CARILLON Mitral Contour System® (XE2)

Instructions for Use

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INSTRUCTIONS FOR USE

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

I. Intended Purpose

The CARILLON Mitral Contour System is intended to reduce secondary mitral regurgitation within 12 months of implantation.

II. Indication

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; and
- Presence of annulus dilatation as primary contributor to the significant MR; and
- 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 have a mitral annuloplasty ring implant

IV. Intended Users

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

V. 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 Section IX, 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.

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- 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.

VI. 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 corona[illegible] vessel
- Embolism of air, tissue, device or thrombus
- Hematoma
- Hemodynamic deterioration
- Implant fracture
- Inability to permanently place th[illegible]impla
- Infection
- Inflammation
- Lack of mitral regurgitati[illegible]edu[illegible]on
- Loss of mitral regurgi[illegible]tion [illegible]duction
- Mitral stenosis
- Multi-organ failure
- Myocardial i[illegible]arction
- Myocardial isc[illegible]mia
- Occlus[illegible]n of a co[illegible]y vessel
- Peric[illegible]dial[illegible]ion
- Pneumothorax
- Prolonged [illegible]posure to fluoroscopic radiation
- Renal failure
- Stroke
- Surgical removal of the implant
- Tissue necrosis
- Tissue penetration
- Transient ischemic attack
- Vasovagal reaction
- Vessel erosion
- Vessel spasm
- Worsening heart failure

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VII. 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.
- **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

- The Carillon implant is recommended for use when a multi-disciplinary and specialized heart team determines that a reduction in Regurgitant Volume can be reasonably expected within 12 months of implantation. The expected reduction in Regurgitant Volume can be inferred from previous study data. Reference Section XIV for clinical study safety and performance information.
- 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-obstruction 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.

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- Results from clinical studies indicate that some patients may have a coronary artery near the great cardiac vein which can lead to acute coronary compromise and recapture of the implant during the Carillon procedure. The expected occurrence rate can be inferred from previous study data. Reference Section XIV for clinical study safety and performance information.
- 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.
- 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 snares 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.

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VIII. System Description

The Cardiac Dimensions 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.

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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). The implant is designed to be deployed, tensioned, and secured in the coronary vein.

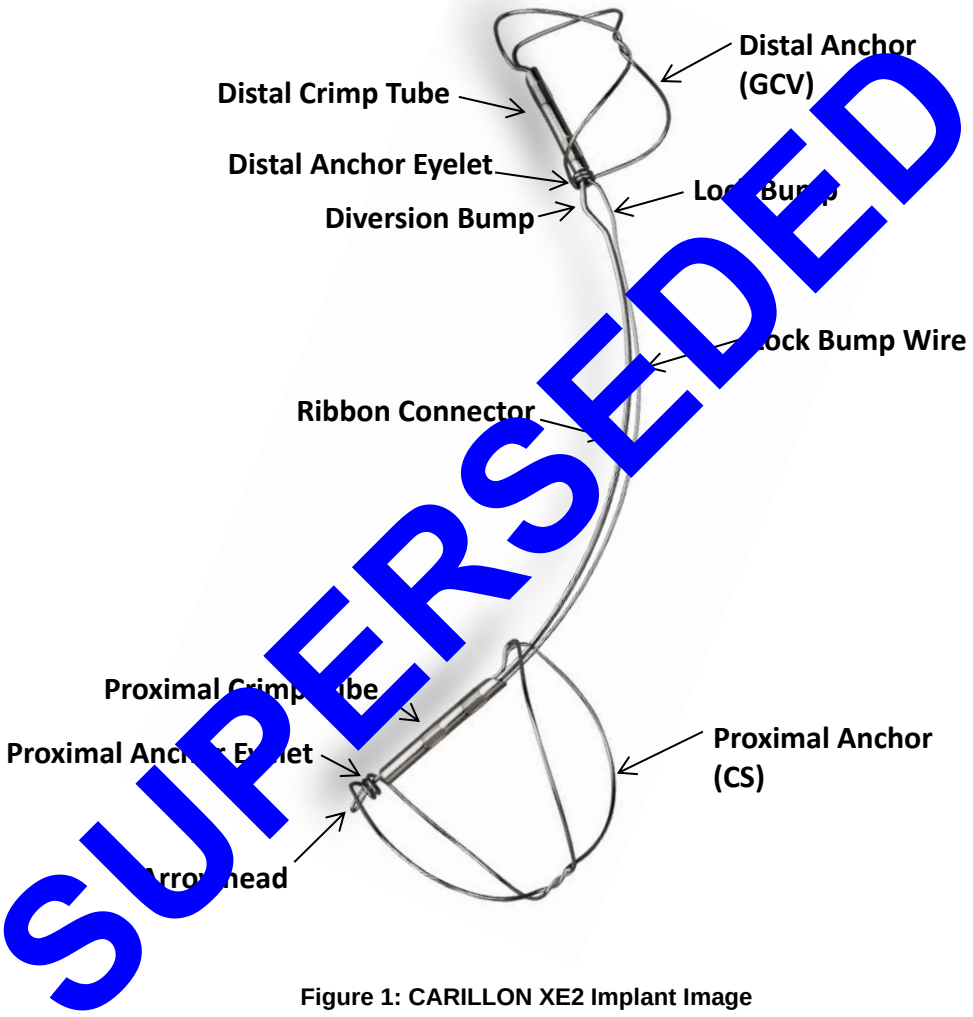

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Figure 1: CARILLON XE2 Implant Image

- **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 (Figure 2). 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.

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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.

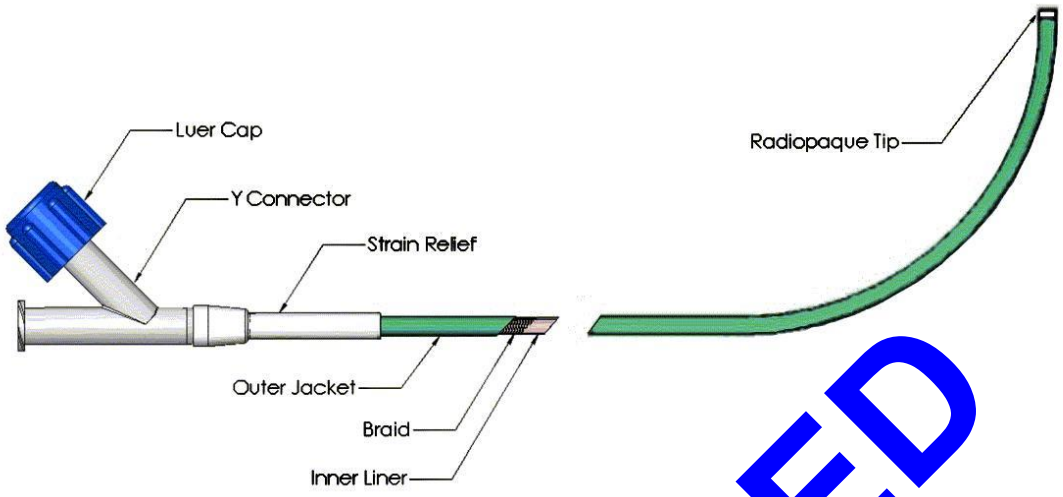

Figure 2: CMCS Delivery Cath

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Handle Assembly:

The handle assembly is composed of a cartridge, a heat/pusher assembly and a handle assembly with cartridge window, rotating knobs, and release safety (Figure 3). The distal end of the cartridge (male luer) connects to the luer fitting of the strain 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).
- 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.

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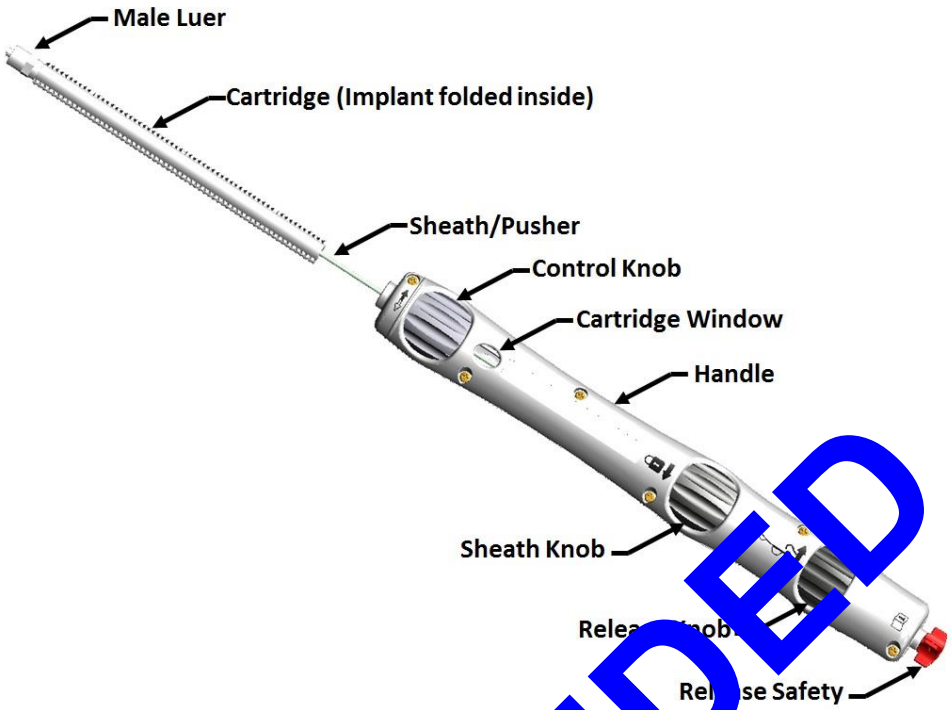

Figure 3: CARILLON [illegible] Assembly

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- **Sizing Catheter**

  The sizing catheter is used to estima[illegible] the [illegible]verall CS/GCV dimensions so that an appropriately sized implant may be selected. The [illegible]er is inserted into the delivery catheter and advanced until the most distal [illegible]rker b[illegible]d is aligned with the radiopaque marker at the tip of the delivery catheter. Venous si[illegible]estim[illegible]ates a[illegible]e then determined by the physician using venograms captured with fluoroscopy.

  The sizing catheter co[illegible]sist[illegible]f po[illegible]er shaft, a hub with a luer connector at the proximal end, a polymer strain relief, [illegible]dio[illegible]que marker bands, and a clear distal sleeve covering the marker bands (Figure 4).

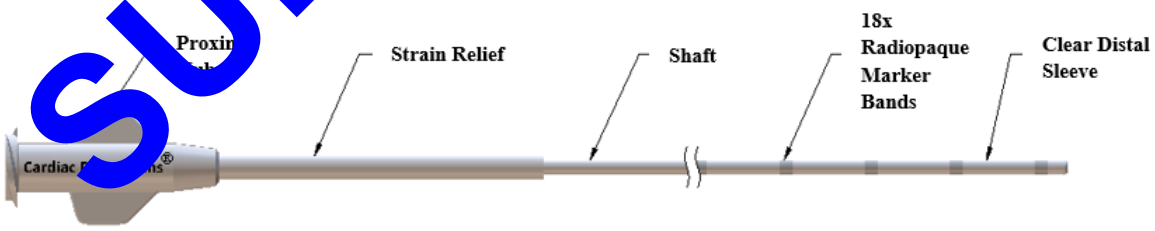

Figure 4: CARILLON Sizing Catheter

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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 pattern

   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 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.

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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 fluoroscopy 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.

c. 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.

d. 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.

e. If the CMCS delivery catheter needs to be advanced in order to cross 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.**

f. 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.

g. 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.

h. 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 (Figure 5). 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 6) 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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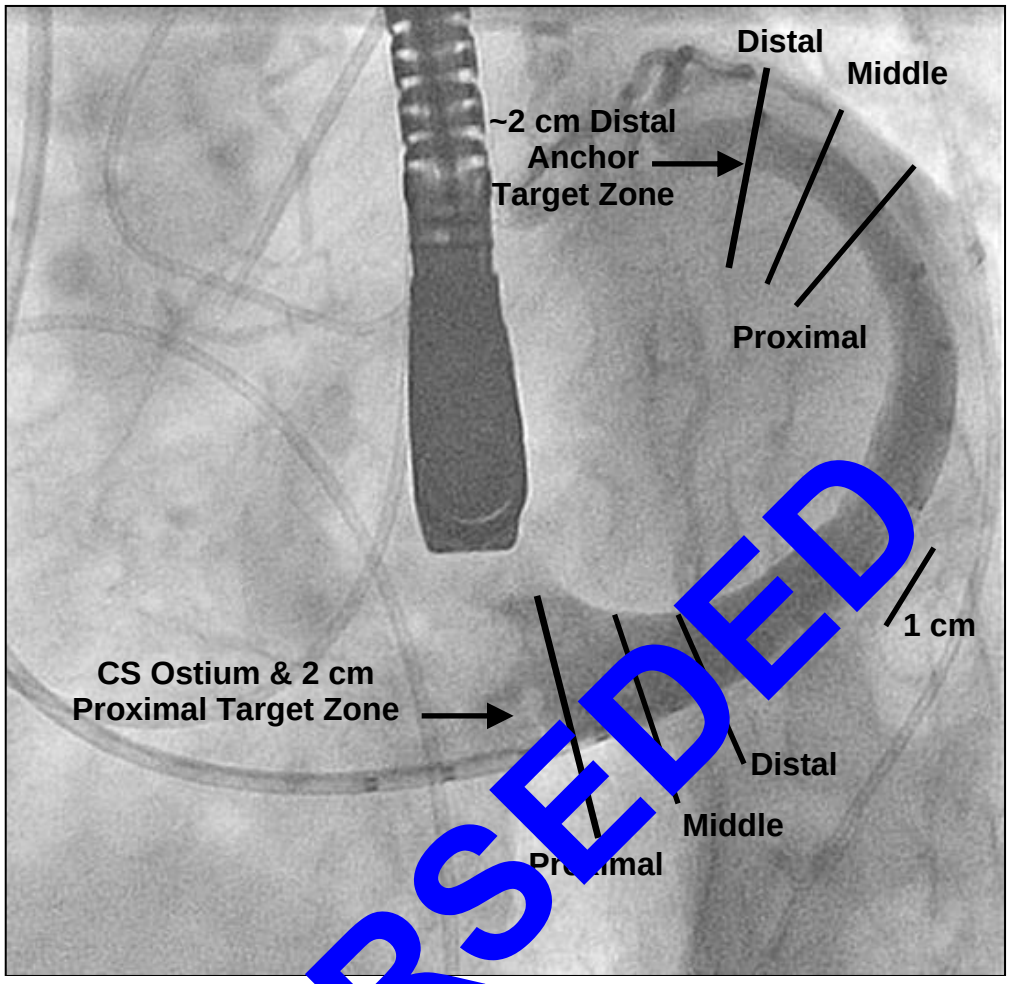

Figure 5: SCV/CS Venogram – Vein Sizing

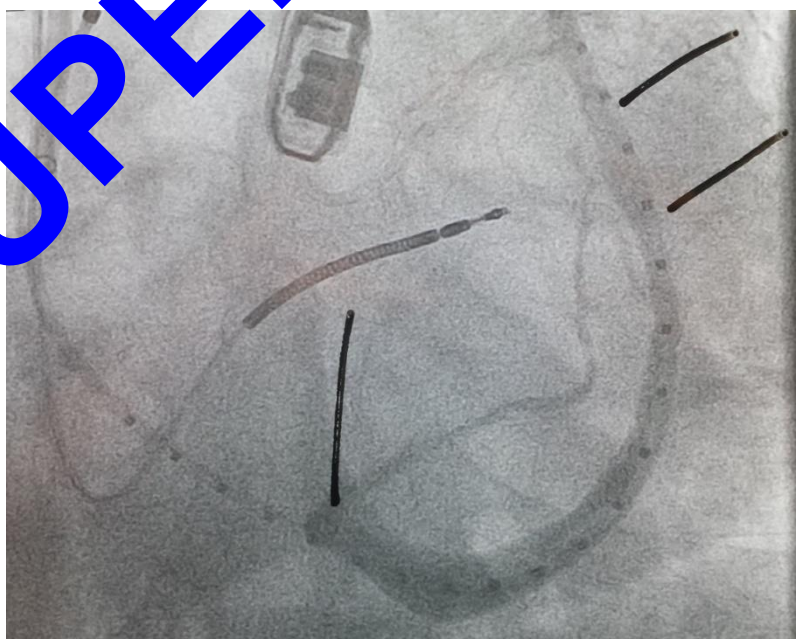

Figure 6: Example of Marked Monitor Screen for Anchor Placement

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i. 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 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 1: CARILLON XE2 Anchor Sizing Recommendation

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 – [illegible]	12
4.0 – 4.4	8	[illegible] – 7.9	14
4.5 – 4.9	9	8.0 – [illegible].9	16
5.0 – 5.6	10	[illegible].0 – 10.9	18
5.7 – 6.3	11	11 – 13.5	20
6.4 – 7.2	12		
7.3 – 7.8	13		
7.9 – 8.4	14		

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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 clockwise direction, opposite the black locking arrow (Figure 7), ensuring the proximal locking sheath is fully retracted.

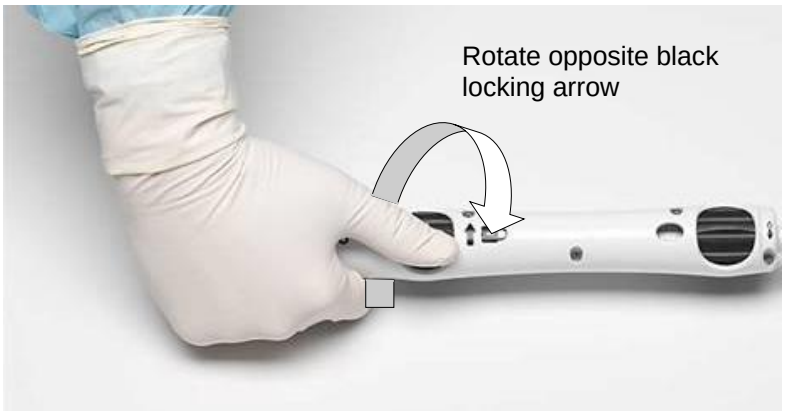

Figure 7: Counter-Rotating the Sheath Locking Knob

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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 8).

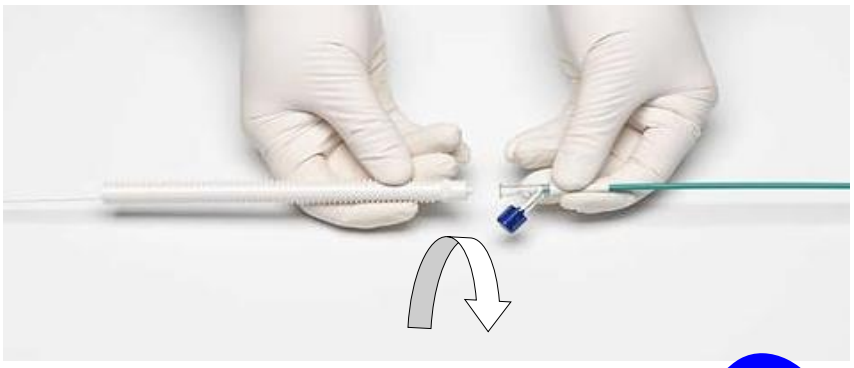

Figure 8: Connecting the Cartridge to the Straight Port of the Delivery Catheter

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 9). Continue to advance the sheath/pusher assembly until the handle and cartridge come together.

Figure 9: 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 10).

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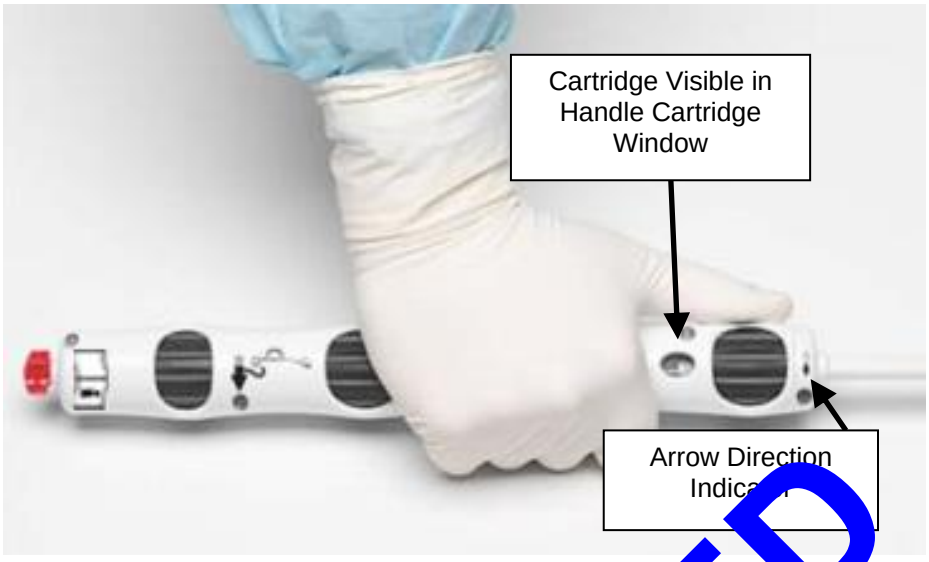

Figure 10: Cartridge is Visible in the Handle Cartridge Window

ATTENTION: The remaining Device Implantation steps must be performed with fluoroscopic guidance.

f. Using fluoroscopy (and/or cinefluoroscopy), confirm correct distal anchor orientation prior to unsheathing the distal anchor from the delivery catheter. The diversion bump should be closer to (and pointing towards) the inner curvature of the delivery catheter (Figure 11a). If the diversion bump is closer to (and pointing towards) the outer curvature of the delivery catheter (Figure 11b), then the distal anchor is incorrectly oriented and the distal anchor should not be deployed.

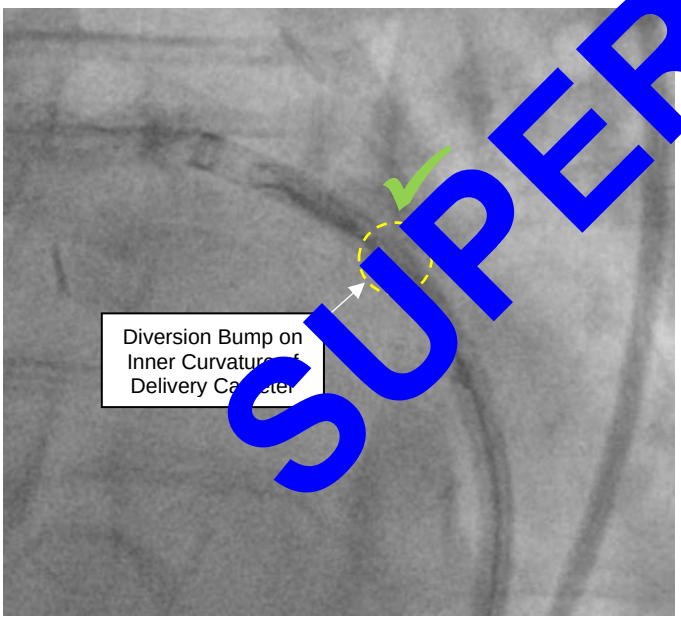

Figure 11a: Correct Distal Anchor Orientation

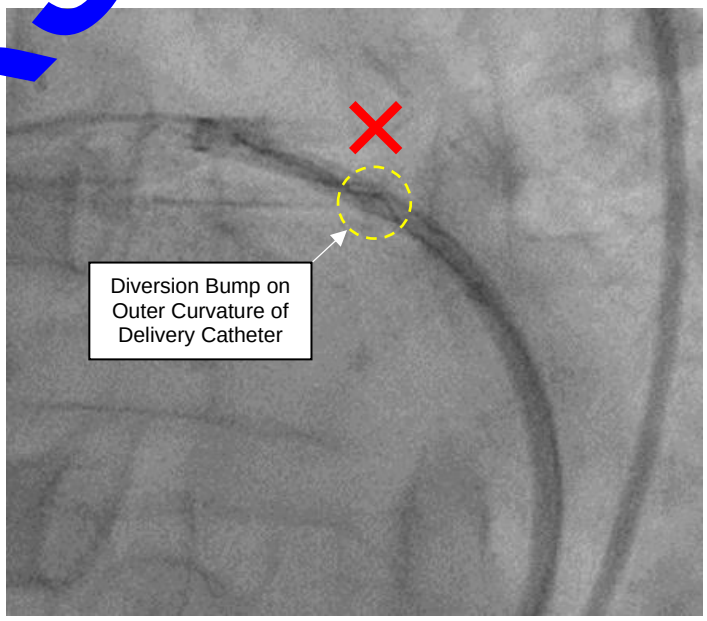

Figure 11b: Incorrect Distal Anchor Orientation

If a distal anchor with incorrect orientation is inadvertently unsheathed from the delivery catheter, recapture the implant. See Section IX, Step 5 – Implant Recapture.

g. 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 control knob to accurately deliver the distal anchor to the target location. Continue to rotate the control knob in

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the same direction until the distal anchor eyelet is completely out of the delivery catheter (Figure 12).

Figure 12: Rotating the Control Knob to Deploy the Distal Anchor

h. 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

i. 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.

j. 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.

k. 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 fluoroscopy screen) in the CS as guided by fluoroscopy.

l. 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.

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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).

m. 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 13).

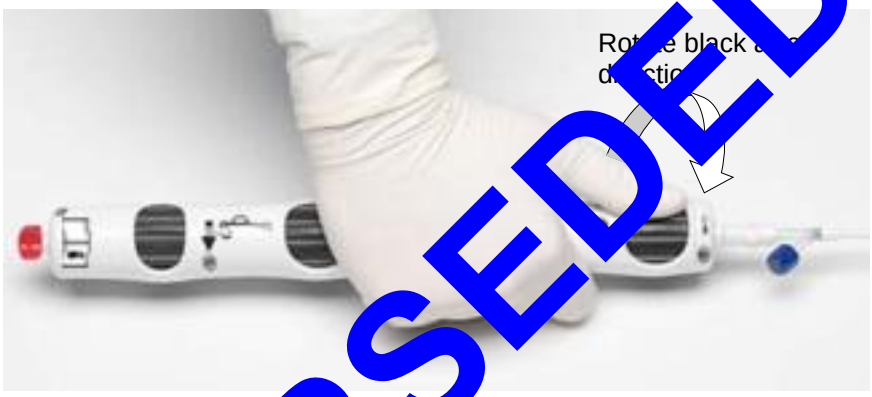

Figure 13: Rotating the Control Knob to Deploy the Proximal Anchor

n. 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 14).

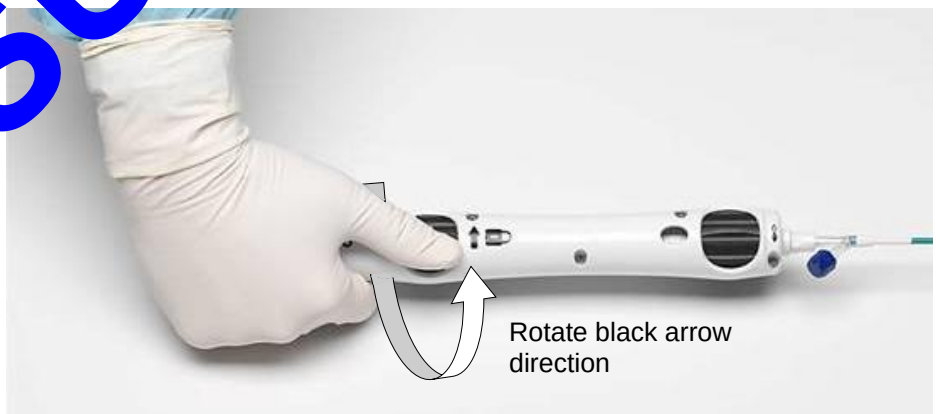

Figure 14: Rotating the Sheath Knob to Lock the Proximal Anchor

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o. 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.

p. 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 15a through 15d.

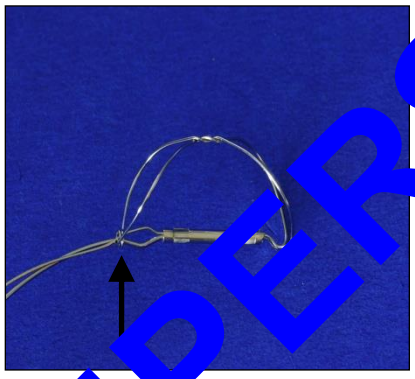

Figure 15a: Unlocked Distal Anchor

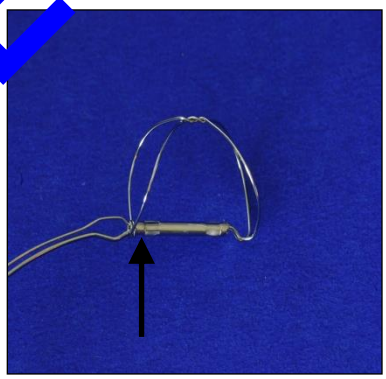

Figure 15b: Locked Distal Anchor

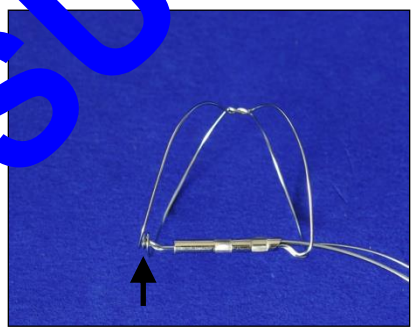

Figure 15c: Unlocked Proximal Anchor

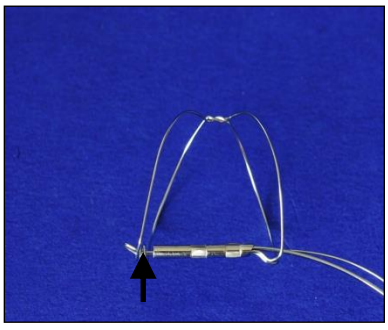

Figure 15d: Locked Proximal Anchor

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.

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

q. 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 16). Then rotate the release knob in the direction indicated by the decouple arrow until the implant is completely separated from the handle assembly (Figure 17).

Figure 16: Rotating and Removing the Release Safety

Figure 17: Rotating the Release Knob to Decouple the Implant from the Handle Assembly

r. With[illegible] the [illegible] assembly and attached CMCS delivery catheter out of the venous introducer sheath. Do not advance the system once the implant has been decoupled.

s. 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 18).

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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.

Figure 18: 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 sinus 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

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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 3.

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	251 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 preloaded 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 SINGLE 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

Cardiac Dimensions has completed three clinical studies (TITAN[1], TITAN II[2], and REDUCE FMR[3]) of the current configuration of the Carillon Mitral Contour System. A synopsis of each of these studies is provided below, with the study designs further summarized in Table 2.

TITAN

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. Thirty-six patients were implanted as part of the TITAN trial.

TITAN II

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. Thirty patients were implanted as part of the TITAN trial.

REDUCE FMR

The objective of this prospective, multi-center, randomized, double-blinded, post-market trial was to assess the efficacy of the Carillon Mitral Contour System in in treating FMR associated with heart failure, as compared to a randomized Control group which was medically managed according to heart failure guidelines. Safety was assessed as a secondary objective. One-hundred and twenty patients were randomized into one of two study groups using a 3:1 (Treatment population to Control population) ratio. Seventy-three patients were implanted as part of the REDUCE FMR post-market trial.

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Table 2: Summary of TITAN, TITAN II and REDUCE FMR Trials

Study	TITAN	TITAN II	REDUCE FMR
Sample Size	ITT (n=53) Implanted (n=36)	ITT (n=36) Implanted (n=30)	ITT (n=87) Implanted (n=73) Control (n=33)
Enrollment Dates	2008 - 2010	2011 – 2013	2015 - 2017
Study Type	Feasibility Prospective, multicenter, non-randomized dual arm Follow-up: Baseline, 1, 6, 12 months and annually through 5 years	Feasibility Prospective, multicenter, single-arm, non-randomized Follow-up: Baseline, 1, 6, & 12 months	Post-market Prospective, multicenter, double-blinded, randomized control Follow-up: Baseline, 1, 6, & 12 months

[1] Siminiak T, et. al. Treatment of functional mitral regurgitation by percutaneous annuloplasty: Results of the TITAN Trial. Eur J Heart Fail. 2012;14:931-38.
[2] Lipiecki J, Siminiak T, Sievert H, et al. Coronary sinus-based percutaneous annuloplasty as treatment for functional mitral regurgitation: the TITAN II trial. BMJ Open Heart. 2016; 3: e000411.
[3] Witte K, et al, A Randomized Sham-Controlled Study of Percutaneous Mitral Annuloplasty in Functional Mitral Regurgitation: The REDUCE FMR Trial. J Am Coll Cardiol, HFI, DOI: 10.1016/j, jchf.2019.06.011

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Table 2: Summary of TITAN, TITAN II, and REDUCE FMR Trials			
Study	TITAN	TITAN II	REDUCE FMR
Main Inclusion and Exclusion Criteria	**Inclusion**: • dilated ischemic/non-ischemic cardiomyopathy • moderate to severe Functional Mitral Regurgitation (2+, 3+, 4+) • LVEF < 40% • NYHA Class II - IV • age 18-80 yrs. • stable HF medication **Exclusion**: • hospitalization within the past three months for myocardial infarction, CABG surgery, or unstable angina • hospitalization within the past 30 days for coronary angioplasty • patients expected to require cardiac surgery with one year	**Inclusion**: • dilated ischemic/non-ischemic cardiomyopathy • moderate to severe Functional Mitral Regurgitation (2+, 3+, 4+) • LVEF < 40% • NYHA Class III - IV • age 18-80 yrs. • stable HF medication **Exclusion**: • hospitalization within the past three months for myocardial infarction, CABG surgery, or unstable angina • hospitalization within the past 30 days for coronary angioplasty • patients expected to require cardiac surgery with one year	**Inclusion**: • dilated ischemic/non-ischemic cardiomyopathy • moderate to severe Functional Mitral Regurgitation (2+, 3+, 4+) • LVEF ≤ 50% • NYHA Class II - IV • age 18-85 yrs. • stable HF medication **Exclusion**: • hospitalization within the past three months for myocardial infarction, CABG surgery, or unstable angina • hospitalization within the past 30 days for coronary angioplasty • patients expected to require cardiac surgery with one year
Endpoints	**Primary**: Major Adverse Event (MAE) Rate through 30 days. • 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)	**Primary**: Major Adverse Event (MAE) Rate through 30 days. • death • myocardial infarction • cardiac perforation necessitating catheter-based or surgical intervention [SEP] • 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	**Primary**: Significant improvement of Regurgitant Volume (RV) relative to the Control population. **Major Secondary**: Major Adverse Event (MAE) Rate through 30 days and 12 months • death • myocardial infarction • device embolization • vessel erosion • cardiac perforation necessitating catheter-based or surgical intervention [SEP] • occurrence of surgery or percutaneous coronary intervention related to the device HF hospitalizations 6-minute walk distance Left ventricular volumes
# of sites and patients	7 sites 53 intent-to-treat patients 36 implanted patients (followed through 5 years) 17 non-implanted patients (followed through 1 year only)	5 sites 36 intent-to-treat patients 30 implanted patients (followed through 1 year only) 6 non-implanted patients (followed through 30 days only)	31 sites 120 randomized patients (followed through 1 year) 87 intent-to treat patients 73 implanted patients 30 control patients

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1. Safety

Key Demographics

Key demographic characteristics of the implanted patient populations for the TITAN, TITAN II, and REDUCE FMR studies is shown below in Table 3.

Table 3: Key Demographic Characteristics of Implanted Patients in the TITAN, TITAN II, and REDUCE FMR Trials (Safety) - ITT

Patient Characteristic	TITAN N=53	TITAN II N=36	REDUCE FMR N=87	All Studies N=176
Age, mean (SD), yrs.	62 ± 12.7	70.6 ± 8.5	70.1 ± 9.7	67.8±11.1
Gender, % (n), Male	77.4% (41)	66.7% (24)	72.4% (63)	72.7% (128)
NYHA Classification, % (n)				
Class I	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Class II	1.9% (1)	5.6% (2)	44.8% (39)	24.0% (42)
Class III	94.2% (49)	88.9% (32)	52.9% (46)	6% (127)
Class IV	3.8% (2)	5.6% (2)	2.3% (	.4% (6)
MR Grade % (n)				
1+	0.0% (0)	0.0% (0)	28.7 (	14.6% (25)
2+	17.0% (9)	32.3% (10)	29.1% (	31.0% (53)
3+	56.6% (30)	45.2% (14)	26. (23	39.2% (67)
4+	26.4% (14)	22.6% (7)	5.7% (5)	15.2% (26)
6-minute walk, mean ± SD, m	313.8 ± 77.9 (53)	287.9 ± 86.8 (35)	30 90.5 (86)	304.9±86.1 (174)
Medical History, % (n)				
Diabetes	16.7% (6)	3 (9)	28.8% (21)	26.1% (58)
Angina	44.4% (16)	0.0%	53.4% (39)	43.2% (76)
Coronary Artery Disease	61.1% (22)	6 % (18	72.6% (53)	52.8% (93)
CABG	*54.5% (12/2*	*28.0% (7/18)*	*41.5% (22/53)*	*44.1% (41/93)*
Ischemic Cardiomyopathy	67.9 (36)	55.6% (20)	67.8% (59)	65.7% (115)
Atrial fibrillation – % (n)	26.4 4)	47.2% (17)	58.6% (51)	46.9% (82)
Echo Parameter, mean ± SD, (				
RV, mL	36 12.2 (53)	34.4 ± 13.5 (24)	40.4 ± 23.9 (79)	38.1±19.3 (156)
LVEDD, cm	7 ± 0.8 (53)	6.3 ± 0.9 (29)	6.6 ± 0.9 (83)	6.5±0.9 (165)
Mitral annular diam. (A-P), cm	4 ± 0.53 (53)	3.82 ± 0.54 (23)	3.9 ± 0.6 (82)	3.8±0.57 (158)
EROA	0.26 ± 0.1 (53)	0.25 ± 0.11 (24)	0.26 ± 0.15 (79)	0.26 ± 0.13 (153)
LVEF, mean (SD) %	28 ± 8 (53)	32 ± 9 (29)	33 ± 9 (71)	31±9 (153)

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Table 4 summarizes the study-specific and pooled procedural safety (30-day) safety outcomes for the TITAN, TITAN II, and REDUCE FMR studies in the intent-to-treat (ITT) populations.

Table 4: Procedural Safety (MAE) - ITT

30-Day Procedural Events	TITAN N=53	TITAN II N=36	REDUCE FMR N=87	All Studies N=176
All MAEs	**1.9% (1)**	**2.8% (1)**	**5.7% (5)**	**4.0% (7)**
Death (all cause)	1.9% (1)	2.8% (1)	2.3% (2)	2.3% (4)

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Table 4: Procedural Safety (MAE) - ITT				
30-Day Procedural Events	**TITAN N=53**	**TITAN II N=36**	**REDUCE FMR N=87**	**All Studies N=176**
Myocardial Infarction	0%	0%	3.4% (3) *	1.7% (3)
Device embolization	0%	0%	0%	0%
Vessel erosion requiring percutaneous or surgical intervention	0%	0%	0%	0%
Cardiac perforation necessitating catheter-based or surgical intervention	0%	0%	0%	0%
Surgery or percutaneous coronary intervention associated with device malfunction	0%	0%	0%	0%

* MI's due to troponin elevation. No clinical sequelae.

Table 5 summarizes the study-specific and pooled long-term safety (1 year) safety outcomes for the TITAN, TITAN II, and REDUCE FMR studies in the intent-to-treat (ITT) populations.

Table 5: Long-Term Safety (MAE) through 12 Months (ITT)				
12-Month Events (MAE)	**TITAN N=53**	**TITAN II N=36**	**REDUCE FMR N=87**	**All Studies N=176**
All Events	**26.4% (14)**	**19.4% (7)**	**16.1% (14)**	**19.9% (35)**
Death (all cause)	22.6% (12)	19.4% (7)	12.6% (11)	**17.0% (30)**
Myocardial Infarction	3.8% (2)	0%	3.5% (3)	**2.8% (5)**
Device Embolism	0%	0%	0%	**0%**
Vessel erosion requiring percutaneous or surgical intervention	0%	0%	0%	**0%**
Cardiac perforation necessitating catheter-based or surgical intervention	0%	0%	0%	**0%**
Surgery or percutaneous coronary intervention associated with device malfunction	0%	0%	0%	**0%**

* MI's due to troponin elevation. No clinical sequelae.

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2. Performance

Key Demographics

Key demographic characteristics of the implanted patient populations for the TITAN, TITAN II, and REDUCE FMR studies is shown below in Table 6.

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Table 6: Key Demographic Characteristics of Implanted Patients in the TITAN, TITAN II, and REDUCE FMR Trials (Performance) - Implanted				
Patient Characteristic	**TITAN N=36**	**TITAN II N=30**	**REDUCE FMR N=73**	**All Studies N=139**
Age, mean (SD), yrs.	62.4 ± 12.7	70.3 ± 8.7	70.0 ± 9.2	68.0±10.7
Gender, % (n), Male	75.0% (27)	70.0% (21/30)	78.1% (57)	75.5% (105)
NYHA Classification, % (n)				
Class I	0% (0)	0% (0)	0% (0)	0% (0)
Class II	0% (0)	3.3% (1)	47.9% (35)	26.1% (36)
Class III	94.4% (34)	90.0% (27)	49.3% (36)	69.6% (96)
Class IV	5.6% (2)	6.7% (2)	2.7% (2)	4.3% (6)
MR Grade % (n)				
1+	0% (0)	0% (0/25)	34.2% (25)	18.7% (25)
2+	19.4% (7)	36.0% (9/25)	37.0% (27)	[illegible]1% (43)
3+	55.6% (20)	36.0% (9/25)	23.3% (17)	3[illegible]% (46)
4+	25.0% (9)	28.0% (7/25)	5.5% (4)	1[illegible]% (20)
6-minute walk, mean ± SD, m	302.5 ± 74	294.07 ± 82.6	314.8 ± [illegible]	[illegible]07.2±85.5 (137)
Medical History, % (n)				
Diabetes	16.7% (6)	30.0% (9)	[illegible].8% [illegible]	25.9% (36)
Angina	44.4% (16)	70.0% (21)	[illegible].4% (3[illegible]	54.7% (76)
Coronary Artery Disease	61.1% (22)	60.0% (18)	7[illegible]% ([illegible]	66.9% (93)
CABG	*54.5% (12/22)*	*38.9% (7/18)*	*41.[illegible]% (22)*	*44.1% (41/93)*
Ischemic Cardiomyopathy	66.7% (24)	60.0[illegible] (30)	69.9% (51)	67.6% (94)
Atrial fibrillation – % (n)	n/a	[illegible].0% (15)	57.5% (42)	49.6% (69)
Echo Parameter, mean ± SD, (n)				
RV, mL	34.5 ± 11.5 (36)	[illegible].6 (24)	38.6 ± 23.5 (66)	36.7±19.0 (126)
LVEDD, cm	6.63 [illegible].85 ([illegible]	5.[illegible] ± 0.77 (24)	6.48 ± 0.91 (42)	6.6±0.9 (129)
Mitral annular diam. A-P, cm	[illegible] ± 0.[illegible] [illegible]6)	3.82 ± 0.54 (23)	4.08 ± 0.47 (72)	3.9±0.6 (127)
EROA	[illegible] ± 0.09 (36)	0.25 ± 0.11 (24)	0.27 ± 0.14 (52)	0.25±0.13 (126)
LVEF, mea[illegible]SD) %	28[illegible] ± 7.5 (36)	30.48 ± 8.7 (23)	33± 9 (48)	31.1±8.4 (118)

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Summary TITAN, TITAN II, and REDUCE FMR Performance Data

Table 7: Summary of TITAN, TITAN II, and REDUCE FMR Performance Data at 12 months (change from baseline)				
Parameter	**TITAN N=36**	**TITAN II N=30 ***	**REDUCE FMR N=73**	**All Studies N=139**
Regurgitant Volume (ΔRV), mL	-16.7±14.21 (25)	-8.6 ± 10.0 (12)	-7.5 ± 15.6 (45)	-10.5 ± 14.9 (82)
LV End Systolic Volume (ΔLVESV), mL	-28.4 ± 56.6 (24)	-13.2 ± 26.0 (11)	-4.8 ± 21.0 (39)	-13.7 ± 38.0 (74)
LV End Diastolic Volume (ΔLVEDV), mL	-28.3 ± 59.9 (25)	-8.5 ± 14.9 (11)	-8.6 ± 26.6 (39)	-15.2 ± 40.6 (75)
MR Grade (equal or better)	100% (25)	100% (14)	73.7% (42)	84.4% (81)
NYHA Class (equal or better)	100% (23)	95.5% (21)	88.1% (52)	92.3% (96)

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Table 7: Summary of TITAN, TITAN II, and REDUCE FMR Performance Data at 12 months (change from baseline)				
Parameter	**TITAN N=36**	**TITAN II N=30 ***	**REDUCE FMR N=73**	**All Studies N=139**
ΔKCCQ Score	17.26 ± 23.6 (23)	n/a	9.35 ± 25.6 (59)	11.6 ± 25.2 (82)

Hemodynamic Measures (RV, LVESV, LVEDV)

Figure 19 below summarizes the change in key hemodynamic measures (Regurgitant Volume, LV End Systolic Volume, and LV End Diastolic Volume) from baseline to 12 months in the pooled TITAN, TITAN II, and REDUCE FMR implanted population.

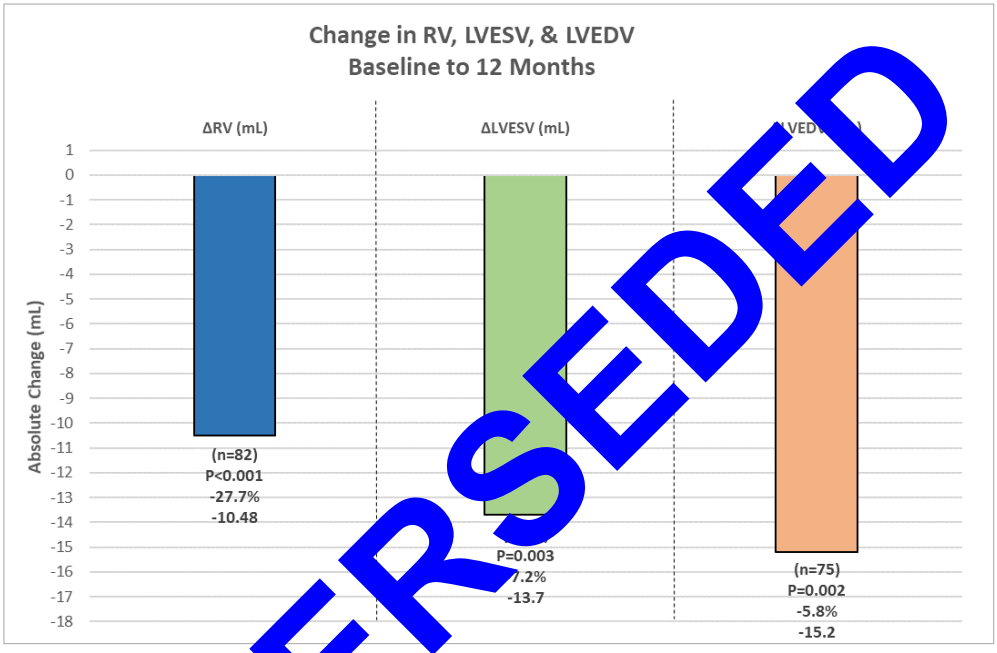

Figure 19: Hemodynamic measures in the pooled TITAN, TITAN II, and REDUCE FMR implanted population

MR Grade

Figure 20 below summarizes the relative change MR Grade from baseline to 12 months in the pooled TITAN, TITAN II, and REDUCE FMR implanted population.

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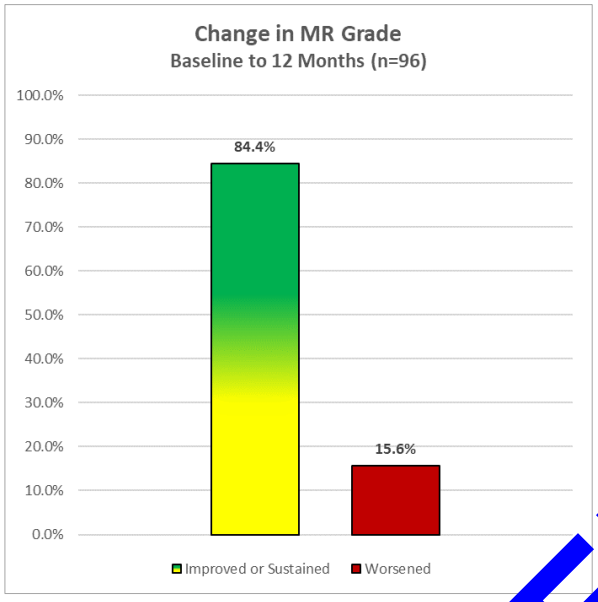

Figure 20: MR Grade in the pooled TITAN, TITAN II, and REDUCE FMR implanted population

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NHYA Classification

Figure 21 below summarizes the relative change in NYHA classification from baseline to 12 months in the pooled TITAN, TITAN II, and REDUCE FMR implanted population.

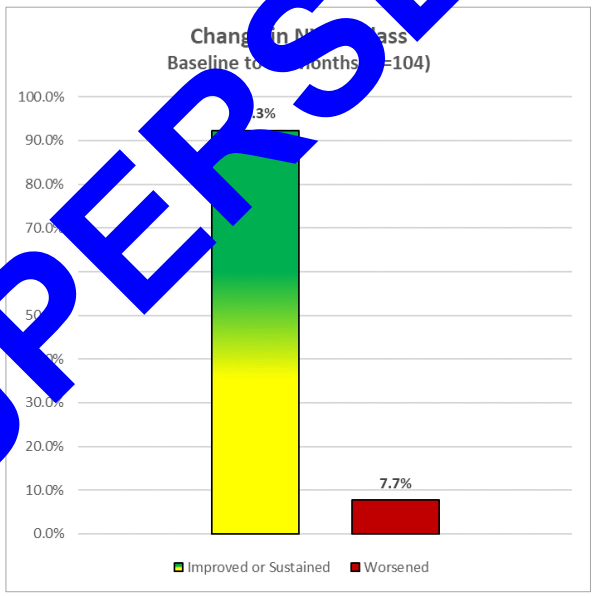

Figure 21: NYHA Classification in the pooled TITAN, TITAN II, and REDUCE FMR implanted population

Quality of Life (KCCQ)

Table 8 below summarizes the relative change in KCCQ scores from baseline to 12 months in the pooled TITAN and REDUCE FMR implanted population.

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Table 8: Change in KCCQ Scores from Baseline to 12 Months				
Time Point	**TITAN**	**TITAN II ***	**REDUCE FMR**	**All Studies**
12 months	+17.3 (n=23)	-	+9.4 (n=59)	**+11.6** **(n=82)**

* KCCQ scores not collected in TITAN II

Exercise Tolerance (6-Minute Walk Distance)

Figure 22 below summarizes the relative change in 6-minute walk distance (6MWD) from baseline to 12 months in the pooled TITAN, TITAN II, and REDUCE FMR implanted population.

Figure 22: 6MWD in the pooled TITAN, TITAN II, and REDUCE FMR implanted population

Clinical Benefits Summary

A summary of the clinical outcomes for the three key clinical parameters and the number of patients benefiting in the pooled TITAN, TITAN II, and REDUCE FMR studies are listed in Tables 9 and 10 below.

Table 9: Clinical Benefits for 6MWD, NYHA, and KCCQ at 12 months (paired pooled data from TITAN, TITAN II, REDUCE FMR)		
Clinical Parameter	**Patients that maintained or improved relative to baseline**	**Patients that improved relative to baseline**
6MWD (n=96)	76.0% (73)	74.0% (71)
NYHA (n=104)	92.3% (96)	54.8% (57)
KCCQ (n=82) *	70.7% (58)	70.7% (58)

* KCCQ not assessed in TITAN II study

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Table 10: Patients with 1 or more clinical benefit at 12 months (paired pooled data from TITAN, TITAN II, REDUCE FMR)		
Occurrence of clinical benefits in 6MWD, NYHA, or KCCQ	**Patients that maintained or improved clinically**	**Patients that improved clinically**
At least 1 clinical benefit	96.2% (102/106)	86.8% (92/106)
At least 2 clinical benefits	80.2% (85/106)	65.1% (69/106)
At least 3 clinical benefits	37.7% (40/106)	23.6% (25/106)

* 106 patients (paired data) were assessed in TITAN, TITAN II, and REDUCE FMR

Device, Implant, and Procedure Success

The overall device, implant, and procedure success rates in the pooled TITAN, TITAN II and REDUCE FMR studies are shown in Table 11.

Table 11: Device, Implant, and Procedure Success Rates – All CARILLON trials				
Patient Characteristics	**TITAN † (n=53)**	**TITAN II (n=36)**	**REDUCE FMR (n=86) ***	**All Studies (n=175)**
Device Success	100% (53/53)	97.2% (35/36)	100% (86/86)	**99.4% (174/175)**
Implant Success *	84.9% (45/53)	83.3% (30/36)	84.9% (73/86)	**84.6% (148/175)**
Procedure Success	98.1% (52/53)	94.4% (34/36)	95.3% (82/86)	**96.0% (168/175)**

* Patent anatomy can lead to coronary compromise and recapture of the implant. This is the primary reason for non-implanted devices and occurred in 12 of the ITT patients.

** Excludes patient not implanted due to sizing error in REDUCE FMR.

† Per TITAN protocol, patients with less than one or more grade reduction in MR were not implanted. This excluded nine (9) patients that would have otherwise received an implant.

Device Success: *Successful delivery and deployment of the investigational device, including recapture of the device if necessary or decoupling delivery system from the device, and retrieval of the investigational delivery catheter.*

Implant Success: *Successful permanent implantation of the CARILLON investigational device.*

Procedure Success: *Device success and no occurrence of 30-day (or hospital discharge if longer* than 30 days) MAEs.

3. Survival

A Kaplan-Meier plot for TITAN, TITAN II, and REDUCE FMR through twelve months is shown below in Figure 23.

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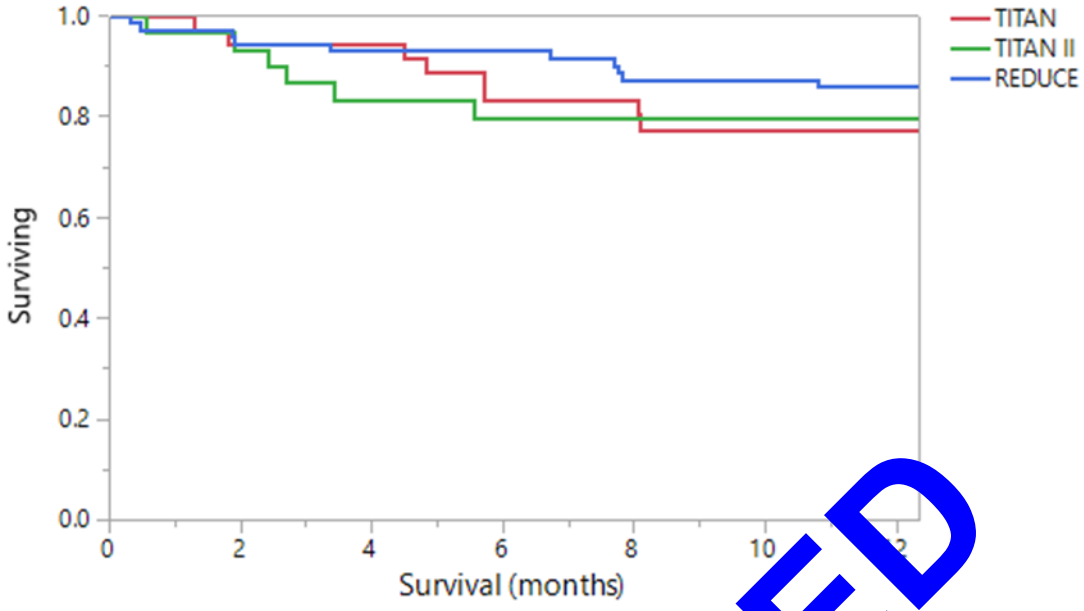

Figure 23: Kaplan-Meier graph showing survival of implanted patients in the TITAN, TITAN II, and REDUCE FMR studies through 12 months.

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4. Efficacy Beyond Twelve Months (Long-Term)

Heart Failure with FMR is a progressive disease with a reported two-year mortality of 34.2 - 46.1%.[4,5,6] A pooled data analysis (TITAN, TITAN II, and REDUCE FMR) has demonstrated a two-year mortality rate of 26.6%. The TITAN study showed that 80% of Carillon patients with NYHA III/IV had improved to NYHA I/II at two years (n=20) compared to baseline.

The effectiveness of the Carillon Mitral Contour System in reducing FMR beyond twelve months is currently under investigation.

The Kaplan-Meier plot for pooled data analysis (TITAN, TITAN II, and REDUCE FMR) through five years (60 months) is shown in Figure 24.

[4] Stone et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. N Engl J Med. 2018 Sep 23; 379:2307-2318
[5] Trichon et al. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003; 91:538-43.
[6] Lung et al. Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years. European Journal of Heart Failure. 2019 Dec; Volume 21, Issue 12: 1619-1627

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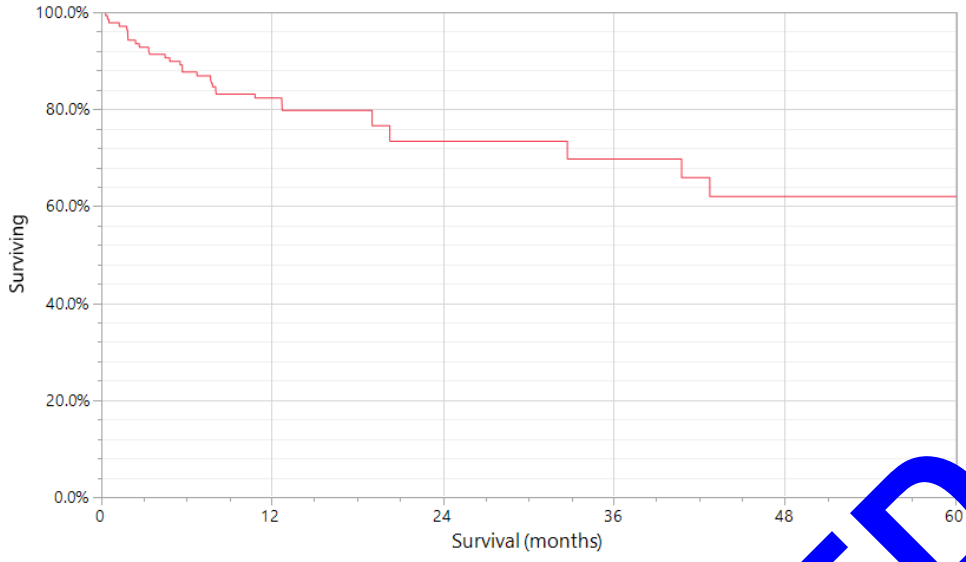

Timepoint	0	12	24	36	48	60
No at risk	139	76	23	20	15	7
P(survival)	100.0% ± 0.0%	82.3% ± 6.4%	73.4% ± 11.2%	69.7% ± 12.7%	62.0% ± 15.2%	62.0% ± 15.2%

Figure 24: Kaplan-Meier graph and at-risk table showing combined survival of implanted patients in the CARILLON studies (TITAN, TITAN II, REDUCE FMR) to 5 years

As published in *Cardiovascular Revascularization Medicine*[7], the Carillon Mitral Contour System has shown to result in a favorable five-year survival rate compared to guideline-directed therapy alone. The survival benefit was greatest among patients with improvement in clinical and hemodynamic parameters during the first year of follow-up.

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

[7] J. Lipiecki, D.M. Kaye, K.K. Witte, et al., Long-term survival following transcatheter mitral valve repair: Pooled analysis of prospective trial..., Cardiovascular Revascularization Medicine, https://doi.org/10.1016/j.carrev.2020.02.012

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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 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

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XVI. Manufacturer

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

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