MitraClip™ NT Clip Delivery System

Rx ONLY

MitraClip™ NT System
Clip Delivery System Ref No. CDS0501
Steerable Guide Catheter Ref No. SGC0101/Ref No. SGC0301
™

MitraClip™ System Accessories
Stabilizer Ref No. SZR01ST
Lift Ref No. LFT01ST
Support Plate Ref No. PLT01ST

Instructions for Use

WARNING: Read all instructions carefully. Failure to follow these instructions, warnings and precautions may lead to device damage or patient injury. Use of the MitraClip™ NT should be restricted to those physicians trained to perform invasive endovascular and transseptal procedures and to those physicians trained in the proper use of the system.

NOTE: The MitraClip NT Clip Delivery System Ref No. CDS0501 is fully compatible with Steerable Guide Catheter Ref No. SGC0101 and Ref No. SGC0301. The procedure step-by-step instructions for the use of the Steerable guide have not changed. Please refer to the instructions for use for Ref No. SGC0101 to obtain information on how Ref No. SGC0101 is supplied.

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1.0 INDICATION FOR USE

- The MitraClip™ NT Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.
- The MitraClip™ NT Clip Delivery System, when used with maximally tolerated guideline-directed medical therapy (GDMT), is indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria) in patients with a left ventricular ejection fraction (LVEF) ≥ 20% and ≤ 50%, and a left ventricular end systolic dimension (LVESD) ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease.

2.0 CONTRAINDICATIONS

The MitraClip™ NT Clip Delivery System is contraindicated in patients with the following conditions:

- Patients who cannot tolerate procedural anticoagulation or post procedural anti-platelet regimen
- Active endocarditis of the mitral valve
- Rheumatic mitral valve disease
- Evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus

3.0 WARNINGS

- **DO NOT use MitraClip™ NT outside of the labeled indication.**
- The MitraClip™ NT Device should be implanted with sterile techniques using fluoroscopy and echocardiography (e.g., transesophageal [TEE] and transthoracic [TTE]) in a facility with on-site cardiac surgery and immediate access to a cardiac operating room.
- Read all instructions carefully. Failure to follow these instructions, warnings and precautions may lead to device damage, user injury or patient injury. Use universal precautions for biohazards and sharps while handling the MitraClip™ NT System to avoid user injury.
- Use of the MitraClip™ NT should be restricted to those physicians trained to perform invasive endovascular and transseptal procedures and those trained in the proper use of the system.
- The Clip Delivery System is provided sterile and designed for single use only. Cleaning, re-sterilization and/or reuse may result in infections, malfunction of the device or other serious injury or death.
- Use caution when treating patients with hemodynamic instability requiring

inotropic support or mechanical heart assistance due to the increased risk of mortality in this patient population. The safety and effectiveness of MitraClip™ in these patients has not been evaluated.

4.0 PRECAUTIONS

- Note the product “Use by” date specified on the package.
- Inspect all product prior to use. Do not use if the package is open or damaged, or if product is damaged.

- Prohibitive Risk Primary (or degenerative) Mitral Regurgitation
  - Prohibitive risk is determined by the clinical judgment of a heart team, including a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, due to the presence of one or more of the following documented surgical risk factors:
    - 30-day STS predicted operative mortality risk score of
      - ≥8% for patients deemed likely to undergo mitral valve replacement or
      - ≥6% for patients deemed likely to undergo mitral valve repair
    - Porcelain aorta or extensively calcified ascending aorta.
    - Frailty (assessed by in-person cardiac surgeon consultation)
    - Hostile chest
    - Severe liver disease / cirrhosis (MELD Score > 12)
    - Severe pulmonary hypertension (systolic pulmonary artery pressure > 2/3 systemic pressure)
    - Unusual extenuating circumstance, such as right ventricular dysfunction with severe tricuspid regurgitation, chemotherapy for malignancy, major bleeding diathesis, immobility, AIDS, severe dementia, high risk of aspiration, internal mammary artery(IMA) at high risk of injury, etc.
    - Evaluable data regarding safety or effectiveness is not available for prohibitive risk DMR patients with an LVEF < 20% or an LVESD > 60 mm. MitraClip™ NT should be used only when criteria for clip suitability for DMR have been met.
    - The heart team should include a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease and may also include appropriate physicians to assess the adequacy of heart failure treatment and valvular anatomy.
- Secondary Mitral Regurgitation
  - Evaluable data regarding safety or effectiveness is not available for secondary MR patients with an LVEF < 20% or an LVESD > 70 mm.
  - The multidisciplinary heart team should be experienced in the evaluation and treatment of heart failure and mitral valve disease and determine that symptoms and MR severity persist despite maximally tolerated GDMT.

5.0 SPECIAL PATIENT POPULATIONS

Pregnancy
The MitraClip™ NT device has not been tested in pregnant women. Effects on the developing fetus have not been studied. The risks and reproductive effects are unknown at this time.

Gender
No safety or effectiveness related gender differences were observed in clinical studies.

Ethnicity
Insufficient subject numbers prevent ethnicity-related analyses on the clinical safety and effectiveness.

Pediatrics
Safety and effectiveness of the MitraClip™ NT device has not been established in pediatric patients.

Anatomic Considerations
For optimal results, the following anatomic patient characteristics should be considered. The safety and effectiveness of the MitraClip™ NT outside of these conditions has not been established. Use outside these conditions may interfere with placement of the MitraClip™ NT Device or mitral valve leaflet insertion.

- The primary regurgitant jet is non-commissural. If a secondary jet exists, it must be considered clinically insignificant
- Mitral valve area ≥ 4.0 cm^2
- Minimal calcification in the grasping area
- No leaflet cleft in the grasping area
- Flail width < 15 mm and flail gap < 10 mm

6.0 POTENTIAL COMPLICATIONS AND ADVERSE EVENTS

The following ANTICIPATED EVENTS have been identified as possible complications of the Mitra Clip™ NT procedure.

Death	Hypotension/hypertension
Allergic reaction (anesthetic, contrast, Heparin, nickel alloy, latex)	Infection
Aneurysm or pseudo-aneurysm	Injury to mitral valve complicating or preventing later surgical repair
Arrhythmias	Lymphatic complications
Atrial fibrillation	Mesenteric ischemia
Atrial septal defect requiring intervention	MitraClip™ NT erosion, migration or malposition
Arterio-venous fistula	MitraClip™ NT Device thrombosis
Bleeding	MitraClip™ NT System component(s) embolization
Cardiac arrest	Mitral stenosis
Cardiac perforation	Mitral valve injury
Cardiac tamponade/Pericardial Effusion	Multi-system organ failure
Chordal entanglement/rupture	Myocardial infarction
Coagulopathy	Nausea/vomiting
Conversion to standard valve surgery	Pain
Deep venous thrombus (DVT)	Peripheral ischemia
Dislodgement of previously implanted devices	Prolonged angina
Dizziness	Prolonged ventilation
Drug reaction to anti-platelet/anticoagulation agents/contrast media	Pulmonary congestion
Dyskinesia	Pulmonary thrombo-embolism
Dyspnea	Renal insufficiency or failure
Edema	Respiratory failure/atelectasis/pneumonia
Emboli (air, thrombus, MitraClip™ NT Device)	Septicemia
Emergency cardiac surgery	Shock, Anaphylactic or Cardiogenic
Endocarditis	Single leaflet device attachment (SLDA)
Esophageal irritation	Skin injury or tissue changes due to exposure to ionizing radiation
Esophageal perforation or stricture	Stroke or transient ischemic attack (TIA)
Failure to deliver MitraClip™ NT to the intended site	Urinary tract infection
Failure to retrieve MitraClip™ NT System components	Vascular trauma, dissection or occlusion
Fever or hyperthermia	Vessel spasm
Gastrointestinal bleeding or infarct	Vessel perforation or laceration
Hematoma	Worsening heart failure
Hemolysis	Worsening mitral regurgitation
Hemorrhage requiring transfusion	Wound dehiscence

7.0 PATIENT COUNSELING

Patients undergoing any procedures known to potentially be associated with bacteremia after implantation of the MitraClip™ NT Device should be prescribed prophylactic antibiotic therapy prior to such procedures.

Short-term anticoagulation therapy may be necessary after mitral valve repair with the MitraClip™ NT Device. Prescribe anticoagulation and other medical therapy per institutional guidelines.

After placement of a MitraClip™ NT Device, the Implant Identification Card should be filled out and the patient should be instructed to carry it at all times.

All patients should be advised to limit strenuous physical activity for at least the first month post-procedure or longer if warranted.

Physicians should consider the following in counseling patients about the MitraClip™ NT Device:

- Discuss the risks associated with MitraClip™ NT Device placement.
- Discuss why surgery is not an option for the patient.
- Discuss the risk/benefit considerations for the patient.

8.0 HOW SUPPLIED

8.1 Contents

One (1) Clip Delivery System with the MitraClip™ NT Device, one (1) MitraClip™ NT Device Implant Card.

8.2 Sterile

For the MitraClip™ NT Clip Delivery System (Ref No. CDS0501) and Steerable Guide Catheter (Ref No. SGC0301) only: these devices are provided sterile, in a thermoformed tray with lid, in a sealed pouch.

Parts of the devices that are in either direct or indirect contact with circulating blood are non-pyrogenic.

Note the product “Use By” date specified on the package. DO NOT use if the “Use by” date has passed.
These devices are intended for single-use only; do not reuse. Do not resterilize, as this can compromise device performance and increase the risk of cross contamination due to inappropriate reprocessing. Inspect all product prior to use. Do not use if the package is open or damaged, or if product is damaged.
The white Guide tip shape retainer and transparent protective tubing are provided sterile and pre-installed on the distal tip of the Steerable Guide Catheter. The Fasteners and the Silicone Pad used with the Stabilizer are provided sterile with the Steerable Guide Catheter. The Dilator, Fasteners and the Silicone Pad are intended for single use only.

Do not reuse. Do not resterilize, as this can compromise device performance and increase the risk of cross contamination due to inappropriate reprocessing.

8.3 Non-Sterile

The Stabilizer, Support Plate and Lift are provided non-sterile. Follow the cleaning and sterilization instructions provided with the Stabilizer, Support Plate and Lift.

9.0 STORAGE

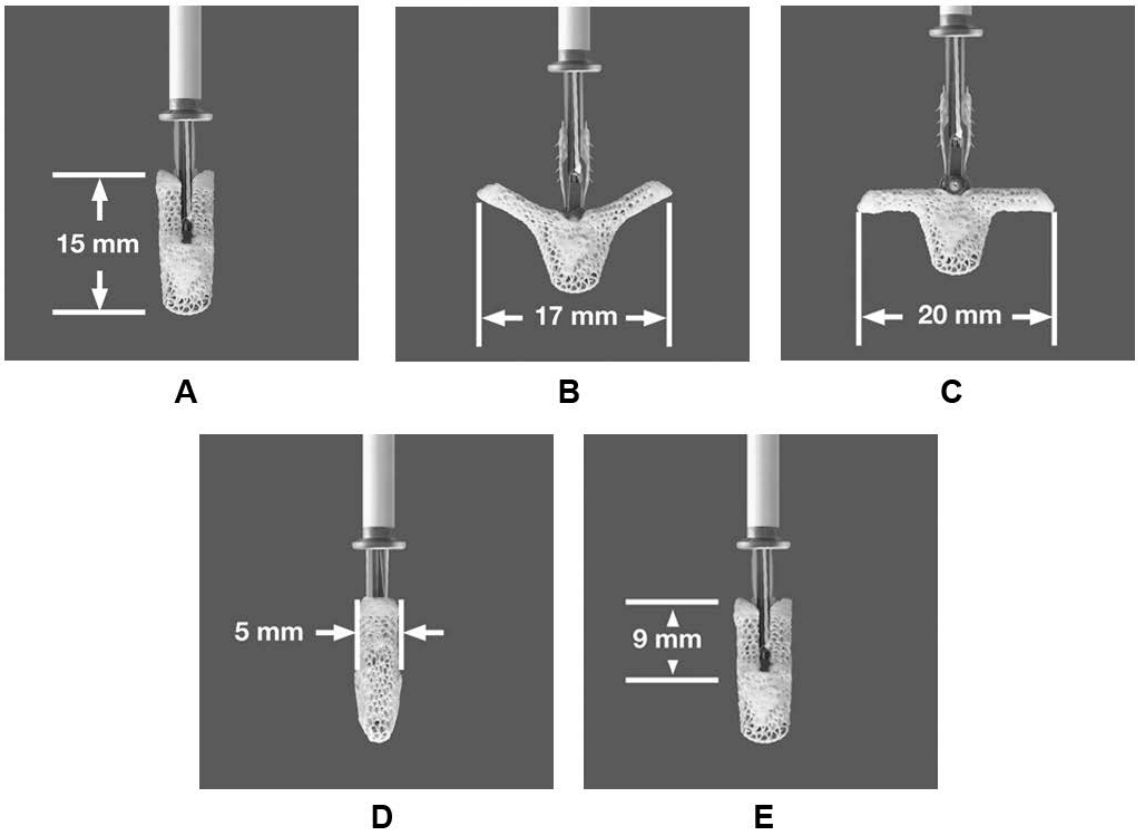
Handle with care. Store in original packaging. Keep dry. Keep away from sunlight.

10.0 MITRACLIP™ NT SYSTEM DIMENSIONS

Table 10.1: MitraClip™ NT Device Dimensions

Component	*Dimension*
Delivery Catheter	
Extended Length (from Sleeve curved at 90 degrees)	*45 mm – 70 mm*
Catheter Shaft Outer Diameter	*3.4 mm (10 Fr)*
Steerable Sleeve	
Working Length	*1095 mm*
Catheter Distal Shaft Outer Diameter	*5.3 mm (16 Fr)*
MitraClip™ NT Device	
Closed Clip Length (Figure 1A)	*15 mm maximum*
Grasping Width at 120 degrees (Figure 1B)	*17 mm minimum*
Clip Width at 180 degrees (Figure 1C)	*20 mm maximum*
Arm Width (Figure 1D)	*5 mm maximum*
Arm Length (Coaptation Length) (Figure 1E)	*9 mm maximum*
Steerable Guide Catheter	
Working Length	*800 mm*
Catheter Shaft Inner Diameter	*5.5 mm (16 Fr)*
Catheter Shaft Outer Diameter	*8.1 mm (24 Fr)*
Catheter Distal Tip Diameter	*7.7 mm (23 Fr)*
Catheter Septal Crossing Diameter	*7.4 mm (22 Fr)*
Dilator	
Working Length	*1220 mm*
Shaft Inner Diameter	*1.0 mm (3 Fr)*
Shaft Outer Diameter	*5.4 mm (16 Fr)*
Distal Tip Outer Diameter	*1.5 mm (4 Fr)*

Figure 10.1: MitraClip™ NT Device Dimensions



11.0 GLOSSARY OF ACRONYMS

Guide:	Steerable Guide Catheter	RA:	Right Atrium
CDS:	Clip Delivery System	LA:	Left Atrium
Sleeve:	Steerable Sleeve	LV:	Left Ventricle
DC:	Delivery Catheter	RO:	Radiopaque
Clip:	MitraClip™ NT Device (Implant)	MR:	Mitral Regurgitation

12.0 DEVICE DESCRIPTION

The MitraClip™ NT System consists of two parts: 1) the Clip Delivery System and 2) the Steerable Guide Catheter.

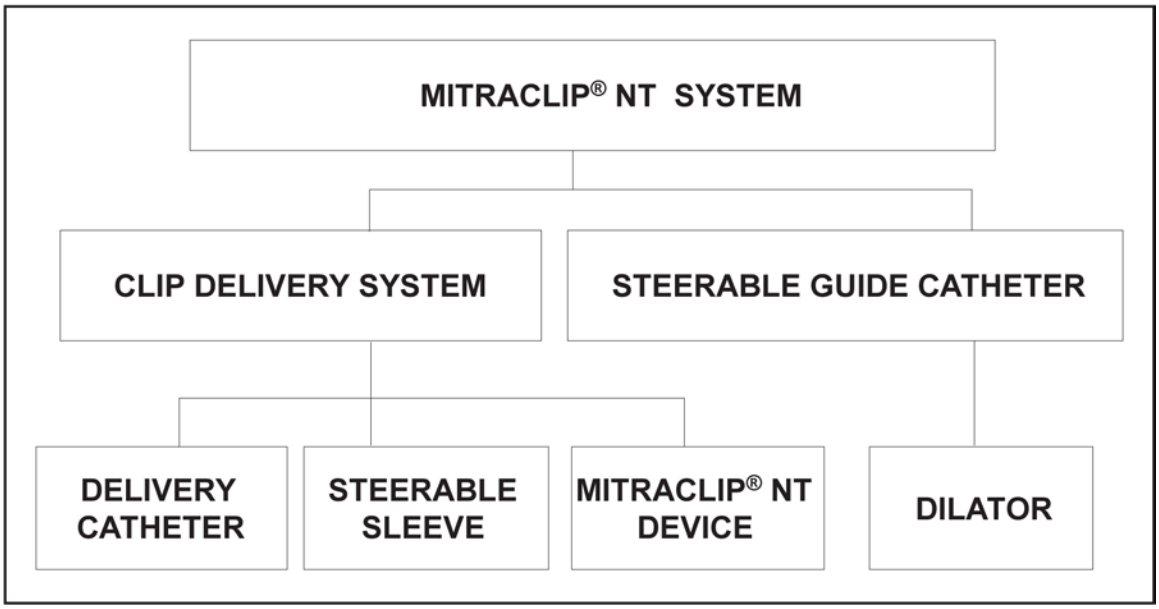
The Clip Delivery System consists of three major components:

1) The Delivery Catheter

2) The Steerable Sleeve and

3) The MitraClip™ NT Device

The Clip Delivery System is introduced into the body through a Steerable Guide Catheter which includes a dilator. The Clip Delivery System and Steerable Guide Catheter constitute the MitraClip™ NT System.



The Clip Delivery System (Figures 2 and 4) is used to advance and manipulate the implantable MitraClip™ NT Device for proper positioning and placement on the mitral valve leaflets. The Clip Delivery System is designed to deploy the implant in a way that requires multiple steps to ensure safe delivery of the device.

The outer surfaces of the Delivery Catheter and the Steerable Guide Catheter have a hydrophilic coating.

The MitraClip™ NT Device (Figure 6) is a percutaneously implanted mechanical Clip. The MitraClip™ NT Device grasps and coapts the mitral valve leaflets resulting in fixed approximation of the mitral leaflets throughout the cardiac cycle. The MitraClip™ NT Device is placed without the need for arresting the heart or cardiopulmonary bypass. The implantable MitraClip™ NT Device is manufactured with metal alloys and polyester fabric (Clip cover) that are commonly used in cardiovascular implants.

The MitraClip™ NT Device arms can be adjusted to any position from fully opened, fully inverted and fully closed. These positions are designed to allow the MitraClip™ NT Device to grasp and approximate the leaflets of the mitral valve using controls on the Delivery Catheter Handle. The MitraClip™ NT Device can be locked, unlocked and repeatedly opened and closed. The Grippers can be raised or lowered repeatedly.

The MitraClip™ NT Device can be removed using standard surgical techniques and can be disposed of according to institutional guidelines.

The Steerable Guide Catheter (Figure 3a) is used to introduce the Clip Delivery System into the left side of the heart through the interatrial septum. The Steerable Guide Catheter is also used to position and orient the Clip Delivery System to the appropriate location above the mitral valve. The Dilator (Figure 3b) is used for the introduction of the Steerable Guide Catheter into the femoral vein and left atrium.

12.1 MRI Safety Information

Non-clinical testing has demonstrated that the MitraClip™ NT is MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 or 3 Tesla
- Maximum spatial field gradient of 2500 Gauss / cm
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 4 W / kg (First Level Controlled Operating Mode).

Under the scan conditions defined above, MitraClip™ NT is expected to produce a maximum temperature rise of less than 3°C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by a pair of devices extends approximately 30 mm beyond MitraClip™ NT when imaged with a spin echo or gradient echo pulse sequence and a 3 T magnetic resonance system. It may be necessary to optimize the magnetic resonance imaging parameters due to the presence of the implant.

12.2 MitraClip™ System Accessories Overview

Several accessories are used in conjunction with the MitraClip™ NT System including: 1) a Stabilizer, 2) a Lift, 3) a Support Plate, 4) a Silicone Pad, and 5) Fasteners. The Stabilizer is provided separately as a non-sterile reusable device and must be cleaned and sterilized prior to each use. The Stabilizer is used on the sterile field to support and position the Steerable Guide Catheter and Clip Delivery System during the procedure. The Lift and Support Plate are provided separately as non-sterile reusable devices and must be cleaned prior to each use. The Lift and Support Plate are used outside the sterile field to provide a stable platform for the Stabilizer and MitraClip™ NT System during the procedure. Follow the cleaning and sterilization instructions provided with the Stabilizer, Support Plate and Lift. The Silicone Pad and Fasteners are single use accessories and are provided sterile with the Steerable Guide Catheter packaging. The Silicone Pad is used on the sterile field under the Stabilizer to prevent incidental movement of the Stabilizer during the procedure. The Fasteners are used on the sterile field to secure the Steerable Guide Catheter and Clip Delivery System to the Stabilizer.

Legend of Figure Labels

Figure 2: Clip Delivery System (CDS) 1 Delivery Catheter Handle 2 Delivery Catheter Fastener 3 A/P Knob 4 M/L Knob 5 Steerable Sleeve Handle 6 Clip Introducer 7 MitraClip™ NT Device **Figure 3a: Steerable Guide Catheter** 8 Hemostasis Valve 9 Alignment Marker 10 Flush Port 11 +/- Knob 12 Proximal Shaft 13 Distal Shaft 14 Radiopaque Tip Ring **Figure 3b: Dilator** 15 Rotating Hemostatic Valve 16 Flush Port 17 Echogenic Spiral Groove	**Figure 4: CDS Handles** 18 Actuator Knob 19 Release Pin 20 Arm Positioner 21 Lock Lever Cap 22 Gripper Lever Cap 23 Lock Lever 24 Gripper Lever 25 Delivery Catheter Top Flush Port (Bottom Flush Port Not Shown) 26 Delivery Catheter Handle 27 Delivery Catheter Fastener 28 Sleeve Flush Port 29 A/P Knob 30 M/L Knob 31 Steerable Sleeve Handle **Figure 5: CDS Distal End** 32 Longitudinal Alignment Marker 33 Key 34 Steerable Sleeve Shaft	35 Radiopaque Alignment Markers 35a Proximal 35b Distal 36 Sleeve Radiopaque Tip Ring 37 Delivery Catheter Shaft 38 Delivery Catheter Radiopaque Ring 39 MitraClip™ NT Device **Figure 6: MitraClip™ NT Device Positions** A Clip fully closed (low profile) B Clip opened to 180 degrees C Clip closed to 120 degrees D Clip closed to 60 degrees E Clip closed to 20 degrees F Clip inverted G Clip fully inverted

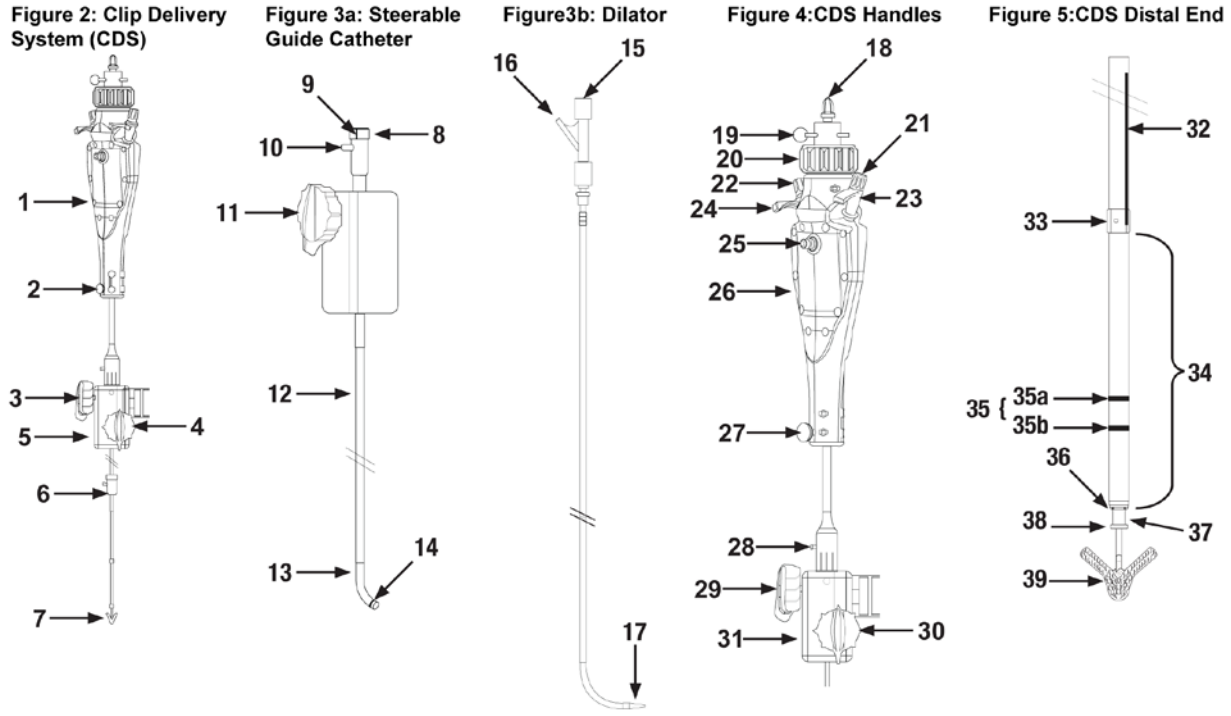
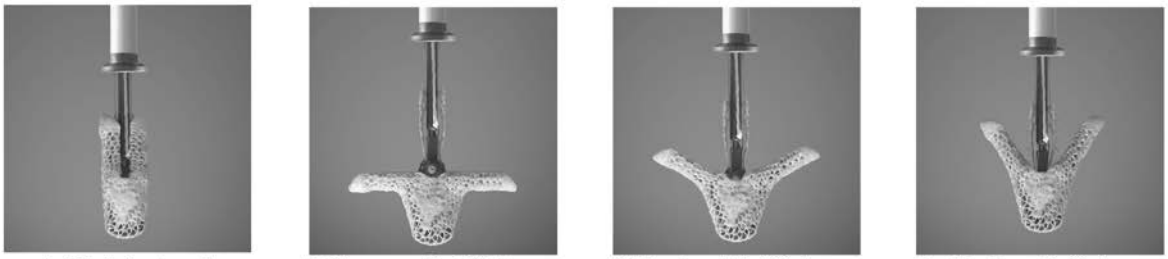


Figure 12.1: MitraClip™ NT Device Positions



A: Clip fully closed

B: Clip opened to 180 degrees

C: Clip closed to 120 degrees

D: Clip closed to 60 degrees

E: Clip closed to 20 degrees

F: Clip inverted

G: Clip fully inverted

The Steerable Guide Catheter and Clip Delivery System (Steerable Sleeve, Delivery Catheter and Clip) are steered and actuated by the use of control knobs, levers and fasteners located on the handles.

Table 12.1: MitraClip™ NT System Handle Controls

Device	Control	Function
Steerable Guide Catheter	+/- Knob	Tip deflection
Steerable Sleeve	M/L Knob	Tip deflection
	A/P Knob	Tip deflection
Delivery Catheter	Lock Lever	Locks-Unlocks Clip via Lock Line
	Gripper Lever	Raises-Lowers Grippers via Gripper Line
	Arm Positioner	Opens-Closes Clip Arms
	DC Fastener	Locks-Unlocks DC translation/torque
	Lock Lever Cap	Controls removal of Lock Line
	Release Pin	Prevents Actuator Knob turning
	Actuator Knob	Turns actuator shaft for Clip deployment
	Gripper Lever Cap	Controls removal of Gripper Line

13.0 REQUIRED ACCESSORIES

SZR01ST: One (1) Stabilizer.
LFT01ST: One (1) Lift.
PLT01ST: One (1) Support Plate.
One (1) Silicone Pad, three (3) Fasteners (All are included sterile with the Steerable Guide Catheter).

14.0 ADDITIONAL REQUIRED EQUIPMENT NOT INCLUDED

Transseptal sheath and guidewire.
Transseptal needle.
Step-up dilators.
260 cm of 0.9 mm (0.035") super stiff exchange length guidewire.
High pressure three way stopcocks (5).
Arterial high pressure extension tubing (3).
50–60 cc syringes with luer fitting (2).
1000 ml pressure bags (2).
Sterile IV tubing with thumbwheel occluders (2).
Heparinized sterile saline solution (2) 1-liter bags.
Rolling IV Pole.
Sterile Basin.

15.0 OVERVIEW OF CLINICAL STUDIES

Table 15.1 presents an overview of the MitraClip clinical program in the United States including study design, enrollment criteria, endpoints and sample size.

Table 15.1: Overview of MitraClip US Clinical Trials

Type	Study	Key Inclusion Criteria	Key Exclusion Criteria	Endpoint	sites	patients
Feasibility	EVEREST I enrollment 2003-2006	• MR≥3+ • Symptomatic or asymptomatic with[a]: LVEF 30-50% and/or LVESD 50-55mm or LVEF 50-60% and LVESD < 45 mm or LVEF>60 and LVESD 45-55 mm • Candidate for mitral valve surgery including cardiopulmonary bypass	• LVEF<30%, and/or LVESD >55mm • Mitral valve orifice area <4.0 cm2 • Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR	• Primary: Major Adverse Event rate through 30 days	11	55
Randomized Control Trial	EVEREST II RCT enrollment 2005-2008	MR≥3+ • Symptomatic with LVEF > 25% and LVESD ≤ 55 mm or asymptomatic with[a]: LVEF 25% to 60% LVESD ≥ 40 mm New onset of atrial fibrillation PASP>50mmHg at rest of >60 mmHg with exercise	• LVEF≤25%, and/or LVESD >55mm • Mitral valve orifice area <4.0 cm^2 • Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR	• Primary Safety: Major Adverse Event rate through 30 days or discharge, whichever is greater Primary Effectiveness: Freedom from death, MV surgery (for Device group) or re-operation (for Control group), and MR > 2+ at 12 months • Secondary Effectiveness: • Measures of LV Function • SF-36 quality of life • NYHA Functional Class	37	60 roll-in 178 [b] Device 80 [b] Surgical Control
Single-Arm Registry	EVEREST II High Risk Registry Study enrollment 2007-2008	MR≥3+ • Predicted procedural mortality risk calculated using the STS surgical risk calculator of ≥ 12% or in the judgment of a cardiac surgeon the patient is considered a high risk surgical candidate due to the presence of one of the following indications: 1. Porcelain aorta, mobile ascending aortic atheroma 2. Post-radiation mediastinum 3. Previous mediastinitis 4. Functional MR with EF<40 5. Over 75 years old with EF<40 6. Re-operation with patent grafts 7. Two or more prior chest surgeries 8. Hepatic cirrhosis 9. Three or more of the following STS high risk factors 9.1 Creatinine > 2.5 mg/dL 9.2 Prior chest surgery 9.3 Age over 75 9.4 EF<35	• LVEF<20% and/or LVESD>60mm • Mitral valve orifice area <4.0 cm^2 • Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR	• Primary Safety: Procedural mortality at 30 days • Major Secondary: • Measures of LV Function • SF-36 quality of life • NYHA Functional Class • CHF Hospitalizations • Secondary Safety: • Major Adverse Event rate at 30 days and 12 months	25	78
Continued Access Registry	REALISM High Risk enrollment 2009-2013	• Same as High Risk Registry with the exception of the requirement for predicted procedural mortality risk ≥ 12%	• Same as High Risk Registry	• Same as High Risk Registry	39	581[c]
	REALISM Non-High Risk enrollment 2009-2011	• Same as RCT	• Same as RCT	• Same as RCT • 6 Minute Walk Test (6MWT) Distance[d]	39	272
Pivotal RCT	COAPT Enrollment 2012-2017	• Ischemic or non-ischemic cardiomyopathy with LVEF 20%-50% and LVESD ≤70 mm • Moderate-to-severe (3+) or severe (4+) secondary MR confirmed by an independent echo core laboratory prior to	• ACC/AHA stage D heart failure, hemodynamic instability or cardiogenic shock • Untreated clinically significant coronary	• Primary Safety: Composite endpointof device-related complications at 12 months • Primary Effectiveness: Recurrent HF hospitalizations through 24 months	84	614 (51 roll-n)

Type	Study	Key Inclusion Criteria	Key Exclusion Criteria	Endpoint	sites	patients
		enrollment • NYHA Functional Class II, III or ambulatory IV despite stable maximally-tolerated GDMT regimen and CRT (if appropriate) • At least one hospitalization for heart failure in the 12 months prior to subject registration and/or a corrected BNP ≥300 pg/ml or corrected NT-proBNP ≥1500 pg/ml measured within 90 days prior to subject registration • Surgery per local heart team assessment • (LVESD) is ≤70 mm assessed by site based on a transthoracic echocardiographic (TTE) • Treating interventionalist believes secondary MR can be successfully treated with MitraClip, •	artery disease requiring revascularization • COPD requiring continuous home oxygen therapy or chronic oral steroid use • Severe pulmonary hypertension or moderate or severe right ventricular dysfunction • Aortic or tricuspid valve disease requiring surgery or transcatheter intervention • Mitral valve orifice area <4.0 cm^2 • Life expectancy < 12 months due to non-cardiac reasons			

[a] Inclusion criteria based on the current indication for mitral valve surgery for mitral regurgitation in the ACC/AHA guidelines for management of valvular dysfunction.
[b] Of the 184 patients randomized to Device, 178 received Device. Of the 95 patients randomized to Control, 80 underwent mitral valve surgery.
[c] As of July 12, 2013.
[d] In protocol version dated November 17, 2008, only patients with NYHA Functional Class III or IV in the Non-High Risk arm were considered for a 6-minute walk test. In the amended protocol version dated September 14, 2010, all patients enrolled in REALISM are required to perform the 6-minute walk test.

15.1 EVEREST I Trial (Feasibility)

The EVEREST I trial was a prospective, multi-center, registry trial designed to evaluate the preliminary safety and effectiveness of the MitraClip device in the treatment of moderate-to-severe (3+) or severe (4+) chronic MR using up to 2 MitraClip devices per patient. The EVEREST I trial demonstrated the preliminary safety and feasibility of the MitraClip device as a percutaneous method for the reduction of MR severity. EVEREST I enrolled 55 patients at 12 US sites. Enrolled patients were required to complete clinical follow up at 30 days, 6, 18 and 24 months, and 3, 4, and 5 years. The primary safety endpoint of EVEREST I was MAE rate through 30 days (acute safety). Multiple additional secondary endpoints were pre-specified for safety and effectiveness for reporting with descriptive statistics. The study is now closed.

15.2 EVEREST II Randomized Clinical Trial (RCT)

The EVEREST II RCT was a landmark trial, being the first randomized trial to compare a percutaneous intervention for the reduction of MR to standard of care mitral valve surgery. The EVEREST II RCT was a prospective, blinded, randomized, controlled, multi-center study of 279 patients (184 MitraClip, 95 surgical control) comparing the safety and effectiveness of the MitraClip to the standard of care mitral valve surgery. The intended population was patients with significant symptomatic mitral regurgitation (MR ≥ 3+) of either secondary MRor primary MR etiology that were non-high risk candidates indicated for and who could undergo mitral valve surgery. Study design elements including key inclusion/exclusion criteria and endpoints are provided in Table 15.1. Patients were evaluated at baseline, discharge, 30 days, 6, 12, 18 and 24 months, and annually thereafter through 5 years. Results of this study showed that the safety advantages of the percutaneous procedure were offset by the diminution of MR reduction with MitraClip compared to surgery, and therefore good surgical candidates should continue to receive surgical intervention.

15.3 EVEREST II High Risk Registry and EVEREST II REALISM Continued Access Study - High Risk (EVEREST II HRR and REALISM HR)

The EVEREST II High Risk Registry (HRR) was a prospective, multi-center, registry designed to be adjunctive to the RCT and to evaluate the safety and effectiveness of the MitraClip device in the treatment of high surgical risk (≥ 12%) patients with moderate-to-severe (3+) or severe (4+) chronic MR using up to 2 MitraClip devices per patient. The EVEREST II HRR enrolled 78 patients at 35 North American sites. Enrolled patients were required to complete clinical follow up at 30 days, 6, 12, 18 and 24 months, and 3, 4, and 5 years. The primary safety endpoint of the EVEREST II HRR was procedural mortality at 30 days or prior to discharge, whichever is longer. REALISM HR was a single-arm, self-controlled adjunctive study enrolling the same patient population as the EVEREST II HRR and designed to continue to collect safety and effectiveness data and allow patients continued access to the MitraClip during review of the PMA application.

15.4 COAPT (Cardiovascular Outcomes Assessment of the MitraClip™Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation)

The COAPT Trial was a prospective, randomized (1:1; MitraClip + GDMT vs. GDMT alone), open-label, multicenter investigational study intended to demonstrate: (1) MitraClip was safe in subjects with secondary MR, and (2) MitraClip could reduce recurrent HF hospitalization as compared to the GDMT Control group. The randomization was further stratified by study site and by cardiomyopathy etiology (e.g., ischemic or non-ischemic). The planned sample size of the trial was 760, including 150 roll-in subjects.

16.0 CLINICAL RESULTS IN PROHIBITIVE RISK PRIMARY MR PATIENTS

Data on 127 patients with significant symptomatic mitral regurgitation due to primary abnormality of the mitral apparatus (primary mitral regurgitation) determined to be at prohibitive risk for mitral valve surgery (Prohibitive Risk primary MR Cohort or PR primary MR Cohort) that were collected from the EVEREST II HRR and REALISM HR studies are provided in detail below. The analysis cohort of 127 subjects was developed post-hoc; this severely limits the statistical interpretability of reported data. These data were determined to adequately establish the safety, effectiveness, and positive benefit-risk profile of the MitraClip for the indicated population (PR primary MR) and are the basis for PMA approval. The totality of evidence demonstrates reasonable assurance of safety and effectiveness of MitraClip to reduce MR and provide patient benefit in this discreet and specific patient population.

Prohibitive Risk primary MR patients treated with the MitraClip were elderly with a high rate of serious comorbidities (Table 16.1).

Table 16.1: Prohibitive Risk Primary MR MitraClip Cohort – Key Baseline Characteristics

Baseline Characteristic[a]	Prohibitive Risk Primary MR MitraClip Patients % (n/N) (N = 127)
Age (years), Mean±SD (N)	82.4±8.7 (127)
Patients over 75 years of age	83.5% (106/127)
Female Gender	44.9% (57/127)
Body Mass Index (kg/m^2), Mean±SD (N)	25.0±5.7 (127)
Coronary Artery Disease	72.8% (91/125)
Prior Myocardial Infarction	24.4% (31/127)
Atrial Fibrillation History	70.5% (86/122)
Prior Stroke	10.2% (13/127)
Diabetes	29.9% (38/127)
Moderate to Severe Renal Disease	28.3% (36/127)
Cardiomyopathy	23.6% (30/127)
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O2)	31.5% (40/127)
Hypertension	88.2% (112/127)
Previous Cardiovascular Surgery	48.0% (61/127)
Previous Percutaneous Coronary Intervention	33.3% (42/126)
NYHA Functional Class III/IV Heart Failure	86.6% (110/127)
LV Ejection Fraction (%), Mean±SD (N)	60.6±9.5 (112)
LV Internal Diameter, systole (cm), Mean±SD (N)	3.4±0.8 (113)
STS Mortality Risk (determined at enrollment for replacement)[b], Mean±SD (N)	13.6±7.9 (127)

[a] Sample sizes or denominators smaller than the N reported for the group reflect missing data.
[b] STS replacement score calculated using the version of the calculator at the time of enrollment.

The mean Procedure Time, defined as the start time of the transseptal procedure to the time the Steerable Guide Catheter is removed, was approximately 2.5 hours (Table 16.2). Device time, defined as the time of insertion of the Steerable Guide Catheter to the time the MitraClip Delivery Catheter is retracted into the Steerable Guide Catheter, averaged 125 minutes. The mean fluoroscopy duration was 46 minutes. Fluoroscopy time was a relatively short proportion of the overall Procedure Time (29%). There were no intra-procedural deaths.

Table 16.2: Prohibitive Risk Primary MR MitraClip Cohort - Procedural Results

Procedural Result [a]	Mean±SD (N) Median (Min, Max)[a]
Procedure Time[b] (min)	157±81 (124) 134 (39, 524)
Device Time[c] (min)	125±75 (124) 110 (9, 511)
Fluoroscopy Duration (min)	46±26 (126) 39 (3, 167)

[a] Sample sizes or denominators smaller than 127 reflect missing data.
[b] Procedure time is measured from the time the transseptal procedure starts until the time the Steerable Guide Catheter is removed.
[c] Device time is measured from the time the Steerable Guide Catheter is placed in the intra-atrial septum until the time the MitraClip Delivery System is retracted into the Steerable Guide Catheter.

The MitraClip device was implanted successfully in a majority (95.3%) of patients (Table 16.3).

Table 16.3: Prohibitive Risk MitraClip Primary MR Cohort – Number of MitraClip Devices Implanted

# Devices Implanted	% (n/N)
0	4.7% (6/127)
1	44.1% (56/127)
2	51.2% (65/127)

Procedural mortality rate was 6.3%, which was less than both the mean and median predicted STS mortality risk using either the repair or replacement calculator.

Table 16.4: Prohibitive Risk Primary MR MitraClip Cohort - Procedural Mortality

Observed Procedural Mortality, % (n/N)	6.3% (8/127)
95% CI[a,c]	(2.8%, 12.0%)
STS v2.73 Replacement Risk Score	
Mean (95% CI[b,c])	13.2% (11.9%, 14.5%)
Median (95% CI[b,c])	12.4% (11.3%, 13.7%)
STS v2.73 Repair Risk Score	
Mean (95% CI[b,c])	9.5% (8.5%, 10.6%)
Median (95% CI[b,c])	8.5% (7.6%, 9.3%)

[a] Based on Clopper-Pearson method.
[b] CI for mean is calculated based on two-sample t-distribution and CI for median is based on non-parametric methods.
[c] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

At 12 months, MAEs occurred at a rate of 35.4% among Prohibitive Risk primary MR MitraClip patients, with deaths (23.6%) and transfusions (19.7%) comprising the majority of events. The rate of stroke was 2.4% and rate of non-elective cardiovascular surgery was 0.8% at 12 months.

Table 16.5: Prohibitive Risk Primary MR MitraClip Cohort - CEC Adjudicated Major Adverse Events at 30 Days and 12 Months

Description of Event	Prohibitive Risk Primary MR MitraClip Patients (N = 127)	
	30 days % (n/N)	12 Months % (n/N)
Death	6.3% (8/127)	23.6% (30/127)
Myocardial infarction	0.8% (1/127)	0.8% (1/127)
Re-operation for failed surgical repair or replacement	0	0
Non-elective cardiovascular surgery for adverse events	0.8% (1/127)	0.8% (1/127)
Stroke	2.4% (3/127)	2.4% (3/127)
Renal Failure	1.6% (2/127)	3.9% (5/127)
Deep wound infection	0	0.0% (0/127)
Ventilation > 48 hours	3.1% (4/127)	4.7% (6/127)
GI complication requiring surgery	0.8% (1/127)	2.4% (3/127)
New onset of permanent AF	0	0.0% (0/127)
Septicemia	0	4.7% (6/127)
Transfusion ≥ 2 units	12.6% (16/127)	19.7% (25/127)
Total[a]	**18.9% (24/127)**	**35.4% (45/127)**
Total[a] (Excluding Transfusions ≥ 2 units)	**9.4% (12/127)**	**26.0% (33/127)**

[a] Total number of patients may not equal the sum of patients in each row since one patient may experience multiple events.

Other secondary safety endpoints occurred at a relatively low rate, consistent with access to the mitral valve achieved via the femoral vein and inferior vena cava. Major vascular complications occurred in 5.5% of patients at 30 days and in 7.1% of patients at 12 months. Major bleeding complications, defined as procedure-related bleeding requiring transfusions of at least 2 units or surgery, occurred at a rate of 12.6% at 30 days. The majority of bleeding events required transfusions rather than surgery. Bleeding events that occurred after 30 days were unrelated to the MitraClip procedure. Clinically significant atrial septal defect requiring treatment occurred at a rate of 2.4% at 12 months. A low rate (2.4%) of mitral stenosis was observed at 12 months, with a total of 3 patients reported to have experienced mitral stenosis defined as Echocardiography Core Laboratory assessed mitral valve area less than 1.5 cm^2 through 12 months. The site did not report mitral stenosis for these patients and none of these patients underwent mitral valve surgery for stenosis.

Table 16.6: Prohibitive Risk Primary MR Cohort - Other Secondary Safety Events at 30 Days and 12 Months

Description of Event	30 Days % (n/N)	12 Months % (n/N)
Major Vascular Complications	5.5% (7/127)	7.1% (9/127)
Major Bleeding Complications	12.6% (16/127)	15.7% (20/127)
Non-Cerebral Thromboembolism	1.6% (2/127)	1.6% (2/127)
New Onset of Persistent Atrial Fibrillation	3.9% (5/127)	3.9% (5/127)
Heart Block/Other Arrhythmia requiring Permanent Pacemaker	0.0% (0/127)	1.6% (2/127)
Endocarditis	0.0% (0/127)	0.0% (0/127)
Thrombosis	0.0% (0/127)	0.0% (0/127)
Hemolysis	0.0% (0/127)	0.0% (0/127)
Atrial Septal Defect	1.6% (2/127)	2.4% (3/127)
Mitral Valve Stenosis	0.0% (0/127)	2.4% (3/127)

The Duke University Medical Center database, which consists of patient-level data with echocardiographic, medical history and follow-up data on a large number of patients with MR ≥ 3+ provides a descriptive comparator for mortality. This database allowed for characterization of survival in patients deemed high risk for surgery and managed non-surgically at the Duke University Medical Center despite clear Class I indications for surgery according to the ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease. Nine hundred and fifty-three (953) patients in the Duke database with 3+ or 4+ MR were identified as too high risk for surgery based on the same high risk criteria as those in the EVEREST II HRR and REALISM studies (i.e. STS mortality risk ≥ 12% or protocol-specified surgical risk factors) and managed non-surgically. This made up the Duke High Risk Cohort, of which 65 patients were identified as primary MR. Table 16.7 shows both groups were comprised of elderly patients, with a majority of patients over the age of 75 years. The Duke High Risk primary MR Cohort reported a lower LVEF at baseline and a higher proportion of female patients than the Prohibitive Risk primary MR Cohort. The Prohibitive Risk primary MR Cohort reported a higher proportion of patients with COPD and NYHA III/IV symptoms at baseline. Both groups had high rates of previous MI, atrial fibrillation and previous cardiovascular surgery.

Figure 16.1 and Table 16.8 display Kaplan-Meier curves comparing survival in the Prohibitive Risk primary MR patients to the Duke High Risk primary MR patients. Based on these Kaplan-Meier curves, mortality in the Prohibitive Risk primary MR Cohort was 6.4% at 30 days and 24.8% at 12 months compared to 10.9% at 30 days and 30.6% at 12 months in the Duke High Risk primary MR patients. While these results are descriptive and limited by differences described above, they suggest that there is no elevated risk of mortality in Prohibitive Risk primary MR patients who undergo the MitraClip procedure over non-surgical management.

Table 16.7: Baseline and Demographic Characteristics – Prohibitive Risk Primary MR and Duke High Risk Primary MR Cohorts

Baseline Characteristic[a]	Prohibitive Risk Primary MR MitraClip Cohort % (n/N) (N = 127)	Duke High Risk Primary MR Medical Therapy Cohort % (n/N) (N = 65)
Age (years), Mean±SD (N)	82.4±8.7 (127)	76.8±11.3 (65)
Patients over 75 years of age	83.5% (106/127)	67.7% (44/65)
Male Gender	55.1% (70/127)	36.9% (24/65)
Body Mass Index (kg/m2), Mean±SD (N)	25.0±5.7 (127)	25.4±5.0(65)
Prior Myocardial Infarction	24.4% (31/127)	33.8% (22/65)
Atrial Fibrillation History	70.5% (86/122)	58.5% (38/65)
Prior Stroke	10.2% (13/127)	18.5% (12/65)
COPD with Home Oxygen	13.4% (17/127)	6.2% (4/65)
Hypertension	88.2% (112/127)	75.4% (49/65)
Diabetes	29.9% (38/127)	36.9% (24/65)
Moderate to Severe Renal Disease	28.3% (36/127)	20.0% (13/65)
Previous Cardiovascular Surgery	48.0% (61/127)	56.9% (37/65)
Previous Percutaneous Coronary Intervention	33.3% (42/126)	58.5% (38/65)
NYHA Functional Class III/IV	86.6% (110/127)	43.8% (28/65)
STS Predicted Mortality Risk	13.2±7.3 (127)	13.3±9.0
LV Ejection Fraction (%), Mean±SD (N)	60.6±9.5 (112)	44.9±11.7 (65)
LV Internal Diameter, systole (cm), Mean±SD (N)	3.4±0.8 (113)	3.4±0.9 (65)

Figure 16.1: Kaplan-Meier Freedom from Mortality – Prohibitive Risk Primary MR MitraClip and Duke High Risk Primary MR Medical Therapy Patients

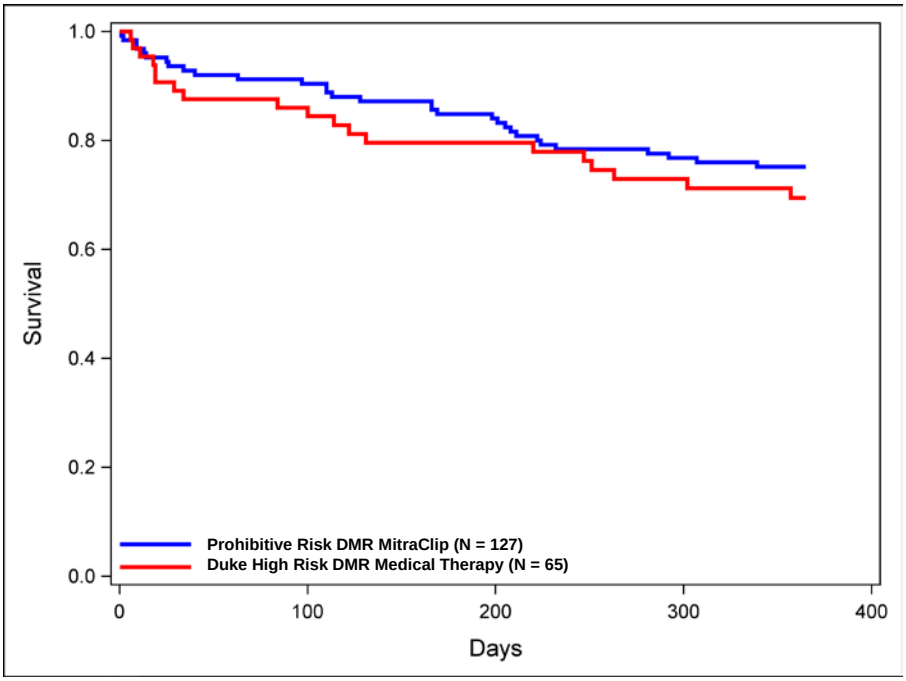


Table 16.8: Number at Risk, Kaplan-Meier Estimates and 95% CIs

Time Post Index Procedure	Baseline	30 Days	6 Months	12 Months
Prohibitive Risk Primary MR MitraClip Patients (N = 127)				
# At Risk	127	117	106	85
# Events	0	8	19	31
% Event Free	100%	93.6%	84.8%	75.2%
95% CI[a]	-	[87.6%, 96.8%]	[77.2%, 90.0%]	[66.1%, 82.1%]
Duke High Risk Primary MR Medical Therapy Patients (N = 65)				
# At Risk	65	57	49	39
# Events	0	7	13	19
% Event Free	100%	89.1%	79.6%	69.4%
95% CI[a]	-	[78.5%, 94.7%]	[67.4%, 87.6%]	[56.3%, 79.3%]

[a] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

MR severity at baseline, discharge and 12 months are presented in Table 16.9 for patients with data available at each follow-up (Completers Analysis). Immediate improvement in MR severity was noted at discharge with 82.1% and 53.7% of surviving patients reporting MR severity ≤ 2+ and ≤ 1+, respectively. This improvement was sustained at 12 months, with the majority (83.3%) of surviving patients reporting MR severity ≤ 2+ and 36.9% reporting MR severity ≤ 1+. At 12 months, freedom from death and MR > 2+ was 61.4% and freedom from death and MR > 1+ was 27.2% patients.

Table 16.9: Prohibitive Risk Primary MR MitraClip Cohort - MR Severity at Baseline and Follow-up
Completers Analysis

MR Severity	Baseline % (n/N)	Discharge[a] % (n/N)	12 Months % (n/N)
0 : None	0	1.6% (2/123)	0
1+: Mild	0	52.0% (64/123)	36.9% (31/84)
2+: Moderate	9.7% (12/124)	28.5% (35/123)	46.4% (39/84)
3+: Moderate-to-severe	58.9% (73/124)	13.0% (16/123)	13.1% (11/84)
4+: Severe	31.5% (39/124)	4.9% (6/123)	3.6% (3/84)
Missing	3	3	13
Death	0	1	30
MR ≤ 2+ in surviving patients	9.7% (12/124)	82.1% (101/123)	83.3% (70/84)
MR ≤ 1+ in surviving patients	0.0% (0/124)	53.7% (66/123)	36.9% (31/84)
Freedom from Death and MR > 2+	9.7% (12/124)	81.5% (101/124)	61.4% (70/114)
Freedom from Death and MR > 1+	0.0% (0/124)	53.2% (66/124)	27.2% (31/114)

[a] 30-day MR severity was used if discharge MR was unavailable.

Reduced preload as a result of the reduction in MR severity achieved with the MitraClip device resulted in reverse left ventricular remodeling (Table 16.10), characterized largely by a clinically important decrease in diastolic volume (-16.6 ml) and dimension (-0.2 cm).

TABLE 16.10: PROHIBITIVE RISK Primary MR MITRACLIP COHORT – LV Measurements at Baseline and 12 Months Patients with Paired Data[a]

LV Measurement	N	Baseline	12-month	Difference (12-month - Baseline)	%Change (12-month - Baseline)
LVEDV, ml					
Mean±SD	69	125.1±40.1	108.5±37.9	-16.6±22.9	-11.5±17.9
Median		119.7	104.7	-12.3	-10.2
95% CI[b,c]				(-22.1, -11.1)	(-15.9, -7.2)
LVIDd, cm					
Mean±SD	80	5.0±0.6	4.8±0.6	-0.2±0.4	-3.7±8.2
Median		5.1	4.9	-0.2	-4.0
95% CI[b,c]				(-0.3, -0.1)	(-5.6, -1.9)
LVESV, ml					
Mean±SD	69	49.1±24.5	46.1±21.4	-3.0±13.7	-1.3±27.0
Median		45.7	41.0	-1.5	-2.7
95% CI[b,c]				(-6.3, 0.3)	(-7.7, 5.2)
LVIDs, cm					
Mean±SD	75	3.4±0.7	3.3±0.7	-0.1±0.5	-0.2±16.4
Median		3.2	3.3	-0.1	-2.3
95% CI[b,c]				(-0.2, 0.1)	(-4.0, 3.6)

[a] Only patients who had a measurement at both Baseline and 12 months are included.
[b] 95% CI is based on a t-distribution.
[c] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

Improvement in LV function resulted in improvements in heart failure symptoms. NYHA Functional Class at baseline and follow-up are presented in Table 16.11 for patients with data available at each follow-up (Completers Analysis). Immediate improvement in NYHA Class was noted at 30 days with 82.3% of surviving patients reporting NYHA Class I or II symptoms. This improvement was sustained at 12 months, with the majority (86.9%) of surviving patients reporting NYHA Class I or II symptoms. At 12 months, freedom from death and NYHA Class III or IV symptoms was 64.0%. This improvement in NYHA Class symptoms is clinically important given that the majority of these patients (86.6%) were enrolled with NYHA Class III or IV symptoms.

Table 16.11: Prohibitive Risk Primary MR MitraClip Cohort - NYHA Functional Class at Baseline and Follow-up Completers Analysis

NYHA Functional Class	Baseline % (n/N)	30 Days % (n/N)	12 Months % (n/N)
I	2.4% (3/127)	33.6% (38/113)	40.5% (34/84)
II	11.0% (14/127)	48.7% (55/113)	46.4% (39/84)
III	63.8% (81/127)	15.9% (18/113)	10.7% (9/84)
IV	22.8% (29/127)	1.8% (2/113)	2.4% (2/84)
Missing	0	5	13
Death	0	9	30
NYHA I/II in surviving patients	13.4% (17/127)	82.3% (93/113)	86.9% (73/84)
Freedom from Death and NYHA Class III/IV	13.4% (17/127)	76.2% (93/122)	64.0% (73/114)

Table 16.12 shows the change in NYHA Class at 12 months from baseline. The table shows that 73 of 83 (88%) surviving patients improved by at least 1 class, and 30 of 83 (36.1%) surviving patients improved by at least 2 classes. Inclusion of deaths in the denominator results in 64.6% of patients alive and improved by at least 1 class and 26.5% alive and improved by at least 2 classes.

Table 16.12: Prohibitive Risk Primary MR MitraClip Cohort – Change in NYHA Class at 12 Months from Baseline

NYHA Class Change	Number of Patients
3 Class Improvement	4
2 Class Improvement	26
1 Class Improvement	43
No Change	9
1 Class Worsening	2
Death	30
Missing	13

Table 16.13 shows a mean change of +6.0 points in the Physical Component Summary (PCS) score and +5.6 points in the Mental Component Summary (MCS) score from baseline to 12 months after the MitraClip procedure. These changes are well above the 2-3 point minimally important difference (MID) threshold reported in the literature.

Table 16.13: Prohibitive Risk Primary MR MitraClip Cohort – SF-36 Quality of Life at Baseline and 12 Months Completers Analysis[a]

Component	N	Baseline	12-month	Difference (12-month - Baseline)
Physical Component Summary Score				
Mean±SD	73	33.4±8.6	39.4±10.5	6.0±8.6
Median		32.4	40.7	5.6
95% CI [b,c]				(4.0, 8.0)
Mental Component Summary Score				
Mean±SD	73	46.6±13.4	52.2±10.2	5.6±14.0
Median		49.8	54.0	3.2
95% CI [b,c]				(2.3, 8.9)

[a] Only patients who had a measurement at both Baseline and 12 months are included.
[b] 95% CI is based on a t-distribution.
[c] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

The proportion of responders for both the PCS and MCS scores are shown in Table 16.14 based on distribution-based methods recommended by the SF-36 authors (Significant Change Criteria, SCC) and the Standard Error of Measurement (SEM) method suggested by the FDA in its 2009 PRO Guidance. The proportion of responders was 63-68% for PCS and 49-53% for MCS.

Table 16.14: Prohibitive Risk Primary MR MitraClip Cohort – SF-36 QOL Responder Rate

Component	Minimally Important Difference	Completers Analysis
Physical Component Summary Score	SCC[a] (3.1)	63.0% (46/73)
	SEM[b] (2.2)	68.5% (50/73)
Mental Component Summary Score	SCC[a] (3.8)	49.3% (36/73)
	SEM[b] (2.7)	53.4% (39/73)

[a] SCC (Significant Change Criteria): Significant change assuming baseline-follow-up correlation of .4 and using a 80% CI.
[b] SEM (Standard Error of Measurement): One SEM equals 68% CI.

A clinically important decrease in the rate of hospitalization for heart failure was observed following discharge from the MitraClip procedure (0.67 to 0.18 per patient-year, a 73% reduction, Table 16.15) between the pre-enrollment and the post-discharge 12-month periods.

Table 16.15: Prohibitive Risk Primary MR MitraClip Cohort - Heart Failure Hospitalizations

	12 months Pre-enrollment	Post-discharge through 12 months
# Patients for Analysis	127	120
# Patients with Events	48	13
# Events	85	17
Follow-up (Patient-Years)	127	97
Rate[a]	0.67	0.18
(95% Two-sided CI [a,b])	(0.54, 0.83)	(0.11, 0.28)
# days hospitalized (Mean±SD)	6.0±4.5	5.9±3.8

[a] CI is obtained from a Poisson regression model.
[b] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

Effectiveness results demonstrate that 82.1% (101/123) of completers experienced MR reduction from 3+ or 4+ to 2+ or less at discharge following the MitraClip procedure (Table 16.16). Reduction of MR at 12 months was sustained to ≤ 2+ in 83.3% (70/84), and to ≤ 1+ in 36.9% (31/84) of patients for whom echocardiographic data was available. Reduction in MR severity was associated with reverse left ventricular remodeling characterized largely by clinically important decreases in diastolic volume and dimension.

Patients also experienced clinically important improvement in NYHA Functional Class at 12 months; more than 80% of patients experienced NYHA Class III or Class IV symptoms at baseline, which reduced to less than 15% at 12 months. Despite the elderly and highly co-morbid nature of the population, quality of life as measured by the SF-36 quality of life physical and mental component scores showed clinically important improvement. Sensitivity analyses showed that these effectiveness results are robust to missing data. Finally, heart failure hospitalizations showed clinically important reduction in the 12 months post-MitraClip procedure from the 12 months pre-MitraClip procedure, including in a sensitivity analysis where death is included in the analysis as a heart failure hospitalization.

Table 16.16: Effectiveness in Prohibitive Risk Primary MR MitraClip Cohort

Effectiveness Measure[§]	Prohibitive Risk DMR MitraClip Cohort (N=127)
Improvement in LVEDV at 1 year	-17±23
Improvement in LVESV at 1 year	-3±14
Improvement in SF-36 PCS at 1 year	6.0±8.6
Improvement in SF-36 MCS at 1 year	5.6±14.0
NYHA Class III or IV: Baseline → 1 year	85% → 13%

[§] LVEDV, LVESV, SF-36 PCS and MCS results are in patients with paired data, and NYHA Class results are in Completers.

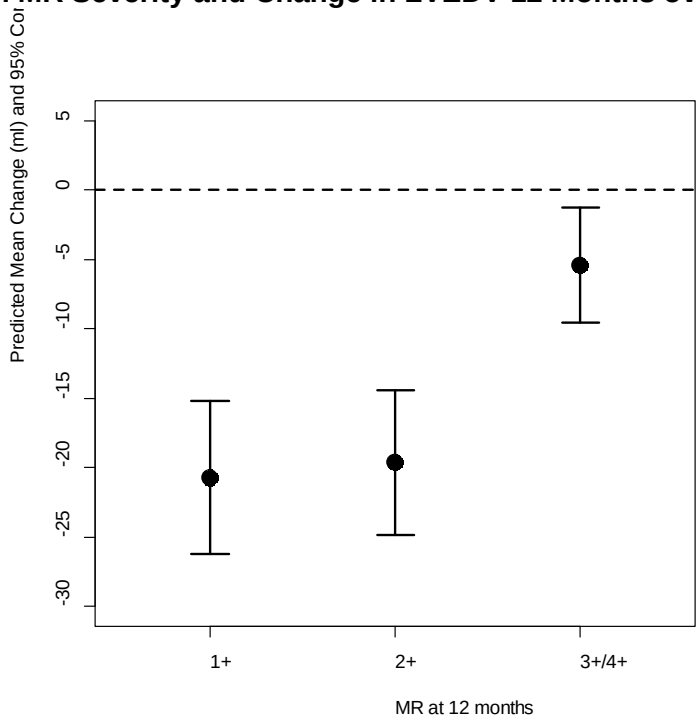
Reduction in MR severity was assessed in patients who have 2-year follow-up available. Table 16.17 shows that MR reduction in surviving patients to ≤ 2+ and ≤ 1+ is 82.5% (33/40) and 35.0%, (14/40) respectively, at 2 years. Therefore, there is no evidence of deterioration of MR severity from 12 months to 2 years in surviving patients.

Table 16.17: Prohibitive Risk Primary MR MitraClip Cohort - Durability of MR Reduction

MR Severity	Baseline % (n/N)	12 Months % (n/N)	2 Years % (n/N)
0 : None	0	0	0
1+: Mild	0	36.9% (31/84)	35.0% (14/40)
2+: Moderate	9.7% (12/124)	46.4% (39/84)	47.5% (19/40)
3+: Moderate-to-severe	58.9% (73/124)	13.1% (11/84)	15.0% (6/40)
4+: Severe	31.5% (39/124)	3.6% (3/84)	2.5% (1/40)
MR ≤ 2+ in surviving patients	9.7% (12/124)	83.3% (70/84)	82.5% (33/40)
MR ≤ 1+ in surviving patients	0.0% (0/124)	36.9% (31/84)	35.0% (14/40)

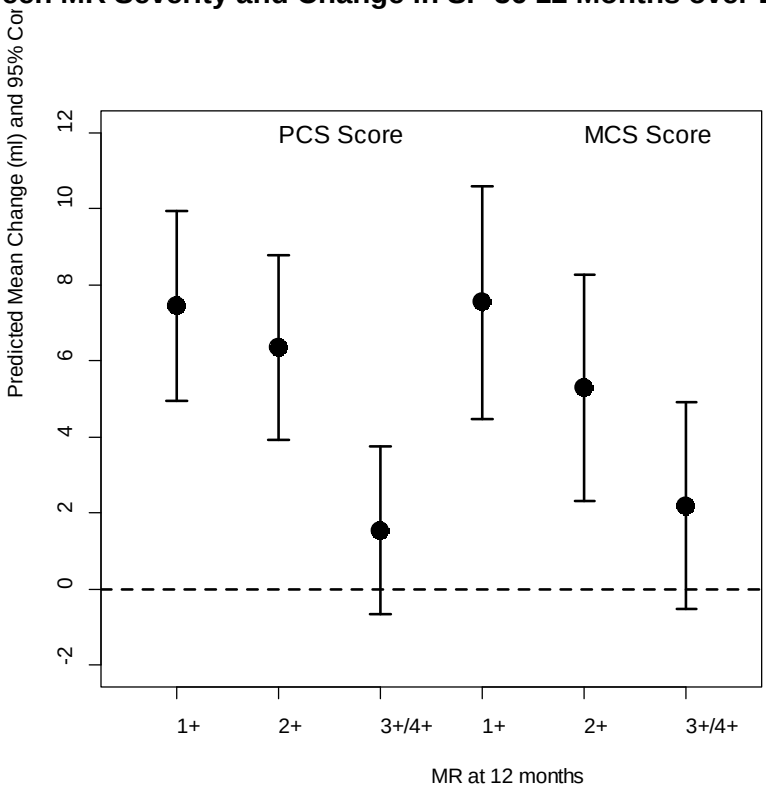
In order to evaluate the relationship between MR severity and measures of effectiveness, statistical models were fit to the effectiveness data. MR severity was importantly associated with LVEDV in the Prohibitive Risk primary MR MitraClip patients (Figure 16.2). Reduction of MR severity to ≤ 2+ at 12 months resulted in clinically important decreases in LVEDV. No clinically important difference in LVEDV reduction is observed between MR 1+ and 2+. Reduction of MR to 2+ or less is associated with a decrease in left ventricular size that is not observed with ongoing MR of 3+ or greater.

Figure 16.2: Prohibitive Risk Primary MR MitraClip Cohort - Dose-Response Relationship between MR Severity and Change in LVEDV 12 Months over Baseline



MR severity was importantly associated with PCS and MCS scores in Prohibitive Risk primary MR MitraClip patients. Reduction of MR severity to ≤ 2+ at 12 months resulted in clinically important improvement in PCS and MCS scores. When MR severity remained 3+/4+, the changes in PCS and MCS scores were small and not clinically important (Figure 16.3). Reduction of MR to 2+ or less is thus associated with an improvement in quality of life that is not observed with ongoing MR of 3+ or greater.

Figure 16.3: Prohibitive Risk Primary MR MitraClip Cohort - Dose-Response Relationship between MR Severity and Change in SF-36 12 Months over Baseline



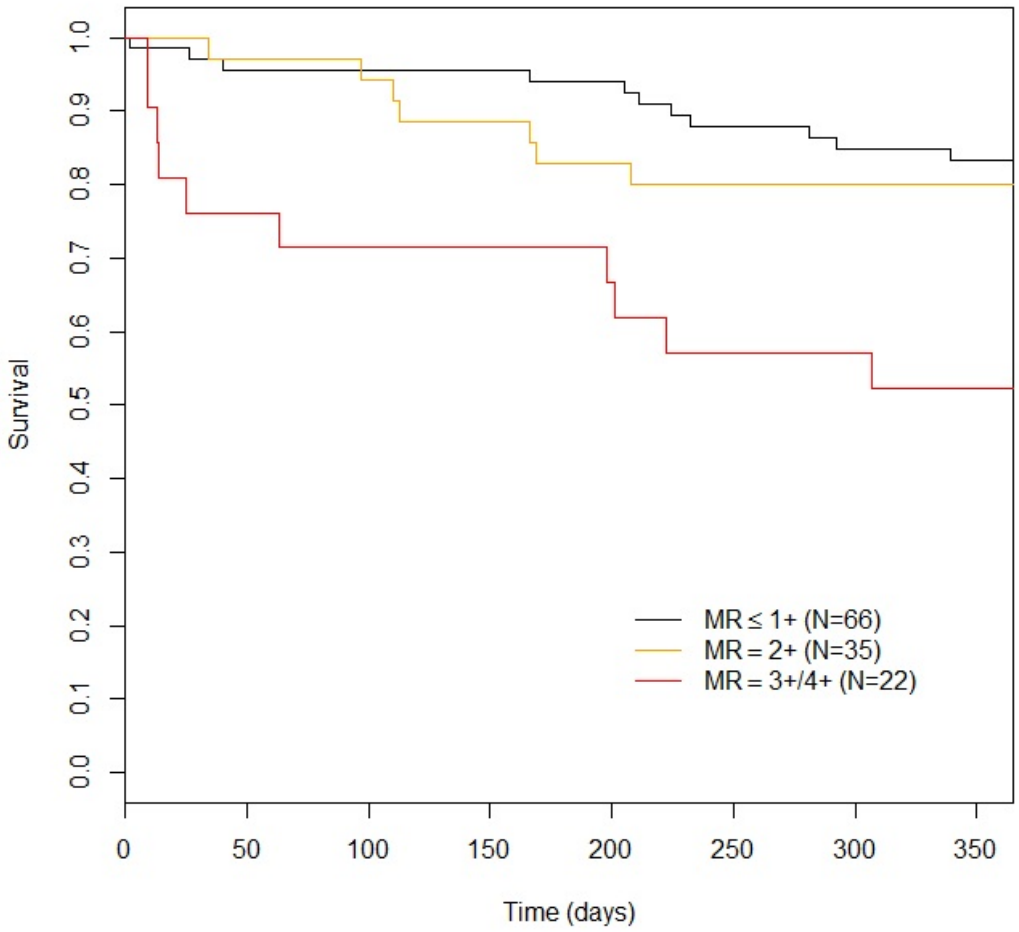
The observed number and corresponding estimated proportions of NYHA Classes at 12 months by two discharge MR groups are summarized in Table 16.18. The results demonstrate that reduction of MR to 2+ or less at discharge is associated with improved NYHA Functional Class that is not observed with MR of 3+ or greater at discharge.

Table 16.18: Prohibitive Risk Primary MR MitraClip Cohort – Summary of Binary NYHA Functional Class Data By Discharge MR Severity

Discharge MR	NYHA Functional Class at 12 Months	
	I/II	III/IV/Death
≤ 2+	66/93 (0.710)	27/93 (0.290)
3+/4+	7/19 (0.368)	12/19 (0.632)

Kaplan-Meier survival curves are plotted by discharge MR severity (Figure 16.4). There was no clinically important difference between the "≤1+" discharge MR group and the "2+" discharge MR group; however, there was a clinically important difference between the "≤1+" discharge MR group and the "3+/4+" discharge MR group and between the "2+" discharge MR group and the "3+/4+" discharge MR group. Reduction of MR to 2+ or less is associated with decreased mortality compared to ongoing MR of 3+ or greater.

Figure 16.4: Prohibitive Risk Primary MR MitraClip Cohort - Kaplan-Meier Survival Curves by Discharge MR Severity (≤1+, 2+, 3+/4+)



17.0 SUMMARY OF THE COAPT RESULTS

A. Study Design

Patients were enrolled between December 27, 2012, and June 23, 2017. The database for this Panel Track Supplement reflected data collected through August 3, 2018, and included 614 randomized patients. There were 78 investigational sites.

The COAPT Trial was a prospective, randomized (1:1; MitraClip + GDMT vs. GDMT alone), open-label, multicenter investigational study intended to demonstrate: (1) MitraClip was safe in subjects with secondary MR, and (2) MitraClip could reduce recurrent HF hospitalization as compared to the GDMT Control group. The randomization was further stratified by study

site and by cardiomyopathy etiology (e.g., ischemic or non-ischemic). The planned sample size of the trial was 760, including 150 roll-in subjects.

The COAPT Trial was conducted under the oversight of several independent committees, including: (1) a Steering Committee, which provided scientific and medical input on trial design, data collection, data analyses, and interpretation of results; (2) an independent Eligibility Committee, which confirmed that each subject was on optimal therapy including GDMT prior to being considered for the trial and that the subject was not appropriate for mitral valve surgery, even if randomized to the Control group; (3) a Central Echocardiography Core Laboratory (ECL), which was responsible for reviewing subject's screening echocardiography images to determine if the subject met the MR severity eligibility criterion prior to the subject being considered eligible for the trial, and for assessing MR severity and left ventricular measurements, along with other measures, at baseline and follow-ups; (4) a Clinical Events Committee (CEC), which adjudicated all adverse events per pre-established definitions (blinding was maintained whenever feasible); (5) a Data Monitoring Committee (DMC), which monitored the safety of subjects throughout trial; and (6) a Contract Research Organization, which participated in source data verification.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the COAPT Trial was limited to patients who met the following inclusion criteria:

- Symptomatic functional MR (≥ 3+) due to cardiomyopathy of either ischemic or non-ischemic etiology determined by assessment of a qualifying transthoracic echocardiogram (TTE) obtained within 90 days and transesophageal echocardiogram (TEE) obtained within 180 days prior to subject registration, with MR severity based principally on the TTE study, confirmed by the ECL. The ECL may request a transesophageal echocardiogram (TEE) to confirm MR etiology.
- In the judgment of the HF specialist investigator at the site, the subject has been adequately treated per applicable standards, including for coronary artery disease, left ventricular dysfunction, mitral regurgitation and HF (e.g., with CRT, revascularization, and/or GDMT. The Eligibility Committee must concur that the subject has been adequately treated.
- New York Heart Association (NYHA) Functional Class II, III or ambulatory IV.
- The Local Site Heart Team (cardiothoracic surgeon and HF specialist investigators) and the Central Eligibility Committee concur that surgery will not be offered as a treatment option and that medical therapy was the intended therapy for the subject, even if the subject was randomized to the Control group.
- Left Ventricular Ejection Fraction (LVEF) was ≥20% and ≤50% within 90 days prior to subject registration, assessed by the site using any one of the following methods: echocardiography, contrast left ventriculography, gated blood pool scan or cardiac magnetic resonance imaging (MRI).
- Left Ventricular End Systolic Dimension (LVESD) was ≤70 mm assessed by site based on a TTE obtained within 90 days prior to subject registration.
- The primary regurgitant jet was non-commissural, and in the opinion of the MitraClip implanting investigator can successfully be treated by the MitraClip. If a secondary jet exists, it must be considered clinically insignificant.
- Creatine Kinase-MB (CK-MB) obtained within prior 14 days < local laboratory ULN (Upper Limit of Normal).

- Transseptal catheterization and femoral vein access was determined to be feasible by the MitraClip implanting investigator.
- Age 18 years or older.
- The subject or the subject's legal representative understands and agrees that should he/she be assigned to the Control group, he/she will be treated with medical therapy and conservative management without surgery and without the MitraClip, either domestically or abroad. If the subject would actively contemplate surgery and/or MitraClip if randomized to Control, he/she should not be registered in this trial.
- The subject or the subject's legal representative has been informed of the nature of the trial and agrees to its provisions, including the possibility of randomization to the Control group and returning for all required post-procedure follow-up visits, and has provided written informed consent.

Patients were <u>not</u> permitted to enroll in the COAPT Trial if they met any of the following clinical or anatomical exclusion criteria:

- Chronic Obstructive Pulmonary Disease (COPD) requiring continuous home oxygen therapy or chronic outpatient oral steroid use.
- Untreated clinically significant coronary artery disease requiring revascularization.
- Coronary artery bypass grafting (CABG) within 30 days prior to subject registration.
- Percutaneous coronary intervention within 30 days prior to subject registration.
- Transcatheter aortic valve replacement (TAVR) within 30 days prior to subject registration.
- Tricuspid valve disease requiring surgery.
- Aortic valve disease requiring surgery or transcatheter intervention.
- Cerebrovascular accident within 30 days prior to subject registration.
- Severe symptomatic carotid stenosis (> 70% by ultrasound).
- Carotid surgery or stenting within 30 days prior to subject registration.
- American College of Cardiology (ACC)/American Heart Association (AHA) Stage D heart failure.
- Presence of any of the following:
    - Estimated pulmonary artery systolic pressure (PASP) > 70 mm Hg assessed by site based on echocardiography or right heart catheterization, unless active vasodilator therapy in the catheterization laboratory was able to reduce the pulmonary vascular resistance (PVR) to < 3 Wood Units or between 3 and 4.5 Wood Units with v wave less than twice the mean of the pulmonary capillary wedge pressure
    - Hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology
    - Infiltrative cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis)
    - Hemodynamic instability requiring inotropic support or mechanical heart assistance
- Physical evidence of right-sided congestive heart failure with echocardiographic evidence of moderate or severe right ventricular dysfunction, as assessed by site.
- Implant of any CRT or CRT with cardioverter-defibrillator (CRT-D) within the last 30 days prior to subject registration.
- Mitral valve orifice area < 4.0 cm^2 assessed by site based on a TTE within 90 days prior to subject registration.

- Leaflet anatomy which may preclude MitraClip implantation, proper MitraClip positioning on the leaflets or sufficient reduction in MR by the MitraClip. This evaluation was based on TEE evaluation of the mitral valve within 180 days prior to subject registration and includes:
  - Insufficient mobile leaflet available for grasping with the MitraClip device
  - Evidence of calcification in the grasping area
  - Presence of a significant cleft in the grasping area
  - Lack of both primary and secondary chordal support in the grasping area
  - Leaflet mobility length < 1 cm
- Hemodynamic instability defined as systolic pressure < 90 mmHg with or without afterload reduction, cardiogenic shock or the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device.
- Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months.
- Life expectancy < 12 months due to non-cardiac conditions.
- Modified Rankin Scale (MRS) ≥ 4 disability.
- Status 1 heart transplant or prior orthotopic heart transplantation.
- Prior mitral valve leaflet surgery or any currently implanted prosthetic mitral valve, or any prior transcatheter mitral valve procedure.
- Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
- Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e., noncompliant, perforated).
- Active infections requiring current antibiotic therapy.
- Subjects in whom TEE was contraindicated or high risk.
- Known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically.
- Pregnant or planning pregnancy within next 12 months.
- Currently participating in an investigational drug or another device study that has not reached its primary endpoint. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
- Subject belongs to a vulnerable population per investigator's judgment or subject has any kind of disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures.

2. Follow-up Schedule

All patients were scheduled for follow-up examinations at 1 week (phone contact), 30 days, 6 months, 12 months, 18 months, 24 months, and annually thereafter through 5 years. Preoperative and post-operative assessments included physical assessment and patient interview, laboratory measurements, imaging tests, and health status/quality of life (QoL) questionnaire. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

Primary Safety Endpoint:

The primary safety endpoint was a composite of SLDA, device embolizations, endocarditis requiring surgery, ECL confirmed mitral stenosis requiring surgery, left ventricular assist device (LVAD) implant, heart transplant, and any device related

complications requiring non-elective cardiovascular surgery at 12 months. The proportion of subjects free from the primary safety endpoint events was tested against a pre-specified performance goal (PG) of 88% for the Safety Analysis population, as defined in Section X.B.

Primary Effectiveness Endpoint:

The primary effectiveness endpoint was recurrent HF hospitalizations through 24 months, with the following null and alternative hypotheses:

$$H_0: RRR \leq 0$$
$$H_A: RRR > 0$$

where *RRR* is the relative risk reduction in the rate of recurrent HF hospitalization due to treatment with the MitraClip device as compared to the Control group. The primary effectiveness endpoint was analyzed when the last subject completed 12 months of follow-up. Hypothesis testing was performed using the Joint Frailty Model to adjust for the competing risk of death.[1-3]

Secondary Endpoints:

An ordered list of powered secondary endpoints, as shown in Table 17.1, was included in a hierarchical testing scheme, which were carried out after both the primary safety and effectiveness endpoints were met.

Table 17.1: Ordered List of Secondary Endpoints for Hierarchical Testing

Order	Secondary Endpoint	Alternative Hypothesis
#1	Proportion of MR severity ≤ 2+ at 12 months	$H_A: P_D - P_C \neq 0$
#2	All-cause mortality at 12 months	$H_A: HR < 1.5$
#3	Hierarchical composite of all-cause mortality and recurrent HF hospitalization (analyzed when the last subject completes 12 months of follow-up)	H_A: Either rate of death or rate of recurrent HF hospitalization is lower in the Device group compared to the Control group.
#4	Change in quality of life (QoL) at 12 months from baseline, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ)	$H_A: \mu_D - \mu_C \neq 0$
#5	Change in distance walked on the 6 Minute Walk Test (6MWT distance or 6MWD) at 12 months over baseline	$H_A: \mu_D - \mu_C \neq 0$
#6	Recurrent hospitalizations - all-cause (analyzed when the last subject completes 12 months of follow-up)	$H_A: RRR \neq 0$
#7	Proportion of New York Heart Association (NYHA) Functional Class I/II at 12 months	$H_A: P_D - P_C \neq 0$
#8	Change in Left Ventricular End Diastolic Volume (LVEDV) at 12 months over baseline	$H_A: \mu_D - \mu_C \neq 0$
#9	All-cause mortality at 24 months	$H_A: HR \neq 1$

Order	Secondary Endpoint	Alternative Hypothesis
#10	Freedom from all-cause mortality, stroke, myocardial infarction, or non-elective cardiovascular surgery for device related complications in the MitraClip group at 30 days	$H_A: P_D(30) > 0.80$
P: proportion; *μ*: mean. *HR*: hazard ratio; *RRR*: relative risk reduction. Subscript D: Device; Subscript C: Control.		

B. Accountability of PMA Cohort

At the time of database lock, a total of 614 subjects were randomized in this trial, including 302 Device subjects and 312 Control subjects.

There were four different analysis populations defined in the protocol: Intention-to-Treat (ITT) population, Per Protocol (PP) population, As Treated (AT) population, and Safety Analysis (SA) population, as summarized in Table 17.2 and Figure 17.1. The primary analysis for safety was the Safety Analysis, and that for effectiveness was the ITT analysis.

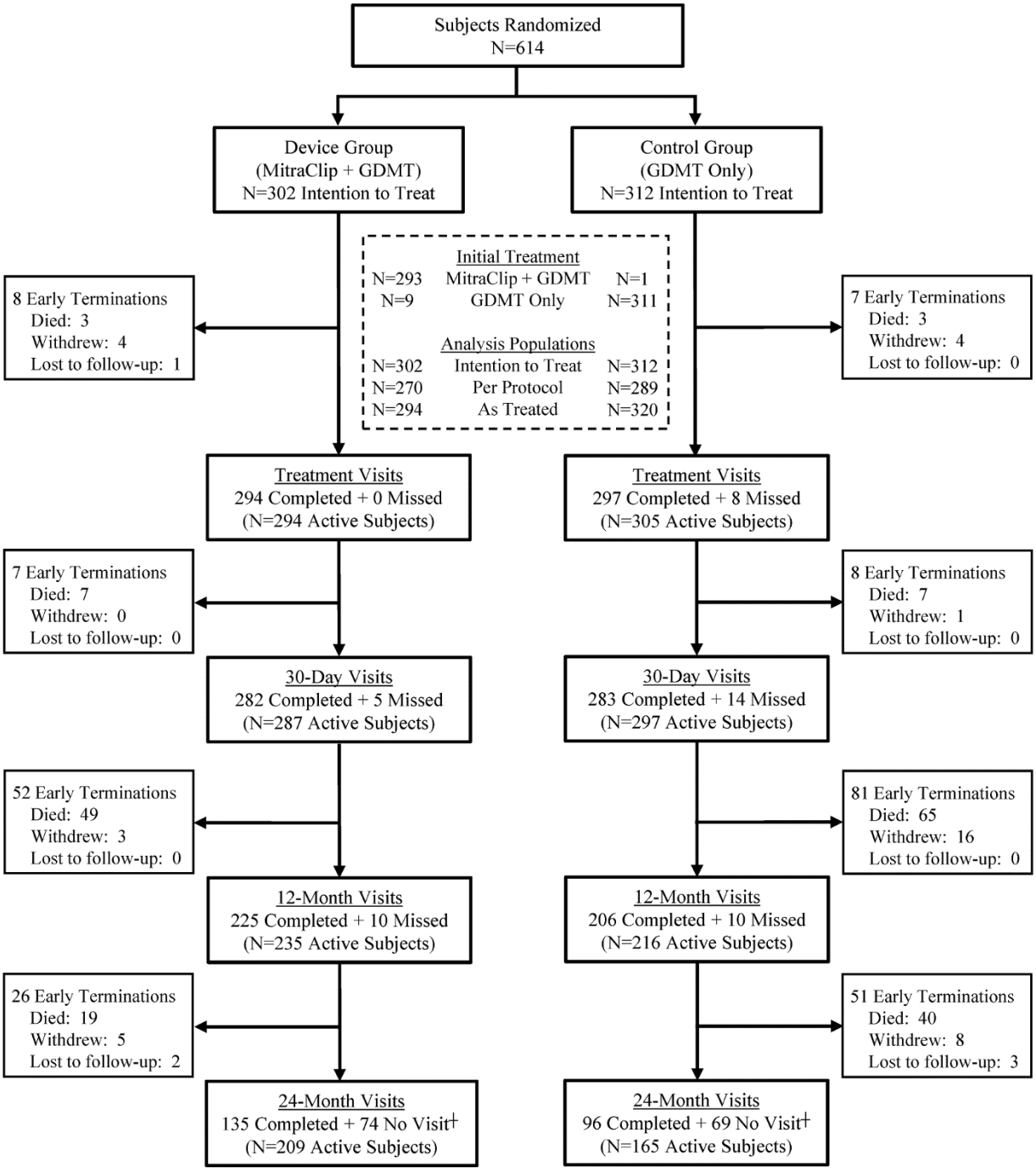
Table 17.2: Analysis Populations

Analysis Population	Definition	Number of Patients	
		Device	Control
Intention-to-Treat (ITT)	All randomized subjects	302	312
As Treated (AT)	Randomized subjects who received the treatment as randomized	294	320
Per Protocol (PP)	Subjects who met major inclusion and none of the major exclusion criteria and received the treatment as randomized	270	289
Safety Analysis (SA)	All ITT subjects in the Device group with an attempted implant procedure*	293	
*Attempted implant procedure is defined as administration of anesthesia for the MitraClip procedure.			

C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics of the study population are typical for an HF study performed in the U.S., as shown in Table 17.3. The two study groups were well-balanced, with no significant difference in patient demographics and baseline characteristics.

Figure 17.1: Disposition of COAPT Randomized Subjects



†Denotes visits that were expected from, missed by or not due from subjects active in the study at the time of the data cut-off.

Table 17.3: Patient Demographics and Baseline Characteristics (ITT Population)

Demographics and Baseline Characteristics	Summary Statistics*		P-Value†
	Device (N=302)	Control (N=312)	
Age at Registration (year)	71.7 ± 11.8 (302)	72.8 ± 10.5 (312)	0.2186
Male	66.6% (201/302)	61.5% (192/312)	0.1953
Race/Ethnicity			
White or Caucasian	74.5% (225/302)	74.4% (232/312)	0.9673
Non-white	25.5% (77/302)	25.6% (80/312)	
Height (cm)	170.8 ± 10.4 (301)	169.9 ± 10.8 (306)	0.2500
Weight (kg)	78.8 ± 17.2 (301)	78.4 ± 20.1 (307)	0.8002
Body Mass Index (kg/m^2)	27.0 ± 5.8 (300)	27.1 ± 5.9 (305)	0.9880
Serum Creatinine (mg/dL)	1.8 ± 1.2 (300)	1.8 ± 1.4 (306)	0.8362
Creatinine Clearance (mL/min)	50.9 ± 28.5 (299)	47.8 ± 25.0 (302)	0.1552
Creatinine Clearance ≤ 60 mL/min	71.6% (214/299)	75.2% (227/302)	0.3189
BNP (pg/mL)	1014.8 ± 1086.0 (208)	1017.1 ± 1212.8 (209)	0.9833
NT-proBNP (pg/mL)	5174.3 ± 6566.6 (74)	5943.9 ± 8437.6 (85)	0.5194
Elevated BNP or NT-proBNP prior to Enrollment	93.4% (267/286)	93.1% (282/303)	0.8898
Extremely High Risk for MV Surgery	68.6% (205/299)	69.9% (218/312)	0.7258
KCCQ Overall Summary Score	53.2 ± 22.8 (302)	51.6 ± 23.3 (309)	0.3907
Six Minute Walk Test Distance (meters)	249.6 ± 123.8 (296)	234.5 ± 123.5 (305)	0.1359
NYHA Functional Class			
Class I	0.3% (1/302)	0.0% (0/311)	0.4927
Class II	42.7% (129/302)	35.4% (110/311)	0.0623
Class III	51.0% (154/302)	54.0% (168/311)	0.4532
Class IV	6.0% (18/302)	10.6% (33/311)	0.0371
SF-36 Quality of Life Physical Component Score	33.0 ± 9.1 (299)	32.6 ± 10.0 (308)	0.6336
SF-36 Quality of Life Mental Component Score	46.7 ± 12.7 (299)	45.3 ± 13.0 (308)	0.1883
Cardiovascular Event History			
Ischemic Cardiomyopathy	60.9% (184/302)	60.6% (189/312)	0.9292
Non-Ischemic Cardiomyopathy	39.1% (118/302)	39.4% (123/312)	
Prior TIA	8.6% (26/302)	5.4% (17/312)	0.1250
Prior Stroke	12.3% (37/302)	11.2% (35/312)	0.6906
Prior Stroke or TIA	18.5% (56/302)	15.7% (49/312)	0.3505
Prior Myocardial Infarction	51.7% (156/302)	51.3% (160/312)	0.9262

Demographics and Baseline Characteristics	Summary Statistics*		P-Value†
	Device (N=302)	Control (N=312)	
Coronary Artery Disease (CAD)	72.2% (218/302)	73.1% (228/312)	0.8044
Hypertension	80.5% (243/302)	80.4% (251/312)	0.9963
Hypercholesterolemia	55.0% (166/302)	52.2% (163/312)	0.4988
Angina	16.9% (51/302)	23.4% (73/312)	0.0446
Chronic Obstructive Pulmonary Disease	23.5% (71/302)	23.1% (72/312)	0.8990
Arrhythmia Event History	66.6% (201/302)	64.4% (201/312)	0.5783
Ventricular Fibrillation	5.6% (17/302)	8.0% (25/312)	0.2421
Ventricular Flutter	0.0% (0/302)	0.0% (0/312)	1.0000
Ventricular Tachycardia	24.8% (75/302)	22.4% (70/312)	0.4842
Atrial Flutter	10.3% (31/302)	10.9% (34/312)	0.7990
Atrial Fibrillation	55.6% (168/302)	51.0% (159/312)	0.2465
Atrial Fibrillation or Flutter	57.3% (173/302)	53.2% (166/312)	0.3095
Any Hospitalization 12 months prior to enrollment	67.5% (204/302)	65.1% (203/312)	0.5148
Heart Failure	58.3% (176/302)	56.1% (175/312)	0.5838
Other-Cardiovascular	11.6% (35/302)	9.3% (29/312)	0.3523
Non-Cardiovascular	7.9% (24/302)	7.1% (22/312)	0.6734
Co-morbidity			
Diabetes	35.1% (106/302)	39.4% (123/312)	0.2680
Peripheral Vascular Disease	17.2% (52/302)	18.3% (57/312)	0.7334
Renal Disease	57.0% (172/302)	56.7% (177/312)	0.9555
History of Anemia	22.5% (68/302)	24.4% (76/312)	0.5901
History of Major Bleeds or Bleeding Disorder	7.6% (23/302)	7.1% (22/312)	0.7884
STS Replacement Score (%)	7.8 ± 5.5 (302)	8.5 ± 6.2 (312)	0.1565
STS Repair Score (%)	5.6 ± 5.6 (302)	6.0 ± 5.4 (312)	0.3939
Prior Cardiac Interventions			
Coronary Artery Bypass Craft (CABG)	40.1% (121/302)	40.4% (126/312)	0.9359
PTCA/Stents/Atherectomy	43.0% (130/302)	49.0% (153/312)	0.1364
Device Implantation			
None	33.1% (100/302)	33.0% (103/312)	0.9790
ICD	30.1% (91/302)	32.4% (101/312)	0.5496
CRT-P	1.7% (5/302)	1.9% (6/312)	0.8028
CRT-D	36.4% (110/302)	33.0% (103/312)	0.3747
Pacemaker	6.0% (18/302)	8.0% (25/312)	0.3191
Defibrillator (ICD or CRT-D)	62.6% (189/302)	61.5% (192/312)	0.7898

Demographics and Baseline Characteristics	Summary Statistics*		P-Value†
	Device (N=302)	Control (N=312)	
Resynchronization (CRT-D or CRT-P)	38.1% (115/302)	34.9% (109/312)	0.4185
Pacing (CRT-P or Pacemaker)	7.3% (22/302)	9.9% (31/312)	0.2422
Prior Cardiac Valve Interventions			
Aortic Valve Intervention	3.3% (10/302)	4.5% (14/312)	0.4523
Pulmonic Valve Intervention	0.0% (0/302)	0.0% (0/312)	1.0000
Tricuspid Valve Intervention	0.0% (0/302)	0.0% (0/312)	1.0000
Mitral Valve Intervention	0.3% (1/302)	0.0% (0/312)	0.4919
Echocardiographic Core Laboratory Measures			
Mitral regurgitation severity			
3+: Moderate-to-Severe	49.0% (148/302)	55.3% (172/311)	0.1186
4+: Severe	51.0% (154/302)	44.7% (139/311)	
Effective Regurgitant Orifice Area (EROA, cm^2)	0.41 ± 0.15 (289)	0.40 ± 0.15 (302)	0.4203
Left Ventricular Ejection Fraction (LVEF, %)	31.3 ± 9.1 (281)	31.3 ± 9.6 (294)	0.9717
≤ 40 %	82.2% (231/281)	82.0% (241/294)	0.9418
Left Ventricular End Systolic Dimension (LVESD, cm)	5.3 ± 0.9 (301)	5.3 ± 0.9 (306)	0.8172
Left Ventricular End Diastolic Dimension (LVEDD, cm)	6.2 ± 0.7 (301)	6.2 ± 0.8 (307)	0.7958
Left Ventricular End Systolic Volume (LVESV, mL)	135.5 ± 56.1 (281)	134.3 ± 60.3 (294)	0.8085
Left Ventricular End Diastolic Volume (LVEDV, mL)	194.4 ± 69.2 (281)	191.0 ± 72.9 (294)	0.5667
LVEDV Index (mL/m^2)	102.3 ± 33.7 (279)	100.6 ± 35.0 (288)	0.5570
Right Ventricular Systolic Pressure (RVSP, mmHg)	44.0 ± 13.4 (253)	44.6 ± 14.0 (275)	0.6090
Medication Use at Baseline			
Beta-blocker	91.1% (275/302)	89.7% (280/312)	0.5802
ACEI, ARB or ARNI	71.5% (216/302)	62.8% (196/312)	0.0218
Mineralocorticoid receptor antagonist	50.7% (153/302)	49.7% (155/312)	0.8076
Nitrate	6.3% (19/302)	8.0% (25/312)	0.4084
Hydralazine	16.6% (50/302)	17.6% (55/312)	0.7243
Diuretic	89.4% (270/302)	88.8% (277/312)	0.8048
Chronic oral anticoagulant	46.4% (140/302)	40.1% (125/312)	0.1155
Aspirin	57.6% (174/302)	64.7% (202/312)	0.0699
P2Y12 receptor inhibitor	25.2% (76/302)	22.8% (71/312)	0.4843
Statin	62.6% (189/302)	60.6% (189/312)	0.6095

*Continuous measures - Mean ± SD; categorical measures - % (no./total no.).
†P-values are from *t*-test for continuous variables and from Chi-square test or Fisher's exact test when

Demographics and Baseline Characteristics	Summary Statistics*		P-Value†
	Device (N=302)	Control (N=312)	

Cochran's rule is not met for categorical variables. All p-values displayed are two-sided and for information only.

D. Safety and Effectiveness Results

1. Primary Safety Endpoint

The rate of freedom from device-related complications at 12 months was 96.6%, with a lower 95% confidence limit of 94.8%, which was higher than the pre-specified performance goal of 88% (p<0.0001), as shown in Figure 17.2. As such, the COAPT Trial met its primary safety endpoint. A breakdown of the composite primary safety endpoint events is presented in Table 17.2.

Figure 17.2: Kaplan-Meier Curve of the Primary Safety Endpoint (SA Population)

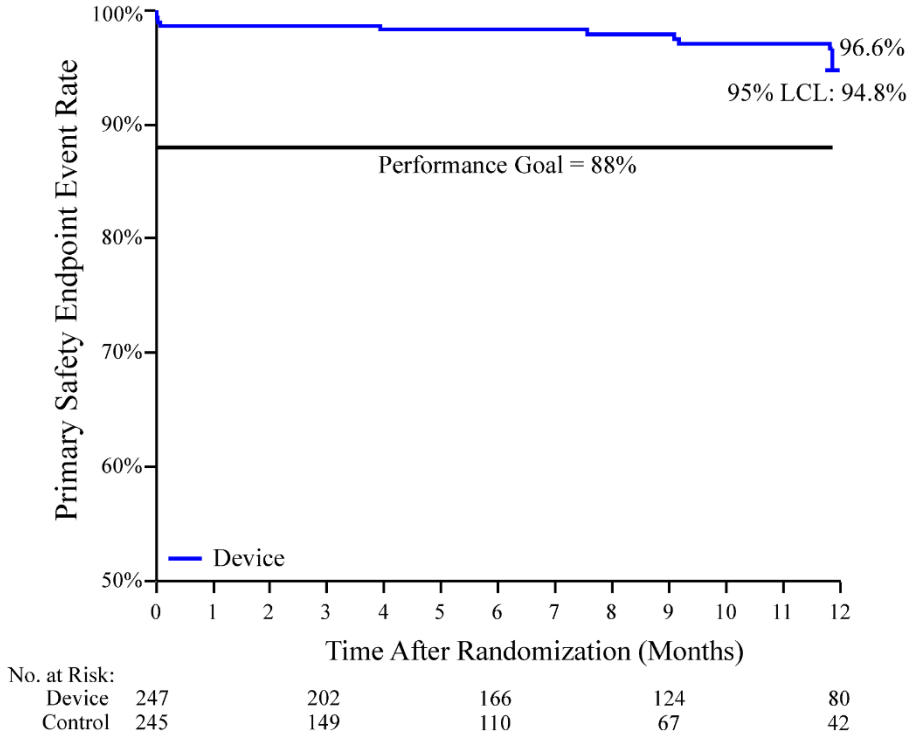


Table 17.4: Outcomes of the Primary Safety Endpoint Components (SA Population)

Event	Summary Statistics* (N = 293)
Device-related complications at 12 months	9 (3.4%)
-- Single leaflet device attachment	2 (0.7%)
-- Device embolization	1 (0.3%)

-- Endocarditis requiring surgery	0 (0.0%)
-- Mitral stenosis requiring surgery	1 (0.3%)
-- LVAD implant	3 (1.2%)
-- Heart transplant	2 (0.8%)
-- Any device-related complication requiring non-elective cardiovascular surgery	1 (0.3%)

*# events (Kaplan-Meier rate)

2. Primary Effectiveness Endpoint

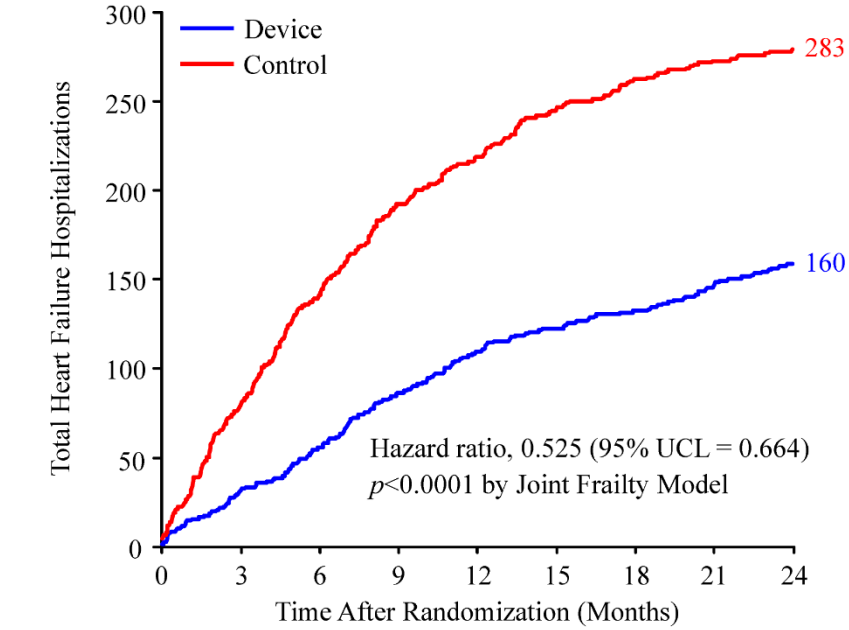
A total of 160 and 283 HF hospitalizations occurred within 24 months in the Device and Control groups, respectively. The annualized rates (events per patient-year) of HF hospitalization were 0.358 in the Device group and 0.679 in the Control group, with a hazard ratio (HR) of 0.525 (upper 95% confidence limit: 0.664), representing a 47.5% reduction in the risk of recurrent HF hospitalization by the Joint Frailty Model in favor of the Device (p<0.0001), as summarized in Table 17.5 and Figure 17.3. Therefore, the COAPT Trial met its primary effectiveness endpoint. The successes of the primary safety endpoint and the primary effectiveness endpoint were confirmed by the AT analysis, PP analysis, and sensitivity analysis.

Table 17.5: Recurrent HF Hospitalization through 24 Months – Primary Effectiveness Endpoint (ITT Population)

	Device (N=302)	Control (N=312)	Hazard Ratio - Device vs. Control [95% CI]	Relative Risk Reduction - Device vs. Control [95% CI]	P-Value
Number of Subjects*	92 (30.5%)	151 (48.4%)			
Number of Events	160	283			
Total Follow-Up (patient-years)*	446.5	416.8			
Annualized Rate [95% CI]†	0.358 [0.307, 0.418]	0.679 [0.604, 0.763]			
Joint Frailty Model			0.525 [-, 0.664]	0.475 [0.336, -]	< 0.0001

*The total follow-up in patient-years was calculated as the sum of follow-up patient-years for each subject through 24 months at the time of data cut-off or end of study, whichever was earlier.
†The annualized rate was calculated as total number of HF hospitalization events divided by total follow-up years through 24 months.
Note: (1) Hospitalizations that were adjudicated by the CEC as related to HF using the pre-specified protocol definition were included as events in the analysis; (2) Hospitalizations for MV surgery, LVAD implant or heart transplant during the follow-up period were treated as HF hospitalizations; and (3) For subjects in the Control group who received the MitraClip device due to HF or cardiac symptoms, the hospitalizations for the MitraClip procedure were treated as HF hospitalizations.

Figure 17.3: Total HF Hospitalization through 24 Months (ITT Population)



3. Powered Secondary Endpoints

Hypothesis testing was performed on 10 pre-specified secondary endpoints using a hierarchical test procedure, as shown in Table 17.6.

Table 17.6: Summary of Hierarchical Secondary Endpoints (ITT Population)

Secondary Endpoints (hierarchical order)	Device (N=302)	Control (N=312)	HR or Difference [95% CI]	Lower 95% confidence limit	P-Value*
#1 Proportion of MR Severity ≤ 2+ at 12 Months; % (no./total no.) [95% CI]	94.8% (199/210) [90.82%, 97.36%]	46.9% (82/175) [39.29%, 54.53%]	-	-	< 0.0001
#2 All-Cause Mortality at 12 Months (Non-inferiority);† Kaplan-Meier estimate (SE) of event rate	19.1% (2.3%)	23.2% (2.4%)	0.809 [-, 1.085]	-	0.0003
#3 Finkelstein-Schoenfeld Analysis of a Hierarchical Composite of All-Cause Mortality and Recurrent HF Hospitalization through 24 Months	-	-	-	-	< 0.0001
#4 Change in KCCQ Overall Summary	12.50 (1.82) [8.93, 16.08]	-3.56 (1.85) [-7.21, 0.08]	16.07 [10.97, 21.17]	-	< 0.0001

Secondary Endpoints (hierarchical order)	Device (N=302)	Control (N=312)	HR or Difference [95% CI]	Lower 95% confidence limit	P-Value*
Score at 12 Months over Baseline; least square means (SE) [95% CI]					
#5 Change in 6MWD at 12 Months over Baseline; least square means (SE) [95% CI]	-2.17 (9.12) [-20.10, 15.76]	-60.03 (8.99) [-77.69, -42.36]	57.86 [32.67, 83.05]	-	< 0.0001
#6 All-Cause Recurrent Hospitalizations through 24 Months;† annualized rate [95% CI]	1.062 [0.970, 1.162]	1.464 [1.352, 1.585]	0.760 [0.602, 0.960]	-	0.0213
#7 Proportion of NYHA Functional Class of I/II at 12-Month; % (no./total no.) [95% CI]	72.2% (171/237) [65.98%, 77.76%]	49.6% (115/232) [42.96%, 56.19%]	-	-	< 0.0001
#8 Change in Left Ventricular End Diastolic Volume at 12 Months over Baseline; least square means (SE) [95% CI]	-3.71 (5.08) [-13.71, 6.28]	17.06 (5.10) [7.03, 27.08]	-20.77 [-34.93, -6.62]	-	0.0041
#9 All-Cause Mortality through 24 Months;† Kaplan-Meier estimate (SE) of event rate	29.1% (2.8%)	46.1% (3.2%)	0.615 [0.463, 0.816]	-	0.0008
#10 Estimate of Freedom from All-Cause Mortality, Stroke, MI or Non-Elective Cardiovascular Surgery for Device-Related Complications at 30 Days; % (no./total no.)	96.9% (284/293)	-	-	94.7%	<0.0001

*All p-values were tests for superiority, except for the secondary endpoint of mortality at 12 months (#2), which was a test for non-inferiority, and for the secondary endpoint of freedom from composite of all-cause mortality, stroke, MI or non-elective cardiovascular surgery for device-related complications at 30 days (#10), which was compared against a performance goal.

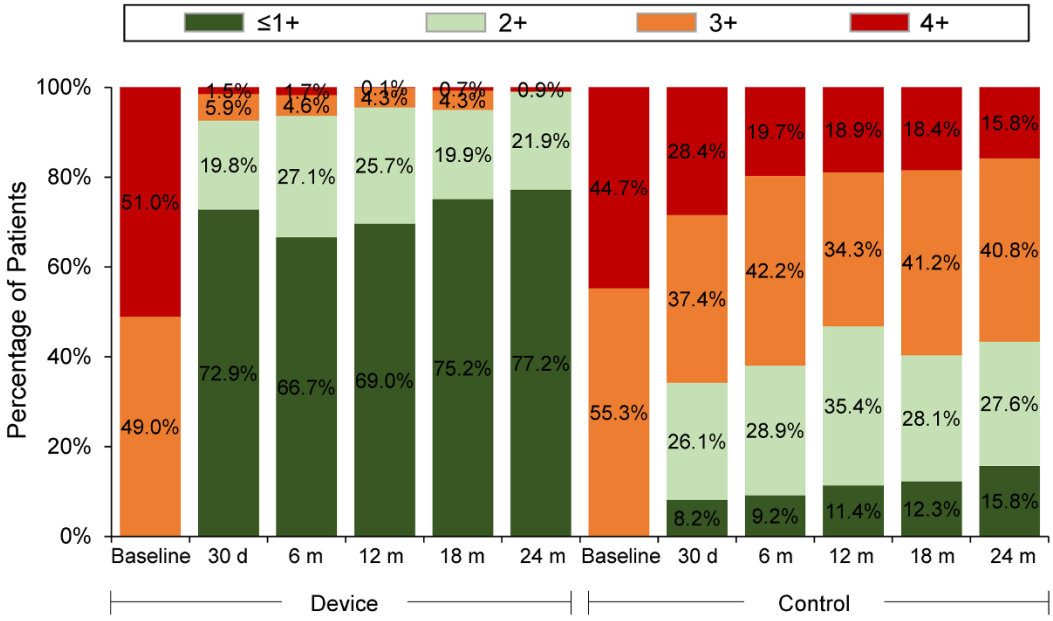
†Analyzed when the last subject completed the 12-month follow-up.

Note: (1) Imputation of worst clinical outcomes for subjects experiencing HF death prior to 12 months for the changes in KCCQ, 6MWD, LVEDV and NYHA class. (2) Continuous endpoints (KCCQ, 6MWD, and LVEDV) were analyzed using Analysis of Covariance (ANCOVA). (3) HR – Hazard Ratio; CI – Confidence Interval; SE – Standard Error.

All powered secondary endpoints were met, as summarized below:

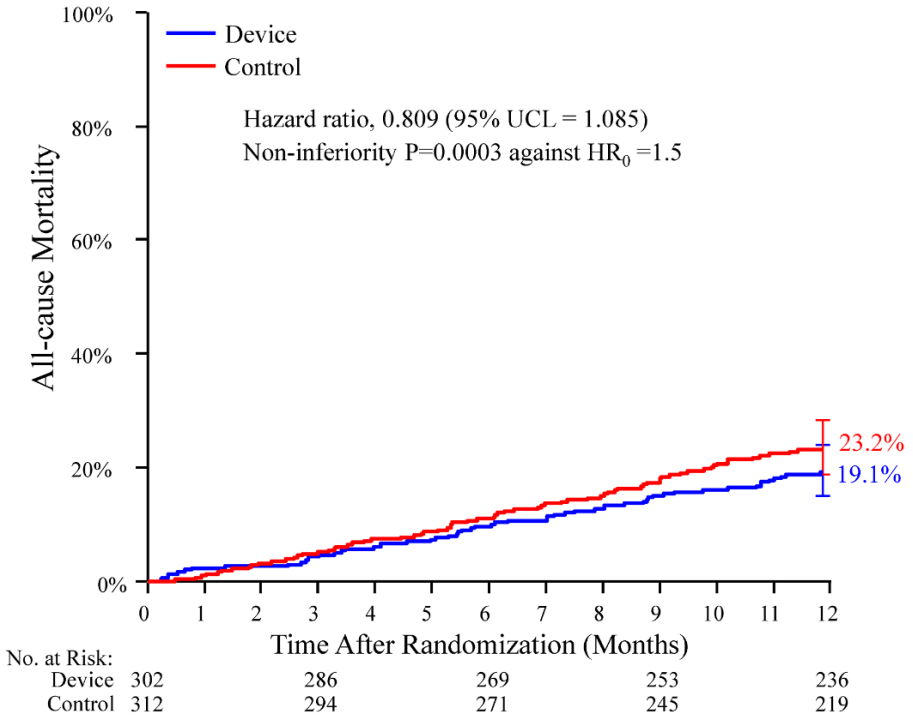
1. There were significantly more subjects with MR severity ≤ 2+ in the Device group than in the Control group at 12 months (94.8% vs. 46.9%). The MR severity grades over time in both groups are shown in Figure 17.4.

Figure 17.4: MR Severity Grades over Time (ITT Population)



2. The Device group was found to be non-inferior to the Control group in all-cause mortality at 12 months (19.1% vs. 23.2%), as shown in Figure 17.5.

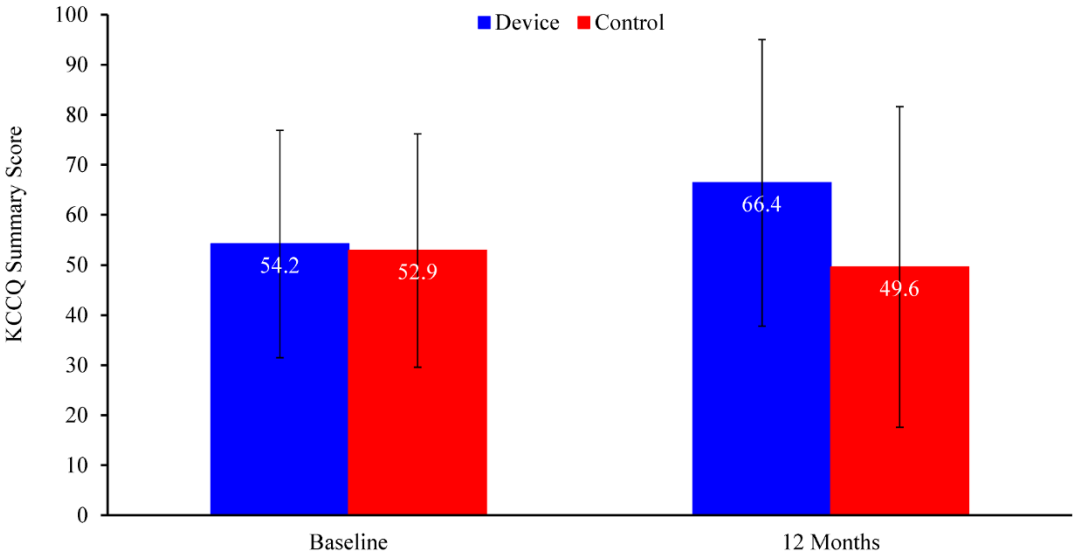
Figure 17.5: Kaplan-Meier Curve of All-Cause Mortality through 12 Months (ITT Population)



3. Subjects in the Device group experienced a significant reduction in the hierarchical composite of all-cause mortality and recurrent HF hospitalization compared to those in the Control group.

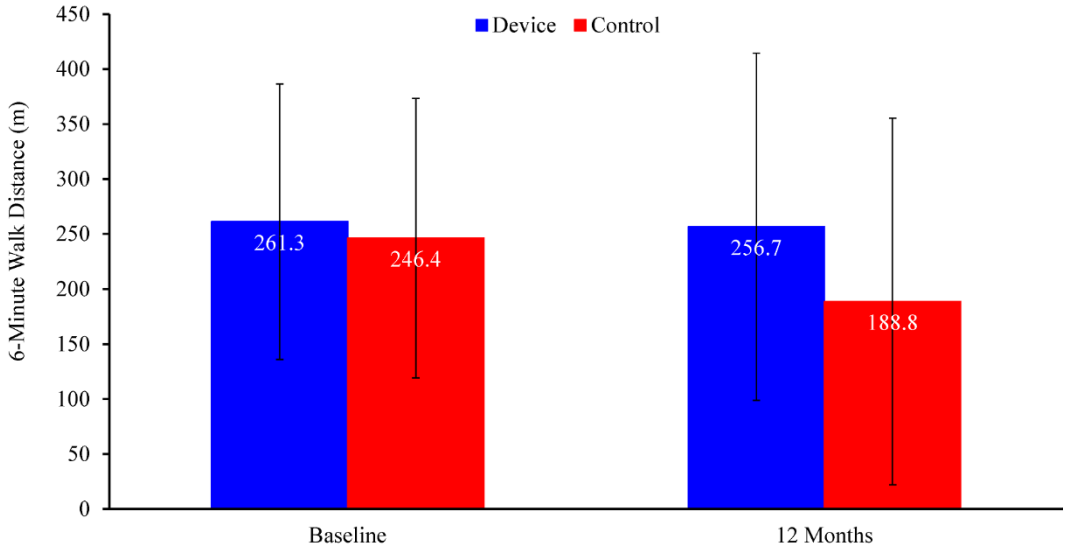
4. Subjects in the Device group experienced a significantly greater improvement in QoL (as assessed by the change in KCCQ Overall Summary Score at 12 months over baseline) compared to those in the Control group (12.50 vs. -3.56), as shown in Figure 17.6.

Figure 17.6: KCCQ Overall Summary Score at Baseline and 12 Months (ITT Population)



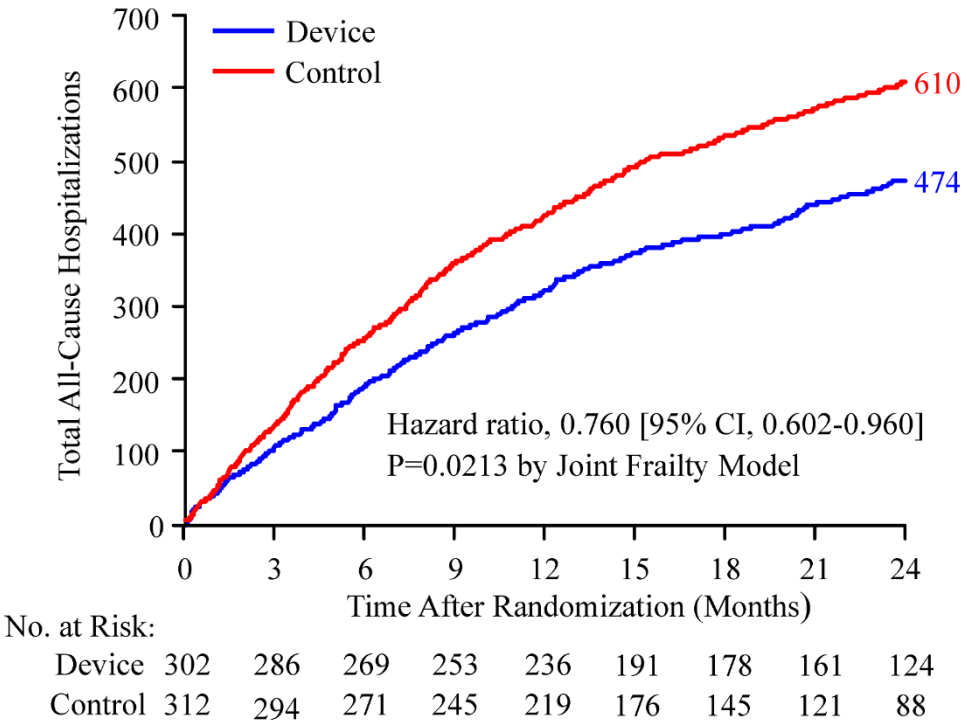
5. Subjects in the Device group experienced significantly greater preservation of functional capacity (as assessed by the change in 6MWD at 12 months over baseline) compared to those in the Control group (-2.17 m vs. -60.03 m), as shown in Figure 17.7.

Figure 17.7: 6MWD at Baseline and 12 Months (ITT Population)



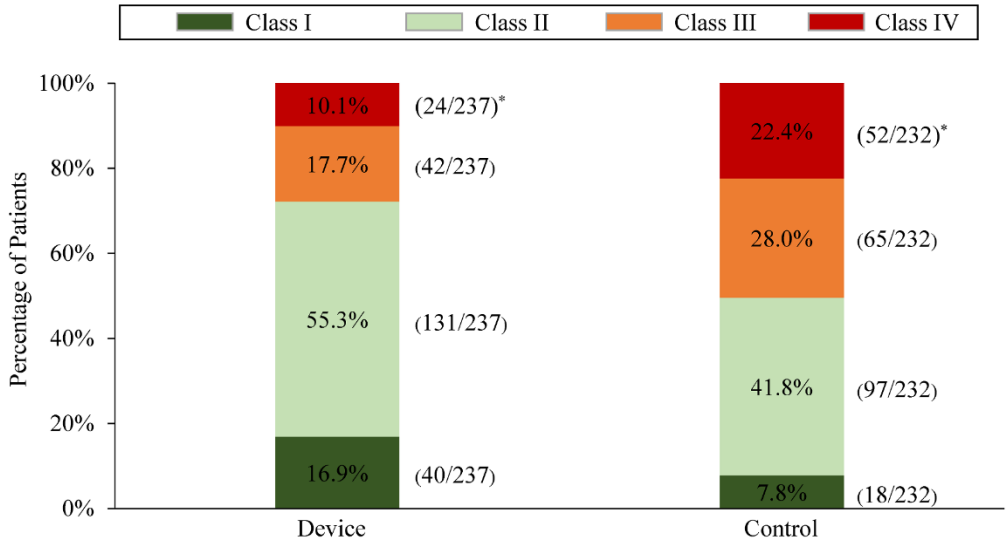
6. Subjects in the Device group experienced a significantly lower annualized rate (events per patient-year) of all-cause hospitalizations compared to those in the Control group (1.062 vs. 1.464). The total all-cause hospitalization through 24 months is shown in Figure 17.8.

Figure 17.8: Total All-Cause Hospitalization through 24 Months (ITT Population)



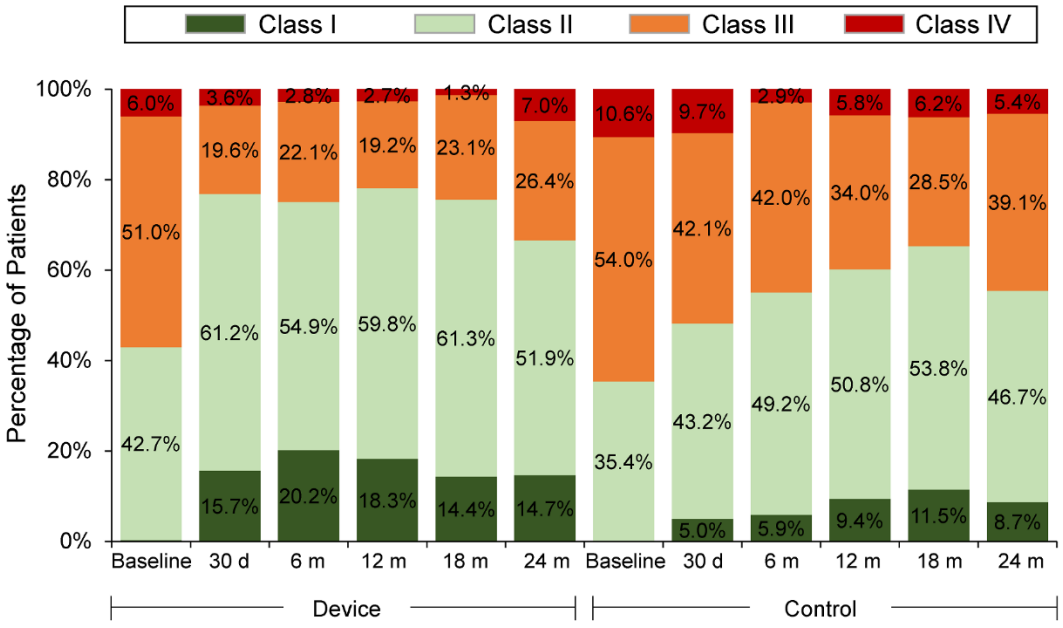
7. Subjects in the Device group experienced a significantly greater improvement in NYHA Functional Class at 12 months compared to those in the Control group (Class I or II: 72.2% vs. 49.6%), as shown in Figure 17.9A, where subjects who died prior to 12 months were imputed as having NYHA Class IV. The NYHA Functional Class (unimputed) through 24 months is shown in Figure 17.9B.

Figure 17.9A: NYHA Functional Class at 12 Months (ITT Population)



*Subjects died of HF prior to 12 months were imputed as having NYHA Class IV (Device group: 18; Control group: 41)

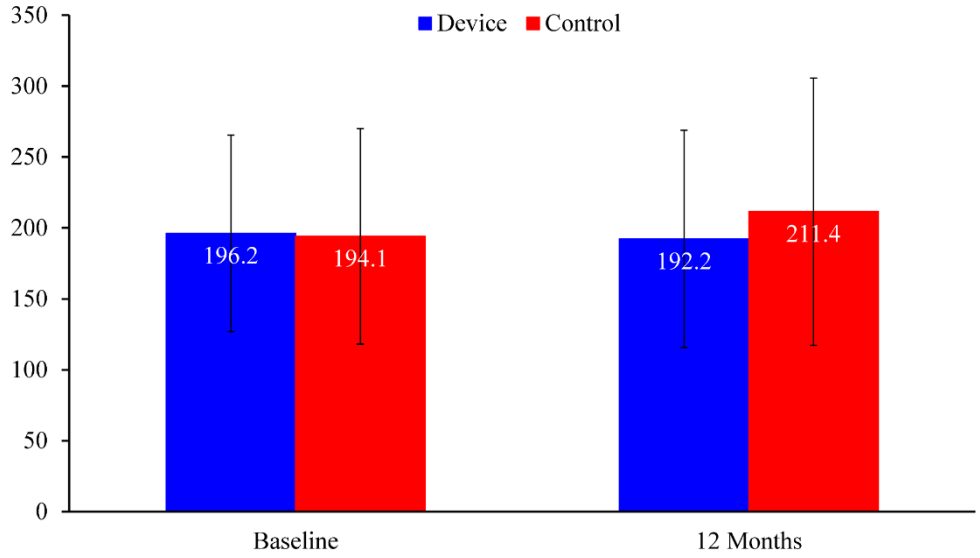
Figure 17.9B: NYHA Functional Class through 24 Months (ITT Population)



8. Subjects in the Device group experienced significantly greater reduction in LVEDV between baseline and 12 months compared to those in the Control group (-3.71 mL vs. 17.06 mL), as shown in Figure 17.10. However, while per protocol this endpoint passes, this finding appears to be primarily related to pre-specified imputation of LVEDV values for subjects who died of HF prior to completing the 12-month follow-up where these subjects were assigned the worst LVEDV change between baseline

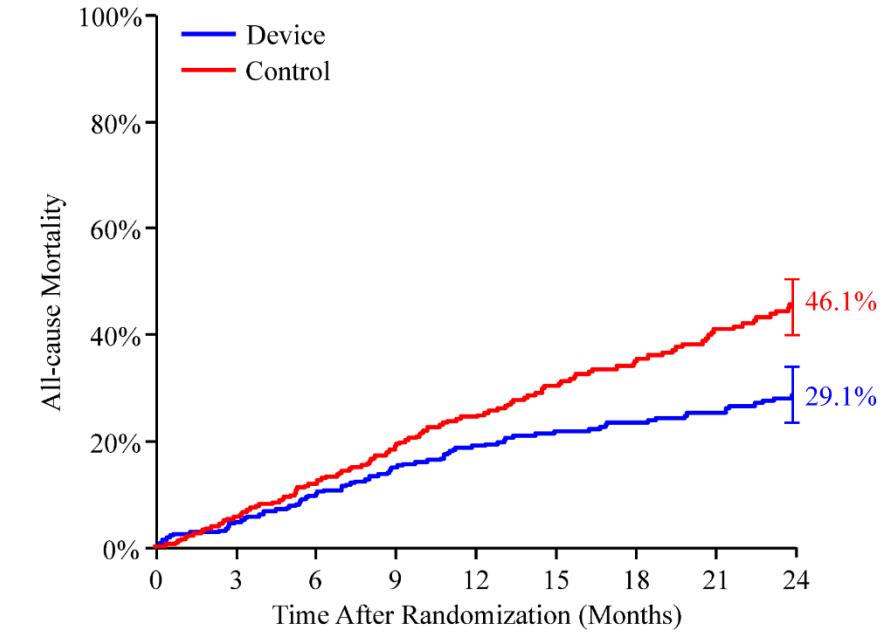
and 12 months observed for any subject in the analysis (126 mL). Because subjects in the Control group had a numerically higher (41 vs. 18) incidence of HF-related mortality than those in the Device group and the worst change in LVEDV was extreme, calculations for the LVEDV change from baseline in the Control group patients could be skewed mathematically to the larger end. It should be noted that neither clinically nor statistically significant difference in LVEDV change from baseline to 12 months was observed between the Device and Control groups based on un-imputed unpaired and paired analyses, or based on a responder analysis.

Figure 17.10: LVEDV Change from Baseline to 12 Months (ITT Population)



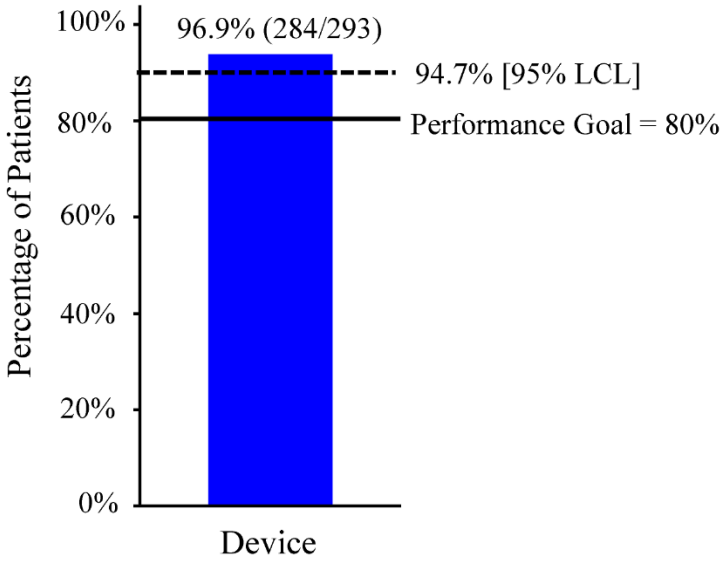
9. Subjects in the Device group experienced significantly lower all-cause mortality at 24 months compared to those in the Control group (Kaplan-Meier estimate: 29.1% vs. 46.1%), as shown in Figure 17.11. The number needed to treat (NNT) to save one life within 24 months was 5.9 (95% CI: [3.9, 11.7]).

Figure 17.11: Kaplan-Meier Curve of All-Cause Mortality through 24 Months (ITT Population)



10. The rate of freedom from all-cause mortality, stroke, MI, or non-elective cardiovascular surgery for device-related complications at 30 days was 96.9%, with a lower 95% confidence limit of 94.7%, which met the prespecified performance goal of 80%, as shown in Figure 17.12.

Figure 17.12: Freedom from All-Cause Mortality, Stroke, MI or Non-Elective Cardiovascular Surgery for Device-Related Complications at 30 Days (SA Population)



4. Adverse Events

The adverse events that occurred in the trial through 24 months are presented in Table 17.7.

Table 17.7: CEC-Adjudicated Adverse Events through 24 Months (SA Population)

Events	0-30 Days		0-12 Months		0-24 Months	
	Device	Control	Device	Control	Device	Control
All-cause mortality*	2.3% (7)	1.0% (3)	19.1% (57)	23.2% (70)	29.1% (80)	46.1% (121)
Cardiovascular	2.3% (7)	0.6% (2)	13.8% (40)	19.4% (57)	23.2% (60)	37.0% (93)
Heart failure	0.7% (2)	0.6% (2)	6.2% (17)	13.8% (39)	12.0% (28)	25.9% (61)
Stroke	0.7% (2)	0.0% (0)	2.9% (8)	2.9% (8)	4.4% (11)	5.1% (11)
Transient ischemic attack	0.0% (0)	0.0% (0)	1.1% (3)	1.1% (3)	1.1% (3)	1.1% (3)
Endocarditis requiring surgery	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
ECL confirmed mitral stenosis requiring surgery	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
LVAD implant	0.0% (0)	1.0% (3)	0.8% (2)	3.9% (11)	3.0% (6)	7.1% (16)
Heart transplant	0.0% (0)	0.0% (0)	0.8% (2)	2.2% (6)	1.4% (3)	3.6% (8)
Myocardial Infarction†	0.3% (1)	0.0% (0)	NA	NA	NA	NA
Major bleeding†	5.0% (15)	1.0% (3)	NA	NA	NA	NA
Iatrogenic ASD requiring	0.7%	NA	0.7%	NA	0.7%	NA

Events	0-30 Days		0-12 Months		0-24 Months	
intervention	(2)		(2)		(2)	
Device-related complications requiring non-elective CV surgery	0.3% (1)	NA	0.3% (1)	NA	0.3% (1)	NA

*Include adjudicated death events and deaths from the national death registry (for subjects who were lost to follow-up or withdrew from the COAPT study).
†Events were adjudicated up to 30 days post treatment visit.
Note: (1) Kaplan-Meier rate (# patients with events). Include only each patient's first occurrence of each event. (2) The follow-up duration was calculated from the randomization date. (3) ECL: Echocardiography Core Laboratory; LVAD: Left Ventricular Assists Device; ASD: Atrial Septal Defect; CV: Cardiovascular.

5. Subgroup Analyses

Pre-specified Analyses:

The primary safety and primary effectiveness endpoints were examined across the following 4 subgroups:

- Sex (male vs. female)
- Etiology of cardiomyopathy (ischemic vs. non-ischemic)
- LVEF (> 40% vs. ≤ 40%)
- Extreme surgical risk status (yes vs. no, as determined by the Central Eligibility Committee)

There was no clinically significant difference among the subgroups for the primary safety outcome, and there were no clinically significant interaction effects between treatment and subgroups for the primary effectiveness outcome.

Post hoc Analyses:

In light of publication of another study of the MitraClip device in literature, entitled "Mitra-FR Trial" (see reference [4]), a comparison of the baseline characteristics of the subjects enrolled in the COAPT Trial and Mitra-FR Trial was performed to further define the proper patient population for the MitraClip SMR indication. The comparison suggested there were some differences between the two trials as shown in Table 17.8.

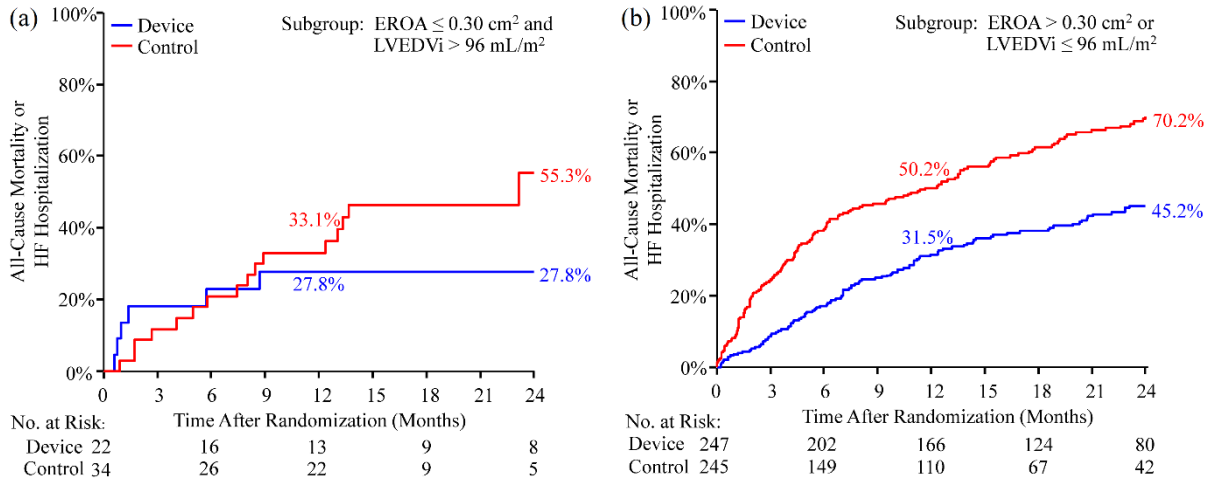
Table 17.8: Comparison in EROA and LVEDVi between Mitra-FR and COAPT

Baseline Characteristics	Mitra-FR	COAPT
EROA (mean ± SD; cm^2)	0.31 ± 0.11	0.41 ± 0.15
LVEDVi (mean ±SD; mL/m^2)	135 ± 35	101 ± 34

To explore whether there was any correlation between the clinical outcomes and the baseline EROA and LVEDVi, a *post hoc* subgroup analysis was conducted on the COAPT dataset, by comparing the composite rate of all-cause mortality or HF hospitalization between subjects with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2 and those with an EROA > 0.30 cm^2 or an LVEDVi ≤ 96 mL/m^2, where 0.30 was the lower bound of the EROA

defining, along with other parameters, Grade III (or 3+) MR as per the 2017 ASE Recommendation for Noninvasive Evaluation of Native Valvular Regurgitation and 96 was the median LVEDVi value in the COAPT Trial.[5] A total of 22 subjects in the Device group and 34 subjects in the Control group had an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2. The results of the subgroups analysis are shown in Figure 17.13. COAPT subjects with relatively less severe MR and larger left ventricles (Fig 17.13A) did not show a clinically meaningful benefit of the Device for all-cause mortality or HF hospitalization at the 12-month timepoint. For the remaining COAPT subjects (those with an EROA > 0.3cm^2 or an LVEDVI ≤ 96mL/m^2; Figure 17.13B), the difference in all-cause mortality or HF hospitalization seen in the overall population was maintained.

Figure 17.13: Subgroup Analysis Stratified by EROA and LVEDVi



Despite the absence of benefit of reduced all-cause mortality or HF hospitalization in the subgroup with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2, clinically meaningful improvements in the overall 6MWD (as shown in Figure 17.14; 11 subjects in the Device group and 26 subjects in the Control group had 6MWD values) and KCCQ (as shown in Figure 17.15; 15 subjects in the Device group and 27 subjects in the Control group had KCCQ values) compared to baseline were observed in Device group patients, an effect not observed in the same sub-population of the Control group. However, because of the nature of the *post hoc* subgroup analysis and the small sample size in the subgroup with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2, no statistical or clinical intra-group inferences can be made.

Figure 17.14: 6MWD for Subjects with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2

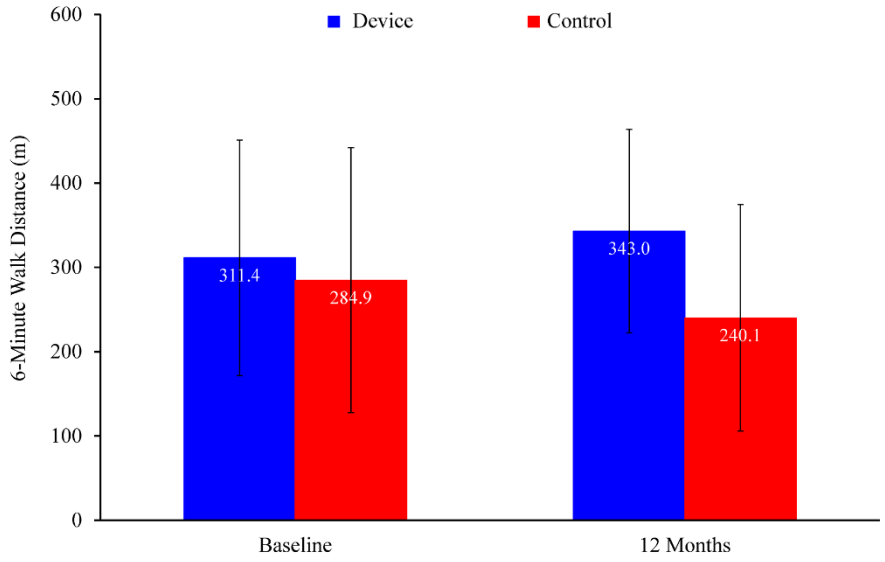
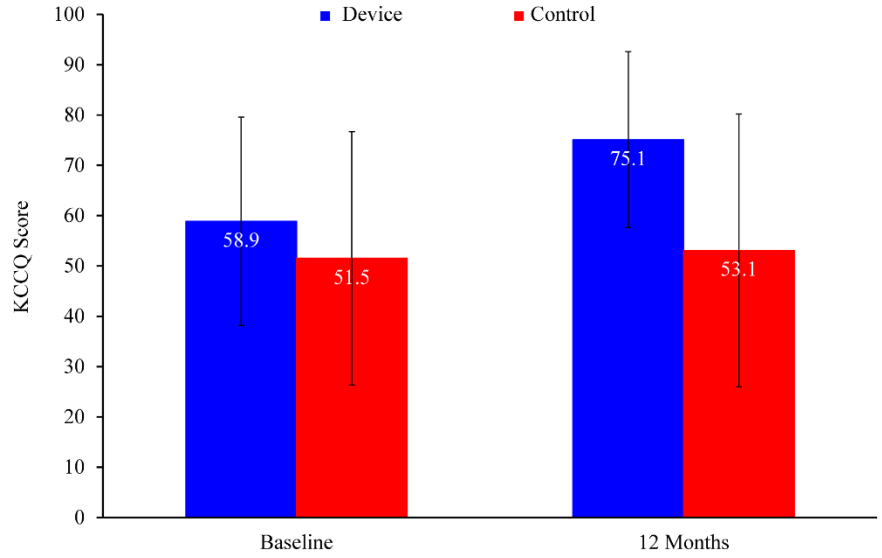


Figure 17.15: KCCQ Score for Subjects with an EROA ≤ 0.30 cm² and an LVEDVi > 96 mL/m²



6. Procedural Data

The procedural data of the Device group are summarized in Table 17.9.

Table 17.9: Procedural Data Summary for Device Subjects – AT Population

Procedure Data	Device (N=294)
MitraClip Procedure Attempted	100.0%
Implant Rate	98.0%

Procedure Data	Device (N=294)
Number of Clips Implanted	
0 Clip	2.0%
1 Clip	36.4%
2 Clips	53.1%
3 Clips	8.2%
4 Clips	0.3%
Total Number of Clips Implanted	495
Total Procedure Time (min) Mean ± SD (n) Median (Q1, Q3)	 163.0 ± 117.5 (294) 146.5 (108.0, 199.0)
Device Procedure Time (min) Mean ± SD (n) Median (Q1, Q3)	 118.8 ± 63.3 (283) 106.0 (73.0, 148.0)
Device Time (min) Mean ± SD (n) Median (Q1, Q3)	 82.6 ± 80.6 (288) 65.5 (40.0, 100.0)
Fluoroscopy Duration (min) Mean ± SD (n) Median (Q1, Q3)	 33.91 ± 23.15 (285) 29.50 (18.60, 43.00)

7. REFERENCES

[1] Rogers JK, Pocock SJ, McMurray JJV, Granger CB, Michelson EL, Östergren J, et al. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology with application to charm-preserved. *European Journal of Heart Failure* 2014; 16:33–40.

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[3] Rogers JK, Yaroshinsky A, Pocok SJ, Stokard D, Pogodae Janice. Analysis of recurrent events with an associated informative dropout time: Application of the joint frailty model. *Statistics in Medicine* 2016; 35:2195-205.

[4] Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *New England Journal of Medicine* 2018; 379:2297-2306.

[5] Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *New England Journal of Medicine* 2018;379:2307-2318.

[6] Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *Journal of the American Society of Echocardiography* 2017;30:303-371.

18.0 MITRACLIP™ NT PROCEDURE STEP-BY-STEP INSTRUCTIONS

18.1 DEFINITION OF TERMS

Defined Terms are in italics throughout document.

TERM	DEFINITION AND RELATED TECHNIQUE
Lock the Clip	1. Rotate the Lock Lever outward. 2. Fully advance the Lock Lever. 3. Rotate the Lock Lever inward to engage the lever.
Unlock the Clip and Open the Clip Arms	1. Rotate the Lock Lever outward and then retract the lever until the mark on the lever is fully exposed. 2. Rotate the Lock Lever inward to engage the lever. 3. Turn the Arm Positioner at least 1/2 turn in the "Close" (clockwise) direction. 4. Turn the Arm Positioner in the "Open" (counter-clockwise) direction until the desired *Clip Arm Angle* is achieved. 5. *Lock the Clip.* **WARNING:** Always *Lock the Clip* immediately after the desired *Clip Arm Angle* is achieved. Clip could be damaged and not unlock or open. Inability to open the Clip may result in valve injury, single leaflet device attachment (SLDA), worsening of mitral regurgitation, deployment of the Clip in an unintended location, or conversion to surgical intervention. **NOTE 1**: If Clip does not open smoothly, retract the Lock Lever farther, then repeat steps 2 – 5. **NOTE 2**: If the Clip Arms fail to open visibly (as observed under fluoroscopic guidance), use the following techniques in the order provided, as needed: A. Stop and return *Arm Positioner to Neutral*. Retract Lock Lever farther, then turn the Arm Positioner farther in the "Close" direction before turning in the "Open" direction. B. Turn the *Arm Positioner to Neutral*, then incrementally iterate the amount of Arm Positioner rotation in the "Close" direction followed by rotation in the "Open" direction. Iterate until Clip opens or until it is no longer possible to rotate the Arm Positioner in the "Close" direction. C. Turn the *Arm Positioner to Neutral*, iterate the amount of Lock Lever retraction past the mark in 5 mm increments, and rotate the Arm Positioner fully in the "Close" direction, before rotating in the "Open" direction, until Clip opens. D. Advance the Gripper Lever and repeat NOTE 2, Step C. Retract the Gripper Lever after Clip opens. E. If in the LA and free of tissue, release the DC Fastener, then release the Sleeve curves and repeat NOTE 2, Step C.

TERM	DEFINITION AND RELATED TECHNIQUE
	WARNING: Failure to release the DC Fastener before releasing Sleeve curves may result in device damage and/or embolization. F. If the Clip does not open after performing all steps in NOTE 2, DO NOT use the device.
Arm Positioner to Neutral	Turn the Arm Positioner in the "Close" or "Open" direction until no resistance to turning is noted.
Invert the Clip Arms	1. Unlock the Clip. 2. Turn the Arm Positioner at least 1/2 turn in the "Close" direction. 3. Turn the Arm Positioner in the "Open" direction until the Clip Arms invert (see Figure 6F). DO NOT over-invert the Clip Arms; stop turning the Arm Positioner when resistance is first noted. 4. *Lock the Clip*.
Raise the Grippers	1. Rotate the Gripper Lever outward. 2. Slowly retract the Gripper Lever (under fluoroscopic observation) until the mark on the lever is just exposed. **NOTE:** If pulling beyond the mark is required, advance the Gripper Lever back to the mark once the Grippers are fully raised. 3. Rotate the Gripper Lever inward to engage the lever.
Lower the Grippers	1. Rotate the Gripper Lever outward. 2. Fully advance the Gripper Lever. 3. Rotate the Gripper Lever inward to engage the lever.
Clip Arm Angle	• Angle between the inner edges of both Clip Arms. • All *Clip Arm Angles* are measured using fluoroscopy with optimal view allowing clear observation of the tip of the Clip and both arms in the same plane so they appear as a "V" (see Figure 6).
Grasping Arm Angle	A *Clip Arm Angle* of approximately 120 degrees. **NOTE:** Establish *Grasping Arm Angle* after closing the Clip from a larger *Clip Arm Angle.*
Fully Close the Clip Arms	Turn the Arm Positioner in the "Close" direction until the Clip Arms contact the DC. • Under direct visualization, the Clip is fully closed when the Clip Covering contacts the DC. • Under fluoroscopic observation, the Clip is fully closed when the inner edges of the Clip Arms are parallel. **WARNING:** Never close the Clip while the Lock Lever is in an unlocked state. Clip could be damaged and not unlock or open. Inability to open the Clip may result in valve injury, single leaflet device attachment (SLDA), worsening of mitral regurgitation, deployment of the Clip in an unintended location, or conversion to surgical intervention.

TERM	DEFINITION AND RELATED TECHNIQUE
Establish Final Arm Angle	Pre-deployment *Clip Arm Angle* that reflects the *Clip Arm Angle* post-deployment. 1. With the Lock Lever fully advanced, turn the Arm Positioner in the "Open" direction until resistance is first noted. The Clip Arms may open slightly and then remain in a stable position. 2. Confirm that the Clip is locked by observing slight Delivery Catheter shaft deflection using fluoroscopy. **NOTE:** If continued opening of the Clip Arms is noted, reconfirm that the Lock Lever is completely advanced. Close the Clip Arms, and *Establish Final Arm Angle*.

19.0 PATIENT PREPARATION

19.1 Prepare the patient per institution's standard practice for transseptal catheterization.

19.2 Place support plate under patient's leg in the region between the area of the upper leg and the knee and place the Lift over the ipsilateral lower extremity prior to draping the patient.

19.3 Place the Lift on the Support Plate such that the front edge (i.e., the edge that corresponds with the shorter legs of the Lift) is approximately 80 cm from the patient's mid sternum.

19.4 Adjust the height of the Lift so that the front edge of the Lift is close to the patient's leg, but is not impinging on it. Adjust the back legs to be 2 or 3 notches above the front legs (i.e., the back legs of the Lift are taller than the front legs).

19.5 Ensure the Lift and Support Plate are covered completely by sterile drape during the procedure. Use towels as necessary to minimize direct contact between the patient and all surfaces of both the Lift and Support Plate.

19.6 Prepare the patient for invasive hemodynamic monitoring.

20.0 MITRACLIP™ NT SYSTEM PREPARATION BEFORE USE

WARNING: DO NOT use the MitraClip™ NT System after the "Use By" date stated on the package label, and never reuse or re-sterilize the system. Use of expired, reused, or re-sterilized devices may result in infection, endocarditis, and/or sepsis.

WARNING: Always inspect the MitraClip™ NT System and its packaging to verify no damage has occurred as a result of shipping and handling and that the sterile barrier has not been compromised. DO NOT use the device if damage is detected. Use of product with a compromised sterile barrier may result in infection, endocarditis, and/or sepsis. Use of damaged product may result in patient injury.

- DO NOT remove the protective cover placed over the Clip.

WARNING: DO NOT handle the Clip directly; leave it in the protective cover to avoid potential contamination. Removal of the protective cover may result in infection, endocarditis, and/or sepsis. Removal of the protective cover may result in damaged product which may result in patient injury.

- The preparation is most easily accomplished with the aid of an assistant.

20.1 Steerable Guide Catheter Preparation

WARNING: All lumens contain air when shipped. Use proper de-airing techniques before and during use to minimize the risk of air embolism.

20.1.1 Carefully remove the white Guide tip shape retainer and transparent protective tubing from the Guide tip.

20.1.2 Inspect Steerable Guide Catheter and Dilator to verify they are undamaged.

WARNING: DO NOT use if damage is detected. Use of damaged product may result in air embolism, vascular and/or cardiac injury.

20.1.3 Remove the sterile package containing Fasteners and Silicone Pad from the Steerable Guide Catheter tray.

20.1.4 Fill a basin with 1000 cc of heparinized saline.

20.1.5 Flush and de-air the Guide and Dilator with heparinized saline:

20.1.5.1 Connect 3-way stopcocks to the Guide and Dilator flush ports.

20.1.5.2 De-air the Dilator, then close the stopcock and the Rotating Hemostatic Valve.

20.1.5.3 Hydrate 5-10 cm of the distal end of the Dilator with heparinized saline.

20.1.5.4 Insert the Dilator approximately 10 cm into Guide then remove.

20.1.5.5 Connect high pressure tubing and a 50–60 cc syringe filled with heparinized saline to the Guide flush port.

20.1.5.6 De-air the Guide.

20.1.5.6.1 With the tip raised, displace all air from the Guide while tapping along the length of the catheter shaft.

20.1.5.6.2 Cover the Guide tip with finger once heparinized saline exits the Guide.

20.1.5.6.3 Close the Guide stopcock.

20.1.6 Submerge the Guide tip in the basin of heparinized saline.

20.1.7 While the Guide tip is submerged in the basin of heparinized saline, remove finger from Guide tip and check the Guide valve for leaks by raising the handle to a vertical position for a minimum of 30 seconds.

20.1.8 Hydrate 5-10 cm of the distal end of the Dilator with heparinized saline.

20.1.9 Cover the Guide tip with finger and insert the Dilator into the Guide while Guide tip remains submerged in the basin of heparinized saline.

20.1.9.1 While advancing the Dilator, continually watch for air in the Guide Hemostasis Valve housing. If needed, remove finger from Guide tip and aspirate while assuring the Guide tip is submerged.

20.1.9.2 Remove finger from tip of Guide when the Dilator tip approaches the Guide tip.

20.1.9.3 Advance the Dilator until the curve is extended from the Guide tip.

20.2 Steerable Guide Catheter Functional Inspection

- The functional inspection is most easily accomplished with the aid of an assistant.
- The Guide functional inspection should be performed with the Guide tip and Dilator tip submerged in a basin of heparinized saline to prevent air from entering the lumens. If the Guide tip and/or Dilator tip fails to remain submerged during inspection, flush the Guide and/or Dilator with heparinized saline to completely remove air.

WARNING: Failure to completely remove air may result in air embolism.

WARNING: All catheter manipulations should be done with care. DO NOT continue to rotate or manipulate any of the handle controls if significant resistance is noted. Use of damaged product may result in air embolism, vascular and/or cardiac injury.

Guide Inspection

20.2.1 Inspect all Guide parts to verify they are undamaged.

WARNING: DO NOT use device if damage is detected. Use of damaged product may result in air embolism, vascular and/or cardiac injury.

20.2.2 To confirm proper tip deflection with "+" knob rotation:

20.2.2.1 Rotate the +/- Knob in the "+" direction until the Guide is curved to approximately 80 degrees.

20.2.2.2 Remove hand from the +/- Knob and check that the knob does not slip.

20.2.2.3 Return the +/- Knob to the neutral position.

20.2.2.4 Repeat steps 19.2.2.1 through 19.2.2.3.

20.2.3 To confirm proper tip deflection with "-" knob rotation:

20.2.3.1 Rotate the +/- Knob in the "-" direction until the Guide curve is substantially straightened.

20.2.3.2 Remove hand from the +/- Knob and check that the knob does not slip.

20.2.3.3 Return the +/- Knob to the neutral position.

20.2.3.4 Repeat steps 19.2.3.1 through 19.2.3.3.

20.2.4 Retract the Dilator until the tip is 3-5 cm beyond the Guide tip. Position the Dilator to create a smooth transition.

20.3 Stabilizer Preparation

20.3.1 Assemble the sterilized Stabilizer by placing the two Fasteners in the Stabilizer. Ensure that the Fasteners can be fully threaded into the Stabilizer holes. Set the Stabilizer aside in a protected sterile environment for later use.

20.4 Clip Delivery System Preparation

20.4.1 Inspect the Clip, DC shaft, and Sleeve tip to verify they are undamaged.

WARNING: DO NOT use the device if damage is detected. Use of damaged product may result in air embolism, device or device component embolization, vascular and/or cardiac injury.

Sleeve Preparation

20.4.2 Connect 3-way stopcocks to the Sleeve flush port and bottom DC flush port.

20.4.3 Remove the cap from the Clip Introducer.

20.4.4 Place the cap on the top flush port of the DC Handle.

20.4.5 Connect a 3-way stopcock to the Clip Introducer flush port.

20.4.6 Connect one high pressure tube to each drip line from the pressurized bags with sterile heparinized saline; flush and de-air the lines.

20.4.7 Connect one high pressure tube to the 3-way stopcock on the bottom flush port of the DC Handle and one high pressure tube to the 3-way stopcock on the flush port of the Sleeve Handle.

20.4.8 Flush and de-air the Sleeve with heparinized saline.

20.4.8.1 With the tip raised and the shaft held taut, displace all air from the Sleeve lumen while tapping along the length of the catheter shaft.

20.4.8.2 While flushing, release the DC Fastener, retract and advance the DC Handle to remove residual air from the lumen.

WARNING: Using excessive force when pulling the DC Radiopaque Ring against the Sleeve tip, while translating the DC shaft, may result in device damage including distal tip embolization.

20.4.8.3 Secure the DC Fastener with DC Handle fully advanced.

Delivery Catheter Preparation

WARNING: DO NOT handle the Clip directly; leave in the protective cover to avoid potential contamination. Removal of the protective cover may result in damaged product which may result in patient injury.

20.4.9 Attach a 50–60 cc syringe filled with heparinized saline to the 3-way stopcock on the Clip Introducer.

20.4.10 De-air the Clip Introducer, then close the stopcock.

20.4.11 Temporarily remove the cap from top flush port of the DC Handle.

20.4.12 Flush and de-air DC Handle and all lumens of the DC with heparinized saline.

20.4.13 After de-airing the DC Handle chamber, replace the cap to close off top flush port of the DC Handle.

20.4.14 Retract and advance the Lock Lever several times to remove residual air from the lumens.

20.4.15 Loosen the Lock Lever and the Gripper Lever Caps to de-air. DO NOT turn lever caps more than 1/2 turn in the “Open” direction. After de-airing, tighten the lever caps.

20.4.16 With the tip raised and the shaft held taut, displace all air from the DC while tapping along the length of the catheter shaft.

20.4.17 Confirm continuous flow from the distal end of the DC.

20.5 Clip Delivery System Functional Inspection

- The functional inspection is most easily accomplished with the aid of an assistant.

20.5.1 Inspect all Clip Delivery System parts, including the Clip, to verify they are undamaged.

WARNING: DO NOT use device if damage is detected. Use of damaged product may result in air embolism, device or device component embolization, vascular and/or cardiac injury.

WARNING: All catheter manipulations should be done with care. DO NOT continue to rotate or manipulate any of the handle controls if significant resistance is noted. Use of damaged product may result in air embolism, vascular and/or cardiac injury.

Sleeve Inspection

WARNING: DO NOT deflect the Sleeve more than 90 degrees during the inspections below. Use of damaged product may result in cardiac injury.

20.5.2 To confirm proper tip deflection with “A” knob rotation:

20.5.2.1 With the DC handle fully advanced and the shaft held taut, rotate the A/P Knob approximately 3/4 turn in the "A" direction from neutral to confirm that the distal tip deflects.

20.5.2.2 Remove hand from the A/P Knob and check that the knob does not slip.

20.5.2.3 Return the A/P Knob to the neutral position.

20.5.2.4 Repeat steps 20.5.2.1 through 20.5.2.3.

20.5.3 To confirm proper tip deflection with “P” knob rotation:

20.5.3.1 With the DC handle fully advanced and the shaft held taut, rotate the A/P Knob approximately 3/4 turn in the "P" direction from neutral to confirm that the distal tip deflects.

20.5.3.2 Remove hand from the A/P Knob and check that the knob does not slip.

20.5.3.3 Return the A/P Knob to the neutral position.

20.5.3.4 Repeat steps 20.5.3.1 through 20.5.3.3.

19.5.4 To confirm proper tip deflection with “M” knob rotation:

20.5.4.1 With the DC Handle fully advanced and the shaft held taut, rotate the M/L Knob in the "M" direction until the distal tip deflects to approximately 90 degrees to confirm distal tip deflection.

20.5.4.2 Remove hand from the M/L Knob and check that the knob does not slip.

20.5.4.3 Return the M/L Knob to the neutral position.

20.5.4.4 Repeat steps 20.5.4.1 through 20.5.4.3.

Delivery Catheter and Clip Inspection

WARNING: DO NOT handle the Clip directly, leave in the protective cover to avoid potential contamination. Removal of the protective cover may result in infection, endocarditis, and/or sepsis. Removal of the protective cover may result in damaged product which may result in patient injury.

NOTE: If *Clip Arm Angle* is greater than *Grasping Arm Angle,* close the Clip to *Grasping Arm Angle*; if *Clip Arm Angle* is less than *Grasping Arm Angle*, *Unlock the Clip and Open the Clip Arms* to 180 degrees then close the Clip to *Grasping Arm Angle*.

29.5.5 Carefully inspect the Grippers to confirm the cover is intact and not damaged.

WARNING: DO NOT use the device if damage is detected. Use of damaged product may result in cardiac injury and/or may lead to inability to reduce MR.

20.5.6 *Raise the Grippers*.

CAUTION: Raising the Grippers more often than needed, retracting the Gripper Lever forcefully, or retracting the Gripper Lever more than 1.5 cm beyond the mark may damage the Gripper cover and impair CDS performance.

20.5.7 Unlock the Clip.

WARNING: Retracting the Lock Lever forcefully may result in the inability to lock or unlock the Clip. Damage could occur causing the Clip to not unlock or open. Inability to open the Clip may result in valve injury or lead to deployment of the Clip in an unintended location.

20.5.8 *Invert the Clip Arms*.

WARNING: DO NOT continue turning the Arm Positioner if resistance is felt. Use of damaged product may result in cardiac injury.

20.5.9 Lock the Clip.

20.5.10 Close the Clip to *Grasping Arm Angle*.

20.5.11 *Lower the Grippers* once to de-air the lumens.

20.5.12 Release the DC Fastener and torque the DC Handle clockwise and counterclockwise 1/4 turn while translating the shaft.

WARNING: Using excessive force when pulling the DC Radiopaque Ring against the Sleeve tip, while translating the DC shaft, may result in device damage including distal tip embolization.

20.5.13 Secure the DC Fastener with DC Handle fully advanced.

20.5.14 Close the Clip to a *Clip Arm Angle* of approximately 20 degrees.

20.5.15 *Establish Final Arm Angle*.

20.5.16 Return the *Arm Positioner to Neutral*.

20.5.17 Unlock the Clip.

20.5.18 Open the Clip to *Grasping Arm Angle*.

20.5.19 *Lock the Clip*.

20.5.20 Return the *Arm Positioner to Neutral*.

20.5.21 Release the DC Fastener and retract the DC fully against the Sleeve.

20.5.22 Secure the DC Fastener.

20.5.23 Temporarily discontinue heparinized saline flushes.

The following steps should be performed just before use of the CDS:

20.5.24 Re-start heparinized saline flushes.

20.5.25 *Raise the Grippers*.

20.5.26 *Fully Close the Clip Arms*.

20.5.27 *Lower the Grippers*.

20.5.28 Without removing the protective cover, carefully slide the Clip Introducer over the Clip.

WARNING: DO NOT compress the Clip Arms. Compressing the Clip Arms may result in inability to open the Clip. Inability to open the Clip may result in valve injury or lead to deployment of the Clip in an unintended location.

20.5.29 Stop when the tip of the Clip is just proximal to the tip of the Clip Introducer.

20.5.30 Turn the *Arm Positioner to Neutral*.

WARNING: Failure to *Fully Close the Clip Arms*, before insertion or retraction into the Clip Introducer, may result in difficulty or inability to advance or retract the Clip, which may result in vascular and/or cardiac injury, air embolism, and/or the need for surgical intervention.

WARNING: Heparinized saline flush should be continuous throughout the procedure. Ensure flow is visible through the drip chamber, that the tubing is free from kinks and/or obstruction and appropriate pressure of 300 mm Hg is maintained. Discontinuing flush may result in air embolism and/or thrombus formation.

21.0 ACCESS TO THE MITRAL VALVE

NOTE: This is a suggested sequence for the procedure. Variations may be used based upon patient anatomy.

21.1 Access the LA to accommodate the Guide tip using transvenous, transseptal techniques and equipment.

21.2 Heparinize the patient.

WARNING: Failure to administer heparin once transseptal access has been achieved may result in thrombus formation.

21.3 Carefully place a 260 cm super stiff 0.9 mm (0.035") exchange length guidewire in the left upper pulmonary vein or LA. Dilate the subcutaneous tissue and femoral vein to accommodate the Guide shaft using standard dilation technique.

22.0 STEERABLE GUIDE CATHETER INSERTION

WARNING: Confirm a smooth transition between the Dilator and the tip of the Guide to minimize the risk of vascular and/or cardiovascular injury.

CAUTION: Always use pressure monitoring, echocardiography and fluoroscopy for guidance and observation during use of the MitraClip™ NT System.

WARNING: Always use a careful, deliberate, and iterative approach to positioning the MitraClip™ NT System. It is recommended to make multiple small adjustments rather than single large adjustments. Large adjustments may result in vascular and/or cardiac injury.

22.1 Rotate the +/- Knob in the "-" direction until the Guide curve is substantially straightened.

22.2 Wet the surface of the Guide shaft with sterile saline.

22.3 Insert the Guide-Dilator assembly over the stationary guidewire into the femoral vein.

WARNING: DO NOT use excessive force to advance or manipulate the Guide-Dilator assembly. If resistance is encountered, use echocardiography and/or fluoroscopy to assess before proceeding. Use of excessive force may result in arrhythmias, vascular and/or cardiac injury, including creation of a clinically significant atrial septal defect.

22.4 Advance the Guide-Dilator assembly to the RA. Rotate the +/- Knob to Neutral, then place tip of the Dilator partially across the atrial septum.

22.5 Slowly dilate the atrial septum by gradually advancing the tip of the Guide-Dilator assembly.

WARNING: DO NOT rapidly advance the Guide-Dilator assembly across the atrial septum. Rapid advancement may result in vascular and/or cardiac injury**.**

22.6 Advance the Guide-Dilator assembly until the tip of the Guide extends approximately 3 cm in the LA.

22.7 Adjust Guide deflection and torque to position the tip away from adjacent tissues.

22.8 Place the Silicone Pad on the sterile drape over the Lift. Place the Stabilizer onto the Silicone Pad.

22.9 Secure the Guide in the Stabilizer slot using the Fastener. Ensure the Fastener engages the metallic tube on the Guide shaft. The Guide handle should be immediately adjacent to the Stabilizer, such that they are in contact with each other.

2.10 Retract the Dilator approximately 5 cm into the Guide, leaving the guide wire in the left upper pulmonary vein or LA.

CAUTION: Always loosen the Fastener before torquing the Guide to prevent stripping the screw.

22.11 Retract the guidewire into the tip of the Dilator. Remove the Dilator and guidewire while gently aspirating the Guide (starting when the Dilator is approximately halfway retracted into the Guide, approximately 40 cm) using a 50–60 cc syringe. Cover Guide Hemostasis Valve with finger upon Dilator removal.

NOTE: Avoid contacting tissue or creating a vacuum in the Guide lumen. If necessary, position the Guide handle below the level of the LA to allow blood to fill the Guide lumen.

WARNING: DO NOT create a vacuum while removing the dilator from the Guide; air may enter the lumen of the Guide which may result in air embolism.

WARNING: Failure to fully retract guidewire into the Dilator may result in air embolism.

23.0 CLIP DELIVERY SYSTEM INSERTION

23.1 Confirm the Guide lumen is completely de-aired.

WARNING: To minimize the potential of air embolism**,** DO NOT introduce the CDS into the Guide until the Guide lumen has been completely de-aired.

23.2 Confirm there is a slow, continuous heparinized saline flush through both the Sleeve and the DC.

CAUTION: Failure to continuously flush the CDS with heparinized saline may reduce device performance.

WARNING: Heparinized saline flush should be continuous throughout the procedure. Ensure flow is visible through the drip chamber and that tubing is free from kinks and/or obstruction and pressure of 300 mm Hg is maintained. Discontinuing flush may result in air embolism and/or thrombus formation.

23.3 Confirm tip of the Clip is just proximal to the tip of the Clip Introducer.

23.4 Carefully remove the protective cover surrounding the Clip and the Clip Introducer.

23.5 Confirm that the stopcock on the Clip Introducer flush port is closed and that the Clip Introducer is de-aired.

23.6 While flushing heparinized saline on the Guide Hemostasis Valve, place the tip of the Clip Introducer against the Guide Hemostasis Valve and advance the Clip Introducer straight into the valve in a continuous motion while rotating the Clip Introducer in small clockwise and counterclockwise motions until the Clip can be observed distal to the valve.

WARNING: DO NOT continue to advance the Clip Introducer if resistance is felt; the Guide Hemostasis Valve, Clip Introducer or the Clip may be damaged. Damage to these components may result in air embolism, vascular or cardiac injury.

WARNING: To minimize the potential of air embolism, ensure proper de-airing when inserting the Clip Introducer into the Guide Hemostasis Valve.

23.7 Leave the Clip Introducer fully inserted in the Guide Hemostasis Valve throughout the procedure.

23.8 Align the Longitudinal Alignment Marker on the Sleeve shaft with the Alignment Marker on the Guide Hemostasis Valve.

23.9 Turn the +/- Knob to neutral then carefully advance the CDS through the Guide under fluoroscopic guidance. Stop when the tip of the Clip is even with the tip of the Guide.

NOTE: If resistance to CDS advancement is felt, reduce Guide deflection.

23.10 Under echocardiographic guidance, advance the CDS and retract the Guide iteratively as needed while maintaining the Guide in the LA. Stop when the Guide RO Tip Ring is between the RO Alignment Markers of the Sleeve, as confirmed under fluoroscopic guidance.

23.11 Position the Sleeve Handle in the Stabilizer slot.

23.12 Confirm that the Clip is free from the left atrial wall and valve tissue.

WARNING: Failure to confirm that the Clip is free from the left atrial wall and valve tissue may result in cardiac injury.

24.0 INITIAL MITRACLIP™ NT SYSTEM POSITIONING IN THE LEFT ATRIUM

NOTE: Positioning is achieved with iterative adjustments of the Guide and CDS using torque, translation and knob adjustments. The goals of positioning are:

A. Positioning the Clip centrally over the valve with respect to anterior-posterior and medial-lateral directions.

B. Aligning the Clip so the DC Shaft is perpendicular to the plane of the mitral valve.

C. Positioning the distal tip of the Clip at least 1 cm above the leaflets.

WARNING: Excessive torque on the Guide and translation of the MitraClip™ NT System may inadvertently displace the tip of the Guide from the LA, which may result in arrhythmias or cardiac injury.

WARNING: DO NOT continue to rotate or manipulate any of the handle knobs if significant resistance is noted; device damage may occur and result in cardiac injury.

24.1 Adjust the Guide position as necessary to maintain that the Clip is free from adjacent tissue.

24.2 Adjust Sleeve deflection using the M/L Knob and/or the A/P Knob to deflect the Clip towards the apex. Retract the DC Radiopaque Ring against the Sleeve tip as necessary.

24.3 During Sleeve deflections confirm that the Guide RO Tip Ring is between the RO Alignment Markers of the Sleeve prior to making maximum Sleeve deflections.

WARNING: DO NOT deflect the Sleeve tip more than 90 degrees as device damage may occur. Use of damaged product may result in cardiac injury.

24.4 Secure the Sleeve handle in the Stabilizer using the Fastener.

24.5 To reposition the MitraClip™ NT System, move the Stabilizer and the system together until positioning is adequate.

24.6 Adjust the MitraClip™ NT System position to maintain adequate height above the mitral valve in the LA.

WARNING: Maintain the Clip above the leaflets until ready to grasp to minimize the risk of Clip entanglement in the chordal apparatus. Clip entanglement may result in cardiac injury, worsening mitral regurgitation, difficulty or inability to remove the Clip and conversion to surgical intervention.

25.0 FINAL MITRACLIP™ NT SYSTEM POSITIONING

25.1 *Raise the Grippers*

CAUTION: Raising the Grippers more often than needed, retracting the Gripper Lever forcefully, or retracting the Gripper Lever more than 1.5 cm beyond the mark may damage the Gripper cover and impair CDS performance.

25.2 *Unlock the Clip and Open the Clip Arms* to approximately 180 degrees.

WARNING: Retracting the Lock Lever forcefully may result in the inability to unlock Clip. Inability to open the Clip may result in valve injury or lead to deployment of the Clip in an unintended location.

25.3 *Lock the Clip*.

CAUTION: Failure to immediately advance the Lock Lever after Clip Arm opening may affect DC shaft straightness.

25.4 Adjust the MitraClip™ NT System to reposition the Clip as necessary. Confirm that the distal tip of the Clip is at least 1 cm above the leaflets.

25.5 Rotate the DC handle to align the Clip Arms perpendicular to the line of coaptation. DO NOT rotate the Clip more than 90 degrees in each direction.

25.6 Carefully translate the DC shaft multiple times to release stored torque. Fully retract the DC.

WARNING: Failure to fully release stored torque may result in unwanted Clip Arm orientation changes during grasping. Torque of the DC Handle more than 180 degrees may result in DC damage and cardiac injury.

25.7 Complete final MitraClip™ NT System positioning in the LA using multiple imaging planes. Re-secure the Guide and Sleeve Fasteners.

26.0 GRASPING THE LEAFLETS AND VERIFYING THE GRASP

26.1 Advance the DC distally to position the Clip approximately 2 cm below the valve. Ensure that the Clip Arms are oriented perpendicular to the line of coaptation.

WARNING: Failure to confirm that the Clip Arms are perpendicular to the line of coaptation may result in loss of leaflet capture and insertion. Loss of leaflet capture and insertion may result in inadequate reduction of mitral regurgitation and may result in a single leaflet device attachment (SLDA).

WARNING: DO NOT make substantial Clip Arm orientation adjustment in the LV. Clip entanglement in sub-valvular apparatus may result in cardiac injury and worsening mitral regurgitation; and may result in difficulty or inability to remove the Clip, and conversion to surgical intervention.

WARNING: Always ensure that either the Grippers are raised or that the Clip is closed while in the LV to avoid potential cardiac injury.

26.2 Close the Clip to the *Grasping Arm Angle*.

26.3 Without using excessive force, retract the DC to grasp both anterior and posterior leaflets.

WARNING: An improper grasp will allow one or both leaflets to move freely. Closing and deploying the Clip in this situation may result in loss of leaflet capture and insertion. Loss of leaflet capture and insertion may result in inadequate reduction of mitral regurgitation and may result in a single leaflet device attachment (SLDA).

26.4 If the grasp appears satisfactory, *Lower the Grippers* onto the leaflets.

WARNING: Failure to confirm that both Grippers have been lowered onto the leaflets prior to closing the Clip may result in loss of leaflet capture and insertion. Loss of leaflet capture and insertion may result in inadequate reduction of mitral regurgitation and may result in a single leaflet device attachment (SLDA).

WARNING: DO NOT adjust the position of the MitraClip™ NT System after grasping the leaflets, valve injury may occur.

26.5 Close the Clip until the *Clip Arm Angle* is approximately 60 degrees. Release tension on the DC and secure the DC Fastener.

26.6 Use echocardiographic imaging to verify insertion of both leaflets and satisfactory grasp by observation of:

- Leaflet immobilization
- Single or multiple valve orifice(s)
- Limited leaflet mobility relative to the tips of both Clip Arms
- Adequate MR reduction.

26.6.1 If grasping fails to hold both leaflets and the Clip retracts to the LA, reposition the MitraClip™ NT System.

26.6.1.1 *Unlock the Clip and Open the Clip Arms* to approximately 180 degrees and reorient the Clip Arms in the LA, as needed, then repeat grasping steps.

26.6.1.1.1 If significant repositioning is necessary, *Fully Close the Clip Arms* and *Lower the Grippers* then repeat positioning and grasping steps.

26.6.2 If the Sleeve limits DC travel during grasping, an inadequate grasp may require repositioning of the MitraClip™ NT System.

26.6.2.1 *Raise the Grippers*, *Unlock the Clip and Open the Clip Arms* to 180 degrees, and advance the DC handle. Repeat positioning and grasping steps as necessary.

27.0 CLOSING THE CLIP AND EVALUATING CLIP POSITION

27.1 Slowly close the Clip just until the leaflets are coapted and MR is sufficiently reduced. The Clip should maintain a distinct “V” shape.

WARNING: DO NOT use excessive force to close the Clip further than is necessary to adequately reduce MR. Leaflet injury may occur.

WARNING: Closing the Clip too tightly may result in inability to deploy the Clip. Inability to deploy the Clip may result in worsening mitral regurgitation, cardiac injury, a single leaflet device attachment (SLDA), and/or conversion to surgical intervention.

27.2 Use echocardiographic imaging to verify valve function, satisfactory coaptation, and insertion of both leaflets by observation of:

- Leaflet immobilization;
- Single or multiple valve orifice(s);
- Limited leaflet mobility relative to the tips of both Clip Arms;
- Adequate MR reduction.

27.2.1 If the Clip position is not satisfactory, *Raise the Grippers* and *Invert the Clip Arms*.

27.2.2 Retract the inverted Clip into the LA.

27.2.3 Confirm both leaflets move freely.

27.2.4 Repeat positioning steps, as necessary, then repeat grasping steps.

28.0 MITRACLIP™ NT DEVICE PRE-DEPLOYMENT CLIP ASSESSMENT

28.1 Confirm DC Handle is secure.

WARNING: Failure to secure the DC Handle may result in leaflet injury or loss of leaflet insertion with resultant worsening mitral regurgitation, single leaflet device attachment (SLDA), and/or conversion to surgical intervention.

28.2 *Establish Final Arm Angle*.

WARNING: DO NOT turn the Arm Positioner more than 1/2 turn in the “Open” direction once initial resistance is felt to prevent device deployment. Inability to deploy the Clip may result in worsening mitral regurgitation, cardiac injury, a single leaflet device attachment (SLDA), and/or conversion to surgical intervention.

28.3 Turn the Arm Positioner to the “closed” side of the neutral position.

28.3.1 Use echocardiographic imaging to verify valve function, satisfactory coaptation, and insertion of both leaflets by observation of:

- Leaflet immobilization;
- Single or multiple valve orifice(s);
- Limited leaflet mobility relative to the tips of both Clip Arms;
- Adequate MR reduction.

28.4 Perform mean pressure gradient assessment prior to proceeding to deployment.

28.5 Establish Gripper Line Removability.

WARNING: Failure to Establish Gripper Line Removability prior to deployment of the Clip may result in inability to remove the Gripper Line. Intervention may be required.

28.5.1 Confirm the Gripper Lever is fully advanced.

28.5.2 Increase the flush rate to the DC and Sleeve. Remove the Gripper Lever Cap and "O" ring. Unwrap the two ends of the Gripper Line. Remove the plastic cover from the lines and separate the two ends so that no twists or knots are present.

28.5.3 With one free end of the Gripper Line in each hand, confirm that the Gripper Line is removable by pulling slowly on one end until the other end of the Gripper Line moves approximately 3-5 cm. If the Gripper Line is confirmed to be removable, continue to Clip Deployment.

NOTE: If excessive resistance is noted, stop, and pull on the other free end.

WARNING: While Establishing Gripper Line Removability, ensure that both ends of the Gripper Line remain exposed. Failure to maintain exposure of both Gripper Line ends may result in an inability to remove the Gripper Line in its entirety and could lead to conversion to surgical intervention.

WARNING: Pulling the Gripper Line too quickly or with excessive force may raise the Grippers, break the Gripper Line and/or disturb leaflet capture and insertion. This may result in worsening mitral regurgitation, and could lead to a single leaflet device attachment (SLDA), and/or conversion to surgical intervention.

28.5.3.1 If excessive resistance is noted at both ends of the Gripper Line (resulting in failure to Establish Gripper Line Removability), stop and remove the Clip Delivery System.

NOTE: The removal of the Clip Delivery System is most easily accomplished with the aid of an assistant.

28.5.3.1.1 Hold both free ends of the Gripper Lines together and apply tension to maintain the Grippers in a raised position through Step 28.5.3.1.4.

28.5.3.1.2 *Invert the Clip Arms* and then *Lock the Clip*.

28.5.3.1.3 Release the DC Fastener and retract the inverted Clip into the LA. Retract DC shaft until the DC Radiopaque Ring is fully against the tip of the Sleeve.

28.5.3.1.4 *Fully Close the Clip Arms* and continue to turn the Arm Positioner until it is no longer possible to rotate the Arm Positioner. Return the Arm Positioner to Neutral.

WARNING: Failure to follow Step 28.5.3.1.4 prior to retraction into the Guide may result in device damage, inability to remove the CDS and/or vascular and cardiac injury

28.5.3.1.5 Continue to Section 30.2.1.5: MITRACLIP™ NT SYSTEM REMOVAL WITH CLIP ATTACHED to remove the Clip.

29.0 CLIP DEPLOYMENT

29.1 Deployment Step 1: Lock Line Removal

29.1.1 While holding the ends of the lock line remove the Lock Lever Cap and "O" ring. Unwrap the two ends of the Lock Line in a counterclockwise direction. Separate the ends of the lock line and remove the plastic cover from the lines so that that no twists or knots are present.

WARNING: Do not let Line unravel freely. Do not remove Lock Line or plastic covers if line is bunched. Letting Line unravel freely may result in knots in the line. Removing Line if it is bunched may result in difficulty or inability to remove line due to knots or twists.

29.1.2 Grasp one of the free ends of the Lock Line, confirm the line moves freely, and slowly remove the Lock Line. Pull the Lock Line coaxial to the Lock Lever. If resistance is noted, stop and pull on the other free end to remove the Lock Line.

29.1.3 *Establish Final Arm Angle*.

NOTE: The Clip Arms may open slightly before remaining in a stable position. If Arms open more than slightly, close the Clip to the desired Arm position and re-*Establish Final Arm Angle*.

29.1.4 Turn the *Arm Positioner to Neutral*.

29.2 Deployment Step 2: Delivery Catheter Shaft Detachment

29.2.1 Confirm that the Arm Positioner is Neutral and that the two ends of the Gripper Line have been unwrapped from under the cap and are not twisted or knotted. Remove the Release Pin from the DC Handle.

29.2.2 Turn the Arm Positioner in the "Open" direction until the Release Pin groove is fully exposed.

NOTE: After the Release Pin is removed, turning the Arm Positioner in the "Open" direction will not open the Clip Arms.

29.2.3 Turn the Actuator Knob of the DC approximately 8 turns in the direction of the arrow printed on the Actuator Knob.

If it is difficult to turn the Actuator Knob, STOP and confirm that the Arm Positioner has been turned in the "Open" direction, such that the Release Pin groove is fully exposed.

WARNING: Failure to stop turning the Actuator Knob when resistance is felt may result in inability to deploy the Clip. Inability to deploy the Clip may result in worsening mitral regurgitation, cardiac injury, a single leaflet device attachment (SLDA), and/or conversion to surgical intervention.

29.2.4 Release the DC Fastener then retract the Actuator Knob approximately 0.5 cm after it is fully unthreaded.

29.2.5 Retract the DC Handle such that the Clip has separated at least 1 cm from the DC tip.

29.2.6 Secure the DC Fastener.

29.2.7 Allow several minutes after catheter shaft detachment before proceeding to the final Clip deployment step. Use echocardiographic imaging to verify valve function, satisfactory coaptation, and insertion of both leaflets by observation of:

- Leaflet immobilization;
- Single or multiple valve orifice(s);
- Limited leaflet mobility relative to the tips of both Clip Arms;
- Adequate MR reduction.

WARNING: If Clip placement and/or MR reduction is not satisfactory after Deployment Step 2: Delivery Catheter Shaft Detachment, DO NOT proceed to Deployment Step 3: Gripper Line Removal. Intervention may be required to remove the Clip.

29.3 Deployment Step 3: Gripper Line Removal

29.3.1 Grasp one of the free ends of the Gripper Line, confirm the line moves freely and slowly remove the line. Pull the Gripper Line coaxial to the Gripper Lever. If resistance is noted, stop and pull on the other free end to remove the Gripper Line. Maintain at least 1 cm separation between the DC tip and the Clip while slowly removing the Gripper Line.

WARNING: If less than 1 cm separation is present between the DC tip and the Clip before or during Gripper Line retraction, it may be difficult to remove the Gripper Line in its entirety.

WARNING: Pulling the Gripper Line too quickly or with excessive force may raise the Grippers, resulting in device damage and/or compromise leaflet capture and insertion. This may result in worsening mitral regurgitation, and could lead to a single leaflet device attachment (SLDA).

29.3.1.1 If the Gripper Line does not move easily, release the DC Fastener and incrementally release Sleeve curves (M/L Knob and A/P Knob). Secure DC Fastener once Sleeve curves are released.

WARNING: Failure to release the DC Fastener before releasing Sleeve curves may result in device damage and/or embolization.

29.3.1.2 If the Gripper Line still does not move easily, partially release Guide curves.

29.3.1.3 If the Gripper Line still does not move easily, the CDS may also be partially retracted into the tip of the Guide, or completely removed by pulling only on the Sleeve Handle, to facilitate Gripper Line removal.

WARNING: Retracting the CDS by pulling on the DC Handle may result in device damage and/or embolization.

29.3.2 Release the DC Fastener and retract the DC Handle until the DC Radiopaque Ring is against the tip of the Sleeve.

29.3.3 Secure the DC Fastener.

29.3.4 Confirm that the Clip position is stable.

29.3.5 Use echocardiographic imaging to verify valve function, satisfactory coaptation, and insertion of both leaflets by observation of:

- Leaflet immobilization;
- Single or multiple valve orifice(s);
- Limited leaflet mobility relative to the tips of both Clip Arms;
- Adequate MR reduction.

29.4 If placing an additional Clip proceed to Section 30.0. If not placing an additional Clip proceed to section 31.0.

30.0 ADDITIONAL MITRACLIP™ NT DEVICE PLACEMENT

WARNING: Use caution not to displace or dislodge an implanted Clip when placing an additional Clip; Clip detachment from leaflet(s) may occur which may result in a single leaflet device attachment (SLDA) or device embolization.

30.1 When placing an additional Clip, the following are recommended:

30.1.1 In the LA, ensure Clip Arms are oriented perpendicular to the line of coaptation and Grippers are raised.

30.1.2 Cross into the LV with a *Clip Arm Angle* of < 90 degrees.

30.1.3 Use both fluoroscopy and echocardiography when crossing into the LV and during grasping.

30.1.4 *Unlock the Clip* and *Open the Clip Arms* to 180 degrees. Ensure that the Clip Arms are oriented perpendicular to the line of coaptation then Close the Clip to the *Grasping Arm Angle*.

WARNING: DO NOT use excessive force or retraction distance during grasping. This may compromise leaflet capture and insertion. Loss of leaflet capture and insertion may result in inadequate reduction of mitral regurgitation and may result in a single leaflet device attachment (SLDA).

31.0 MITRACLIP™ NT SYSTEM REMOVAL

WARNING: During MitraClip™ NT System removal always retract the CDS by pulling only on the Sleeve Handle. Retracting the CDS by pulling on the DC Handle may result in device damage and/or device or component embolization, and may result in vascular and/or cardiac injury.

WARNING: Failure to release the DC Fastener before releasing Sleeve curves may result in device damage and/or device or component embolization.

WARNING: Failure to utilize echocardiographic guidance while releasing Sleeve deflection may result in cardiac injury.

31.1 MitraClip™ NT System Removal After Clip Deployment

31.1.1 Removal of the CDS While Leaving the Guide in Place.

31.1.1.1 Release the DC Fastener.

31.1.1.2 Slowly release Sleeve deflection by rotating the M/L Knob and the A/P Knob to neutral.

31.1.1.3 Secure DC Fastener once Sleeve curves are released.

31.1.1.4 Straighten the Guide with the +/- Knob when the Delivery Catheter tip is free from the left atrial wall and the mitral valve.

31.1.1.5 Release the Sleeve Fastener and retract the CDS approximately 10 cm into the Guide by pulling only on the Sleeve Handle.

31.1.1.6 Confirm that the Clip Introducer is still fully advanced in the Guide Hemostasis Valve.

31.1.1.7 Retract the CDS by pulling only on the Sleeve Handle and position the Delivery Catheter tip inside the Clip Introducer. Begin gently aspirating the Guide (starting when the CDS is approximately halfway into the Guide, approximately 40 cm retracted) using a 50–60 cc syringe.

31.1.1.8 Remove the CDS and the Clip Introducer simultaneously from the Guide by pulling on the Sleeve shaft and Clip Introducer. Ensure the Delivery Catheter tip is inside the Clip Introducer by visualizing the Proximal Sleeve alignment marker just outside the Clip Introducer. Aspirate the Guide during removal of the CDS and Clip Introducer. Cover Guide Hemostasis Valve with finger upon CDS removal. If necessary, position the Guide Handle below the level of the LA to allow blood to fill the Guide Lumen.

WARNING: DO NOT remove the tip of the CDS from the Guide without removing the Clip Introducer simultaneously. Failure to remove the Clip Introducer simultaneously may result in air embolism.

WARNING: DO NOT create a vacuum while removing the CDS from the Guide; air may enter the lumen of the Guide which may result in air embolism.

31.1.1.9 Aspirate using a 50–60 cc syringe to remove any remaining air from the Guide.

31.1.2 Removal of the CDS and Guide simultaneously.

31.1.2.1 Release the DC Fastener.

31.1.2.2 Slowly release Sleeve curves by rotating the M/L Knob and the A/P Knob to neutral.

31.1.2.3 Secure the DC Fastener once Sleeve curves are released.

31.1.2.4 Straighten the Guide with the +/- Knob when the Delivery Catheter tip is free from the left atrial wall and the mitral valve.

31.1.2.5 Release the Sleeve Fastener and retract the CDS approximately 10 cm into the Guide by pulling only on the Sleeve Handle.

31.1.2.6 Carefully retract the Guide tip into the RA. The Guide may be straightened further with the +/- Knob if desired.

31.1.2.7 Remove the MitraClip™ NT System from the femoral vein, while providing hemostasis.

31.2 MitraClip™ NT System Removal with Clip Attached

31.2.1 Removal of the CDS while leaving the Guide in place.

31.2.1.1 Confirm Clip is locked.

31.2.1.2 *Fully Close the Clip Arms* and continue to turn the Arm Positioner until it is no longer possible to rotate the Arm Positioner. Return the Arm Positioner to Neutral.

WARNING: Failure to follow Step 31.2.1.2 prior to retraction into the Guide may result in device damage, inability to remove the CDS and/or vascular and cardiac injury.

31.2.1.3 *Lower the Grippers*.

31.2.1.4 Release the DC Fastener and retract the DC Handle until the DC Radiopaque Ring is fully against the tip of the Sleeve.

31.2.1.5 Slowly release Sleeve deflection by rotating the M/L Knob and the A/P Knob to neutral.

31.2.1.6 Rotate DC handle such that the clip arms are perpendicular to the guide curve plane.

31.2.1.7 Secure the DC Fastener once Sleeve curves are released.

31.2.1.8 Straighten the Guide with the +/- Knob when the tip of the MitraClip™ NT Device is free from the left atrial wall and the mitral valve.

WARNING: Failure to straighten the Guide prior to retracting the Clip into the Guide may result in device damage, inability to remove the CDS and/or vascular and cardiac injury.

31.2.1.9 Release the Sleeve Fastener and retract the CDS into the Guide by pulling only on the Sleeve Handle.

NOTE: If resistance is noted, advance and rotate the Clip by rotating the DC Handle then retract the CDS into the Guide. The Guide and/or Sleeve position may also be adjusted to facilitate Clip entry into the Guide. If necessary, retract the Sleeve or advance the Clip to create a 2–3 cm separation to facilitate Clip entry into the Guide.

WARNING: Failure to utilize fluoroscopic guidance while retracting the CDS into the Guide may result in device damage, inability to remove the CDS and/or vascular and cardiac injury.

31.2.1.10 Confirm that the Clip Introducer is still fully advanced in the Guide Hemostasis Valve.

31.2.1.11 Retract the CDS by pulling only on the Sleeve Handle and position the Clip inside the Clip Introducer. Begin gently aspirating the Guide (starting when the CDS is approximately halfway into the Guide, approximately 40 cm retracted) using a 50–60 cc syringe.

31.2.1.12 Remove CDS and Clip Introducer simultaneously from the Guide by pulling on the Sleeve shaft and Clip Introducer. Ensure the Clip is inside the Clip Introducer by visualizing the Proximal Sleeve alignment marker just outside the Clip Introducer. Aspirate the Guide during removal of the CDS and Clip Introducer. If necessary, position the Guide Handle below the level of the LA to allow blood to fill the Guide lumen.

WARNING: DO NOT remove the tip of the CDS from the Guide without removing the Clip Introducer simultaneously and with the Clip inside the Clip Introducer. Failure to remove the Clip Introducer simultaneously may result in air embolism.

WARNING: DO NOT create a vacuum while removing the CDS from the Guide; air may enter the lumen of the Guide which may result in air embolism.

WARNING: DO NOT re-use the CDS after removal. Replace the CDS with a new device. Reinserting the CDS after removal may result in inability to open the Clip. Inability to open the Clip may result in valve injury or lead to deployment of the Clip in an unintended location.

31.2.1.13 Aspirate using a 50–60 cc syringe to remove any remaining air from the Guide.

31.2.2 Simultaneous removal of CDS and Guide.

31.2.2.1 Confirm Clip is locked.

31.2.2.2 *Fully Close the Clip Arms* and continue to turn the Arm Positioner until it is no longer possible to rotate the Arm Positioner. Return the Arm Positioner to Neutral.

WARNING: Failure to follow Step 31.2.2.2 prior to retraction into the Guide may result in device damage, inability to remove the CDS and/or vascular and cardiac injury.

31.2.2.3 *Lower the Grippers*.

31.2.2.4 Release the DC Fastener and retract the DC Handle until the DC Radiopaque Ring is fully against the tip of the Sleeve.

31.2.2.5 Slowly release Sleeve deflection by rotating the M/L Knob and the A/P Knob to neutral.

31.2.2.6 Rotate DC handle such that the clip arms are perpendicular to the guide curve plane.

31.2.2.7 Secure the DC Fastener once Sleeve curves are released.

31.2.2.8 Straighten the Guide with the +/- Knob when the tip of the MitraClip™ NT Device is free from the left atrial wall and the mitral valve.

WARNING: Failure to straighten the Guide prior to retracting the Clip into the Guide may result in device damage, inability to remove the CDS and/or vascular and cardiac injury.

31.2.2.9 Release the Sleeve Fastener and retract the CDS approximately 10 cm into the Guide by pulling only on the Sleeve Handle.

NOTE: If resistance is noted, advance and rotate the Clip by rotating the DC Handle then retract the CDS into the Guide. The Guide and/or Sleeve position may also be adjusted to facilitate Clip entry into the Guide. If necessary, retract the Sleeve or advance the Clip to create a 2–3 cm separation to facilitate Clip entry into the Guide.

WARNING: Failure to utilize fluoroscopic guidance while retracting the CDS into the Guide may result in device damage, inability to remove the CDS and/or vascular and cardiac injury.

31.2.2.10 Carefully retract the Guide tip into the RA. The Guide may be straightened further with the +/- Knob if desired.

31.2.2.11 Remove the MitraClip™ NT System from the femoral vein, while providing hemostasis.

32.0 PATENTS AND TRADEMARKS

This product and / or its use are covered by one or more of the following United States Patents: 8,057,493; 7,736,388; 7,682,369; 7,666,204; 7,655,015; 7,608,091; 7,604,646; 7,563,267; 7,288,097; 7,226,467; 7,048,754; 6,770,083; 6,752,813; 6,629,534; 6,461,366. Other U.S. patents pending. Foreign patents issued and pending.

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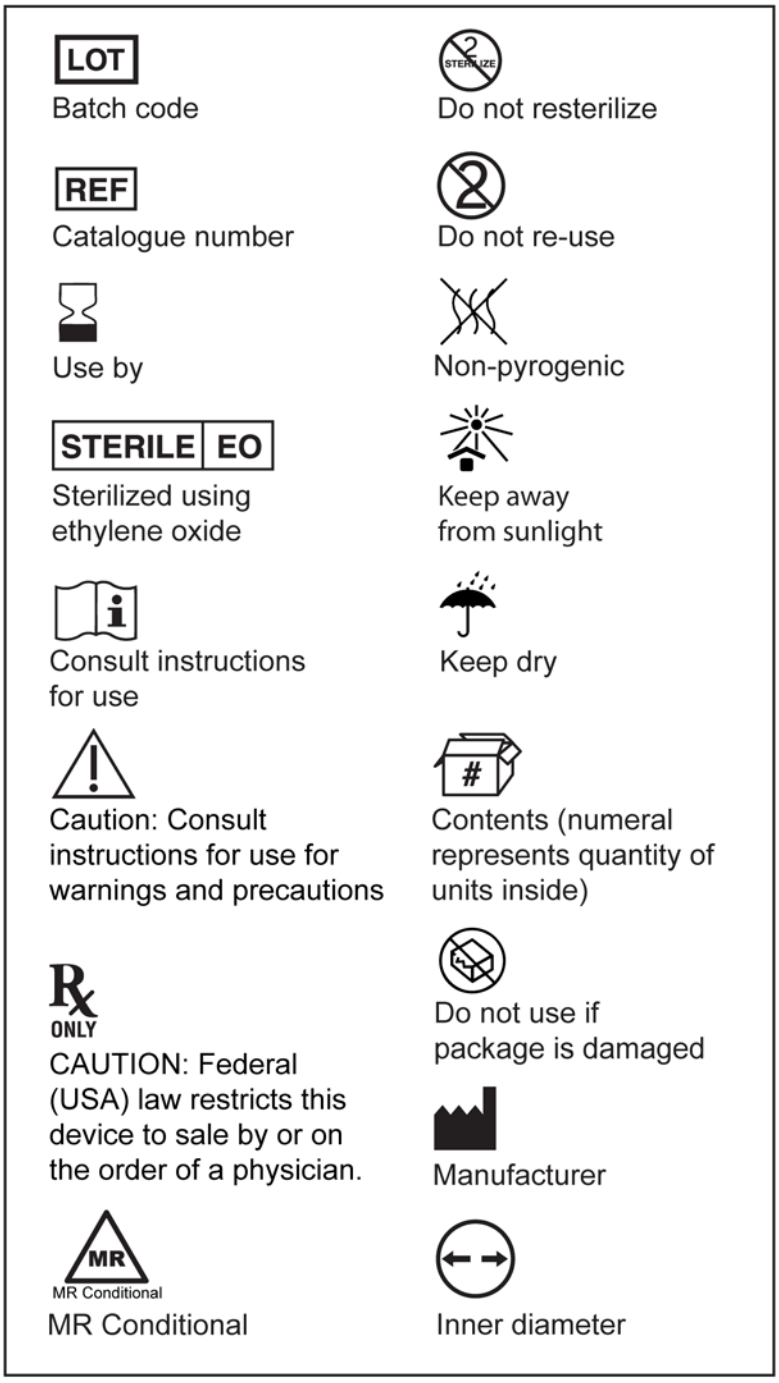
GRAPHICAL SYMBOLS FOR MEDICAL DEVICE LABELING



Rx ONLY

MitraClip™ NTR/XTR Clip Delivery System
Clip Delivery System REF CDS06
Steerable Guide Catheter REF SGC0301

MitraClip™ System Accessories
Stabilizer REF SZR01ST
Lift REF LFT01ST
Support Plate REF PLT01ST

Instructions for Use

WARNING: Read all instructions carefully. Failure to follow these instructions, warnings and precautions may lead to device damage or patient injury. Use of the MitraClip™ System should be restricted to those physicians trained to perform invasive endovascular and transseptal procedures and to those physicians trained in the proper use of the system.

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1.0 INDICATION FOR USE

- The MitraClip™ NTR/XTR Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.
- The MitraClip™ NTR/XTR Clip Delivery System, when used with maximally tolerated guideline-directed medical therapy (GDMT), is indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria) in patients with a left ventricular ejection fraction (LVEF) ≥ 20% and ≤ 50%, and a left ventricular end systolic dimension (LVESD) ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease.

2.0 CONTRAINDICATIONS

The MitraClip™ NTR/XTR Clip Delivery System is contraindicated in patients with the following conditions:

- Patients who cannot tolerate procedural anticoagulation or post procedural anti-platelet regimen
- Active endocarditis of the mitral valve
- Rheumatic mitral valve disease
- Evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus

3.0 WARNINGS

- **DO NOT use MitraClip™ outside of the labeled indication.**
- The MitraClip™ Implant should be implanted with sterile techniques using fluoroscopy and echocardiography (e.g., transesophageal [TEE] and transthoracic [TTE]) in a facility with on-site cardiac surgery and immediate access to a cardiac operating room.
- Read all instructions carefully. Failure to follow these instructions, warnings and precautions may lead to device damage, user injury or patient injury. Use universal precautions for biohazards and sharps while handling the MitraClip™ System to avoid user injury.
- Use of the MitraClip™ should be restricted to those physicians trained to perform invasive endovascular and transseptal procedures and those trained in the proper use of the system.
- The Clip Delivery System is provided sterile and designed for single use only. Cleaning, re-sterilization and / or reuse may result in infections, malfunction of the device or other serious injury or death.
- Use caution when treating patients with hemodynamic instability requiring inotropic support or mechanical heart assistance due to the increased risk of mortality in this

patient population. The safety and effectiveness of MitraClip™ in these patients has not been evaluated.

4.0 PRECAUTIONS

- Note the product “Use by” date specified on the package.
- Inspect all product prior to use. Do not use if the package is open or damaged, or if product is damaged.
-
- Prohibitive Risk Primary (or degenerative) Mitral Regurgitation
    - Prohibitive risk is determined by the clinical judgment of a heart team, including a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, due to the presence of one or more of the following documented surgical risk factors:
    - 30-day STS predicted operative mortality risk score of
        - ≥8% for patients deemed likely to undergo mitral valve replacement or
        - ≥6% for patients deemed likely to undergo mitral valve repair
    - Porcelain aorta or extensively calcified ascending aorta.
    - Frailty (assessed by in-person cardiac surgeon consultation)
    - Hostile chest
    - Severe liver disease / cirrhosis (MELD Score > 12)
    - Severe pulmonary hypertension (systolic pulmonary artery pressure > 2/3 systemic pressure)
    - Unusual extenuating circumstance, such as right ventricular dysfunction with severe tricuspid regurgitation, chemotherapy for malignancy, major bleeding diathesis, immobility, AIDS, severe dementia, high risk of aspiration, internal mammary artery(IMA) at high risk of injury, etc.
    - Evaluable data regarding safety or effectiveness is not available for prohibitive risk DMR patients with an LVEF < 20% or an LVESD > 60 mm. MitraClip® should be used only when criteria for clip suitability for DMR have been met.
    - The heart team should include a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease and may also include appropriate physicians to assess the adequacy of heart failure treatment and valvular anatomy.
- Secondary Mitral Regurgitation
    - Evaluable data regarding safety or effectiveness is not available for secondary MR patients with an LVEF < 20% or an LVESD > 70 mm.
    - The multidisciplinary heart team should be experienced in the evaluation and treatment of heart failure and mitral valve disease and determine that symptoms and MR severity persist despite maximally tolerated GDMT.

5.0 SPECIAL PATIENT POPULATIONS

Pregnancy
The MitraClip™ device has not been tested in pregnant women. Effects on the developing fetus have not been studied. The risks and reproductive effects are unknown at this time.

Gender

No safety or effectiveness related gender differences were observed in clinical studies.

Ethnicity
Insufficient subject numbers prevent ethnicity-related analyses on the clinical safety and effectiveness.

Pediatrics
Safety and effectiveness of the MitraClip™ device has not been established in pediatric patients.

Anatomic Considerations
For optimal results, the following anatomic patient characteristics should be considered. The safety and effectiveness of the MitraClip™ outside of these conditions has not been established. Use outside these conditions may interfere with placement of the MitraClip™ Implant or mitral valve leaflet insertion.

- The primary regurgitant jet is non-commissural. If a secondary jet exists, it must be considered clinically insignificant
- Mitral valve area ≥ 4.0 cm^2
- Minimal calcification in the grasping area
- No leaflet cleft in the grasping area
- Flail width < 15 mm and flail gap < 10 mm

6.0 POTENTIAL COMPLICATIONS AND ADVERSE EVENTS

The following ANTICIPATED EVENTS have been identified as possible complications of the MitraClip™ procedure.

Death	Hypotension / hypertension
Allergic reaction (anesthetic, contrast, Heparin, nickel alloy, latex)	Infection
Aneurysm or pseudo-aneurysm	Injury to mitral valve complicating or preventing later surgical repair
Arrhythmias	Lymphatic complications
Atrial fibrillation	Mesenteric ischemia
Atrial septal defect requiring intervention	MitraClip™ Implant erosion, migration or malposition
Arterio-venous fistula	MitraClip™ Implant thrombosis
Bleeding	MitraClip™ System component(s) embolization
Cardiac arrest	Mitral stenosis
Cardiac perforation	Mitral valve injury
Cardiac tamponade / Pericardial Effusion	Multi-system organ failure
Chordal entanglement / rupture	Myocardial infarction
Coagulopathy	Nausea / vomiting
Conversion to standard valve surgery	Pain
Deep venous thrombus (DVT)	Peripheral ischemia
Dislodgement of previously implanted devices	Prolonged angina
Dizziness	Prolonged ventilation
Drug reaction to anti-platelet / anticoagulation agents / contrast media	Pulmonary congestion
Dyskinesia	Pulmonary thrombo-embolism
Dyspnea	Renal insufficiency or failure
Edema	Respiratory failure / atelectasis / pneumonia
Emboli (air, thrombus, MitraClip™ Implant)	Septicemia
Emergency cardiac surgery	Shock, Anaphylactic or Cardiogenic
Endocarditis	Single leaflet device attachment (SLDA)
Esophageal irritation	Skin injury or tissue changes due to exposure to ionizing radiation
Esophageal perforation or stricture	Stroke or transient ischemic attack (TIA)
Failure to deliver MitraClip™ to the intended site	Urinary tract infection
Failure to retrieve MitraClip™ System components	Vascular trauma, dissection or occlusion
Fever or hyperthermia	Vessel spasm
Gastrointestinal bleeding or infarct	Vessel perforation or laceration
Hematoma	Worsening heart failure
Hemolysis	Worsening mitral regurgitation
Hemorrhage requiring transfusion	Wound dehiscence

7.0 PATIENT COUNSELING

Patients undergoing any procedures known to potentially be associated with bacteremia after implantation of the MitraClip™ Implant should be prescribed prophylactic antibiotic therapy prior to such procedures.

Short-term anticoagulation therapy may be necessary after mitral valve repair with the MitraClip™ Implant. Prescribe anticoagulation and other medical therapy per institutional guidelines.

After placement of a MitraClip™ Implant, the Implant Identification Card should be filled out and the patient should be instructed to carry it at all times.

All patients should be advised to limit strenuous physical activity for at least the first month post-procedure or longer if warranted.

Physicians should consider the following in counseling patients about the MitraClip™ Implant:

- Discuss the risks associated with MitraClip™ Implant placement.
- Discuss why surgery is not an option for the patient.
- Discuss the risk / benefit considerations for the patient.

8.0 HOW SUPPLIED

8.1 Contents

One (1) Clip Delivery System with the MitraClip™ Implant, one (1) MitraClip™ Implant Card.

8.2 Sterile

The Clip Delivery System and Steerable Guide Catheter are sterilized with ethylene oxide gas and provided in a thermoformed tray with lid, in a sealed pouch.
Parts of the devices that are in either direct or indirect contact with circulating blood are non-pyrogenic.

Note the product “Use By” date specified on the package. DO NOT use if the “Use by” date has passed.
These devices are intended for single-use only. Do not reuse. Do not resterilize. This single use device cannot be reused on another patient, as it is not designed to perform as intended after the first usage. Changes in mechanical, physical, and / or chemical characteristics introduced under conditions of repeated use, cleaning, and / or resterilization may compromise the integrity of the design and / or materials, leading to contamination due to narrow gaps and / or spaces and diminished safety and / or performance of the device. Absence of original labeling may lead to misuse and eliminate traceability. Absence of original packaging may lead to device damage, loss of sterility, and risk of injury to the patient and / or user. Inspect all product prior to use. Do not use if the package is open or damaged, or if product is damaged.
The white Guide tip shape retainer and transparent protective tubing are provided sterile and pre-installed on the distal tip of the Steerable Guide Catheter. The Fasteners and the Silicone Pad used with the Stabilizer are provided sterile with the Steerable Guide Catheter. The Dilator, Fasteners and the Silicone Pad are intended for single use only.

Do not reuse. Do not resterilize, as this can compromise device performance and increase the risk of cross contamination due to inappropriate reprocessing.

8.3 Non-Sterile

The Stabilizer, Support Plate and Lift are provided non-sterile. Follow the cleaning and sterilization instructions provided with the Stabilizer, Support Plate and Lift.

9.0 STORAGE

Handle with care. Store in original packaging. Keep dry. Keep away from sunlight.

10.0 MITRACLIP™ SYSTEM DIMENSIONS

Table 10.1: MitraClip™ System Dimensions

Component	***Dimension***	
Delivery Catheter		
Extended Length (from Sleeve curved at 90 degrees)	*> 65 mm*	
Steerable Sleeve		
Working Length	*1095 mm*	
Catheter Distal Shaft Outer Diameter	*5.3 mm (16 Fr)*	
MitraClip™ Implant	*NTR*	*XTR*
Closed Clip Length (Figure 1A, Figure 2A)	*15 mm maximum*	*18 mm maximum*
Grasping Width at 120 degrees (Figure 1B, Figure 2B)	*17 mm minimum*	*22 mm minimum*
Clip Width at 180 degrees (NTR) or (Figure 1C)	*20 mm maximum*	--
Clip Width at 60 degrees (XTR) (Figure 2C)	--	*20 mm maximum*
Arm Width (Figure 1D, Figure 2D)	*5 mm maximum*	*5 mm maximum*
Arm Length (Coaptation Length) (Figure 1E, Figure 2E)	*9 mm maximum*	*12 mm maximum*
Steerable Guide Catheter		
Working Length	*800 mm*	
Catheter Shaft Inner Diameter	*5.5 mm (16 Fr)*	
Catheter Shaft Outer Diameter	*8.1 mm (24 Fr)*	
Catheter Distal Tip Diameter	*7.7 mm (23 Fr)*	
Catheter Septal Crossing Diameter	*7.4 mm (22 Fr)*	
Dilator		
Working Length	*1220 mm*	
Shaft Inner Diameter	*1.0 mm (3 Fr)*	
Shaft Outer Diameter	*5.4 mm (16 Fr)*	
Distal Tip Outer Diameter	*1.5 mm (4 Fr)*	

Figure 10.1: MitraClip™ NTR Implant Dimensions

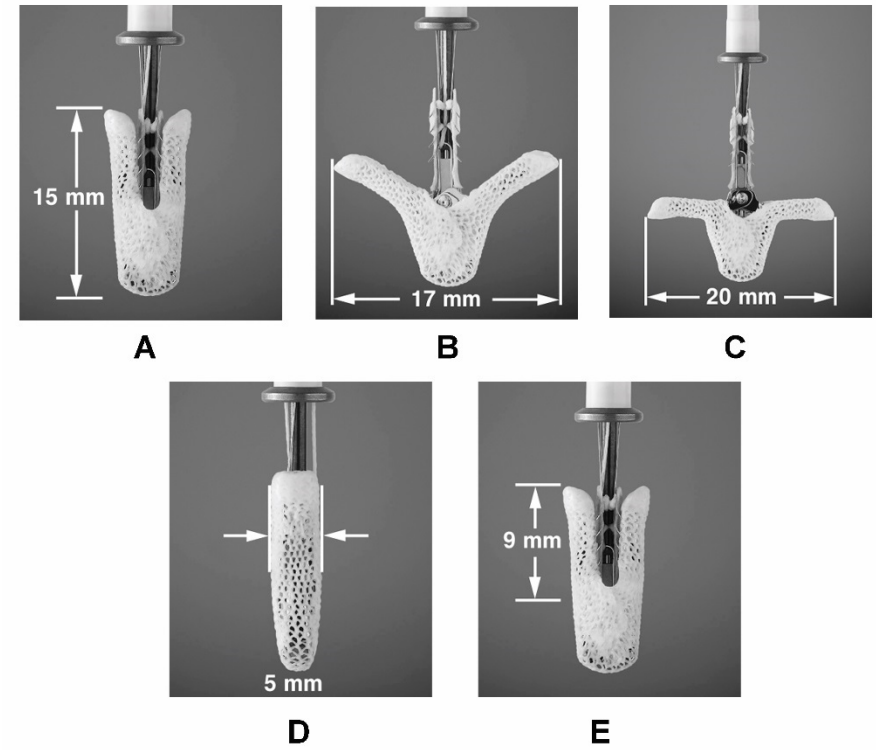
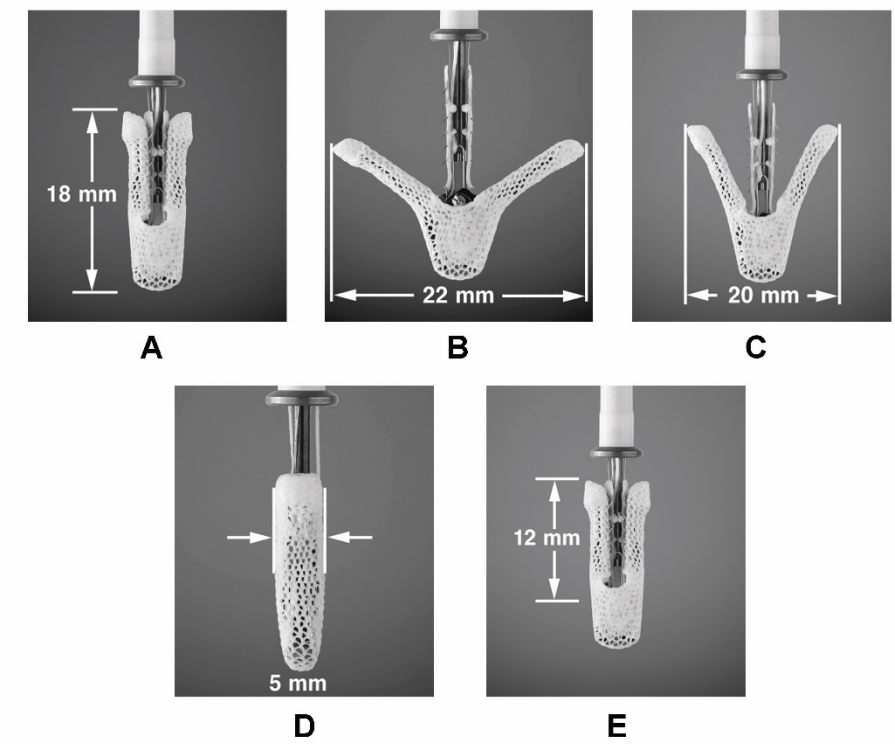


Figure 10.2: MitraClip™ XTR Implant Dimensions



11.0 GLOSSARY OF ACRONYMS

Guide:	Steerable Guide Catheter	RA:	Right Atrium
SGC:	Steerable Guide Catheter		
CDS:	Clip Delivery System	LA:	Left Atrium
Sleeve:	Steerable Sleeve	LV:	Left Ventricle
DC:	Delivery Catheter	RO:	Radiopaque
Clip:	MitraClip™ Implant	MR:	Mitral Regurgitation

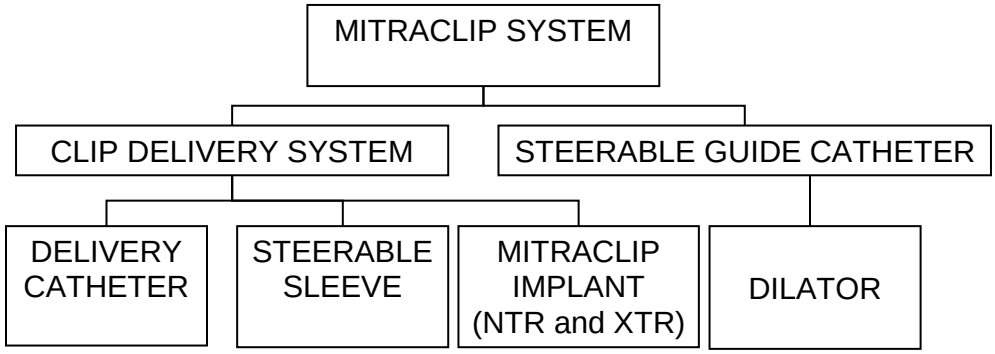
12.0 DEVICE DESCRIPTION

The MitraClip™ System consists of two parts: 1) the Clip Delivery System and 2) the Steerable Guide Catheter.

The Clip Delivery System consists of three major components:

1) The Delivery Catheter
2) The Steerable Sleeve and
3) The MitraClip™ Implant

The Clip Delivery System is introduced into the body through a Steerable Guide Catheter which includes a dilator. The Clip Delivery System and Steerable Guide Catheter constitute the MitraClip™ System.



The Clip Delivery System (Figures 3, 5 and 6) is used to advance and manipulate the implantable MitraClip™ Implant for proper positioning and placement on the mitral valve leaflets. The Clip Delivery System is designed to deploy the implant in a way that requires multiple steps to ensure safe delivery of the device.

The outer surfaces of the Delivery Catheter and the Steerable Guide Catheter have a hydrophilic coating.

The MitraClip™ Implant (Figure 10.1 and Figure 10.2) is a percutaneously implanted mechanical Clip. The MitraClip™ Implant grasps and coapts the mitral valve leaflets resulting in fixed approximation of the mitral leaflets throughout the cardiac cycle. The MitraClip™ Implant is placed without the need for arresting the heart or cardiopulmonary bypass. The implantable MitraClip™ Implant is manufactured with metal alloys and polyester fabric (Clip cover) that are commonly used in cardiovascular implants.

The MitraClip™ Implant arms can be adjusted to any position from fully opened, fully inverted and fully closed. These positions are designed to allow the MitraClip™ Implant to grasp and approximate the leaflets of the mitral valve using controls on the Delivery Catheter Handle. The MitraClip™ Implant can be locked, unlocked and repeatedly opened and closed. The Grippers can be raised or lowered repeatedly.

The MitraClip™ Implant can be removed using standard surgical techniques and can be disposed of according to institutional guidelines.

The Steerable Guide Catheter (Figure 4a) is used to introduce the Clip Delivery System into the left side of the heart through the interatrial septum. The Steerable Guide Catheter is also used to position and orient the Clip Delivery System to the appropriate location above the mitral valve. The Dilator (Figure 4b) is used for the introduction of the Steerable Guide Catheter into the femoral vein and left atrium.

12.1 MRI Safety Information

Non-clinical testing has demonstrated that the MitraClip Implants are MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5-Tesla (1.5 T) or 3-Tesla (3.0 T)
- Maximum spatial field gradient of 4,000 Gauss/cm (40 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode).

Under the scan conditions defined above, MitraClip Implants are expected to produce a maximum temperature rise of less than or equal to 3.1°C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by a pair of MitraClip Implants extends approximately 40 mm beyond the MitraClip Implants when imaged with a spin echo or gradient echo pulse sequence in a 3 T magnetic resonance imaging system. The presence of additional implants in a patient's valve may increase the image artifact size when imaged in an MRI system.

12.2 MitraClip™ System Accessories Overview

Several accessories are used in conjunction with the MitraClip™ System including: 1) a Stabilizer, 2) a Lift, 3) a Support Plate, 4) a Silicone Pad, and 5) Fasteners. The Stabilizer is provided separately as a non-sterile reusable device and must be cleaned and sterilized prior to each use. The Stabilizer is used on the sterile field to support and position the Steerable Guide Catheter and Clip Delivery System during the procedure. The Lift and Support Plate are provided separately as non-sterile reusable devices and must be cleaned prior to each use. The Lift and Support Plate are used outside the sterile field to provide a stable platform for the Stabilizer and MitraClip™ System during the procedure. Follow the cleaning and sterilization instructions provided with the Stabilizer, Support Plate and Lift. The Silicone Pad and Fasteners are single use accessories and are provided sterile with the Steerable Guide Catheter packaging. The Silicone Pad is used on the sterile field under the Stabilizer to prevent incidental movement of the Stabilizer during the procedure. The Fasteners are used on the sterile field to secure the Steerable Guide Catheter and Clip Delivery System to the Stabilizer.

Legend of Figure Labels

Figure 3: Clip Delivery System (CDS)
1 Delivery Catheter Handle
2 Delivery Catheter Fastener
3 A/P Knob
4 M/L Knob
5 Steerable Sleeve Handle
6 Clip Introducer
7 MitraClip™ Implant

Figure 4a: Steerable Guide Catheter
8 Hemostasis Valve
9 Alignment Marker
10 Flush Port
11 +/- Knob
12 Proximal Shaft
13 Distal Shaft
14 Radiopaque Tip Ring

Figure 4b: Dilator
15 Rotating Hemostatic Valve
16 Flush Port
17 Echogenic Spiral Groove

Figure 5: CDS Handles
18 Actuator Knob
19 Release Pin
20 Arm Positioner
21 Lock Lever Cap
22 Gripper Lever Cap
23 Lock Lever
24 Gripper Lever
25 Delivery Catheter Top Flush Port (Bottom Flush Port Not Shown)
26 Delivery Catheter Handle
27 Delivery Catheter Fastener
28 Sleeve Flush Port
29 A/P Knob
30 M/L Knob
31 Steerable Sleeve Handle

Figure 6: CDS Distal End
32 Longitudinal Alignment Marker
33 Key
34 Steerable Sleeve Shaft
35 Radiopaque Alignment Markers
35a Proximal
35b Distal
36 Sleeve Radiopaque Tip Ring
37 Delivery Catheter Shaft
38 Delivery Catheter Radiopaque Ring
39 MitraClip™ Implant

Figure 7: MitraClip™ Implant Positions
A Clip fully closed (low profile)
B Clip at 180 degrees
C Clip at 120 degrees
D Clip at 60 degrees
E Clip at 20 degrees
F Clip inverted
G Clip fully inverted

Figure 3: Clip Delivery System (CDS)

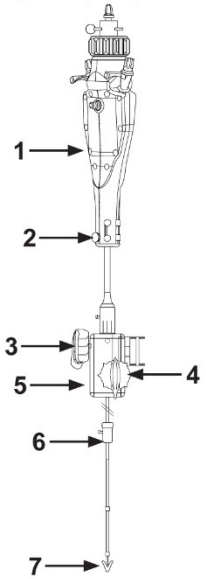


Figure 4a: Steerable Guide Catheter

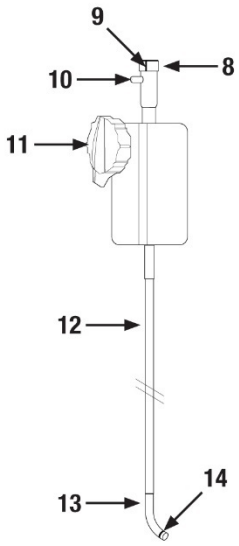


Figure 4b: Dilator

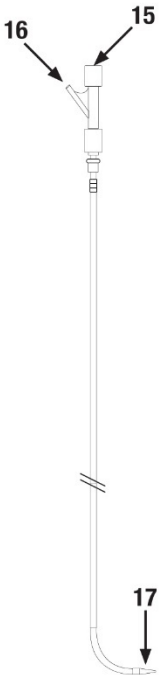


Figure 5:CDS Handles

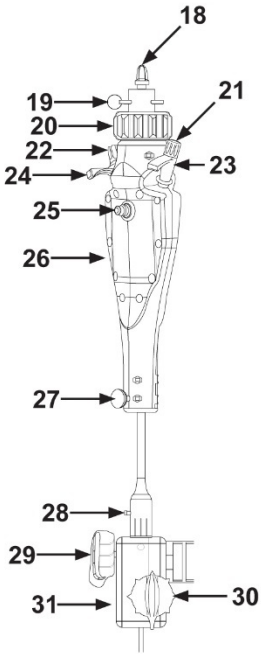


Figure 6:CDS Distal End

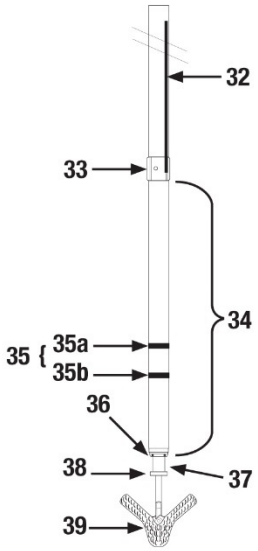


Figure 12.1: MitraClip™ Implant Positions

A: Clip fully closed

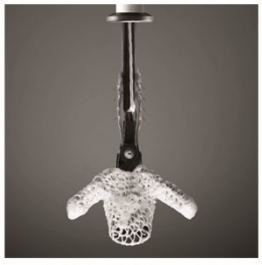
B: Clip at 180 degrees

C: Clip at 120 degrees

D: Clip at 60 degrees

E: Clip at 20 degrees

F: Clip inverted



G: Clip fully inverted

The Steerable Guide Catheter and Clip Delivery System (Steerable Sleeve, Delivery Catheter and Clip) are steered and actuated by the use of control knobs, levers and fasteners located on the handles.

Table 12.1: MitraClip™ System Handle Controls

Device	Control	Function
Steerable Guide Catheter	+/- Knob	Tip deflection
Steerable Sleeve	M/L Knob A/P Knob	Tip deflection Tip deflection
Delivery Catheter	Lock Lever Gripper Lever Arm Positioner DC Fastener Lock Lever Cap Release Pin Actuator Knob Gripper Lever Cap	Locks-Unlocks Clip via Lock Line Raises-Lowers Grippers via Gripper Line Opens-Closes Clip Arms Locks-Unlocks DC translation/torque Controls removal of Lock Line Prevents Actuator Knob turning Turns actuator shaft for Clip deployment Controls removal of Gripper Line

13.0 REQUIRED ACCESSORIES

SZR01ST: One (1) Stabilizer
LFT01ST: One (1) Lift
PLT01ST: One (1) Support Plate
One (1) Silicone Pad, three (3) Fasteners (All are included sterile with the Steerable Guide Catheter)

14.0 ADDITIONAL REQUIRED EQUIPMENT NOT INCLUDED

Transseptal sheath and guidewire
Transseptal needle
Step-up dilators
260 cm of 0.9 mm (0.035") super stiff exchange length guidewire
High pressure three way stopcocks (5)
Arterial high pressure extension tubing (3)
50–60 cc syringes with luer fitting (2)
1000 ml pressure bags (2)
Sterile IV tubing with thumbwheel occluders (2)
Heparinized sterile saline solution (2) 1 liter bags
Rolling IV Pole
Sterile Basin

15.0 OVERVIEW OF CLINICAL STUDIES

Table 15.1 presents an overview of the MitraClip clinical program in the United States including study design, enrollment criteria, endpoints and sample size.

Table 15.1: Overview of MitraClip US Clinical Trials

Type	Study	Key Inclusion Criteria	Key Exclusion Criteria	Endpoint	sites	patients
Feasibility	EVEREST I enrollment 2003-2006	• MR≥3+ • Symptomatic or asymptomatic with[a]: LVEF 30-50% and / or LVESD 50-55mm or LVEF 50-60% and LVESD < 45 mm or LVEF>60 and LVESD 45-55 mm • Candidate for mitral valve surgery including cardiopulmonary bypass	• LVEF<30%, and / or LVESD >55mm • Mitral valve orifice area <4.0 cm2 • Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR	• Primary: Major Adverse Event rate through 30 days	11	55
Randomized Control Trial	EVEREST II RCT enrollment 2005-2008	MR≥3+ • Symptomatic with LVEF > 25% and LVESD ≤ 55 mm or asymptomatic with[a]: LVEF 25% to 60% LVESD ≥ 40 mm New onset of atrial fibrillation PASP>50mmHg at rest of >60 mmHg with exercise	• LVEF≤25%, and / or LVESD >55mm • Mitral valve orifice area <4.0 cm^2 • Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR	• Primary Safety: Major Adverse Event rate through 30 days or discharge, whichever is greater Primary Effectiveness: Freedom from death, MV surgery (for Device group) or re-operation (for Control group), and MR > 2+ at 12 months • Secondary Effectiveness: • Measures of LV Function • SF-36 quality of life • NYHA Functional Class	37	60 roll-in 178 [b] Device 80 [b] Surgical Control
Single-Arm Registry	EVEREST II High Risk Registry Study enrollment 2007-2008	MR≥3+ • Predicted procedural mortality risk calculated using the STS surgical risk calculator of ≥ 12% or in the judgment of a cardiac surgeon the patient is considered a high risk surgical candidate due to the presence of one of the following indications: 1. Porcelain aorta, mobile ascending aortic atheroma 2. Post-radiation mediastinum 3. Previous mediastinitis 4. Functional MR with EF<40 5. Over 75 years old with EF<40 6. Re-operation with patent grafts 7. Two or more prior chest surgeries 8. Hepatic cirrhosis 9. Three or more of the following STS high risk factors 9.1 Creatinine > 2.5 mg/dL 9.2 Prior chest surgery 9.3 Age over 75 9.4 EF<35	• LVEF<20% and / or LVESD>60mm • Mitral valve orifice area <4.0 cm^2 • Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR	• Primary Safety: Procedural mortality at 30 days • Major Secondary: • Measures of LV Function • SF-36 quality of life • NYHA Functional Class • CHF Hospitalizations • Secondary Safety: • Major Adverse Event rate at 30 days and 12 months	25	78
Continued Access Registry	REALISM High Risk enrollment 2009-2013	• Same as High Risk Registry with the exception of the requirement for predicted procedural mortality risk ≥ 12%	• Same as High Risk Registry	• Same as High Risk Registry	39	581[c]
	REALISM Non-High Risk enrollment 2009-2011	• Same as RCT	• Same as RCT	• Same as RCT • 6 Minute Walk Test (6MWT) Distance[d]	39	272

Type	Study	Key Inclusion Criteria	Key Exclusion Criteria	Endpoint	sites	patients
Pivotal RCT	COAPT Enrollment 2012-2017	• Ischemic or non-ischemic cardiomyopathy with LVEF 20%-50% and LVESD ≤70 mm • Moderate-to-severe (3+) or severe (4+) secondary MR confirmed by an independent echo core laboratory prior to enrollment • NYHA Functional Class II, III or ambulatory IV despite stable maximally-tolerated GDMT regimen and CRT (if appropriate) • At least one hospitalization for heart failure in the 12 months prior to subject registration and/or a corrected BNP ≥300 pg/ml or corrected NT-proBNP ≥1500 pg/ml measured within 90 days prior to subject registration • Surgery per local heart team assessment • (LVESD) is ≤70 mm assessed by site based on a transthoracic echocardiographic (TTE) • Treating interventionalist believes secondary MR can be successfully treated with MitraClip	• ACC/AHA stage D heart failure, hemodynamic instability or cardiogenic shock • Untreated clinically significant coronary artery disease requiring revascularization • COPD requiring continuous home oxygen therapy or chronic oral steroid use • Severe pulmonary hypertension or moderate or severe right ventricular dysfunction • Aortic or tricuspid valve disease requiring surgery or transcatheter intervention • Mitral valve orifice area <4.0 cm^2 • Life expectancy < 12 months due to non-cardiac reasons	• Primary Safety: Composite of device-related complications at 12 months • Primary Effectiveness: Recurrent HF hospitalizations through 24 months	84	614 (51 roll-n)

[a] Inclusion criteria based on the current indication for mitral valve surgery for mitral regurgitation in the ACC/AHA guidelines for management of valvular dysfunction.
[b] Of the 184 patients randomized to Device, 178 received Device. Of the 95 patients randomized to Control, 80 underwent mitral valve surgery.
[c] As of July 12, 2013.
[d] In protocol version dated November 17, 2008, only patients with NYHA Functional Class III or IV in the Non-High Risk arm were considered for a 6-minute walk test. In the amended protocol version dated September 14, 2010, all patients enrolled in REALISM are required to perform the 6-minute walk test.

15.1 EVEREST I Trial (Feasibility)

The EVEREST I trial was a prospective, multi-center, registry trial designed to evaluate the preliminary safety and effectiveness of the MitraClip device in the treatment of moderate-to-severe (3+) or severe (4+) chronic MR using up to 2 MitraClip devices per patient. The EVEREST I trial demonstrated the preliminary safety and feasibility of the MitraClip device as a percutaneous method for the reduction of MR severity. EVEREST I enrolled 55 patients at 12 US sites. Enrolled patients were required to complete clinical follow up at 30 days, 6, 18 and 24 months, and 3, 4, and 5 years. The primary safety endpoint of EVEREST I was MAE rate through 30 days (acute safety). Multiple additional secondary endpoints were pre-specified for safety and effectiveness for reporting with descriptive statistics. The study is now closed.

15.2 EVEREST II Randomized Clinical Trial (RCT)

The EVEREST II RCT was a landmark trial, being the first randomized trial to compare a percutaneous intervention for the reduction of MR to standard of care mitral valve surgery. The EVEREST II RCT was a prospective, blinded, randomized, controlled, multi-center study of 279 patients (184 MitraClip, 95 surgical control) comparing the safety and effectiveness of the MitraClip to the standard of care mitral valve surgery. The intended population was patients with significant symptomatic mitral regurgitation (MR ≥ 3+) of either secondary MR or primary MR etiology that were non-high risk candidates indicated for and who could undergo mitral valve surgery. Study design elements including key inclusion/exclusion criteria and endpoints are provided in Table 15.1. Patients were evaluated at baseline, discharge, 30 days, 6, 12, 18 and 24 months, and annually thereafter through 5 years. Results of this study showed that the safety advantages of the percutaneous procedure were offset by the diminution of MR reduction with MitraClip compared to surgery, and therefore good surgical candidates should continue to receive surgical intervention.

15.3 EVEREST II High Risk Registry and EVEREST II REALISM Continued Access Study - High Risk (EVEREST II HRR and REALISM HR)

The EVEREST II High Risk Registry (HRR) was a prospective, multi-center, registry designed to be adjunctive to the RCT and to evaluate the safety and effectiveness of the MitraClip device in the treatment of high surgical risk (≥ 12%) patients with moderate-to-severe (3+) or severe (4+) chronic MR using up to 2 MitraClip devices per patient. The EVEREST II HRR enrolled 78 patients at 35 North American sites. Enrolled patients were required to complete clinical follow up at 30 days, 6, 12, 18 and 24 months, and 3, 4, and 5 years. The primary safety endpoint of the EVEREST II HRR was procedural mortality at 30 days or prior to discharge, whichever is longer. REALISM HR was a single-arm, self-controlled adjunctive study enrolling the same patient population as the EVEREST II HRR and designed to continue to collect safety and effectiveness data and allow patients continued access to the MitraClip during review of the PMA application.

15.4 COAPT (Cardiovascular Outcomes Assessment of the MitraClip™Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation)

The COAPT Trial was a prospective, randomized (1:1; MitraClip + GDMT vs. GDMT alone), open-label, multicenter investigational study intended to demonstrate: (1) MitraClip was safe in subjects with secondary MR, and (2) MitraClip could reduce recurrent HF hospitalization as compared to the GDMT Control group. The randomization was further stratified by study site and by cardiomyopathy etiology (e.g., ischemic or non-ischemic). The planned sample size of the trial was 760, including 150 roll-in subjects.

16.0 CLINICAL RESULTS IN PROHIBITIVE RISK PRIMARY MR PATIENTS

Data on 127 patients with significant symptomatic mitral regurgitation due to primary abnormality of the mitral apparatus (primary mitral regurgitation) determined to be at prohibitive risk for mitral valve surgery (Prohibitive Risk primary MR Cohort or PR primary MR Cohort) that were collected from the EVEREST II HRR and REALISM HR studies are provided in detail below. The analysis cohort of 127 subjects was developed post-hoc; this severely limits the statistical interpretability of reported data. These data were determined to adequately establish the safety, effectiveness, and positive benefit-risk profile of the MitraClip for the indicated population (PR primary MR) and are the basis for PMA approval. The totality of evidence demonstrates reasonable assurance of safety and effectiveness of MitraClip to reduce MR and provide patient benefit in this discreet and specific patient population.

Prohibitive Risk primary MR patients treated with the MitraClip were elderly with a high rate of serious comorbidities (Table 16.1).

Table 16.1: Prohibitive Risk Primary MR MitraClip Cohort – Key Baseline Characteristics

Baseline Characteristic[a]	Prohibitive Risk Primary MR MitraClip Patients % (n/N) (N = 127)
Age (years), Mean±SD (N)	82.4±8.7 (127)
Patients over 75 years of age	83.5% (106/127)
Female Gender	44.9% (57/127)
Body Mass Index (kg/m^2), Mean±SD (N)	25.0±5.7 (127)
Coronary Artery Disease	72.8% (91/125)
Prior Myocardial Infarction	24.4% (31/127)
Atrial Fibrillation History	70.5% (86/122)
Prior Stroke	10.2% (13/127)
Diabetes	29.9% (38/127)
Moderate to Severe Renal Disease	28.3% (36/127)
Cardiomyopathy	23.6% (30/127)
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O2)	31.5% (40/127)
Hypertension	88.2% (112/127)
Previous Cardiovascular Surgery	48.0% (61/127)
Previous Percutaneous Coronary Intervention	33.3% (42/126)
NYHA Functional Class III/IV Heart Failure	86.6% (110/127)
LV Ejection Fraction (%), Mean±SD (N)	60.6±9.5 (112)
LV Internal Diameter, systole (cm), Mean±SD (N)	3.4±0.8 (113)
STS Mortality Risk (determined at enrollment for replacement)[b], Mean±SD (N)	13.6±7.9 (127)

[a] Sample sizes or denominators smaller than the N reported for the group reflect missing data.
[b] STS replacement score calculated using the version of the calculator at the time of enrollment.

The mean Procedure Time, defined as the start time of the transseptal procedure to the time the Steerable Guide Catheter is removed, was approximately 2.5 hours (Table 16.2). Device time, defined as the time of insertion of the Steerable Guide Catheter to the time the MitraClip Delivery Catheter is retracted into the Steerable Guide Catheter, averaged 125 minutes. The mean fluoroscopy duration was 46 minutes. Fluoroscopy time was a relatively short proportion of the overall Procedure Time (29%). There were no intra-procedural deaths.

Table 16.2: Prohibitive Risk Primary MR MitraClip Cohort - Procedural Results

Procedural Result [a]	Mean±SD (N) Median (Min, Max)[a]
Procedure Time[b] (min)	157±81 (124) 134 (39, 524)
Device Time[c] (min)	125±75 (124) 110 (9, 511)
Fluoroscopy Duration (min)	46±26 (126) 39 (3, 167)

[a] Sample sizes or denominators smaller than 127 reflect missing data.
[b] Procedure time is measured from the time the transseptal procedure starts until the time the Steerable Guide Catheter is removed.
[c] Device time is measured from the time the Steerable Guide Catheter is placed in the intra-atrial septum until the time the MitraClip Delivery System is retracted into the Steerable Guide Catheter.

The MitraClip device was implanted successfully in a majority (95.3%) of patients (Table 16.3).

Table 16.3: Prohibitive Risk MitraClip Primary MR Cohort – Number of MitraClip Devices Implanted

# Devices Implanted	% (n/N)
0	4.7% (6/127)
1	44.1% (56/127)
2	51.2% (65/127)

Procedural mortality rate was 6.3%, which was less than both the mean and median predicted STS mortality risk using either the repair or replacement calculator.

Table 16.4: Prohibitive Risk Primary MR MitraClip Cohort - Procedural Mortality

Observed Procedural Mortality, % (n/N)	6.3% (8/127)
95% CI[a,c]	(2.8%, 12.0%)
STS v2.73 Replacement Risk Score	
Mean (95% CI[b,c])	13.2% (11.9%, 14.5%)
Median (95% CI[b,c])	12.4% (11.3%, 13.7%)
STS v2.73 Repair Risk Score	
Mean (95% CI[b,c])	9.5% (8.5%, 10.6%)
Median (95% CI[b,c])	8.5% (7.6%, 9.3%)

[a] Based on Clopper-Pearson method.
[b] CI for mean is calculated based on two-sample t-distribution and CI for median is based on non-parametric methods.
[c] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

At 12 months, MAEs occurred at a rate of 35.4% among Prohibitive Risk primary MR MitraClip patients, with deaths (23.6%) and transfusions (19.7%) comprising the majority of events. The rate of stroke was 2.4% and rate of non-elective cardiovascular surgery was 0.8% at 12 months.

Table 16.5: Prohibitive Risk Primary MR MitraClip Cohort - CEC Adjudicated Major Adverse Events at 30 Days and 12 Months

Description of Event	Prohibitive Risk Primary MR MitraClip Patients (N = 127)	
	30 days % (n/N)	12 Months % (n/N)
Death	6.3% (8/127)	23.6% (30/127)
Myocardial infarction	0.8% (1/127)	0.8% (1/127)
Re-operation for failed surgical repair or replacement	0	0
Non-elective cardiovascular surgery for adverse events	0.8% (1/127)	0.8% (1/127)
Stroke	2.4% (3/127)	2.4% (3/127)
Renal Failure	1.6% (2/127)	3.9% (5/127)
Deep wound infection	0	0.0% (0/127)
Ventilation > 48 hours	3.1% (4/127)	4.7% (6/127)
GI complication requiring surgery	0.8% (1/127)	2.4% (3/127)
New onset of permanent AF	0	0.0% (0/127)
Septicemia	0	4.7% (6/127)
Transfusion ≥ 2 units	12.6% (16/127)	19.7% (25/127)
Total[a]	**18.9% (24/127)**	**35.4% (45/127)**
Total[a] (Excluding Transfusions ≥ 2 units)	**9.4% (12/127)**	**26.0% (33/127)**

[a] Total number of patients may not equal the sum of patients in each row since one patient may experience multiple events.

Other secondary safety endpoints occurred at a relatively low rate, consistent with access to the mitral valve achieved via the femoral vein and inferior vena cava. Major vascular complications occurred in 5.5% of patients at 30 days and in 7.1% of patients at 12 months. Major bleeding complications, defined as procedure-related bleeding requiring transfusions of at least 2 units or surgery, occurred at a rate of 12.6% at 30 days. The majority of bleeding events required transfusions rather than surgery. Bleeding events that occurred after 30 days were unrelated to the MitraClip procedure. Clinically significant atrial septal defect requiring treatment occurred at a rate of 2.4% at 12 months. A low rate (2.4%) of mitral stenosis was observed at 12 months, with a total of 3 patients reported to have experienced mitral stenosis defined as Echocardiography Core Laboratory assessed mitral valve area less than 1.5 cm^2 through 12 months. The site did not report mitral stenosis for these patients and none of these patients underwent mitral valve surgery for stenosis.

Table 16.6: Prohibitive Risk Primary MR Cohort - Other Secondary Safety Events at 30 Days and 12 Months

Description of Event	30 Days % (n/N)	12 Months % (n/N)
Major Vascular Complications	5.5% (7/127)	7.1% (9/127)
Major Bleeding Complications	12.6% (16/127)	15.7% (20/127)
Non-Cerebral Thromboembolism	1.6% (2/127)	1.6% (2/127)
New Onset of Persistent Atrial Fibrillation	3.9% (5/127)	3.9% (5/127)
Heart Block/Other Arrhythmia requiring Permanent Pacemaker	0.0% (0/127)	1.6% (2/127)
Endocarditis	0.0% (0/127)	0.0% (0/127)
Thrombosis	0.0% (0/127)	0.0% (0/127)
Hemolysis	0.0% (0/127)	0.0% (0/127)
Atrial Septal Defect	1.6% (2/127)	2.4% (3/127)
Mitral Valve Stenosis	0.0% (0/127)	2.4% (3/127)

The Duke University Medical Center database, which consists of patient-level data with echocardiographic, medical history and follow-up data on a large number of patients with MR ≥ 3+ provides a descriptive comparator for mortality. This database allowed for characterization of survival in patients deemed high risk for surgery and managed non-surgically at the Duke University Medical Center despite clear Class I indications for surgery according to the ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease. Nine hundred and fifty-three (953) patients in the Duke database with 3+ or 4+ MR were identified as too high risk for surgery based on the same high risk criteria as those in the EVEREST II HRR and REALISM studies (i.e. STS mortality risk ≥ 12% or protocol-specified surgical risk factors) and managed non-surgically. This made up the Duke High Risk Cohort, of which 65 patients were identified as primary MR. Table 16.7 shows both groups were comprised of elderly patients, with a majority of patients over the age of 75 years. The Duke High Risk primary MR Cohort reported a lower LVEF at baseline and a higher proportion of female patients than the Prohibitive Risk primary MR Cohort. The Prohibitive Risk primary MR Cohort reported a higher proportion of patients with COPD and NYHA III/IV symptoms at baseline. Both groups had high rates of previous MI, atrial fibrillation and previous cardiovascular surgery.

Figure 16.1 and Table 16.8 display Kaplan-Meier curves comparing survival in the Prohibitive Risk primary MR patients to the Duke High Risk primary MR patients. Based on these Kaplan-Meier curves, mortality in the Prohibitive Risk primary MR Cohort was 6.4% at 30 days and 24.8% at 12 months compared to 10.9% at 30 days and 30.6% at 12 months in the Duke High Risk primary MR patients. While these results are descriptive and limited by differences described above, they suggest that there is no elevated risk of mortality in Prohibitive Risk primary MR patients who undergo the MitraClip procedure over non-surgical management.

Table 16.7: Baseline and Demographic Characteristics – Prohibitive Risk Primary MR and Duke High Risk Primary MR Cohorts

Baseline Characteristic[a]	Prohibitive Risk Primary MR MitraClip Cohort % (n/N) (N = 127)	Duke High Risk Primary MR Medical Therapy Cohort % (n/N) (N = 65)
Age (years), Mean±SD (N)	82.4±8.7 (127)	76.8±11.3 (65)
Patients over 75 years of age	83.5% (106/127)	67.7% (44/65)
Male Gender	55.1% (70/127)	36.9% (24/65)
Body Mass Index (kg/m2), Mean±SD (N)	25.0±5.7 (127)	25.4±5.0(65)
Prior Myocardial Infarction	24.4% (31/127)	33.8% (22/65)
Atrial Fibrillation History	70.5% (86/122)	58.5% (38/65)
Prior Stroke	10.2% (13/127)	18.5% (12/65)
COPD with Home Oxygen	13.4% (17/127)	6.2% (4/65)
Hypertension	88.2% (112/127)	75.4% (49/65)
Diabetes	29.9% (38/127)	36.9% (24/65)
Moderate to Severe Renal Disease	28.3% (36/127)	20.0% (13/65)
Previous Cardiovascular Surgery	48.0% (61/127)	56.9% (37/65)
Previous Percutaneous Coronary Intervention	33.3% (42/126)	58.5% (38/65)
NYHA Functional Class III/IV	86.6% (110/127)	43.8% (28/65)
STS Predicted Mortality Risk	13.2±7.3 (127)	13.3±9.0
LV Ejection Fraction (%), Mean±SD (N)	60.6±9.5 (112)	44.9±11.7 (65)
LV Internal Diameter, systole (cm), Mean±SD (N)	3.4±0.8 (113)	3.4±0.9 (65)

Figure 16.1: Kaplan-Meier Freedom from Mortality – Prohibitive Risk Primary MR MitraClip and Duke High Risk Primary MR Medical Therapy Patients

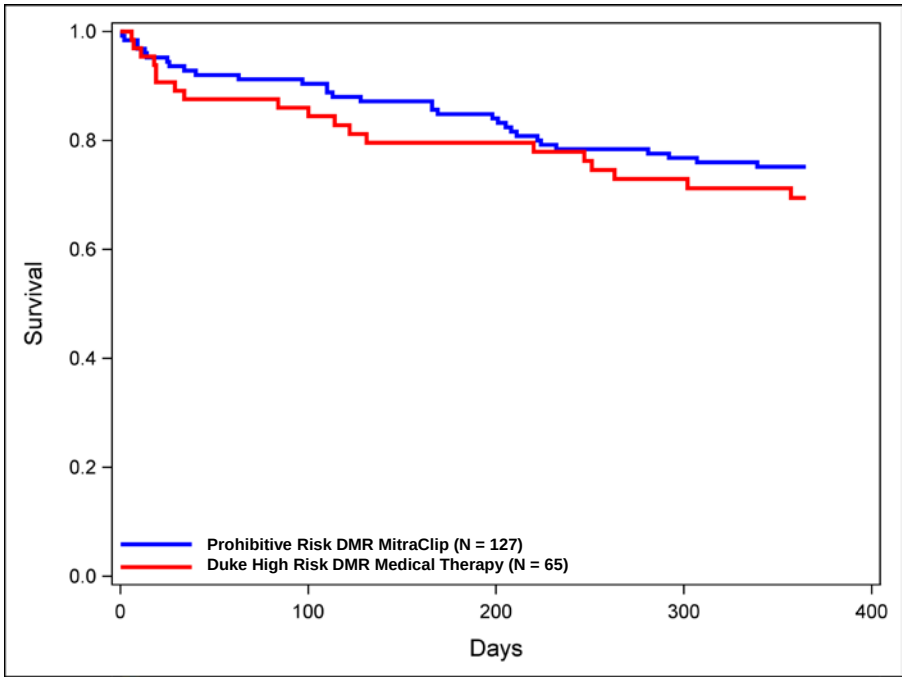


Table 16.8: Number at Risk, Kaplan-Meier Estimates and 95% CIs

Time Post Index Procedure	Baseline	30 Days	6 Months	12 Months
Prohibitive Risk Primary MR MitraClip Patients (N = 127)				
# At Risk	127	117	106	85
# Events	0	8	19	31
% Event Free	100%	93.6%	84.8%	75.2%
95% CI[a]	-	[87.6%, 96.8%]	[77.2%, 90.0%]	[66.1%, 82.1%]
Duke High Risk Primary MR Medical Therapy Patients (N = 65)				
# At Risk	65	57	49	39
# Events	0	7	13	19
% Event Free	100%	89.1%	79.6%	69.4%
95% CI[a]	-	[78.5%, 94.7%]	[67.4%, 87.6%]	[56.3%, 79.3%]

[a] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

MR severity at baseline, discharge and 12 months are presented in Table 16.9 for patients with data available at each follow-up (Completers Analysis). Immediate improvement in MR severity was noted at discharge with 82.1% and 53.7% of surviving patients reporting MR severity ≤ 2+ and ≤ 1+, respectively. This improvement was sustained at 12 months, with the majority (83.3%) of surviving patients reporting MR severity ≤ 2+ and 36.9% reporting MR severity ≤ 1+. At 12 months, freedom from death and MR > 2+ was 61.4% and freedom from death and MR > 1+ was 27.2% patients.

Table 16.9: Prohibitive Risk Primary MR MitraClip Cohort - MR Severity at Baseline and Follow-up
Completers Analysis

MR Severity	Baseline % (n/N)	Discharge[a] % (n/N)	12 Months % (n/N)
0 : None	0	1.6% (2/123)	0
1+: Mild	0	52.0% (64/123)	36.9% (31/84)
2+: Moderate	9.7% (12/124)	28.5% (35/123)	46.4% (39/84)
3+: Moderate-to-severe	58.9% (73/124)	13.0% (16/123)	13.1% (11/84)
4+: Severe	31.5% (39/124)	4.9% (6/123)	3.6% (3/84)
Missing	3	3	13
Death	0	1	30
MR ≤ 2+ in surviving patients	9.7% (12/124)	82.1% (101/123)	83.3% (70/84)
MR ≤ 1+ in surviving patients	0.0% (0/124)	53.7% (66/123)	36.9% (31/84)
Freedom from Death and MR > 2+	9.7% (12/124)	81.5% (101/124)	61.4% (70/114)
Freedom from Death and MR > 1+	0.0% (0/124)	53.2% (66/124)	27.2% (31/114)

[a] 30-day MR severity was used if discharge MR was unavailable.

Reduced preload as a result of the reduction in MR severity achieved with the MitraClip device resulted in reverse left ventricular remodeling (Table 16.10), characterized largely by a clinically important decrease in diastolic volume (-16.6 ml) and dimension (-0.2 cm).

TABLE 16.10: PROHIBITIVE RISK Primary MR MITRACLIP COHORT – LV Measurements at Baseline and 12 Months Patients with Paired Data[a]

LV Measurement	N	Baseline	12-month	Difference (12-month - Baseline)	%Change (12-month - Baseline)
LVEDV, ml					
Mean±SD	69	125.1±40.1	108.5±37.9	-16.6±22.9	-11.5±17.9
Median		119.7	104.7	-12.3	-10.2
95% CI[b,c]				(-22.1, -11.1)	(-15.9, -7.2)
LVIDd, cm					
Mean±SD	80	5.0±0.6	4.8±0.6	-0.2±0.4	-3.7±8.2
Median		5.1	4.9	-0.2	-4.0
95% CI[b,c]				(-0.3, -0.1)	(-5.6, -1.9)
LVESV, ml					
Mean±SD	69	49.1±24.5	46.1±21.4	-3.0±13.7	-1.3±27.0
Median		45.7	41.0	-1.5	-2.7
95% CI[b,c]				(-6.3, 0.3)	(-7.7, 5.2)
LVIDs, cm					
Mean±SD	75	3.4±0.7	3.3±0.7	-0.1±0.5	-0.2±16.4
Median		3.2	3.3	-0.1	-2.3
95% CI[b,c]				(-0.2, 0.1)	(-4.0, 3.6)

[a] Only patients who had a measurement at both Baseline and 12 months are included.
[b] 95% CI is based on a t-distribution.
[c] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

Improvement in LV function resulted in improvements in heart failure symptoms. NYHA Functional Class at baseline and follow-up are presented in Table 16.11 for patients with data available at each follow-up (Completers Analysis). Immediate improvement in NYHA Class was noted at 30 days with 82.3% of surviving patients reporting NYHA Class I or II symptoms. This improvement was sustained at 12 months, with the majority (86.9%) of surviving patients reporting NYHA Class I or II symptoms. At 12 months, freedom from death and NYHA Class III or IV symptoms was 64.0%. This improvement in NYHA Class symptoms is clinically important given that the majority of these patients (86.6%) were enrolled with NYHA Class III or IV symptoms.

Table 16.11: Prohibitive Risk Primary MR MitraClip Cohort - NYHA Functional Class at Baseline and Follow-up Completers Analysis

NYHA Functional Class	Baseline % (n/N)	30 Days % (n/N)	12 Months % (n/N)
I	2.4% (3/127)	33.6% (38/113)	40.5% (34/84)
II	11.0% (14/127)	48.7% (55/113)	46.4% (39/84)
III	63.8% (81/127)	15.9% (18/113)	10.7% (9/84)
IV	22.8% (29/127)	1.8% (2/113)	2.4% (2/84)
Missing	0	5	13
Death	0	9	30
NYHA I/II in surviving patients	13.4% (17/127)	82.3% (93/113)	86.9% (73/84)
Freedom from Death and NYHA Class III/IV	13.4% (17/127)	76.2% (93/122)	64.0% (73/114)

Table 16.12 shows the change in NYHA Class at 12 months from baseline. The table shows that 73 of 83 (88%) surviving patients improved by at least 1 class, and 30 of 83 (36.1%) surviving patients improved by at least 2 classes. Inclusion of deaths in the denominator results in 64.6% of patients alive and improved by at least 1 class and 26.5% alive and improved by at least 2 classes.

Table 16.12: Prohibitive Risk Primary MR MitraClip Cohort – Change in NYHA Class at 12 Months from Baseline

NYHA Class Change	Number of Patients
3 Class Improvement	4
2 Class Improvement	26
1 Class Improvement	43
No Change	9
1 Class Worsening	2
Death	30
Missing	13

Table 16.13 shows a mean change of +6.0 points in the Physical Component Summary (PCS) score and +5.6 points in the Mental Component Summary (MCS) score from baseline to 12 months after the MitraClip procedure. These changes are well above the 2-3 point minimally important difference (MID) threshold reported in the literature.

Table 16.13: Prohibitive Risk Primary MR MitraClip Cohort – SF-36 Quality of Life at Baseline and 12 Months Completers Analysis[a]

Component	N	Baseline	12-month	Difference (12-month - Baseline)
Physical Component Summary Score				
Mean±SD	73	33.4±8.6	39.4±10.5	6.0±8.6
Median		32.4	40.7	5.6
95% CI [b,c]				(4.0, 8.0)
Mental Component Summary Score				
Mean±SD	73	46.6±13.4	52.2±10.2	5.6±14.0
Median		49.8	54.0	3.2
95% CI [b,c]				(2.3, 8.9)

[a] Only patients who had a measurement at both Baseline and 12 months are included.
[b] 95% CI is based on a t-distribution.
[c] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

The proportion of responders for both the PCS and MCS scores are shown in Table 16.14 based on distribution-based methods recommended by the SF-36 authors (Significant Change Criteria, SCC) and the Standard Error of Measurement (SEM) method suggested by the FDA in its 2009 PRO Guidance. The proportion of responders was 63-68% for PCS and 49-53% for MCS.

Table 16.14: Prohibitive Risk Primary MR MitraClip Cohort – SF-36 QOL Responder Rate

Component	Minimally Important Difference	Completers Analysis
Physical Component Summary Score	SCC[a] (3.1)	63.0% (46/73)
	SEM[b] (2.2)	68.5% (50/73)
Mental Component Summary Score	SCC[a] (3.8)	49.3% (36/73)
	SEM[b] (2.7)	53.4% (39/73)

[a] SCC (Significant Change Criteria): Significant change assuming baseline-follow-up correlation of .4 and using a 80% CI.
[b] SEM (Standard Error of Measurement): One SEM equals 68% CI.

A clinically important decrease in the rate of hospitalization for heart failure was observed following discharge from the MitraClip procedure (0.67 to 0.18 per patient-year, a 73% reduction, Table 16.15) between the pre-enrollment and the post-discharge 12-month periods.

Table 16.15: Prohibitive Risk Primary MR MitraClip Cohort - Heart Failure Hospitalizations

	12 months Pre-enrollment	Post-discharge through 12 months
# Patients for Analysis	127	120
# Patients with Events	48	13
# Events	85	17
Follow-up (Patient-Years)	127	97
Rate[a]	0.67	0.18
(95% Two-sided CI [a,b])	(0.54, 0.83)	(0.11, 0.28)
# days hospitalized (Mean±SD)	6.0±4.5	5.9±3.8

[a] CI is obtained from a Poisson regression model.
[b] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

Effectiveness results demonstrate that 82.1% (101/123) of completers experienced MR reduction from 3+ or 4+ to 2+ or less at discharge following the MitraClip procedure (Table 16.16). Reduction of MR at 12 months was sustained to ≤ 2+ in 83.3% (70/84), and to ≤ 1+ in 36.9% (31/84) of patients for whom echocardiographic data was available. Reduction in MR severity was associated with reverse left ventricular remodeling characterized largely by clinically important decreases in diastolic volume and dimension.

Patients also experienced clinically important improvement in NYHA Functional Class at 12 months; more than 80% of patients experienced NYHA Class III or Class IV symptoms at baseline, which reduced to less than 15% at 12 months. Despite the elderly and highly co-morbid nature of the population, quality of life as measured by the SF-36 quality of life physical and mental component scores showed clinically important improvement. Sensitivity analyses showed that these effectiveness results are robust to missing data. Finally, heart failure hospitalizations showed clinically important reduction in the 12 months post-MitraClip procedure from the 12 months pre-MitraClip procedure, including in a sensitivity analysis where death is included in the analysis as a heart failure hospitalization.

Table 16.16: Effectiveness in Prohibitive Risk Primary MR MitraClip Cohort

Effectiveness Measure[§]	Prohibitive Risk DMR MitraClip Cohort (N=127)
Improvement in LVEDV at 1 year	-17±23
Improvement in LVESV at 1 year	-3±14
Improvement in SF-36 PCS at 1 year	6.0±8.6
Improvement in SF-36 MCS at 1 year	5.6±14.0
NYHA Class III or IV: Baseline → 1 year	85% → 13%

[§] LVEDV, LVESV, SF-36 PCS and MCS results are in patients with paired data, and NYHA Class results are in Completers.

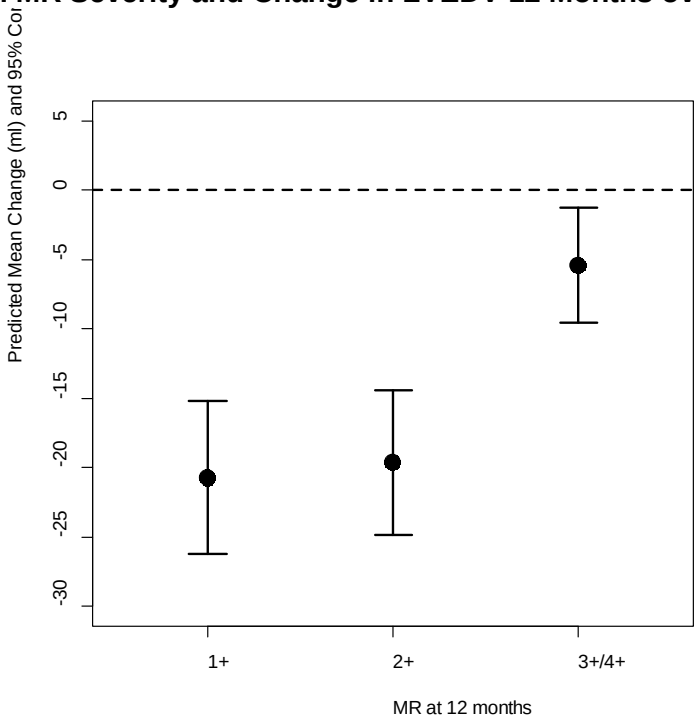
Reduction in MR severity was assessed in patients who have 2-year follow-up available. Table 16.17 shows that MR reduction in surviving patients to ≤ 2+ and ≤ 1+ is 82.5% (33/40) and 35.0%, (14/40) respectively, at 2 years. Therefore, there is no evidence of deterioration of MR severity from 12 months to 2 years in surviving patients.

Table 16.17: Prohibitive Risk Primary MR MitraClip Cohort - Durability of MR Reduction

MR Severity	Baseline % (n/N)	12 Months % (n/N)	2 Years % (n/N)
0 : None	0	0	0
1+: Mild	0	36.9% (31/84)	35.0% (14/40)
2+: Moderate	9.7% (12/124)	46.4% (39/84)	47.5% (19/40)
3+: Moderate-to-severe	58.9% (73/124)	13.1% (11/84)	15.0% (6/40)
4+: Severe	31.5% (39/124)	3.6% (3/84)	2.5% (1/40)
MR ≤ 2+ in surviving patients	9.7% (12/124)	83.3% (70/84)	82.5% (33/40)
MR ≤ 1+ in surviving patients	0.0% (0/124)	36.9% (31/84)	35.0% (14/40)

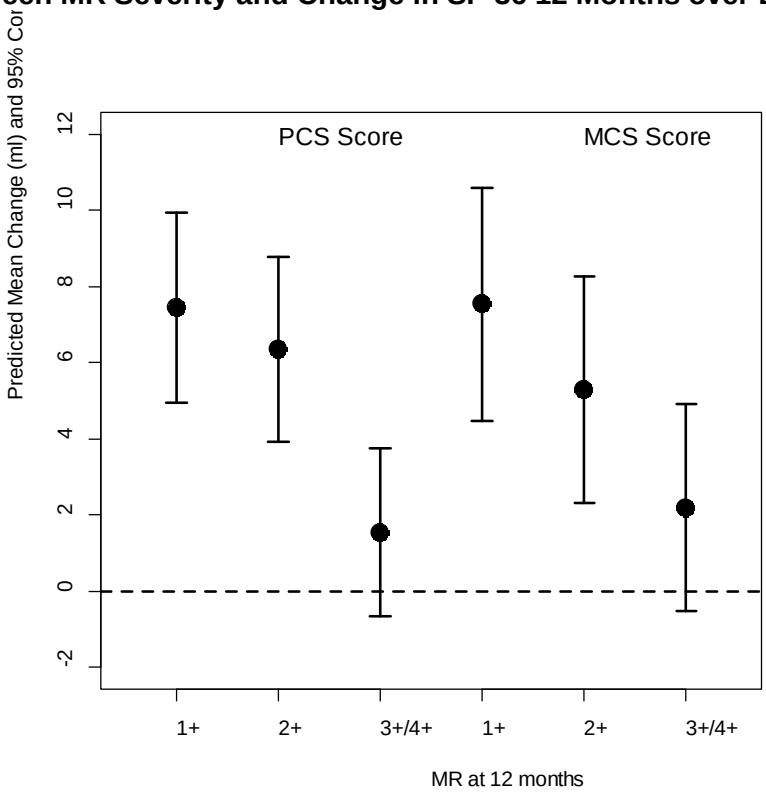
In order to evaluate the relationship between MR severity and measures of effectiveness, statistical models were fit to the effectiveness data. MR severity was importantly associated with LVEDV in the Prohibitive Risk primary MR MitraClip patients (Figure 16.2). Reduction of MR severity to ≤ 2+ at 12 months resulted in clinically important decreases in LVEDV. No clinically important difference in LVEDV reduction is observed between MR 1+ and 2+. Reduction of MR to 2+ or less is associated with a decrease in left ventricular size that is not observed with ongoing MR of 3+ or greater.

Figure 16.2: Prohibitive Risk Primary MR MitraClip Cohort - Dose-Response Relationship between MR Severity and Change in LVEDV 12 Months over Baseline



MR severity was importantly associated with PCS and MCS scores in Prohibitive Risk primary MR MitraClip patients. Reduction of MR severity to ≤ 2+ at 12 months resulted in clinically important improvement in PCS and MCS scores. When MR severity remained 3+/4+, the changes in PCS and MCS scores were small and not clinically important (Figure 16.3). Reduction of MR to 2+ or less is thus associated with an improvement in quality of life that is not observed with ongoing MR of 3+ or greater.

Figure 16.3: Prohibitive Risk Primary MR MitraClip Cohort - Dose-Response Relationship between MR Severity and Change in SF-36 12 Months over Baseline



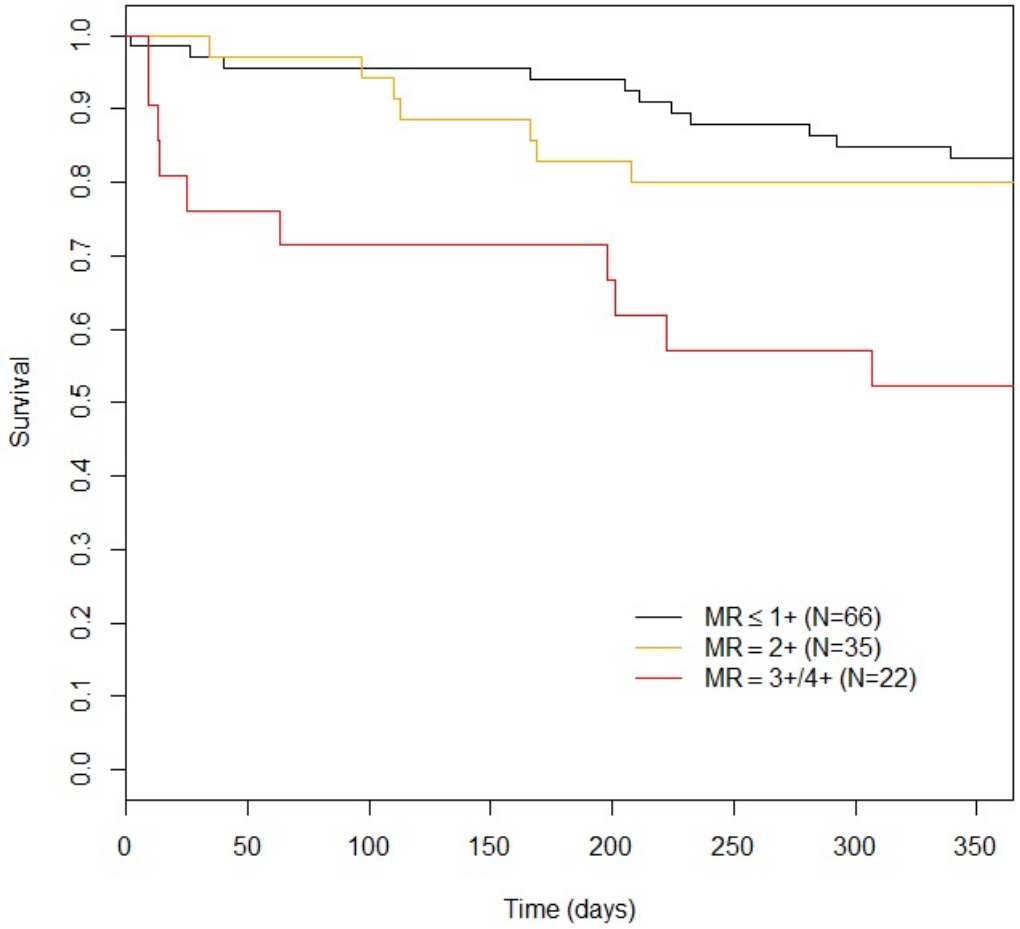
The observed number and corresponding estimated proportions of NYHA Classes at 12 months by two discharge MR groups are summarized in Table 16.18. The results demonstrate that reduction of MR to 2+ or less at discharge is associated with improved NYHA Functional Class that is not observed with MR of 3+ or greater at discharge.

Table 16.18: Prohibitive Risk Primary MR MitraClip Cohort – Summary of Binary NYHA Functional Class Data By Discharge MR Severity

Discharge MR	NYHA Functional Class at 12 Months	
	I/II	III/IV/Death
≤ 2+	66/93 (0.710)	27/93 (0.290)
3+/4+	7/19 (0.368)	12/19 (0.632)

Kaplan-Meier survival curves are plotted by discharge MR severity (Figure 16.4). There was no clinically important difference between the "≤1+" discharge MR group and the "2+" discharge MR group; however, there was a clinically important difference between the "≤1+" discharge MR group and the "3+/4+" discharge MR group and between the "2+" discharge MR group and the "3+/4+" discharge MR group. Reduction of MR to 2+ or less is associated with decreased mortality compared to ongoing MR of 3+ or greater.

Figure 16.4: Prohibitive Risk Primary MR MitraClip Cohort - Kaplan-Meier Survival Curves by Discharge MR Severity (≤1+, 2+, 3+/4+)



17.0 SUMMARY OF THE COAPT RESULTS

A. Study Design

Patients were enrolled between December 27, 2012, and June 23, 2017. The database for this Panel Track Supplement reflected data collected through August 3, 2018, and included 614 randomized patients. There were 78 investigational sites.

The COAPT Trial was a prospective, randomized (1:1; MitraClip + GDMT vs. GDMT alone), open-label, multicenter investigational study intended to demonstrate: (1) MitraClip was safe

in subjects with secondary MR, and (2) MitraClip could reduce recurrent HF hospitalization as compared to the GDMT Control group. The randomization was further stratified by study site and by cardiomyopathy etiology (e.g., ischemic or non-ischemic). The planned sample size of the trial was 760, including 150 roll-in subjects.

The COAPT Trial was conducted under the oversight of several independent committees, including: (1) a Steering Committee, which provided scientific and medical input on trial design, data collection, data analyses, and interpretation of results; (2) an independent Eligibility Committee, which confirmed that each subject was on optimal therapy including GDMT prior to being considered for the trial and that the subject was not appropriate for mitral valve surgery, even if randomized to the Control group; (3) a Central Echocardiography Core Laboratory (ECL), which was responsible for reviewing subject's screening echocardiography images to determine if the subject met the MR severity eligibility criterion prior to the subject being considered eligible for the trial, and for assessing MR severity and left ventricular measurements, along with other measures, at baseline and follow-ups; (4) a Clinical Events Committee (CEC), which adjudicated all adverse events per pre-established definitions (blinding was maintained whenever feasible); (5) a Data Monitoring Committee (DMC), which monitored the safety of subjects throughout trial; and (6) a Contract Research Organization, which participated in source data verification.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the COAPT Trial was limited to patients who met the following inclusion criteria:

   - Symptomatic functional MR (≥ 3+) due to cardiomyopathy of either ischemic or non-ischemic etiology determined by assessment of a qualifying transthoracic echocardiogram (TTE) obtained within 90 days and transesophageal echocardiogram (TEE) obtained within 180 days prior to subject registration, with MR severity based principally on the TTE study, confirmed by the ECL. The ECL may request a transesophageal echocardiogram (TEE) to confirm MR etiology.
   - In the judgment of the HF specialist investigator at the site, the subject has been adequately treated per applicable standards, including for coronary artery disease, left ventricular dysfunction, mitral regurgitation and HF (e.g., with CRT, revascularization, and/or GDMT. The Eligibility Committee must concur that the subject has been adequately treated.
   - New York Heart Association (NYHA) Functional Class II, III or ambulatory IV.
   - The Local Site Heart Team (cardiothoracic surgeon and HF specialist investigators) and the Central Eligibility Committee concur that surgery will not be offered as a treatment option and that medical therapy was the intended therapy for the subject, even if the subject was randomized to the Control group.
   - Left Ventricular Ejection Fraction (LVEF) was ≥20% and ≤50% within 90 days prior to subject registration, assessed by the site using any one of the following methods: echocardiography, contrast left ventriculography, gated blood pool scan or cardiac magnetic resonance imaging (MRI).
   - Left Ventricular End Systolic Dimension (LVESD) was ≤70 mm assessed by site based on a TTE obtained within 90 days prior to subject registration.
   - The primary regurgitant jet was non-commissural, and in the opinion of the MitraClip implanting investigator can successfully be treated by the MitraClip. If a secondary jet exists, it must be considered clinically insignificant.

- Creatine Kinase-MB (CK-MB) obtained within prior 14 days < local laboratory ULN (Upper Limit of Normal).
- Transseptal catheterization and femoral vein access was determined to be feasible by the MitraClip implanting investigator.
- Age 18 years or older.
- The subject or the subject's legal representative understands and agrees that should he/she be assigned to the Control group, he/she will be treated with medical therapy and conservative management without surgery and without the MitraClip, either domestically or abroad. If the subject would actively contemplate surgery and/or MitraClip if randomized to Control, he/she should not be registered in this trial.
- The subject or the subject's legal representative has been informed of the nature of the trial and agrees to its provisions, including the possibility of randomization to the Control group and returning for all required post-procedure follow-up visits, and has provided written informed consent.

Patients were not permitted to enroll in the COAPT Trial if they met any of the following clinical or anatomical exclusion criteria:

- Chronic Obstructive Pulmonary Disease (COPD) requiring continuous home oxygen therapy or chronic outpatient oral steroid use.
- Untreated clinically significant coronary artery disease requiring revascularization.
- Coronary artery bypass grafting (CABG) within 30 days prior to subject registration.
- Percutaneous coronary intervention within 30 days prior to subject registration.
- Transcatheter aortic valve replacement (TAVR) within 30 days prior to subject registration.
- Tricuspid valve disease requiring surgery.
- Aortic valve disease requiring surgery or transcatheter intervention.
- Cerebrovascular accident within 30 days prior to subject registration.
- Severe symptomatic carotid stenosis (> 70% by ultrasound).
- Carotid surgery or stenting within 30 days prior to subject registration.
- American College of Cardiology (ACC)/American Heart Association (AHA) Stage D heart failure.
- Presence of any of the following:
  - Estimated pulmonary artery systolic pressure (PASP) > 70 mm Hg assessed by site based on echocardiography or right heart catheterization, unless active vasodilator therapy in the catheterization laboratory was able to reduce the pulmonary vascular resistance (PVR) to < 3 Wood Units or between 3 and 4.5 Wood Units with v wave less than twice the mean of the pulmonary capillary wedge pressure
  - Hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology
  - Infiltrative cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis)
  - Hemodynamic instability requiring inotropic support or mechanical heart assistance
- Physical evidence of right-sided congestive heart failure with echocardiographic evidence of moderate or severe right ventricular dysfunction, as assessed by site.
- Implant of any CRT or CRT with cardioverter-defibrillator (CRT-D) within the last 30 days prior to subject registration.

- Mitral valve orifice area < 4.0 cm^2 assessed by site based on a TTE within 90 days prior to subject registration.
- Leaflet anatomy which may preclude MitraClip implantation, proper MitraClip positioning on the leaflets or sufficient reduction in MR by the MitraClip. This evaluation was based on TEE evaluation of the mitral valve within 180 days prior to subject registration and includes:
  - Insufficient mobile leaflet available for grasping with the MitraClip device
  - Evidence of calcification in the grasping area
  - Presence of a significant cleft in the grasping area
  - Lack of both primary and secondary chordal support in the grasping area
  - Leaflet mobility length < 1 cm
- Hemodynamic instability defined as systolic pressure < 90 mmHg with or without afterload reduction, cardiogenic shock or the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device.
- Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months.
- Life expectancy < 12 months due to non-cardiac conditions.
- Modified Rankin Scale (MRS) ≥ 4 disability.
- Status 1 heart transplant or prior orthotopic heart transplantation.
- Prior mitral valve leaflet surgery or any currently implanted prosthetic mitral valve, or any prior transcatheter mitral valve procedure.
- Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
- Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e., noncompliant, perforated).
- Active infections requiring current antibiotic therapy.
- Subjects in whom TEE was contraindicated or high risk.
- Known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically.
- Pregnant or planning pregnancy within next 12 months.
- Currently participating in an investigational drug or another device study that has not reached its primary endpoint. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
- Subject belongs to a vulnerable population per investigator's judgment or subject has any kind of disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures.

2. Follow-up Schedule

   All patients were scheduled for follow-up examinations at 1 week (phone contact), 30 days, 6 months, 12 months, 18 months, 24 months, and annually thereafter through 5 years. Preoperative and post-operative assessments included physical assessment and patient interview, laboratory measurements, imaging tests, and health status/quality of life (QoL) questionnaire. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

Primary Safety Endpoint:

The primary safety endpoint was a composite of SLDA, device embolizations, endocarditis requiring surgery, ECL confirmed mitral stenosis requiring surgery, left ventricular assist device (LVAD) implant, heart transplant, and any device related complications requiring non-elective cardiovascular surgery at 12 months. The proportion of subjects free from the primary safety endpoint events was tested against a pre-specified performance goal (PG) of 88% for the Safety Analysis population, as defined in Section X.B.

Primary Effectiveness Endpoint:

The primary effectiveness endpoint was recurrent HF hospitalizations through 24 months, with the following null and alternative hypotheses:

$$H_0: RRR \leq 0$$
$$H_A: RRR > 0$$

where *RRR* is the relative risk reduction in the rate of recurrent HF hospitalization due to treatment with the MitraClip device as compared to the Control group. The primary effectiveness endpoint was analyzed when the last subject completed 12 months of follow-up. Hypothesis testing was performed using the Joint Frailty Model to adjust for the competing risk of death.[1-3]

Secondary Endpoints:

An ordered list of powered secondary endpoints, as shown in Table 17.1, was included in a hierarchical testing scheme, which were carried out after both the primary safety and effectiveness endpoints were met.

Table 17.1: Ordered List of Secondary Endpoints for Hierarchical Testing

Order	Secondary Endpoint	Alternative Hypothesis
#1	Proportion of MR severity ≤ 2+ at 12 months	$H_A: P_D - P_C \neq 0$
#2	All-cause mortality at 12 months	$H_A: HR < 1.5$
#3	Hierarchical composite of all-cause mortality and recurrent HF hospitalization (analyzed when the last subject completes 12 months of follow-up)	H_A: Either rate of death or rate of recurrent HF hospitalization is lower in the Device group compared to the Control group.
#4	Change in quality of life (QoL) at 12 months from baseline, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ)	$H_A: \mu_D - \mu_C \neq 0$
#5	Change in distance walked on the 6 Minute Walk Test (6MWT distance or 6MWD) at 12 months over baseline	$H_A: \mu_D - \mu_C \neq 0$
#6	Recurrent hospitalizations - all-cause (analyzed when the last subject completes 12 months of follow-up)	$H_A: RRR \neq 0$
#7	Proportion of New York Heart Association (NYHA) Functional Class I/II at 12 months	$H_A: P_D - P_C \neq 0$

Order	Secondary Endpoint	Alternative Hypothesis
#8	Change in Left Ventricular End Diastolic Volume (LVEDV) at 12 months over baseline	$H_A: \mu_D - \mu_C \neq 0$
#9	All-cause mortality at 24 months	$H_A: HR \neq 1$
#10	Freedom from all-cause mortality, stroke, myocardial infarction, or non-elective cardiovascular surgery for device related complications in the MitraClip group at 30 days	$H_A: P_D(30) > 0.80$
P: proportion; *μ*: mean. *HR*: hazard ratio; *RRR*: relative risk reduction. Subscript D: Device; Subscript C: Control.		

B. Accountability of PMA Cohort

At the time of database lock, a total of 614 subjects were randomized in this trial, including 302 Device subjects and 312 Control subjects.

There were four different analysis populations defined in the protocol: Intention-to-Treat (ITT) population, Per Protocol (PP) population, As Treated (AT) population, and Safety Analysis (SA) population, as summarized in Table 17.2 and Figure 17.1. The primary analysis for safety was the Safety Analysis, and that for effectiveness was the ITT analysis.

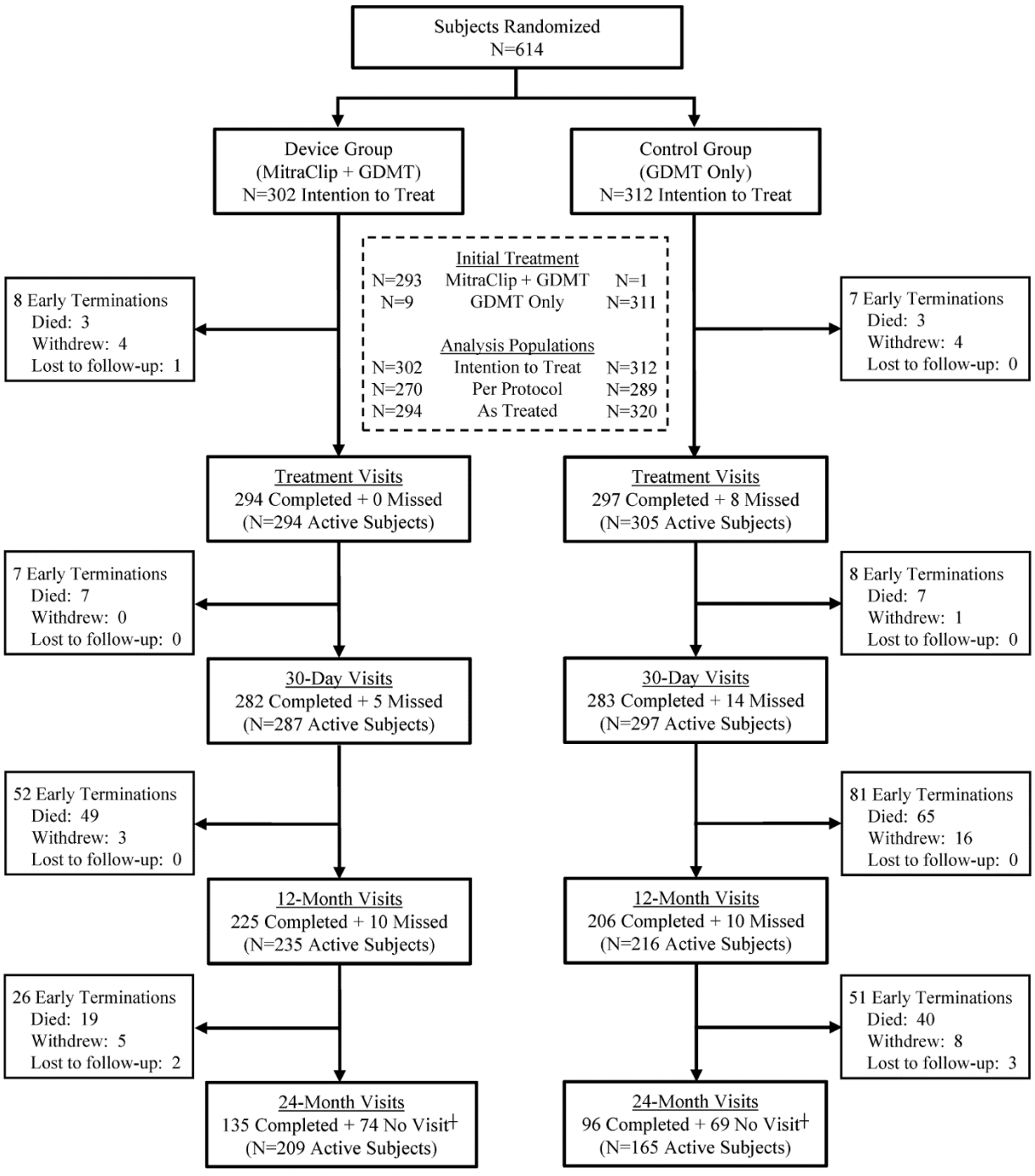
Table 17.2: Analysis Populations

Analysis Population	Definition	Number of Patients	
		Device	Control
Intention-to-Treat (ITT)	All randomized subjects	302	312
As Treated (AT)	Randomized subjects who received the treatment as randomized	294	320
Per Protocol (PP)	Subjects who met major inclusion and none of the major exclusion criteria and received the treatment as randomized	270	289
Safety Analysis (SA)	All ITT subjects in the Device group with an attempted implant procedure*	293	
*Attempted implant procedure is defined as administration of anesthesia for the MitraClip procedure.			

C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics of the study population are typical for an HF study performed in the U.S., as shown in Table 17.3. The two study groups were well-balanced, with no significant difference in patient demographics and baseline characteristics.

Figure 17.1: Disposition of COAPT Randomized Subjects



†Denotes visits that were expected from, missed by or not due from subjects active in the study at the time of the data cut-off.

Table 17.3: Patient Demographics and Baseline Characteristics (ITT Population)

Demographics and Baseline Characteristics	Summary Statistics*		P-Value†
	Device (N=302)	Control (N=312)	
Age at Registration (year)	71.7 ± 11.8 (302)	72.8 ± 10.5 (312)	0.2186
Male	66.6% (201/302)	61.5% (192/312)	0.1953
Race/Ethnicity			
White or Caucasian	74.5% (225/302)	74.4% (232/312)	0.9673
Non-white	25.5% (77/302)	25.6% (80/312)	
Height (cm)	170.8 ± 10.4 (301)	169.9 ± 10.8 (306)	0.2500
Weight (kg)	78.8 ± 17.2 (301)	78.4 ± 20.1 (307)	0.8002
Body Mass Index (kg/m^2)	27.0 ± 5.8 (300)	27.1 ± 5.9 (305)	0.9880
Serum Creatinine (mg/dL)	1.8 ± 1.2 (300)	1.8 ± 1.4 (306)	0.8362
Creatinine Clearance (mL/min)	50.9 ± 28.5 (299)	47.8 ± 25.0 (302)	0.1552
Creatinine Clearance ≤ 60 mL/min	71.6% (214/299)	75.2% (227/302)	0.3189
BNP (pg/mL)	1014.8 ± 1086.0 (208)	1017.1 ± 1212.8 (209)	0.9833
NT-proBNP (pg/mL)	5174.3 ± 6566.6 (74)	5943.9 ± 8437.6 (85)	0.5194
Elevated BNP or NT-proBNP prior to Enrollment	93.4% (267/286)	93.1% (282/303)	0.8898
Extremely High Risk for MV Surgery	68.6% (205/299)	69.9% (218/312)	0.7258
KCCQ Overall Summary Score	53.2 ± 22.8 (302)	51.6 ± 23.3 (309)	0.3907
Six Minute Walk Test Distance (meters)	249.6 ± 123.8 (296)	234.5 ± 123.5 (305)	0.1359
NYHA Functional Class			
Class I	0.3% (1/302)	0.0% (0/311)	0.4927
Class II	42.7% (129/302)	35.4% (110/311)	0.0623
Class III	51.0% (154/302)	54.0% (168/311)	0.4532
Class IV	6.0% (18/302)	10.6% (33/311)	0.0371
SF-36 Quality of Life Physical Component Score	33.0 ± 9.1 (299)	32.6 ± 10.0 (308)	0.6336
SF-36 Quality of Life Mental Component Score	46.7 ± 12.7 (299)	45.3 ± 13.0 (308)	0.1883
Cardiovascular Event History			
Ischemic Cardiomyopathy	60.9% (184/302)	60.6% (189/312)	0.9292
Non-Ischemic Cardiomyopathy	39.1% (118/302)	39.4% (123/312)	
Prior TIA	8.6% (26/302)	5.4% (17/312)	0.1250
Prior Stroke	12.3% (37/302)	11.2% (35/312)	0.6906
Prior Stroke or TIA	18.5% (56/302)	15.7% (49/312)	0.3505
Prior Myocardial Infarction	51.7% (156/302)	51.3% (160/312)	0.9262

Demographics and Baseline Characteristics	Summary Statistics*		P-Value†
	Device (N=302)	Control (N=312)	
Coronary Artery Disease (CAD)	72.2% (218/302)	73.1% (228/312)	0.8044
Hypertension	80.5% (243/302)	80.4% (251/312)	0.9963
Hypercholesterolemia	55.0% (166/302)	52.2% (163/312)	0.4988
Angina	16.9% (51/302)	23.4% (73/312)	0.0446
Chronic Obstructive Pulmonary Disease	23.5% (71/302)	23.1% (72/312)	0.8990
Arrhythmia Event History	66.6% (201/302)	64.4% (201/312)	0.5783
Ventricular Fibrillation	5.6% (17/302)	8.0% (25/312)	0.2421
Ventricular Flutter	0.0% (0/302)	0.0% (0/312)	1.0000
Ventricular Tachycardia	24.8% (75/302)	22.4% (70/312)	0.4842
Atrial Flutter	10.3% (31/302)	10.9% (34/312)	0.7990
Atrial Fibrillation	55.6% (168/302)	51.0% (159/312)	0.2465
Atrial Fibrillation or Flutter	57.3% (173/302)	53.2% (166/312)	0.3095
Any Hospitalization 12 months prior to enrollment	67.5% (204/302)	65.1% (203/312)	0.5148
Heart Failure	58.3% (176/302)	56.1% (175/312)	0.5838
Other-Cardiovascular	11.6% (35/302)	9.3% (29/312)	0.3523
Non-Cardiovascular	7.9% (24/302)	7.1% (22/312)	0.6734
Co-morbidity			
Diabetes	35.1% (106/302)	39.4% (123/312)	0.2680
Peripheral Vascular Disease	17.2% (52/302)	18.3% (57/312)	0.7334
Renal Disease	57.0% (172/302)	56.7% (177/312)	0.9555
History of Anemia	22.5% (68/302)	24.4% (76/312)	0.5901
History of Major Bleeds or Bleeding Disorder	7.6% (23/302)	7.1% (22/312)	0.7884
STS Replacement Score (%)	7.8 ± 5.5 (302)	8.5 ± 6.2 (312)	0.1565
STS Repair Score (%)	5.6 ± 5.6 (302)	6.0 ± 5.4 (312)	0.3939
Prior Cardiac Interventions			
Coronary Artery Bypass Craft (CABG)	40.1% (121/302)	40.4% (126/312)	0.9359
PTCA/Stents/Atherectomy	43.0% (130/302)	49.0% (153/312)	0.1364
Device Implantation			
None	33.1% (100/302)	33.0% (103/312)	0.9790
ICD	30.1% (91/302)	32.4% (101/312)	0.5496
CRT-P	1.7% (5/302)	1.9% (6/312)	0.8028
CRT-D	36.4% (110/302)	33.0% (103/312)	0.3747
Pacemaker	6.0% (18/302)	8.0% (25/312)	0.3191
Defibrillator (ICD or CRT-D)	62.6% (189/302)	61.5% (192/312)	0.7898

Demographics and Baseline Characteristics	Summary Statistics*		P-Value†
	Device (N=302)	Control (N=312)	
Resynchronization (CRT-D or CRT-P)	38.1% (115/302)	34.9% (109/312)	0.4185
Pacing (CRT-P or Pacemaker)	7.3% (22/302)	9.9% (31/312)	0.2422
Prior Cardiac Valve Interventions			
Aortic Valve Intervention	3.3% (10/302)	4.5% (14/312)	0.4523
Pulmonic Valve Intervention	0.0% (0/302)	0.0% (0/312)	1.0000
Tricuspid Valve Intervention	0.0% (0/302)	0.0% (0/312)	1.0000
Mitral Valve Intervention	0.3% (1/302)	0.0% (0/312)	0.4919
Echocardiographic Core Laboratory Measures			
Mitral regurgitation severity			
3+: Moderate-to-Severe	49.0% (148/302)	55.3% (172/311)	0.1186
4+: Severe	51.0% (154/302)	44.7% (139/311)	
Effective Regurgitant Orifice Area (EROA, cm^2)	0.41 ± 0.15 (289)	0.40 ± 0.15 (302)	0.4203
Left Ventricular Ejection Fraction (LVEF, %)	31.3 ± 9.1 (281)	31.3 ± 9.6 (294)	0.9717
≤ 40 %	82.2% (231/281)	82.0% (241/294)	0.9418
Left Ventricular End Systolic Dimension (LVESD, cm)	5.3 ± 0.9 (301)	5.3 ± 0.9 (306)	0.8172
Left Ventricular End Diastolic Dimension (LVEDD, cm)	6.2 ± 0.7 (301)	6.2 ± 0.8 (307)	0.7958
Left Ventricular End Systolic Volume (LVESV, mL)	135.5 ± 56.1 (281)	134.3 ± 60.3 (294)	0.8085
Left Ventricular End Diastolic Volume (LVEDV, mL)	194.4 ± 69.2 (281)	191.0 ± 72.9 (294)	0.5667
LVEDV Index (mL/m^2)	102.3 ± 33.7 (279)	100.6 ± 35.0 (288)	0.5570
Right Ventricular Systolic Pressure (RVSP, mmHg)	44.0 ± 13.4 (253)	44.6 ± 14.0 (275)	0.6090
Medication Use at Baseline			
Beta-blocker	91.1% (275/302)	89.7% (280/312)	0.5802
ACEI, ARB or ARNI	71.5% (216/302)	62.8% (196/312)	0.0218
Mineralocorticoid receptor antagonist	50.7% (153/302)	49.7% (155/312)	0.8076
Nitrate	6.3% (19/302)	8.0% (25/312)	0.4084
Hydralazine	16.6% (50/302)	17.6% (55/312)	0.7243
Diuretic	89.4% (270/302)	88.8% (277/312)	0.8048
Chronic oral anticoagulant	46.4% (140/302)	40.1% (125/312)	0.1155
Aspirin	57.6% (174/302)	64.7% (202/312)	0.0699
P2Y12 receptor inhibitor	25.2% (76/302)	22.8% (71/312)	0.4843
Statin	62.6% (189/302)	60.6% (189/312)	0.6095

*Continuous measures - Mean ± SD; categorical measures - % (no./total no.).

Demographics and Baseline Characteristics	Summary Statistics*		P-Value†
	Device (N=302)	Control (N=312)	

†P-values are from *t*-test for continuous variables and from Chi-square test or Fisher's exact test when Cochran's rule is not met for categorical variables. All p-values displayed are two-sided and for information only.

D. Safety and Effectiveness Results

1. Primary Safety Endpoint

The rate of freedom from device-related complications at 12 months was 96.6%, with a lower 95% confidence limit of 94.8%, which was higher than the pre-specified performance goal of 88% (p<0.0001), as shown in Figure 17.2. As such, the COAPT Trial met its primary safety endpoint. A breakdown of the composite primary safety endpoint events is presented in Table 17.2.

Figure 17.2: Kaplan-Meier Curve of the Primary Safety Endpoint (SA Population)

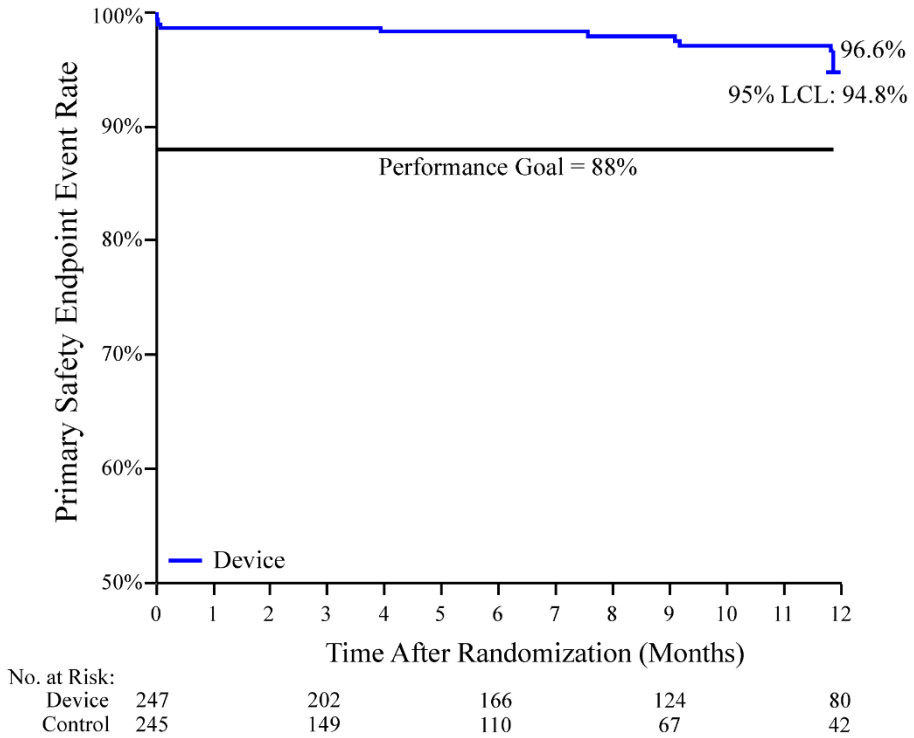


Table 17.4: Outcomes of the Primary Safety Endpoint Components (SA Population)

Event	Summary Statistics* (N = 293)
Device-related complications at 12 months	9 (3.4%)
-- Single leaflet device attachment	2 (0.7%)

-- Device embolization	1 (0.3%)
-- Endocarditis requiring surgery	0 (0.0%)
-- Mitral stenosis requiring surgery	1 (0.3%)
-- LVAD implant	3 (1.2%)
-- Heart transplant	2 (0.8%)
-- Any device-related complication requiring non-elective cardiovascular surgery	1 (0.3%)

*# events (Kaplan-Meier rate)

2. Primary Effectiveness Endpoint

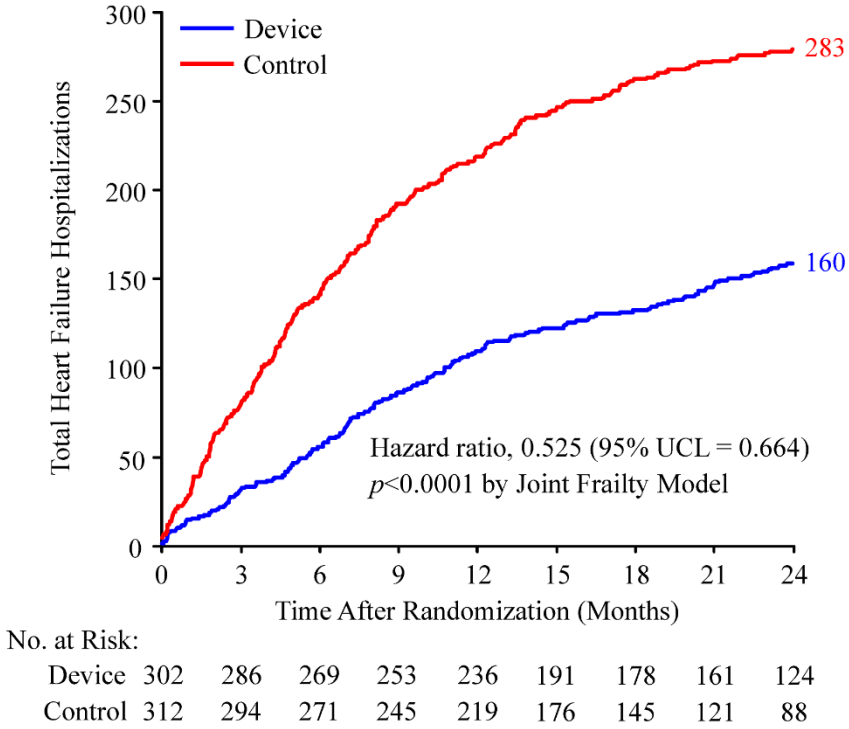
A total of 160 and 283 HF hospitalizations occurred within 24 months in the Device and Control groups, respectively. The annualized rates (events per patient-year) of HF hospitalization were 0.358 in the Device group and 0.679 in the Control group, with a hazard ratio (HR) of 0.525 (upper 95% confidence limit: 0.664), representing a 47.5% reduction in the risk of recurrent HF hospitalization by the Joint Frailty Model in favor of the Device (p<0.0001), as summarized in Table 17.5 and Figure 17.3. Therefore, the COAPT Trial met its primary effectiveness endpoint. The successes of the primary safety endpoint and the primary effectiveness endpoint were confirmed by the AT analysis, PP analysis, and sensitivity analysis.

Table 17.5: Recurrent HF Hospitalization through 24 Months – Primary Effectiveness Endpoint (ITT Population)

	Device (N=302)	Control (N=312)	Hazard Ratio - Device vs. Control [95% CI]	Relative Risk Reduction - Device vs. Control [95% CI]	P-Value
Number of Subjects*	92 (30.5%)	151 (48.4%)			
Number of Events	160	283			
Total Follow-Up (patient-years)*	446.5	416.8			
Annualized Rate [95% CI]†	0.358 [0.307, 0.418]	0.679 [0.604, 0.763]			
Joint Frailty Model			0.525 [-, 0.664]	0.475 [0.336, -]	< 0.0001

*The total follow-up in patient-years was calculated as the sum of follow-up patient-years for each subject through 24 months at the time of data cut-off or end of study, whichever was earlier.
†The annualized rate was calculated as total number of HF hospitalization events divided by total follow-up years through 24 months.
Note: (1) Hospitalizations that were adjudicated by the CEC as related to HF using the pre-specified protocol definition were included as events in the analysis; (2) Hospitalizations for MV surgery, LVAD implant or heart transplant during the follow-up period were treated as HF hospitalizations; and (3) For subjects in the Control group who received the MitraClip device due to HF or cardiac symptoms, the hospitalizations for the MitraClip procedure were treated as HF hospitalizations.

Figure 17.3: Total HF Hospitalization through 24 Months (ITT Population)



3. Powered Secondary Endpoints

Hypothesis testing was performed on 10 pre-specified secondary endpoints using a hierarchical test procedure, as shown in Table 17.6.

Table 17.6: Summary of Hierarchical Secondary Endpoints (ITT Population)

Secondary Endpoints (hierarchical order)	Device (N=302)	Control (N=312)	HR or Difference [95% CI]	Lower 95% confidence limit	P-Value*
#1 Proportion of MR Severity ≤ 2+ at 12 Months; % (no./total no.) [95% CI]	94.8% (199/210) [90.82%, 97.36%]	46.9% (82/175) [39.29%, 54.53%]	-	-	< 0.0001
#2 All-Cause Mortality at 12 Months (Non-inferiority);† Kaplan-Meier estimate (SE) of event rate	19.1% (2.3%)	23.2% (2.4%)	0.809 [-, 1.085]	-	0.0003
#3 Finkelstein-Schoenfeld Analysis of a Hierarchical Composite of All-Cause Mortality and Recurrent HF Hospitalization through 24 Months	-	-	-	-	< 0.0001

Secondary Endpoints (hierarchical order)	Device (N=302)	Control (N=312)	HR or Difference [95% CI]	Lower 95% confidence limit	P-Value*
#4 Change in KCCQ Overall Summary Score at 12 Months over Baseline; least square means (SE) [95% CI]	12.50 (1.82) [8.93, 16.08]	-3.56 (1.85) [-7.21, 0.08]	16.07 [10.97, 21.17]	-	< 0.0001
#5 Change in 6MWD at 12 Months over Baseline; least square means (SE) [95% CI]	-2.17 (9.12) [-20.10, 15.76]	-60.03 (8.99) [-77.69, -42.36]	57.86 [32.67, 83.05]	-	< 0.0001
#6 All-Cause Recurrent Hospitalizations through 24 Months;† annualized rate [95% CI]	1.062 [0.970, 1.162]	1.464 [1.352, 1.585]	0.760 [0.602, 0.960]	-	0.0213
#7 Proportion of NYHA Functional Class of I/II at 12-Month; % (no./total no.) [95% CI]	72.2% (171/237) [65.98%, 77.76%]	49.6% (115/232) [42.96%, 56.19%]	-	-	< 0.0001
#8 Change in Left Ventricular End Diastolic Volume at 12 Months over Baseline; least square means (SE) [95% CI]	-3.71 (5.08) [-13.71, 6.28]	17.06 (5.10) [7.03, 27.08]	-20.77 [-34.93, -6.62]	-	0.0041
#9 All-Cause Mortality through 24 Months;† Kaplan-Meier estimate (SE) of event rate	29.1% (2.8%)	46.1% (3.2%)	0.615 [0.463, 0.816]	-	0.0008
#10 Estimate of Freedom from All-Cause Mortality, Stroke, MI or Non-Elective Cardiovascular Surgery for Device-Related Complications at 30 Days; % (no./total no.)	96.9% (284/293)	-	-	94.7%	<0.0001

*All p-values were tests for superiority, except for the secondary endpoint of mortality at 12 months (#2), which was a test for non-inferiority, and for the secondary endpoint of freedom from composite of all-cause mortality, stroke, MI or non-elective cardiovascular surgery for device-related complications at 30 days (#10), which was compared against a performance goal.

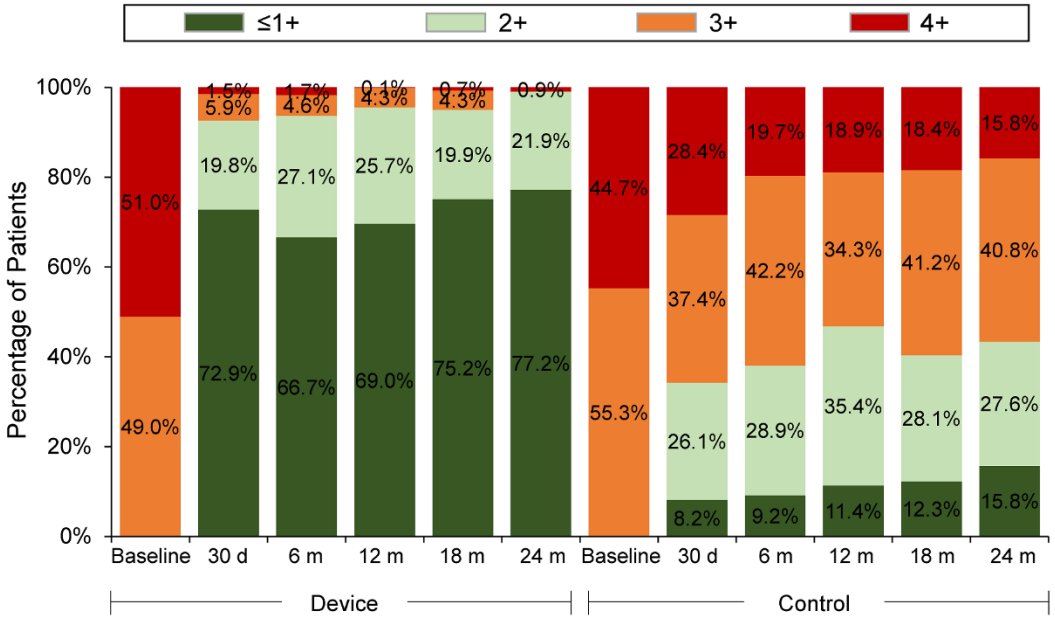
†Analyzed when the last subject completed the 12-month follow-up.

Note: (1) Imputation of worst clinical outcomes for subjects experiencing HF death prior to 12 months for the changes in KCCQ, 6MWD, LVEDV and NYHA class. (2) Continuous endpoints (KCCQ, 6MWD, and LVEDV) were analyzed using Analysis of Covariance (ANCOVA). (3) HR – Hazard Ratio; CI – Confidence Interval; SE – Standard Error.

All powered secondary endpoints were met, as summarized below:

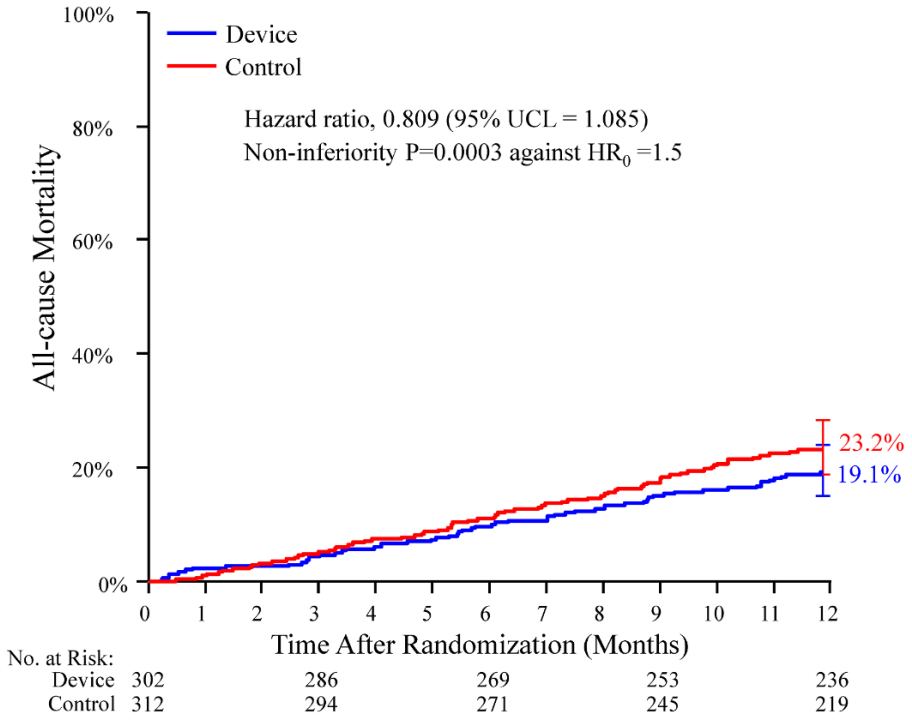
1. There were significantly more subjects with MR severity ≤ 2+ in the Device group than in the Control group at 12 months (94.8% vs. 46.9%). The MR severity grades over time in both groups are shown in Figure 17.4.

Figure 17.4: MR Severity Grades over Time (ITT Population)



2. The Device group was found to be non-inferior to the Control group in all-cause mortality at 12 months (19.1% vs. 23.2%), as shown in Figure 17.5.

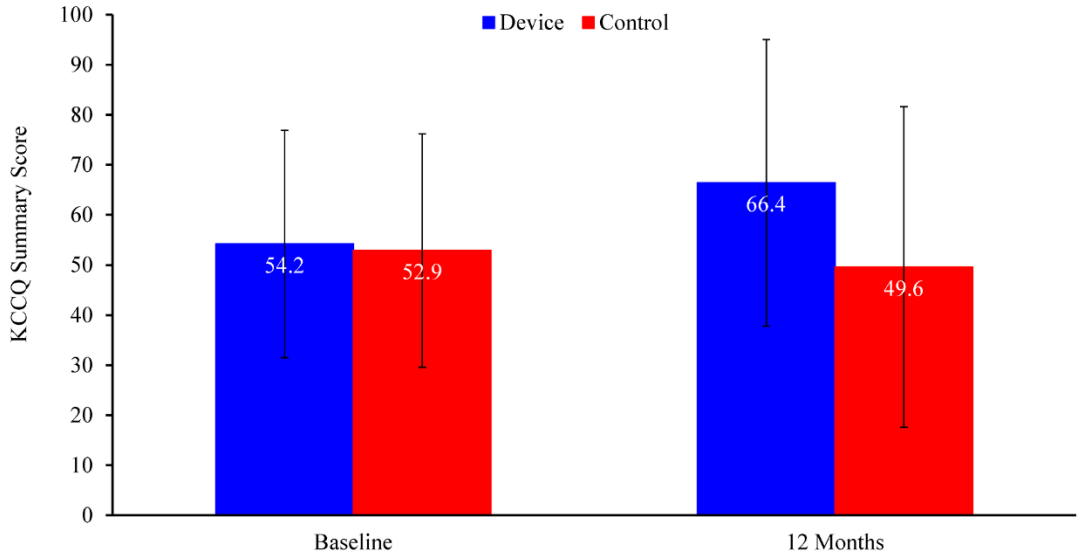
Figure 17.5: Kaplan-Meier Curve of All-Cause Mortality through 12 Months (ITT Population)



3. Subjects in the Device group experienced a significant reduction in the hierarchical composite of all-cause mortality and recurrent HF hospitalization compared to those in the Control group.

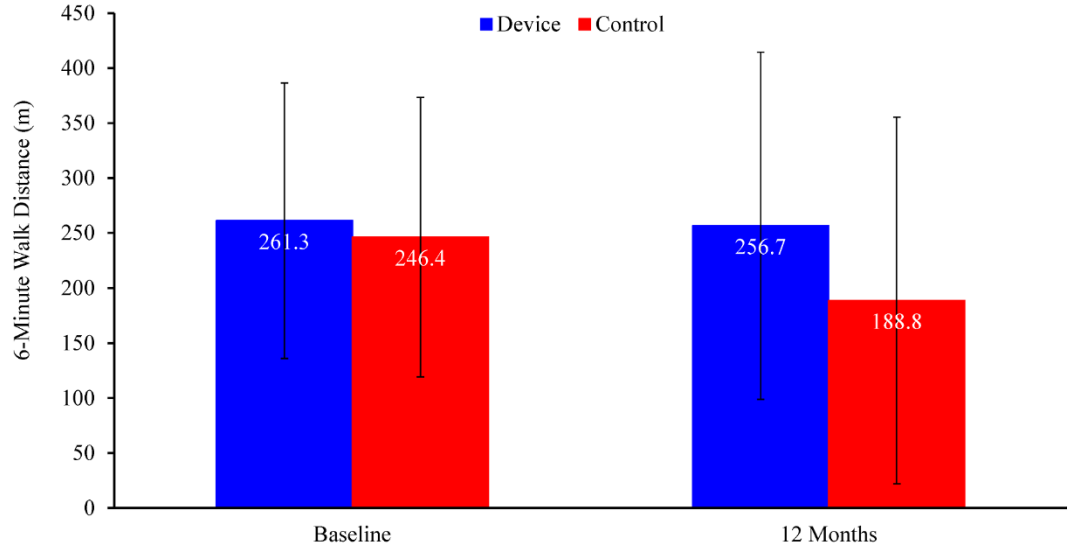
4. Subjects in the Device group experienced a significantly greater improvement in QoL (as assessed by the change in KCCQ Overall Summary Score at 12 months over baseline) compared to those in the Control group (12.50 vs. -3.56), as shown in Figure 17.6.

Figure 17.6: KCCQ Overall Summary Score at Baseline and 12 Months (ITT Population)



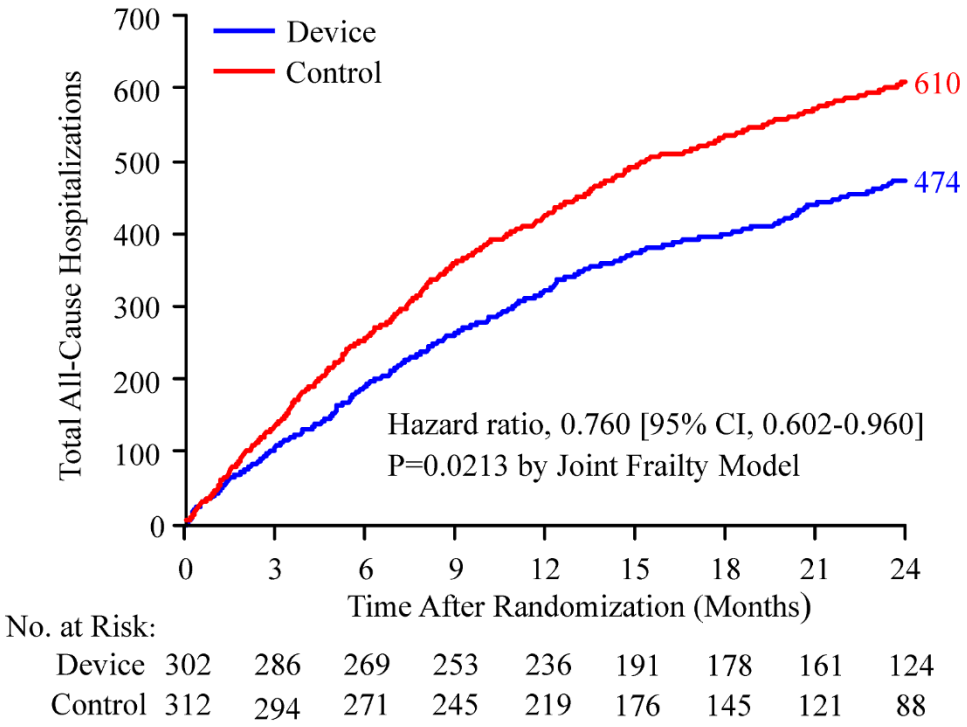
5. Subjects in the Device group experienced significantly greater preservation of functional capacity (as assessed by the change in 6MWD at 12 months over baseline) compared to those in the Control group (-2.17 m vs. -60.03 m), as shown in Figure 17.7.

Figure 17.7: 6MWD at Baseline and 12 Months (ITT Population)



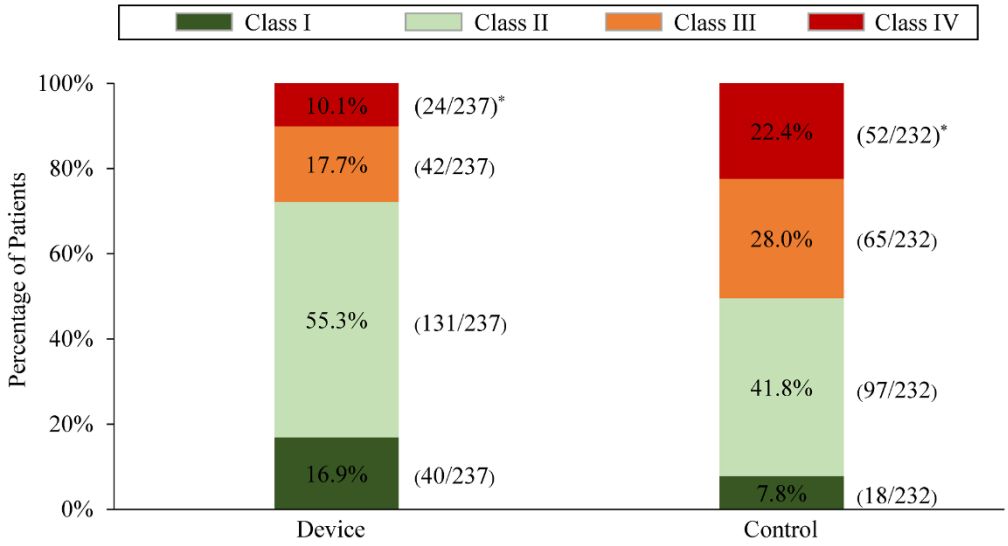
6. Subjects in the Device group experienced a significantly lower annualized rate (events per patient-year) of all-cause hospitalizations compared to those in the Control group (1.062 vs. 1.464). The total all-cause hospitalization through 24 months is shown in Figure 17.8.

Figure 17.8: Total All-Cause Hospitalization through 24 Months (ITT Population)



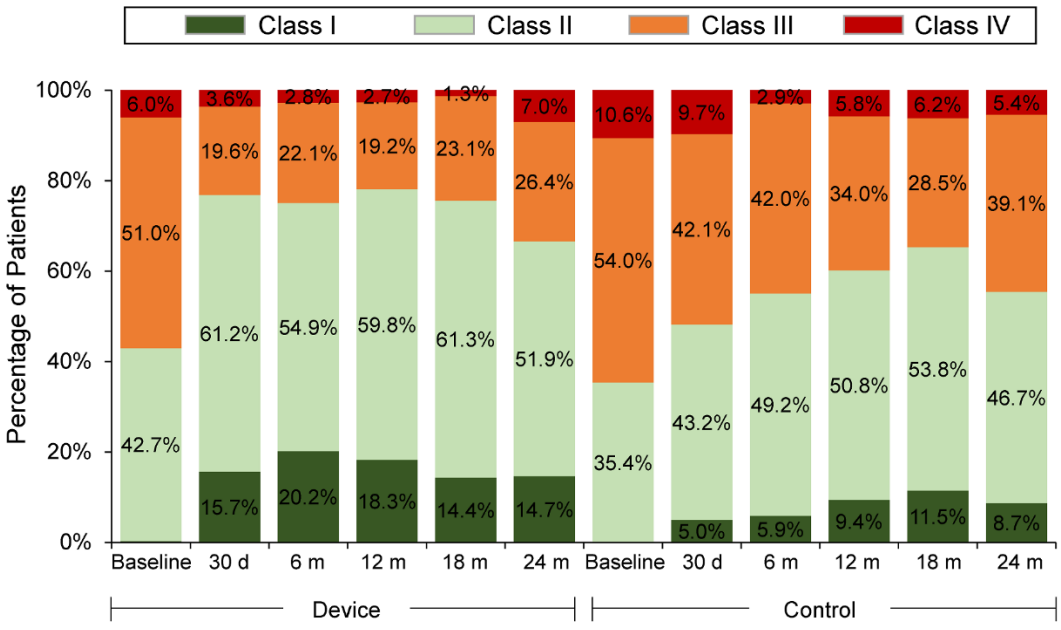
7. Subjects in the Device group experienced a significantly greater improvement in NYHA Functional Class at 12 months compared to those in the Control group (Class I or II: 72.2% vs. 49.6%), as shown in Figure 17.9A, where subjects who died prior to 12 months were imputed as having NYHA Class IV. The NYHA Functional Class (unimputed) through 24 months is shown in Figure 17.9B.

Figure 17.9A: NYHA Functional Class at 12 Months (ITT Population)



*Subjects died of HF prior to 12 months were imputed as having NYHA Class IV (Device group: 18; Control group: 41)

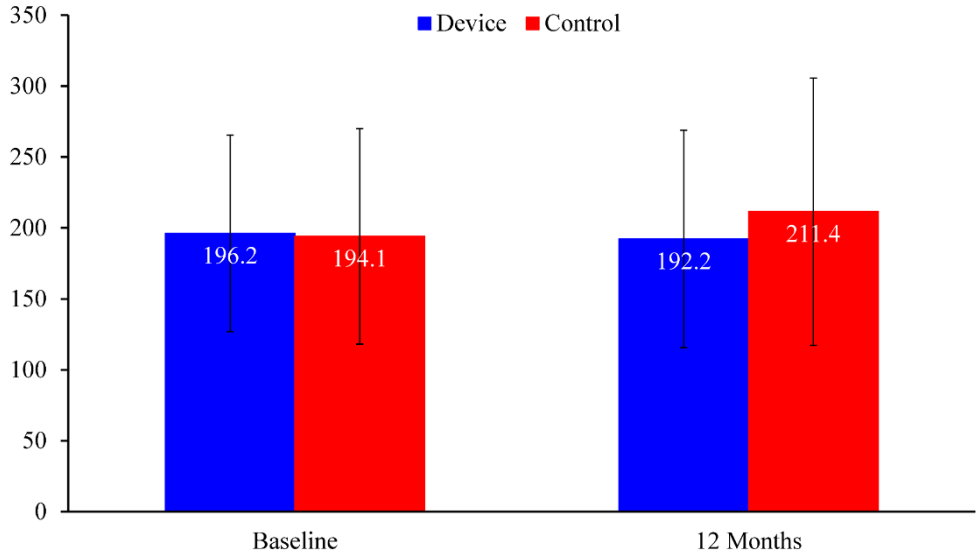
Figure 17.9B: NYHA Functional Class through 24 Months (ITT Population)



8. Subjects in the Device group experienced significantly greater reduction in LVEDV between baseline and 12 months compared to those in the Control group (-3.71 mL vs. 17.06 mL), as shown in Figure 17.10. However, while per protocol this endpoint passes, this finding appears to be primarily related to pre-specified imputation of LVEDV values for subjects who died of HF prior to completing the 12-month follow-up where these subjects were assigned the worst LVEDV change between baseline and

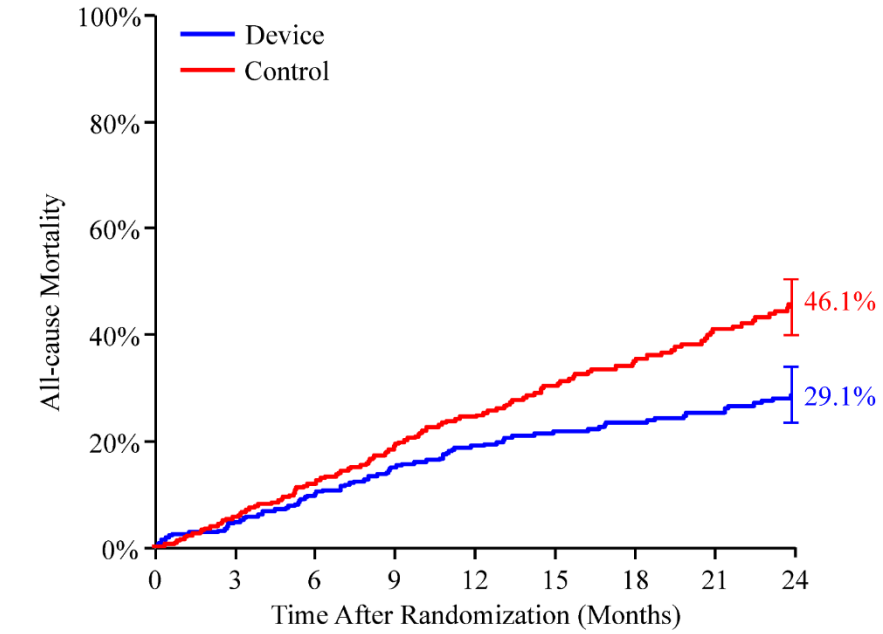
12 months observed for any subject in the analysis (126 mL). Because subjects in the Control group had a numerically higher (41 vs. 18) incidence of HF-related mortality than those in the Device group and the worst change in LVEDV was extreme, calculations for the LVEDV change from baseline in the Control group patients could be skewed mathematically to the larger end. It should be noted that neither clinically nor statistically significant difference in LVEDV change from baseline to 12 months was observed between the Device and Control groups based on un-imputed unpaired and paired analyses, or based on a responder analysis.

Figure 17.10: LVEDV Change from Baseline to 12 Months (ITT Population)



9. Subjects in the Device group experienced significantly lower all-cause mortality at 24 months compared to those in the Control group (Kaplan-Meier estimate: 29.1% vs. 46.1%), as shown in Figure 17.11. The number needed to treat (NNT) to save one life within 24 months was 5.9 (95% CI: [3.9, 11.7]).

Figure 17.11: Kaplan-Meier Curve of All-Cause Mortality through 24 Months (ITT Population)

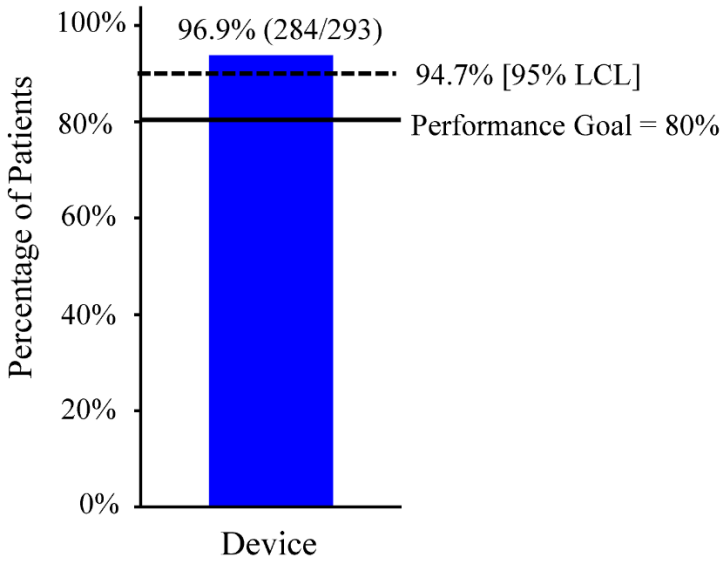


No. at Risk:

Device	302	286	269	253	236	191	178	161	124
Control	312	294	271	245	219	176	145	121	88

10. The rate of freedom from all-cause mortality, stroke, MI, or non-elective cardiovascular surgery for device-related complications at 30 days was 96.9%, with a lower 95% confidence limit of 94.7%, which met the prespecified performance goal of 80%, as shown in Figure 17.12.

Figure 17.12: Freedom from All-Cause Mortality, Stroke, MI or Non-Elective Cardiovascular Surgery for Device-Related Complications at 30 Days (SA Population)



4. Adverse Events

The adverse events that occurred in the trial through 24 months are presented in Table 17.7.

Table 17.7: CEC-Adjudicated Adverse Events through 24 Months (SA Population)

Events	0-30 Days		0-12 Months		0-24 Months	
	Device	Control	Device	Control	Device	Control
All-cause mortality*	2.3% (7)	1.0% (3)	19.1% (57)	23.2% (70)	29.1% (80)	46.1% (121)
Cardiovascular	2.3% (7)	0.6% (2)	13.8% (40)	19.4% (57)	23.2% (60)	37.0% (93)
Heart failure	0.7% (2)	0.6% (2)	6.2% (17)	13.8% (39)	12.0% (28)	25.9% (61)
Stroke	0.7% (2)	0.0% (0)	2.9% (8)	2.9% (8)	4.4% (11)	5.1% (11)
Transient ischemic attack	0.0% (0)	0.0% (0)	1.1% (3)	1.1% (3)	1.1% (3)	1.1% (3)
Endocarditis requiring surgery	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
ECL confirmed mitral stenosis requiring surgery	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
LVAD implant	0.0% (0)	1.0% (3)	0.8% (2)	3.9% (11)	3.0% (6)	7.1% (16)
Heart transplant	0.0% (0)	0.0% (0)	0.8% (2)	2.2% (6)	1.4% (3)	3.6% (8)
Myocardial Infarction†	0.3% (1)	0.0% (0)	NA	NA	NA	NA
Major bleeding†	5.0% (15)	1.0% (3)	NA	NA	NA	NA
Iatrogenic ASD requiring intervention	0.7% (2)	NA	0.7% (2)	NA	0.7% (2)	NA

Events	0-30 Days		0-12 Months		0-24 Months	
	Device	Control	Device	Control	Device	Control
Device-related complications requiring non-elective CV surgery	0.3% (1)	NA	0.3% (1)	NA	0.3% (1)	NA

*Include adjudicated death events and deaths from the national death registry (for subjects who were lost to follow-up or withdrew from the COAPT study).
†Events were adjudicated up to 30 days post treatment visit.
Note: (1) Kaplan-Meier rate (# patients with events). Include only each patient's first occurrence of each event. (2) The follow-up duration was calculated from the randomization date. (3) ECL: Echocardiography Core Laboratory; LVAD: Left Ventricular Assists Device; ASD: Atrial Septal Defect; CV: Cardiovascular.

5. Subgroup Analyses

Pre-specified Analyses:

The primary safety and primary effectiveness endpoints were examined across the following 4 subgroups:

- Sex (male vs. female)
- Etiology of cardiomyopathy (ischemic vs. non-ischemic)
- LVEF (> 40% vs. ≤ 40%)
- Extreme surgical risk status (yes vs. no, as determined by the Central Eligibility Committee)

There was no clinically significant difference among the subgroups for the primary safety outcome, and there were no clinically significant interaction effects between treatment and subgroups for the primary effectiveness outcome.

Post hoc Analyses:

In light of publication of another study of the MitraClip device in literature, entitled "Mitra-FR Trial" (see reference [4]), a comparison of the baseline characteristics of the subjects enrolled in the COAPT Trial and Mitra-FR Trial was performed to further define the proper patient population for the MitraClip SMR indication. The comparison suggested there were some differences between the two trials as shown in Table 17.8.

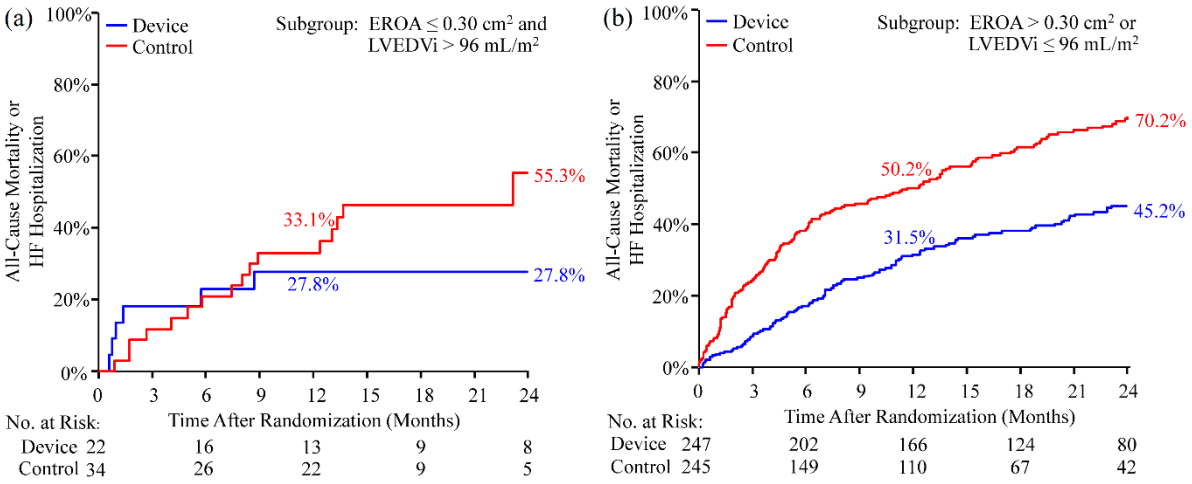
Table 17.8: Comparison in EROA and LVEDVi between Mitra-FR and COAPT

Baseline Characteristics	Mitra-FR	COAPT
EROA (mean ± SD; cm^2)	0.31 ± 0.11	0.41 ± 0.15
LVEDVi (mean ±SD; mL/m^2)	135 ± 35	101 ± 34

To explore whether there was any correlation between the clinical outcomes and the baseline EROA and LVEDVi, a *post hoc* subgroup analysis was conducted on the COAPT dataset, by comparing the composite rate of all-cause mortality or HF hospitalization between subjects with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2 and those with an EROA > 0.30 cm^2 or an LVEDVi ≤ 96 mL/m^2, where 0.30 was the lower bound of the EROA

defining, along with other parameters, Grade III (or 3+) MR as per the 2017 ASE Recommendation for Noninvasive Evaluation of Native Valvular Regurgitation and 96 was the median LVEDVi value in the COAPT Trial.[5] A total of 22 subjects in the Device group and 34 subjects in the Control group had an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2. The results of the subgroups analysis are shown in Figure 17.13. COAPT subjects with relatively less severe MR and larger left ventricles (Fig 17.13A) did not show a clinically meaningful benefit of the Device for all-cause mortality or HF hospitalization at the 12-month timepoint. For the remaining COAPT subjects (those with an EROA > 0.3cm^2 or an LVEDVI ≤ 96mL/m^2; Figure 17.13B), the difference in all-cause mortality or HF hospitalization seen in the overall population was maintained.

Figure 17.13: Subgroup Analysis Stratified by EROA and LVEDVi



Despite the absence of benefit of reduced all-cause mortality or HF hospitalization in the subgroup with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2, clinically meaningful improvements in the overall 6MWD (as shown in Figure 17.14; 11 subjects in the Device group and 26 subjects in the Control group had 6MWD values) and KCCQ (as shown in Figure 17.15; 15 subjects in the Device group and 27 subjects in the Control group had KCCQ values) compared to baseline were observed in Device group patients, an effect not observed in the same sub-population of the Control group. However, because of the nature of the *post hoc* subgroup analysis and the small sample size in the subgroup with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2, no statistical or clinical intra-group inferences can be made.

Figure 17.14: 6MWD for Subjects with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2

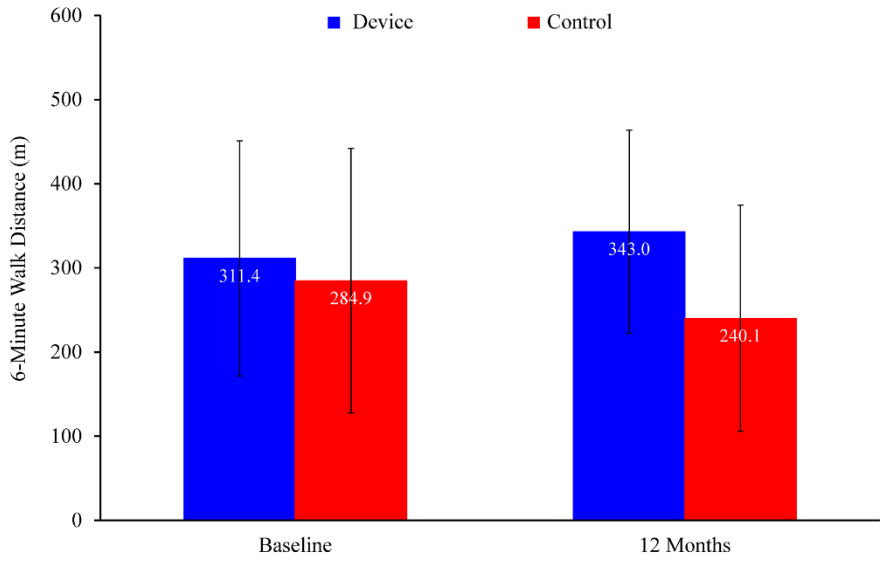
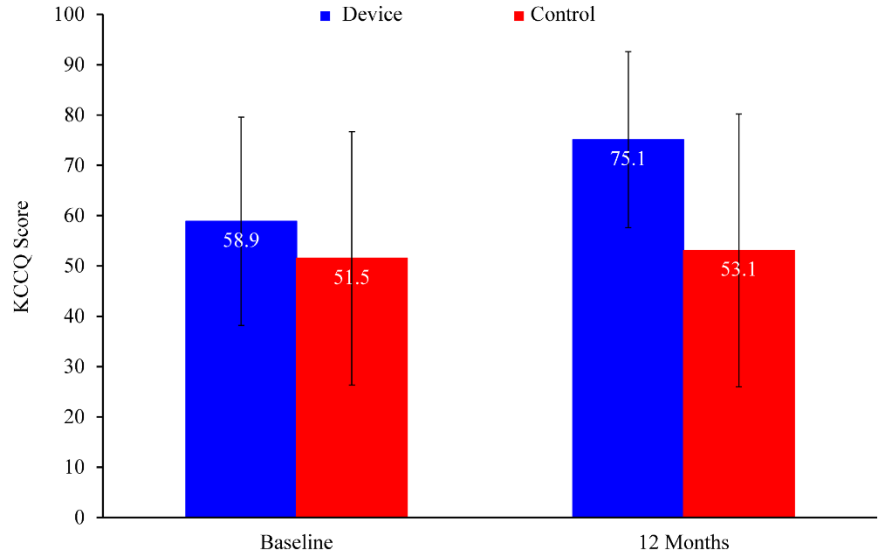


Figure 17.15: KCCQ Score for Subjects with an EROA ≤ 0.30 cm² and an LVEDVi > 96 mL/m²



6. Procedural Data

The procedural data of the Device group are summarized in Table 17.9.

Table 17.9: Procedural Data Summary for Device Subjects – AT Population

Procedure Data	Device (N=294)
MitraClip Procedure Attempted	100.0%
Implant Rate	98.0%

Procedure Data	Device (N=294)
Number of Clips Implanted	
0 Clip	2.0%
1 Clip	36.4%
2 Clips	53.1%
3 Clips	8.2%
4 Clips	0.3%
Total Number of Clips Implanted	495
Total Procedure Time (min) Mean ± SD (n) Median (Q1, Q3)	 163.0 ± 117.5 (294) 146.5 (108.0, 199.0)
Device Procedure Time (min) Mean ± SD (n) Median (Q1, Q3)	 118.8 ± 63.3 (283) 106.0 (73.0, 148.0)
Device Time (min) Mean ± SD (n) Median (Q1, Q3)	 82.6 ± 80.6 (288) 65.5 (40.0, 100.0)
Fluoroscopy Duration (min) Mean ± SD (n) Median (Q1, Q3)	 33.91 ± 23.15 (285) 29.50 (18.60, 43.00)

7. REFERENCES

[1] Rogers JK, Pocock SJ, McMurray JJV, Granger CB, Michelson EL, Östergren J, et al. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology with application to charm-preserved. *European Journal of Heart Failure* 2014; 16:33–40.

[2] Rogers JK, Jhund PS, Perez A, Böhm M, Cleland JG, Gullestad L, et al. Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA trial (controlled rosuvastatin multinational trial in heart failure). *Journal of the American College of Cardiology Heart Failure* 2014; 2:289–297.

[3] Rogers JK, Yaroshinsky A, Pocok SJ, Stokard D, Pogodae Janice. Analysis of recurrent events with an associated informative dropout time: Application of the joint frailty model. *Statistics in Medicine* 2016; 35:2195-205.

[4] Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *New England Journal of Medicine* 2018; 379:2297-2306.

[5] Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *New England Journal of Medicine* 2018;379:2307-2318.

[6] Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *Journal of the American Society of Echocardiography* 2017;30:303-371.

18.0 MITRACLIP™ PROCEDURE STEP-BY-STEP INSTRUCTIONS

18.1 DEFINITION OF TERMS

Defined Terms are in italics throughout document.

TERM	DEFINITION AND RELATED TECHNIQUE
Lock the Clip	1. Rotate the Lock Lever outward. 2. Fully advance the Lock Lever. 3. Rotate the Lock Lever inward to engage the lever.
Unlock the Clip	1. Rotate the Lock Lever outward and then retract the lever until the mark on the lever is fully exposed. 2. Rotate the Lock Lever inward to engage the lever.
Open the Clip Arms	1. Confirm the Clip is unlocked. 2. Turn the Arm Positioner at least 1/2 turn in the "Close" (clockwise) direction. 3. Turn the Arm Positioner in the "Open" (counter-clockwise) direction until the desired *Clip Arm Angle* is achieved. **NOTE 1**: If Clip does not open smoothly, retract the Lock Lever farther, then repeat steps 2 – 3. **NOTE 2**: If the Clip Arms fail to open visibly (as observed under fluoroscopic guidance), use the following techniques in the order provided, as needed: A. Stop and return *Arm Positioner to Neutral*. Retract Lock Lever farther, then turn the Arm Positioner farther in the "Close" direction before turning in the "Open" direction. Advance the lock lever just enough so that the mark on the lever is still fully exposed. B. Turn the *Arm Positioner to Neutral*, then incrementally iterate the amount of Arm Positioner rotation in the "Close" direction followed by rotation in the "Open" direction. Iterate until Clip opens or until it is no longer possible to rotate the Arm Positioner in the "Close" direction. Advance the lock lever just enough so that the mark on the lever is still fully exposed. C. Turn the *Arm Positioner to Neutral*, iterate the amount of Lock Lever retraction past the mark in 5 mm increments, and rotate the Arm Positioner fully in the "Close" direction, before rotating in the "Open" direction, until Clip opens. Advance the lock lever just enough so that the mark on the lever is still fully exposed. D. Advance the Gripper Lever and repeat NOTE 2, Step C. Retract the Gripper Lever after Clip opens. E. If in the LA and free of tissue, release the DC Fastener, then release the Sleeve curves and repeat NOTE 2, Step C.

TERM	DEFINITION AND RELATED TECHNIQUE
	WARNING: Failure to release the DC Fastener before releasing Sleeve curves may result in device damage and / or embolization. F. If the Clip does not open after performing all steps in NOTE 2, DO NOT use the device.
Arm Positioner to Neutral	Turn the Arm Positioner in the "Close" or "Open" direction until no resistance to turning is noted.
Invert the Clip Arms	1. Confirm the Clip is unlocked. 2. Turn the Arm Positioner at least 1/2 turn in the "Close" direction. 3. Turn the Arm Positioner in the "Open" direction until the Clip Arms invert (see Figure 7G). DO NOT over-invert the Clip Arms; stop turning the Arm Positioner when resistance is first noted.
Raise the Grippers	1. Rotate the Gripper Lever outward. 2. Slowly retract the Gripper Lever (under fluoroscopic observation) until the mark on the lever is just exposed. **NOTE:** If pulling beyond the mark is required, advance the Gripper Lever back to the mark once the Grippers are fully raised. 3. Rotate the Gripper Lever inward to engage the lever.
Lower the Grippers	1. Rotate the Gripper Lever outward. 2. Fully advance the Gripper Lever. 3. Rotate the Gripper Lever inward to engage the lever.
Clip Arm Angle	• Angle between the inner edges of both Clip Arms. • All *Clip Arm Angles* are measured using fluoroscopy with optimal view allowing clear observation of the tip of the Clip and both arms in the same plane so they appear as a "V" (see Figure 7).
Grasping Arm Angle	A *Clip Arm Angle* of approximately 120 degrees. **NOTE:** Establish *Grasping Arm Angle* after closing the Clip from a larger *Clip Arm Angle.*
Fully Close the Clip Arms	Turn the Arm Positioner in the "Close" direction until the Clip Arms contact the DC. • Under direct visualization, the Clip is fully closed when the Clip Covering contacts the DC. • Under fluoroscopic observation, the Clip is fully closed when the inner edges of the Clip Arms are parallel.
Establish Final Arm Angle	Pre-deployment *Clip Arm Angle* that reflects the *Clip Arm Angle* post-deployment. With the Lock Lever fully advanced, turn the Arm Positioner approximately ½ turn in the "Open" direction once initial resistance is felt. The Clip Arms may open slightly and then remain in a stable position.

TERM	DEFINITION AND RELATED TECHNIQUE
	NOTE: If continued opening of the Clip Arms is noted, reconfirm that the Lock Lever is completely advanced. Close the Clip Arms, and *Establish Final Arm Angle*.

19.0 PATIENT PREPARATION

19.1 Prepare the patient per institution's standard practice for transseptal catheterization.

19.2 Place support plate under patient's leg in the region between the area of the upper leg and the knee and place the Lift over the ipsilateral lower extremity prior to draping the patient.

19.3 Place the Lift on the Support Plate such that the front edge (i.e., the edge that corresponds with the shorter legs of the Lift) is approximately 80 cm from the patient's mid sternum.

19.4 Adjust the height of the Lift so that the front edge of the Lift is close to the patient's leg, but is not impinging on it. Adjust the back legs to be 2 or 3 notches above the front legs (i.e., the back legs of the Lift are taller than the front legs).

19.5 Ensure the Lift and Support Plate are covered completely by sterile drape during the procedure. Use towels as necessary to minimize direct contact between the patient and all surfaces of both the Lift and Support Plate.

19.6 Prepare the patient for invasive hemodynamic monitoring.

20.0 MITRACLIP™ SYSTEM PREPARATION BEFORE USE

WARNING: DO NOT use the MitraClip™ System after the "Use By" date stated on the package label, and never reuse or re-sterilize the system. Use of expired, reused, or re-sterilized devices may result in infection, endocarditis, and / or sepsis.

WARNING: Always inspect the MitraClip™ System and its packaging to verify no damage has occurred as a result of shipping and handling and that the sterile barrier has not been compromised. DO NOT use the device if damage is detected. Use of product with a compromised sterile barrier may result in infection, endocarditis, and / or sepsis. Use of damaged product may result in patient injury.

- DO NOT remove the protective cover placed over the Clip.

WARNING: DO NOT handle the Clip directly; leave it in the protective cover to avoid potential contamination. Removal of the protective cover may result in infection, endocarditis, and / or sepsis. Removal of the protective cover may result in damaged product which may result in patient injury.

- The preparation is most easily accomplished with the aid of an assistant.

20.1 Steerable Guide Catheter Preparation

WARNING: All lumens contain air when shipped. Use proper de-airing techniques before and during use to minimize the risk of air embolism.

20.1.1 Carefully remove the white Guide tip shape retainer and transparent protective tubing from the Guide tip.

20.1.2 Inspect Steerable Guide Catheter and Dilator to verify they are undamaged.

WARNING: DO NOT use if damage is detected. Use of damaged product may result in air embolism, vascular and / or cardiac injury.

20.1.3 Remove the sterile package containing Fasteners and Silicone Pad from the Steerable Guide Catheter tray.

20.1.4 Fill a basin with 1000 cc of heparinized saline.

20.1.5 Flush and de-air the Guide and Dilator with heparinized saline:

20.1.5.1 Connect 3-way stopcocks to the Guide and Dilator flush ports.

20.1.5.2 De-air the Dilator, then close the stopcock and the Rotating Hemostatic Valve.

20.1.5.3 Hydrate 5-10 cm of the distal end of the Dilator with heparinized saline.

20.1.5.4 Insert the Dilator approximately 10 cm into Guide then remove.

20.1.5.5 Connect high pressure tubing and a 50–60 cc syringe filled with heparinized saline to the Guide flush port.

20.1.5.6 De-air the Guide.

20.1.5.6.1 With the tip raised, displace all air from the Guide while tapping along the length of the catheter shaft.

20.1.5.6.2 Cover the Guide tip with finger once heparinized saline exits the Guide.

20.1.5.6.3 Close the Guide stopcock.

20.1.6 Submerge the Guide tip in the basin of heparinized saline.

20.1.7 While the Guide tip is submerged in the basin of heparinized saline, remove finger from Guide tip and check the Guide valve for leaks by raising the handle to a vertical position for a minimum of 30 seconds.

20.1.8 Hydrate 5-10 cm of the distal end of the Dilator with heparinized saline.

20.1.9 Cover the Guide tip with finger and insert the Dilator into the Guide while Guide tip remains submerged in the basin of heparinized saline.

20.1.9.1 While advancing the Dilator, continually watch for air in the Guide Hemostasis Valve housing. If needed, remove finger from Guide tip and aspirate while assuring the Guide tip is submerged.

20.1.9.2 Remove finger from tip of Guide when the Dilator tip approaches the Guide tip.

20.1.9.3 Advance the Dilator until the curve is extended from the Guide tip.

20.2 Steerable Guide Catheter Functional Inspection

- The functional inspection is most easily accomplished with the aid of an assistant.
- The Guide functional inspection should be performed with the Guide tip and Dilator tip submerged in a basin of heparinized saline to prevent air from entering the lumens. If the Guide tip and / or Dilator tip fails to remain submerged during inspection, flush the Guide and / or Dilator with heparinized saline to completely remove air.

WARNING: Failure to completely remove air may result in air embolism.

WARNING: All catheter manipulations should be done with care. DO NOT continue to rotate or manipulate any of the handle controls if significant resistance is noted. Use of damaged product may result in air embolism, vascular and / or cardiac injury.

Guide Inspection

20.2.1 Inspect all Guide parts to verify they are undamaged.

WARNING: DO NOT use device if damage is detected. Use of damaged product may result in air embolism, vascular and / or cardiac injury.

20.2.2 To confirm proper tip deflection with "+" knob rotation:

20.2.2.1 Rotate the +/- Knob in the "+" direction until the Guide is curved to approximately 80 degrees.

20.2.2.2 Remove hand from the +/- Knob and check that the knob does not slip.

20.2.2.3 Return the +/- Knob to the neutral position.

20.2.2.4 Repeat steps 20.2.2.1 through 20.2.2.3.

20.2.3 To confirm proper tip deflection with "-" knob rotation:

20.2.3.1 Rotate the +/- Knob in the "-" direction until the Guide curve is substantially straightened.

20.2.3.2 Remove hand from the +/- Knob and check that the knob does not slip.

20.2.3.3 Return the +/- Knob to the neutral position.

20.2.3.4 Repeat steps 20.2.3.1 through 20.2.3.3.

20.2.4 Retract the Dilator until the tip is 3-5 cm beyond the Guide tip. Position the Dilator to create a smooth transition.

20.3 Stabilizer Preparation

20.3.1 Assemble the sterilized Stabilizer by placing the two Fasteners in the Stabilizer. Ensure that the Fasteners can be fully threaded into the Stabilizer holes. Set the Stabilizer aside in a protected sterile environment for later use.

20.4 Clip Delivery System Preparation

20.4.1 Inspect the Clip, DC shaft, and Sleeve tip to verify they are undamaged.

WARNING: DO NOT use the device if damage is detected. Use of damaged product may result in air embolism, device or device component embolization, vascular and / or cardiac injury.

Sleeve Preparation

20.4.2 Connect 3-way stopcocks to the Sleeve flush port and bottom DC flush port.

20.4.3 Remove the cap from the Clip Introducer.

20.4.4 Place the cap on the top flush port of the DC Handle.

20.4.5 Connect a 3-way stopcock to the Clip Introducer flush port.

20.4.6 Connect one high pressure tube to each drip line from the pressurized bags with sterile heparinized saline; flush and de-air the lines.

20.4.7 Connect one high pressure tube to the 3-way stopcock on the bottom flush port of the DC Handle and one high pressure tube to the 3-way stopcock on the flush port of the Sleeve Handle.

20.4.8 Flush and de-air the Sleeve with heparinized saline.

20.4.8.1 With the tip raised and the shaft held taut, displace all air from the Sleeve lumen while tapping along the length of the catheter shaft.

20.4.8.2 While flushing, release the DC Fastener, retract and advance the DC Handle to remove residual air from the lumen.

WARNING: Using excessive force when pulling the DC Radiopaque Ring against the Sleeve tip, while translating the DC shaft, may result in device damage including distal tip embolization.

20.4.8.3 Secure the DC Fastener with DC Handle fully advanced.

Delivery Catheter Preparation

WARNING: DO NOT handle the Clip directly; leave in the protective cover to avoid potential contamination. Removal of the protective cover may result in damaged product which may result in patient injury.

20.4.9 Attach a 50–60 cc syringe filled with heparinized saline to the 3-way stopcock on the Clip Introducer.

20.4.10 De-air the Clip Introducer, then close the stopcock.

20.4.11 Temporarily remove the cap from top flush port of the DC Handle.

20.4.12 Flush and de-air DC Handle and all lumens of the DC with heparinized saline.

20.4.13 After de-airing the DC Handle chamber, replace the cap to close off top flush port of the DC Handle.

20.4.14 Retract and advance the Lock Lever several times to remove residual air from the lumens.

20.4.15 Loosen the Lock Lever and the Gripper Lever Caps to de-air. DO NOT turn lever caps more than 1/2 turn in the “Open” direction. After de-airing, tighten the lever caps.

20.4.16 With the tip raised and the shaft held taut, displace all air from the DC while tapping along the length of the catheter shaft.

20.4.17 Confirm continuous flow from the distal end of the DC.

20.5 Clip Delivery System Functional Inspection

- The functional inspection is most easily accomplished with the aid of an assistant.

20.5.1 Inspect all Clip Delivery System parts, including the Clip, to verify they are undamaged.

WARNING: DO NOT use device if damage is detected. Use of damaged product may result in air embolism, device or device component embolization, vascular and / or cardiac injury.

WARNING: All catheter manipulations should be done with care. DO NOT continue to rotate or manipulate any of the handle controls if significant resistance is noted. Use of damaged product may result in air embolism, vascular and / or cardiac injury.

Sleeve Inspection

WARNING: DO NOT deflect the Sleeve more than 90 degrees during the inspections below. Use of damaged product may result in cardiac injury.

20.5.2 To confirm proper tip deflection with “A” knob rotation:

20.5.2.1 With the DC handle fully advanced and the shaft held taut, rotate the A/P Knob approximately 3/4 turn in the "A" direction from neutral to confirm that the distal tip deflects.

20.5.2.2 Remove hand from the A/P Knob and check that the knob does not slip.

20.5.2.3 Return the A/P Knob to the neutral position.

20.5.2.4 Repeat steps 20.5.2.1 through 20.5.2.3.

20.5.3 To confirm proper tip deflection with “P” knob rotation:

20.5.3.1 With the DC handle fully advanced and the shaft held taut, rotate the A/P Knob approximately 3/4 turn in the "P" direction from neutral to confirm that the distal tip deflects.

20.5.3.2 Remove hand from the A/P Knob and check that the knob does not slip.

20.5.3.3 Return the A/P Knob to the neutral position.

20.5.3.4 Repeat steps 19.5.3.1 through 19.5.3.3.

20.5.4 To confirm proper tip deflection with “M” knob rotation:

20.5.4.1 With the DC Handle fully advanced and the shaft held taut, rotate the M/L Knob in the "M" direction until the distal tip deflects to approximately 90 degrees to confirm distal tip deflection.

20.5.4.2 Remove hand from the M/L Knob and check that the knob does not slip.

20.5.4.3 Return the M/L Knob to the neutral position.

20.5.4.4 Repeat steps 20.5.4.1 through 23205.4.3.

Delivery Catheter and Clip Inspection

WARNING: DO NOT handle the Clip directly, leave in the protective cover to avoid potential contamination. Removal of the protective cover may result in infection, endocarditis, and / or sepsis. Removal of the protective cover may result in damaged product which may result in patient injury.

NOTE: If *Clip Arm Angle* is greater than *Grasping Arm Angle,* close the Clip to *Grasping Arm Angle*; if *Clip Arm Angle* is less than *Grasping Arm Angle*, *Unlock the Clip and Open the Clip Arms* to 180 degrees then close the Clip to *Grasping Arm Angle*.

20.5.5 Carefully inspect the Grippers to confirm the cover is intact and not damaged.

WARNING: DO NOT use the device if damage is detected. Use of damaged product may result in cardiac injury and / or may lead to inability to reduce MR.

20.5.6 *Raise the Grippers*.

CAUTION: Raising the Grippers more often than needed, retracting the Gripper Lever forcefully, or retracting the Gripper Lever more than 1.5 cm beyond the mark may damage the Gripper cover and impair CDS performance.

20.5.7 Unlock the Clip.

WARNING: Retracting the Lock Lever forcefully may result in the inability to lock or unlock the Clip. Damage could occur causing the Clip to not unlock or open. Inability to open the Clip may result in valve injury or lead to deployment of the Clip in an unintended location.

20.5.8 *Invert the Clip Arms*.

WARNING: DO NOT continue turning the Arm Positioner if resistance is felt. Use of damaged product may result in cardiac injury.

20.5.9 *Lock the Clip*.

20.5.10 Close the Clip to *Grasping Arm Angle*.

20.5.11 *Lower the Grippers* once to de-air the lumens.

20.5.12 Release the DC Fastener and torque the DC Handle clockwise and counterclockwise 1/4 turn while translating the shaft.

WARNING: Using excessive force when pulling the DC Radiopaque Ring against the Sleeve tip, while translating the DC shaft, may result in device damage including distal tip embolization.

20.5.13 Secure the DC Fastener with DC Handle fully advanced.

20.5.14 Close the Clip to a *Clip Arm Angle* of approximately 20 degrees.

20.5.15 *Establish Final Arm Angle*.

20.5.16 Return the *Arm Positioner to Neutral*.

20.5.17 *Unlock the Clip*.

20.5.18 *Open the Clip Arms* to *Grasping Arm Angle*.

20.5.19 *Lock the Clip*.

20.5.20 Return the *Arm Positioner to Neutral*.

20.5.21 Release the DC Fastener and retract the DC fully against the Sleeve.

20.5.22 Secure the DC Fastener.

20.5.23 Temporarily discontinue heparinized saline flushes.

The following steps should be performed just before use of the CDS:

20.5.24 Re-start heparinized saline flushes.

20.5.25 *Raise the Grippers*.

20.5.26 *Fully Close the Clip Arms*.

20.5.27 *Lower the Grippers*.

20.5.28 Without removing the protective cover, carefully slide the Clip Introducer over the Clip.

WARNING: DO NOT compress the Clip Arms. Compressing the Clip Arms may result in inability to open the Clip. Inability to open the Clip may result in valve injury or lead to deployment of the Clip in an unintended location.

20.5.29 Stop when the tip of the Clip is just proximal to the tip of the Clip Introducer.

20.5.30 Turn the *Arm Positioner to Neutral*.

WARNING: Failure to *Fully Close the Clip Arms*, before insertion or retraction into the Clip Introducer may result in difficulty or inability to advance or retract the Clip, which may result in vascular and / or cardiac injury, air embolism, and / or the need for surgical intervention.

WARNING: Heparinized saline flush should be continuous throughout the procedure. Ensure flow is visible through the drip chamber, that the tubing is free from kinks and / or obstruction and appropriate pressure of 300 mm Hg is maintained. Discontinuing flush may result in air embolism and / or thrombus formation.

21.0 ACCESS TO THE MITRAL VALVE

NOTE: This is a suggested sequence for the procedure. Variations may be used based upon patient anatomy.

21.1 Access the LA to accommodate the Guide tip using transvenous, transseptal techniques and equipment.

21.2 Heparinize the patient.

WARNING: Failure to administer heparin once transseptal access has been achieved may result in thrombus formation.

21.3 Carefully place a 260 cm super stiff 0.9 mm (0.035") exchange length guidewire in the left upper pulmonary vein or LA. Dilate the subcutaneous tissue and femoral vein to accommodate the Guide shaft using standard dilation technique.

22.0 STEERABLE GUIDE CATHETER INSERTION

WARNING: Confirm a smooth transition between the Dilator and the tip of the Guide to minimize the risk of vascular and / or cardiac injury.

CAUTION: Always use pressure monitoring, echocardiography and fluoroscopy for guidance and observation during use of the MitraClip™ System.

WARNING: Always use a careful, deliberate, and iterative approach to positioning the MitraClip™ System. It is recommended to make multiple small adjustments rather than single large adjustments. Large adjustments may result in vascular and / or cardiac injury.

22.1 Rotate the +/- Knob in the "-" direction until the Guide curve is substantially straightened.

22.2 Wet the surface of the Guide shaft with sterile saline.

22.3 Insert the Guide-Dilator assembly over the stationary guidewire into the femoral vein.

WARNING: DO NOT use excessive force to advance or manipulate the Guide-Dilator assembly. If resistance is encountered, use echocardiography and / or fluoroscopy to assess before proceeding. Use of excessive force may result in arrhythmias, vascular and / or cardiac injury, including creation of a clinically significant atrial septal defect.

22.4 Advance the Guide-Dilator assembly to the RA. Rotate the +/- Knob to Neutral, then place tip of the Dilator partially across the atrial septum.

22.5 Slowly dilate the atrial septum by gradually advancing the tip of the Guide-Dilator assembly.

WARNING: DO NOT rapidly advance the Guide-Dilator assembly across the atrial septum. Rapid advancement may result in vascular and / or cardiac injury**.**

22.6 Advance the Guide-Dilator assembly until the tip of the Guide extends approximately 3 cm in the LA.

22.7 Adjust Guide deflection and torque to position the tip away from adjacent tissues.

22.8 Place the Silicone Pad on the sterile drape over the Lift. Place the Stabilizer onto the Silicone Pad.

22.9 Secure the Guide in the Stabilizer slot using the Fastener. Ensure the Fastener engages the metallic tube on the Guide shaft. The Guide handle should be immediately adjacent to the Stabilizer, such that they are in contact with each other.

22.10 Retract the Dilator approximately 5 cm into the Guide, leaving the guide wire in the left upper pulmonary vein or LA.

CAUTION: Always loosen the Fastener before torquing the Guide to prevent stripping the screw.

22.11 Retract the guidewire into the tip of the Dilator. Remove the Dilator and guidewire while gently aspirating the Guide (starting when the Dilator is approximately halfway retracted into the Guide, approximately 40 cm) using a 50–60 cc syringe. Cover Guide Hemostasis Valve with finger upon Dilator removal.

NOTE: Avoid contacting tissue or creating a vacuum in the Guide lumen. If necessary, position the Guide handle below the level of the LA to allow blood to fill the Guide lumen.

WARNING: DO NOT create a vacuum while removing the dilator from the Guide; air may enter the lumen of the Guide which may result in air embolism.

WARNING: Failure to fully retract guidewire into the Dilator may result in air embolism.

23.0 CLIP DELIVERY SYSTEM INSERTION

23.1 Confirm the Guide lumen is completely de-aired.

WARNING: To minimize the potential of air embolism**,** DO NOT introduce the CDS into the Guide until the Guide lumen has been completely de-aired.

23.2 Confirm there is a slow, continuous heparinized saline flush through both the Sleeve and the DC.

CAUTION: Failure to continuously flush the CDS with heparinized saline may reduce device performance.

WARNING: Heparinized saline flush should be continuous throughout the procedure. Ensure flow is visible through the drip chamber and that tubing is free from kinks and / or obstruction and pressure of 300 mm Hg is maintained. Discontinuing flush may result in air embolism and / or thrombus formation.

23.3 Confirm tip of the Clip is just proximal to the tip of the Clip Introducer.

23.4 Carefully remove the protective cover surrounding the Clip and the Clip Introducer.

23.5 Confirm that the stopcock on the Clip Introducer flush port is closed and that the Clip Introducer is de-aired.

23.6 While flushing heparinized saline on the Guide Hemostasis Valve, place the tip of the Clip Introducer against the Guide Hemostasis Valve and advance the Clip Introducer straight into the valve in a continuous motion while rotating the Clip Introducer in small clockwise and counterclockwise motions until the Clip can be observed distal to the valve.

WARNING: DO NOT continue to advance the Clip Introducer if resistance is felt; the Guide Hemostasis Valve, Clip Introducer or the Clip may be damaged. Damage to these components may result in air embolism, vascular or cardiac injury.

WARNING: To minimize the potential of air embolism, ensure proper de-airing when inserting the Clip Introducer into the Guide Hemostasis Valve.

23.7 Leave the Clip Introducer fully inserted in the Guide Hemostasis Valve throughout the procedure.

23.8 Align the Longitudinal Alignment Marker on the Sleeve shaft with the Alignment Marker on the Guide Hemostasis Valve.

23.9 Turn the +/- Knob to neutral then carefully advance the CDS through the Guide under fluoroscopic guidance. Stop when the tip of the Clip is even with the tip of the Guide.

NOTE: If resistance to CDS advancement is felt, reduce Guide deflection.

23.10 Under echocardiographic guidance, advance the CDS and retract the Guide iteratively as needed while maintaining the Guide in the LA. Stop when the Guide RO Tip Ring is between the RO Alignment Markers of the Sleeve, as confirmed under fluoroscopic guidance.

23.11 Position the Sleeve Handle in the Stabilizer slot.

23.12 Confirm that the Clip is free from the left atrial wall and valve tissue.

WARNING: Failure to confirm that the Clip is free from the left atrial wall and valve tissue may result in cardiac injury.

24.0 INITIAL MITRACLIP™ SYSTEM POSITIONING IN THE LEFT ATRIUM

NOTE: Positioning is achieved with iterative adjustments of the Guide and CDS using torque, translation and knob adjustments. The goals of positioning are:

A. Positioning the Clip centrally over the valve with respect to anterior-posterior and medial-lateral directions.

B. Aligning the Clip so the DC Shaft is perpendicular to the plane of the mitral valve.

C. Positioning the distal tip of the Clip at least 1 cm above the leaflets.

WARNING: Excessive torque on the Guide and translation of the MitraClip™ System may inadvertently displace the tip of the Guide from the LA, which may result in arrhythmias or cardiac injury.

WARNING: DO NOT continue to rotate or manipulate any of the handle knobs if significant resistance is noted; device damage may occur and result in cardiac injury.

24.1 Adjust the Guide position as necessary to maintain that the Clip is free from adjacent tissue.

24.2 Adjust Sleeve deflection using the M/L Knob and / or the A/P Knob to deflect the Clip towards the apex. Retract the DC Radiopaque Ring against the Sleeve tip as necessary.

24.3 During Sleeve deflections confirm that the Guide RO Tip Ring is between the RO Alignment Markers of the Sleeve prior to making maximum Sleeve deflections.

WARNING: DO NOT deflect the Sleeve tip more than 90 degrees as device damage may occur. Use of damaged product may result in cardiac injury.

24.4 Secure the Sleeve handle in the Stabilizer using the Fastener.

24.5 To reposition the MitraClip™ System, move the Stabilizer and the system together until positioning is adequate.

24.6 Adjust the MitraClip™ System position to maintain adequate height above the mitral valve in the LA.

WARNING: Maintain the Clip above the leaflets until ready to grasp to minimize the risk of Clip entanglement in the chordal apparatus. Clip entanglement may result in cardiac injury, worsening mitral regurgitation, difficulty or inability to remove the Clip and conversion to surgical intervention.

25.0 FINAL MITRACLIP™ SYSTEM POSITIONING

25.1 *Raise the Grippers.*

CAUTION: Raising the Grippers more often than needed, retracting the Gripper Lever forcefully, or retracting the Gripper Lever more than 1.5 cm beyond the mark may damage the Gripper cover and impair CDS performance.

25.2 *Unlock the Clip* and *Open the Clip Arms*.

25.2.1 For MitraClip™ NTR: *Open the Clip Arms* to approximately 180 degrees.

25.2.2 For MitraClip™ XTR: *Open the Clip Arms* to approximately 60 degrees.

WARNING: Retracting the Lock Lever forcefully may result in the inability to unlock Clip. Inability to open the Clip may result in valve injury or lead to deployment of the Clip in an unintended location.

25.3 Adjust the MitraClip™ System to reposition the Clip as necessary. Confirm that the distal tip of the Clip is at least 1 cm above the leaflets.

25.4 Rotate the DC handle to align the Clip Arms perpendicular to the line of coaptation. DO NOT rotate the Clip more than 90 degrees in each direction.

25.5 Carefully translate the DC shaft multiple times to release stored torque. Fully retract the DC.

WARNING: Failure to fully release stored torque may result in unwanted Clip Arm orientation changes during grasping. Torque of the DC Handle more than 180 degrees may result in DC damage and cardiac injury.

25.6 For MitraClip™ NTR: Close the Clip to a *Clip Arm Angle* of approximately 60 degrees.

25.7 Complete final MitraClip™ System positioning in the LA using multiple imaging planes. Re-secure the Guide and Sleeve Fasteners.

26.0 GRASPING THE LEAFLETS AND VERIFYING THE GRASP

26.1 Advance the DC distally to position the Clip approximately 2 cm below the valve. Ensure that the Clip Arms are oriented perpendicular to the line of coaptation.

WARNING: Failure to confirm that the Clip Arms are perpendicular to the line of coaptation may result in loss of leaflet capture and insertion. Loss of leaflet capture and insertion may result in inadequate reduction of mitral regurgitation and may result in a single leaflet device attachment (SLDA).

WARNING: DO NOT make substantial Clip Arm orientation adjustment in the LV. Clip entanglement in chordae may result in cardiac injury and worsening mitral regurgitation; and may result in difficulty or inability to remove the Clip, and conversion to surgical intervention.

WARNING: Always ensure that either the Grippers are raised or that the Clip is closed while in the LV to avoid potential cardiac injury.

26.2 *Open the Clip Arms* to the *Grasping Arm Angle*.

26.3 Without using excessive force, retract the DC to grasp both anterior and posterior leaflets.

WARNING: An improper grasp will allow one or both leaflets to move freely. Closing and deploying the Clip in this situation may result in loss of leaflet capture and insertion. Loss of leaflet capture and insertion may result in inadequate reduction of mitral regurgitation and may result in a single leaflet device attachment (SLDA).

26.4 If the grasp appears satisfactory, *Lower the Grippers* onto the leaflets.

26.4.1 If both Grippers have not lowered:

26.4.1.1 *Lock the Clip.*

26.4.1.2 Confirm both Grippers have lowered.

26.4.1.3 *Unlock the Clip.*

WARNING: Failure to confirm that both Grippers have been lowered onto the leaflets prior to closing the Clip may result in loss of leaflet capture and insertion. Loss of leaflet capture and insertion may result in inadequate reduction of mitral regurgitation and may result in a single leaflet device attachment (SLDA).

WARNING: DO NOT adjust the position of the MitraClip™ System after grasping the leaflets, valve injury may occur.

26.5 Close the Clip until the *Clip Arm Angle* is approximately 60 degrees. Release tension on the DC and secure the DC Fastener.

26.6 Use echocardiographic imaging to verify insertion of both leaflets and satisfactory grasp by observation of:

- Leaflet immobilization
- Single or multiple valve orifice(s)
- Limited leaflet mobility relative to the tips of both Clip Arms
- Adequate MR reduction.

26.6.1 If grasping fails to hold both leaflets and the Clip retracts to the LA, reposition the MitraClip™ System.

26.6.1.1 *Open the Clip Arms* and reorient the Clip Arms in the LA, as needed, then repeat grasping steps (refer to Section 25.0 and 26.0).

26.6.1.1.1 If significant repositioning is necessary, *Fully Close the Clip Arms* and *Lower the Grippers* then repeat positioning and grasping steps.

26.6.2 If the Sleeve limits DC travel during grasping, an inadequate grasp may require repositioning of the MitraClip™ System.

26.6.2.1 *Raise the Grippers* and *Open the Clip Arms* to approximately 180 degrees for MitraClip™ NTR or 60 degrees for MitraClip™ XTR and advance the DC handle.

26.6.2.2 Repeat positioning and grasping steps as necessary (refer to Section 25.0 and 26.0)

27.0 CLOSING THE CLIP AND EVALUATING CLIP POSITION

27.1 *Lock the Clip.*

WARNING: Failure to *Lock the Clip* may result in loss of leaflet capture and insertion. Loss of leaflet capture and insertion may result in inadequate reduction of mitral regurgitation and may result in a single leaflet device attachment (SLDA).

27.2 Slowly close the Clip just until the leaflets are coapted and MR is sufficiently reduced. The Clip should maintain a distinct “V” shape.

WARNING: DO NOT use excessive force to close the Clip further than is necessary to adequately reduce MR. Leaflet injury may occur.

WARNING: Closing the Clip too tightly may result in inability to deploy the Clip. Inability to deploy the Clip may result in worsening mitral regurgitation, cardiac injury, a single leaflet device attachment (SLDA), and / or conversion to surgical intervention.

WARNING: Failure to turn the Arm Positioner at least ½ turn in the “Close” direction after locking the Clip may result in loss of leaflet capture and insertion. Loss of leaflet capture and insertion may result in inadequate reduction of mitral regurgitation and may result in a single leaflet device attachment (SLDA).

27.3 Use echocardiographic imaging to verify valve function, satisfactory coaptation, and insertion of both leaflets by observation of:

- Leaflet immobilization
- Single or multiple valve orifice(s)
- Limited leaflet mobility relative to the tips of both Clip Arms
- Adequate MR reduction.

27.3.1 If the Clip position is not satisfactory, *Raise the Grippers, Unlock the Clip* and *Invert the Clip Arms*.

27.3.2 Retract the inverted Clip into the LA.

27.3.3 Confirm both leaflets move freely.

27.3.4 Repeat positioning steps, as necessary, then repeat grasping steps.

28.0 MITRACLIP™ IMPLANT PRE-DEPLOYMENT CLIP ASSESSMENT

28.1 Confirm DC Handle is secure.

WARNING: Failure to secure the DC Handle may result in leaflet injury or loss of leaflet insertion with resultant worsening mitral regurgitation, single leaflet device attachment (SLDA), and / or conversion to surgical intervention.

28.2 *Establish Final Arm Angle*.

WARNING: DO NOT turn the Arm Positioner more than 1/2 turn in the "Open" direction once initial resistance is felt to prevent device deployment. Inability to deploy the Clip may result in worsening mitral regurgitation, cardiac injury, a single leaflet device attachment (SLDA), and / or conversion to surgical intervention.

28.3 Turn the Arm Positioner to the "closed" side of the neutral position.

28.3.1 Use echocardiographic imaging to verify valve function, satisfactory coaptation, and insertion of both leaflets by observation of:

- Leaflet immobilization
- Single or multiple valve orifice(s)
- Limited leaflet mobility relative to the tips of both Clip Arms
- Adequate MR reduction.

28.4 Perform mean pressure gradient assessment prior to proceeding to deployment.

28.5 Establish Gripper Line Removability.

WARNING: Failure to Establish Gripper Line Removability prior to deployment of the Clip may result in inability to remove the Gripper Line. Intervention may be required.

28.5.1 Confirm the Gripper Lever is fully advanced.

28.5.2 Increase the flush rate to the DC and Sleeve. Remove the Gripper Lever Cap and "O" ring. Unwrap the two ends of the Gripper Line. Remove the plastic cover from the lines and separate the two ends so that no twists or knots are present.

28.5.3 With one free end of the Gripper Line in each hand, confirm that the Gripper Line is removable by pulling slowly on one end until the other end of the Gripper Line moves approximately 3-5 cm. If the Gripper Line is confirmed to be removable, continue to Clip Deployment.

NOTE: If excessive resistance is noted, stop, and pull on the other free end.

WARNING: While Establishing Gripper Line Removability, ensure that both ends of the Gripper Line remain exposed. Failure to maintain exposure of both Gripper Line ends may result in an inability to remove the Gripper Line in its entirety and could lead to conversion to surgical intervention.

WARNING: Pulling the Gripper Line too quickly or with excessive force may raise the Grippers, break the Gripper Line and / or disturb leaflet capture and insertion. This may result in worsening mitral regurgitation, and could lead to a single leaflet device attachment (SLDA), and / or conversion to surgical intervention.

28.5.3.1 If excessive resistance is noted at both ends of the Gripper Line (resulting in failure to Establish Gripper Line Removability), stop and remove the Clip Delivery System.

NOTE: The removal of the Clip Delivery System is most easily accomplished with the aid of an assistant.

28.5.3.1.1 Hold both free ends of the Gripper Lines together and apply tension to maintain the Grippers in a raised position through Step 28.5.3.1.4.

28.5.3.1.2 *Unlock the Clip, Invert the Clip Arms* and then *Lock the Clip*.

28.5.3.1.3 Release the DC Fastener and retract the inverted Clip into the LA. Retract DC shaft until the DC Radiopaque Ring is fully against the tip of the Sleeve.

28.5.3.1.4 *Fully Close the Clip Arms* and continue to turn the Arm Positioner until it is no longer possible to rotate the Arm Positioner. Return the *Arm Positioner to Neutral.*

WARNING: Failure to follow Step 28.5.3.1.4 prior to retraction into the Guide may result in device damage, inability to remove the CDS and / or vascular and cardiac injury.

28.5.3.1.5 Continue to Section 31.2: MITRACLIP™ SYSTEM REMOVAL WITH CLIP ATTACHED to remove the Clip.

29.0 CLIP DEPLOYMENT

29.1 Deployment Step 1: Lock Line Removal

29.1.1 While holding the ends of the Lock Line remove the Lock Lever Cap and “O” ring. Unwrap the two ends of the Lock Line in a counterclockwise direction. Separate the ends of the Lock Line and remove the plastic cover from the lines so that no twists or knots are present.

WARNING: Do not let Line unravel freely. Do not remove Lock Line or plastic covers if line is bunched. Letting Line unravel freely may result in knots in the line. Removing Line if it is bunched may result in difficulty or inability to remove line due to knots or twists.

29.1.2 Grasp one of the free ends of the Lock Line, confirm the line moves freely, and slowly remove the Lock Line. Pull the Lock Line coaxial to the Lock Lever. If resistance is noted, stop and pull on the other free end to remove the Lock Line.

29.1.3 *Establish Final Arm Angle*.

NOTE: The Clip Arms may open slightly before remaining in a stable position. If Arms open more than slightly, close the Clip to the desired Arm position and re-*Establish Final Arm Angle*.

29.1.4 Turn the *Arm Positioner to Neutral*.

29.2 Deployment Step 2: Delivery Catheter Shaft Detachment

29.2.1 Confirm that the Arm Positioner is Neutral and that the two ends of the Gripper Line have been unwrapped from under the cap and are not twisted or knotted. Remove the Release Pin from the DC Handle.

29.2.2 Turn the Arm Positioner in the “Open” direction until the Release Pin groove is fully exposed.

NOTE: After the Release Pin is removed, turning the Arm Positioner in the “Open” direction will not open the Clip Arms.

29.2.3 Turn the Actuator Knob of the DC approximately 8 turns in the direction of the arrow printed on the Actuator Knob.

If it is difficult to turn the Actuator Knob, STOP and confirm that the Arm Positioner has been turned in the “Open” direction, such that the Release Pin groove is fully exposed.

WARNING: Failure to stop turning the Actuator Knob when resistance is felt may result in inability to deploy the Clip. Inability to deploy the Clip may result in worsening mitral regurgitation, cardiac injury, a single leaflet device attachment (SLDA), and / or conversion to surgical intervention.

29.2.4 Release the DC Fastener then retract the Actuator Knob approximately 0.5 cm after it is fully unthreaded.

29.2.5 Retract the DC Handle such that the Clip has separated at least 1 cm from the DC tip.

29.2.5.1 If resistance is felt during DC Detachment, confirm the Actuator Knob is retracted approximately 0.5 cm beyond the fully exposed Release Pin groove.

29.2.5.2 If resistance is still felt during DC Detachment, secure the DC fastener. Slowly re-position the Stabilizer and / or rotate the SGC until the angulation between the DC Shaft and the Clip is reduced or eliminated (as observed under fluoroscopic imaging).

29.2.5.3 If resistance is still felt during DC Detachment, release the DC Fastener, retract the Actuator Knob an additional 0.5 cm beyond the fully exposed Release Pin groove and repeat step 29.2.5.2 as needed.

29.2.6 Secure the DC Fastener.

29.2.7 Allow several minutes after catheter shaft detachment before proceeding to the final Clip deployment step. Use echocardiographic imaging to verify valve function, satisfactory coaptation, and insertion of both leaflets by observation of:

- Leaflet immobilization
- Single or multiple valve orifice(s)
- Limited leaflet mobility relative to the tips of both Clip Arms
- Adequate MR reduction.

WARNING: If Clip placement and / or MR reduction is not satisfactory after Deployment Step 2: Delivery Catheter Shaft Detachment, DO NOT proceed to Deployment Step 3: Gripper Line Removal. Intervention may be required to remove the Clip.

29.3 Deployment Step 3: Gripper Line Removal

29.3.1 Grasp one of the free ends of the Gripper Line, confirm the line moves freely and slowly remove the line. Pull the Gripper Line coaxial to the Gripper Lever. If resistance is noted, stop and pull on the other free end to remove the Gripper Line. Maintain at least 1 cm separation between the DC tip and the Clip while slowly removing the Gripper Line.

WARNING: If less than 1 cm separation is present between the DC tip and the Clip before or during Gripper Line retraction, it may be difficult to remove the Gripper Line in its entirety.

WARNING: Pulling the Gripper Line too quickly or with excessive force may raise the Grippers, resulting in device damage and / or compromise leaflet capture and insertion. This may result in worsening mitral regurgitation, and could lead to a single leaflet device attachment (SLDA).

29.3.1.1 If the Gripper Line does not move easily, release the DC Fastener and incrementally release Sleeve curves (M/L Knob and A/P Knob). Secure DC Fastener once Sleeve curves are released.

WARNING: Failure to release the DC Fastener before releasing Sleeve curves may result in device damage and / or embolization.

29.3.1.2 If the Gripper Line still does not move easily, partially release Guide curves.

29.3.1.3 If the Gripper Line still does not move easily, the CDS may also be partially retracted into the tip of the Guide, or completely removed by pulling only on the Sleeve Handle, to facilitate Gripper Line removal.

WARNING: Retracting the CDS by pulling on the DC Handle may result in device damage and / or embolization.

29.3.2 Release the DC Fastener and retract the DC Handle until the DC Radiopaque Ring is against the tip of the Sleeve.

29.3.3 Secure the DC Fastener.

29.3.4 Confirm that the Clip position is stable.

29.3.5 Use echocardiographic imaging to verify valve function, satisfactory coaptation, and insertion of both leaflets by observation of:

- Leaflet immobilization
- Single or multiple valve orifice(s)
- Limited leaflet mobility relative to the tips of both Clip Arms
- Adequate MR reduction.

29.4 If placing an additional Clip proceed to Section 30.0. If not placing an additional Clip proceed to Section 31.0.

30.0 ADDITIONAL MITRACLIP™ IMPLANT PLACEMENT

WARNING: Use caution not to displace or dislodge an implanted Clip when placing an additional Clip; Clip detachment from leaflet(s) may occur which may result in a single leaflet device attachment (SLDA) or device embolization.

30.1 When placing an additional Clip, the following are recommended:

30.1.1 In the LA, ensure Clip Arms are oriented perpendicular to the line of coaptation and Grippers are raised.

30.1.2 Cross into the LV with a *Clip Arm Angle* of < 60 degrees.

30.1.3 Use both fluoroscopy and echocardiography when crossing into the LV and during grasping.

30.1.4 *Open the Clip Arms* to approximately 180 degrees for MitraClip™ NTR or 60 degrees for MitraClip™ XTR.

30.1.5 Repeat positioning steps as necessary (refer to Section 25.0). Complete grasping steps (refer to Section 26.0)

WARNING: DO NOT use excessive force or retraction distance during grasping. This may compromise leaflet capture and insertion. Loss of leaflet capture and insertion may result in inadequate reduction of mitral regurgitation and may result in a single leaflet device attachment (SLDA).

31.0 MITRACLIP™ SYSTEM REMOVAL

WARNING: During MitraClip™ System removal always retract the CDS by pulling only on the Sleeve Handle. Retracting the CDS by pulling on the DC Handle may result in device damage and / or device or component embolization, and may result in vascular and / or cardiac injury.

WARNING: Failure to release the DC Fastener before releasing Sleeve curves may result in device damage and / or device or component embolization.

WARNING: Failure to utilize echocardiographic guidance while releasing Sleeve deflection may result in cardiac injury.

31.1 MitraClip™ System Removal After Clip Deployment

31.1.1 Removal of the CDS While Leaving the Guide in Place.

31.1.1.1 Release the DC Fastener.

31.1.1.2 Slowly release Sleeve deflection by rotating the M/L Knob and the A/P Knob to neutral.

31.1.1.3 Secure DC Fastener once Sleeve curves are released.

31.1.1.4 Straighten the Guide with the +/- Knob when the Delivery Catheter tip is free from the left atrial wall and the mitral valve.

31.1.1.5 Release the Sleeve Fastener and retract the CDS approximately 10 cm into the Guide by pulling only on the Sleeve Handle.

31.1.1.6 Confirm that the Clip Introducer is still fully advanced in the Guide Hemostasis Valve.

31.1.1.7 Retract the CDS by pulling only on the Sleeve Handle and position the Delivery Catheter tip inside the Clip Introducer. Begin gently aspirating the Guide (starting when the CDS is approximately halfway into the Guide, approximately 40 cm retracted) using a 50–60 cc syringe.

31.1.1.8 Remove the CDS and the Clip Introducer simultaneously from the Guide by pulling on the Sleeve shaft and Clip Introducer. Ensure the Delivery Catheter tip is inside the Clip Introducer by visualizing the Proximal Sleeve alignment marker just outside the Clip Introducer. Aspirate the Guide during removal of the CDS and Clip Introducer. Cover Guide Hemostasis Valve with finger upon CDS removal. If necessary, position the Guide Handle below the level of the LA to allow blood to fill the Guide Lumen.

WARNING: DO NOT remove the tip of the CDS from the Guide without removing the Clip Introducer simultaneously. Failure to remove the Clip Introducer simultaneously may result in air embolism.

WARNING: DO NOT create a vacuum while removing the CDS from the Guide; air may enter the lumen of the Guide which may result in air embolism.

31.1.1.9 Aspirate using a 50–60 cc syringe to remove any remaining air from the Guide.

31.1.2 Removal of the CDS and Guide simultaneously.

31.1.2.1 Release the DC Fastener.

31.1.2.2 Slowly release Sleeve curves by rotating the M/L Knob and the A/P Knob to neutral.

31.1.2.3 Secure the DC Fastener once Sleeve curves are released.

31.1.2.4 Straighten the Guide with the +/- Knob when the Delivery Catheter tip is free from the left atrial wall and the mitral valve.

31.1.2.5 Release the Sleeve Fastener and retract the CDS approximately 10 cm into the Guide by pulling only on the Sleeve Handle.

31.1.2.6 Carefully retract the Guide tip into the RA. The Guide may be straightened further with the +/- Knob if desired.

31.1.2.7 Remove the MitraClip™ System from the femoral vein, while providing hemostasis.

31.2 MitraClip™ System Removal with Clip Attached

31.2.1 Removal of the CDS while leaving the Guide in place.

31.2.1.1 Confirm Clip is locked.

31.2.1.2 *Fully Close the Clip Arms* and continue to turn the Arm Positioner until it is no longer possible to rotate the Arm Positioner. Return the *Arm Positioner to Neutral*.

WARNING: Failure to follow Step 31.2.1.2 prior to retraction into the Guide may result in device damage, inability to remove the CDS and / or vascular and cardiac injury.

31.2.1.3 *Lower the Grippers*.

31.2.1.4 Release the DC Fastener and retract the DC Handle until the DC Radiopaque Ring is fully against the tip of the Sleeve.

31.2.1.5 Slowly release Sleeve deflection by rotating the M/L Knob and the A/P Knob to neutral.

31.2.1.6 Rotate DC handle such that the clip arms are perpendicular to the guide curve plane.

31.2.1.7 Secure the DC Fastener once Sleeve curves are released.

31.2.1.8 Straighten the Guide with the +/- Knob when the tip of the MitraClip™ Implant is free from the left atrial wall and the mitral valve.

WARNING: Failure to straighten the Guide prior to retracting the Clip into the Guide may result in device damage, inability to remove the CDS and / or vascular and cardiac injury.

31.2.1.9 Release the Sleeve Fastener and retract the CDS into the Guide by pulling only on the Sleeve Handle.

NOTE: If resistance is noted, advance and rotate the Clip by rotating the DC Handle then retract the CDS into the Guide. The Guide and / or Sleeve position may also be adjusted to facilitate Clip entry into the Guide. If necessary, retract the Sleeve or advance the Clip to create a 2–3 cm separation to facilitate Clip entry into the Guide.

WARNING: Failure to utilize fluoroscopic guidance while retracting the CDS into the Guide may result in device damage, inability to remove the CDS and / or vascular and cardiac injury.

31.2.1.10 Confirm that the Clip Introducer is still fully advanced in the Guide Hemostasis Valve.

31.2.1.11 Retract the CDS by pulling only on the Sleeve Handle and position the Clip inside the Clip Introducer. Begin gently aspirating the Guide (starting when the CDS is approximately halfway into the Guide, approximately 40 cm retracted) using a 50–60 cc syringe.

31.2.1.12 Remove CDS and Clip Introducer simultaneously from the Guide by pulling on the Sleeve shaft and Clip Introducer. Ensure the Clip is inside the Clip Introducer by visualizing the Proximal Sleeve alignment marker just outside the Clip Introducer. Aspirate the Guide during removal of the CDS and Clip Introducer. If necessary, position the Guide Handle below the level of the LA to allow blood to fill the Guide lumen.

WARNING: DO NOT remove the tip of the CDS from the Guide without removing the Clip Introducer simultaneously and with the Clip inside the Clip Introducer. Failure to remove the Clip Introducer simultaneously may result in air embolism.

WARNING: DO NOT create a vacuum while removing the CDS from the Guide; air may enter the lumen of the Guide which may result in air embolism.

WARNING: DO NOT re-use the CDS after removal. Replace the CDS with a new device. Reinserting the CDS after removal may result in inability to open the Clip. Inability to open the Clip may result in valve injury or lead to deployment of the Clip in an unintended location.

31.2.1.13 Aspirate using a 50–60 cc syringe to remove any remaining air from the Guide.

31.2.2 Simultaneous removal of CDS and Guide.

31.2.2.1 Confirm Clip is locked.

31.2.2.2 *Fully Close the Clip Arms* and continue to turn the Arm Positioner until it is no longer possible to rotate the Arm Positioner. Return the *Arm Positioner to Neutral*.

WARNING: Failure to follow Step 31.2.2.2 prior to retraction into the Guide may result in device damage, inability to remove the CDS and / or vascular and cardiac injury.

31.2.2.3 *Lower the Grippers*.

31.2.2.4 Release the DC Fastener and retract the DC Handle until the DC Radiopaque Ring is fully against the tip of the Sleeve.

31.2.2.5 Slowly release Sleeve deflection by rotating the M/L Knob and the A/P Knob to neutral.

31.2.2.6 Rotate DC handle such that the Clip Arms are perpendicular to the guide curve plane.

31.2.2.7 Secure the DC Fastener once Sleeve curves are released.

31.2.2.8 Straighten the Guide with the +/- Knob when the tip of the MitraClip™ Implant is free from the left atrial wall and the mitral valve.

WARNING: Failure to straighten the Guide prior to retracting the Clip into the Guide may result in device damage, inability to remove the CDS and / or vascular and cardiac injury.

31.2.2.9 Release the Sleeve Fastener and retract the CDS approximately 10 cm into the Guide by pulling only on the Sleeve Handle.

NOTE: If resistance is noted, advance and rotate the Clip by rotating the DC Handle then retract the CDS into the Guide. The Guide and / or Sleeve position may also be adjusted to facilitate Clip entry into the Guide. If necessary, retract the Sleeve or advance the Clip to create a 2–3 cm separation to facilitate Clip entry into the Guide.

WARNING: Failure to utilize fluoroscopic guidance while retracting the CDS into the Guide may result in device damage, inability to remove the CDS and / or vascular and cardiac injury.

31.2.2.10 Carefully retract the Guide tip into the RA. The Guide may be straightened further with the +/- Knob if desired.

31.2.2.11 Remove the MitraClip™ System from the femoral vein, while providing hemostasis.

32.0 PATENTS AND TRADEMARKS

This product and / or its use are covered by one or more of the following United States Patents: 8,057,493; 7,736,388; 7,682,369; 7,666,204; 7,655,015; 7,608,091; 7,604,646; 7,563,267; 7,288,097; 7,226,467; 7,048,754; 6,770,083; 6,752,813; 6,629,534; 6,461,366. Other U.S. patents pending. Foreign patents issued and pending.

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GRAPHICAL SYMBOLS FOR MEDICAL DEVICE LABELING - Source reference for recognized symbols retained at the manufacturer in the Medical Device File.

	Batch code		Do not resterilize
	Catalogue number		Do not reuse
	Use-by date		Non-pyrogenic
	Sterilized using ethylene oxide.		Keep away from sunlight
	Consult instructions for use		Keep dry
	Caution		Do not use if package is damaged.
	MR Conditional		Manufacturer
	Date of manufacture		Inner diameter
	Packaging Unit (numeral represents quantity of units inside)		CAUTION: Federal law restricts this device to sale by or on the order of a physician.