CARILLON® Mitral Contour System® (XE2)

Instructions for Use

CE 0344

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INSTRUCTIONS FOR USE

Cardiac Dimensions®, Inc. CARILLON® Mitral Contour System® (XE2)

I. System Description

The Cardiac Dimensions®, Inc. CARILLON® Mitral Contour System® (CMCS™) is a medical device and consists of the following components:

1) A proprietary implant intended for permanent placement in the coronary sinus (CS)/great cardiac vein (GCV)
2) A catheter-based delivery system which consists of a curved CMCS delivery catheter (3.2mm outer diameter) and a handle assembly
3) A sizing catheter to enable the physician to estimate the overall CS/GCV dimensions so that an appropriately sized implant may be selected

The implant is attached to the handle assembly and is delivered through the CMCS delivery catheter to the coronary vein along the posterolateral aspect of the mitral annulus. The implant is designed to re-shape the mitral annulus to reduce annular dilation and mitral regurgitation.

The specific components of the CARILLON Mitral Contour System are described as follows.

- **Implant**

  The XE2 implant is made of nitinol and titanium and is manufactured in different lengths and with different anchor sizes to accommodate individual venous anatomy. The implant is composed of a distal anchor (positioned in the GCV), proximal anchor (positioned in the CS), ribbon connector (joining the anchors), proximal crimp tube, and distal crimp tube. The lock bump and arrowhead help secure their respective eyelets in the locked position (Figure 1.1). The implant is designed to be deployed, tensioned, and secured in the coronary vein.

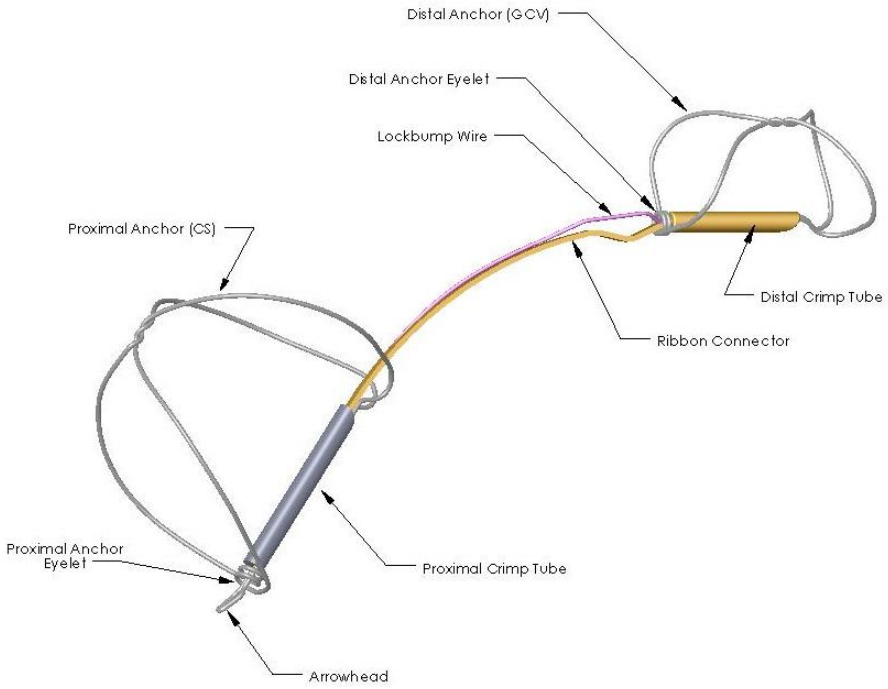

Figure 1.1: CARILLON XE2 Implant Illustration (actual device is uniform silver in color)

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- **Delivery System**

  CMCS Delivery Catheter:

  The delivery catheter facilitates percutaneous entry of the sizing catheter, attachment of the cartridge, delivery of the implant, engagement of the locking mechanism of the distal anchor, and recapture of the implant (if necessary).

  The delivery catheter is composed of a metal braid reinforced polymer sheath with a luer "Y" connector and will withstand a maximum of 1700 KPa (246 psi) injection pressure. The catheter tip is radiopaque. The delivery catheter is curved at its distal end and has a 3.2 mm outer diameter and 70 cm effective length. The inside diameter is 2.5 mm and will accept a 0.035" (0.89 mm) guidewire or a 7F (2.3 mm) outer diameter diagnostic or deflectable catheter (Figure 1.2).

  The straight port is used for advancement and removal of a measuring device and introduction of the implant. The side port may be used for injection of radiopaque contrast medium.

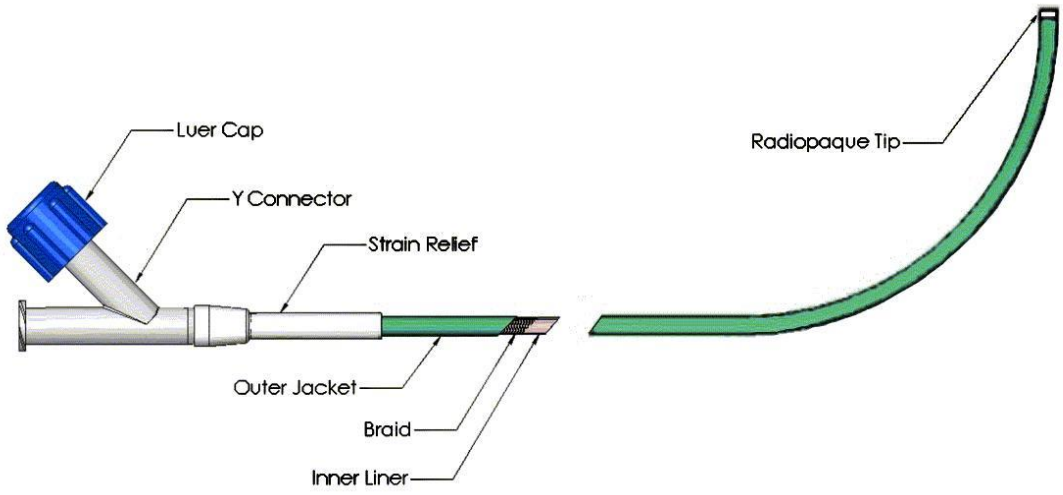

Figure 1.2: CMCS Delivery Catheter

Handle Assembly:

The handle assembly is composed of a cartridge, a sheath/pusher assembly and a handle assembly with cartridge window, rotating knobs, and release safety (Figure 1.3). The distal end of the cartridge (male luer) connects to the luer fitting of the straight port on the proximal end of the delivery catheter.

- In its packaging, the cartridge contains the implant, which is folded in the unlocked position within the cartridge lumen. It also houses the distal portion of the sheath/pusher assembly, which is connected to the implant. During delivery, the implant is manually pushed from the cartridge into the delivery catheter.
- The sheath/pusher assembly is composed of a lock wire and tether wire, a pusher, and a polymeric sheath for locking the proximal anchor. The combination of the pusher and wires aid in the placement, deployment, and decoupling of the implant from the handle assembly. They provide a mechanism for assuring that the implant is connected to the handle assembly until the appropriate time for decoupling (using the release safety & release knob).

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- The handle facilitates deployment, locking, decoupling, and recapture of the implant. This is accomplished by rotating knobs that enable controlled movements of the delivery catheter, the implant, the sheath/pusher, and the decoupling mechanism. The release safety must be removed prior to decoupling the implant from the handle assembly.

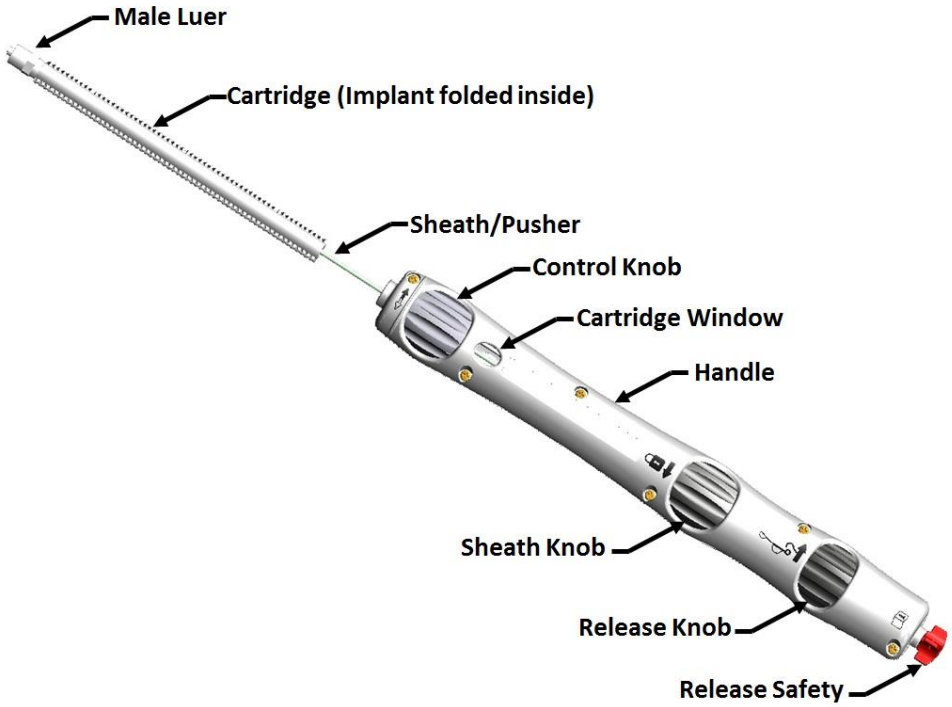

Figure 1.3: CARILLON Handle Assembly

- **Sizing Catheter**

  The sizing catheter is used to estimate the overall CS/GCV dimensions so that an appropriately sized implant may be selected. The sizing catheter is inserted into the delivery catheter and advanced until the most distal marker band is aligned with the radiopaque marker at the tip of the delivery catheter. Venous size estimates are then determined by the physician using venograms captured with fluoroscopy.

  The sizing catheter consists of polymer shaft, a hub with a luer connector at the proximal end, a polymer strain relief, radiopaque marker bands, and a clear distal sleeve covering the marker bands (Figure 1.4).

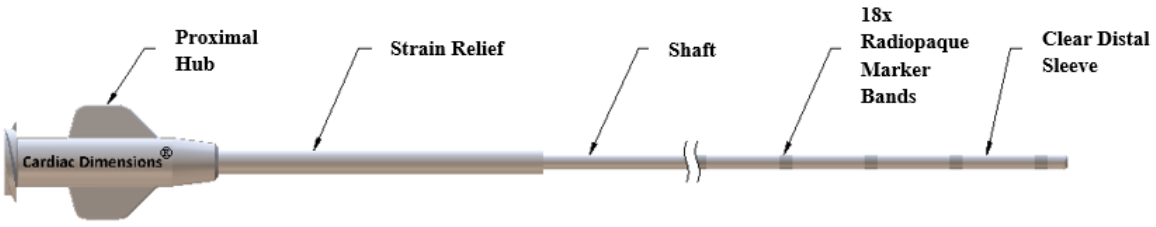

Figure 1.4: CARILLON Sizing Catheter

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II. Indications

The CARILLON Mitral Contour System is indicated for use in patients with functional mitral regurgitation who are symptomatic (NYHA Grade ≥ 2) despite treatment with guideline directed medical therapy.

CARILLON Mitral Contour System implantation can be considered in case of:

- Presence of symptomatic secondary mitral regurgitation not amenable by conventional guideline directed treatment.
- Presence of annulus dilatation as primary contributor to the significant MR.
- Absence of mitral valve leaflet abnormalities where the effect of the abnormalities outweighs any beneficial effects of (partial) annulus reduction achieved by the CARILLON implant.

III. Contraindications

The CARILLON Mitral Contour System is contraindicated for use in:

- Patients with existing devices in the CS/GCV
- Patients who have had a mitral valve replacement or a mitral annuloplasty ring implant

IV. Intended Use

The CARILLON Mitral Contour System is intended to reduce secondary mitral regurgitation. The Carillon implant is recommended for use when a multi-disciplinary and specialized heart team has determined that a reduction of ≥1 MR grade is reasonably expected within 12 months of implantation.

- Results from pre-market clinical studies suggest that not all improvements due to the Carillon implant are observed acutely during the implant procedure. Results from TITAN show that 80% of implanted patients (59%-92% with 95% confidence) have ≥1 MR grade reduction at 12 months, as well as a 31% relative reduction in mitral annular area at 12 months. NYHA scores were also improved in implanted patients at 12 months and sustained at 24 months.[1] Cardiac Dimensions is in the process of conducting post-market clinical follow up studies to further evaluate the effectiveness of the Carillon permanent implant.

V. User Requirements

The CARILLON Mitral Contour System is intended for use only by physicians who have expertise in the techniques of vascular catheterizations and who have been trained on the proper use of the CARILLON system.

Implant placement should only be performed at institutions where emergency surgery can be readily arranged (either within the implanting institution, or via patient transport to an alternate institution with emergency surgery capability).

The decision to implant the CARILLON Mitral Contour System should be determined by a multidisciplinary and specialized heart team.

[1] Siminiak, T, Wu JC, Haude M, Hoppe UC, Sadowski J, Lipiecki J, Fajadet J, Shah AM, Feldman T, Kaye DM, Goldberg SL, Levy WC, Solomon SD, Reuter DG. Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN Trial. Eur J Heart Fail. 2012 Aug; 14(8): 931-8.

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VI. Warnings

- If the patient experiences prolonged third degree A-V block or asystole at any point during the procedure, terminate the procedure.
- If the distal anchor struts are inadvertently collapsed by over advancement of the delivery catheter to the DA twist, recapture and remove the entire implant. See Step 5 – Implant Recapture.
- The implant cannot be recaptured with the handle assembly once it is decoupled from the handle assembly.
- If, at any point during the procedure, a coronary venogram demonstrates evidence of a clinically significant venous dissection in the implant target zone, terminate the implant procedure and monitor the patient.
- If, at any point during the procedure, a coronary venogram or echocardiogram demonstrates evidence of a clinically significant venous perforation, terminate the implant procedure. Monitor the patient for pericardial effusion and assess the need for pericardial drainage.
- If clinically significant denuded venous tissue is observed on a component of the CARILLON Mitral Contour System following implant recapture, terminate the implant procedure. Monitor the patient for pericardial effusion.
- If placement of the implant causes a significant change in the electrocardiogram (ECG), recapture and remove the implant.
- If placement of the implant causes a significant reduction in the coronary arterial dimensions of a clinically significant artery and unresponsive to intracoronary nitroglycerine, then recapture and remove the implant. Confirm a return to baseline arterial dimensions.

VII. Potential Complications and Adverse Events

The following anticipated events (in alphabetical order) have been identified as possible complications of the CARILLON Mitral Contour System procedure and includes those associated with diagnostic coronary angiography as well as those associated with the delivery, permanent placement, and recapture of the CARILLON implant in the coronary venous system.

- Allergic reaction
- Angina pectoris
- Aortic stenosis
- Bleeding
- Cardiac arrhythmia
- Cardiac tamponade
- Carotid artery trauma
- Chronic nerve damage
- Death
- Denudation of venous tissue
- Dissection, perforation, or rupture of a coronary vessel
- Embolism of air, tissue, device or thrombus

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- Hematoma
- Hemodynamic deterioration
- Implant fracture
- Inability to permanently place the implant
- Infection
- Inflammation
- Lack of mitral regurgitation reduction
- Loss of mitral regurgitation reduction
- Mitral stenosis
- Myocardial infarction
- Myocardial ischemia
- Occlusion of a coronary vessel
- Pericardial effusion
- Pneumothorax
- Prolonged exposure to fluoroscopic radiation
- Renal failure
- Stroke
- Surgical removal of the implant
- Tissue necrosis
- Tissue penetration
- Transient ischemic attack
- Vasovagal reaction
- Vessel erosion
- Vessel spasm

VIII. Precautions

General Precautions

- Store all CARILLON Mitral Contour System components in their shelf boxes in a location that is cool, dry, and away from direct sunlight.
- Inspect packaging prior to use. Do not use a component if its peel pouch is damaged or opened.
- Do not use a component if it appears to be damaged.

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- **For SINGLE USE ONLY.** Do not re-sterilize and reuse the implant, delivery catheter, sizing catheter, or handle assembly.
- Recapture of the implant can impair the performance of the implant and delivery catheter. Reuse may result in inability to deploy the implant, inability to recapture the implant, a compromise in implant function, and implant fracture.
- Use the product prior to the “Use By” date shown on the device labeling.
- Use sterile technique when handling the CARILLON Mitral Contour System.

Precautions Specific to Patient Selection

- Patients with a history of atrial fibrillation should undergo a trans-esophageal echo prior to the procedure to rule-out left atrial appendage clot to minimize the risk of thrombo-embolism caused by the tissue plication.
- Patients with nickel, titanium or nickel/titanium (nitinol) sensitivity may have a reaction to the implant.
- Permanent placement of the implant may affect future cardiac procedures such as percutaneous coronary intervention or placement of a pacing lead through the coronary sinus for resynchronization therapy. . Patients with known conduction system disease, especially left bundle branch block, should be considered for temporary transvenous RV pacing prior to cannulation of the coronary sinus.
- Patients with a left dominant or co-dominant coronary artery circulation may be more likely to experience acute transient coronary artery compression during the procedure.
- Patients who have significant mitral annular calcification may be less likely to have mitral regurgitation reduction.
- Patients with non-compaction cardiomyopathy.
- The amount of MR change caused by the CARILLON implant has not been correlated to anatomical morphology. Valve tethering and tenting have been associated with recurrent MR after mitral valve surgical repair. The impact of these abnormalities on the performance of the CARILLON implant have not been demonstrated. Imaging data should not be used to predict the amount of benefit from this device.
- Patients with hyperdynamic venous compression; when any portion of the coronary sinus vein lumen fully contracts during the cardiac cycle.

Precautions Specific to Implant Procedure

- Implant placement should only be performed at institutions where emergency cardiac surgery can be readily arranged (either within the implanting institution, or via patient transport to an alternate institution with emergency surgery capability).
- Only cannulate the right internal jugular vein for introducing the CARILLON Mitral Contour System.
- The distal end of the distal anchor must be placed at least 9 cm from the CS ostium.
- Ensure accurate sizing of the coronary vein and appropriate implant selection.
- Do not advance or withdraw the CARILLON Mitral Contour System when resistance is met. Determine the cause of the resistance through fluoroscopic examination or other means.
- Always advance the CMCS delivery catheter over a 6F or 7F outer diameter catheter such as a multi-purpose angiographic (MPA) diagnostic catheter or deflectable catheter.

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NOTE: A 7F catheter is preferred to a 6F as it minimizes the luminal transition between the diagnostic catheter and the CMCS delivery catheter.

- Follow standard interventional cardiology anticoagulation protocols when using the CARILLON Mitral Contour System.
- Minimize bending of the handle assembly and delivery catheter during the advancement, delivery, deployment, and recapture of the implant.
- Do not place an implant in a location which may compromise the integrity of a coronary artery stent. Use coronary angiography to check for coronary artery obstruction as part of the implant procedure.
- Confirm both anchors are locked prior to decoupling the implant from the handle assembly.
- Consider recapturing and removing the implant if the final location of the implant is not in the intended coronary sinus anatomy, if the anchors do not lock, or if implant anchor wireforms appear severely misshaped.
- Do not reuse a delivery catheter, handle assembly, or implant for an additional implant procedure attempt.
- Implant retrieval methods (i.e. use of wires or snares) post implant decoupling from the handle assembly have not been assessed and may result in trauma to the coronary vasculature and/or the vascular access site.

Precautions Specific to Post-Procedure Care

- Employ proper access site management post procedure and post hospital discharge to prevent infection.
- Encapsulation of the implant should be considered prior to conducting future coronary sinus interventions.
- If the patient requires post-procedure imaging see Section XI, Magnetic Resonance Imaging (MRI) Compatibility

IX. Implant Procedure

WARNING: If the patient experiences prolonged third degree A-V block or asystole at any point during the procedure, terminate the procedure.

1. Procedure Preparation

a. Perform a procedure baseline echocardiogram.

b. Cannulate a peripheral artery with a vascular introducer sheath for coronary artery injections.

c. Cannulate the right internal jugular vein with a 10F vascular introducer sheath. Do not use a different vein for access.

d. Administer heparin to the patient and maintain adequate heparinization throughout the procedure according to standard interventional cardiology anticoagulation protocols for diagnostic catheterization procedures.

e. Perform baseline left and right coronary arteriograms to:

   i. Evaluate relevant arterial disease

   ii. Record the baseline arterial dimensions and flow patterns

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iii. Record the CS ostium location during the venous phase of the injection

2. Coronary Venous Access

a. Attach a rotating hemostatic valve (RHV) to a 6F (2.0 mm) or 7F (2.3 mm) outer diameter shaped diagnostic catheter (e.g., MPA-1 or MPA-2) and flush the catheter with heparinized saline.

b. Insert a 0.035" (0.89 mm) soft tip guidewire through the RHV and into the diagnostic catheter.

c. Attach a rotating hemostatic valve to the straight port of the CMCS (3.2 mm) outer diameter delivery catheter and flush the catheter with heparinized saline.

d. Insert and advance the diagnostic catheter/wire assembly through the RHV on the CMCS delivery catheter.

e. Insert the entire access assembly through the 10F venous introducer sheath.

f. Cannulate the coronary sinus (CS) using the telescoping system of the CMCS delivery catheter, 6F or 7F shaped diagnostic catheter, and soft tip guidewire. Use the venous phase of a previous arteriogram as an angiographic guide for cannulation of the CS ostium.

g. Advance the guidewire through the CS and GCV into the anterior interventricular vein (AIV).

h. Advance the diagnostic catheter over the guidewire to the GCV/AIV junction.

i. Advance the CMCS delivery catheter over the diagnostic catheter to the GCV/AIV junction.

j. Remove the diagnostic catheter and guidewire from the CMCS delivery catheter.

k. Confirm bleed back through the CMCS delivery catheter, indicating a luminal position of the catheter tip. If necessary, withdraw the delivery catheter until bleed back occurs.

l. As an alternative coronary sinus access method, load a 7F (2.3 mm) outside diameter deflectable catheter (with or without guidewire lumen) through the RHV into the CMCS delivery catheter. Cannulate the CS with the 7F deflectable catheter. Advance the 7F deflectable catheter (over the guidewire, if present) to the GCV/AIV junction. Advance the CMCS delivery catheter over the 7F deflectable catheter to the GCV/AIV junction. Remove the 7F deflectable catheter from the CMCS delivery catheter. Confirm bleed back through the CMCS delivery catheter, indicating a luminal position of the catheter tip. If necessary, withdraw the delivery catheter until bleed back occurs.

3. Implant Target Location and Implant Selection

a. Carefully remove the sizing catheter from its packaging to avoid kinking. Advance the sizing catheter through the RHV and align its distal radiopaque band with the delivery catheter distal radiopaque band.

b. Perform a small volume, low-pressure contrast venogram through the CMCS delivery catheter to verify that the catheter tip is not located in a vein side branch or occluding the vein lumen. Retract the CMCS delivery catheter, if necessary. If the catheter position is appropriate, perform and record a contrast venogram through the delivery catheter to opacify the venous anatomy, noting the position of the GCV/AIV junction, the CS ostium, and to determine the combined length of the CS/GCV. Venograms should be recorded in projections sufficient to visualize vein geometry. Consider LAO/caudal, RAO/caudal and AP/caudal. The final arteriogram and follow-through venogram should be in the LAO/caudal (or AP/caudal) position such that the fluoro screen can be marked for anchor positioning. The table or image intensifier should not be moved until the Carillon Mitral Contour System has been completely unsheathed and locked.

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If the CS ostium is inadequately visualized with the venogram performed from the GCV, consider repeating the venogram with the CMCS delivery catheter in the CS.

Alternatively, perform the CS venogram in the LAO caudal projection prior to cannulation of the GCV. After the CS venogram, continue to cannulate the GCV as described in section 2.

c. If the CMCS delivery catheter needs to be advanced in order to be closer to the GCV/AIV junction, first remove the sizing catheter and reinsert the diagnostic catheter and guidewire (or deflectable catheter (and guidewire, if present)) into the CMCS delivery catheter.

CAUTION: Always advance the CMCS delivery catheter over a 6F or 7F diagnostic or deflectable catheter.

d. Perform arteriograms, in RAO and LAO caudal views with the sizing catheter positioned in the CMCS delivery catheter to determine the relationship of the coronary arteries to the CS/GCV. Loosen the RHV and remove the sizing catheter.

e. Implant target zones are determined by considering available vein length, vein geometry, location of venous side branches, venous valves, venous tortuosity, dynamic venous compression, location of coronary arteries, and location of coronary artery stents.

f. Use the fluoroscopic projection and venogram frame or frames yielding the largest vein diameters to measure the vein diameters in the implant target zones. Compute the average of 3 equally spaced diameter measurements to determine the average GCV diameter in the 1.5 cm - 2 cm distal anchor target zone. If venograms from complementary projections suggest an ovalized vein, consider averaging vein diameters from these complementary projections to account for asymmetric venous anatomy. Determine the CS diameter at three positions over a 2 cm proximal anchor target zone. Mark the monitor screen (Figure 3.2) to indicate the distal anchor and proximal anchor targets.

NOTE: Do not move the table or the image intensifier once the monitor screen has been marked, or ensure that the table and image intensifier can be returned to the precise position as present when the monitor is marked. Consider using anatomical landmarks to aid in returning the table and image intensifier to the original location, when necessary.

i. Do not place a distal anchor in a vein segment with an average diameter of less than 3.5 mm.

ii. Do not place a proximal anchor apex at a vein location with a diameter of greater than 13.5 mm.

iii. The distal end of the distal anchor must be placed at least 9 cm from the CS ostium.

CAUTION: If the delivery catheter causes a localized vein distention, do not measure the vein diameter at the distended location.

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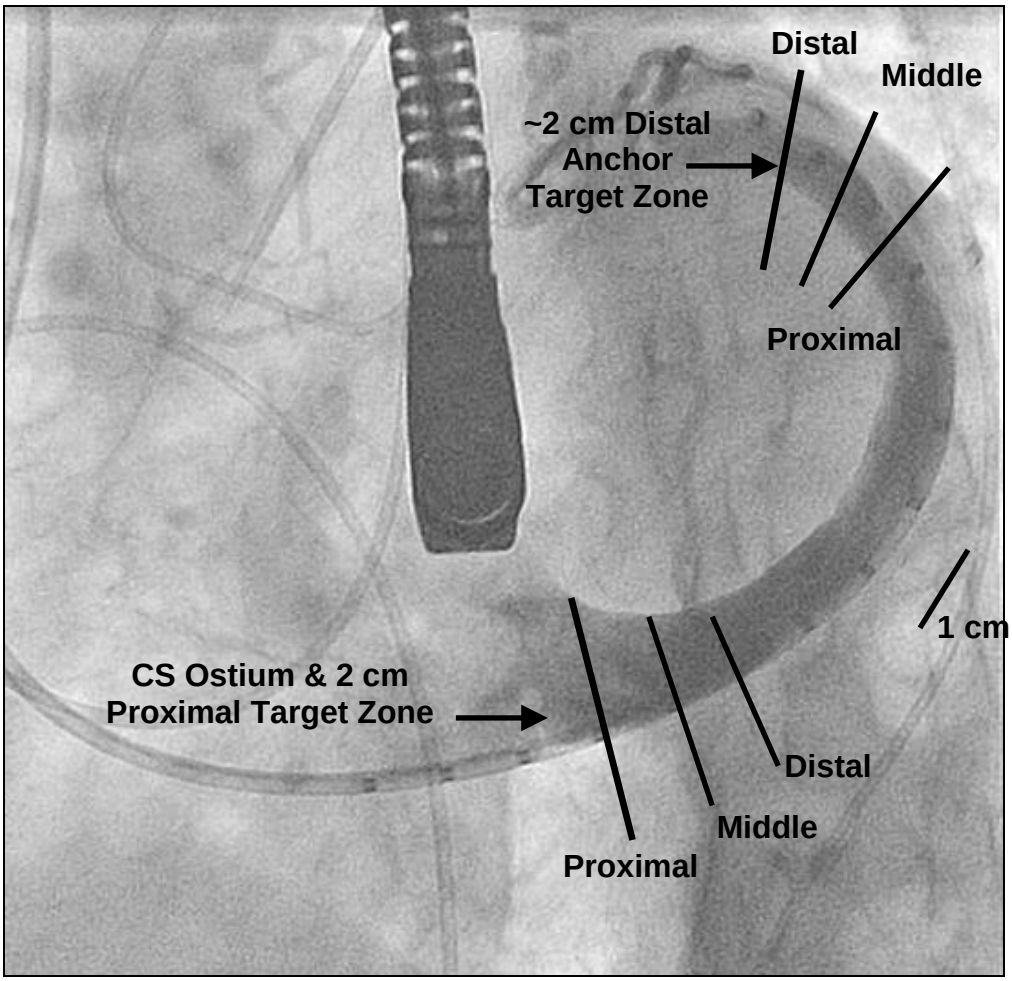

Figure 3.1: GCV/CS Venogram – Vein Sizing

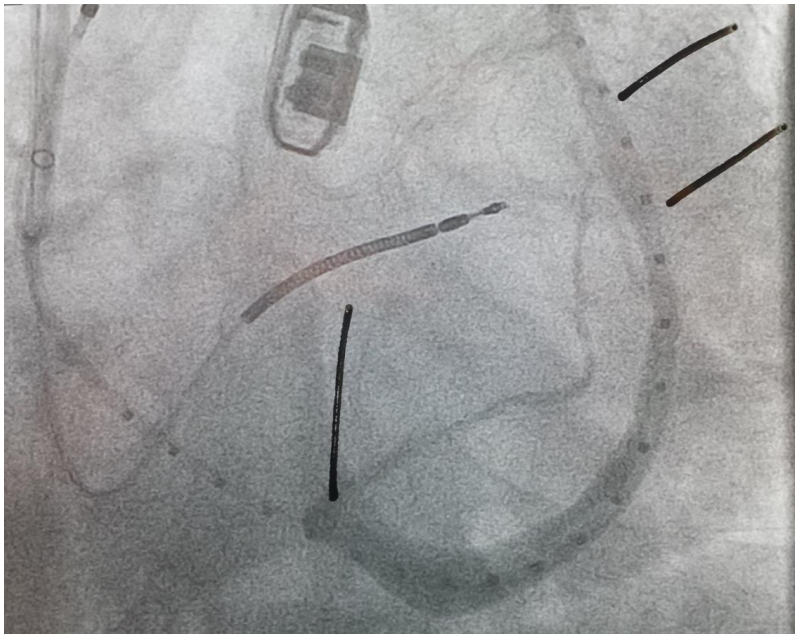

Figure 3.2: Example of Marked Monitor Screen for Anchor Placement

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g. Select an appropriate implant based on vein diameters and available vein length. Available vein length is determined by total vein length (CS ostium to GCV/AIV junction), vein diameters, vein geometry, and relevant arterial anatomy. Available vein length may be less than total vein length.

Table 3.1 contains the anchor sizing recommendations. The recommendations for choosing an implant length are as follows:

- If available vein length is ≤ 12 cm, use a 60 or 70 mm length implant for the first attempt
- If available vein length is ≥ 13 cm, use an 80 mm length implant for the first attempt, unless placement of the distal anchor is less than 12cm from CS ostium (for example, to avoid a coronary artery)
- If additional implants attempts are made, either length may be chosen
- Note that implants with 13 or 14 mm distal anchors are available only in 70 or 80 mm lengths

Table 3.1: CARILLON XE2 Anchor Sizing Recommendations

Average GCV Diameter in the Distal Anchor Target Zone (mm)	Distal Anchor (GCV) Height (mm)	Average CS Diameter in the Proximal Anchor Target Zone (mm)	Proximal Anchor (CS) Height (mm)
3.5 – 3.9	7	6.0 – 6.9	12
4.0 – 4.4	8	7.0 – 7.9	14
4.5 – 4.9	9	8.0 – 8.9	16
5.0 – 5.6	10	9.0 – 10.9	18
5.7 – 6.3	11	11.0 – 13.5	20
6.4 – 7.2	12		
7.3 – 7.8	13		
7.9 – 8.4	14		

4. Device Implantation

a. Carefully remove the handle assembly and cartridge from the packaging tray and do not allow the cartridge to move relative to the handle. Ensure the implant remains sheathed in the cartridge and that it is not advanced out of the cartridge prematurely. If the implant becomes inadvertently partially unsheathed during handling, the device should be replaced by a new device.

b. After removal of the handle assembly and cartridge from the packaging, rotate the sheath locking knob in a clockwise direction, opposite the black locking arrow (Figure 4.1), ensuring the proximal locking sheath is fully retracted.

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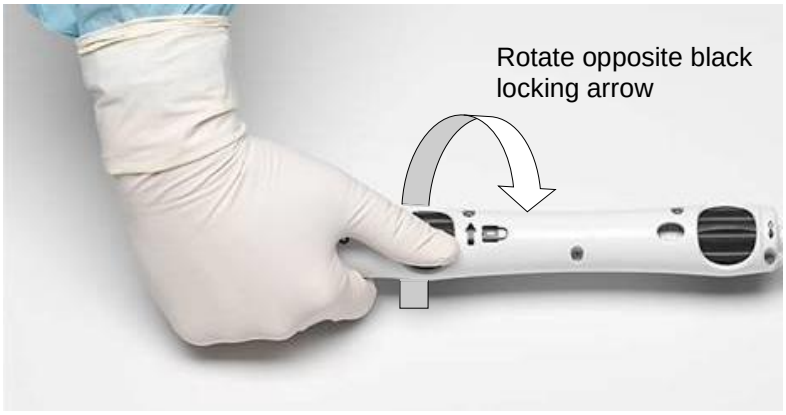

Figure 4.1: Counter-Rotating the Sheath Locking Knob

c. Remove the RHV from the straight port of the CMCS delivery catheter and connect the male luer at the distal end of the cartridge to the delivery catheter (Figure 4.2).

Figure 4.2: Connecting the Cartridge to the Straight Port of the Delivery Catheter

d. Advance the implant out of the cartridge and into the delivery catheter by manually advancing the sheath/pusher assembly at the proximal end of the cartridge. Push in small increments (1cm - 2 cm increments) so as not to kink the sheath/pusher assembly (Figure 4.3). Continue to advance the sheath/pusher assembly until the handle and cartridge come together.

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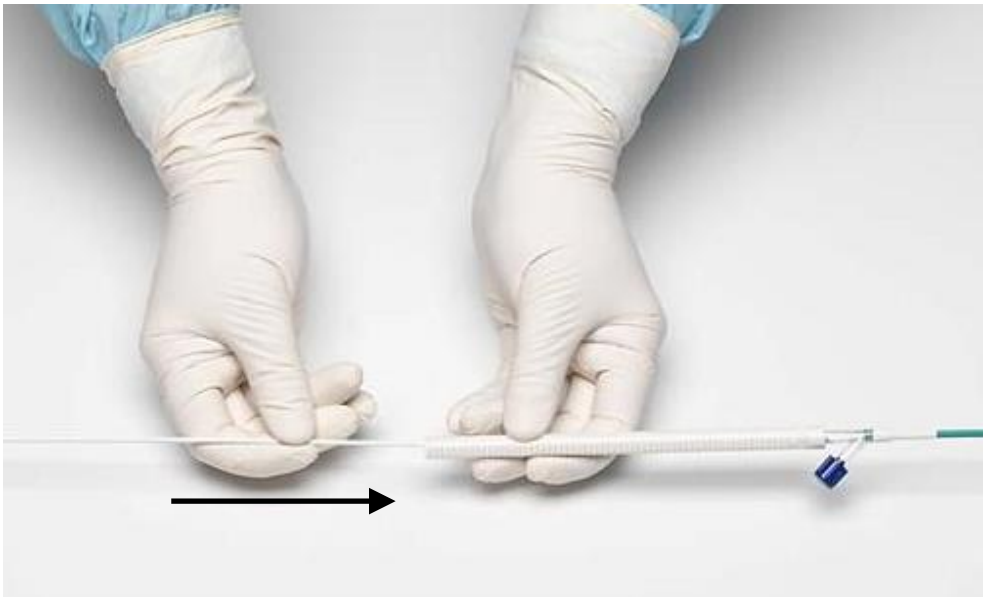

Figure 4.3: Advancing the Implant into the Delivery Catheter

e. Insert the proximal end of the cartridge into the distal socket of the handle and rotate the control knob in the direction indicated by the black arrow to engage the cartridge. Ensure that the delivery catheter remains in a fixed position at the introducer sheath while rotating the control knob and engaging the cartridge. Stop rotating the control knob once the proximal end of the cartridge is visible in the cartridge window (Figure 4.4).

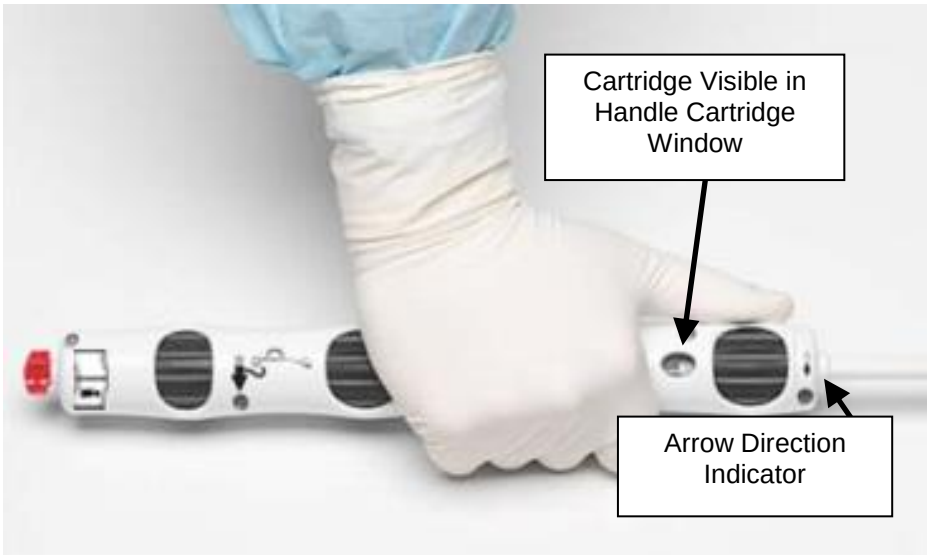

Figure 4.4: Cartridge is Visible in the Handle Cartridge Window

ATTENTION: The remaining Device Implantation steps (f-p) must be performed with fluoroscopic guidance.

f. Deploy the distal anchor in the target location in the GCV by rotating the control knob in the direction indicated by the black arrow until the distal anchor is exposed. Typically it is necessary to gently pull back on the handle and delivery catheter during rotation of the

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control knob to accurately deliver the distal anchor to the target location. Continue to rotate the control knob in the same direction until the distal anchor eyelet is completely out of the delivery catheter (Figure 4.5).

Figure 4.5: Rotating the Control Knob to Deploy the Distal Anchor

g. Lock the distal anchor at the target location by rotating the control knob in the direction indicated by the white arrow until the delivery catheter pushes the eyelet flush against the distal crimp tube. Retract the delivery catheter by rotating the control knob in the direction indicated by the black arrow to verify that the distal anchor eyelet remains flush against the distal crimp tube in the locked position. If necessary, rotate the control knob in the direction of the white arrow to advance the delivery catheter again for another attempt at locking.

CAUTION: Once the distal anchor is locked, additional rotation of the control knob in the direction of the white arrow will cause the delivery catheter to begin recapturing the anchor.

WARNING: If the distal anchor struts are inadvertently collapsed by over advancement of the delivery catheter to the DA twist, recapture and remove the entire implant. See Step 5 – Implant Recapture

h. Perform arteriograms, as needed, to assess the arterial dimensions and flow in the region around the implant. If there is a significant impact on arterial dimensions or flow that is not resolved by pulling tension on the system, recapture and remove the implant (See step 5 – Implant Recapture).

NOTE: Consider administration of intracoronary nitroglycerine to rule out vessel spasm whenever coronary compromise due to the implant is suspected.

i. Retract the delivery catheter to the distal end of the proximal anchor crimp tube by rotating the control knob in the direction indicated by the black arrow. To ensure the proximal anchor remains sheathed in the delivery catheter, only rotate the control knob until ~2 cm of exposed thread length is visible on the cartridge.

j. Place gradual tension on the implant by gently pulling on the handle assembly and/or the CMCS delivery catheter while stabilizing the venous introducer sheath. Continue slowly pulling tension until the proximal anchor crimp tube is at the proximal anchor target location (demarcated on the fluoro screen) in the CS as guided by fluoroscopy.

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k. Do not pull the proximal anchor crimp tube into the right atrium. Use the venous phase of the arteriogram to help confirm that the proximal anchor remains in the coronary sinus. Alternatively, inject contrast through the side-port of the delivery catheter to assess the position of the proximal anchor's crimp tube relative to the CS anatomy. Careful attention must be made to ensure that the tension in the system is not altered during these maneuvers.

NOTE: Before unsheathing and deploying the proximal anchor, perform arteriograms as needed to assess relevant arterial dimensions and flow. If there is a significant impact on arterial dimensions or flow not relieved by partial release of tension, then release the tension on the implant to restore arterial dimensions. Recapture and remove the implant. If the coronary vessels are obscured by any portion of the CARILLON device, consider performing arteriograms in an alternative projection, such as RAO caudal, to adequately visualize coronary vessels and flow. This maneuver requires careful planning to ensure that the location of the table and image intensifier are returned to the same position when returning from the RAO caudal to the LAO caudal position, to allow the proximal anchor to be placed in the intended location.

NOTE: If the distal anchor slips during tensioning, recapture and remove the implant (See step 5 – Implant Recapture).

l. While maintaining tension on the handle assembly and/or the CMCS delivery catheter, deploy the proximal anchor at the target position in the CS by rotating the control knob in the direction indicated by the black arrow. Adjust tension as needed to keep the proximal anchor at the target position. Continue to rotate the control knob until no more rotations are possible (Figure 4.6).

Figure 4.6: Rotating the Control Knob to Deploy the Proximal Anchor

m. Lock the proximal anchor at the CS target location by rotating the sheath knob in the direction indicated by the locking arrow until the sheath pushes the proximal anchor eyelet flush against the proximal crimp tube. Retract the sheath by rotating the sheath knob in the reverse direction, opposite the locking arrow. Verify that the proximal anchor eyelet remains against the proximal crimp tube in the locked position. To better visualize and confirm proximal anchor locking, consider viewing the proximal anchor in an LAO cranial projection. If necessary, rotate the sheath knob in the direction of the lock arrow to advance the sheath again for another attempt at locking (Figure 4.7).

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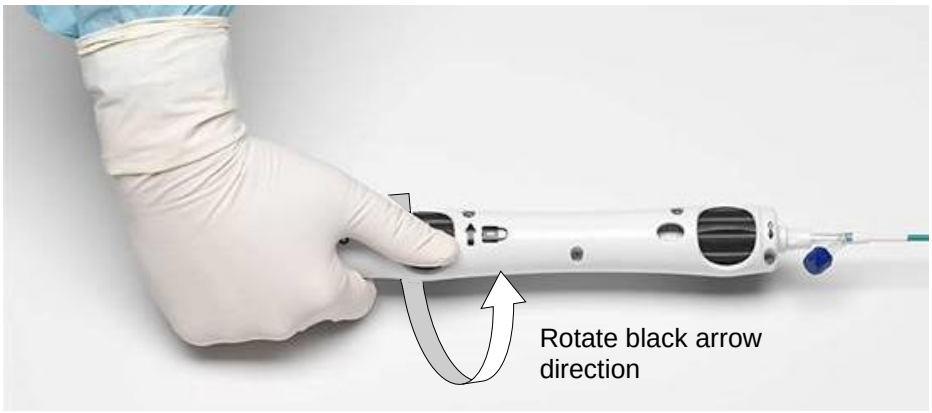

Figure 4.7: Rotating the Sheath Knob to Lock the Proximal Anchor

n. Remove any external tension on the system by gently advancing the delivery catheter at the introducer sheath. Confirm that when excess external system tension is relieved the implant does not migrate or change position in the CS/GCV.

o. Prior to decoupling the implant from the handle assembly, perform each of the following steps:

   i. Assess hemodynamics and patient stability.

   ii. Perform arteriograms to confirm no significant impact on the left and right coronary arteries.

WARNING: If placement of the implant causes a significant change in the electrocardiogram (ECG), recapture and remove the implant.

WARNING: If placement of the implant causes a significant reduction in the coronary arterial dimensions of a clinically significant artery, recapture and remove the implant. Confirm a return to baseline arterial dimensions.

   iii. Confirm both anchors are locked by utilizing multiple fluoroscopic views.

   Examples of locked and unlocked anchors are shown in figures 4.8 through 4.11.

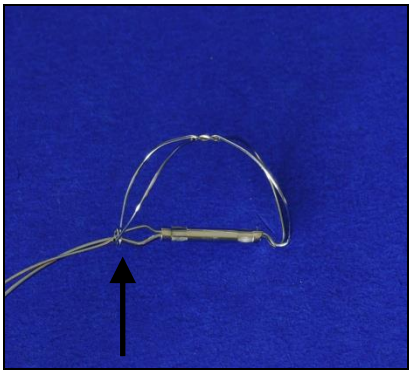

Figure 4.8: Unlocked Distal Anchor

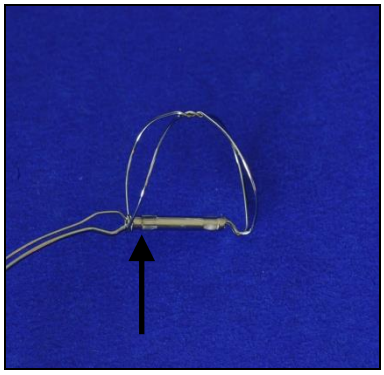

Figure 4.9: Locked Distal Anchor

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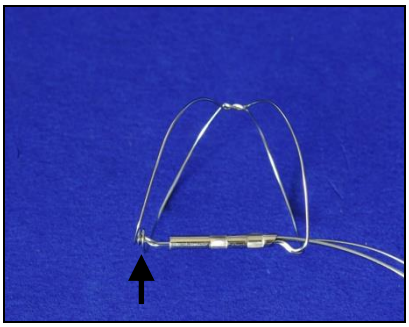

Figure 4.10: Unlocked Proximal Anchor

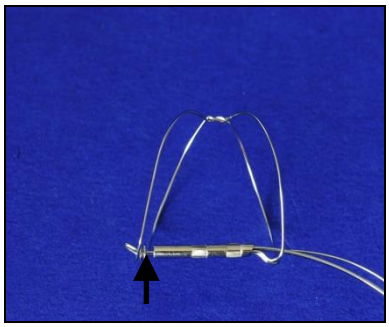

Figure 4.11: Locked Proximal Anchor

iv. Use an echocardiogram to quantify MR reduction.

WARNING: The implant cannot be recaptured with the handle assembly once it is decoupled from the handle assembly.

Consider recapturing and removing the implant if final location of the implant is not in the intended coronary sinus anatomy, or if implant anchor wireforms appear severely misshaped (See step 5 – Implant Recapture).

p. To decouple the implant from the delivery system, turn the red release safety in the direction of the arrow and remove the safety from the handle (Figure 4.12). Then rotate the release knob in the direction indicated by the decouple arrow until the implant is completely separated from the handle assembly (Figure 4.13).

Figure 4.12: Rotating and Removing the Release Safety

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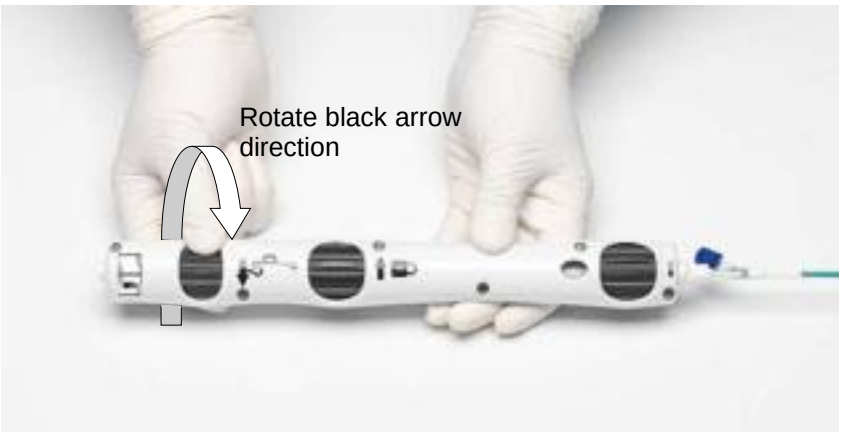

Figure 4.13: Rotating the Release Knob to Decouple the Implant from the Handle Assembly

q. Withdraw the handle assembly and attached CMCS delivery catheter out of the venous introducer sheath. Do not advance the system once the implant has been decoupled.

r. Remove the delivery system.

5. Implant Recapture

If clinical circumstances warrant, the implant may be recaptured and removed from the coronary vein **prior** to decoupling from the handle assembly. Recapture and remove the implant if implant performance, appearance or final location is unsatisfactory.

a. If the proximal anchor has been deployed, rotate the sheath knob in the direction indicated by the lock arrow until the sheath is firmly against the proximal anchor crimp tube. Do not over tighten. Then proceed to (b). If the proximal anchor has not been deployed proceed directly to (d).

b. Rotate the control knob in the direction indicated by the white arrow to advance the CMCS delivery catheter over the proximal anchor wireforms (Figure 5.1).

c. Next, retract the catheter approximately 1 cm by rotating the control knob in the direction indicated by the black arrow, exposing the tip of the proximal anchor wireforms beyond the tip of the delivery catheter. This is done to “normalize”, or remove any inversion of the tip of the delivery catheter prior to capturing the distal anchor.

d. To recapture the distal anchor, rotate the control knob in the direction indicated by the white arrow to advance the CMCS delivery catheter over the remainder of the implant. Prevent excess tension on the system during recapture by manually advancing the delivery catheter at the introducer sheath while rotating the control knob. Tension on the system can be monitored by the location of the proximal anchor crimp tube with respect to cardiac anatomy.

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Figure 5.1: Rotating the Control Knob to Recapture the Implant

NOTE: If significant resistance is encountered while trying to recapture an anchor, retract the catheter approximately 2 cm from the anchor by rotating the control knob in the direction indicated by the black arrow. Place tension on the handle assembly or CMCS delivery catheter to straighten the angle between the delivery catheter and the anchor. Then rotate the control knob in the direction indicated by the white arrow to advance the delivery catheter to initiate recapture of the anchor. Once the anchor begins to collapse, release the extra tension on the system by manually advancing the delivery catheter at the introducer sheath. Then continue rotating the control knob to complete the recapture.

e. Once the entire implant is inside the CMCS delivery catheter, disconnect the cartridge from the delivery catheter and stabilize the delivery catheter. Pull on the handle assembly to withdraw the implant completely out of the delivery catheter, thus leaving the used delivery catheter in the coronary vein and maintaining coronary venous access. A venogram may be done to assess for a venous dissection. Alternatively, once the entire implant is inside the delivery catheter, withdraw the handle assembly and delivery catheter together through the venous introducer sheath.

WARNING: If a venogram shows evidence of a clinically significant venous dissection or perforation following recapture, do not attempt to place an additional implant.

WARNING: If clinically significant denuded venous tissue is observed on a component of the CARILLON Mitral Contour System following recapture, do not attempt to place an additional implant. Monitor the patient for pericardial effusion.

f. If an additional implant procedure attempt is planned, repeat the implant procedure with a new delivery catheter, handle assembly, and implant. Components of the CARILLON Mitral Contour System are single use only. If the delivery catheter was left in the coronary vein after recapture, use an appropriate exchange length guidewire (e.g., a 0.035” (0.89 mm) soft tip guidewire) to remove the used catheter and bring in a new CMCS delivery catheter over a diagnostic catheter for the next procedure attempt. Repeat the implant procedure beginning with Section IX, 3.

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X. Follow-up Procedures

The following patient assessments are recommended post-implant:

- Chest X-ray or cinefluoroscopy to assess proper position and integrity of the implant
- Echocardiogram to assess left ventricular (LV) function and mitral regurgitation
- Electrocardiogram (ECG) to assess potential myocardial infarction
- Patient history to assess for symptoms of ischemia

XI. Magnetic Resonance Imaging (MRI) Compatibility: MR Conditional

Non-clinical testing has demonstrated the CARILLON XE2 implant is MR Conditional according to the terminology specified in the ASTM International Standard F2503. It can be safely scanned under the following conditions:

- Static magnetic field of 3.0 Tesla
- Spatial gradient field of 720 Gauss/cm
- Maximum whole body averaged specific absorption rate (SAR) of 2.9 W/kg for 15 minutes of scanning

In non-clinical testing, the CARILLON XE2 implant produced a temperature rise of less than or equal to 2.3°C at a maximum whole body absorption rate (SAR) of 2.9 W/kg, as assessed by calorimetry for 15 minutes of MR scanning in a 3.0 Tesla (3.0 Tesla/128 MHz, Excite, HDX, Software 14x.M5, General Electric Healthcare, Milwaukee, WI) MR system.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the CARILLON XE2 implant. Therefore, optimization of MR imaging parameters to compensate for the presence of this device may be necessary. Artifacts were in the form of signal voids as follows:

Pulse Sequence	T1-SE	T1-SE	GRE	GRE
Signal Void Size	1,951 mm^2	384 mm^2	2,279 mm^2	644 mm^2
Plane Orientation	Parallel	Perpendicular	Parallel	Perpendicular

XII. Sterilization

The implant, handle assembly, delivery catheter, and sizing catheter are provided sterile and non-pyrogenic. The implant is loaded in the cartridge and attached to the handle assembly. The delivery catheter and sizing catheter are packaged separately. All system components are sterilized with ethylene oxide and are for SINLGE USE ONLY—DO NOT RESTERILIZE. Do not use if the package is opened or damaged.

XIII. Storage Conditions

Store all CARILLON Mitral Contour System components in their shelf boxes in a location that is cool, dry, and away from direct sunlight.

Do not use after expiration date.

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XIV. Clinical Study Information

6. Overview of Clinical Studies

This Clinical Evaluation includes a summary of the results of the CARILLON Mitral Contour System prospective clinical trials.

Results from the AMADEUS study using an earlier iteration of the CARILLON Mitral Contour System have been published in Circulation.[2]

Clinical data in this section includes information obtained from the TITAN and TITAN II feasibility clinical trials.

The TITAN and TITAN II trials were conducted exclusively on patients with functional mitral regurgitation and heart failure who remained symptomatic (NYHA Grade ≥ 2) despite treatment with guideline directed medical therapy.

Table 6.1: Summary of TITAN and TITAN II Clinical Trials

Study Name & Enrollment Dates	Study Type	Device Name	Main Inclusion and Exclusion Criteria	Endpoints	# of sites and patients
TITAN [1] 2008 - 2009	Feasibility. Prospective, non-randomized, dual arm Follow-up: Baseline, 1, 6, 12 months and annually through 5 years	CARILLON XE2	**Inclusion**: • dilated ischemic/non-ischemic cardiomyopathy • moderate to severe Functional Mitral Regurgitation (2+ - 4+) • LVEF < 40% • NYHA Class II - IV • age 18-80 • stable HF medication **Exclusion**: • hospitalization within the past three months for: ○ myocardial infarction, CABG surgery, unstable angina • hospitalization within the past 30 days for coronary angioplasty • patients expected to require cardiac surgery with one year	**Primary**: Major Adverse Event (MAE) Rate through 30 days. MAE defined as: • death • myocardial infarction • cardiac perforation necessitating catheter-based or surgical intervention • device embolization • occurrence of surgery or percutaneous coronary intervention related to the device **Major Secondary**: • mortality through 5 years • quantitative MR • measures of LV function • NYHA functional class • 6 minute walk distance • quality of life (KCCQ)	7 sites 53 intent-to-treat patients 36 implanted patients (followed through 5 years) 17 non-implanted patients (followed through 1 year only)

[2] Schofer J, Siminiak T, Haude M, et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: Results of the CARILLON mitral annuloplasty device European Union study. Circulation. 2009;120:326-333.

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Study Name & Enrollment Dates	Study Type	Device Name	Main Inclusion and Exclusion Criteria	Endpoints	# of sites and patients
TITAN II 2011 - 2013	Feasibility. Prospective, single-arm confirmatory Follow-up: Baseline, 1, 6, & 12 months	CARILLON mXE2	Same as TITAN	**Primary**: Major Adverse Event (MAE) Rate through 30 days. MAE defined as: • death • myocardial infarction • cardiac perforation necessitating catheter-based or surgical intervention • device embolization • occurrence of surgery or percutaneous coronary intervention related to the device **Major Secondary**: • mortality through 5 years • quantitative MR • measures of LV function • NYHA functional class • 6 minute walk distance	5 sites 36 intent-to-treat patients 30 implanted patients (followed through 1 year only) 6 non-implanted patients (followed through 30 days only)

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7. TITAN Clinical Trial

The results of the TITAN Trial have been published in the **European Journal of Heart Failure**.[1]

TITAN Clinical Trial Development

The primary objective of the TITAN trial was to evaluate the safety of deploying and implanting the CARILLON Mitral Contour System in patients with FMR. Secondary objectives included an evaluation of long-term safety, as well as an assessment of hemodynamic and clinical changes. Hemodynamic changes were characterized by echocardiography. Clinical efficacy was assessed by changes in NYHA classification, exercise tolerance, and quality of life.

Independent Oversight

The protocol, Informed Consent form, and other study documentation were approved by the appropriate European Member Competent Authority and the respective Ethics Committees. This study included an independent Data and Safety Monitoring Board (DSMB). The DSMB reviewed the safety data against the established criteria and in the context of safety data accumulated and the continued validity of the study. The DSMB also reviewed the adverse event rates and evaluates study progress when unexpected adverse events occur. If the safety data appeared to demonstrate that there is harm being done, the DSMB had the right and responsibility to stop the study.

Statistical Analysis

Data collected in this study were documented using summary tables and patient data listings. Statistical significance testing is reported where appropriate and provides a comparison between the implanted and non-implanted cohorts. Computations were performed using SAS version 9.1.

The specific statistical testing used is detailed as footnotes to the relevant tables and graphs. All statistical testing was based on a two-sided alpha = 0.05 significance level. There was no imputation for missing data.

TITAN Clinical Trial Results

Patient Disposition

The patient disposition flow diagram for all patients who met the final eligibility criteria is shown below.

Definitions:

Intent to Treat Population (ITT): Fully qualified subjects in whom CARILLON implantation was attempted.

Successful Implantation Population: Subjects permanently implanted, five-year follow-up.

Non-implanted population: Subjects who were enrolled to the study and in whom CARILLON implantation was attempted, but who did not receive a permanent implant.

LTFU: Lost to Follow Up

A total of 53 patients were fully qualified to undergo a CARILLON implant procedure and comprise the intent-to-treat population (“ITT patients”).

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Thirty-six (36) patients were successfully implanted with the CARILLON Mitral Contour System (“implanted patients”) for a 68% implant success rate.

Of the 36 implanted patients:

- Twenty-six (26) patients required just one device attempt to gain sufficient MR reduction with no coronary artery compromise resulting in permanent placement of the CARILLON device.
- Ten (10) patients required more than one attempt in order to meet the requirements for permanent placement.

Seventeen (17) patients did not meet the criteria for a successful implant (no MR reduction and/or coronary artery compromise) and did not receive a permanent implant (“non-implanted patients”).

Of the 17 non-implanted patients:

- Nine (9) patients did not receive a permanent implant due to a protocol specified reason - insufficient peri-procedural MR reduction - defined as a one or more grade reduction in MR in at least one echo derived MR parameter (vena contracta, regurgitant volume, effective regurgitant orifice area or MR jet area/left atrial area) at the time of the procedure.
- Seven (7) patients did not receive a device due to coronary artery compromise.
- One (1) patient had both no MR reduction and coronary artery compromise precluding permanent device placement.

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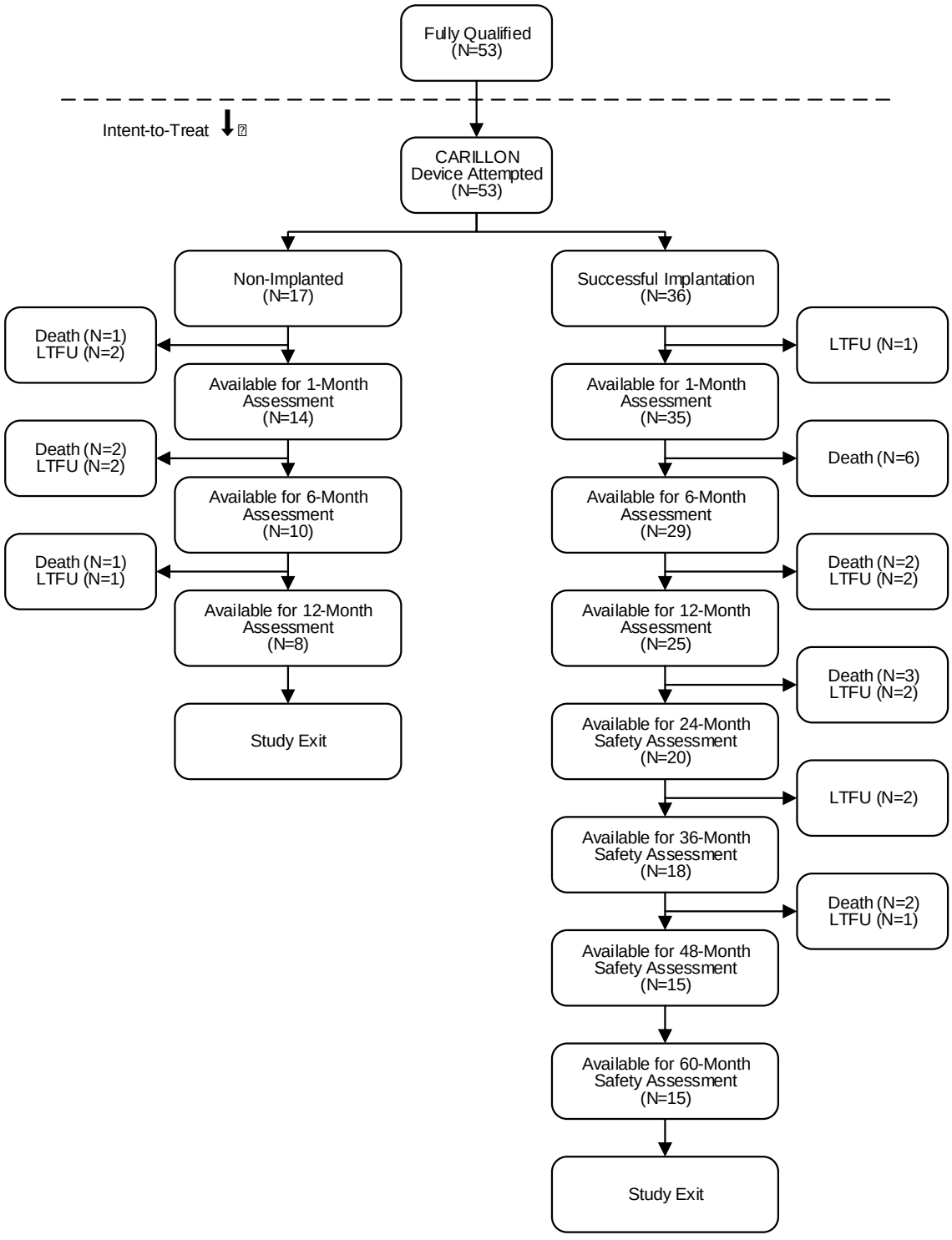

Figure 7.1: TITAN Trial Patient Disposition

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Patient Demographics

The key patient demographics for both the implanted and non-implanted patients are summarized in Table 7.1.

Table 7.1: Key Demographic Characteristics

Patient Characteristic	Implanted Patients (N=36)	Non-Implanted Patients (N=17)	P-value*
Age, mean (SD), yr	62 (13)	63 (13)	0.95
Gender, n (%), Male			
Male	27 (75)	14 (82)	0.73
NYHA Classification, % (n)			0.55
Class I	0% (0/35)	0% (0/17)	
Class II	0.0% (0/36)	5.9% (1/17)	
Class III	94.4% (34/36)	94.1% (16/17)	
Class IV	5.6% (2/36)	0.0% (0/17)	
6 minute walk, mean (SD), m	302.5 (74)	337.9 (83)	0.12
Medical History, n (%)			
Hx of Diabetes	6 (16.7%)	5 (29.4%)	0.30
Hx of Angina	16 (44.4%)	9 (52.9%)	0.77
Hx of CAD	22 (61.1%)	12 (70.6%)	0.56
Hx of CABG	12/22 (54.5%)	4/12 (33.3%)	0.30
Number of HF admissions in past 12 months, mean (SD)	0.8 (0.8)	3.0 (6.2)	0.13
Echo Parameter, mean (SD)			
LVEDD, cm	6.63 (0.85)	6.72 (0.77)	0.70
Mitral annular diam., cm	3.74 (0.56)	3.74 (0.48)	0.95
LVEF, mean (SD) %	28.7 (7.5)	27.0 (7.8)	0.46

* Ordinal measures were assessed using the mean score Cochran-Mantel-Haenszel (CMH) test, dichotomous measures were assessed using Fisher's test, and continuous measures were assessed using t-test or Wilcoxon rank sum test.

The majority of patients were male, NYHA class III, with a six minute walk distance consistent with moderate heart failure. There was no statistical difference in the co-morbidities between the two patient cohorts. There were no statistically significant differences in echo parameters between the implanted and non-implanted patients.

CARILLON Device and Procedure Characteristics

The overall device, implant, and procedure success are shown in Table 7.2.

Implant success was defined as:

- Successful permanent implantation of the CARILLON investigational device and was further categorized into cases requiring just one attempt and cases requiring more than one attempt.

Overall implant success was 68%, with 36 of 53 patients receiving a permanent implant. However, it should be noted that in 9 of the 17 cases in which a CARILLON device was not implanted was due to a protocol specified rationale for removing the device, namely, if a one grade reduction in MR was not achieved. In only 8 cases was an implant recaptured and not implanted due to coronary artery compromise.

In 72% of the implanted cases (26/36) the device was able to reduce MR and be implanted on the first attempt. In the remaining 10 cases, the device was able to be recaptured appropriately

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(either due to lack of MR reduction or coronary artery compromise) and a subsequent attempt(s) resulted in a satisfactory MR result allowing permanent implant.

Table 7.2: Device and Procedure Success Rate

Patient Characteristics	Intent to Treat Population (N=53)
Implant Success	67.9% (36/53)
At first attempt	72.2% (26/36)
Requiring >1 attempts	27.8% (10/36)

Safety – Major Adverse Events

Key adverse events have been identified as relating specifically to the safety of the CARILLON Mitral Contour System. These adverse events were termed major adverse events (MAE). Safety was evaluated as the 30-day (or hospital discharge date, whichever was longer) rate of MAEs defined as the composite endpoint of:

- Death
- Myocardial infarction
- Cardiac perforation necessitating catheter-based or surgical intervention
- Device embolization
- The occurrence of surgery or percutaneous coronary intervention related to the device (e.g., device related infection/septicemia)

The 30-day MAE rate for the ITT population is listed in Table 7.3.

Table 7.3: Principal Safety Results at 30 days – Intent to Treat Population

Primary Safety Endpoint through 30 days of follow up (or hospital discharge date)	Intent to Treat Population (N=53)	Kaplan Meier Event Rate	Kaplan Meier 95% CI
Major Adverse Events	**1.9% (1/53)**	**98.1%**	**[87.4%, 99.7%]**
Death	1.9% (1/53)		
Myocardial Infarction	0% (0/53)		
Cardiac Perforation Necessitating Catheter-based or Surgical Intervention	0% (0/53)		
Device Embolization	0% (0/53)		
Surgery or Percutaneous Coronary Intervention Related to the Device	0% (0/53)		

* ITT patients include all subjects who were enrolled to the study and in whom CARILLON implantation was attempted.

At 30 days, the MAE rate was 1.9% (1/53) in the ITT population. This consisted of one death in a patient with LVEF of 32.5% and MR grade 4+ who experienced transient asystole during CS access prior to an unsuccessful placement of the CARILLON device on April 24, 2008. The patient developed renal failure and died as a result of multi organ failure on May 2, 2008. This

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MAE event was reviewed by the DSMB and noted as a non-cardiac operative mortality related to the procedure.

Table 7.4 shows the principal safety results (30-day MAE rate) separated into the implanted and non-implanted groups. The results show that at 30 days, the MAE rate in the implanted population was 0% (0/36).

Table 7.4: Principal Safety Results at 30 days – Comparison of Implanted & Non-Implanted Patients

Primary Safety Endpoint through 30 days of follow up (or hospital discharge date)*	Subjects with Successful Implantation (N=36) Proportion				Non Implanted Population (N=17) Proportion				P-Value***
	Device Related	Procedure Related	Total	95% CI**	Device Related	Procedure Related	Total	95% CI**	
Major Adverse Events	0% (0/36)	0% (0/36)	0% (0/36)	[0.0%, 9.7%]	0% (0/17)	5.9% (1/17)	5.9% (1/17)	[0.1%, 28.7%]	0.3208
Death	0% (0/36)	0% (0/36)	0% (0/36)	[0.0%, 9.7%]	0% (0/17)	5.9% (1/17)	5.9% (1/17)	[0.1%, 28.7%]	0.3208
Myocardial Infarction	0% (0/36)	0% (0/36)	0% (0/36)	[0.0%, 9.7%]	0% (0/17)	0% (0/17)	0% (0/17)	[0.0%, 19.5%]	
Cardiac Perforation Necessitating Catheter-based or Surgical Intervention	0% (0/36)	0% (0/36)	0% (0/36)	[0.0%, 9.7%]	0% (0/17)	0% (0/17)	0% (0/17)	[0.0%, 19.5%]	
Device Embolization	0% (0/36)	0% (0/36)	0% (0/36)	[0.0%, 9.7%]	0% (0/17)	0% (0/17)	0% (0/17)	[0.0%, 19.5%]	
Surgery or Percutaneous Coronary Intervention Related to the Device	0% (0/36)	0% (0/36)	0% (0/36)	[0.0%, 9.7%]	0% (0/17)	0% (0/17)	0% (0/17)	[0.0%, 19.5%]	

*The data presented in the table include all subjects with successful implantation and with 30-day follow-up (defined as subjects with at least 24 days of follow-up) or subjects with successful implantation, who experienced MAE at 30 days post procedure or before discharge.
** 95% CI was computed for total proportions of subjects with successful implantation and non-implanted population.
*** Comparison of Implanted vs. Non-Implanted populations. Fisher's test p-value was computed for comparing total proportions for subjects who experienced MAE through 30 days.

The 12-month (365 + 30 days) MAE rate for implanted patients was 27.8% (10/36), which consisted of eight (8) deaths and two (2) non ST segment MIs (Table 7.5). The 12-month MAE rate for the non-implanted patients was 23.5% (4/17), which consisted of four deaths. There was no statistically significant difference in either the overall MAE or mortality rate between the two patient populations.

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Table 7.5: Long Term Safety Results – Comparison of Implanted & Non-Implanted Patients at 1 year

MAE through 365 days of follow up (or hospital discharge date)*	Subjects with Successful Implantation (N=36) Proportion				Non Implanted Population (N=17) Proportion				P-Value***
	Device Related	Procedure Related	Total	95% CI**	Device Related	Procedure Related	Total	95% CI**	
Major Adverse Events	0% (0/36)	2.8% (1/36)	27.8% (10/36)	[14.2%, 45.2%]	0% (0/17)	5.9% (1/17)	23.5% (4/17)	[6.8%, 49.9%]	1.0000
Death	0% (0/36)	2.8% (1/36)	22.2% (8/36)	[10.1%, 39.2%]	0% (0/17)	5.9% (1/17)	23.5% (4/17)	[6.8%, 49.9%]	1.0000
Myocardial Infarction	0% (0/36)	0% (0/36)	5.6% (2/36)	[0.7%, 18.7%]	0% (0/17)	0% (0/17)	0% (0/17)	[0.0%, 19.5%]	
Cardiac Perforation Necessitating Catheter-based or Surgical Intervention	0% (0/36)	0% (0/36)	0% (0/36)	[0.0%, 9.7%]	0% (0/17)	0% (0/17)	0% (0/17)	[0.0%, 19.5%]	
Device Embolization	0% (0/36)	0% (0/36)	0% (0/36)	[0.0%, 9.7%]	0% (0/17)	0% (0/17)	0% (0/17)	[0.0%, 19.5%]	
Surgery or Percutaneous Coronary Intervention Related to the Device	0% (0/36)	0% (0/36)	0% (0/36)	[0.0%, 9.7%]	0% (0/17)	0% (0/17)	0% (0/17)	[0.0%, 19.5%]	

*The data presented in the table includes all subjects with 365-day follow-up or subjects who experienced MAE at 365±30 days post procedure.
** 95% CI was computed for total proportions of subjects with successful implantation and non-implanted population.
*** Comparison of Implanted vs. Non-Implanted populations. Fisher's test p-value was computed for comparing total proportions for subjects who experienced MAE through 365±30 days.

Beyond the one-year follow-up in the implanted population, there have only been five additional deaths.

- Two (2) of these deaths occurred after the 2-year follow-up was completed and three (3) deaths occurred after the 3-year follow-up was completed.
- Three (3) of these deaths were designated as unrelated to the device. In the remaining two (2) the cause of death was not divulged by the patient's family members, despite numerous requests.

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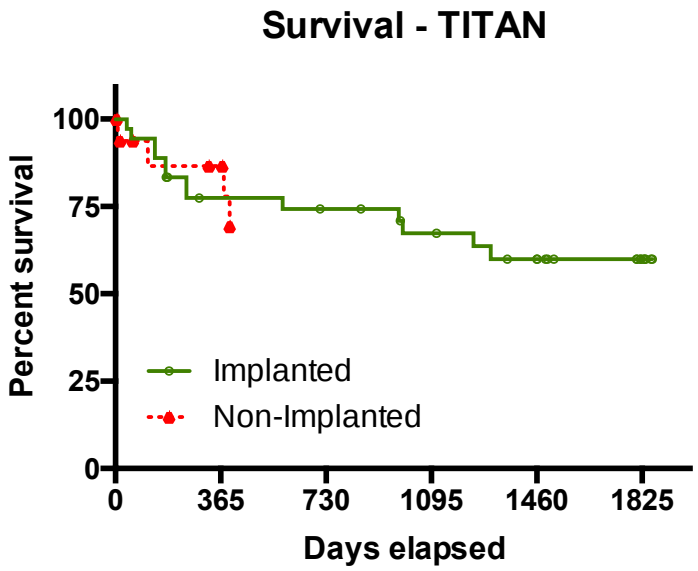

Figure 7.2: TITAN Survival Curve

Apart from mortality, there were no other long-term major adverse events, notably no late myocardial infarctions were noted through the end of the study follow-up.

At the end of the 5-year study follow-up, of the original 36 implanted patients:

- 15 patients were still alive
- 13 patients had died
- 8 patients were lost-to-follow-up (1 @1M, 2 @12M, 2 @18M, 2 @36M and 1 @48M)

Device Integrity

The TITAN trial completed patient enrollment in February 2009 and follow-up data collection in February 2014.

Cardiac Dimensions noted the occurrence of device integrity issues (broken wireforms) in a small percentage of the patients implanted with the CARILLON XE2 device in the TITAN trial. Broken wireforms are a potential risk and clearly documented in TITAN protocol, Instructions-For-Use and the Patient Informed Consent.

The loss of device integrity has not been associated with any adverse clinical events and the CARILLON devices remain implanted in 5 of the 9 patients with fractures through the 5-year follow-up with no fracture related adverse events noted. Efficacy Data

This analysis report presents efficacy data on all patients (implanted and non-implanted) through the 12-month follow-up assessments.

Effects of CARILLON Device on MR Assessments

In the implanted group, mitral annular diameter (measured in the anteroseptal-posterolateral plane) decreased markedly at 1 month, showing a 13.5% decrease from baseline. This decrease in annular diameter remained through the 6 and 12-month follow-ups.

In contrast, the non-implanted group showed no change or a slight increase in annular diameter through the 12-month follow-up. The difference in annular diameter changes between groups was highly statistically different (P<0.001) across all follow-up time points.

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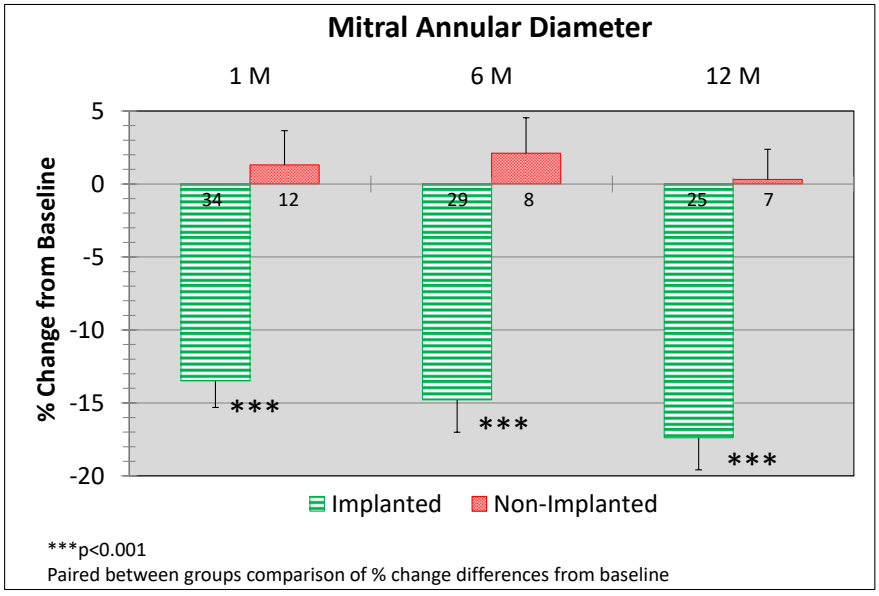

Figure 7.3: Mitral Annular Diameter – Implanted vs. Non-Implanted Patients

The four key echocardiographic indices of MR – effective regurgitant orifice area (EROA), vena contracta, regurgitant volume (RV), and regurgitant fraction (RF) – all showed decreases from baseline through 1 month ranging between -17% and -28%. These changes decreased further for all these parameters at 12 months (ranging from decreases of -34% to -46%). In marked contrast, the non-implanted group showed increases in all MR parameters.

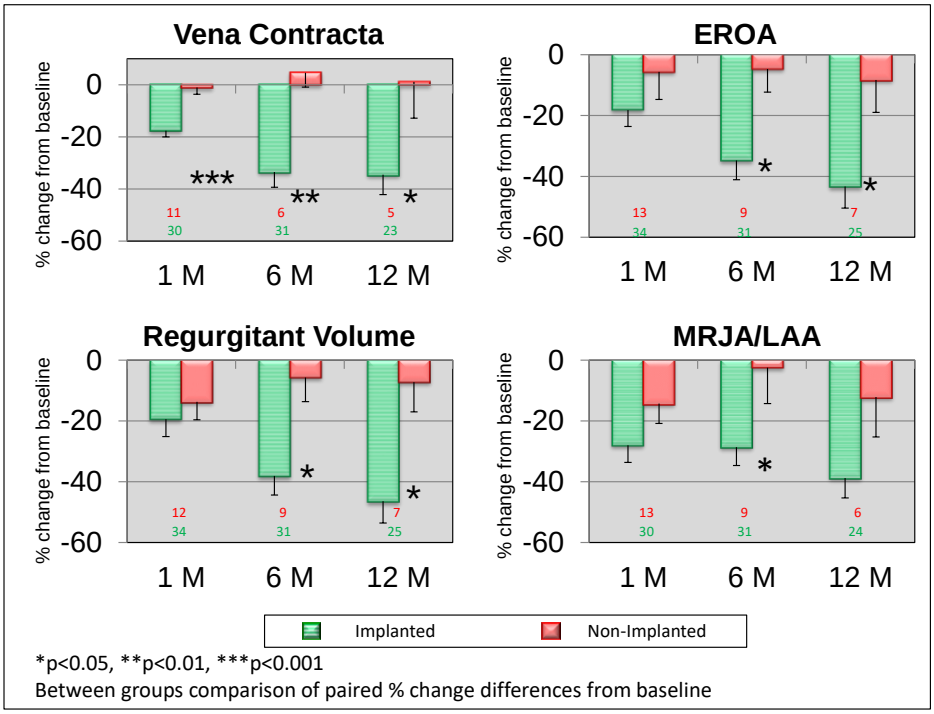

Figure 7.4: Mitral Regurgitation Parameters – Implanted vs. Non-Implanted Patients

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The overall MR grade in the implanted group improved from baseline such that 81% of patients were MR grade 3+ or 4+ at baseline, by 1 month this decreased to only 45% and by 12 months to only 20%. At 12 months the majority of patients (80%) now being MR grade 2+ or better. Notably, 12% (3/25) of patients in the implanted group at 12 months showed none or only trace amounts of MR (MR grade 0).

There was no indication of systolic anterior motion or of mitral stenosis in any of the implanted patients at any of the follow-up time intervals.

Effects of CARILLON Device on Hemodynamic Assessments

The mean left ventricular end diastolic and end systolic volumes decreased from baseline in the implanted group, showing the largest decreases at 12 months of -9.5% and -12.1%, respectively. This was reflected in increases in left ventricular ejection fraction of 18.7% at 12 months. These changes suggest reverse remodeling of the left ventricle in response to the reduction in mitral regurgitation.

In marked contrast, the non-implanted group showed further enlargement in both left ventricular end diastolic and end systolic volumes at 12 months of 12.2% and 9.6%, respectively, characteristic of heart failure progression.

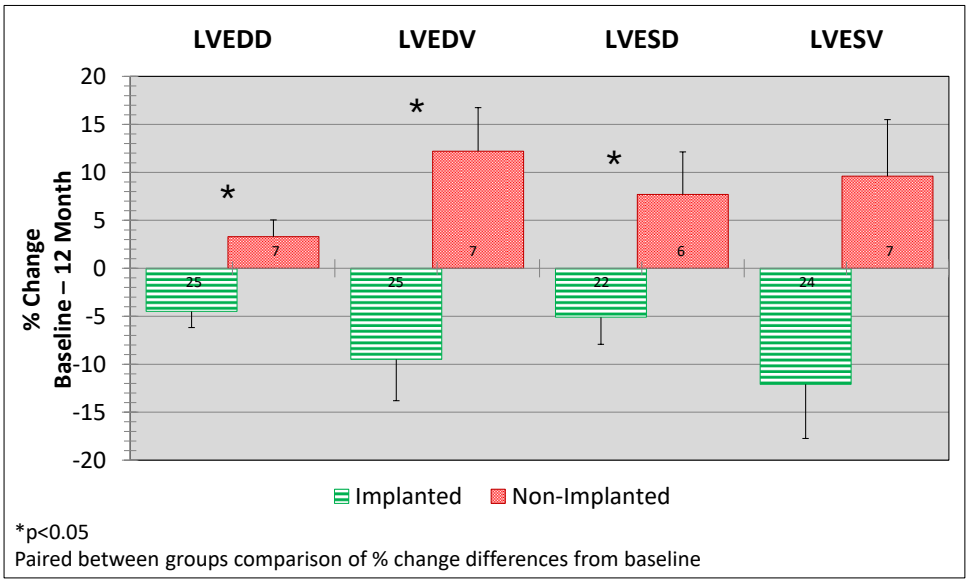

Figure 7.5: Left Ventricular Dimensions – Implanted vs. Non-Implanted Patients

Effects of CARILLON Device on Functional Assessments

The effects of the CARILLON Mitral Contour System on improvement in functional performance are described by the changes in NYHA class, exercise tolerance as measured by the Six Minute Walk Test (6MWT), and Quality of Life (QOL) as assessed by the KCCQ assessment.

<u>6MWT</u>

In the implanted group, the 6MWT showed appreciable increases across all time points. The mean absolute increases in walking distance at 1, 6 months and 12 months compared to baseline were 93.7 meters (34.5% increase), 114.6 meters (40.1% increase) and 102.5 meters (36.7%), respectively.

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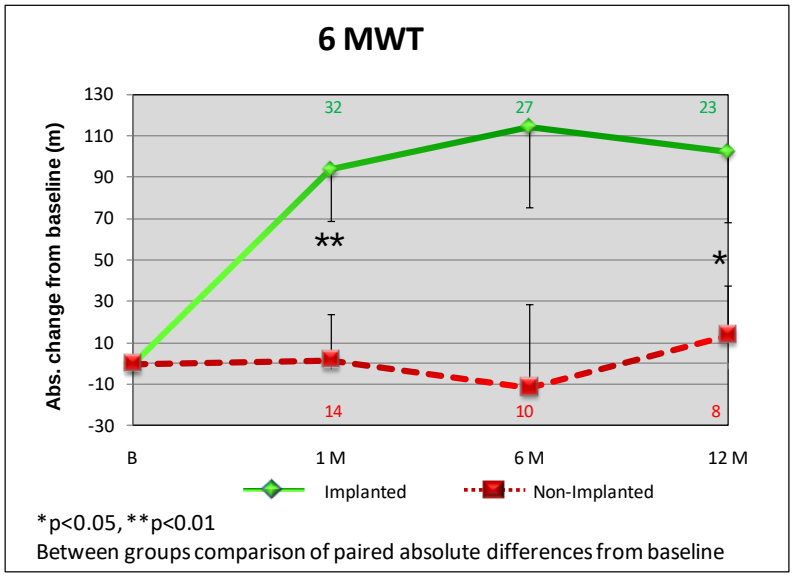

Figure 7.6: 6 Minute Walk Distance – Implanted vs. Non-Implanted Patients

In marked contrast, the non-implanted cohort showed a mean absolute change compared to baseline of only 1.8 meters (3.2% increase) at 1 month, a decrease in walking distance of 11.5 meters (5.4%) at 6 months and an increase of 13.9 meters (1.4%) at 12 months, indicating no improvement in exercise capacity for the non-implanted group.

NYHA

The NYHA class improved in the implanted group from baseline such that at 1 month 84.4% of patients showed an improvement of at least one NYHA class; this improvement is maintained at 6 and 12 months where 75.9% and 76%, respectively, still benefited from a one class improvement in NYHA class.

In contrast, the non-implanted group showed only 15.4% of patients had improved by one NYHA class at 1 month, only 40% improved at 6 months and 62.5% improved at 12 months. The percent improvement seen at 12 months is probably a reflection of low evaluable numbers.

KCCQ

The KCCQ data, a reflection of the quality of life in these patients showed a mean 20 point 109% improvement at 1 month which was maintained at 6 (21.5 point, 73% improvement) and 12 months (17.3 point, 62% improvement). In contrast, the non-implanted cohort showed only a 5 point change at 1 month, with no additional change at 6 (4 point change) and 12 months (6 point change).

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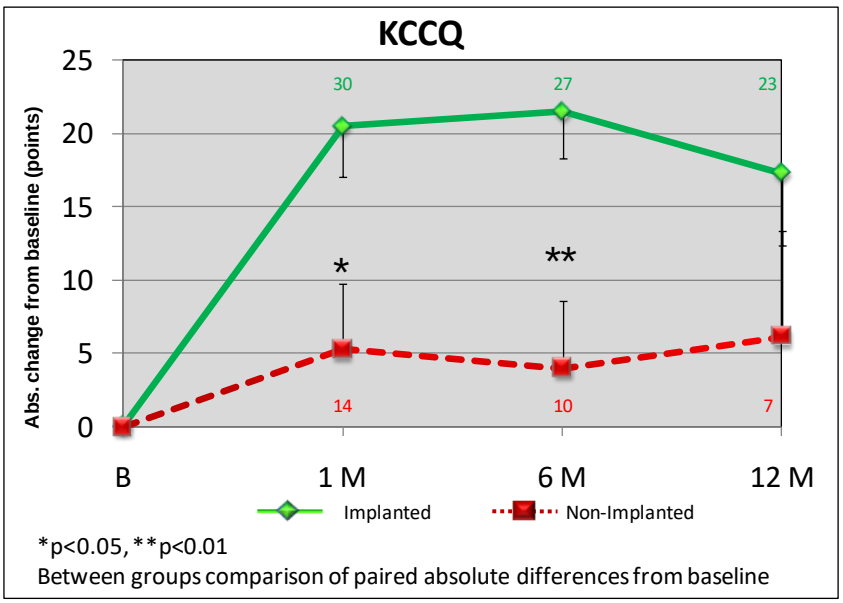

Figure 7.7: KCCQ Score (QoL assessment) – Implanted vs. Non-Implanted Patients

8. TITAN II Clinical Trial

The TITAN II trial was initiated as a confirmatory study to assess the modified CARILLON device. In particular, to determine if the modified device either resolved or minimized the rate associated with loss of device integrity, while still preserving the improvements in mitral valve regurgitation, leading to concomitant improvements in functional performance and left ventricular hemodynamics, as seen in the TITAN trial.

TITAN II Clinical Trial Development

As with the TITAN trial, the primary objective of the TITAN II trial was to evaluate the safety of deploying and implanting the CARILLON device in the coronary sinus/great cardiac vein in patients with functional mitral regurgitation. The secondary objectives were to determine the long-term safety of the device, and the effect of the device on hemodynamics and patient function.

Study Safety Oversight

This study included an independent Data and Safety Monitoring Board (DSMB). The DSMB reviewed the safety data against the established criteria and in the context of other safety data accumulated to date and the continued validity of the study. The DSMB also reviewed the adverse event rates and evaluated study progress when unexpected adverse events occurred.

Statistical Analysis

Data collected in this study were documented using summary tables and patient data listings. Statistical significance testing is reported where appropriate. There was no imputation for missing data.

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TITAN II Clinical Trial Results

Patient Disposition

The patient disposition flow diagram for all patients enrolled in the TITAN II trial is shown below in Figure 8.1.

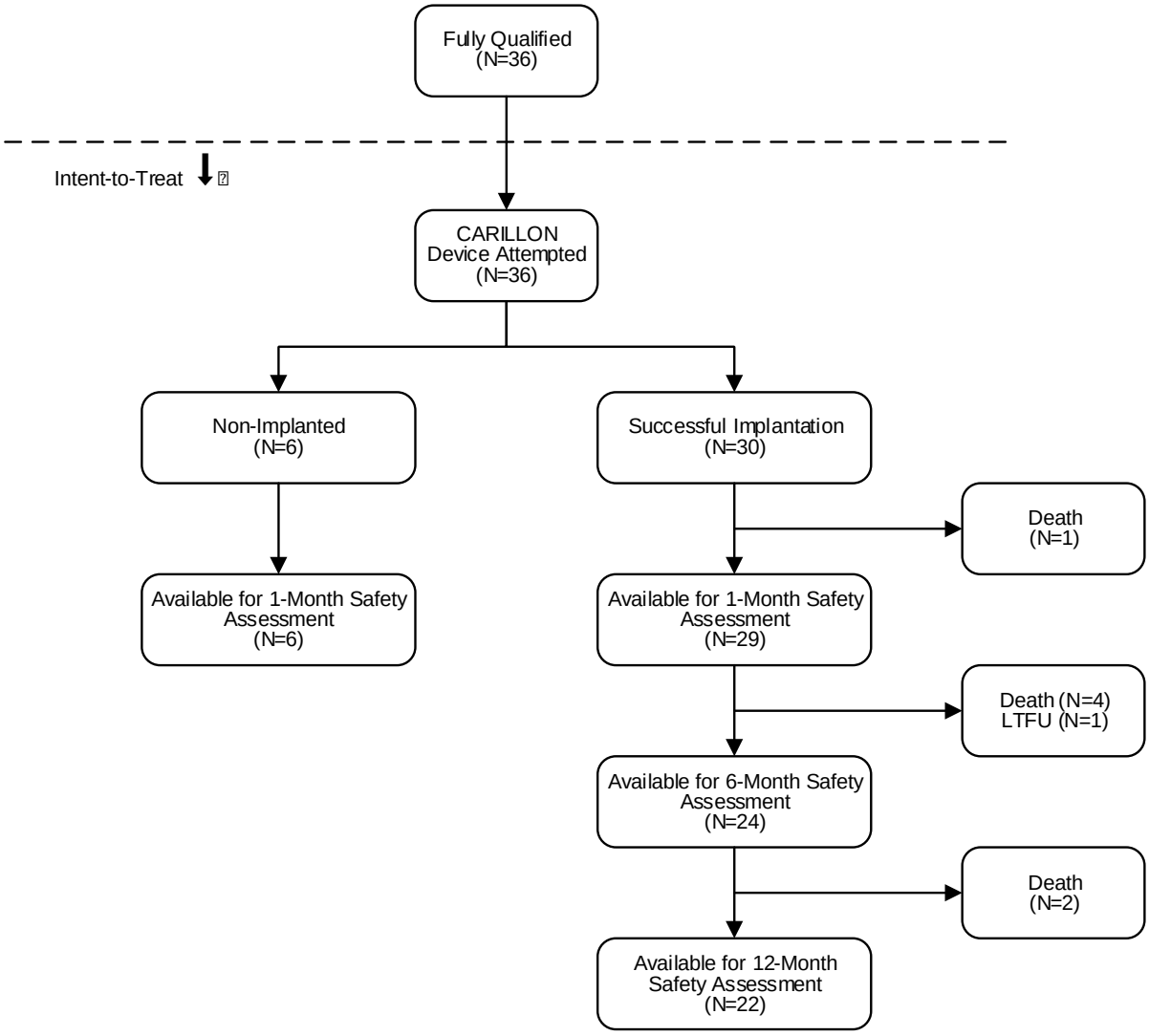

Figure 8.1: TITAN II Patient Disposition

A total of 36 patients comprised the intent-to-treat population ("ITT patients"). Of these, 30 patients were successfully implanted with the CARILLON Mitral Contour System ("implanted patients") for an 83% implant success rate and 6 patients did not receive a permanent implant ("non-implanted patients"). Non-implanted patients were followed through discharge and assessed for adverse events through 30 days before being exited from the study. Implanted patients were followed through the protocol specified duration of 12 months.
Of the 30 implanted patients:

- Twenty-two (22) patients required just one device attempt to gain sufficient MR reduction with no coronary artery compromise resulting in permanent placement of the CARILLON device.

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- Seven (7) patients required two implant attempts in order to meet the requirements for permanent placement
- One (1) patient required three implant attempts in order to meet the requirements for permanent placement

Of the 6 non-implanted patients:

- Three (3) patients had one implant attempt, but did not receive a device due to coronary artery compromise.

Of the remaining three (3) patients, two (2) patients had two implant attempts and one patient had three implant attempts. All of these patients did not receive a device due to coronary artery compromise.

Patient Demographics

The key patient demographics for both the implanted and non-implanted patients are summarized in Table 8.1.

Table 8.1: Key Demographic Characteristics

Patient Characteristic	Implanted Patients (N=30)	Non-Implanted Patients (N=6)
Age, mean & SD, yr	70.3 ±8.7	72.0 ±7.6
Gender, n (%), Male		
Male	70.0% (21/30)	50.0% (3/6)
NYHA Classification, % (n)		
Class I	0% (0/30)	0% (0/6)
Class II	3.3% (1/30)	16.7% (1/6)
Class III	90.0% (27/30)	83.3% (5/6)
Class IV	6.7% (2/30)	0.0% (0/6)
6 minute walk, mean & SD, m	294.07 ±82.59 (29)	258.33 ±108.38 (6)
Medical History, n (%)		
Hx of Diabetes	30.0% (9/30)	33.3% (2/6)
Hx of Hypertension	70.0% (21/30)	66.7% (4/6)
Hx of CAD	60.0% (18/30)	33.3% (2/6)
Hx of CABG	38.9% (7/18)	0.0% (0/2)
Ischemic Cardiomyopathy	60.0% (18/30)	50.0% (3/6)
Number of HF admissions in past 12 months, mean (SD)	1.48 ±1.19 (27)	1.75 ±1.7 (4)

The majority of patients were male, NYHA class III, with a six minute walk distance consistent with a patient population having moderate heart failure.

CARILLON Device and Procedure Characteristics

The overall device, implant and procedure success are shown in Table 8.2.

Implant success was defined as:

- Successful permanent implantation of the CARILLON investigational device and was further categorized into cases requiring just one attempt and cases requiring more than one attempt.

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Overall implant success was 83%, with 30 of 36 patients receiving a permanent implant. In 73% of these cases (22/30) the device was able to reduce MR and be implanted on the first attempt. In the remaining 8 cases, the device was able to be recaptured appropriately (due to coronary artery compromise) and a subsequent attempt(s) resulted in a satisfactory MR result allowing permanent implant.

Table 8.2: Device and Procedure Success Rate

Patient Characteristics	Intent to Treat Population (N=36)
Implant Success	83.3% (30/36)
At first attempt	73.3% (22/30)
Requiring >1 attempts	26.7% (8/30)

There were a total of 47 device deployment attempts in the 36 patients who underwent the implant procedure. In the implanted population, eight (8) of 30 patients (27%) required more than one device attempt. In the non-implanted population, two (2) of 6 patients (33%) required more than one device attempt.

Safety – Major Adverse Events

Key adverse events have been identified as relating specifically to the safety of the CARILLON Mitral Contour System. These adverse events were termed major adverse events (MAE). Safety was evaluated as the 30-day (or hospital discharge date, whichever was longer) rate of MAEs defined as the composite endpoint of:

- Death
- Myocardial infarction
- Cardiac perforation necessitating catheter-based or surgical intervention
- Device embolization
- The occurrence of surgery or percutaneous coronary intervention related to the device (e.g., device related infection/septicemia).

The 30-day MAE rate for the ITT population is listed in Table 8.3.

Table 8.3: Principal Safety Results – Intent to Treat Population

Primary Safety Endpoint: < 30 days post-procedure (or hospital discharge date)	Intent to Treat Population (N=36)
Major Adverse Events	**2.8% (1/36)**
Death	2.8% (1/36)
Myocardial Infarction	0% (0/26)
Cardiac Perforation Necessitating Catheter-based or Surgical Intervention	0% (0/36)
Device Embolization	0% (0/36)
Surgery or Percutaneous Coronary Intervention Related to the Device	0% (0/36)

* ITT patients include all subjects who were enrolled to the study and in whom CARILLON implantation was attempted (non-implanted and implanted patients).

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At 30 days, the MAE rate was 2.8% (1/36) in the ITT population. This consisted of one death (patient 802-001) in a patient having a history of ischemic cardiomyopathy, NYHA class III, atrial fibrillation, ICD implant, CABG, myocardial infarction, smoking, and hyperlipidemia. Successful placement of the CARILLON device occurred on March 28, 2012. The patient died on April 14, 2012 as a result of an initial GI infection/inflammation which in combination with the patient's existing severe heart failure, previously compromised renal function and poor cardiac reserve, caused a multi-system cardiac decompensation ultimately leading to the patient's death. The adverse event was adjudicated to be unrelated to either the procedure or the device.

Table 8.4 shows the principal safety results (30-day MAE rate) separated into the implanted and non-implanted groups. The results show that at 30 days, the MAE rate in the implanted population was 3.3% (1/30). There were no MAEs in the non-implanted population through the 30-day follow-up. Thus, the CARILLON procedure overall has a very good safety profile.

Table 8.4: Principal Safety Results – Comparison of Implanted and Non-Implanted Patients

Primary Safety Endpoint: < 30 days post-procedure (or hospital discharge date)	**Subjects with Successful Implantation (N=30)**			**Non Implanted Population* (N=6)**		
	Device Related	**Procedure Related**	**Total**	**Device Related**	**Procedure Related**	**Total**
Major Adverse Events	**0% (0/30)**	**0% (0/30)**	**5.9% (1/30)**	**0% (0/6)**	**0% (0/6)**	**0% (0/6)**
Death	0% (0/30)	0% (0/30)	5.9% (1/30)	0% (0/6)	0% (0/6)	0% (0/6)
MI	0% (0/30)	0% (0/30)	0% (0/30)	0% (0/6)	0% (0/6)	0% (0/6)
Cardiac Perforation Necessitating Catheter-based or Surgical Intervention	0% (0/30)	0% (0/30)	0% (0/30)	0% (0/6)	0% (0/6)	0% (0/6)
Device Embolization	0% (0/30)	0% (0/30)	0% (0/30)	0% (0/6)	0% (0/6)	0% (0/6)
Surgery or Percutaneous Coronary Intervention Related to the Device	0% (0/30)	0% (0/30)	0% (0/30)	0% (0/6)	0% (0/6)	0% (0/6)

The total MAE rate (all MAEs through the data lock for this report) for implanted patients is shown in Table 8.5. The long-term MAE rate in implanted patients was 23.3% (7/30 patients). All of these events resulted in deaths, however, none of these MAEs were adjudicated to be either procedure or device related.

Table 8.5: Long-Term Safety Results –Implanted Patients

Total MAEs*	**Implanted Population (N=30)** ---------- **Proportion**		
	Device Related	**Procedure Related**	**Total**
Major Adverse Events	0% (0/30)	0% (0/30)	23.3% (7/30)
Death	0% (0/30)	0% (0/30)	23.3% (7/30)
MI	0% (0/30)	0% (0/30)	0% (0/30)
Cardiac Perforation Necessitating Catheter-based or Surgical Intervention	0% (0/30)	0% (0/30)	0% (0/30)
Device Embolization	0% (0/30)	0% (0/30)	0% (0/30)
Surgery or Percutaneous Coronary Intervention Related to the Device	0% (0/30)	0% (0/30)	0% (0/30)

*Includes all implanted subjects who experienced a MAE through the final data lock for this study – 23 September 2014.

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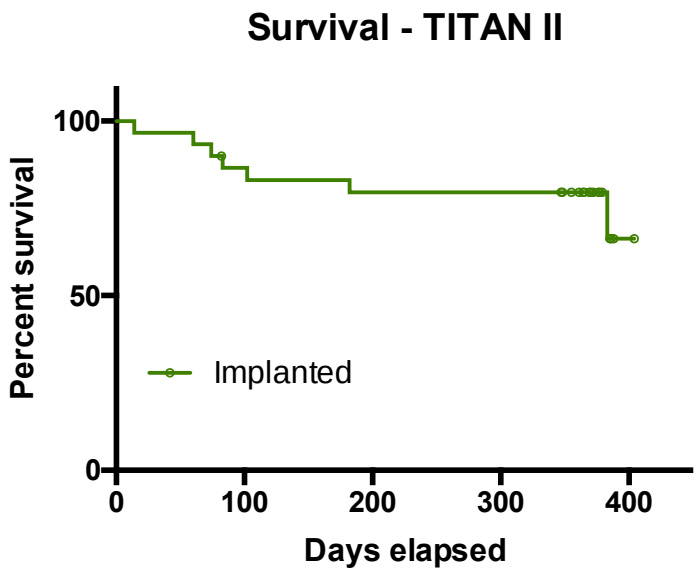

Figure 8.2: TITAN II Survival Curve

Device Integrity

Twenty-nine (29) of the 30 patients successfully implanted with the CARILLON Mitral Contour System in Titan II showed no anchor wireform fracture at follow-up. There was one implant anchor fracture observed at 3 month follow-up that was most likely due to damage from implant redeployment following implant recapture, which is contrary to the instructions for use and physician training.

Effects of CARILLON Device on MR Assessments

The effects of the CARILLON Mitral Contour System on echocardiographic derived MR parameters (evaluated at baseline, 1 month, 6 months and 12 months of follow-up) for the implanted group are presented below.

Mitral Annular Diameter

Mitral annular diameter (measured in the anteroseptal-posterolateral plane) decreased markedly at 1 month, showing a 15.3% decrease from baseline. This decrease in annular diameter remained through the 6 and 12 month follow-ups. This change in mitral annular diameter is similar to that found in the previous TITAN study.

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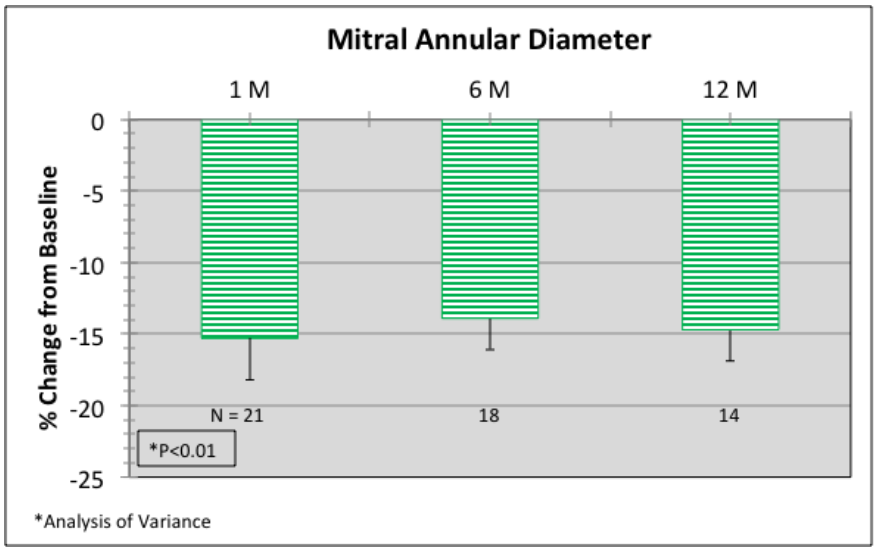

Figure 8.3: Mitral Annular Diameter - Change from Baseline

MR Parameters

The overall MR grade in the implanted group improved from baseline such that 64% of patients were MR grade 3+ or 4+ at baseline, by 1 month this decreased to 42% and by 12 months to only 25%.

At 12 months the majority of patients (75%) now being MR grade 2+ or better (lower). Notably, 13% (2/16) of patients at 12 months showed none or only trace amounts of MR (MR grade 0).

The four key echocardiographic indices of MR – vena contracta, effective regurgitant orifice area (EROA), regurgitant volume (RV), and MR jet area/left atrial are (MRJA/LAA) – all showed decreases from baseline through 1 month ranging between -17% and -25%. These changes decreased further for all these parameters at 12 months (ranging from decreases of -24% to -37%).

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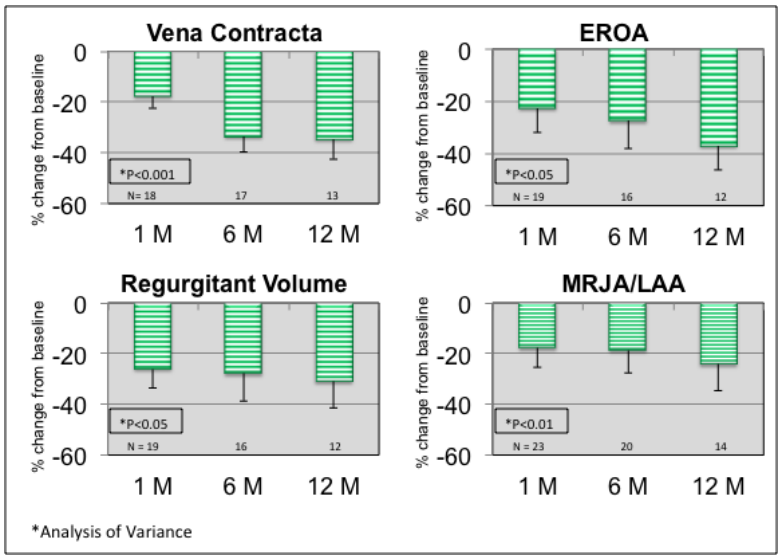

Figure 8.4: Quantitative Mitral Regurgitation Parameters – Change from Baseline

There was no indication of systolic anterior motion or of mitral stenosis in any of the implanted patients at any of the follow-up time intervals.

Effects of CARILLON Device on Hemodynamic Assessments

The mean left ventricular end diastolic (LVEDV) and end systolic volumes (LVESV) decreased from baseline, showing the largest decreases at 12 months of -5.2% and -9.4%, respectively. This was reflected in increases in left ventricular ejection fraction of 18.7% at 12 months. Although not statistically significant, these changes suggest reverse remodeling of the left ventricle in response to the reduction in mitral regurgitation.

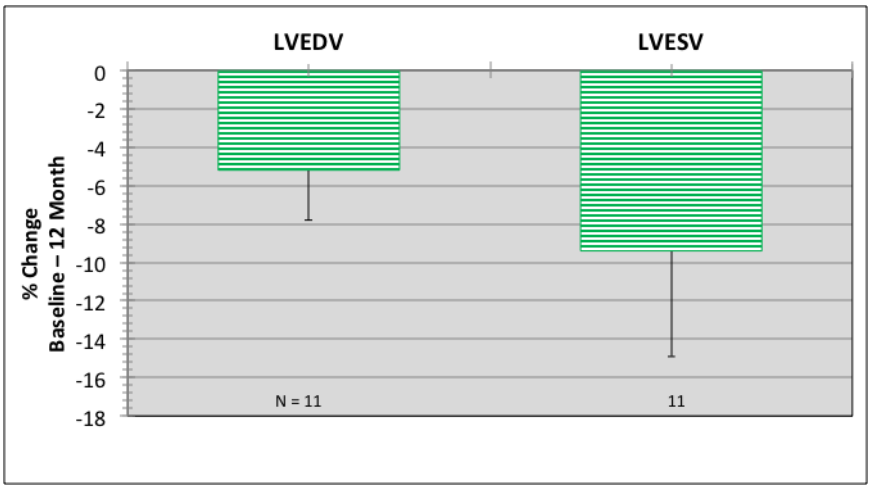

Figure 8.5: Left Ventricular Volumetric Parameters – Change from Baseline

Effects of CARILLON Device on Functional Assessments

The effects of the CARILLON Mitral Contour System on improvement in NYHA class and exercise tolerance as measured by the 6MWT are shown below.

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NYHA

The NYHA class improved from baseline such that at 1 month 79.3% of patients showed an improvement of at least one NYHA class; this improvement is maintained at 6 and 12 months where 83.3% and 77.3%, respectively, still benefited from a one class improvement in NYHA class.

6MWT

The 6MWT showed an immediate increase at 1 month post procedure and this remained durable through the 12-month follow-up. The mean absolute increases in walking distance at 1, 6 months and 12 months compared to baseline were 77.3 meters (28.4% increase), 84.3 meters (27.2% increase) and 77.6 meters (26.4%), respectively.

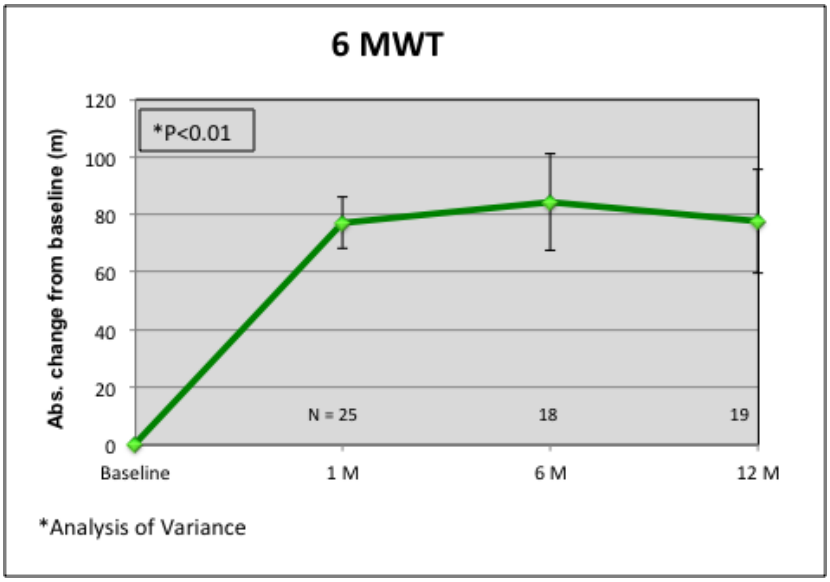

Figure 8.6: 6 Minute Walk Distance – Change from Baseline

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XV. Definitions

The symbols used on the handle assembly and their definitions are listed below:

Symbol	Definition
	Caution, see instructions for use
	Control symbol
	Lock symbol
	Release symbol

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The symbols used in the product labeling and their definitions are listed below:

Symbol	Definition
	Do not reuse - Single use
	Do not use if package is damaged
	Use by
	Method of sterilization using ethylene oxide
	Lot number
	Catalogue (model) number
http://www.cardiacdimensions.com /physicians/instructions-for-use/	Consult instructions for use on this website.
	Manufacturer
	MR conditional
	Keep dry
	Keep away from sunlight

XVI. Manufacturer

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Patent- http://www.cardiacdimensions.com/company/IP.html

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