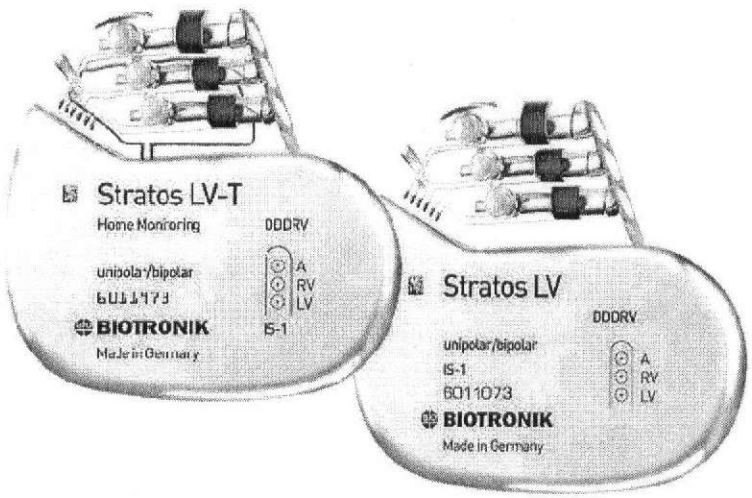
Stratos

Family of Cardiac Resynchronization Therapy Pacemakers



Technical Manual

BIOTRONIK
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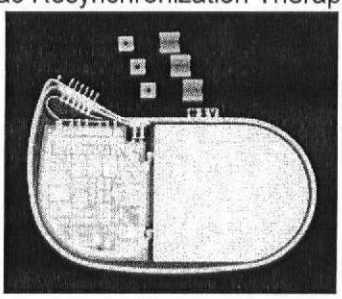
Stratos CRT-Ps

Implantable Cardiac Resynchronization Therapy Pacemakers



Stratos
X-Ray identification

Radiopaque Identification

A radiopaque identification code is visible on standard x-ray, and identifies the pulse generator:

Stratos LV/LV-T SV

CAUTION

Lead / CRT-P Compatibility – Because of the numerous available 3.2-mm configurations (e.g., the IS-1 and VS-1 standards), lead/ CRT-P compatibility should be confirmed with the CRT-P and/or lead manufacturer prior to the implantation of the system.

IS-1, wherever stated in this manual, refers to the international standard, whereby leads and generators from different manufacturers are assured a basic fit. [Reference ISO 5841-3:1992(E)].

Contents

1. General

1.1 Device Description

The Stratos LV and Stratos LV-T CRT-Ps are rate adaptive pacemakers designed to provide Cardiac Resynchronization Therapy (CRT). The Stratos CRT-Ps provide all standard bradycardia pacemaker therapy with the additional capabilities of biventricular pacing for CRT. Biventricular pacing in the Stratos CRT-Ps can be programmed to initially pace in either the right or left ventricular chambers with separately programmable outputs for both left and right channels. Sensing of cardiac signals only occurs in the right ventricular chamber.

The Stratos CRT-Ps can also provide single and dual chamber pacing in a variety of rate-adaptive and non-rate adaptive pacing modes. Pacing capability is supported by an extensive diagnostic set. For motion-based rate-adaptation, the Stratos CRT-Ps are equipped with an internal accelerometer. This sensor produces an electric signal during physical activity of the patient. If a rate-adaptive (R) mode is programmed, then the accelerometer sensor signal controls the stimulation rate.

The Stratos LV-T additionally also employs BIOTRONIK's Home Monitoring™ technology, which is an automatic, wireless, remote monitoring system for management of patients with implantable devices. With Home Monitoring, physicians can review data about the patient's cardiac status and CRT-P's functionality between regular follow-up visits, allowing the physician to optimize the therapy process. Stratos CRT-Ps are also designed to collect diagnostic data to aid the physician's assessment of a patient's condition and the performance of the implanted device.

The bipolar IS-1 connections are used for pacing and sensing (right atrial and ventricle) and the additional IS-1 connection is used for pacing in the left ventricle in either a bipolar or unipolar configuration depending on the left ventricular lead. The pulse amplitude and pulse width of each of the three channels is separately programmable.

Stratos CRT-Ps are designed to meet all indications for Cardiac Resynchronization Therapy in CHF patients as well as those for bradycardia therapy as exhibited in a wide variety of patients. The Stratos family is comprised of two CRT-Ps that are designed to handle a multitude of situations.

Stratos LV	Triple chamber, rate-adaptive, unipolar/bipolar pacing CRT-P
Stratos LV-T	Triple chamber, rate-adaptive, unipolar/bipolar pacing CRT-P with Home Monitoring

Throughout this manual, specific feature and function descriptions may only be applicable to the Stratos LV-T and those features will be referenced as such. Otherwise, reference to Stratos CRT-Ps refers to both devices.

1.2 Indications

The Stratos LV and Stratos LV-T Cardiac Resynchronization Therapy Pacemakers (CRT-Ps) are indicated for patients who have moderate to severe heart failure (NYHA Class III/IV), including left ventricular dysfunction (EF ≤ 35%) and QRS ≥ 120 ms and remain symptomatic despite stable, optimal heart failure drug therapy.

1.3 Contraindications

Use of Stratos LV and Stratos LV-T CRT-Ps are contraindicated for the following patients:

- Unipolar pacing is contraindicated for patients with an implanted cardioverter-defibrillator (ICD) because it may cause unwanted delivery or inhibition of ICD therapy.
- Single chamber atrial pacing is contraindicated for patients with impaired AV nodal conduction.
- Dual chamber and single chamber atrial pacing is contraindicated for patients with chronic refractory atrial tachyarrhythmias.

1.4 Note to Physician

As with any implantable pulse generator, there are certain infrequent risks associated with Stratos CRT-Ps. Section 1.6 lists the adverse events that have been observed or may potentially occur with these Cardiac Resynchronization Therapy Pacemakers. The warnings and precautions listed in Section 1.5 should be taken under serious consideration in order to aid in avoiding device failures and harm to the patient.

Regular monitoring of the patient and their implanted device should be conducted to identify performance concerns and ensure appropriate therapy is being administered to the patient. Please communicate any performance concerns to BIOTRONIK and to FDA.

All explanted devices should be returned to the manufacturer for testing to help understand device reliability and performance. Refer to Section 10 for recommended procedures for handling explanted devices.

1.5 Warnings and Precautions

Certain therapeutic and diagnostic procedures may cause undetected damage to a Cardiac Resynchronization Therapy Pacemakers, resulting in malfunction or failure at a later time. Please note the following warnings and precautions:

Magnetic Resonance Imaging (MRI) – Avoid use of magnetic resonance imaging as it has been shown to cause movement of the CRT-Ps within the subcutaneous pocket and may cause pain and injury to the patient and damage to the CRT-P. If the procedure must be used, constant monitoring is recommended, including monitoring the peripheral pulse.

Rate Adaptive Pacing – Use rate adaptive pacing with care in patients unable to tolerate increased pacing rates.

NIPS – Life threatening ventricular arrhythmias can be induced by stimulation in the ventricle. Ensure that an external cardiac defibrillator is accessible during tachycardia testing. Only physicians trained and experienced in tachycardia induction and reversion protocols should use non-invasive programmed stimulation (NIPS).

High Output Settings – High output settings combined with extremely low lead impedance may reduce the life expectancy of the Stratos CRT-Ps. Programming of pulse amplitudes, higher than 4.8 V, in combination with long pulse widths and/or high pacing rates may lead to premature activation of the replacement indicator.

1.5.1 Interactions with Other Medical Therapy

Before applying one of the following procedures, a detailed analysis of the advantages and risks should be made. Cardiac activity during one of these procedures should be confirmed by continuous monitoring of peripheral pulse or blood pressure. Following the procedures, CRT-P function and stimulation threshold must be checked.

Therapeutic Diathermy Equipment – Use of therapeutic diathermy equipment is to be avoided for pacemaker patients due to possible heating effects of the CRT-P and at the implant site. If diathermy therapy must be used, it should not be applied in the immediate vicinity of the CRT-P or leads. The patient's peripheral pulse should be monitored continuously during the treatment.

Transcutaneous Electrical Nerve Stimulation (TENS) – Transcutaneous electrical nerve stimulation may interfere with CRT-P function. If necessary, the following measures may reduce the possibility of interference:

- Place the TENS electrodes as close to each other as possible.
- Place the TENS electrodes as far from the CRT-P/lead system as possible.
- Monitor cardiac activity during TENS use.

Defibrillation – The following precautions are recommended to minimize the inherent risk of CRT-P operation being adversely affected by defibrillation:

- The paddles should be placed anterior-posterior or along a line perpendicular to the axis formed by the CRT-P and the implanted lead.
- The energy setting should not be higher than required to achieve defibrillation.
- The distance between the paddles and the CRT-P/leads should not be less than 10 cm (4 inches).

Radiation – The CRT-P's internal electronics may be damaged by exposure to radiation during radiotherapy. To minimize this risk when using such therapy, the CRT-P should be protected with local radiation shielding.

Lithotripsy – Lithotripsy treatment should be avoided for CRT-P patients since electrical and/or mechanical interference with the CRT-P is possible. If this procedure must be used, the greatest possible distance from the point of electrical and mechanical strain should be chosen in order to minimize a potential interference with the CRT-P.

Electrocautery – Electrocautery should never be performed within 15 cm (6 inches) of an implanted CRT-P or leads because of the danger of introducing fibrillatory currents into the heart and/or damaging the CRT-P. Pacing should be asynchronous and above the patient's intrinsic rate to prevent inhibition by interference signals generated by the cautery. When possible, a bipolar electrocautery system should be used.

For transurethral resection of the prostate, it is recommended that the cautery ground plate be placed under the buttocks or around the thigh, but not in the thoracic area where the current pathway could pass through or near the CRT-P system.

1.5.2 Storage and Sterilization

Storage (temperature) – Recommended storage temperature range is 5° to 55°C (41°-131°F). Exposure to temperatures outside this range may result in CRT-P malfunction (see Section 7.1).

Low Temperatures – Exposure to **low temperatures** (below 0°C) may cause a false elective replacement indication to be present. If this occurs, warm the device to room temperature and reset the ERI with magnet application (see Section 7.1).

Handling – Do not drop. If an unpackaged CRT-P is dropped onto a hard surface, return it to BIOTRONIK (see Section 7.1).

FOR SINGLE USE ONLY - Do not re-sterilize the CRT-P or accessories packaged with the CRT-P, they are intended for one-time use.

Device Packaging – Do not use the device if the packaging is wet, punctured, opened or damaged because the integrity of the sterile packaging may be compromised. Return the device to BIOTRONIK.

Storage (magnets) – Store the device in a clean area, away from magnets, kits containing magnets, and sources of electromagnetic interference (EMI) to avoid damage to the device.

Temperature Stabilization – Allow the device to reach room temperature before programming or implanting the device. Temperature extremes may affect the initial device function.

Use Before Date – Do not implant the device after the USE BEFORE DATE because the device may have reduced longevity.

1.5.3 Lead Connection and Evaluation

Lead Check –

Feature Description: Lead Check is a feature that, when activated, automatically measures the lead impedance with every pace. Based on these measurements, the lead configuration will be set to either unipolar or bipolar. Refer to Section 2.5 for more details regarding this feature.

Caution: Lead check will not lead to disabling of cardiac resynchronization therapy. It limits the use of the resynchronization features.

1. Lead check is possible only when the right ventricle is paced first.
2. Lead check works only when the pacing voltages are programmed between 2.4 and 4.8 V. The lead check feature can be programmed OFF in patients that require cardiac resynchronization therapy.

Care should be taken when programming Stratos CRT-Ps with Lead Check ON as the device may switch from bipolar to unipolar pacing and sensing without warning. This situation may be inappropriate when using a Stratos CRT-P for patients with an Implantable Cardioverter Defibrillator (ICD). The following associated message appears when programming this feature:

> "Lead check may result in a switch to unipolar pacing and sensing, which may be inappropriate for patients with an ICD."

Additionally, Lead Check should be programmed OFF before lead connection as the feature will automatically reprogram the device to unipolar in the absence of a lead.

Lead / CRT-P Compatibility – Because of the numerous available 3.2-mm configurations (e.g., the IS-1 and VS-1 standards), lead/ CRT-P compatibility should be confirmed with the CRT-P and/or lead manufacturer prior to the implantation of the system.

IS-1, wherever stated in this manual, refers to the international standard, whereby leads and generators from different manufacturers are assured a basic fit. [Reference ISO 5841-3:1992(E)].

Lead Configuration – The polarity of the implanted lead dictates what lead configuration can be programmed for the CRT-P. Pacing will not occur with a unipolar lead if the lead configuration of the respective channel is programmed to bipolar (see Section 8).

Setscrew Adjustment – Back-off the setscrew(s) prior to insertion of lead connector(s) as failure to do so may result in damage to the lead(s), and/or difficulty connecting lead(s).

Cross Threading Setscrew(s) – To prevent cross threading the setscrew(s), do not back the setscrew(s) completely out of the threaded hole. Leave the torque wrench in the slot of the setscrew(s) while the lead is inserted.

Tightening Setscrew(s) – Do not overtighten the setscrew(s). Use only the BIOTRONIK supplied torque wrench.

Sealing System – Be sure to properly insert the torque wrench into the perforation at an angle perpendicular to the connector receptacle. Failure to do so may result in damage to the plug and its self-sealing properties.

1.5.4 Programming and Operation

IEGM – Due to the compression processes that the signals undergo, the IEGM recordings are not suitable for making some specific cardiac diagnoses, such as ischemia; although, these tracings may be useful in diagnosing arrhythmias, device behavior or programming issues.

Post AES - Before activating post-AES, check whether the selected program can cause Pacemaker Mediated Tachycardia (PMT) and whether post-AES pacing results.

Overdrive Pacing Mode - When programming the overdrive pacing mode, check whether the selected program can cause PMT, and whether atrial over drive pacing would result. Corresponding to the measured retrograde conduction time, the PMT protection interval must be programmed to a correct value.

AV Hysteresis – If the AV hysteresis is enabled along with the algorithm for recognizing and terminating PMTs (PMT management), the AV delay for recognizing and terminating a PMT has a higher priority than the AV hysteresis.

Sensing – The Stratos CRT-Ps do not sense in the left ventricle.

AV Conduction – In patients with intact AV conduction, the intrinsic atrial tachycardia is conducted to the ventricle 1:1. With the resynchronization mode activated, spontaneous rate of the right ventricle mode is synchronized for a rate up to 200 ppm in the left ventricle. For this reason, biventricular pacing mode should be turned OFF in such cases.

Unipolar/Bipolar – If the pacing or sensing function is to be programmed to **bipolar** in the atrial channel, it must be verified that **bipolar leads** have been implanted in that chamber. If the atrial lead is **unipolar**, **unipolar** sensing and pacing functions must be programmed in that chamber. Failure to program the appropriate lead configuration could result in patient experiencing entrance and/or exit block.

In addition, if the atrial lead polarity setting within the Patient Data Memory has been set to **bipolar**, the polarity of the corresponding implanted lead must be confirmed to be **bipolar**.

Safe Program – Activating the "Safe Program" is a way of quickly programming the device to multiple settings in the event of an emergency. These settings include unipolar pacing with pacing output OFF in the left ventricular channel. Refer to Section 6.3 for further details.

Programmers – Use only BIOTRONIK's ICS 3000 programmer equipped with appropriate software to program Stratos CRT-Ps. Do not use programmers from other manufacturers.

Pulse Amplitude – Programming of pulse amplitudes, higher than 4.8 V, in combination with long pulse widths and/or high pacing rates can lead to premature activation of the replacement indicator. If a pulse amplitude of 7.2 V or higher is programmed and high pacing rates are reached, output amplitudes may differ from programmed values.

Pacing thresholds – When decreasing programmed output (pulse amplitude and/or pulse width), the pacing threshold must first be accurately assessed to provide a 2:1 safety margin.

EMI – Computerized systems are subject to (Electromagnetic Interference (EMI) or "noise". In the presence of such interference, telemetry communication may be interrupted and prevent programming of the Stratos CRT-P.

Programming Modifications – Extreme programming changes should only be made after careful clinical assessment. Clinical judgment should be used when programming permanent pacing rates below 40 ppm or above 100 ppm.

Short Pacing Intervals – Use of short pacing intervals (high pacing rates) with long atrial and/or ventricular refractory periods may result in intermittent asynchronous pacing and, therefore, may be contraindicated in some patients.

OFF Mode – The OFF mode can be transmitted as a temporary program only to permit evaluation of the patient's spontaneous rhythm. (see Section 2.1.11)

Myopotential Sensing – The filter characteristics of BIOTRONIK implantable devices have been optimized to sense electrical potentials generated by cardiac activity and to reduce the possibility of sensing skeletal myopotentials. However, the risk of CRT-P's operation being affected by myopotentials cannot be eliminated, particularly in unipolar systems. Myopotentials may resemble cardiac activity, resulting in inhibition of pacing, triggering and/or emission of asynchronous pacing pulses, depending on the pacing mode and the interference pattern. Certain follow-up procedures, such as monitoring CRT-P performance while the patient is doing exercises involving the use of pectoral muscles, as well as Holter monitoring, have been recommended to check for interference caused by myopotentials. If sensing of myopotentials is encountered, corrective actions may include selection of a different pacing mode or sensitivity setting.

Muscle or Nerve Stimulation – Inappropriate muscle or nerve stimulation may occur with unipolar pacing when using a non-coated Stratos CRT-P.

Atrial Sensitivity – In dual chamber systems, the atrial sensitivity of 0.1 mV should only be programmed in conjunction with a bipolar lead configuration.

Programmed to Triggered Modes – When programmed to triggered modes, pacing rates up to the programmed upper limit may occur in the presence of either muscle or external interference.

Triggered Modes – While the triggered modes (DDT, DVT, DDTR/A, DDTR/V, DDI/T, VDT, VVT, and AAT) can be programmed permanently, these modes are intended for use as temporary programming for diagnostic purposes. In triggered pacing modes, pacing pulses are emitted in response to sensed signals, and therefore the pacing pulse can be used as an indicator, or marker of sensed events for evaluating the sensing function of the pulse generator using surface ECG. However, real-time telemetry of marker channels and/or intracardiac electrogram via the programmer and programming wand is recommended over the use of a triggered pacing mode in the clinical setting. A triggered pacing mode may be preferred in situations where positioning the programming head over the pulse generator would be impossible or impractical (i.e., during exercise testing or extended Holter monitoring).

Another possible application of triggered modes is to ensure pacing as a short term solution during a period of inhibition of pacing by extracardiac interference, mechanical noise signals, or other sensing abnormalities. Because triggered modes emit pacing pulses in response to sensed events, this may result in unnecessary pacing during the absolute refractory period of the myocardium, inappropriate pacing in response to oversensing of cardiac or extracardiac signals. The risks associated with triggered pacing include excessive pacing, arrhythmias due to the R-on-T phenomenon, and early battery depletion. Therefore, it is important that the triggered modes are not used for long term therapy, and that the CRT-P is always returned to a non-triggered permanent program.

1.5.5 Home Monitoring

Patient's Ability - Use of the Home Monitoring system requires the patient and/or caregiver to follow the system instructions and cooperate fully when transmitting data.

If the patient cannot understand or follow the instructions because of physical or mental challenges, another adult who can follow the instructions will be necessary for proper transmission.

Electromagnetic Interference (EMI) – Precautions for EMI interference with the Stratos CRT-Ps are provided in Section 1.5.6. Sources of EMI including cellular telephones, electronic article surveillance systems, and others are discussed therein.

Use in Cellular Phone Restricted Areas - The mobile patient device (transmitter/receiver) should not be utilized in areas where cellular phones are restricted or prohibited (i.e., commercial aircraft).

Event Triggered Report - A timely receipt of the event report cannot be guaranteed. The receipt is also dependent on whether the patient was physically situated in the required coverage range of the patient device at the time the event information was sent.

Patient-Activated Report - The magnet effect must be programmed "synchronous" if the [Patient Report] function is activated.

Not for Conclusive Diagnosis - Because not all information available in the implant is being transmitted, the data transmitted by Home Monitoring should be evaluated in conjunction with other clinical indicators (i.e., in-office follow-up, patient symptoms, etc.) in order to make a proper diagnosis.

Frequency of Office Follow-Ups When Using Home Monitoring - The use of Home Monitoring does not replace regular follow-up examinations. When using Home Monitoring, the time period between follow-up visits may not be extended.

1.5.6 Electromagnetic Interference (EMI)

The operation of any implanted device may be affected by certain environmental sources generating signals that resemble cardiac activity. This may result in inhibition of pacing and/or triggering or in asynchronous pacing depending on the pacing mode and the interference pattern. In some cases (i.e., diagnostic or therapeutic medical procedures), the interference sources may couple sufficient energy into a pacing system to damage the device and/or cardiac tissue adjacent to the leads.

BIOTRONIK CRT-Ps have been designed to significantly reduce susceptibility to electromagnetic interference (EMI). However, due to the variety and complexity of sources creating interference, there is no absolute protection against EMI. Generally, it is assumed that EMI produces only minor effects, if any, in CRT-P patients. If the patient may be exposed to one of the following environmental conditions, then the patient should be given the appropriate warnings.

1.5.7 Home and Occupational Environments

The following equipment (and similar devices) may affect normal CRT-P operation: electric arc welders, electric melting furnaces, radio/television and radar transmitters, power-generating facilities, high-voltage transmission lines, electrical ignition systems (also of gasoline-powered devices) if protective hoods, shrouds, etc., are removed, electrical tools, anti-theft devices at retail stores and electrical appliances, if not in proper condition or not correctly grounded and encased.

Patients should exercise reasonable caution in avoidance of devices which generate a strong electric or magnetic field. If EMI inhibits pacing or causes a reversion to asynchronous pacing or pacing at magnet rate, moving away from the source or turning it off should allow the CRT-P to return to its normal mode of operation. Some potential EMI sources include:

High Voltage Power Transmission Lines – High voltage power transmission lines may generate enough EMI to interfere with CRT-P operation if approached too closely.

Home Appliances – Home appliances normally do not affect CRT-P operation if the appliances are in proper condition and correctly grounded and encased. There are reports of CRT-P disturbances caused by electrical tools and by electric razors that have touched the skin directly over the CRT-P.

Communication Equipment – Communication equipment such as microwave transmitters, linear power amplifiers, or high-power amateur transmitters may generate enough EMI to interfere with CRT-P operation if approached too closely.

Commercial Electrical Equipment – Commercial electrical equipment such as arc welders, induction furnaces, or resistance welders may generate enough EMI to interfere with CRT-P operation if approached too closely.

Electrical Appliances – Electric hand-tools and electric razors (used over the skin directly above the CRT-P) have been reported to cause pacemaker disturbances. Home appliances that are in good working order and properly grounded do not usually produce enough EMI to interfere with implanted device operation.

Electronic Article Surveillance (EAS) – Equipment such as retail theft prevention systems may interact with the CRT-Ps. Patients should be advised to walk directly through and not to remain near an EAS system longer than necessary.

Radio-Frequency Identification (RFID) – RFID tags may interact with the CRT-Ps. Patients should be advised to avoid leaving a device containing such a tag within close proximity to the CRT-P (i.e., inside a shirt pocket).

1.5.8 Cellular Phones

Recent studies have indicated there may be a potential interaction between cellular phones and pacemaker operation. Potential effects may be due to either the radio frequency signal or the magnet within the phone and could include inhibition or asynchronous pacing when the phone is within close proximity (within 6 inches [15 cm]) to the CRT-P.

Based on testing to date, effects resulting from an interaction between cellular phones and the implanted pacemakers have been temporary. Simply moving the phone away from the implanted device will return it to its previous state of operation. Because of the great variety of cellular phones and the wide variance in patient physiology, an absolute recommendation to cover all patients cannot be made.

Patients having an implanted CRT-P who operate a cellular phone should:

- Maintain a minimum separation of 6 inches (15 cm) between a hand-held personal cellular phone and the implanted device. Portable and mobile cellular phones generally transmit at higher power levels compared to hand held models. For phones transmitting above 3 watts, maintain a minimum separation of 12 inches (30 cm) between the antenna and the implanted device.
- Patients should hold the phone to the ear opposite the side of the implanted device. Patients should not carry the phone in a breast pocket or on a belt over or within 6 inches (15 cm) of the implanted device as some phones emit signals when they are turned ON but not in use (i.e., in the listen or standby mode). Store the phone in a location opposite the side of implant.

1.5.9 Hospital and Medical Environments

Refer to Section 1.5.1 for information regarding CRT-P interaction with the following medical procedures / environments:

- Electrosurgical Cautery
- Lithotripsy
- External Defibrillation
- High Radiation Sources

1.5.10 Device Explant and Disposal

Device Incineration - Never incinerate a CRT-P. Be sure the CRT-P is explanted before a patient who has died is cremated. (see Section 10)

Explanted Devices – Return all explanted devices to BIOTRONIK.

1.6 Potential Effects of the Device on Health

The following possible adverse events may occur with this type of CRT-P based on implant experience including:

Potential Adverse Events

- Air embolism
- Allergic reactions to contrast media
- Arrhythmias
- Bleeding
- Body rejection phenomena
- Cardiac tamponade
- Chronic nerve damage
- Damage to heart valves
- Elevated pacing thresholds
- Extrusion
- Fluid accumulation
- Infection
- Keloid formation
- Lead dislodgment
- Lead fracture / insulation damage
- Lead-related thrombosis
- Local tissue reaction / fibrotic tissue formation
- Muscle or nerve stimulation
- Myocardial damage
- Myopotential sensing
- Pacemaker mediated tachycardia
- Pneumothorax
- Pocket erosion
- Hematoma
- Device migration
- Thromboembolism
- Undersensing of intrinsic signals
- Venous occlusion
- Venous or cardiac perforation

1.7 Clinical Studies

The subsequent sections summarize the following three clinical studies that were used to support the safety and effectiveness of the Stratos LV/LV-T CRT-Ps.

- The AVAIL CLS/CRT clinical study
- The OVID clinical study (OUS)
- The OPTION CRT/ATx clinical study

Two of the studies, AVAIL CLS/CRT and OVID, collected significant safety data supporting use of the Stratos LV/LV-T CRT-P system. The third study, OPTION CRT/ATx, supports the effectiveness of cardiac resynchronization therapy (CRT). The OPTION CRT/ATx study was conducted on a device that delivers CRT but, in addition, also offers defibrillation therapy (CRT-D).

1.7.1 Stratos LV Clinical Study – AVAIL CLS/CRT

Study Design

The AVAIL CLS/CRT was a multi-center, prospective, randomized, blinded clinical study designed to support approval for cardiac resynchronization therapy for a Heart Failure (HF) patient population not requiring back up defibrillation and that are indicated for an ablate and pace procedures. All patients enrolled into the clinical study were randomly assigned to one of three groups using a 2:2:1 ratio for randomization.

- Patients assigned to Group 1 received biventricular pacing with CLS-based rate adaptive pacing using BIOTRONIK's Protos DR/CLS, which is a dual-chamber pulse generator with CLS-based rate adaptive pacing. During this study, the Protos DR/CLS devices were implanted with two ventricular leads: the right ventricular lead was connected to the ventricular port, and the left ventricular lead was connected to the atrial port. Protos DR/CLS was included in this study to evaluate biventricular pacing with a different type of rate adaptive sensor technology.
- Patients assigned to Group 2 received biventricular pacing with accelerometer-based rate adaptive pacing using the Stratos LV.
- Patients assigned to Group 3 (control group) received right ventricular pacing with accelerometer-based rate adaptive pacing using the Stratos LV. Therefore, 60% of the patients received a Stratos LV device.

Primarily, the study evaluated and compared the functional benefits of CRT between the three randomized groups using a composite endpoint consisting of a six-minute walk test (meters walked) and quality of life measurement (assessed using the Minnesota Living with Heart Failure Questionnaire). Relevant measurements were completed twice for each patient: once at the Baseline evaluation (prior to implant and ablation) and again at a six-month follow-up evaluation. The data collected during this clinical study was used to demonstrate superiority of CRT to RV only pacing. This study also evaluated the safety of both the Protos DR/CLS and Stratos LV devices through an analysis of the complication-free rate through six months. Secondarily, the study also evaluated the superiority of CRT with CLS rate adaptation compared to CRT with accelerometer rate adaptation.

Clinical Inclusion Criteria

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrollment:

- Meet the indications for therapy
- Persistent (documented for more than 7 days), symptomatic AF with poorly controlled rapid ventricular rates or permanent, (documented for more than 30 days with failed cardioversion, or longstanding AF of 6 months or more) symptomatic AF with poorly controlled rapid ventricular rates.
- Eligible for AV nodal ablation and permanent pacemaker implantation
- NYHA Class II or III heart failure
- Age ≥ 18 years
- Understand the nature of the procedure
- Ability to tolerate the surgical procedure required for implantation
- Give informed consent
- Able to complete all testing required by the clinical protocol
- Available for follow-up visits on a regular basis at the investigational site

Clinical Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following:

- Meet one or more of the contraindications
- Have a life expectancy of less than six months
- Expected to receive heart transplantation within six months
- Enrolled in another cardiovascular or pharmacological clinical investigation
- Patients with an ICD, or being considered for an ICD
- Patients with previously implanted biventricular pacing systems
- Patients with previously implanted single or dual chamber pacing system with > 50% documented ventricular pacing
- Patients with previous AV node ablation
- Six-minute walk test distance greater than 450 meters
- Any condition preventing the patient from being able to perform required testing
- Presence of another life-threatening, underlying illness separate from their cardiac disorder
- Conditions that prohibit placement of any of the lead systems

Follow-Up Schedule

At the enrollment screening, the physician evaluated the patient to verify that all inclusion/exclusion criteria have been met in accordance to the protocol and the patient has signed the informed consent. After successful enrollment, all patients were implanted with either a Stratos LV CRT-P or Protos DR/CLS device. Evaluations at the Four Week, Three and Six Month follow-ups included NYHA classification, medications, and percentage of ventricular pacing.

Clinical Endpoints

Primary Endpoint: Complication-free Rate (Safety)
The safety of the Stratos LV was evaluated based on complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Stratos LV, the right ventricular, the left ventricular lead, lead ventricular lead adapters (if used) and the implant procedure. The target complication-free rate at six months is 85%.

Primary Endpoint: Six Minute Walk Test & QOL (Effectiveness)
The purpose of Primary Endpoint 1 was to evaluate the effectiveness of the CRT (Groups 1 and 2) compared to RV only (Group 3) pacing as measured by the average composite rate of improvement in six minute walk test and QOL.

Accountability of PMA Cohorts

After randomization and enrollment, 23 patients (8 in Group 1, 8 in Group 2 and 7 in Group 3) did not receive an implant. The reasons for patients not receiving an implant are outlined in **Figure 1**. Two additional patients in Group 1 had an unsuccessful first implant attempt (unable to implant the LV lead), but follow up data was not received.

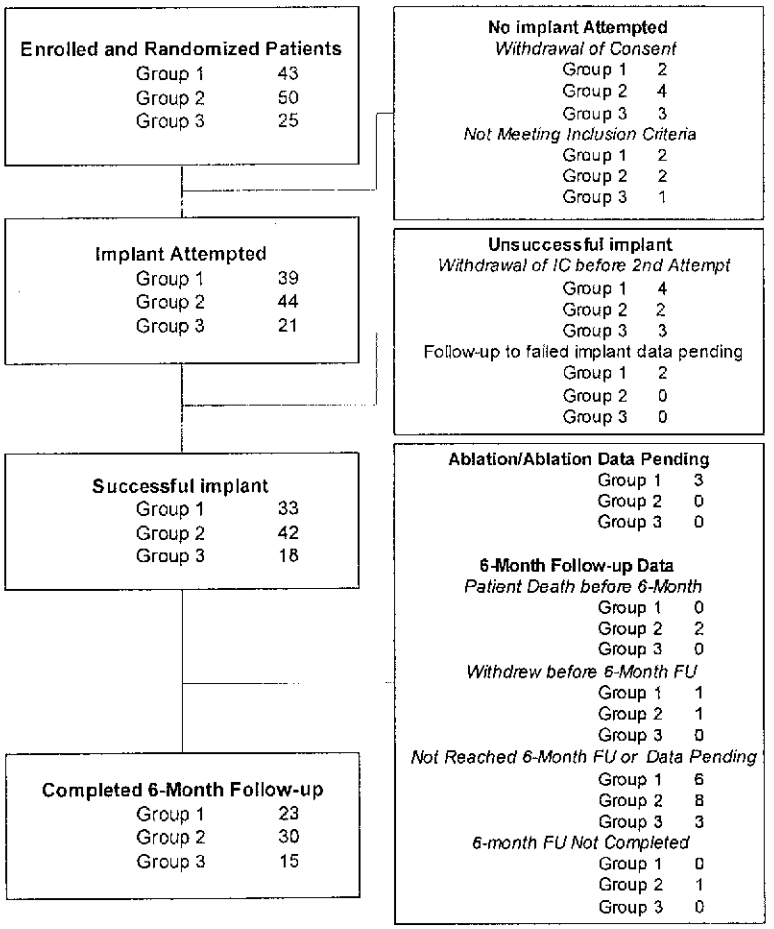


Figure 1: Patient Accountability

Demographics and Baseline Parameters

Table 1 provides a summary of the patient demographics at enrollment. There were no statistical differences in enrollment demographics between the 3 groups.

Table 1: Patient Demographics at Enrollment				
Characteristic	**Group1**	**Group 2**	**Group 3**	**P-value**
Age @ Enrollment (Yrs) Mean ± SE Range	N=42 73.7 ± 1.3 56 to 90	N=50 72.3 ± 1.2 51 to 86	N=25 71.5 ± 1.6 52 to 85	0.534*
Gender Male Female	N=42 18 (42.9%) 24 (57.1%)	N=50 19 (38.0%) 31 (62.0%)	N=25 13 (52.0%) 12 (48.0%)	0.553**
Six-Minute Walk Distance (meters) Mean ± SE Range	N=42 262.7 ± 15.1 78 to 420	N=50 283.6 ± 13.8 37 to 438	N=25 267.8 ± 22.9 23 to 420	0.395*
New York Heart Association Class Class II Class III	N=42 23 (54.8%) 19 (45.2%)	N=50 18 (36.0%) 32 (64.0%)	N=25 10 (40.0%) 15 (60.0%)	0.189**
Underlying Heart Disease Dilated Cardiomyopathy Hypertrophic Cardiomyopathy Valvular Heart Disease Coronary Artery Disease Hypertension No underlying structural heart disease	N=42 8 (19.0%) 4 (9.5%) 12 (28.6%) 19 (45.2%) 37 (88.1%) 3 (7.1%)	N=49 11 (22.4%) 1 (2.0%) 12 (24.5%) 28 (57.7%) 37 (75.5%) 2 (4.1%)	N=25 1 (4.0%) 2 (8.0%) 5 (20.0%) 6 (24.0%) 19 (76.0%) 7 (28.0%)	 0.125** 0.216** 0.792** 0.031** 0.348** 0.007**

Table 1: Patient Demographics at Enrollment				
Characteristic	**Group1**	**Group 2**	**Group 3**	**P-value**
Other Medical History	N=29	N=36	N=17	
Diabetes	13 (44.8%)	9 (25.0%)	4 (23.5%)	0.287**
Chronic Lung Disease	7 (24.1%)	16 (44.4%)	7 (41.2%)	0.211**
Thyroid Disease	12 (41.4%)	12 (33.3%)	5 (29.4%)	0.791**
Chronic Kidney Disease	4 (13.8%)	5 (13.9%)	1 (5.9%)	0.836**
Prior Ischemic Stroke or TIA	7 (24.1%)	10 (27.8%)	6 (35.3%)	0.726**
Prior Embolic Events (non-cerebrovascular)	1 (2.3%)	3 (6.0%)	2 (8.0%)	0.653**

*One-way ANOVA, ** Chi-Square test (2-sided)

Table 2 provides a summary of the AF medical history. **Table 3** provides a summary of cardiac medications patients were taking at the time of enrollment. Please note some categories may equal more than 100% as several categories allow more than one response. In some cases, complete demographic data was not provided for all patients. There were no statistical differences in AF medical history and cardiac medication at enrollment between the 3 groups.

Table 2: Atrial Fibrillation Demographics at Enrollment				
Characteristic	**Group 1**	**Group 2**	**Group 3**	**P-value***
Classification of Atrial Fibrillation	N=42	N=50	N=24	0.537
Persistent AF	10 (23.8%)	17 (34%)	6 (25%)	
Permanent AF	32 (76.2%)	33 (66%)	18 (75%)	
Classification of Symptoms Related to AF	N=42	N=49	N=25	
Palpitations	32 (76.2%)	34 (69.4%)	14 (56.0%)	0.236
Chest Pain	6 (14.3%)	7 (14.3%)	3 (12.0%)	1.000
Dyspnea or shortness of breath	36 (85.7%)	40 (81.6%)	19 (76.0%)	0.568
Fatigue	34 (81.0%)	45 (91.8%)	18 (72.0%)	0.149
Lightheadedness or syncope	17 (40.5%)	13 (26.5%)	9 (36.0%)	0.329
Other	9 (21.4%)	11 (22.4%)	10 (40.0%)	0.205
Previous AF Ablation	N=42	N=50	N=25	0.354
No	37 (88.1%)	47 (94.0%)	21 (84.0%)	
Yes	5 (11.9%)	3 (6.0%)	4 (16.0%)	
Past Medications for Rate or Rhythm Control				
Amiodarone	N=41	N=48	N=24	
Digoxin	12 (29.3%)	10 (20.8%)	10 (41.7%)	0.192
Diltiazem	17 (41.5%)	22 (45.8%)	13 (54.2%)	0.683
Disopyramide	17 (41.5%)	23 (47.9%)	12 (50.0%)	0.804
Dofetilide	0 (0.0%)	3 (6.3%)	0 (0.0%)	0.228
Flecanide	4 (9.8%)	3 (6.3%)	2 (8.3%)	0.895
Ibutilide	5 (12.2%)	5 (10.4%)	1 (4.2%)	0.656
Procainamide	0 (0.0%)	0 (0.0%)	1 (4.2%)	0.215
Propafenone	0 (0.0%)	2 (4.2%)	0 (0.0%)	0.506
Sotolol	2 (4.9%)	4 (8.3%)	0 (0.0%)	0.423
Verapamil	9 (22.0%)	10 (20.8%)	2 (8.3%)	0.389
Metoprolol	5 (12.2%)	8 (16.7%)	3 (12.5%)	0.829
Propranolol	19 (46.3%)	28 (58.3%)	10(41.7%)	0.382
Other Beta-Blockers	0 (0.0%)	0 (0.0%)	1 (4.2%)	0.215
Other Medications	7 (17.1%)	15 (31.3%)	4 (16.7%)	0.248
	5 (12.2%)	5 (10.4%)	1 (4.2%)	0.656

Table 2: Atrial Fibrillation Demographics at Enrollment				
Characteristic	**Group 1**	**Group 2**	**Group 3**	**P-value***
Rate Control Medication, Reasons for Discontinuation	N=17	N=20	N=12	
Ineffective	10 (58.8%)	13 (65.0%)	9 (75.0%)	0.558
Not tolerated	8 (47.1%)	7 (35.0%)	3 (25.0%)	0.760
Other	1 (5.9%)	2 (10.0%)	0 (0.0%)	0.800
Rhythm Control Medication, Reasons for Discontinuation	N=22	N=25	N=13	
Ineffective	17 (77.3%)	20 (80.0%)	8 (61.5%)	0.759
Not tolerated	6 (27.3%)	7 (28.0%)	6 (46.2%)	0.530
Other	1 (4.5%)	1 (4.0%)	2 (15.4%)	0.430
Cardioversion History	N=42	N=49	N=25	
Successful prior electrical cardioversion	13 (31.0%)	16 (32.7%)	10 (40.0%)	0.760
Transthoracic	13 (100.0%)	15 (93.8%)	10 (100.0%)	0.808
Transvenous	0 (0.0%)	1 (6.3%)	0 (0.0%)	
Unsuccessful prior electrical cardioversion	15 (35.7%)	14 (28.6%)	7 (28.0%)	0.680
Transthoracic	15 (100.0%)	14 (93.3%)	7 (100.0%)	0.741
Transvenous	0 (0.0%)	2 (13.3%)	0 (0.0%)	
No electrical cardioversion attempted	17 (40.5%)	20 (40.8%)	9 (36.0%)	0.936
Successful prior pharmacological cardioversion	5 (11.9%)	3 (6.1%)	3 (12.0%)	0.547
Unsuccessful prior pharmacological cardioversion	8 (19.0%)	11 (22.4%)	7 (28.0%)	0.678
No pharmacological cardioversion attempted	23 (54.8%)	29 (59.2%)	15 (60.0%)	0.915

*Chi-Square test (2-sided)

Table 3: Current Cardiac Medications at Enrollment				
Drug Category	Group 1 N=42	Group 2 N=50	Group 3 N=25	P-value*
Anti-Arrhythmics	12 (28.6%)	10 (20.4%)	4 (16.0%)	0.480
Rate Control Medications	32 (76.2%)	43 (87.8%)	20(80.0%)	0.462
Anti-thrombic Agents	17 (40.5%)	19(38.8%)	11 (44.0%)	0.863
Anti-Coagulants	36 (85.7%)	40 (81.6%)	22 (88.0%)	0.686
ACE Inhibitors	16 (38.1%)	16 (32.7%)	8 (32.0%)	0.848
Angiotensin-Receptor Blockers	10 (23.8%)	7 (14.3%)	4 (16.0%)	0.491
Diuretics	30 (71.4%)	34 (69.4%)	13 (52.0%)	0.255
Inotropes	1 (2.4%)	2 (4.1%)	0 (0.0%)	0.803
Nitrates	3 (7.1%)	6 (12.2%)	2 (8.0%)	0.714
Beta-Blockers for CHF	6 (14.3%)	9 (18.4%)	4 (16.0%)	0.947
Other	23 (54.8%)	26 (53.1%)	14 (56.0%)	0.941

*Chi-Square test (2-sided)

Safety and Effectiveness Results

A total of 118 patients were enrolled in the AVAIL CLS/CRT clinical study at 20 sites:

There were 43 Group 1, 50 Group 2, and 25 Group 3 patients in this prospective, multi-center, randomized clinical study. For Group 1, there were 33 successful implants (76.7%) of the Protos DR/CLS system. For Groups 2 and 3, there were 44 and 21 successful implants (88.0% and 84.0%) respectively of the Stratos LV CRT-P system.

- The study was designed to enroll 265 patients. However, the study was terminated early due to slow patient enrollment. There were no safety issues involved in the termination decision. Due to the lack of patient data, the AVAIL CLS/CRT study alone was insufficient to support CRT pacing effectiveness or an ablate and pace indication.
- The cumulative enrollment duration was 416.7 months with a mean duration of 9.7 months for Group 1, 522.4 months with a mean duration of 10.4 months for Group 2, and 261.1 months with a mean duration of 10.4 months for Group 3. 73 (61.9%) of the study patients had enrollment durations greater than 6 months.
- There were 158 adverse events (115 observations in 68 patients and 43 complications in 34 patients). There were no unanticipated adverse device effects reported.
- The overall protocol violation non-compliance rate is 0.4% in Group 1, 0.5% in Group 2, and 0.4% in Group 3. The overall follow-up compliance rate is 99.8% in all groups.
- There were 3 patient deaths reported, two in Group 2 and one in Group 3. The clinical investigators and clinical events committee determined that none of these deaths were related to the study devices.
- Both the CRT pacing and the RV pacing only groups showed improvements in the primary composite endpoint of quality of life and six-minute walk distance between the baseline evaluation and the six-month follow-up. In addition, there was a trend towards improvement between the combined CRT pacing groups compared to the RV pacing only group at six months.

Primary Endpoint—Complication-free Rate (Safety)

The safety of the Stratos LV was evaluated based on complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Stratos LV, the right ventricular, the left ventricular lead, lead ventricular lead adapters (if used) and the implant procedure. The target complication-free rate at six months is 85%.

13 complications in these categories were seen in 11 patients with cumulative enrollment duration of 783.5 months (64.4 patient-years). 14.7% of the patients had a reported complication in these categories. The rate of complications per patient-year is 0.20. Details of the Stratos LV complications in the AVAIL CLS/CRT study are listed in **Table 4**.

Table 4: AVAIL CLS/CRT Complication-Free Rate at 6 months – Stratos LV

Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Device-Related				
Pocket Infection/Pain	1	1.3%	2	0.03
Total	**1**	**1.3%**	**2**	**0.03**
LV Lead Related				
High Threshold No Capture	1	1.3%	1	0.02
Diaphragmatic Stimulation	1	1.3%	1	0.02
Dislodgement	2	2.7%	2	0.03
Total	**4**	**5.3%**	**4**	**0.06**
RV Lead Related				
High Threshold / No Capture	4	5.3%	4	0.06
Total	**4**	**5.3%**	**4**	**0.06**
Procedure				
Pneumothorax	1	1.3%	1	0.02
User error	1	1.3%	1	0.02
Hematoma	1	1.3%	1	0.02
Total	**3**	**4.0%**	**3**	**0.05**
Total Lead and Procedure Related	**11**	**14.7%**	**13**	**0.20**

Table 4: AVAIL CLS/CRT Complication-Free Rate at 6 months – Stratos LV				
Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Other Medical				
Worsening CHF	2	2.7%	2	0.03
Repeat Ablation	3	4.0%	3	0.05
Non-CHF cardiac symptoms	3	4.0%	3	0.05
Other Medical	3	4.0%	3	0.05
Total	**10**	**13.3%**	**11**	**0.17**
Total—All Patients and Categories	**19**	**25.3%**	**24**	**0.37**

Number of Patients = 75 Number of Patient-Years = 64.4

The freedom from Stratos LV system-related and procedure-related complications was 85.33%, with a one sided lower 95% confidence bound of 76.89%. Therefore, the procedure, lead and device related complication-free rate at 6 months met the pre-specified acceptance criterion of equivalence (non-inferiority) within 10% of 85% (p = 0.0196).

Observed Adverse Events

Adverse events are classified as either observations or complications. Observations are defined as clinical events that do not require additional invasive intervention to resolve. Complications are defined as clinical events that require additional invasive intervention to resolve.

Of the 104 adverse events reported in the Stratos LV study groups, there have been 76 observations in 45 patients and 28 complications in 20 patients with a cumulative enrollment duration of 64.4 patient-years. 26.7% of the enrolled Stratos LV patients have experienced a complication. The rate of complications per patient-year is 0.43. 60.0% of the enrolled study patients have a reported observation. The rate of observations per patient-year is 1.18.

Complications and observations for the Stratos LV study groups are summarized in **Table 5** and **Table 6**. The total number of patients may not equal the sum of the number of patients listed in each category, as an individual patient may have experienced more than one complication or observation.

Table 5: Summary of Complications – Stratos LV				
Category	**Number of Patients**	**% of Patients**	**Number of Complications**	**Complications per patient-year**
Device-Related				
Pocket Infection or Pain	2	2.7%	3	0.05
Total	2	**2.7%**	3	0.05
LV Lead-Related				
High Threshold / No Capture	1	1.3%	1	0.02
Diaphragmatic Stimulation	1	1.3%	1	0.02
Dislodgement	2	2.7%	2	0.03
Total	**4**	**5.3%**	**4**	**0.06**
RV Lead Related				
High Threshold / No Capture	4	5.3%	4	0.06
Total	**4**	**5.3%**	**4**	**0.06**
Procedure				
Pneumothorax	1	1.3%	1	0.02
User error	1	1.3%	1	0.02
Hematoma	1	1.3%	1	0.02
Total	**3**	**4.0%**	**3**	**0.05**
Total Lead and Procedure Related	**11**	**14.7%**	**14**	**0.22**
Other Medical				
Worsening CHF	2	2.7%	2	0.03
Non-CHF cardiac symptoms	5	6.7%	5	0.08
Repeated ablation	3	4.0%	3	0.05

Table 5: Summary of Complications – Stratos LV				
Category	**Number of Patients**	**% of Patients**	**Number of Complications**	**Complications per patient-year**
Lead addition	1	1.3%	1	0.02
Other medical	3	4.0%	3	0.05
Total	**12**	**16.0%**	**14**	**0.22**
Total—All Patients and Categories	**20**	**26.7%**	**28**	**0.43**

Number of Patients = 75, Number of Patient-Years = 64.4

Table 6: Summary of Observations – Stratos LV				
Category	Number of Patients	% of Patients	Number of Complications	Observations per patient-year
LV Lead-Related				
High Threshold / No Capture	1	1.3%	1	0.02
Diaphragmatic Stimulation	13	17.3%	13	0.20
Total	**14**	**18.7%**	**14**	**0.22**
Device Related				
Pocket Infection or pain	5	6.7%	5	0.08
Total	**5**	**6.7%**	**5**	**0.08**
Procedure				
Pneumothorax	1	1.3%	1	0.02
Atrial edema	1	1.3%	1	0.02
User error	1	1.3%	1	0.02
Total	**3**	**4.0%**	**3**	**0.05**
Total Lead, Device and Procedure Related	**19**	**25.3%**	**22**	**0.34**

Table 6: Summary of Observations – Stratos LV				
Category	**Number of Patients**	**% of Patients**	**Number of Complications**	**Observations per patient-year**
Other Medical				
Dizziness	3	4.0%	3	0.05
Other Medical	24	32.0%	34	0.53
Worsening CHF	8	10.7%	8	0.12
Ventricular arrhythmias	2	2.7%	2	0.03
Shortness of Breath	5	6.7%	5	0.08
Stroke / TIA	1	1.3%	1	0.02
Non-CHF cardiac symptoms	1	1.3%	1	0.02
Total	**35**	**46.7%**	**54**	**0.84**
Total—All Patients and Categories	**45**	**60.0%**	**76**	**1.18**

Number of Patients = 75 Number of Patient-Years = 64.4

There have been 3 patient deaths reported for the Stratos LV groups (out of 75 Stratos LV patients). None of the deaths were related to the implanted CRT-P system. Table 7 provides a summary of reported patient deaths.

Table 7: Summary of Patient Deaths	
	Stratos LV Patients (N = 75)
Sudden Cardiac	1
Non-Cardiac	2
All Causes	**3**

Primary Endpoint: Six Minute Walk Test & QOL (Effectiveness)

The purpose of Primary Endpoint 1 was to evaluate the effectiveness of the CRT (Groups 1 and 2) compared to RV only (Group 3) pacing as measured by the average composite rate of improvement in six minute walk test and QOL.

- Stratos LV Effectiveness (Group 2 compared to Group 3): The average composite rate for Group 2 (N=30) was 48.1% with a standard error of 12.3%. The average composite rate for Group 3 (N=15) was 33.0% with a standard error of 12.3%. The difference in the mean composite rate between Group 2 and Group 3 is 15.1%. The p value for superiority is 0.442.
- Protos DR/CLS Effectiveness (Group 1 compared to Group 3): The average composite rate for the Group 1 (N=23) is 36.8% with a standard error of 7.9%. The average composite rate for Group 3 (N=15) is 33.0% with a standard error of 12.3%. The difference in the mean composite rate between Group 1 and Group 3 is 3.8%. The p value for superiority is 0.788.

Table 8 presents the average composite rate of improvement in six minute walk test distance and QOL score, the average 6-minute walk test distance and the average QOL score at Baseline and at the Six-Month follow-up, as well as the average difference in 6-minute walk test distance and QOL score between Baseline and the Six-Month follow-up for the CRT (Groups 1 and 2) and RV only (Group 3) for those patients with six minute walk test data and complete QOL data at both Baseline and the Six-Month follow-up.

Table 8: Composite of Six Minute Walk Test and QOL (Effectiveness)			
Category	CRT (Group 1 & 2) (N = 53) Mean ± SE	RV only Group 3 (N = 15) Mean ± SE	p value (student's t-test, 2-sided)
Distance Walked at Baseline	262.8 ± 13.7	288.5 ± 22.4	0.369*
Distance Walked at Six-Months	312.8 ± 14.6	345.8 ± 30.0	0.303*
Δ Distance Walked (meters)	50.0 ± 12.2	57.2 ± 26.7	0.790*
Δ Distance Walked (%)	39.0% ± 13.1%	25.7% ± 15.0%	0.610*
QOL Score at Baseline	58.5 ± 2.9	49.3 ± 5.5	0.137*
QOL Score at Six-Months	30.1 ± 3.2	27.7 ± 6.5	0.731*
Δ in QOL Score	28.4 ± 3.4	21.6 ± 7.7	0.367*
Δ in QOL Score (%)	47.4% ± 5.1%	40.4% ± 11.1%	0.537*
Composite Rate	**43.2% ± 7.7%**	**33.0% ± 12.3%**	**0.525***

* p value is provided for informational purposes to show trends only; clinical significance is not indicated by p values for analyses that were not prespecified.

Primary Effectiveness Endpoint Analysis and Conclusions

The primary effectiveness endpoint evaluated CRT effectiveness (Groups 1 and 2) compared to RV only effectiveness (Group 3), as measured by the composite rate of the six minute walk test and QOL improvement from Baseline to the Six-Month follow-up (**Table 8**). For this analysis, both six minute walk test and QOL were equally weighted at 50%. Due to the small number of patients with data available for the analysis of the primary endpoint, the results lack power to demonstrate that biventricular pacing with either the Protos DR/CLS or Stratos LV device is statistically different from RV only pacing with the Stratos LV device in patients undergoing an "ablate and pace" procedure.

Multi-site Poolability and Gender Analysis

The AVAIL CLS/CRT clinical report included data from multiple centers with centralized coordination, data processing, and reporting at BIOTRONIK. All of the clinical centers followed the requirements of an identical clinical protocol, and all of the clinical centers used the same methods to collect and report the clinical data, including New York Heart Association evaluation, six-minute walk test, Minnesota Living with Heart Failure questionnaire, and echocardiographic measurements. In order to justify pooling of the data from multiple centers, several analyses were completed. All of the centers were divided into two groups (Small and Large sites) based on implant volume. Comparisons were then made between the patient populations based on the results of the safety and effectiveness endpoints. Additionally, analyses were performed on the data collected in the AVAIL clinical investigation in order to compare results between males and females. The first type of analysis compared enrollment by patient gender in each of the study groups. The second type of analysis compared effectiveness and safety outcomes in each gender.

The results of these analyses demonstrated poolability of the data between sites. There were no significant differences in the primary safety or effectiveness endpoints between high and low volume implant centers.

The gender distribution in this clinical investigation was consistent within the study groups and included a representative proportion of enrolled female participants (57.2% versus 42.7% male). There were no significant differences in the primary safety or effectiveness endpoints between the male and female population.

1.7.2 Stratos LV Clinical Study – OVID study

The OVID clinical study collected significant safety data supporting the Stratos LV/LV-T CRT-P system.

Study Design

BIOTRONIK conducted the Corox Over-the-Wire Lead Evaluation (OVID) prospective registry outside the United States (OUS) of the Corox OTW Steroid LV lead in a multi-center trial with legally marketed CRT-D and CRT-P pulse generators that provide biventricular pacing therapy. Data from this registry is presented in the following sections to support the safety of the Stratos LV CRT-P.

The multi-center investigation was designed to validate the safety of the Corox OTW Steroid LV lead through a comparison of successfully implanted LV leads against a pre-defined success rate threshold, when no anatomical restrictions prevent access to the coronary sinus. The evaluation of safety is based on the analysis of the incidence of adverse events, defined as any complications or observations judged by the investigator to be in probable relationship with Corox OTW Steroid LV lead system. Additionally, the effectiveness of the leads was evaluated using lead parameter data, including sensing amplitudes, pacing thresholds, and impedance values.

In the OVID study, enrolled patients could be implanted with any legally marketed CRT-P or CRT-D device. There were 121 patients enrolled in the OVID clinical study, and 89 patients were implanted with a Stratos LV device.

Clinical Inclusion Criteria

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrollment:

- Meet the indications for bi-ventricular pacing
- Age ≥ 18 years
- Receiving optimal drug therapy for Congestive Heart Failure treatment
- Give informed consent

Clinical Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following requirements:

- Myocardial infarction or unstable angina pectoris
- Acute myocarditis
- Life expectancy ≤ 6 months
- Planned cardiac surgical procedures or interventional measures within the next 6 months
- Pregnancy

Follow-Up Schedule

All patients were implanted with the Corox OTW/Steroid LV lead system and a CRT-P or CRT-D pulse generator capable of providing bi-ventricular pacing for the treatment of CHF. The specific study procedures were performed at:

- Pre-operative Visit
- Implantation
- Pre-discharge follow-up
- One-month follow-up
- Three-month follow-up
- Six-month follow-up
- Twelve-month follow-up

Clinical Endpoints

The safety of the Stratos LV was evaluated based on complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Stratos LV device, the atrial lead, the right ventricular lead the left ventricular lead and the implant procedure. The target complication-free rate at six months was 85%.

Accountability of PMA Cohorts

During the OVID study, 84 patients were implanted with the Stratos LV CRT-P and Corox OTW/Steroid LV lead system. Additionally, 5 other patients were implanted with a Stratos LV CRT-P device following an unsuccessful Corox OTW/Steroid LV lead implant attempt. Of these 5 patients, three were not implanted with any LV pacing lead, one was implanted with a non-study LV pacing lead and one was implanted with a BIOTRONIK Elox P 60 BP placed in the RV outflow tract for bi-focal ventricular pacing. These 5 patients were excluded from the OVID study at 1 month post-implant, because the primary endpoint of the OVID study was the evaluation of the safety and effectiveness of the Corox OTW/Steroid lead.

Demographics and Baseline Parameters

Table 9 provides a summary of the patient demographics and medical history for the 89 enrolled patients implanted with a Stratos LV. The typical patient implanted with a Stratos LV CRT-P was a 68 year old male with NYHA Class III heart failure, Left Bundle Branch Block (LBBB), a mean QRS duration of 160 ms, and non-ischemic cardiomyopathy.

Table 9: Patient Demographics	
Characteristic	**Results**
Age at Implant (Years)	**n=88**
Mean ± SD	68 ± 10
Range	34 to 84
Gender	**n=89**
Male	66 (74%)
Female	23 (26%)
QRS-width (ms)	**n=70**
Mean ± SD	160 ± 23
Range	110 to 210
Etiology of Heart Failure	**n=87**
Ischemic	32 (37%)
Non-Ischemic	55 (63%)
New York Heart Association (NYHA) Classification	**n=87**
Class III	73 (84%)
Class IV	14 (16%)
Atrial Tachyarrhythmias	**N=87**
None	48 (55%)
Atrial flutter	5 (5.7%)
Paroxysmal atrial fibrillation	19 (22%)
Persistent atrial fibrillation	10 (11.5%)
Other	5 (5.7%)
Ventricular Tachyarrhythmias	**N=87**
None	80 (92%)
Ventricular fibrillation	-
Sustained or non-sustained VT	5 (5.7%)[1)]
Other VT	2 (2.3%)[2)]
Existing/chronic leads prior to Corox OTW/Steroid	**n=88**
None	73 (83%)
Yes, due to previous pacemaker therapy	15 (17%)

[1)] non-sustained VT (n=4); no further information available (n=1); [2)] VES (n=2)

Safety and Effectiveness Results

- The cumulative implant duration was 760 months with a mean duration of 9.2 months. Sixty-five (77%) of the patients had implant durations greater than 6 months.
- The implant success rate for the Stratos LV CRT-P was 100% (89 out of 89). The implant success of the Stratos LV CRT-P in combination with the Corox OTW/Steroid LV lead was 94.4% (84 out of 89).
- The mean LV pacing threshold at implant was 0.9 and at 6-months was 0.9 volts.
- The mean R-wave at implant was 15.7 mV.
- The mean LV lead impedance at implant was 729 ohms and at 6-months was 603 ohms.
- There were 29 adverse events (18 observations in 17 patients and 11 complications in 10 patients). There were no unanticipated adverse device effects reported.
- There were 10 patient deaths reported in the OVID study. The clinical investigators have determined that no deaths were related to the Stratos LV CRT-P system.
- The overall follow-up compliance rate for the OVID study is 93%.

Primary Endpoint—Complication-free Rate (Safety)

The safety of the Stratos LV was evaluated based on complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Stratos LV device, the atrial lead, the right ventricular lead, the left ventricular lead and the implant procedure. The target complication-free rate at six months was 85%.

Ten (10) complications in these categories were seen in 10 patients with cumulative implant duration of 760 months (63.3 patient-years). 11.2% of the patients had a reported complication in these categories. The rate of complications per patient-year was 0.16. Details of the Stratos LV complications in the OVID study are listed in **Table 10**.

The freedom from Stratos LV system-related and procedure-related complications was 88.76% with a one sided lower 95% confidence bound of 81.69%. Therefore, the null hypothesis was rejected, and it was concluded that the complication-free rate at 6 months is equivalent to 85% within 10% (p = 0.0014).

Observed Adverse Events

Adverse events are classified as either observations or complications. Observations are defined as clinical events that do not require additional invasive intervention to resolve. Complications are defined as clinical events that require additional invasive intervention to resolve.

Of the 29 adverse events reported, there were 18 observations and 11 complications in a total of 89 patients. **Table 10** and **Table 11** provide a summary by category of each type of adverse event (complications and observations).

Table 10: Summary of Complications at 6 months

Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Corox OTW/Steroid Lead-Related				
Loss of capture	2	2.2%	2	0.03
Phrenic nerve stimulation	1	1.1%	1	0.02
Total	**3**	**3.3%**	**3**	**0.05**
Atrial Lead Related				
Loss of capture	1	1.1%	1	0.02
Total	**1**	**1.1%**	**1**	**0.02**
RV Lead Related				
Loss of capture	3	3.3%	3	0.05
Elevated Pacing thresholds	2	2.2%	2	0.03
Total	**5**	**5.6%**	**5**	**0.08**

Table 10: Summary of Complications at 6 months				
Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Device Related				
Pocket infection	1	1.1%	1	0.02
Total	1	1.1%	1	0.02
Total System Related	**10**	**11.2%**	**10**	**0.16**
Other Medical				
Arrhythmias	1	1.1%	1	0.02
Total	1	1.1%	1	0.02
Overall Complication Totals	**10**	**11.2%**	**11**	**0.17**

Number of Patients = 89; Number of Patient-Years = 63.3

Table 11: Summary of Observations at 6 months				
Category	Number of Patients	% of Patients	Number of Observations	Observations per patient-year
Corox OTW/Steroid Lead-Related				
Implant failure	5	5.6%	5	0.08
Phrenic nerve stimulation	4	4.5%	4	0.06
Total	**9**	**10.1%**	**9**	**0.14**
Atrial Lead Related				
Loss of capture	1	1.1%	1	0.02
Total	**1**	**1.1%**	**1**	**0.02**
RV Lead Related				
Elevated Pacing thresholds	2	2.2%	2	0.03
Total	**2**	**2.2%**	**2**	**0.03**

Table 11: Summary of Observations at 6 months				
Category	Number of Patients	% of Patients	Number of Observations	Observations per patient-year
Device Related				
Pocket infection/ Pericardial Effusion	1	1.1%	1	0.02
Total	**1**	**1.1%**	**1**	**0.02**
Total System Related	**12**	**13.5%**	**13**	**0.21**
Medical				
Arrhythmias	2	2.2%	2	0.03
Shortness of breath, palpitations	1	1.1%	1	0.02
Total	**3**	**3.3%**	**3**	**0.05**
Miscellaneous				
Malfunction of hemostatic valve	1	1.1%	1	0.02
Improper Lead preparation	1	1.1%	1	0.02
Total	**2**	**2.2%**	**2**	**0.04**
Overall Observation Totals	**17**	**19.1%**	**18**	**0.28**

Number of Patients = 89; Number of Patient-Years = 63.3

There were a total of 10 patient deaths reported in the OVID study for patients with the Stratos LV device. The clinical investigators determined that no deaths were related to the Stratos LV device system.

1.7.3 AVAIL and OVID Combined Primary Endpoint-Complication-free Rate (Safety)

The results from for the AVAIL CLS/CRT and OVID studies were pooled to evaluate the safety of the Stratos LV device. The safety of the Stratos LV was evaluated based on complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Stratos LV, the atrial lead, the right ventricular lead, the left ventricular lead and the implant procedure. The target complication-free rate at six months was 85%.

Twenty-three (23) complications in these categories were seen in 21 patients with cumulative implant duration of 127.7 years. 12.8% of the patients had a reported complication in these categories. The rate of complications per patient-year was 0.18. Details of the Stratos LV complications in the AVAIL CLS/CRT and OVID studies are listed in **Table 12**.

Table 12: OVID and AVAIL Complication-Free Rate - Stratos LV

Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
LV Lead-Related				
High Threshold / No Capture	3	1.8%	3	0.02
Diaphragmatic Stimulation	2	1.2%	2	0.02
Dislodgement	1	1.2%	2	0.01
Total	**7**	**4.3%**	**7**	**0.06**
RV Lead Related				
High Threshold / No Capture	9	5.5%	9	0.07
Total	**9**	**5.5%**	**9**	**0.07**
Atrial Lead Related				
No Capture	1	0.6%	1	0.01
Total	**1**	**0.6%**	**1**	**0.01**

Table 12: OVID and AVAIL Complication-Free Rate - Stratos LV				
Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Device Related				
Pocket Infection	2	1.2%	3	0.02
Total	**2**	**1.2%**	**3**	**0.02**
Procedure				
Pneumothorax	1	0.6%	1	0.01
User error	1	0.6%	1	0.01
Hematoma	1	0.6%	1	0.01
Total	**3**	**1.8%**	**3**	**0.02**
Total Lead, Device and Procedure Related	**21**	**12.8%**	**23**	**0.18**
Other Medical				
Arrhythmias	1	0.6%	1	0.01
Repeated ablation	3	1.8%	3	0.02
Worsening CHF	2	1.2%	2	0.02
Other Medical	3	1.8%	3	0.02
Non-CHF cardiac symptoms	3	1.8%	3	0.02
Total	**11**	**6.7%**	**12**	**0.09**
Total—All Patients and Categories	**29**	**17.7%**	**35**	**0.27**

Number of Patients = 164 Number of Patient-Years = 127.7

The freedom from Stratos LV system-related and procedure-related complications was 87.2% with a one sided lower 95% confidence bound of 82.09%. Therefore, the null hypothesis was rejected, and it was concluded that the complication-free rate at 6 months is equivalent to 85% within 10% and the primary safety endpoint was met ($p = 0.0002$)*.

1.7.4 Tupos LV/ATx Clinical IDE Study - OPTION CRT/ATx

The CRT functionality of the Stratos CRT-P devices is based on the FDA approved Tupos LV/ATx. Therefore, the data from the OPTION CRT/ATx study supports the effectiveness of CRT. The OPTION CRT/ATx study was conducted on the Tupos LV/ATx, a device that delivers CRT but, in addition, also offers defibrillation therapy (CRT-D).

Study Design

The purpose of the prospective, randomized, multi-center OPTION CRT/ATx study was to demonstrate the safety and effectiveness of the investigational Tupos LV/ATx Cardiac Resynchronization Therapy Defibrillator (CRT-D) in patients with congestive heart failure (CHF) and atrial tachyarrhythmias. Patients in the study group were implanted with a BIOTRONIK Tupos LV/ATx. Patients in the control group were implanted with any legally marketed CRT-D. Patients in both the study and control groups were implanted with a legally marketed left ventricular lead.

* p value is provided for informational purposes to show trends only; clinical significance is not indicated by p values for analyses that were not prespecified.

Primarily, the study evaluates and compares the functional benefits of CRT between the two randomized groups using a composite endpoint consisting of a six-minute walk test (meters walked) and quality of life measurement (assessed using the Minnesota Living with Heart Failure Questionnaire). Relevant measurements were completed twice for each patient: once at the Baseline evaluation (two-week post implant follow-up) and again at a six-month follow-up evaluation. The data collected during this clinical study was used to demonstrate equivalent treatment of CHF in both the study and control groups. This study also evaluated other outcomes including: the percentage of time CRT is delivered, and other measures of CHF status, including NYHA classification, peak oxygen consumption during metabolic exercise testing, and the rate of hospitalization for CHF.

Clinical Inclusion Criteria

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrollment:

- Stable, symptomatic CHF status
- NYHA Class III or IV congestive heart failure
- Left ventricular ejection fraction ≤ 35% (measured within six-months prior to enrollment)
- Intraventricular conduction delay (QRS duration greater than or equal to 130 ms)
- For patients with an existing ICD, optimal and stable CHF drug regimen including ACE-inhibitors and beta-blockers unless contraindicated (stable is defined as changes in dosages less than 50% during the last 30 days)
- Indicated for ICD therapy
- History or significant risk of atrial tachyarrhythmias
- Willing to receive possibly uncomfortable atrial shock therapy for the treatment of atrial tachyarrhythmias
- Able to understand the nature of the study and give informed consent

- Ability to tolerate the surgical procedure required for implantation
- Ability to complete all required testing including the six-minute walk test and cardiopulmonary exercise testing
- Available for follow-up visits on a regular basis at the investigational site
- Age greater than or equal to 18 years

Clinical Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following:

- Previously implanted CRT device
- ACC/AHA/NASPE indication for bradycardia pacing (sinus node dysfunction)
- Six-minute walk test distance greater than 450 meters
- Chronic atrial tachyarrhythmias refractory to cardioversion shock therapy
- Receiving intermittent, unstable intravenous inotropic drug therapy (patients on stable doses of positive inotropic outpatient therapy for at least one-month are permitted)
- Enrolled in another cardiovascular or pharmacological clinical investigation
- Expected to receive a heart transplant within 6 months
- Life expectancy less than 6 months
- Presence of another life-threatening, underlying illness separate from their cardiac disorder
- Acute myocardial infarction, unstable angina or cardiac revascularization within the last 30 days prior to enrollment
- Conditions that prohibit placement of any of the lead systems

Follow-Up Schedule

After successful enrollment, all patients were randomly assigned to either the study group or the control group. The specific procedures of this study were:

- Pre-enrollment screening
- Randomization
- System implantation
- Pre-discharge follow-up
- Baseline evaluation / CRT activation
- One-Month follow-up
- Three-Month follow-up
- Six-Month follow-up
- Subsequent routine follow-ups (every three months)

Clinical Endpoints

Primary Endpoint 1: Six Minute Walk Test & QOL (Effectiveness)
The purpose of Primary Endpoint 1 is to evaluate the effectiveness of the Tupos LV/ATx system in providing CRT as measured by the average composite rate of improvement in six minute walk test and QOL.

Secondary Endpoint Results

1. The purpose of this secondary endpoint is to evaluate improvement in functional capacity as measured by the six minute walk test. The six minute walk test is a well-accepted measure of functional capacity and exercise tolerance. Also, this test more closely mimics the patient's day-to-day activities than maximal exercise testing.
2. The purpose of this secondary endpoint is to evaluate the improvement in the patient's NYHA classification.

Accountability of PMA Cohorts

After randomization and enrollment, 7 patients (4 in the study group and 3 in the control group) did not receive an implant. The reasons for patients not receiving an implant are outlined in **Figure 2**.

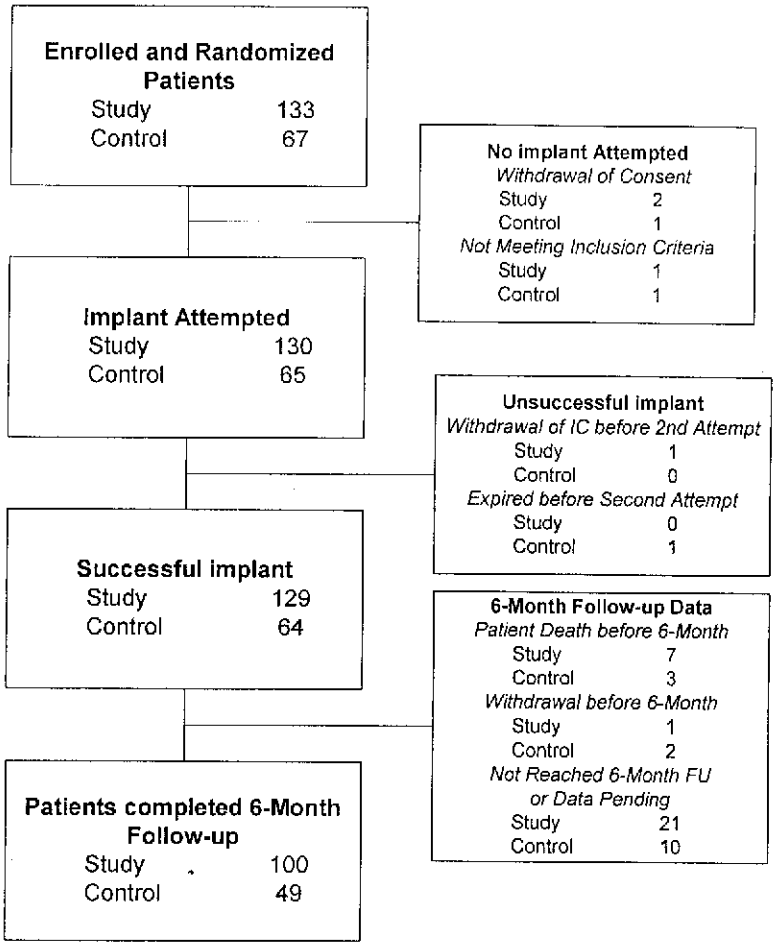


Figure 2: Patient Accountability

Demographics and Baseline Parameters

Table 13 provides a summary of the pre-enrollment demographics of enrolled patients.

Table 13: Patient Demographics at Pre-Enrollment			
Characteristic	**Study N=133**	**Control N=67**	**P-value**
Age at Enrollment (Years) Mean ± SE Range	69.5 ± 0.9 43 to 88	69.1 ± 1.2 38 to 84	0.781*
Gender Male Female	93 (69.9%) 40 (30.1%)	51 (76.1%) 16 (23.9%)	0.407**
Underlying Heart Disease Ischemic Cardiomyopathy Nonischemic Cardiomyopathy	100 (75.2%) 34 (25.6%)	54 (80.6%) 15 (22.4%)	0.294** *
Type of Bundle Branch Block Left Bundle Branch Block Right Bundle Branch Block Other	91 (68.4%) 26 (19.5%) 19 (14.3%)	49 (73.1%) 10 (14.9%) 11 (16.4%)	0.877** *
New York Heart Association Class Class III Class IV	121 (91.0%) 12 (9.0%)	60 (89.6%) 7 (10.4%)	0.800**
Intrinsic QRS Duration (ms) Mean ± SE Range	161.9 ± 2.0 130 to 252	156.1 ± 2.3 130 to 200	0.073*
Left Ventricular Ejection Fraction (%) Mean ± SE Range	22.1 ± 0.6 5 to 35	23.3 ± 0.8 10 to 35	0.255*
Six Minute Walk Distance (meters) Mean ± SE Range	254.8 ± 8.9 20 to 451	250.5 ± 11.9 27 to 447	0.775*
Quality of Life Questionnaire Score Mean ± SE Range	54.3 ± 2.1 0 to 105	52.5 ± 3.1 0 to 102	0.638*

*Student's t-test (2-sided) for means, **Fisher's Exact Test (2-sided) for 2 possible answers, ***Chi-Square test (2-sided) for more than 2 possible answers

Table 14 provides a summary of cardiac medications patients were taking at the time of enrollment. Some categories may be more than 100% as several categories allow more than one response.

Table 14: Cardiac Medications at Pre-Enrollment

Drug Category	Study (N=133)	Control (N=67)	P-value
Specific CHF Medications			
ACE inhibitors	89 (66.9%)	45 (67.2%)	1.000**
Angiotensin receptor blockers	21 (15.8%)	16 (23.9%)	0.180**
Beta blockers	111 (83.5%)	55 (82.1%)	0.843**
Cardiac glycosides (Digoxin)	60 (45.1%)	35 (52.2%)	0.370**
Diuretic	114 (85.7%)	57 (85.1%)	1.000**
Inotropes	1 (0.8%)	3 (4.5%)	0.110**
Anti-arrhythmics	34 (25.6%)	19 (28.4%)	0.735**
Nitrates	36 (27.1%)	14 (20.9%)	0.390**

*Student's t-test (2-sided) for means, **Fisher's Exact Test (2-sided) for 2 possible answers, ***Chi-Square test (2-sided) for more than 2 possible answers

Safety and Effectiveness Results

A total of 200 patients were enrolled in the OPTION CRT/ATx clinical study at 25 sites:

There were 133 study patients and 67 active control patients in this prospective, multi-center, randomized clinical study. For the study group, there were 129 successful implants (91.4%) of the Tupos LV/ATx CRT-D system. For the active control group, there were 64 successful implants (92.2%) of the legally marketed CRT-D systems.

- There were 192 endocardial and 19 epicardial leads implanted in 193 patients. Investigators were allowed to choose among any legally marketed LV lead according to their familiarity with the lead and patient anatomy. The Tupos LV/ATx CRT-D was implanted with 7 endocardial and 4 epicardial lead models from 6 different manufacturers. There were no adverse events reported attributable to lead-generator incompatibility.
- The cumulative implant duration is 1240.4 months with a mean duration of 9.6 months for the study group. The cumulative implant duration is 596.5 months with a mean duration of 9.3 months for the control group.
- The overall protocol compliance rate is 79.2% in the study group and 85.9% in the control group. The overall follow-up compliance rate is 99.4% in the study group and 98.3% in the control group.
- There have been 10 patient deaths reported in the study group and 4 patient deaths reported in the control group. The clinical investigators have determined that no deaths were related to the study device.

Primary Endpoint 1: Six Minute Walk Test & QOL (Effectiveness)

The purpose of Primary Endpoint 1 is to evaluate the effectiveness of the Tupos LV/ATx system in providing CRT as measured by the average composite rate of improvement in six minute walk test and QOL.

Table 15 presents the average composite rate of improvement in six minute walk test distance and QOL score, the average 6-minute walk test distance and the average QOL score at Baseline and at the Six-Month follow-up, as well as the average difference in 6-minute walk test distance and QOL score between Baseline and the Six-Month follow-up for the Study and Control Groups for those patients with six minute walk test data and complete QOL data at both Baseline and the Six-Month follow-up.

Table 15: Composite of Six Minute Walk Test and QOL (Effectiveness)			
Category	**Study Group (N = 74)** Mean ± SE	**Control Group (N = 38)** Mean ± SE	**P-value***
Distance Walked at Baseline	310.51 ± 10.89	288.76 ± 15.37	0.249
Distance Walked at Six-Months	340.77 ± 12.32	301.84 ± 17.02	0.067
Δ Distance Walked	30.26 ± 10.40 17.27% ± 5.59%	13.08 ± 13.05 8.71% ± 5.26%	0.322 0.326
QOL Score at Baseline	44.39 ± 2.78	45.53 ± 4.13	0.817
QOL Score at Six-Months	28.68 ± 2.66	33.95 ± 4.35	0.279
Δ in QOL Score†	15.72± 2.83 19.08% ± 12.21%	11.58 ± 3.45 -13.42% ± 34.54%	0.376 0.281
Composite Rate‡	**18.18% ± 7.07%**	**-2.36% ± 17.73%**	**0.030**

* The calculated p-values are associated with a Student's t-test (2-sided) of the equality of means in the two groups, except for the p-value of the composite rate, which is associated with a test of equivalence (non-inferiority).

† Δ in QOL Score is calculated as the average of the individual differences between Baseline and Six-Months for each patient. Negative values for mean Δ QOL in percent are possible when positive mean values for absolute changes in QOL are recorded. In some cases, small, negative changes in absolute QOL scores resulted in relatively large percentage changes.

‡ The Composite Rate (=(Δ Distance Walked (%) + Δ QOL Score (%)) / 2) is calculated for each patient and then averaged to obtain the Composite Rates. For all calculations, a positive number represents improvement from Baseline to Six-Months.

Primary Effectiveness Endpoint Analysis and Conclusions

A composite rate of six minute walk test and QOL improvement from Baseline to the Six-Month follow-up is evaluated as a measure of CRT effectiveness. For this analysis both six minute walk test and QOL are equally weighted at 50%.

The mean difference in the composite rate between study and control group was 20.53% with an associated one-sided, 95% confidence bound of (-6.10%). The p-value for non-inferiority within 10% is 0.030. The analysis of the composite rate in six minute walk test distance and QOL score demonstrates that the study group is non-inferior to the control group and that the primary effectiveness endpoint was met (p=0.030).

Secondary Endpoint Results

1. The purpose of this secondary endpoint is to evaluate improvement in functional capacity as measured by the six minute walk test. The six minute walk test is a well-accepted measure of functional capacity and exercise tolerance. Also, this test more closely mimics the patient's day-to-day activities than maximal exercise testing.

   Table 16 summarizes the six minute walk test distance at Baseline and the Six-Month follow-up for patients in the study group and the control group.

Table 16: Six Minute Walk Distance

Distance (meters)	Study	Control
Baseline		
N	127	61
Mean ± SE	283.14 ± 9.27	269.43 ± 13.77
Range	23 to 511	29 to 507
Median	302.00	244.00
Six-Month		
N	93	44
Mean ± SE	329.73 ± 10.82	310.70 ± 15.49
Range	78 to 596	91 to 489
Median	335.00	313.00

* Student's t-test, 2-sided

There are no clinically relevant differences in the six minute walk test results between the study and the control group.

2. The purpose of this secondary endpoint is to evaluate the improvement in the patient's NYHA classification. Table 17 summarizes the average improvement in NYHA from Baseline to Six-Months for 140 patients that were able to complete both NYHA classification evaluations.

Table 17: Improvement in NYHA Classification at Six-Months from Baseline

Change in NYHA class	Study (N=97)		Control (N=43)	
	Number of Patients	% of Total Patients	Number of Patients	% of Total Patients
Improved 2 classes	10	10.3%	2	4.7%
Improved 1 class	47	48.5%	20	46.5%
Total improved	57	58.8%	23	51.2%
No change	39	40.2%	20	46.5%
Worsened 1 class	1	1.0%	1	2.3%

The study and the control group have similar NYHA classes and similar rates of improvement in NYHA class from Baseline to the Six-Month follow-up.

Multi-site Poolability and Gender Analysis

The OPTION CRT/ATx clinical report includes data from multiple centers with centralized coordination, data processing, and reporting at BIOTRONIK. All of the clinical centers followed the requirements of an identical clinical protocol, and all of the clinical centers used the same methods to collect and report the clinical data. In order to justify pooling of the data from multiple centers, several analyses were completed. All of the centers were divided into two groups based on implant volume. Comparisons were then made between the patient populations based on the results of each of the endpoints. Additionally, analyses were performed on the data collected in the OPTION CRT/ATx clinical investigation in order to compare results between males and females. The first type of analysis compared enrollment by patient gender in each of the study and control groups. The second type of analysis compared effectiveness outcomes in each gender.

The results of these analyses demonstrate poolability of the data between sites. There were no significant differences in the second primary endpoint or any of the secondary endpoints between high and low volume implant centers.

The gender distribution in this clinical investigation is consistent within the study groups and includes a representative proportion of enrolled female participants (28.0% versus 72.0% male). There were no significant differences in any of the primary or secondary endpoints between the male and female population.

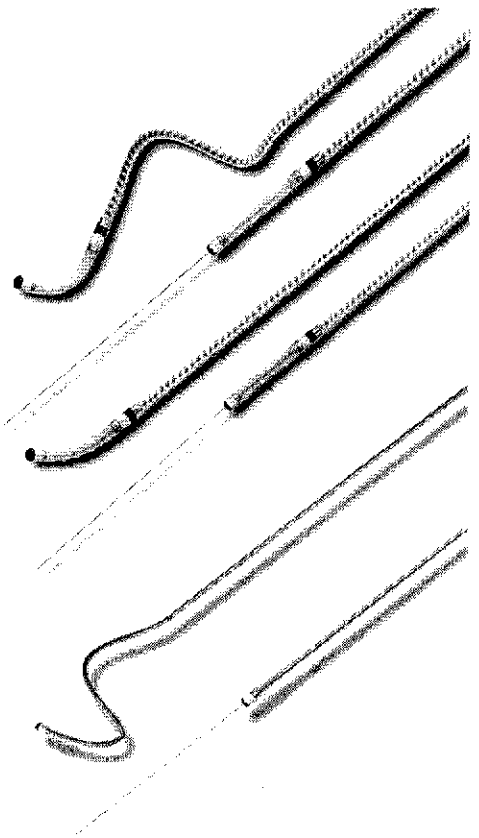
1.7.5 Conclusions Drawn from Studies

The clinical study results support the safety and effectiveness of the Stratos LV CRT-P device.

- The OPTION CRT/ATx clinical study completed and reviewed under P050023 provided a reasonable assurance that bi-ventricular pacing is effective in NYHA class III/IV heart failure patients with a prolonged QRS and a left ventricular ejection fraction <35%. The addition of ICD back-up therapy does not affect the biventricular pacing performance of the device.
- The AVAIL CLS/CRT and Corox (OVID) clinical studies demonstrated the safety of the Stratos LV CRT-P in NYHA class III/IV heart failure patients with a prolonged QRS and a left ventricular ejection fraction <35%.(OVID).

Corox Family of OTW Left Ventricular Leads

Steroid-Eluting Left Ventricular Pacing Leads
IS-1 Connector



Technical Manual

BIOTRONIK
excellence for life

CAUTION

Federal (U.S.A.) law restricts this device to sale by, or on the order of, a physician.

Contents

1. Device Description

BIOTRONIK's Corox OTW leads are transvenous, steroid-eluting left ventricular pacing leads designed for use with a compatible cardiac resynchronization therapy (CRT) device that accepts leads with a unipolar (UP) or bipolar (BP) IS-1 connector configurations. The leads can be positioned in the target vein using either the over-the-wire techniques or stylet driven methods.

The leads are constructed with multifilar conductors insulated with medical grade silicone and coated with polyurethane. There are two separate distal ends available with the Corox OTW leads, as described below. In addition to the unipolar and bipolar leads that are helix shaped at the lead tip (Corox OTW BP and Corox OTW UP Steroid), the Corox OTW-S BP has a bend in the distal tip that fixates by "wedging" across a vessel.

- Corox OTW BP and Corox OTW UP Steroid left ventricular leads have distal ends that are helix shaped at the lead tip, which is designed to adhere to the coronary vein when the stylet or guide wire is removed. This system provides for flexible control and positioning of the lead during implantation while the stylet or guidewire is in place. Additionally, the helical shape of the distal end of the lead fixates the electrode within the vessel after the stylet or guide wire is removed. This fixation design is a clinically proven fixation mechanism for larger vessels.
- Corox OTW-S BP has a silicone thread attached to the lead body between the tip and ring electrodes, which fixates by "wedging" across a vessel. The distal end between the electrodes also exhibits a slight two dimensional bend, which facilitates the steering of the lead in the coronary venous system. This fixation option is designed for implantation in smaller coronary vessels.

Steroid Collar with DXA: The distal tip of all of the Corox OTW leads consists of a steroid-eluting collar, containing 0.5 mg of Dexamethasone Acetate (DXA). Upon exposure to body fluids, the steroid elutes from the collar into the body tissue by diffusion. The bipolar Corox OTW leads have an additional steroid-eluting collar, containing 0.5 mg of dexamethasone acetate (DXA) at the ring electrode.

The Corox OTW leads feature electrodes with a fractal surface structure of iridium that provides a larger effective tissue interface. The electrode is comprised of a platinum/iridium alloy base.

The Corox OTW leads are available in the following configurations:

- Corox OTW 75-UP Steroid (77 cm in length)
- Corox OTW 85-UP Steroid (87 cm in length)
- Corox OTW 75-BP (77 cm in length)
- Corox OTW 85-BP (87 cm in length)
- Corox OTW-S 75-BP (77 cm in length)
- Corox OTW –S 85-BP (87 cm in length)

The Corox OTW leads are designed for transvenous implantation within the coronary sinus system to provide pacing stimulation to the left ventricle in a CRT system. Implantation is facilitated using the standard stylet method or with the over-the-wire (OTW) technology.

CAUTION

Because of the numerous available 3.2 mm configurations, e.g., the IS-1 and VS-1 standards, lead/pulse generator compatibility should be confirmed with the pulse generator and/or lead manufacturer prior to the implantation of a pacing system.

NOTE:

IS-1, wherever stated in this manual, refers to the international standard, whereby leads and generators from different manufacturers are assured a basic fit. [Reference ISO 5841-3:1992(E)].

See **Section 10** for technical specifications of the Corox OTW leads.

1.1 Drug Information

The active drug component in the Corox OTW leads is dexamethasone acetate (DXA).

1.1.1 Drug Component Description

Dexamethasone acetate is an anti-inflammatory steroid with a molecular formula of C24H31FO6 that is a white crystalline solid with a melting point of 238-240°C and maximum UV of 239 nm (Merck Index, Twelfth edition 1996). The structural formula is shown in **Figure 1**.

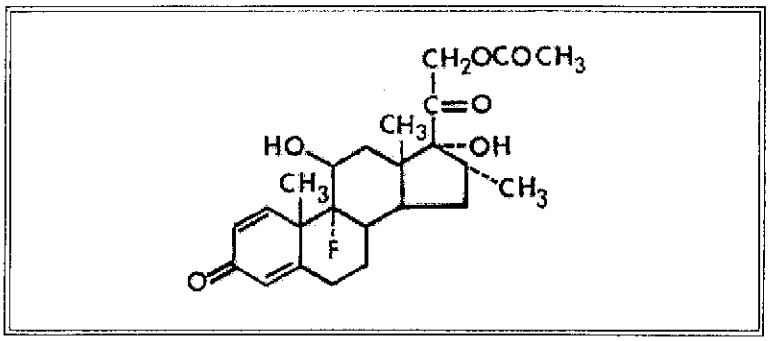


Figure 1: Dexamethasone Acetate Structural Formula

The nominal dose of DXA on the steroid collar is 0.5 mg. Corox OTW UP contains one (1) drug component (steroid collar) at the distal tip, while the Corox OTW BP and Corox OTW-S BP contain two (2) drug components (one steroid collar at the distal tip and one at the ring electrode). Each collar, positioned adjacent and distal to each electrode, consists of DXA in a silicone rubber matrix.

1.1.2 Mechanism of Action

Steroids suppress the inflammatory response that is believed to cause threshold rises typically associated with implanted pacing leads. Dexamethasone acetate is a synthetic steroid of the glucocorticoid family. Glucocorticoid steroids have potent anti-inflammatory actions via direct and indirect effects on major inflammatory cells. While the mechanism of action of glucocorticoids is not fully understood, it is known that glucocorticosteroids bind to a cytoplasmic glucocorticoid receptor as well as to a membrane-bound receptor. Binding to the cytoplasmic receptor, the receptor becomes activated and leads to translocation to the nucleus. The receptor interacts with specific DNA sequences (glucocorticoid responsive elements) within the regulatory regions of affected genes. Thus, glucocorticoids inhibit the production by multiple cells of factors that are critical in generating the inflammatory response, in particular via modulation of transcription factors.

1.1.3 Pharmacokinetics

The pharmacokinetics (local drug levels and systemic levels) of dexamethasone acetate and its metabolites following placement of the Corox OTW leads were not evaluated in a clinical trial.

1.1.4 Mutagenesis, Carcinogenicity and Reproductive Toxicity

Studies on mutagenesis, carcinogenicity and reproductive toxicity have not been performed with Corox OTW leads.

However, the mutagenic, carcinogenic potential and reproductive toxicity of the drug dexamethasone acetate have previously been evaluated. Mutagenesis studies with dexamethasone acetate do not reveal an indication for a clinically relevant genotoxic potential. No adequate studies have been conducted in animals to determine whether dexamethasone acetate has a carcinogenic potential.

Like other glucocorticoids, dexamethasone acetate has been shown to be teratogenic in many animal species. Studies in which dexamethasone acetate has been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. Embryotoxic effects were observed in rats. Effects on fertility were not found.

1.1.5 Pregnancy

Pregnancy Category C – Like other corticosteroids, dexamethasone acetate has been shown to be teratogenic in animal studies. There are no adequate and well-controlled studies in pregnant women of dexamethasone acetate or the Corox OTW leads. The Corox OTW leads should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

1.1.6 Lactation

Corticosteroids like dexamethasone acetate are secreted into human milk and there is a potential for adverse effects. A decision to nurse or not should be made after careful benefit/risk assessment.

2. Indications for Use

COROX OTW UP STEROID LEADS

The Corox OTW UP leads are intended for implantation via the coronary veins to provide long term cardiac pacing when used in conjunction with a compatible pulse generator.

COROX OTW BP AND COROX OTW-S BP LEADS

The Corox OTW BP and Corox OTW-S BP left ventricular pacing leads are bipolar steroid-eluting leads, intended for permanent implantation in the left ventricle via the coronary veins to provide pacing and/or sensing when used in conjunction with a compatible IS-1 pulse generator.

3. Contraindications

The use of the Corox OTW leads is contraindicated under the following circumstances:

- Coronary sinus anomalies
- Tissue in the coronary sinus area that has been damaged by an infarction
- Any anomalies of the venous system that preclude transvenous implantation of the lead
- Patient cannot tolerate a single systemic dose of up to 1.0 mg (0.65 mg for the unipolar version) of dexamethasone acetate (DXA)

4. Warnings and Precautions

The performance of a cardiac pacing system depends on proper interaction of its three components: the pulse generator, the lead(s), and the patient. Abnormalities or changes in the electrical properties of any of the three components, or their interfaces with each other, may directly affect function of the entire system. Correct lead implantation is critical to safe and effective performance of the pacing system.

The pacing system may cease to function at any time due to medical and/or technical complications:

Medical Complications

Medical complications of the pacemaker treatment may include, but are not limited to: fibrotic tissue formation, thrombosis, embolism, elevated thresholds, body rejection phenomena, cardiac tamponade, muscle and nerve stimulation, myocardial perforation, erosion of the pulse generator/lead through the skin, infection and pacemaker-induced dysrhythmia (some of which could be life-threatening such as ventricular fibrillation).

Dexamethasone Acetate (DXA)

The Corox OTW UP leads include one steroid collar with 0.5 mg Dexamethasone Acetate. The Corox OTW BP and Corox OTW-S BP leads each include two steroid collars with a total of 1.0 mg Dexamethasone Acetate. Dexamethasone Acetate is released from these steroid collars very slowly. It has not been determined whether the contraindications, warnings, precautions and side effects usually associated with injectable Dexamethasone Acetate apply to the application of a single, low dose in a very slow released dosage form. For a listing of potentially adverse effects, refer to the Physician's Desk Reference.

Drug Interactions

Drug interactions of Dexamethasone Acetate with the Corox OTW leads have not been studied.

Technical Complications

Incorrect operation of the pacing system may be caused by but is not limited to: improper lead placement, lead dislodgement, lead fracture, loss of insulation integrity, battery depletion, or electrical component failure.

Potentially Harmful Therapeutic and Diagnostic Procedures

As an implanted pacing lead is a direct, low resistance path to the myocardium for electrical current, the observance of high standards of electrical safety is required. Electrosurgical instruments, for example, could generate voltages of such amplitude that a direct coupling between the tip of the electrocautery device and the implanted lead may result, possibly inducing myocardial lesions or serious cardiac arrhythmias (e.g., fibrillation).

Some therapeutic and diagnostic procedures (e.g., diathermy, MRI, electrocautery) may result in latent damage to the pacing system. This damage may not be detected when testing the pulse generator function immediately after the procedure, but may become evident at a later time, resulting in pacing system malfunction or failure.

Prevention of Leakage Current Conduction

Pulse generators and testing equipment connected to the lead must be battery-powered. Proper grounding of line-powered devices in the vicinity of the patient is essential to prevent leakage currents arising from such devices to be conducted via the lead's terminal or any other non-insulated part.

Previously Implanted Leads

It is generally recommended that a chronically implanted lead not be explanted. If it becomes necessary to abandon a lead, the connector pin should be capped to prevent the transmission of electrical signals to the heart.

Storage Temperature

Recommended storage temperature range is 5°– 25° C (41°–77° F). The lead may be stored at a maximum temperature of 50°C (122°F) for only one month. Exposure to temperatures outside this range may result in lead malfunction.

Necessary Equipment for Implantation

During implantation the ECG should be recorded; a pacing system analyzer (PSA) and defibrillation equipment should always be readily available.

Handling the Lead

The lead should be handled very carefully at all times. Any severe application of force (bending, stretching, crimping, etc.) may permanently damage the lead. The metal portion of the lead connector should not be touched.

Lead Lumen

The inner lumen of the Corox OTW leads may not be rinsed with irrigation solution under any circumstances. The resulting excessive pressure inside the lead could damage the silicone insulation.

Stylet Insertion

To avoid damage to the lead, do not insert the stylet too rapidly nor use excessive force when inserting the stylet into the lead.

Only use stylets suitable for the Corox OTW leads. Using unsuitable leads can damage the lead or protrude over the tip electrode and cause injury to the patient.

Lead/Pulse Generator Compatibility

Because of the numerous available 3.2 mm configurations, e.g., the IS-1 and VS-1 standards, lead/pulse generator compatibility should be confirmed with the pulse generator and/or lead manufacturer prior to the implantation of a pacing system.

NOTE:

IS-1, wherever stated in this manual, refers to the international standard, whereby leads and generators from different manufacturers are assured a basic fit. [Reference ISO 5841-3:1992(E)].

Anchoring Sleeve

Always use an anchoring sleeve (lead fixation sleeve) when implanting a lead. Use of the anchoring sleeve, which is provided with the lead, will lessen the possibility of lead dislodgement and protect the lead body from damage by a securing ligature.

Measuring Intracardiac Signals

Depending on the PSA used, pacing may be interrupted during the measurement of the intracardiac signals. BIOTRONIK's ERA 300 Pacing System Analyzer has back-up VVI pacing at a rate of 30 ppm during the intracardiac measurements.

Chronic Repositioning

It is generally recommended that a chronically implanted lead not be explanted. Chronic repositioning or removal of active fixation leads may be difficult due to the presence of blood or fibrotic tissue in the helix. If it becomes necessary to abandon a lead, the connector pin should be capped to prevent the transmission of electrical signals to the heart.

Setscrew Adjustment

The pulse generator's setscrew(s) must be retracted prior to inserting the lead connector. Failure to back off the pulse generator's setscrew(s) may result in damage to the lead(s), and/or difficulty connecting the lead(s).

Cross-Threading Setscrew

To prevent cross-threading the setscrew, do not back the setscrew completely out of the threaded hole. Leave the torque wrench in the slot of the setscrew while the lead is inserted.

Tightening Setscrew

Do not over-tighten the setscrew(s). Use only a torque wrench, which automatically prevents over-tightening.

Sealing Caps

For pacemakers requiring sealing caps, secure a sealing cap over the setscrew(s) to prevent pacemaker malfunction.

5. Potential Adverse Events

Potential complications resulting from the use of left ventricular leads include, but are not limited to: thrombosis, embolism, body rejection phenomena, .cardiac tamponade, pneumothorax, muscle/nerve stimulation, valve damage, fibrillation, infection, skin erosion and ventricular ectopy. Lead perforation through the myocardium has been rarely observed. The table below summarizes some of the potential symptoms indicating a complication and possible corrective actions:

Table 1: Potential Complications and Corrective Actions

Symptom	Potential Complication	Potential Corrective Action
Loss of pacing or sensing	Lead dislodgement	Reposition lead
	Lead fracture	Replace lead
	Setscrew penetration of lead insulation	Replace lead
	Improper lead / pulse generator connection	Reconnect lead to pulse generator
Increase/ decrease in threshold	Fibrotic tissue formation	Adjust pulse generator output; Replace/reposition lead

6. Clinical Studies

The subsequent sections summarize the following clinical studies that were used to support the safety and effectiveness of the Corox OTW UP Steroid and/or Corox OTW(-S) BP Left Ventricular Leads.

- The OVID clinical study (OUS)
- The everesT clinical study (OUS)

The OVID study evaluated the Corox OTW UP Steroid LV lead.

The everesT clinical investigation assessed the clinical safety and effectiveness of Corox OTW(-S) BP bipolar left ventricular leads.

6.1 Overview of OVID Study

An outside the US clinical evaluation of the Corox OTW UP Steroid LV leads (OVID) was conducted in a multi-center trial with legally marketed CRT-D and CRT-P pulse generators that provide biventricular pacing therapy.

6.1.1 Methods

The multi-center investigation was designed to validate the safety of the Corox OTW UP Steroid LV lead through a comparison of successfully implanted LV leads against a pre-defined success rate threshold, when no anatomical restrictions prevent access to the coronary sinus. The evaluation of safety is based on the analysis of the incidence of Corox OTW UP Steroid LV lead related adverse events, defined as any complications or observations judged by the investigator to be in probable relationship with Corox OTW UP Steroid LV lead system. Additionally, the effectiveness of the leads was evaluated using lead parameter data, including sensing amplitudes, pacing thresholds, and impedance values.

INCLUSION CRITERIA

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrollment:

- Meet the indications for bi-ventricular pacing
- Age ≥ 18 years
- Receiving optimal drug therapy for Congestive Heart Failure treatment
- Give informed consent

EXCLUSION CRITERIA

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following requirements:

- Myocardial infarction or unstable angina pectoris
- Acute myocarditis
- Life expectancy ≤ 6 months
- Planned cardiac surgical procedures or interventional measures within the next 6 months
- Pregnancy

6.1.2 Overall Results

The Corox OTW UP Steroid LV clinical evaluation included a total of 132 patients meeting indications for biventricular pacing. The coronary sinus was accessed in all patients, and of these, 121 were successfully implanted with the Corox OTW UP Steroid LV lead. The study population ranged in age from 34 to 84 and included 99 males (75%) and 33 females (25%).

- The cumulative implant duration is 1145 months with a mean duration of 9.6 months. Ninety-six (79%) of the patients have implant durations greater than 6 months.
- The implant success rate for the Corox OTW UP/Steroid LV lead was 91.7% overall.

- The Corox OTW UP/Steroid LV lead was implanted in combination with 8 different CRT-P and CRT-D devices marketed by 4 different manufacturers.
- The mean LV pacing threshold at implant was 0.97 volts and at 6-months was 0.92 volts.
- The mean R-wave at implant was 15 mV.
- The mean LV lead impedance at implant was 796 ohms and at 6-months was 593 ohms.
- There have been 44 adverse events (28 observations in 26 patients and 16 complications in 13 patients). There have been no unanticipated adverse device effects reported.
- There have been 12 patient deaths reported in the OVID study. The clinical investigators have determined that no deaths were related to the Corox OTW/Steroid LV lead.
- The overall follow-up compliance rate for the OVID study is 92.9%.

6.1.3 Primary Endpoint

The primary endpoint was implant success rate, defined as the number of initial and successful Corox OTW UP Steroid LV lead implantations divided by the number of initial Corox OTW UP Steroid LV lead implantation attempts when the coronary sinus was found and when there were no anatomic restrictions making LV lead implantation impossible.

Objective: The lower bound of the one-sided 95% confidence interval of the successful implantation rate of the BIOTRONIK Corox OTW UP Steroid LV lead will not be less than 67%. The success rate was defined as a proportion of patients who received a Corox OTW UP Steroid LV lead during implantation and subsequently it could be confirmed that the Corox OTW UP Steroid LV lead was providing adequate left ventricular stimulation after having finished the implantation procedure.

Results: The coronary sinus was accessed in all 132 enrolled patients. Corox OTW UP Steroid LV leads were successfully placed in 121 patients, which corresponds to an implantation success rate of 91.7% with a 95%-confidence interval of [0.86 - 0.96].

Table 2 provides the Corox OTW UP Steroid implantation success rates within the clinical study.

Table 2: Corox OTW UP Steroid Implantation Success

Results	N	95% Confidence Interval
Coronary Sinus(CS) Found	132 of 132 (100%)	0.97 to 1.0
Successful implantations	121 of 132 (91.7%)	0.86 to 0.96
Success rate when CS was found	121 of 132 (91.7%)	0.86 to 0.96

Corox OTW UP Steroid LV lead implantation was not successful in 11 of 132 (8.3%) patients enrolled into the study. Details for these unsuccessful implant procedures are described in **Table 3:** Reasons for Implant Failure of Corox OTW UP Steroid LV lead

Table 3: Reasons for Implant Failure of Corox OTW UP Steroid LV lead

Reason for Implant Failure of Corox OTW/Steroid LV lead	N
Inability to find a stable position	3 of 132 (2.3%)
Target position not reached	3 of 132 (2.3%)
Coronary vessels too small	2 of 132 (1.5%)
Lead dislodged while removing guide catheter	2 of 132 (1.5%)
Perforation of SVC with pneumothorax	1 of 132 (0.8%)
Total Implant Failures of LV lead	**11 (8.3%)**

Conclusions: The rate of successful implant of the Corox OTW UP Steroid LV lead is 91.7% with a lower 95% confidence bound of 86%. The lower 95% confidence bound of the implant success rate exceeds the limit of 67% and therefore, the null hypothesis is rejected. These results demonstrate that the Corox OTW UP Steroid LV lead has an appropriate implant success rate.

6.1.4 Secondary Endpoints

Reported lead data reflect only the patients with successfully implanted LV leads. LV sensing measurements were performed at implant only because LV sensing cannot be measured through the pulse generators used in the study. These values were all clinically acceptable for LV leads, with an average R-wave amplitude of 15 ± 7 mV. Lead impedance values were collected and also were all clinically acceptable, with an average pacing impedance of 590 ± 136 Ohms at 3 months. **Table 4** provides a summary of the pacing thresholds at implant, one month and three months.

Table 4: Ventricular Pacing Thresholds – Corox OTW UP Steroid LV Lead

Pacing Threshold	Results (Volts @ 0.50 ms)
Implant	
Number of Tests	114
Mean ± SD	0.98 ± 0.8
Range	0.2 - 4.0
One-month Follow-up	
Number of Tests	72
Mean ± SD	0.94 ± 0.7
Range	0.3 - 3.9
Three-month Follow-up	
Number of Tests	71
Mean ± SD	0.89 ± 0.7
Range	0.2 - 3.8

There were 8 LV lead related complications (including the pocket infection which could not be ruled out as related) in 121 patients successfully implanted with the Corox OTW/Steroid LV lead through six months follow-up. The freedom from Corox OTW/Steroid LV lead-related complications is 92.9% with a two-sided lower 95% confidence bound of 86.4%

The complication and observation adverse event rates for the Corox OTW UP Steroid LV lead were 5.3% and 11.4%, respectively during the clinical study. Both these rates are acceptable for prospective biventricular LV pacing lead trials. Furthermore, the overall complication and observation adverse event rates for the patients were 9.8% and 19.7% respectively. This data demonstrates the overall safety performance profile of the Corox OTW Steroid LV lead.

6.1.5 Observed Adverse Events

Adverse events are classified as either observations or complications. Observations are defined as clinical events that do not require additional invasive intervention to resolve. Complications are defined as clinical events that require additional invasive intervention to resolve.

Of the 44 adverse events reported, there were 28 observations and 16 complications in a total of 132 patients. **Table 5** and **Table 6** provide a summary by category of each type of adverse event (complications and observations).

Table 5: OVID - Summary of Complications				
Category	# of Pts	Percentage of Patients	# of Complications	Complication per pt-year
Corox OTW UP Steroid Lead-Related				
Loss of capture	5	3.8%	5	0.05
Phrenic nerve stimulation	2	1.5%	2	0.02
Total LV Lead Related	**7**	**5.3%**	**7**	**0.07**
Atrial Lead Related				
Loss of capture	2	1.5%	2	0.02
Total Atrial Lead Related	**2**	**1.5%**	**2**	**0.02**
RV Lead Related				
Loss of capture	3	2.3%	3	0.03
Elevated Pacing thresholds	2	1.5%	2	0.02
Total RV Lead Related	**5**	**3.8%**	**5**	**0.05**
Medical				
Arrhythmias	1	0.8%	1	0.01
Pocket infection	1	0.8%	1	0.01
Total Medical	**2**	**1.5%**	**2**	**0.02**
Overall Complication Totals	**13**	**9.8%**	**16**	**0.17**

Number of Patients = 132; Number of Patient-Years = 94.1

Table 6: OVID - Summary of Observations				
Category	# of Pts	Percentage of Patients	# of Observations	Observation per pt-year
Corox OTW UP Steroid Lead-Related				
Implant failure	11	8.3%	11	0.12
Phrenic nerve stimulation	4	3.0%	4	0.04
Total LV Lead-Related	**15**	**11.4%**	**15**	**0.16**
Atrial Lead Related				
Loss of capture	1	0.8%	1	0.01
Elevated Pacing thresholds	1	0.8%	1	0.01
Total Atrial Lead Related	**2**	**1.5%**	**2**	**0.02**
RV Lead Related				
Elevated Pacing thresholds	2	1.5%	2	0.02
Total RV Lead Related	**2**	**1.5%**	**2**	**0.02**
Medical				
Arrhythmias	2	1.5%	2	0.02
Pocket infection/ Pericardial Effusion	2	1.5%	2	0.02
Chest pain	1	0.8%	1	0.01
Shortness of breath, palpitations	1	0.8%	1	0.01
Total Medical	**6**	**4.5%**	**6**	**0.06**
Miscellaneous				
Malfunction of hemostatic valve	2	1.5%	2	0.02
Improper Lead preparation	1	0.8%	1	0.01

Table 6: OVID - Summary of Observations				
Category	# of Pts	Percentage of Patients	# of Observations	Observation per pt-year
Total Miscellaneous	**3**	**2.3%**	**3**	**0.03**
Overall Observation Totals	**26**	**19.7%**	**28**	**0.30**

Number of Patients = 132; Number of Patient-Years = 94.1

There were a total of 12 patient deaths reported in the OVID study. The clinical investigators determined that no deaths were related to the Corox OTW UP Steroid LV lead.

6.2 Overview of everesT Study

The clinical investigation everesT: "Evaluation of the new BIOTRONIK Resynchronization + ICD System" was used to support the safety and effectiveness of the Corox OTW BP leads.

6.2.1 Study Design

The clinical investigation everesT was designed to assess the clinical safety and effectiveness of the FDA approved Lumax HF-T 300 and Lumax HF-T 340 CRT-D, as well as the clinical safety and effectiveness of the Corox OTW BP and Corox OTW-S BP polyurethane coated bipolar LV leads. The everesT Study was a multi-center trial conducted Outside the United States (OUS) with legally marked pulse generators and leads to provide biventricular pacing therapy.

While the everesT investigation was designed to study both Lumax devices and Corox OTW(-S) BP LV leads, for purposes of this section, only everesT results from the Corox OTW(-S) BP LV leads are presented.

6.2.2 Clinical Inclusion Criteria

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrolment:

- Patient is willing and able to comply with the protocol and has provided written informed consent
- Indication for cardiac resynchronization therapy (CRT)
- Indication for implantation of an ICD
- Stable residence anticipated for 6 months after enrollment

6.2.3 Clinical Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following:

- Planned cardiac surgical procedures within 6 months after enrollment
- Life expectancy < 6 months
- Pregnant and breast-feeding women
- Age < 18 years or otherwise missing complete contractual capability
- Participation in another clinical study
- Corox BP not yet available on the market
- Any failed LV implant attempt or LV lead implanted prior to enrollment

6.2.4 Follow-Up Schedule

Follow-ups were required for all patients participating in this clinical investigation. Follow-up dates were calculated from initial implantation (day 0). The total follow-up period after implant was 6 months per patient. Study specific procedures were performed at:

- Pre-Hospital Discharge Follow-Up (at the latest five days after implantation)
- One-Month Follow-Up (± 1 week)
- Three-Month Follow-Up (± 2 weeks)
- Six-Month Follow-Up (± 4 weeks)

- Interim Follow-Up (if necessary as long as the patient was enrolled)

6.2.5 Clinical Endpoints

Primary Endpoint: Safety of Corox OTW(-S) BP

The goal was to demonstrate that the Corox BP lead related complication rate is significantly higher than the borderline value of 0.80.

Primary Endpoint: Effectiveness of Corox OTW(-S) BP

The goal was to demonstrate that the probability for successful Corox BP implantation (if the CS was found) is significantly higher than the borderline value of 0.75.

6.2.6 Accountability of PMA Cohorts

During the everesT clinical study, a total of 148 patients were enrolled and implanted with a Lumax HF-T device. There were 131 patients successfully implanted with a Corox BP LV lead. Additionally, there were 17 patients who underwent a Corox BP implant attempt but the procedure was unsuccessful due to anatomy, pacing thresholds, or lead instability. These patients were subsequently implanted with another LV lead and are included in the Corox-relevant sections of this report.

Figure 2 provides a graphical presentation of the patient's accountability.

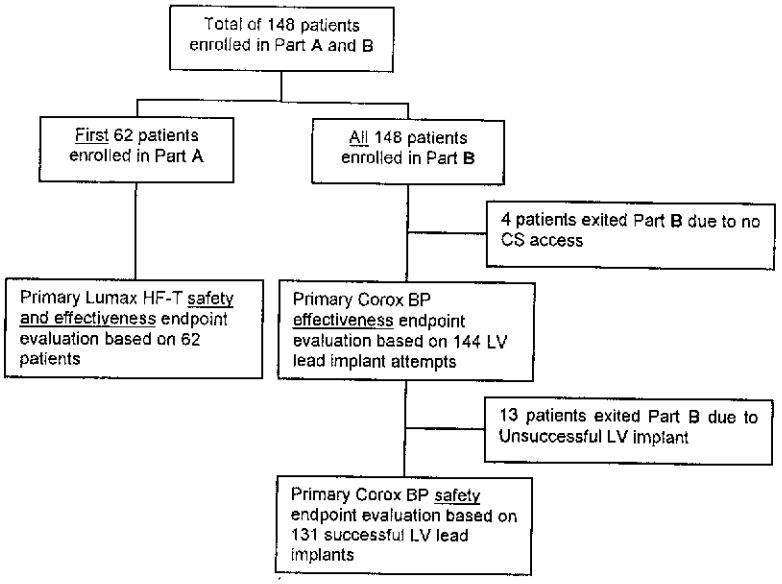


Figure 2: Patient Accountability Flow Chart

6.2.7 Demographics and Baseline Parameters

Table 7 provides a summary of the patient demographics and medical history for the 148 enrolled patients. The typical patient enrolled in the everesT study was a 67 year old male with NYHA Class III heart failure, a mean QRS duration of 162 ms, no AF, and ischemic cardiomyopathy. Note that the percentages in some characteristics may add up to more than 100% because multiple answers per patients were possible.

Table 7: Patient Demographics	
Characteristic	**Patients**
Enrollment in Study Parts	**n=148**
A only	n=0
B only	n=86
A+B	n=62
Age at Implant (years)	**n=148**
Mean ± SD	67 ± 9
Range	33 to 84

Table 7: Patient Demographics	
Characteristic	**Patients**
Gender	**n=148**
male	121 (82%)
female	27 (18%)
NYHA Class	**n=148**
I	0 (0%)
II	27 (18%)
III	114 (77%)
IV	7 (5%)
QRS Duration (ms)	**n=140**
Mean ± SD	162 ± 43
Range	86 to 380
Atrial Rhythm	**n=146**
No AF	88 (60%)
Paroxysmal AF	18 (12%)
Persistent AF	25 (17%)
Permanent AF	15 (10%)
Left Ventricular Ejection Fraction	**n=143**
Mean ± SD	26 ± 7
Range	10 to 44
Ischemic disease	**N=93 (63%)**
Cardiomyopathy	**N=97 (66%)**
Co-Morbidities	**n=148**
Diabetes mellitus	56 (38%)
Renal insufficiency	55 (37%)
Chronic pulmonary disease	33 (22%)
ICD Indication	**n=147**
Survived cardiac arrest	15 (10%)
VT with or without hemodynamic instability	24 (16%)
Non-sustained VT post MI and LVEF≤40%	15 (10%)
Syncope and LVEF≤40%	14 (10%)
Positive family history	1 (1%)
Primary prophylactic indication	95 (65%)
Other	4 (3%)

Table 7: Patient Demographics	
Characteristic	**Patients**
Cardiovascular Medication	**n=148**
ACE Inhibitors / ARBs	127 (86%)
ß-blockers	126 (85%)
Amiodarone	32 (22%)
Calcium antagonists	17 (11%)
Digitalis	56 (38%)
Sotalol	12 (8%)
Other antiarrhythmics	3 (2%)
Anticoagulants	84 (57%)
Platelet aggregation inhibitors	62 (42%)
Lipid lowering drugs	85 (57%)
Nitrates	17 (11%)
Spironolactones	76 (%)
Other diuretics	115 (78%)
Other	15 (10%)

6.2.8 Safety and Effectiveness Results

Data from a total of 148 patients are included in this clinical summary to support the Corox OTW-BP LV lead.

- The cumulative enrollment duration was 683.4 months with a mean duration of 4.6 months. 34/148 (23%) of patients had implant durations greater than 6 months.
- The implant success rate for the Corox OTW(-S) BP LV leads was 91% (131/144)
- The mean bipolar LV pacing threshold was 1.2 V at implant and at 0.8 V at 6-months
- The mean bipolar LV signal amplitude was 7.8 mV at both implant and 6-months
- The mean bipolar LV lead impedance was 839 ohms at implant and 886 ohms at 6-months
- Of the total 46 adverse events reported (e.g. device, lead, procedural, etc), there were 20 complications in 19 patients and 26 observations in 24 patients over cumulative enrollment duration of 57.1 patient-years

- There were 4 patient deaths reported in the everesT study. The clinical investigators have determined that no deaths were related to the Lumax HF-T 300/340 devices or the Corox OTW(-S) BP LV leads.
- The overall follow-up compliance rate for the everesT study was 96%

6.2.8.1 Primary Endpoint: Safety of Corox OTW(-S) BP

Objective: The goal was to demonstrate that the Corox BP lead related complication rate is significantly higher than the borderline value of 0.80.

Results: Out of 131 study patients with a successful Corox BP implant, a total of 2 Corox BP LV lead related complications were seen in 2 patients within 90 days post implant. At 3 months post implant, 1.5% of the study patients with a successful Corox BP implant experienced an LV lead related complication.

Table 8: Summary of Corox BP Complications ≤ 90 days

Category	# of Pts	Percentage of Patients (n = 131)	# of Complications	Complication per pt-year
Corox OTW BP (helix) n = 97				
High Threshold, Loss of capture	1	0.75%	1	0.03
Dislodgement	**1**	**0.75%**	**1**	**0.03**
Corox OTW-S BP (straight) n = 34				
N/A	0	0%	0	0
Total n = 131				
Total Corox BP Complications	**2**	**1.5%**	**2**	**0.06**

Number of Patients = 131 Number of Patient-Years = 31.8

The Corox BP is offered with two different types of fixation mechanisms: a three dimensional pre-shaped helical tip to achieve a stable position in larger veins (Corox OTW BP), or a straight tip for placement in smaller veins, 'wedge position' (Corox OTW-S BP). Out of 97 patients implanted with the Corox OTW BP there were 2 LV lead related complications seen in 2 patients within 90 days post implant. None of the 34 patients implanted with the Corox OTW-S BP experienced a LV lead related complication within 90 days post implant.

The observed total overall Corox BP related complication-free rate at 3 months was 98.5% based on 129 patients without LV lead related complications within the group of 131 patients with a successful Corox BP implant.

Conclusions: The 95% lower bound criterion was found to be 94.6%. This is higher than the pre-determined borderline value of 80%, therefore the respective null hypothesis is rejected and the primary Corox BP LV lead safely endpoint is met.

6.2.8.2 Observed Adverse Events

Adverse events are classified as either observations or complications. Observations are defined as clinical events that do not require additional invasive intervention to resolve. Complications are defined as clinical events that require additional invasive intervention to resolve.

Of the 46 adverse events reported, there have been 20 complications in 19 patients and 26 observations in 24 patients over cumulative enrollment duration of 57.1 patient-years. A total of 12.8% of study patients experienced a complication. The rate of complications per patient-year was 0.35. A total of 16.2% of study patients have a reported observation. The rate of observations per patient-year was 0.46.

Table 9 and **Table 10** provide a summary by category of each type of adverse event (complications and observations) for all 148 patients enrolled in the everesT study.

Table 9: Summary of Complications				
Category	**# of Pts**	**Percentage of Patients**	**# of Complications**	**Complication per pt-year**
Corox BP LV Lead				
Unable to implant LV lead after CS access	2	1.5%	2	0.04
Dislodgement	2	1.5%	2	0.04
High threshold / Loss of capture	1	0.8%	1	0.02
Total LV Lead Related	5	3.4%	5	0.09
RV Lead				
High DFT	1	0.7%	1	0.02
High threshold / Loss of capture	1	0.7%	1	0.02
Sensing / Detection issues	1	0.7%	1	0.02
Total RV Lead Related	2	1.4%	3	0.05
Atrial Lead				
Dislodgement	1	0.7%	1	0.02
Total Atrial Lead Related	1	0.7%	1	0.02
Lumax HF-T CRT-D				
Pocket infection	2	1.4%	2	0.04
Total Device Related	2	1.4%	2	0.04
Procedure				
Hematoma	3	2.0%	3	0.05
Pocket revision	2	1.5%	2	0.04
Pneumothorax	1	0.7%	1	0.02
Total Procedure Related	6	4.0%	6	0.11
Medical				
Atrial tachyarrhythmia	2	1.4%	2	0.04
Ventricular tachyarrhythmia	1	0.7%	1	0.02

Table 9: Summary of Complications				
Category	**# of Pts**	**Percentage of Patients**	**# of Complications**	**Complication per pt-year**
Total Medical Related	3	0.7%	3	0.05
Overall Complication Totals	**19**	**12.8%**	**20**	**0.35**

Number of Patients = 148, Number of Patient-Years = 57.1

Table 10: Summary of Observations				
Category	# of Pts	Percentage of Patients	# of Observations	Observations per patient-year
Corox BP LV Lead				
Phrenic nerve stimulation	4	2.7%	4	0.07
High threshold / Loss of capture	2	1.4%	2	0.04
Total LV Lead Related	6	4.1%	6	0.11
RV Lead				
High threshold / Loss of capture	1	0.7%	1	0.02
Total RV Lead Related	1	0.7%	1	0.02
Atrial Lead				
Dislodgement	1	0.7%	1	0.02
Total Atrial Lead Related	1	0.7%	1	0.02
Lumax HF-T CRT-D				
Sensing / Detection issues	5	3.4%	5	0.09
Total Device Related	5	3.4%	5	0.09
Procedure				
Hematoma	2	1.4%	2	0.04
Dissection of coronary sinus	1	0.7%	1	0.02
Total Procedure Related	3	2.0%	3	0.05
Other Medical				
Stroke	2	1.4%	2	0.04
Worsening CHF	2	1.4%	2	0.04
RA thrombus	2	1.4%	2	0.04
Atrial tachyarrhythmia	1	0.7%	1	0.02
Cardiogenic shock	1	0.7%	1	0.02
Other Medical	2	1.4%	2	0.02
Total Medical	10	6.8%	10	0.18
Overall Observation Totals	**24**	**16.2%**	**26**	**0.46**

Number of Patients = 148, Number of Patient-Years = 57.1

During the everesT trial 4 patient deaths were reported. None of the deaths were related to the devices under investigation.

6.2.8.3 Primary Endpoint: Effectiveness of Corox OTW(-S) BP

Objective: The goal was to demonstrate that the probability for successful Corox BP implantation (if the CS was found) is significantly higher than the borderline value of 0.75.

Results: Out of the 148 study patients, CS access was attained in 144 (97%) patients. Of the attempted Corox BP LV lead implants, 131 (91%) were successful. Of the 106 attempted Corox OTW BP LV lead implants, 97 (91.5%) were successful. Of the 38 attempted Corox OTW-S BP LV lead implants 34 (89.5%) were successful. A two-sided Pearson's asymptotic chi-square test results in a p-value of 0.71 and therefore there is no significant difference for the two models related to implant success. The Corox BP implant success rate of 91% compares well to the 91.7% implant success rate of the market released BIOTRONIK Corox OTW/Steroid Unipolar LV lead (P050023). Additionally, studies with other manufacturer's LV leads report an implant success rate in the range of 85.6 to 94.4%.

Table 11 lists the reasons for the 13 unsuccessful Corox BP LV lead implantations. Note that the percentages for the reasons may add up to more than 100% because multiple answers could be given for implant failure. **Table 12** lists the final outcome for each Corox BP implant failure.

Table 11: Reasons for Corox BP Implant Failure	
Reason	**N**
Inability to find stable position	6 (46%)
Anatomical difficulties	5 (38%)
Inability to advance the lead	4 (31%)
Lead dislodged while removing guide catheter	4 (31%)
High threshold	3 (23%)
Dissection of coronary sinus	1 (8%)
Phrenic nerve stimulation	1 (8%)
No reason given	1 (8%)
Total Corox BP Implant Failures	**13**

Table 12: Final Outcomes for Corox BP Implant Failures	
Final Outcome	**n**
Implantation of Corox OTW Unipolar lead	4 (31%)
Patient received epicardial lead	2 (15%)
Implantation of Corox LV-H lead (not FDA approved)	1 (8%)
Patient received Medtronic LV lead	1 (8%)
Patient was exited from the study by the physician	1 (8%)
Patient withdrew consent	1 (8%)
Information pending	3 (23%)
Total	**13**

Table 13 provides the individual implant success rates for Corox OTW BP and Corox OTW-S BP. There are two types of fixation mechanisms available for the Corox OTW BP LV lead: helical and straight. In order to reveal if the implant success rate was directly related to fixation type, the implant success rate for both mechanisms is presented.

Table 13: Implant Effectiveness of Corox OTW BP and Corox OTW-S BP			
Lead Type	**Successful**	**Unsuccessful**	**% Successful**
Corox OTW BP (helix)	97	9	91.5%
Corox OTW-S BP (straight)	34	4	89.5%
Total LV Implant Results	**131**	**13**	**91.0%**

Conclusions: The 95% lower bound criterion was found to be 85.1%. This is higher than the pre-determined borderline value of 75%, therefore the respective null hypothesis is rejected and the primary Corox BP effectiveness endpoint is met. There is no significant difference (p = 0.71) in complication rates between the Corox OTW BP and the Corox OTW-S BP.

6.2.8.4 Additional Data of Interest: Corox BP LV Lead Measurements

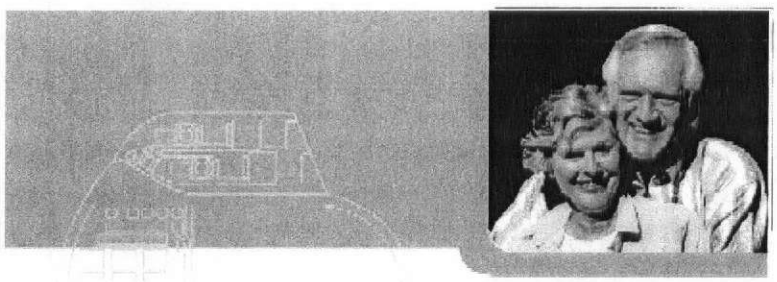
Investigators were required to use the implanted pulse generator to obtain ventricular lead measurements including pacing thresholds, lead impedance, and signal amplitude at implant and all routine follow-ups. Unless indicated, all measurements were made in a bipolar configuration at 0.5 millisecond pulse width. Intra-operative data were measured with the external pacing system analyzer or through the CRT pulse generator.

Table 14 provides a summary of lead measurements.

Table 14: Corox BP LV Lead Measurements at Different Follow-Ups

Pacing threshold @ 0.5 ms (V)					
	Imp.	**PHD**	**1M-FU**	**3M-FU**	6M-FU
n	121	128	108	99	15
Mean ± SD	1.2 ± 0.9	1.5 ± 1.3	1.3 ± 1.2	1.2 ± 1.1	0.8 ± 0.6
Min	0.2	0.3	0.3	0.4	0.4
Median	0.9	1.0	0.9	0.7	0.6
Max	4.5	7.5	7.5	5.2	2.7
Pacing impedance @ 0.5 ms (Ohm)					
	Imp.	**PHD**	**1M-FU**	**3M-FU**	6M-FU
n	115	121	103	94	15
Mean ± SD	839 ± 262	732 ± 219	806 ± 245	788 ± 202	886 ± 194
Min	362	305	374	346	646
Median	795	686	756	755	850
Max	1720	1748	1652	1379	1407
Bipolar Signal Amplitude (mV)					
	Imp.	**PHD**	**1M-FU**	**3M-FU**	6M-FU
n	105	122	95	83	11
Mean ± SD	7.8 ± 3.9	7.5 ± 4.0	8.3 ± 3.9	8.2 ± 4.0	7.8 ± 2.8
Min	2.1	0.9	1.0	0.7	4.4
Median	7.2	6.7	7.3	7.2	7.1
Max	22.0	22.0	22.0	21.7	12.9

What You Should Know About Your Pacemaker



Patient Manual

BIOTRONIK
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Doctor Name	
Doctor Phone Number	
Hospital Name	
Hospital Phone Number	
Pacemaker (Pulse Generator)	
Model Number	
Serial Number	
Date Implanted	

BIOTRONIK, Inc.
6024 Jean Road
Lake Oswego, OR 97035-5369
For more information contact:
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Table of Contents

***** NOTE *****

This manual covers multiple pacemaker models. Some features mentioned within this manual may not be available with all pacemaker models. Consult your doctor to identify the features available with your pacemaker.

1. Glossary

Ablation (cardiac) – To remove or destroy the function of cardiac tissue.

Arrhythmia - Any abnormal heart rhythm. The heart rhythm may be too fast, too slow, or irregular in its pattern. This is also known as dysrhythmia.

Asynchrony – see *Mechanical Asynchrony*.

Asystole - No heartbeat; also referred to as standstill.

Atria - The upper chambers of the heart. These act as receiving chambers for blood from the body. The sinus node is found in the right atrium.

Atrial Fibrillation - an irregular and rapid heart rhythm that starts in the upper chambers of the heart. Atrial fibrillation causes the upper chambers to quiver rapidly instead of pumping blood in a regular rhythm.

Atrial Tachycardia - a fast, regular heart rhythm that starts in the upper chambers of the heart. Atrial tachycardias are generally not life threatening.

Bi-ventricular Pacing - Stimulating the right and left ventricle to make them pump at the same time. See also Cardiac Resynchronization Therapy (CRT).

Bradycardia - Refers to a slow heart rate, usually below 60 beats per minute (bpm). Bradycardia may be caused by the sinus node not working properly, heart block, or certain medications.

Cardiac Arrest - Abrupt stop of normal circulation of the blood that could lead to death if not treated. Causes include, but are not limited to, ventricular tachycardia (VT), ventricular fibrillation (VF), or asystole.

Cardiac Resynchronization Therapy (CRT) - is a pacing method that controls the time of contraction between the right and left ventricles. By making the right and left ventricles pump at the same time (bi-ventricular pacing) or at a set delay, a Cardiac Resynchronization Therapy (CRT) device allows them to pump more efficiently. This in turn can help reduce some symptoms of Congestive Heart Failure (CHF).

***** CARDIAC RESYNCHRONIZATION THERAPY IS NOT AVAILABLE WITH ALL PACEMAKER MODELS *****

Consult your doctor to identify the features available with your pacemaker.

Cautery (electrical) - The use of heat or electrical current to cut tissue.

Congestive Heart Failure (CHF) - is a condition in which the heart fails to pump enough blood to the rest of the body, resulting in a congestion of blood in the lungs and other tissue. CHF often involves mechanical asynchrony. Mechanical asynchrony is when the right and left ventricle do not pump at the same time. Usually, both ventricles pump at the same time. With mechanical asynchrony, the right and left ventricles pump at different times and, as a result, are less efficient.

Contraindications – Situations when having this device may be inappropriate.

Coronary Sinus - The main vessel for collecting blood from the heart and returning the blood to the right atrium, the coronary sinus is commonly used for placement of left ventricular pacing leads.

Electrocardiogram (ECG, EKG) - A picture of the electrical activity of the heart that shows the heart rate and the rhythm.

Electrogram - A picture of the electrical activity of the heart as seen from within the heart chamber.

Electromagnetic Interference (EMI) - Produced by manmade invisible forces called an electromagnetic field. If the forces are strong enough, it may affect the pacemaker system. This happens on rare occasions. Please refer to the precautions listed on pages 43 for additional information concerning EMI.

Electrophysiology Testing or Study (EPS) – An electrical recording and stimulation test used to evaluate the heart's electrical system.

Endocardial - The inside surface of the heart. Endocardial leads are inserted through veins into the heart.

Epicardial - Refers to the outside surface of the heart. Epicardial leads are usually placed on the outside surface of the heart during open chest surgery.

GSM – Global System for Mobile communications; international standard for digital radio networks.

Heart Rhythm - Another term for heart beat. This term refers to the rate and regularity of the heartbeat.

Home Monitoring – Pacemakers with the Home Monitoring function are equipped with an antenna and transmitter used to send messages over a specific frequency to a mobile patient device. These messages are then transmitted via a cellular network or landline connection to the BIOTRONIK Service Center and can only be viewed by your physician via the Internet in the form of a Cardio Report.

Implanted - To be placed inside the body. The BIOTRONIK pacemaker is a system that is implanted.

Lead - An insulated wire that is used both to receive signals from the heart and to send electrical pulses to the heart. The lead is connected to the BIOTRONIK pacemaker.

Mechanical Asynchrony - is when the right and left ventricle do not pump at the same time.

Myocardial Infarction (Heart Attack) - Occurs when an artery that supplies heart muscle with blood becomes blocked. Blood does not get to the tissue and the tissue dies. Symptoms include nausea, shortness of breath, and/or pain in the chest, jaw, or arms.

Myocardium - Refers to the muscle of the heart.

Noise - Current or voltage, such as static, that can interfere with an electrical device or system.

Pacemaker - A device used to treat slow heart rates that is implanted in the body. The BIOTRONIK pacemaker consists of a battery and electronic circuitry.

Programmer - A computerized device that allows the doctor to communicate with the BIOTRONIK pacemaker. With the programmer, the doctor can reprogram the device to fit your needs and to help determine when the device needs to be replaced.

Programmer Wand - The portion of the programmer that makes communication possible between the BIOTRONIK pacemaker and the computer of the programmer.

Sinus Node - A small area of tissue in the upper right atrium from where the normal heart beat starts. This is referred to as the "natural pacemaker of the heart."

SMS (Short Message Service) – Digital communication system for the transmission of text messages for cellular telephones.

Syncope - Fainting or a loss of consciousness with recovery after a period of time. Syncope may occur suddenly or over a period of time. It may or may not be caused from your heart condition.

Tachycardia - An abnormal fast heart rate. Tachycardia rates are usually faster than l00 beats per minute (bpm).

Transcutaneous Electrical Nerve Stimulators (TENS) - Small devices used to stimulate nerve tissues to stimulate the healing process.

Transcutaneous - The process of putting a medical device or performing a procedure under the skin.

Transvenous - Placed in the heart through a vein.

Ventricle - One of the two lower chambers of the heart. Blood from the right ventricle is pumped to the lungs to receive oxygen. Blood from the left ventricle is pumped to the body.

Ventricular Fibrillation - Rapid contraction of the ventricles that results in little or no blood being pumped to the body. This is a life-threatening rhythm if left untreated.

Ventricular Pacing - Stimulation in the ventricle to prevent the heart rate from becoming too slow.

Ventricular Standstill - Failure of the ventricles to contract due to a lack of an electrical pulse. Immediate attention is required.

Ventricular Tachycardia (VT) - A fast heartbeat that starts in a single area in the ventricle. The rate is usually faster than 120 beats per minute (bpm).

2. Contraindications

***** NOTE *****

Although the contraindications for this pacemaker are evaluated by your doctor, this information is displayed here in accordance with FDA guidelines.

Contraindication is a term to indicate situations when having this device may be inappropriate.

It may not be appropriate for some patients to receive this device if the patient's anatomy does not allow the placement of this device or the patient has an artificial heart valve or other medical devices that are not compatible with the implanted pulse generator.

3. Risks, Warnings and Precautions: Keeping Safe with your Pacemaker

No medical device is perfect. Performance and reliability of the device model that you have is continuously being monitored. Should you have any concerns, you should discuss them with your physician.

3.1 Risks

Having a pacemaker involves certain risks. There is the possibility of adverse outcomes that may require additional procedures to replace, revise or remove your device.

Below is a list of some of the understood risks. Some of these adverse events are more common, but they are all unlikely to occur. Ask your physician how you can help minimize these potential risks.

Please contact your doctor if you have any uncommon pain or other problems that may be related to your pacemaker.

- bleeding around the heart
- heart damage
- collection of air or gas in the chest cavity
- wearing through the skin by the pacemaker
- infection
- lead dislodgment or movement

- blood clots or other blood vessel blockages
- vein closure
- body rejection
- muscle/nerve stimulation which may cause hiccups
- fluid accumulation around the pacemaker
- scar tissue development around the pacemaker
- pulse generator moving from original site
- faster heart rates

Note that not all risks will be noticeable to you and will require monitoring by your doctor. Therefore, it is important to adhere to your regularly scheduled follow-ups.

3.2 Warnings

A warning is a statement that is intended to make you aware that a severe adverse health consequence can arise if a certain situation is not avoided.

Magnetic Fields

Avoid equipment or other sources that generate strong magnetic fields (i.e., industrial equipment often contain large magnets). Move away from strong magnetic fields as quickly as possible. If your pacemaker is exposed to a strong magnetic field, it could temporarily interfere with your pacemaker.

Magnetic Resonance Imaging (MRI)

Avoid Magnetic Resonance Imaging (MRI) procedures. Always carry your patient identification with you at all times. Inform your heart doctor if anyone recommends a MRI procedure. Magnetic Resonance Imaging devices emit large magnetic fields. These fields can negatively affect the device.

3.3 Precautions

A precaution is a statement that is intended to make you aware of items to avoid to prevent any minor injuries or problems with or damage to your pacemaker.

Cellular Telephones

Cellular phones may be used with the following recommendations:

- Keep the phone more than 6 inches (15 cm) from the pacemaker at all times, even when it is OFF.

- Hold the phone on the ear opposite the side of the pacemaker.
- Do not carry the phone in a breast pocket over the pacemaker.
- Avoid placing the phone or its antenna over the pacemaker.

It is usually acceptable to keep the cellular telephone in any location greater than 6 inches (15 cm) from the implanted pacemaker. Carrying the cellular telephone in a handbag or in a backpack typically is okay. Testing has shown that any effects from cellular telephones have been eliminated when the phone is removed.

Metal Detectors

Avoid metal detectors. These include the walk through and the hand held types that use strong magnetic fields. These may be encountered in an airport or courthouse. Instead, inform the security personnel and show your patient identification card. The personnel will instruct you on what to do during the security check.

Electromagnetic Interference (EMI)

Avoid electromagnetic interference (EMI). These signals (static) may affect the function of any pacemaker. Example products that may emit electromagnetic interference signals are included on the next page. The pacemaker is designed to ignore all types of static. However, due to the wide variety of electromagnetic interference, absolute protection from electromagnetic interference is not possible with this or any other pacemaker.

These types of signals may be sensed by the device as either static or misinterpreted as a heart rhythm. This depends on the electromagnetic interference signal type. The device might even deliver unnecessary therapy or hold back required therapy as a result of these signals. The delivery of unnecessary pacemaker therapy may cause pain or may start a ventricular tachyarrhythmia. For these reasons, you should avoid sources of electromagnetic interference whenever possible. Typically, if you move away from the electromagnetic interference signal source, its effect on your pacemaker will go away.

Household appliances normally do not affect pacemakers. This is if the appliances are in proper working condition.

There have been reports of the interaction of electric tools or other external devices with pacemakers. This occurs when they are not properly shielded or need repair. If you believe these types of devices are affecting your pacemaker, move away as soon as possible.

Theft Detection Systems are used in all types of retail stores to prevent shoplifting. These systems utilize a wide range of methods to detect thefts. Therefore, it is possible that theft detection systems may have an effect on your pacemaker. You should quickly walk straight through this type of equipment when it is present.

Be aware that theft detection systems may be placed throughout retail stores, not just at the exits. If you feel that these systems are affecting your pacemaker, leave the store immediately.

Avoid the following equipment (and similar devices) because they may emit electromagnetic interference signals that could affect normal pacemaker operation:

- electric welders
- electric melting furnaces
- radio/television and radar transmitters
- power-generating facilities
- high-voltage transmission lines
- commercial radio/TV station transmitters (e.g., radio and television towers)
- hand-held transceivers (e.g., walkie-talkies, security, maintenance, emergency)
- microwave communications/data transmitters (e.g., TV dishes)

- paging transmitters or satellite towers
- emergency vehicle two-way radios
- electrical starting systems (of gasoline-powered equipment) if protective hoods, shrouds, etc., are removed, or if non-electromagnetic interference shielding plastic type hoods, shrouds, etc., are used
- electrical tools, anti-theft devices, and electrical appliances, if not in proper condition.

The above listed items in this section could affect normal pacemaker operation, although most general activities are acceptable and the pacemaker will not drastically change your normal daily activities (refer to Section 8 "Living an Active Life and Resuming Daily Activities")

Electro-surgical and Radiation Procedures

Be aware that your heart doctor will assure that the pacemaker's therapy is turned off during any surgical procedure, if necessary. Some electro-surgical procedures (i.e., Ablations or any procedure utilizing electrical cautery) may cause the pacemaker to either delay therapy, or deliver unintended therapy. Pacemakers may also be damaged by high doses of radiation or x-rays. Ensure that any health professional that you see is aware that you have a pacemaker.

Potentially Harmful Procedures

Before undergoing one of the following medical procedures, your doctor will perform a detailed analysis of the advantages and risks associated with the procedure. Proper function of the pacemaker system should be verified following any of these procedures, as deemed appropriate by your doctor.

Some procedures (e.g. external defibrillation, radiation therapy, Magnetic Resonance Imaging, cautery) may result in damage to the pacemaker. This damage may not be detected when testing pacemaker function after the procedure, but may show up as a malfunction or failure at a later date.

To avoid any problems, be sure to attend all scheduled appointments with your doctor.

Diathermy (generation of heat in tissue by electrical currents), transcutaneous electrical nerve stimulation (TENS), Magnetic Resonance Imaging, and electrical cautery have been reported to interfere with electrocardiograph (ECG) monitoring equipment. Your doctor will continuously monitor your cardiac activity during these procedures.

External Defibrillation (Potentially Harmful Procedure)

In the event your doctor is unaware you received an external shock, be sure to notify him/her immediately. The BIOTRONIK pacemaker is protected against energy normally encountered from external defibrillation. However, any implanted device may be damaged by high-energy external defibrillation procedures. After delivery of an external defibrillation shock, your pacemaker should be checked by your doctor.

Diathermy (Potentially Harmful Procedure)

Avoid diathermy therapy (generation of heat in tissue by electrical currents) because it is not recommended for pacemaker patients due to possible heating effects of the pacemaker and at the implant site. If diathermy therapy must be used; it should not be applied in the immediate vicinity of your implant. Following a diathermy procedure, your pacemaker should be checked by your doctor.

Radiation (Potentially Harmful Procedure)

Avoid radiation, because like all pacemakers, BIOTRONIK pacemakers may be damaged by radiation. Your doctor may need to check your pacemaker after exposure to radiation. Two types of radiation examples are used for Imaging (called x-ray and nuclear medicine), and direct application of radiation on affected site (called radio therapy).

Lithotripsy (Potentially Harmful Procedure)

Avoid lithotripsy treatment (sometimes used to treat kidney stones). This procedure is not recommended for pacemaker patients since electrical and/or mechanical interference with the pacemaker is possible. Use the greatest possible distance from the pacemaker if this procedure must be used. The pacemaker system should be checked by your doctor after the procedure.

Cardiac Ablation (Potentially Harmful Procedure)

Avoid applying energy near the implanted lead system whenever possible. Prior to performing an ablation procedure (procedure to eliminate conduction path within heart tissue), your doctor will shut off the pacemaker. The pacemaker system should be checked by your doctor after the procedure.

Patient Conditions

Changes to your heart condition, drug doses, or other health conditions may have an effect on the success of your pacemaker therapy. In order for your doctor to monitor any changes in your condition, please follow your doctor's appointment schedule.

4. The Natural Heart at Work

4.1 The Structure of the Heart

Your heart is a muscle about the size and shape of a clenched fist. It has four chambers. The two upper chambers are called atria and the two lower chambers known as ventricles. The right atrium and ventricle pump blood from your body to your lungs. The left atrium and ventricle pump blood from your lungs to your body.

Your heart is unlike any other muscle in your body. It has the amazing ability to contract, or squeeze, on its own. Every time your heart contracts, oxygen and other nutrients are sent throughout your body. This process is controlled by a unique electrical system.

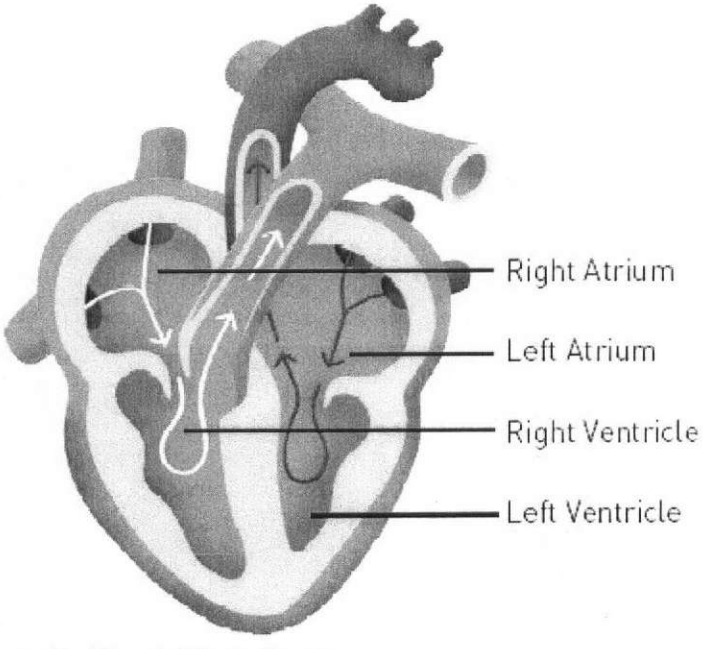


Figure 1. Heart Chambers

4.2 The Heart's Electrical System

The heart's electrical system is found in the walls of the heart itself. The main controller of this system is a natural pacemaker found in the right atrium. It is called the sinoatrial (or S-A) node. Just as a conductor directs a symphony, the SA node directs the rhythmic, regular beating of your heart. It creates small electrical signals in response to messages from your brain.

These signals quickly travel through both atria to the ventricles along the conduction pathway, which consists of the A-V Node, the Bundle of His, and the Purkinje Fibers. The electrical impulse tells your heart to contract. When working normally, your heart beats in a stable, synchronous rhythm. It automatically adjusts itself to supply the oxygen your body needs whether you are reading a book, or going up a set of stairs.

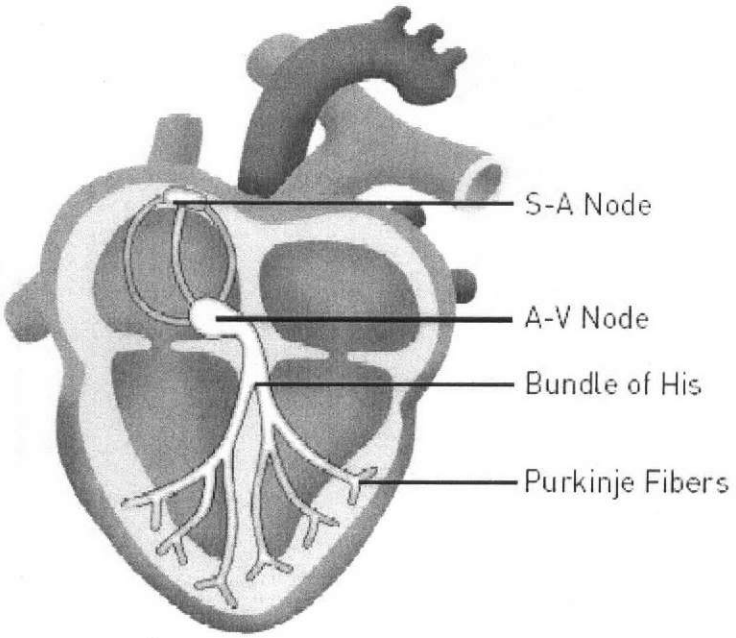


Figure 2. Heart Electrical System When a Pacemaker is Needed

Sometimes, the heart's ability to beat regularly is compromised. The natural pacemaker may be unable to supply electrical impulses, or the natural electrical pathways in the heart's walls may be blocked. Without the ability to rhythmically beat, the heart is unable to supply all the fuel your body needs to walk, swim, garden or cook. This is where a BIOTRONIK pacemaker is designed to help.

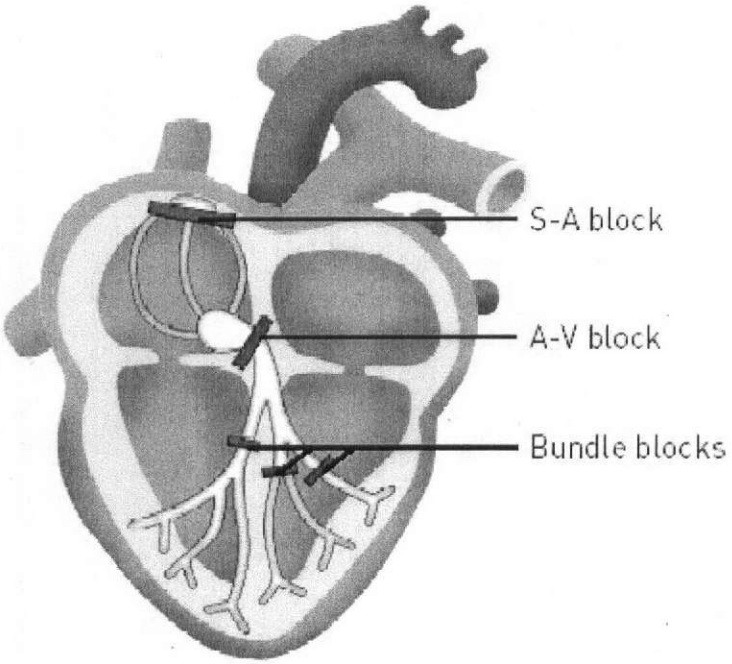


Figure 3. Blocks in Heart Electrical System

5. Types of Heart Conditions

Congestive Heart Failure (CHF)

Congestive Heart Failure (CHF) is a condition in which the heart fails to pump enough blood to the rest of the body, resulting in a congestion of blood in the lungs and other tissue. Congestive Heart Failure often involves mechanical asynchrony. Mechanical asynchrony is when the right and left ventricle do not pump at the same time. Usually, both ventricles pump at the same time. With mechanical asynchrony, the right and left ventricles pump at different times and, as a result, are less efficient.

Cardiac Arrhythmias

A cardiac arrhythmia is an abnormal heart rhythm. This is when the heart beats too fast, too slow, or irregular in its pattern. The following sections explain the types of arrhythmias a pacemaker can treat.

Bradycardia

In addition to fast heartbeats, there are times when a patient's heart may beat too slowly. This condition, called bradycardia, occurs when there is a slowing or block in the electrical system of the heart. During bradycardia, the heart does not contract fast enough to supply sufficient blood to your body. As a result, people may feel tired or even faint.

Ventricular Tachycardia (VT)

A number of medical disorders can disrupt the normal rhythm of your heart. An electrical pulse may start from a place in the lower portion of your heart called the ventricle. These pulses may speed up your heart to a rate greater than 100 beats per minute for more than three beats, a condition that doctors call ventricular tachycardia (VT). During ventricular tachycardia, each heart beat pumps less blood than normal. Therefore, the body and brain receive less oxygen. Ventricular tachycardia may cause blurred vision, dizziness, blackouts, or even unconsciousness.

Ventricular Fibrillation (VF)

It is possible that many electrical pulses start from different places in the ventricles at a very fast rate. Each pulse causes the heart muscle nearby to contract (tighten-up). When this happens, the heart rate becomes very irregular causing little or no blood to be pumped through the body. This condition is known as ventricular fibrillation (VF). Ventricular fibrillation (VF) may result in heart rates of greater than 300 beats per minute and cause patients with this condition to faint due to the lack of oxygen carrying blood to the brain. Eventually, if left untreated, ventricular fibrillation will cause the heart to stop beating completely.

Atrial Tachycardia (AT)

Atrial Tachycardia or Flutter is a rapid, regular rhythm. This is where the atria (upper chambers of the heart) beat very rapidly. Although the atria beat at a rate greater than 200 beats per minute during atrial tachycardias, the ventricles (lower chambers) beat at about half that rate. Therefore, blood is not pumped as efficiently during atrial tachycardias as it is during normal heart rhythms. Symptoms may include pounding of the heart, heart palpitations or feeling clammy or rundown. Atrial tachycardias are generally not life threatening and often stop on their own. However, they can also last for long periods of time (several days). Many times, you might not even notice that these types of arrhythmias are occurring.

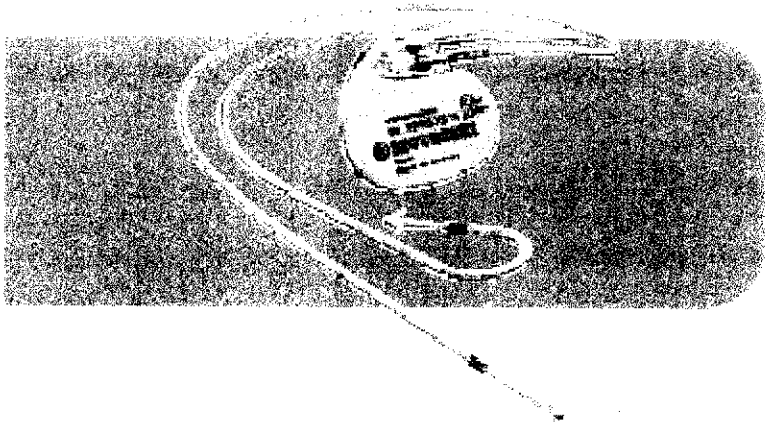
Atrial Fibrillation (AF)

Atrial Fibrillation is an irregular and rapid heart rhythm originating in the atria that occurs in over 2 million Americans. During Atrial Fibrillation, the atria quiver and do not pump blood effectively. Blood in the atria may pool and clot. If a clot breaks loose and moves to the brain, a stroke can result. About 15 percent of strokes occur in people with atrial fibrillation.

When Atrial Fibrillation occurs, the heart's electrical signals begin from multiple locations (sites) in the atria. These signals travel erratically throughout the atria. This causes the upper chambers to quiver rapidly instead of pumping in a regular rhythm. When Atrial Fibrillation occurs, the ventricular rate (felt as your pulse) may also be irregular and can range up to 200 beats per minute.

Atrial Fibrillation can prevent the atria and ventricles from working together - the synchronized beating of your heart is lost and the heart's pumping efficiency is reduced. This is why you may feel tired and weak. Not everyone experiences the same symptoms. Some people may have Atrial Fibrillation without knowing it. Symptoms may include heart palpitations (described as a sudden pounding, fluttering, or racing feeling in the chest), feeling tired, dizziness, shortness of breath, and/or pressure or discomfort in the chest. Atrial Fibrillation may interrupt household duties, work schedules, and other activities. These types of arrhythmias should be treated because if allowed to occur too long or too frequently they can lead to serious health consequences (e.g., stroke).

6. A Look at a Pacemaker



A pacemaker is a small medical device that provides electrical signals much like your natural pacemaker. In this way, your heart is able to continue its job of pumping blood. Moreover, you're able to continue leading an active and productive life.

6.1 The Pacing System

A pacemaker is only one part of a pacing system. A pacing system is made up of a pulse generator, commonly referred to as a pacemaker, and one or two thin insulated wires called leads.

6.2 The Pulse Generator

A pulse generator is a small, thin device that typically weighs less than an ounce. It is usually placed just under the skin near your shoulder. Inside the pulse generator is a highly advanced microcircuit and a battery. The microcircuit is a tiny computer that senses the heart's natural activity. When necessary, it delivers very small electrical impulses called pacing pulses to the heart. These pacing impulses cause your heart to beat, just as your natural pacemaker would. The battery is a Lithium Iodide cell that is designed to last a long time, commonly five to ten years. When the battery is getting close to the end of its useful life, the pacemaker will notify your doctor during a normal check-up visit. When this occurs, you will be scheduled to receive a new pacemaker (with a fresh battery) in a procedure similar to when you received your current device.

An overview of the different types of pacemaker systems is provided in Section 7.2.

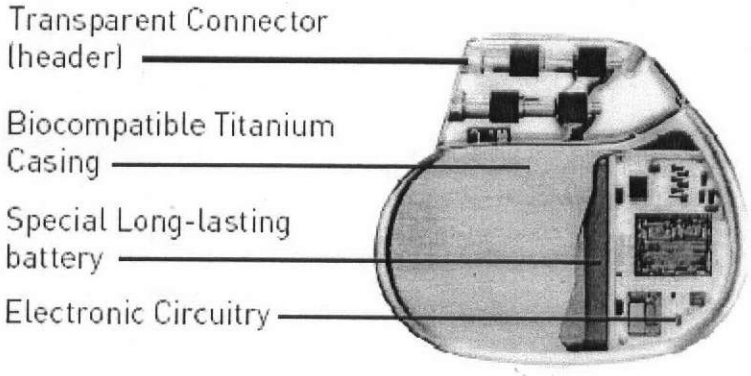


Figure 4. Pacemaker Components

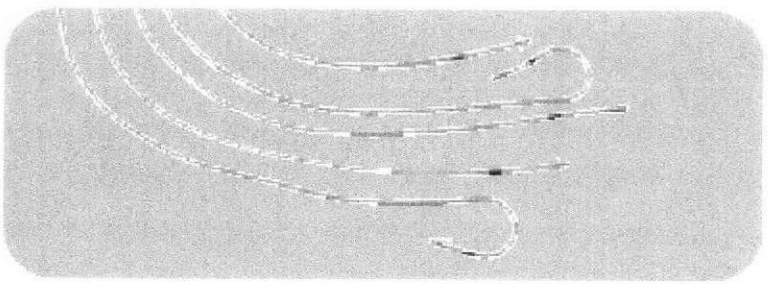
6.3 The Lead

The lead is a very thin, strong, wire coil covered with insulation that connects the pulse generator to your heart. The wire allows the pacemaker to sense your heart's natural rhythm, and carries the small electrical impulses from the pulse generator to your heart.

There are three types of pacemakers:

- Single-chamber pacemakers
- Dual-chamber pacemakers
- CRT-Ps (Cardiac Resynchronization Therapy Pacemakers)

Your doctor chooses which type of pacemaker will give you the greatest benefit. Single-chamber pacemakers have only one lead that is inserted into either the right atrium or the right ventricle. Most dual-chamber pacemakers have two leads with one going to the right atrium and the other to the right ventricle. A CRT-P consists of three leads: one in the right atrium, one in the right ventricle, and one in the coronary sinus to pace the left ventricle.



7. How the Heart and Pacemaker Work Together

7.1 Implantation of Your Pacemaker

Although the method of implantation varies a little with each physician, the procedure is relatively routine. For most people, only a local anesthesia is needed. There is usually an incision under the collar bone and the pacemaker is placed in a small "pocket" in the skin near your shoulder, as shown in Figure 5. You may expect to be in the hospital for a day or two, although on occasion your stay may be a little longer.

7.1.1 Possible Complications

Although unlikely, some possible complications with implanted pacemakers include:

- Air in the vein
- Lead dislodgement
- Heart wall puncture
- Muscle or nerve stimulation
- Ventricular tachyarrhythmias
- Allergic reaction
- Infection
- Lead perforation
- Lung puncture
- Excess blood around the pacemaker

Your doctor will describe the procedure to you, including any possible complications you should know about. A detailed list of risks associated with implanted pacemakers is provided in Section 3.

7.2 Types of Pacemaker Systems

The interaction between your heart and the pacemaker is determined by:

- How many chambers are being monitored and paced. For example whether your pacemaker is a single-chamber system, dual-chamber or three-chamber.
- How the pulse generator is programmed.
- The status of your natural conduction system.

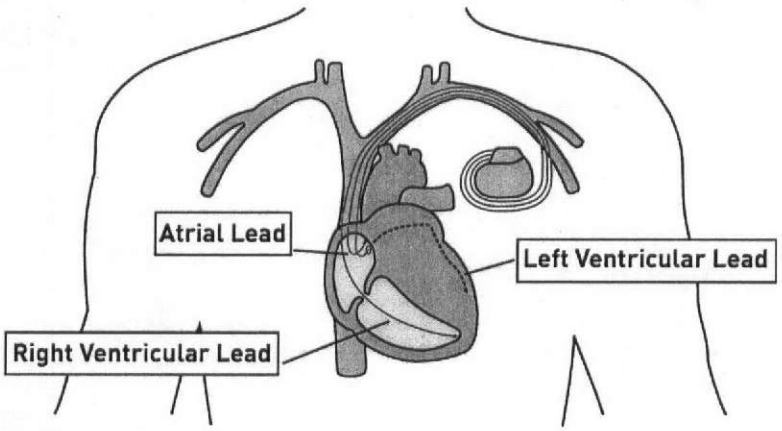


Figure 5. Pacemaker System Configuration

Referring to Figure 5 the different systems are defined as follows:

- A single-chamber system senses the natural electrical signals in only one chamber of your heart, either the atrium or the ventricle. It uses only one lead. If it does not detect a natural signal within a certain period, it sends a pacing pulse. In this way, that chamber should never contract at a rate slower than is considered safe by your doctor.

- A dual-chamber system senses the natural electrical signals in both the atrium and the ventricle by using two leads. It can send pacing pulses to one or both chambers. In this way, it coordinates the contractions of all the chambers of your heart.

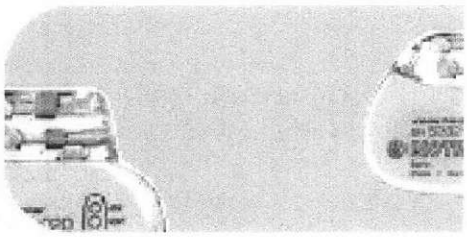
- A three-chamber system is capable of Cardiac Resynchronization Therapy (CRT). This pacemaker uses a pacing method that controls the relative time of contraction of the right and left ventricles. By re-synchronizing the right and left ventricles, a Cardiac Resynchronization Therapy device allows them to pump more efficiently. This in turn can help ease some symptoms of Congestive Heart Failure.

Many pacemakers today have features designed to enhance the pacing system. One example is rate adaptation. This feature uses a special sensor that detects when your body may need a faster heart rate. When this happens, the pacemaker sends pacing pulses to the heart at a faster rate. This helps to get more oxygen and nutrients to your muscles when you exercise.

Figure 6. Example of a Pacemaker Programmer

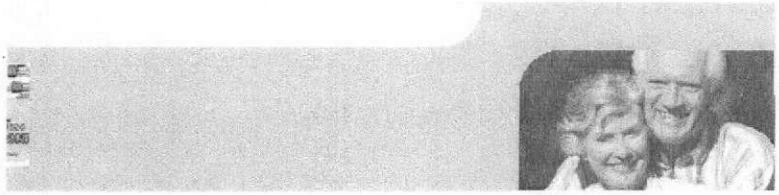
Almost all pacemakers today are programmable. This means that your doctor can change the behavior of the pacemaker to meet any changes in your heart's natural conduction system. Your doctor does this with a programmer that communicates with your pacemaker by using specially coded radio waves. That means the pacemaker can be reprogrammed safely without another surgical procedure or any discomfort to you.

8. Living an Active Life and Resuming Daily Activities



You and your doctor have determined you need a pacemaker. Naturally, you are wondering how this small device will affect your life. As a pacemaker recipient, you join a special group of over two million people worldwide who enjoy active lives, thanks in part to their implanted pacemakers. Many of these people have pacemakers manufactured by BIOTRONIK. BIOTRONIK has over 40 years of experience building reliable, high quality pacemakers.

Reading this booklet may help you in your effort to regain a productive, active life with your new pacemaker. It will answer many commonly asked questions and provide some information about how pacemakers work. After reading this booklet, be sure to ask your doctor any remaining questions.



Immediately After Surgery

For the most part, you should be able to resume all normal activities after just a short wait. Here are a few things to consider immediately after your pacemaker is implanted:

- Carefully follow instructions from your doctor on how to keep the incision clean and dry.
- You may experience redness, swelling or mild soreness at the site of the implant.
- Avoid wearing tight clothing around the areas of the implanted device, i.e., one-piece swimsuits, etc. This will help to avoid irritating the skin near the implant site. In rare cases, implantable devices have worn through the patient's skin.
- Avoid unnecessary contact to your pacemaker site. Take care to ensure that the area around the device is not hit or bumped against anything.
- Avoid making sudden or strenuous movements (i.e., gardening, some exercises, golf swing, housework, picking up grandchildren). Such movements could possibly cause your wound to reopen or delay healing of the area around your pacemaker.

- Avoid lifting and carrying heavy objects from your shoulder (i.e., backpacks, purses), as these activities may put pressure on the pacemaker site and reopen or delay healing around your pacemaker.

- It may take a couple of weeks for the leads to become secure in your heart. Quick movements of your arms or activities such as raising one's arms above the head may lead to movement of the wires (leads) that connect the pacemaker to your heart. To prevent the leads from moving during the first few days after the implantation, you should avoid any sudden or strenuous activity during that time. Your physician will let you know when you may resume the activities that interest you.

- After your physician releases you to resume your normal activities, you will still want to refrain from or modify activities that could affect your pacemaker. For example, when shooting firearms, you should never place the butt of the gun directly over your pacemaker.

A list of activities that should be avoided after implantation is provided in Section 3.3. When you have recovered from the implantation of your pacemaker, you should be able to return to normal activities, including:

- Moderate exercise as indicated by your doctor
- Return to your job
- Drive your own car and other travel
- Yard work
- Sports and hobbies
- Bathe and shower - water will not be a threat to your pacemaker
- Normal sexual activity

Keep in mind that if an activity makes you feel worse, you should discontinue the activity immediately, and talk to your doctor about it.

8.1 Electromagnetic Interference

Examples of sources of electromagnetic interference that could affect the function of your pacemaker are listed below.

Electrical Equipment:

BIOTRONIK pacemakers are specially designed to avoid interference caused by electrical equipment. In general, any electrical device normally used at home, at the office, or in your car is safe to use.

This includes:

- Computers and typewriters
- Fax and copy machines
- Vacuum cleaners
- Washers and dryers
- Kitchen appliances
- Stereo equipment and televisions

If an electrical or magnetic field is strong enough, it could potentially cause temporary interference with your pacemaker. This interference typically causes either an unusually slow or fast pulse rate. The following contains information about specific situations.

Vehicle Ignition Systems:

Although driving a car is safe, it is a good idea to stay 12 inches away from the ignition system found under the hood. If you do get too close and feel any symptoms, simply step away from the hood. The symptoms should go away immediately.

Power Tools:

Although most power tools should be safe, any could potentially interact with your pacemaker. You might consider having a person who is aware of your condition be with you when you use any of these devices for the first time. Should you become lightheaded or dizzy, turn off the tool or move away from it. The symptoms should go away immediately.

Radio Transmitters:

Normal "ham" and CB radios should be safe to use. However, it is a good idea to stay away from high-power transmitters like military radar installations, microwave dishes, and radio towers. In addition, you should avoid arc welders and electric smelting furnaces.

Airport Metal Detectors:

Avoid airport metal detectors. These include the walk through and the hand held types that use strong magnetic fields. Instead, inform the security personnel and show your patient identification card. The personnel will instruct you on what to do during the security check.

Electronic Article Surveillance:

Some stores have anti-theft devices called Electronic Article Surveillance systems, or EAS, that could interfere with your pacemaker. Although you should be able to safely walk through an EAS, you should not linger in-between the device's vertical walls. Again, any interference your pacemaker receives should disappear as soon as you move away from the devices.

Cellular Telephones:

Most cellular telephones today should be safe to use. As a precaution, you should not store a cellular telephone in a breast pocket. In addition, you should make sure that while using the telephone, it is held up to the ear that is on the opposite side of the pacemaker. For example, if your pacemaker incision is on your left side, you should hold the telephone to your right ear.

8.2 Medical Devices and Procedures

Some medical devices and procedures could affect your pacemaker adversely. Refer to Section 3 for a full list of risks, warnings, and precautions.

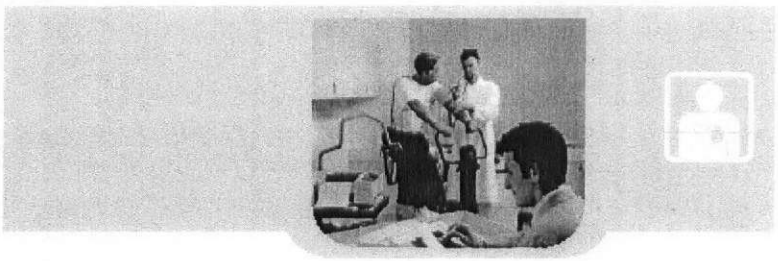
If you have any questions or concerns, consult your doctor. He or she is best suited to answer your question. You may contact BIOTRONIK 24-hours a day at 1-800-547-0394.

9. Follow-up Care

Today's pacemakers are designed to provide reliable therapy for extended periods. However, your doctor will need to check your pacemaker on a regular basis. This check is called a follow-up. Regular follow-ups will ensure that the pacemaker's programming continues to meet your heart's needs.

Your pacemaker should last many years. However, since it uses a battery, it does have limits to how long it will be of service. Each time your doctor checks your pacemaker, the status of the battery will be checked. The pacemaker will indicate to your doctor when the battery has reached "Elective Replacement Indicator". At this time, your pacemaker will still have several months of service. However, to be safe, your doctor will probably schedule you to have your pacemaker replaced with a new one.

Your pacemaker will be programmed to best meet your needs when it is implanted. Over time, those needs may change. Visiting your doctor regularly will ensure that your pacemaker continues to meet your pacing needs. In addition, your doctor will be able to assess the conditions of the leads with each visit, giving you peace of mind that your pacemaker system is functioning appropriately.



If you should feel any symptoms similar to how you felt before receiving a pacemaker, you should immediately contact your doctor. In addition, you should contact your doctor if you notice any of the following signs or symptoms:

- Red, draining, hot, or unusually tender incision
- Fatigue
- Difficulty breathing
- Swelling of your legs, ankles or wrists
- Chest pain or discomfort
- Dizziness
- Lightheadedness
- Shortness of breath
- Fainting spells
- Persistent hiccups
- A very fast, slow, or abnormal pulse

10. BIOTRONIK Home Monitoring

***** NOT AVAILABLE WITH ALL PACEMAKER MODELS *****

Consult your doctor to identify the features available with your pacemaker.

Your physician may have selected to implant a special pacemaker (Home Monitoring pacemakers) that monitors your heart and sends information regarding your pacemaker to your physician – all while you are at home or anywhere else. The only thing that you need to do is carry the specialized device (called CardioMessenger, see Section 10.1) that you received with your pacemaker with you.

The Home Monitoring pacemakers are equipped with a special transmitter. Using an antenna in the pacemaker, the implant automatically sends signals containing medical and technical information from your heart to the CardioMessenger. This information is then forwarded from the CardioMessenger to your treating physician. This allows your physician to "keep an eye" on you, even when you are far away, and evaluate your condition based on accurate and up-to-date clinical information.

10.1 CardioMessenger

Your pacemaker sends medical and technical information to a mobile device similar to a cellular telephone called the CardioMessenger. The CardioMessenger automatically forwards data from your implant to BIOTRONIK via the cellular telephone network or landline connection. Your physician can then view this data on a secure BIOTRONIK Internet site.

The CardioMessenger is distributed by your physician and is ready for operation. Please ensure that you have in your possession the following components:

1. CardioMessenger
2. Charging station
3. Wall Mounted Power supply
4. Telephone Cable
5. Belt clip (attached to the CardioMessenger)
6. Carrying straps
7. Technical manual

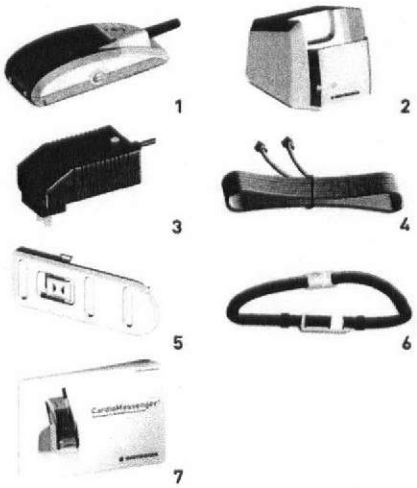


Figure 7. CardioMessenger Components

10.2 Where is a Suitable Place for My CardioMessenger?

There should be a minimum distance of 20 cm (6 inches) and a maximum distance of 2 m (6 feet) between the CardioMessenger and your implant.

Do not carry your CardioMessenger in your breast pocket.

Verify that the CardioMessenger can connect to the cellular telephone network (for data transmission) at its place of storage, for example, on your bedside table. To do this, turn on the CardioMessenger at the place where you plan to keep it. If you succeed in connecting to the cellular telephone network, a green light will begin slowly blinking in approximately 5 minutes. This indicates that the data can be transmitted without problems.

The CardioMessenger must be turned off in airplanes, hospitals, and in the vicinity of sensitive measuring devices. As with every electrical device, the CardioMessenger should be kept away from water.

10.3 How the Device Contacts Your Physician

Your physician programs your implant to transmit its data daily at a certain time, for example, every night at 2a.m. This provides your physician an overview about the progress of your illness and your treatment. It also allows your physician to detect any changes in your physical status early on and adjust your implant to suit your needs.

In case of sudden changes in your heart rhythm or your implant, your physician can be immediately informed via email, fax, or text message for cellular telephones.

10.4 Patient Triggered Report

Your physician may want you to send (transmit) data manually. He will give you specific instructions on when and how this is done. Typically your physician will turn this feature on in the event you're feeling fatigued or not feeling well.

10.5 How Do I Charge My CardioMessenger?

As a rule, the CardioMessenger is charged and ready for operation when you receive it from your physician. To recharge, just place the CardioMessenger in the charging station. Plug the power supply into the power outlet (wall socket), and then connect the small plug from the power adaptor into the charging station. The CardioMessenger is automatically charged as it sits in the charging cradle.

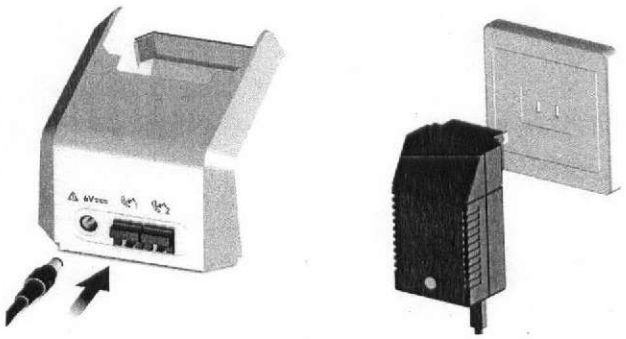


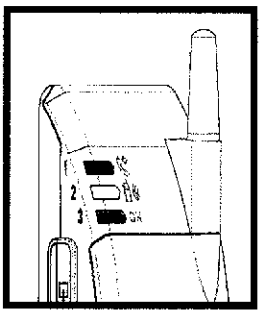
Figure 8. Connections for Charging

10.6 The Function of the Lights: At a Glance

Your CardioMessenger has five lights: four on the mobile part of the CardioMessenger and one on the charging station.

The Lights

The three top lights on your CardioMessenger resemble a traffic light and thus simplify use. The following is a short description of the lights' functions.



Red: Your physician can activate this light. When the red light flashes, your physician is requesting that you call their office.

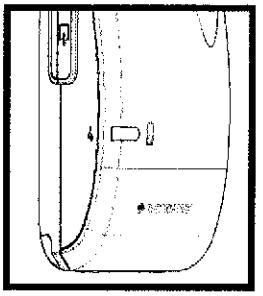
Yellow: When the yellow light flashes or becomes illuminated for a short period of time, your CardioMessenger is not ready for operation. If this status persists for longer than one day, then try to find another suitable place to keep your CardioMessenger.

Green: When the green light flashes, your CardioMessenger is working properly. The data can be transmitted.

Green/Yellow:

The green and yellow lights will flash together if a message is pending. A pending message is a message sent from the implant that has been received by the CardioMessenger, but could not be relayed to the service center within 24 hours. In this case, the mobile part of the CardioMessenger will need to be returned to the charging station in order to transmit the message via the landline connection.

The Battery Status Light



The fourth light is the battery status light and is located at the bottom of the CardioMessenger. This light can be red, yellow, or green.

Red: The CardioMessenger needs to be charged.

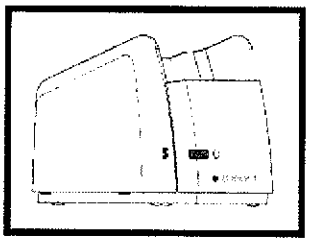
Yellow: The CardioMessenger is being charged. However, if the light is flashing yellow, there is a problem. Please contact your physician if this is the case.

Green: The CardioMessenger is charged and ready for operation.

The Light on the Charging Station

The fifth light is located on the charging station of the CardioMessenger. The display can only be illuminated when the charging station is connected to a power supply via the power adaptor.

Green: The charging station of the CardioMessenger is ready for operation.



11. Questions For My Doctor:

- **What kind of pacemaker do I have?**
- **Do I have a Home Monitoring pacemaker?**
- **Is my pacemaker a Cardiac Resynchronization Therapy (CRT) device?**
- **How often do I have to see my physician for follow-up visits?**
- **Can I partake in my favorite activities?**

Other:

NOTES

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