the security operator not to hold it over or wave it back and forth over your cardiac device.
  - If you have concerns about security screening methods, show your cardiac device ID card to the security operator, request alternative screening, and then follow the security operator's instructions.

2.8 Potential adverse events

Potential adverse events associated with the use of transvenous leads and pacing systems include, but are not limited to, the following events:

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

- cardiac tamponade
- death
- erosion
- excessive fibrotic tissue growth
- fibrillation or other arrhythmias
- formation of hematomas or cysts
- heart wall or vein wall rupture
- infection
- lead abrasion and discontinuity
- muscle stimulation, nerve stimulation, or both
- myocardial irritability
- pericardial effusion
- pneumothorax
- threshold elevation
- thrombolytic and air embolism
- transvenous lead-related thrombosis
- venous occlusion
- chronic nerve damage
- endocarditis
- erosion through the skin
- extrusion
- fluid accumulation
- heart block
- hematoma/seroma
- keloid formation
- lead migration/dislodgment
- myocardial damage
- myopotential sensing
- pericardial rub
- rejection phenomena (local tissue reaction, fibrotic tissue formation, device migration)
- thromboemboli
- thrombosis
- valve damage (particularly in fragile hearts)
- venous or cardiac perforation

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

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:

Atrial Capture Management (ACM) study – This clinical study, which evaluated the Atrial Capture Management feature in EnPulse pacemakers, provides support for the Atrial Capture Management feature in Consulta CRT-P Model C4TR01 devices.

Atrial Fibrillation Symptoms Mediated by Pacing to Mean Rates (AF SYMPTOMS) – This study evaluated the long-term effects of Conducted AF Response in patients with atrial fibrillation and intact atrioventricular (AV) conduction. It provides support for the Conducted AF Response feature in Consulta CRT-P Model C4TR01 devices. Note that the Ventricular Response Pacing (VRP) feature mentioned in the study is called Conducted AF Response in the Consulta CRT-P Model C4TR01 devices.

Atrial Septal Pacing Efficacy Trial (ASPECT) – This clinical study, which evaluated the safety and efficacy of the Medtronic AT500 DDDRP Pacing System devices, provides support for the atrial intervention pacing therapies.

Atrial Therapy Efficacy and Safety Trial (ATTEST) – This clinical study, which evaluated the safety and efficacy of the Medtronic AT500 DDDRP Pacing System devices, provides support for the Consulta CRT-P Model C4TR01 devices.

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 Consulta CRT-P Model C4TR01 devices.

Care-HF clinical study – This clinical study, which evaluated the effects of cardiac resynchronization therapy (CRT) in InSync and InSync III devices on the mortality and morbidity of patients with moderate or severe heart failure due to left ventricular systolic dysfunction and cardiac dyssynchrony, provides support for CRT pacing in Consulta CRT-P Model C4TR01 devices.

FAST study – This clinical study, which evaluated the OptiVol Fluid Monitoring feature in InSync Marquis devices to corroborate the MIDHeFT clinical data, provides support for the OptiVol Fluid Monitoring feature in Consulta CRT-P Model C4TR01 devices.

InSync clinical study – This clinical study, which was used as the historical control for the cardiac resynchronization therapy evaluation of the InSync III clincial study, provides support for CRT pacing in Consulta CRT-P Model C4TR01 devices.

InSync III clinical study – This clinical study, which evaluated the safety and efficacy of sequential biventricular CRT pacing and the general safety and efficacy of CRT in InSync III devices, provides support for CRT pacing in Consulta CRT-P Model C4TR01 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 Consulta CRT-P Model C4TR01 devices.

Kappa 700 clinical study – This study, which evaluated the safety and clinical performance of the Kappa 700 pacemakers, provides support for the Right Ventricular Capture Management feature and other bradycardia pacing features.

Left Ventricular Capture Management Software Download Clinical Trial (LVCM) – This clinical study, which evaluated the accuracy of the Left Ventricular Capture Management feature in modified InSync II Marquis devices, provides support for the Left Ventricular Capture Management feature in Consulta CRT-P Model C4TR01 devices.

Medtronic Impedance Diagnostics in Heart Failure Trial (MIDHeFT) – This clinical study, which demonstrated the use of intrathoracic impedance as a surrogate measure of fluid status in patients with heart failure, provides support for the OptiVol Fluid Monitoring feature in Consulta CRT-P Model C4TR01 devices.

Reducing Episodes by Septal Pacing Efficacy Confirmation Trial (RESPECT) – This clinical study evaluated the efficacy of the intervention pacing therapies on symptomatic AT/AF episodes in subjects where the lead was placed in the Bachmann's Bundle region. The results of the study failed to demonstrate effectiveness of the intervention pacing therapies. Evaluation of the RESPECT study data indicated that the intervention pacing features did not significantly reduce the rate of symptomatic AT/AF episodes and these results did not confirm the findings from previous trials. The pre-specified subgroups were tested for therapeutic effect, but none had results suggesting benefit. When intervention pacing algorithms were programmed ON, atrial pacing percentage increased by 18.1% ($P<0.001$) with a modest, yet statistically significant, increase in mean heart rate of 2.4 beats per minute ($P<0.001$).

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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 $\geq$ 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

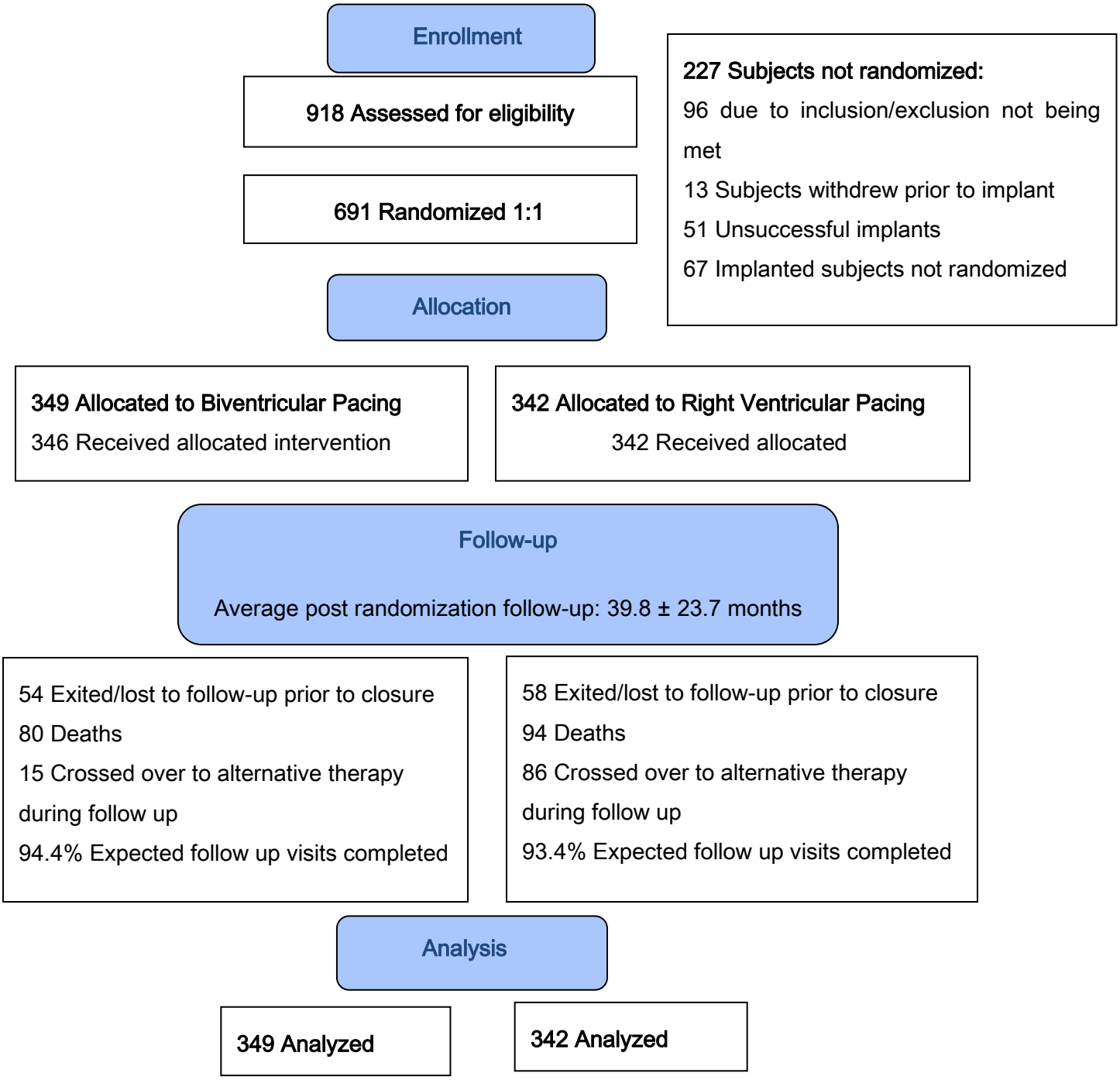
The prespecified statistical approach for the primary objective and stopping rules for data collection and trial completion was an adaptive Bayesian statistical design. Posterior probabilities and 95% credible intervals were the metrics generated in lieu of Frequentist statistical measures such as p-values 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
25th Percentile - 75th 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**.

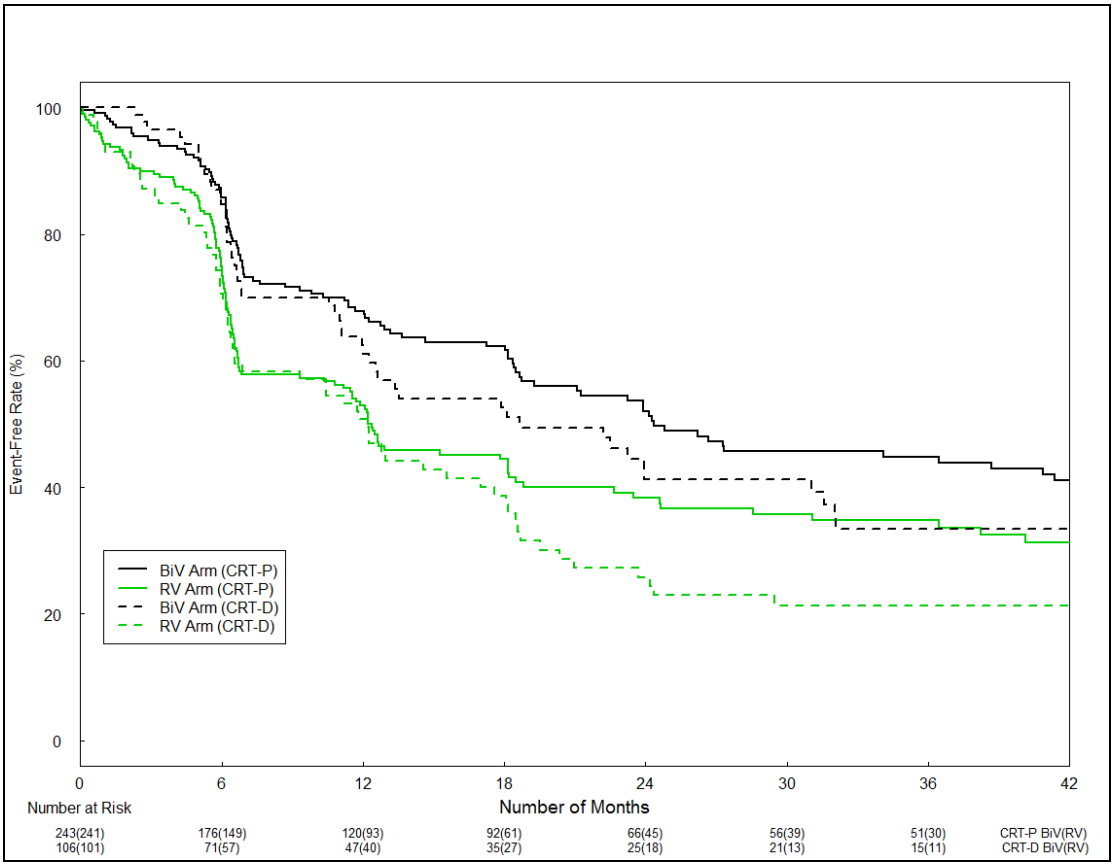
Table 2: Primary Endpoint Events for Analysis of Primary Objective

	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.

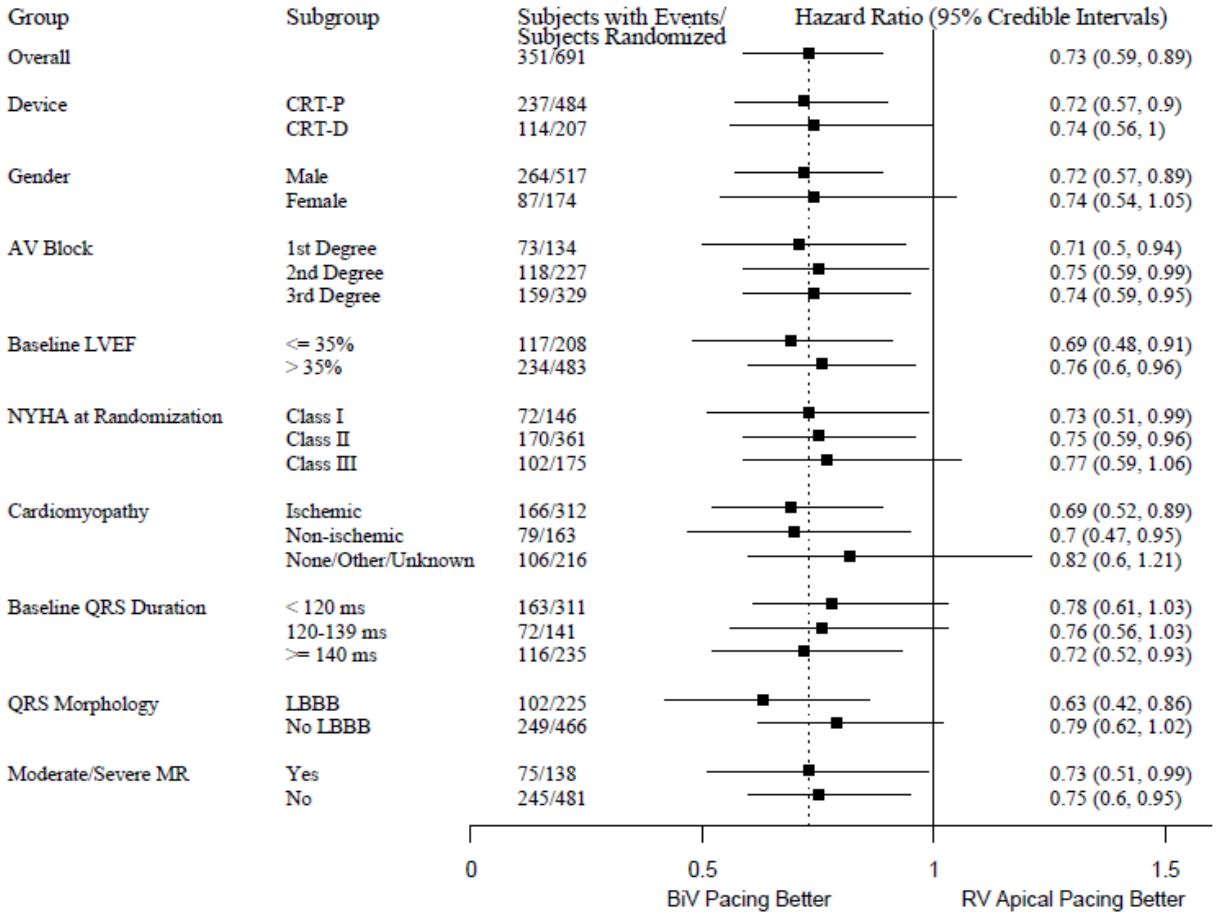
Table 7: Deaths by Device Type and Treatment Arm

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

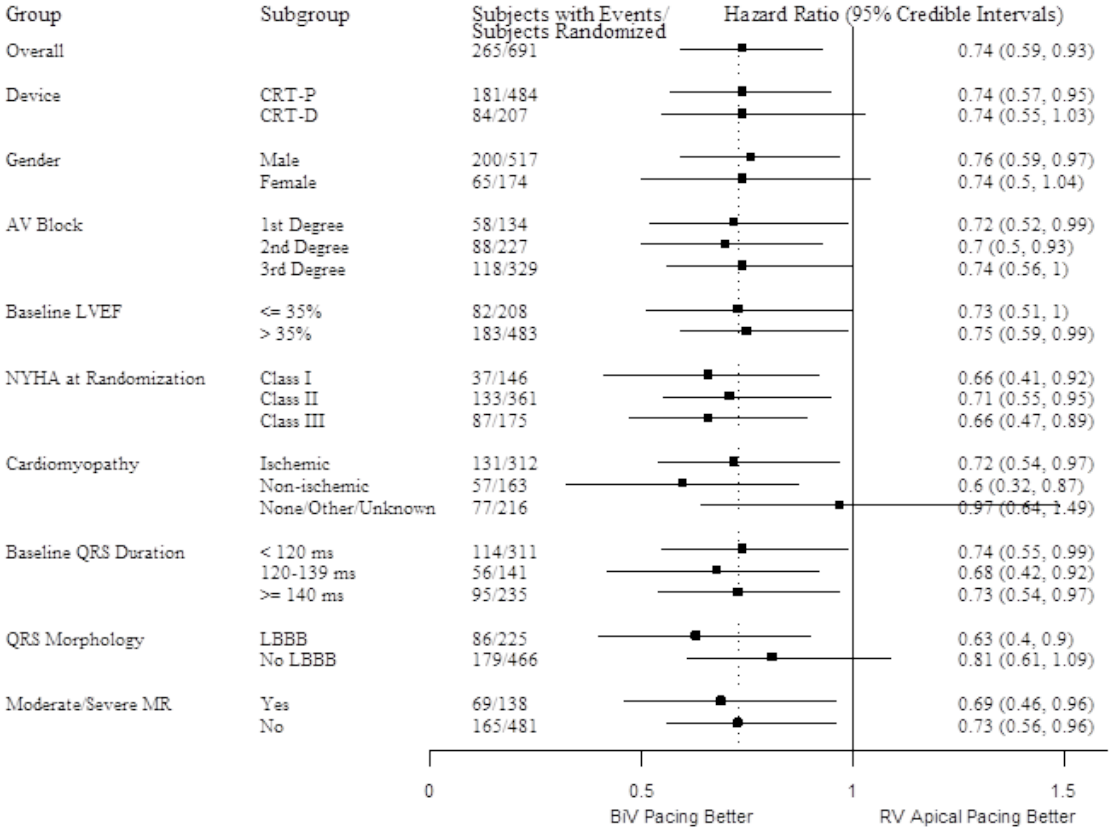
The treatment effect for key clinical subgroups was examined by calculating the hazard ratio in each group as shown in **Figure 3**.

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.

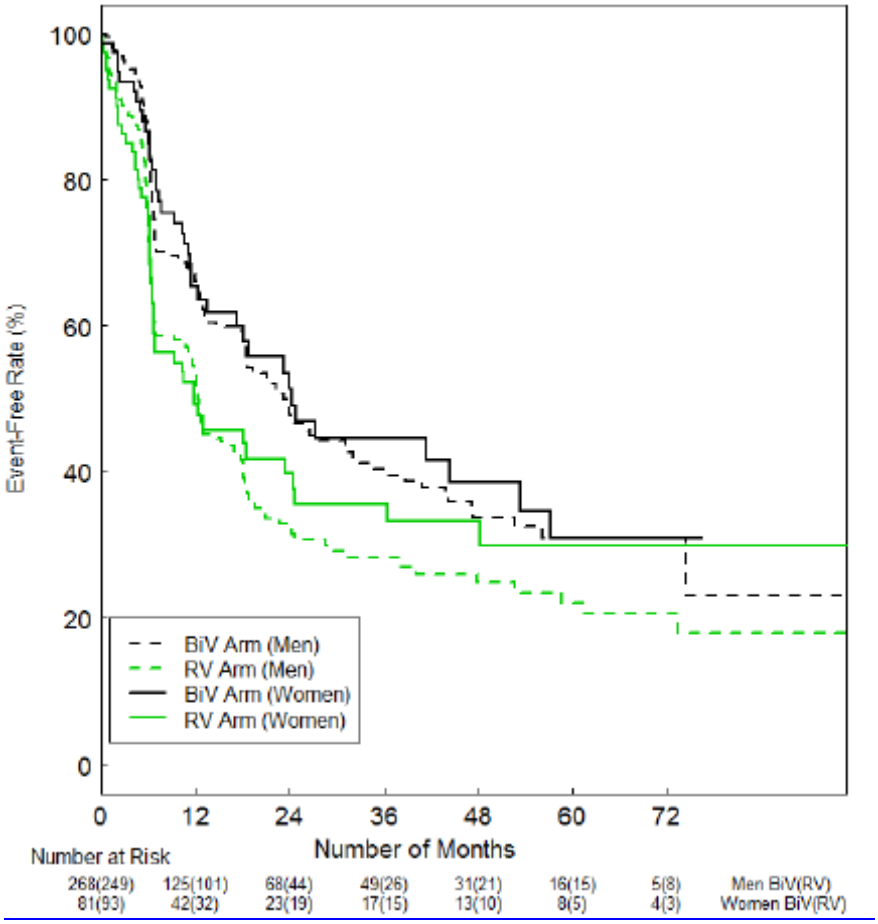
10 Gender Analysis

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.

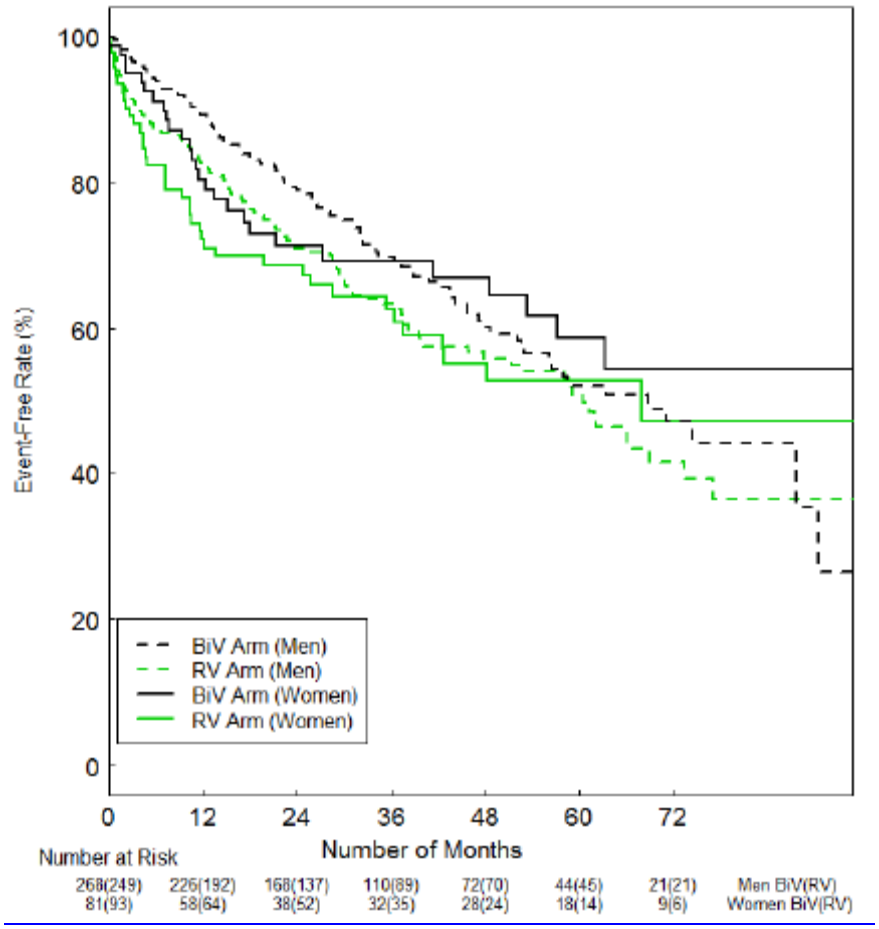
To examine the results of the primary objective by gender, a hierarchical model similar to that used in the main analysis was used to generate the hazard ratios and corresponding 95% two sided credible intervals. In women, biventricular pacing results in an overall 26% reduction in the primary endpoint, 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%)	

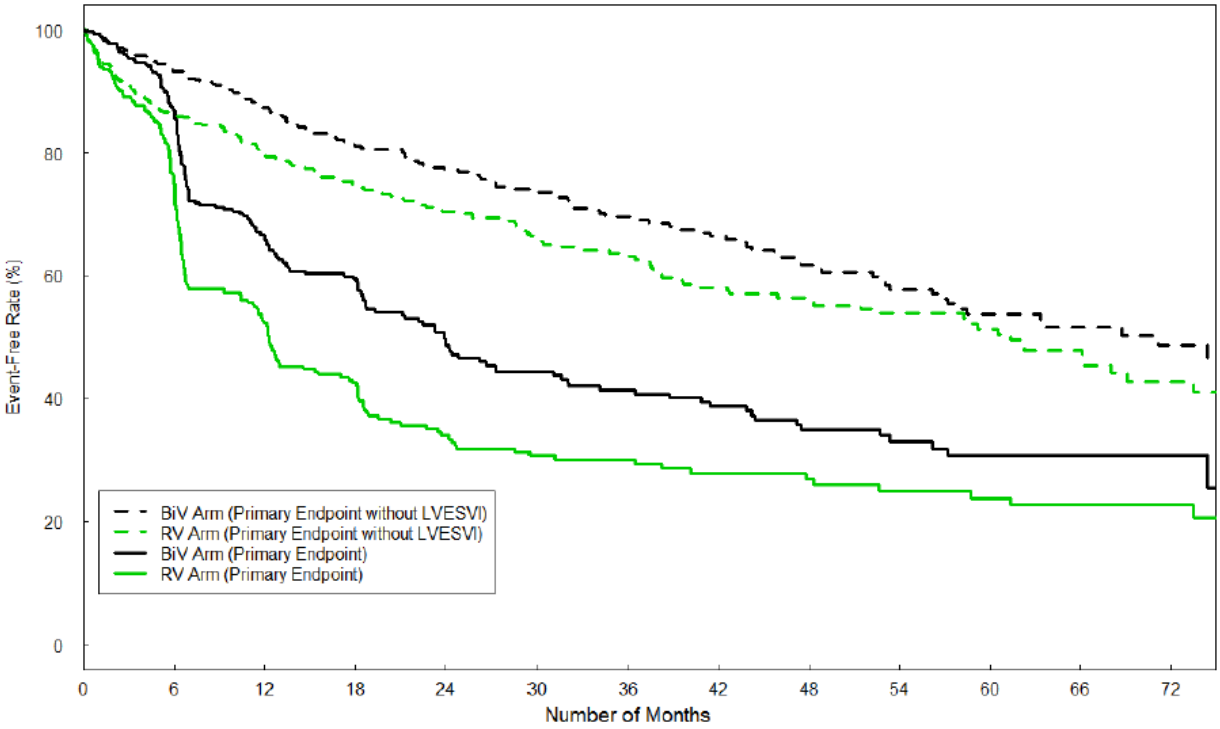
11 Additional Analysis to Understand the Impact of LVESVI

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



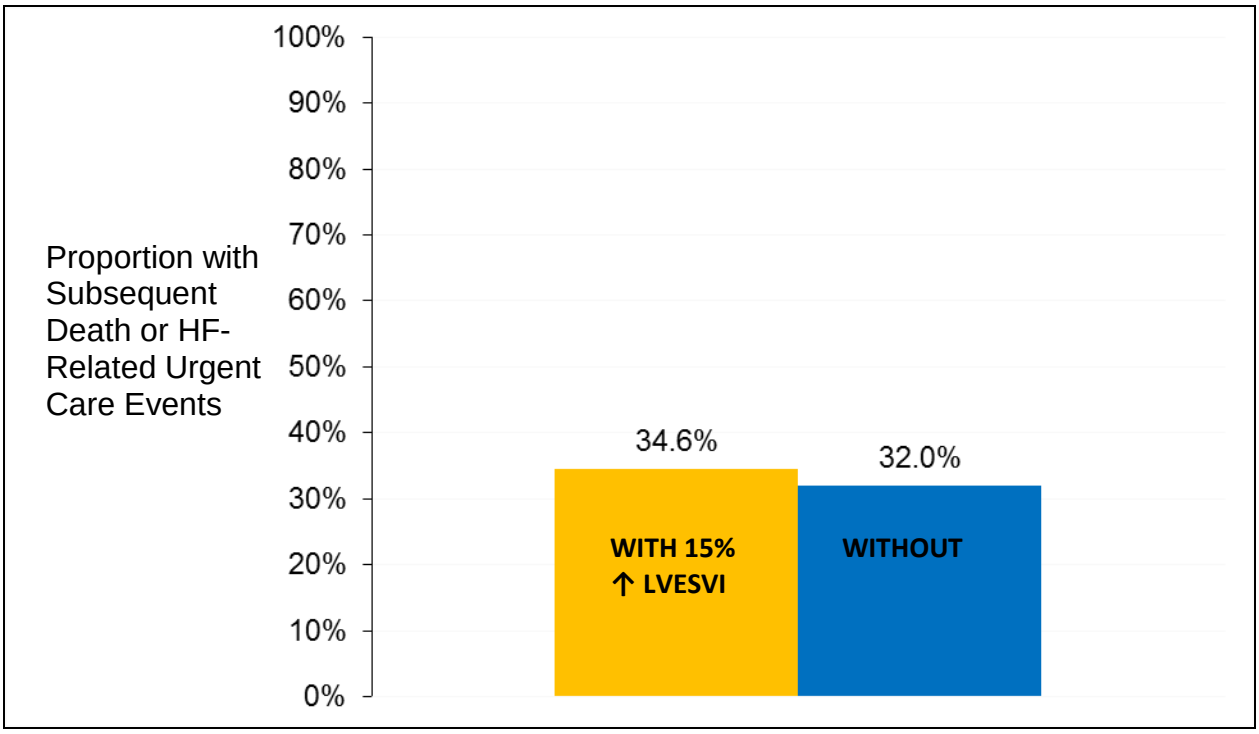
Predictive Value of LVESVI

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

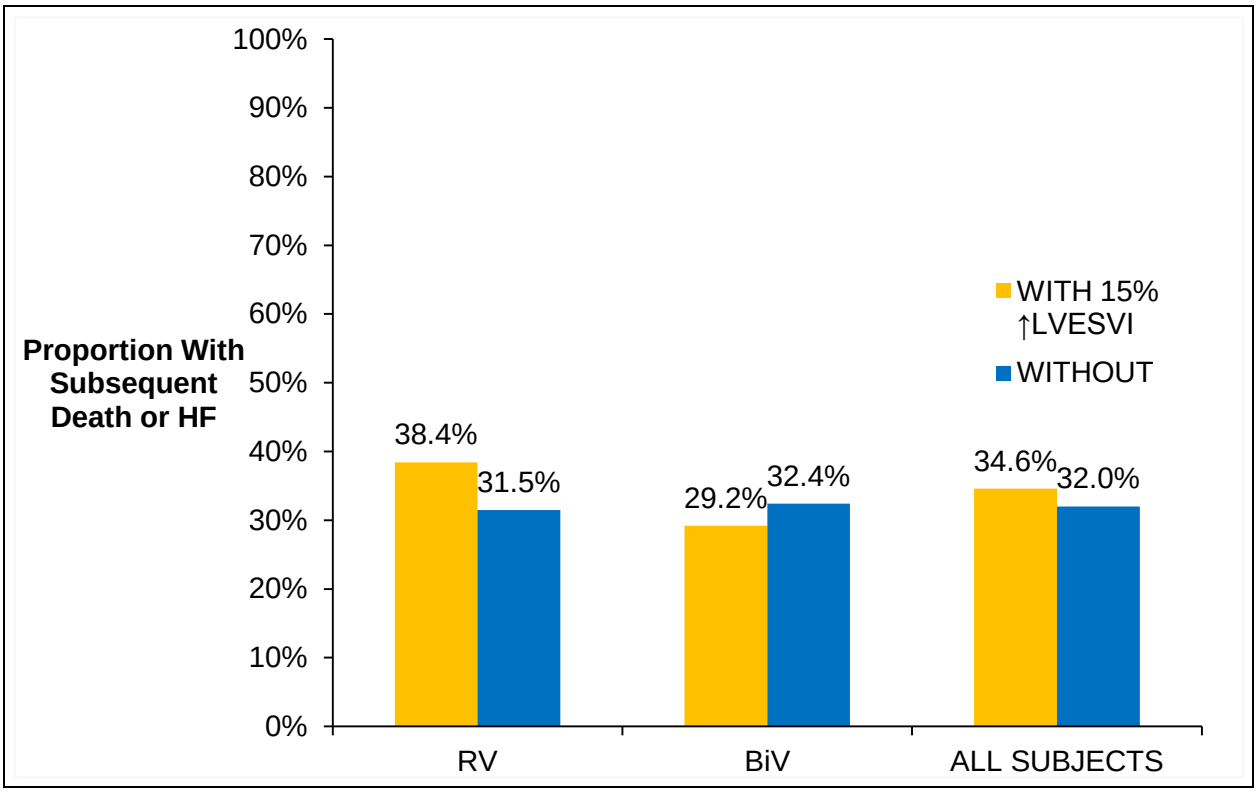
Subjects whose first primary endpoint event was a significant increase in LVESVI were examined for the occurrence of subsequent death or heart failure-related urgent care to assess whether LVESVI changes predicted future death or HF-related urgent care events. This proportion was compared to the proportion 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

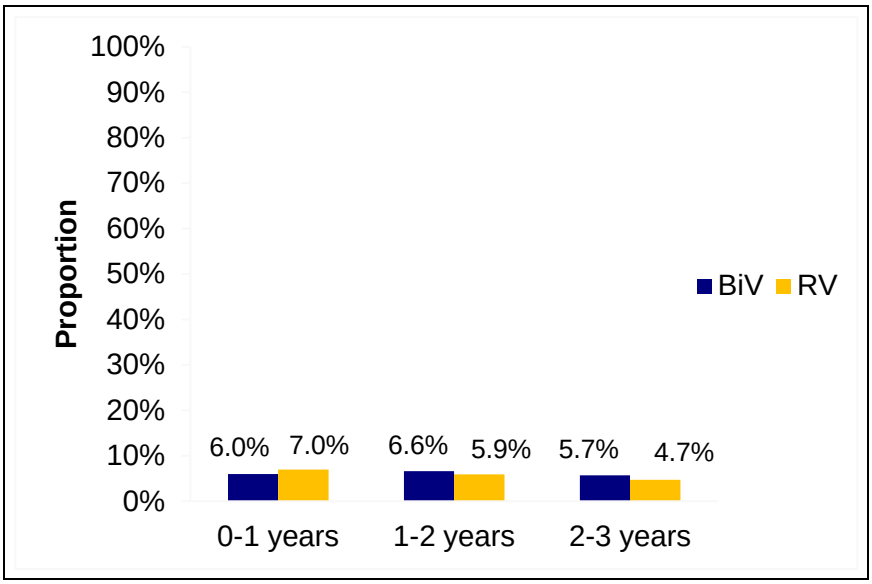
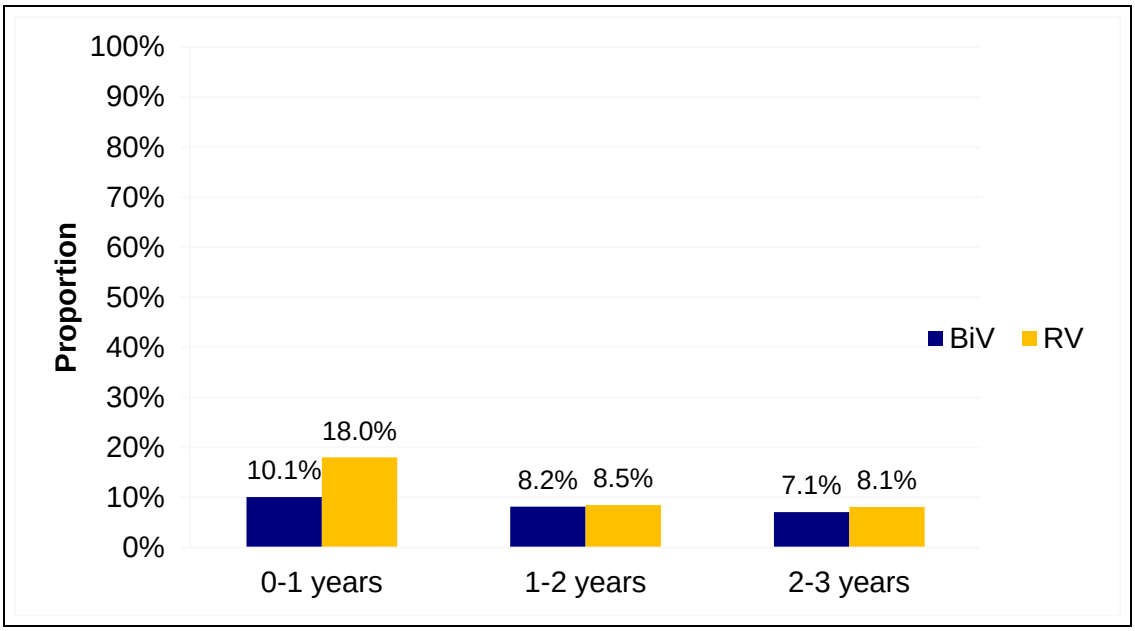


Figure 11: Annualized Heart Failure-Related Urgent Care by Randomization Arm



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 ≤ 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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