# MITRACLIP® CLIP DELIVERY SYSTEM

**MITRACLIP SYSTEM**
**Ref No. CDS0201 Clip Delivery System**
**Ref No. SGC0101 Steerable Guide Catheter**

Rx ONLY

**MITRACLIP SYSTEM ACCESSORIES**
**Ref No. SZR01ST Stabilizer**
**Ref No. LFT01ST Lift**
**Ref No. PLT01ST Support Plate**

***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 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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Abbott


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**Imperative Care Ex. 1075**

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## 1.0 INDICATION FOR USE

The MitraClip 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.

## 2.0 CONTRAINDICATIONS

The MitraClip Clip Delivery System is contraindicated in DMR 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. Treatment of non-prohibitive risk DMR patients should be conducted in accordance with standard hospital practices for surgical repair and replacement.**
- MitraClip is intended to reduce mitral regurgitation. The MitraClip procedure is recommended to be performed when an experienced heart team has determined that reduction of MR to ≤2+ is reasonably expected following the MitraClip. If MR reduction to ≤2+ is not achieved, the benefits of reduced symptoms and hospitalizations, improved quality of life, and reverse LV remodeling expected from MitraClip may not occur.
- The MitraClip 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 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.
- Inspect all product prior to use. DO NOT use if the package is opened or damaged.

## 4.0 PRECAUTIONS

- Patient Selection:
  - 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 > 60mm. MitraClip should be used only when criteria for clip suitability for DMR have been met.
- The major clinical benefits of MitraClip are reduction of MR to ≤2+ resulting in reduced hospitalizations, improved quality of life, reverse LV remodeling and symptomatic relief in patients who have no other therapeutic option. No mortality benefit following MitraClip therapy has been demonstrated.
- 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.
- The heart team may determine an in-person surgical consult is needed to complete the assessment of prohibitive risk. The experienced mitral valve surgeon and heart team should take into account the outcome of this surgical consult when making the final determination of patient risk status.
- For reasonable assurance of device effectiveness, pre-procedural evaluation of the mitral valve and underlying pathologic anatomy and procedural echocardiographic assessment are essential.
- The inside of the outer pouch is not a sterile barrier. The inner pouch within the outer pouch is the sterile barrier. Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.
- Note the “Use by” date specified on the package.

## 5.0 SPECIAL PATIENT POPULATIONS

*Mitral Valve Etiology*
Safety and effectiveness of the MitraClip device has not been established in patients with MR due to underlying ventricular pathology (functional mitral regurgitation or FMR).

*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 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 ≥ 4.0cm$^2$
- 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.

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

## 7.0 PATIENT COUNSELING

Patients undergoing any procedures known to potentially be associated with bacteremia after implantation of the MitraClip 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 Device. Prescribe anticoagulation and other medical therapy per institutional guidelines.

After placement of a MitraClip 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 Device:

- Discuss the risks associated with MitraClip 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) MitraClip Device, one (1) Clip Delivery System, one (1) MitraClip Device Implant Card.

### 8.2 Sterile

For the Clip Delivery System and Steerable Guide Catheter only: these devices are provided sterile, in a thermoformed tray with lid, in sealed pouches.

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

Confirm the “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 re-sterilize. DO NOT use if the package is opened or damaged. Cleaning, re-sterilization and/or re-use may result in infections, malfunction of the device and other serious injury or death.

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 re-sterilize. Cleaning, re-sterilization and/or re-use may result in infections, malfunction of the device and other serious injury or death.

### 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

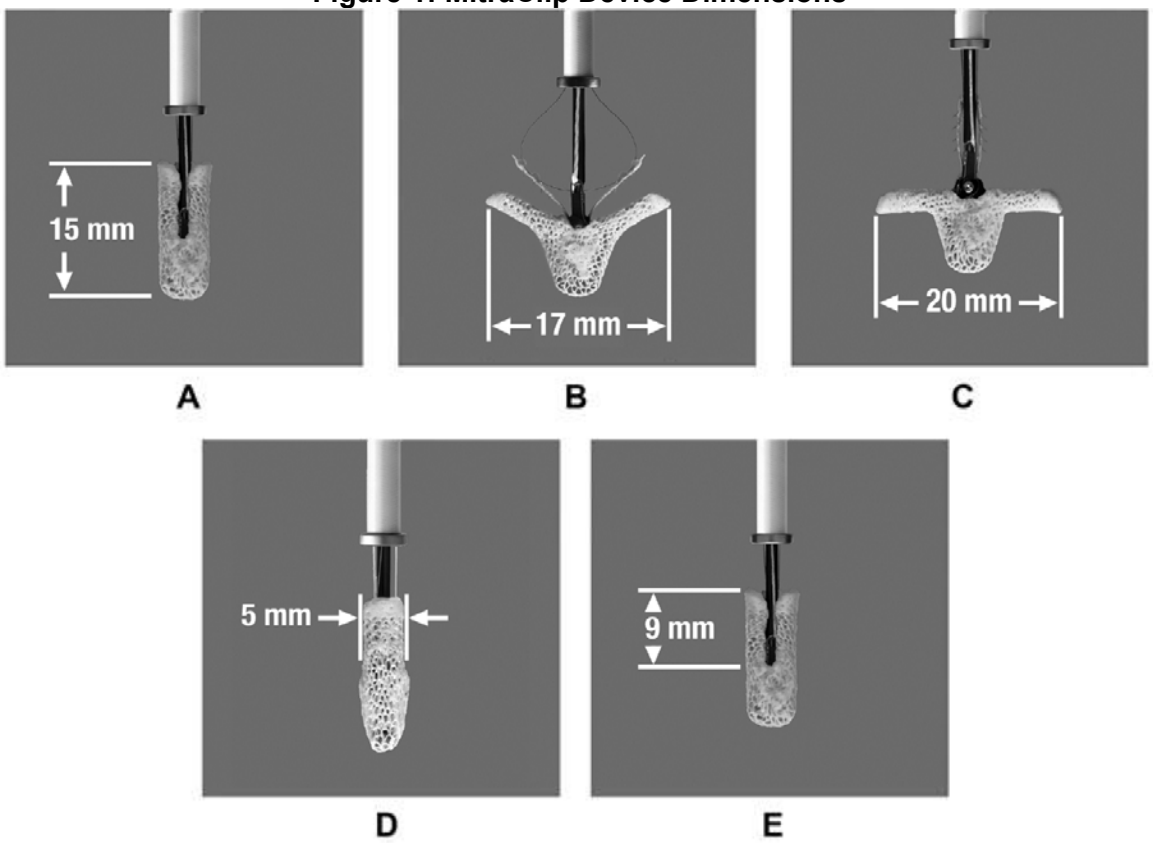
Handle with care. Store in original packaging. Keep dry. Keep away from sunlight.

## 10.0 MITRACLIP SYSTEM DIMENSIONS

**Table 1: MitraClip 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 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 1: MitraClip 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 Device (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.

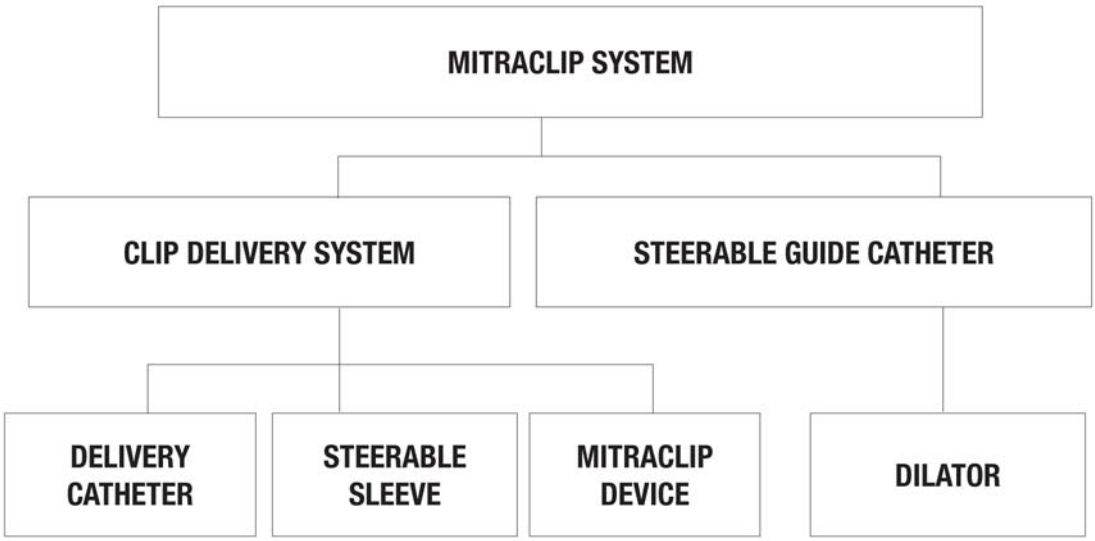
The Clip Delivery System consists of three major components:

1) The Delivery Catheter

2) The Steerable Sleeve and

3) The MitraClip 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 System.




The Clip Delivery System (Figures 2 and 4) is used to advance and manipulate the implantable MitraClip 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 Device (Figure 6) is a percutaneously implanted mechanical Clip. The MitraClip Device grasps and coapts the mitral valve leaflets resulting in fixed approximation of the mitral leaflets throughout the cardiac cycle. The MitraClip Device is placed without the need for arresting the heart or cardiopulmonary bypass. The implantable MitraClip Device is manufactured with metal alloys and polyester fabric (Clip cover) that are commonly used in cardiovascular implants.

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

Non-clinical testing has demonstrated the MitraClip Device is magnetic resonance conditional. It can be scanned safely under the following conditions:

- Static magnetic field up to 3 Tesla;
- Maximum spatial gradient in static field of 2500 gauss/cm or less;
- Maximum whole-body averaged specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of scanning.

In non-clinical testing, the MitraClip produced a temperature rise of less than 1°C at a maximum whole body averaged specific absorption rate (SAR) of 3 W/kg, as assessed by calorimetry for 15 minutes of MR scanning in a 3T system using a GE Signa HDx 3.0 T MR scanner.

Magnetic resonance image quality may be compromised if the area of interest is in the exact same area, or relatively close to the MitraClip Device. A maximum image artifact of 60 x 70 mm was measured in testing conducted in a 3T magnetic resonance system. It may be necessary to optimize the magnetic resonance imaging parameters due to the presence of the implant.

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

Figure 2: Clip Delivery System (CDS)

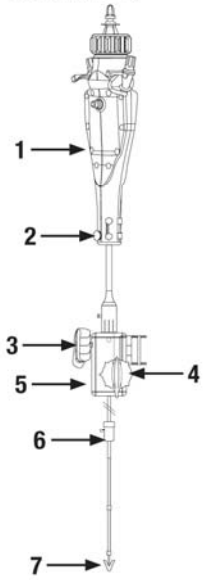



Figure 3a: Steerable Guide Catheter

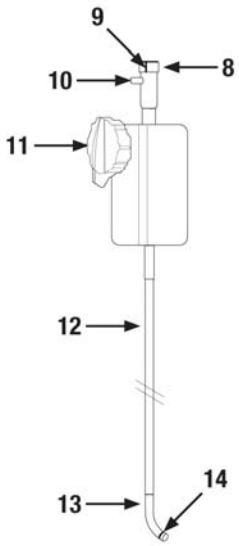



Figure3b: Dilator

Figure 4:CDS Handles

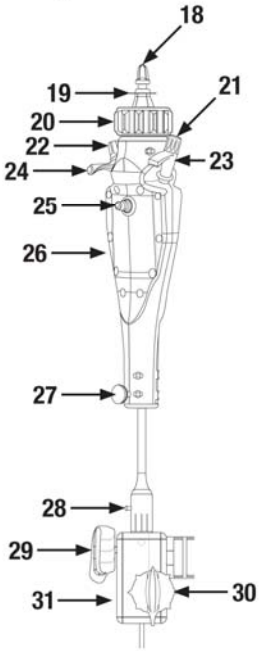



Figure 5:CDS Distal End

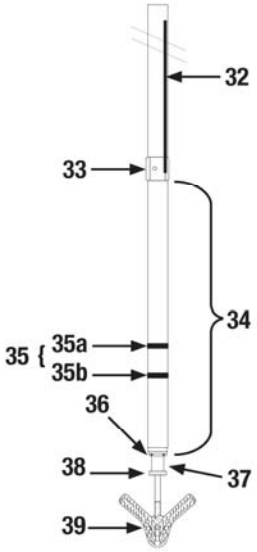



**Figure 6: MitraClip Device Positions**

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 2: MitraClip System Handle Controls**

| Device | Control | Function |
|---|---|---|
| Steerable Guide Catheter | +/- Knob | Tip deflection |
| Steerable Sleeve | M/L Knob<br>A/P Knob | Tip deflection<br>Tip deflection |
| Delivery Catheter | Lock Lever<br>Gripper Lever<br>Arm Positioner<br>DC Fastener<br>Lock Lever Cap<br>Release Pin<br>Actuator Knob<br>Gripper Lever Cap | Locks-Unlocks Clip via Lock Line<br>Raises-Lowers Grippers via Gripper Line<br>Opens-Closes Clip Arms<br>Locks-Unlocks DC translation/torque<br>Controls removal of Lock Lines<br>Prevents Actuator Knob turning<br>Turns actuator shaft for Clip deployment<br>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 0.9mm (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 3 presents an overview of the MitraClip clinical program in the United States including study design, enrollment criteria, endpoints and sample size.

## Table 3: Overview of MitraClip US Clinical Trials

| Type | Study | Key Inclusion Criteria | Key Exclusion Criteria | Endpoint | sites | patients |
|---|---|---|---|---|---|---|
| Feasibility | EVEREST I<br><br>enrollment<br>2003-2006 | • MR≥3+<br>• Symptomatic or asymptomatic with[a]:<br>LVEF 30-50% and/or LVESD 50-55mm or<br>LVEF 50-60% and LVESD < 45 mm or<br>LVEF>60 and LVESD 45-55 mm<br>• Candidate for mitral valve surgery including cardiopulmonary bypass | • LVEF<30%, and/or LVESD >55mm<br>• Mitral valve orifice area <4.0 cm2<br>• 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<br><br>enrollment<br>2005-2008 | MR≥3+<br>• Symptomatic with LVEF > 25% and LVESD ≤ 55 mm or asymptomatic with[a]:<br>LVEF 25% to 60%<br>LVESD ≥ 40 mm<br>New onset of atrial fibrillation<br>PASP>50mmHg at rest of >60 mmHg with exercise | • LVEF≤25%, and/or LVESD >55mm<br>• Mitral valve orifice area <4.0 $cm^2$<br>• 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<br>Primary Effectiveness: Freedom from death, MV surgery (for Device group) or re-operation (for Control group), and MR > 2+ at 12 months<br>• Secondary Effectiveness:<br>• Measures of LV Function<br>• SF-36 quality of life<br>• NYHA Functional Class | 37 | 60<br>roll-in<br><br>178 [b]<br>Device<br><br>80 [b]<br>Surgical<br>Control |
| Single-Arm Registry | EVEREST II High Risk Registry Study<br><br>enrollment<br>2007-2008 | MR≥3+<br>• 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:<br>1. Porcelain aorta, mobile ascending aortic atheroma<br>2. Post-radiation mediastinum<br>3. Previous mediastinitis<br>4. Functional MR with EF<40<br>5. Over 75 years old with EF<40<br>6. Re-operation with patent grafts<br>7. Two or more prior chest surgeries<br>8. Hepatic cirrhosis<br>9. Three or more of the following STS high risk factors<br>9.1 Creatinine > 2.5 mg/dL<br>9.2 Prior chest surgery<br>9.3 Age over 75<br>9.4 EF<35 | • LVEF<20% and/or LVESD>60mm<br>• Mitral valve orifice area <4.0 $cm^2$<br>• 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<br>• Major Secondary:<br>• Measures of LV Function<br>• SF-36 quality of life<br>• NYHA Functional Class<br>• CHF Hospitalizations<br>• Secondary Safety:<br>• Major Adverse Event rate at 30 days and 12 months | 25 | 78 |
| Continued Access Registry | REALISM High Risk<br><br>enrollment<br>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<br><br>enrollment<br>2009-2011 | • Same as RCT | • Same as RCT | • Same as RCT<br>• 6 Minute Walk Test (6MWT) Distance[d] | 39 | 272 |

[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.



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## 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 FMR or DMR 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 3. 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.

## 16.0 CLINICAL RESULTS IN PROHIBITIVE RISK DMR PATIENTS

Data on 127 patients with significant symptomatic mitral regurgitation due to primary abnormality of the mitral apparatus (DMR) determined to be at prohibitive risk for mitral valve surgery (Prohibitive Risk DMR Cohort or PR DMR 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 DMR) 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 DMR patients treated with the MitraClip were elderly with a high rate of serious comorbidities (Table 4).

**Table 4: Prohibitive Risk DMR MitraClip Cohort – Key Baseline Characteristics**

| Baseline Characteristic[a] | Prohibitive Risk DMR 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 5). 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 5: Prohibitive Risk DMR MitraClip Cohort - Procedural Results**

| Procedural Result [a] | Mean±SD (N)<br>Median (Min, Max)[a] |
|---|---|
| Procedure Time[b] (min) | 157±81 (124)<br>134 (39, 524) |
| Device Time[c] (min) | 125±75 (124)<br>110 (9, 511) |
| Fluoroscopy Duration (min) | 46±26 (126)<br>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 6).

**Table 6: Prohibitive Risk MitraClip DMR 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 7: Prohibitive Risk DMR MitraClip Cohort - Procedural Mortality**

| | |
|---|---|
| **Observed Procedural Mortality, % (n/N)**<br>95% CI[a,c] | 6.3% (8/127)<br>(2.8%, 12.0%) |
| **STS v2.73 Replacement Risk Score**<br>Mean (95% CI[b,c])<br>Median (95% CI[b,c]) | <br>13.2% (11.9%, 14.5%)<br>12.4% (11.3%, 13.7%) |
| **STS v2.73 Repair Risk Score**<br>Mean (95% CI[b,c])<br>Median (95% CI[b,c]) | <br>9.5% (8.5%, 10.6%)<br>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 DMR 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 8: Prohibitive Risk DMR MitraClip Cohort - CEC Adjudicated Major Adverse Events at 30 Days and 12 Months**

| Description of Event | Prohibitive Risk DMR 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 cm2 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 9: Prohibitive Risk DMR 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 DMR. Table 10 shows both groups were comprised of elderly patients, with a majority of patients over the age of 75 years. The Duke High Risk DMR Cohort reported a lower LVEF at baseline and a higher proportion of female patients than the Prohibitive Risk DMR Cohort. The Prohibitive Risk DMR 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 7 and Table 11 display Kaplan-Meier curves comparing survival in the Prohibitive Risk DMR patients to the Duke High Risk DMR patients. Based on these Kaplan-Meier curves, mortality in the Prohibitive Risk DMR 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 DMR 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 DMR patients who undergo the MitraClip procedure over non-surgical management.

**Table 10: Baseline and Demographic Characteristics – Prohibitive Risk DMR and Duke High Risk DMR Cohorts**

| Baseline Characteristic[a] | Prohibitive Risk DMR MitraClip Cohort % (n/N) (N = 127) | Duke High Risk DMR 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 7: Kaplan-Meier Freedom from Mortality –**
**Prohibitive Risk DMR MitraClip and Duke High Risk DMR Medical Therapy Patients**

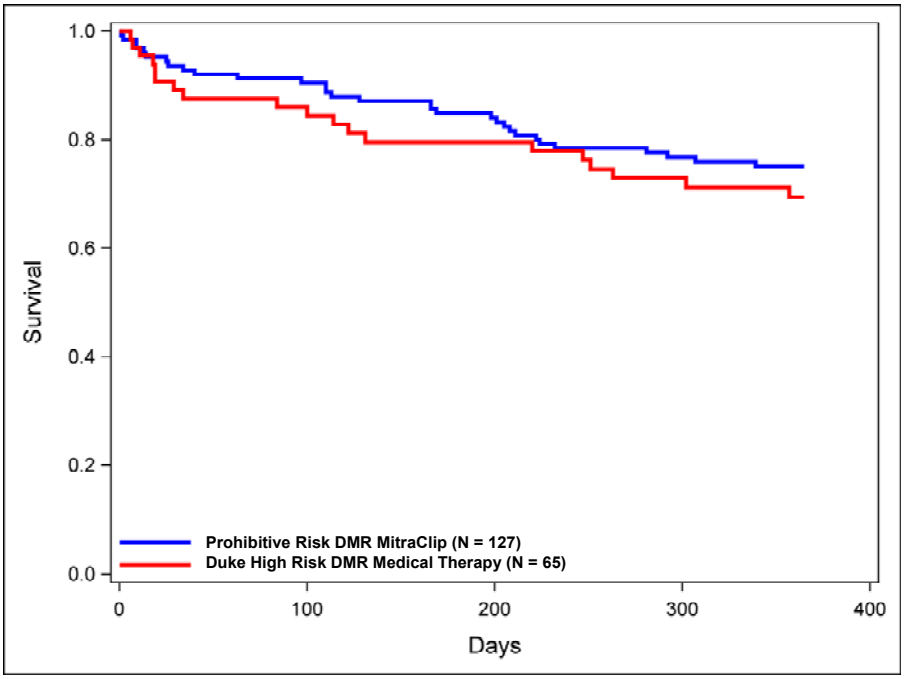



**Table 11: Number at Risk, Kaplan-Meier Estimates and 95% CIs**

| Time Post Index Procedure | Baseline | 30 Days | 6 Months | 12 Months |
|---|---|---|---|---|
| **Prohibitive Risk DMR 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 DMR 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 12 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 12: Prohibitive Risk DMR 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 13), characterized largely by a clinically important decrease in diastolic volume (-16.6 ml) and dimension (-0.2cm).

**TABLE 13: PROHIBITIVE RISK DMR 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 14 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 14: Prohibitive Risk DMR 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 15 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 15: Prohibitive Risk DMR 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 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: Prohibitive Risk DMR 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 17 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 17: Prohibitive Risk DMR 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 18) between the pre-enrollment and the post-discharge 12-month periods.

**Table 18: Prohibitive Risk DMR 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 12). 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 19: Effectiveness in Prohibitive Risk DMR 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.

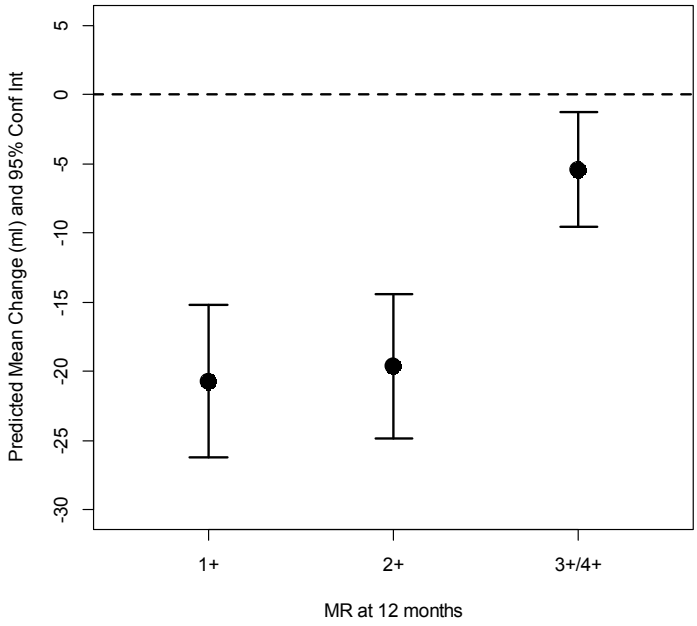
Reduction in MR severity was assessed in patients who have 2-year follow-up available. Table 20 shows that MR reduction in surviving patients to ≤ 2+ and ≤ 1+ is 82.5% (33/40) and 35.0%, (14/40) respectively, at 2 years. Therefore, there is no evidence of deterioration of MR severity from 12 months to 2 years in surviving patients.

**Table 20: Prohibitive Risk DMR 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) |

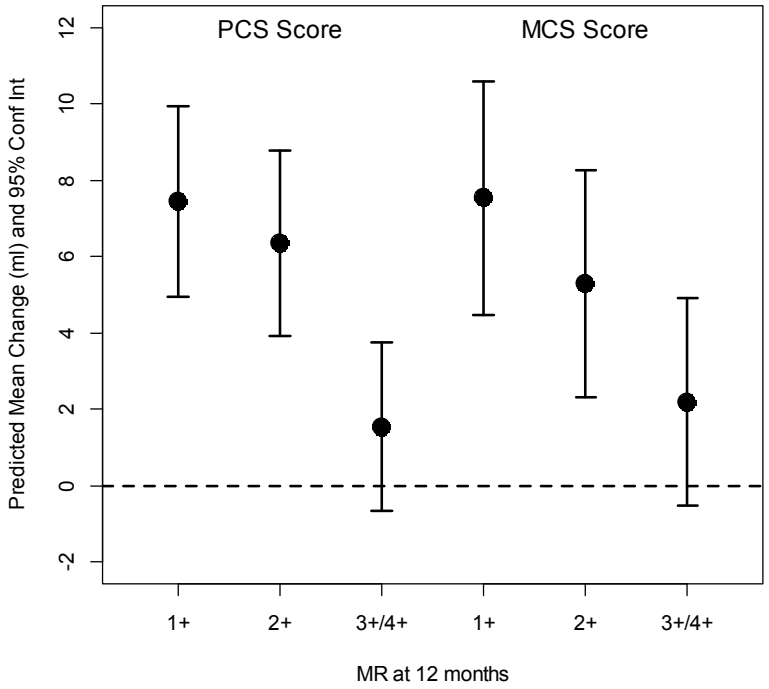
In order to evaluate the relationship between MR severity and measures of effectiveness, statistical models were fit to the effectiveness data. MR severity was importantly associated with LVEDV in the Prohibitive Risk DMR MitraClip patients (Figure 8). Reduction of MR severity to ≤ 2+ at 12 months resulted 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 8: Prohibitive Risk DMR 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 DMR 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 9). 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 9: Prohibitive Risk DMR MitraClip Cohort - Dose-Response Relationship between MR Severity and Change in SF-36 12 Months over Baseline**



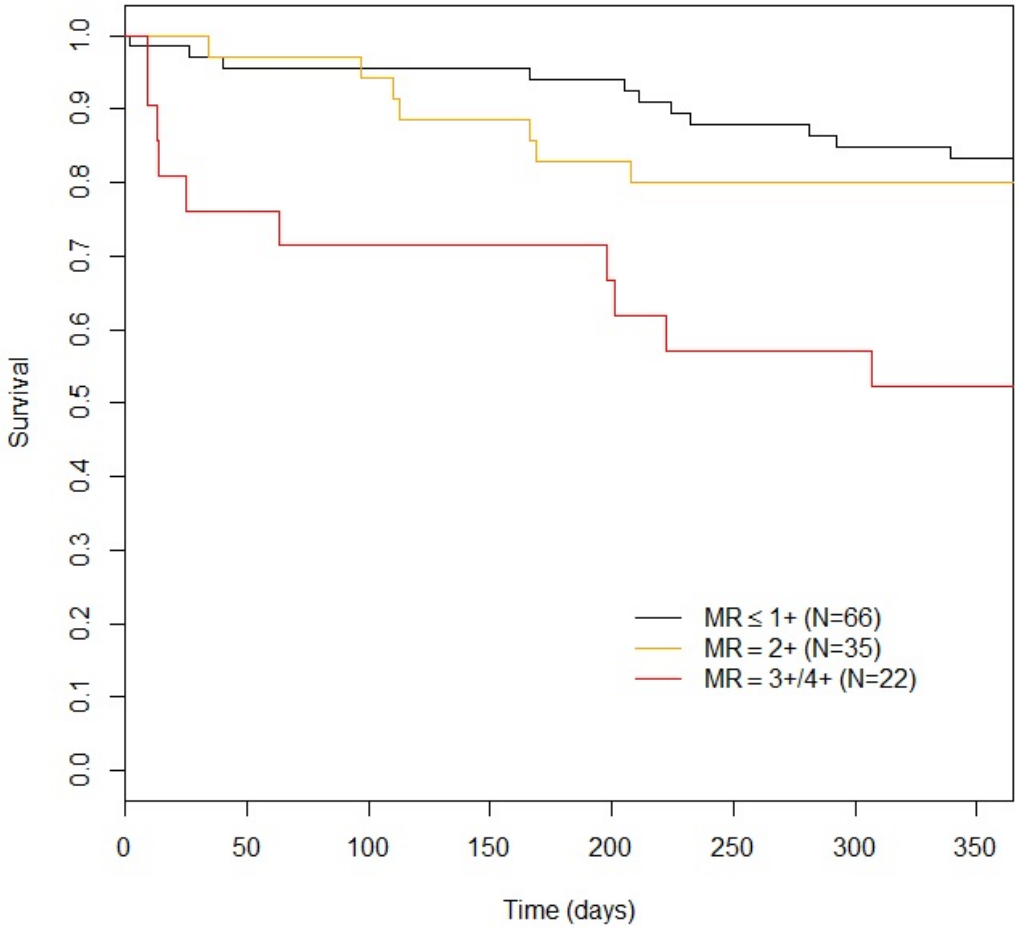

The observed number and corresponding estimated proportions of NYHA Classes at 12 months by two discharge MR groups are summarized in Table 21. The results demonstrate that reduction of MR to 2+ or less at discharge is associated with improved NYHA Functional Class that is not observed with MR of 3+ or greater at discharge.

**Table 21: Prohibitive Risk DMR 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 10). 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 10: Prohibitive Risk DMR MitraClip Cohort - Kaplan-Meier Survival Curves by Discharge MR Severity (≤1+, 2+, 3+/4+)**



## 17.0 MITRACLIP PROCEDURE STEP-BY-STEP INSTRUCTIONS

### 17.1 DEFINITION OF TERMS

***Defined Terms are in italics throughout document.***

| TERM | DEFINITION AND RELATED TECHNIQUE |
|---|---|
| *Lock the Clip* | 1. Rotate the Lock Lever outward.<br>2. Fully advance the Lock Lever.<br>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.<br>2. Rotate the Lock Lever inward to engage the lever.<br>3. Turn the Arm Positioner at least 1/2 turn in the "Close" (clockwise) direction.<br>4. Turn the Arm Positioner in the "Open" (counter-clockwise) direction until the desired *Clip Arm Angle* is achieved.<br>5. *Lock the Clip.*<br>**CAUTION:** Always *Lock the Clip* immediately after the desired *Clip Arm Angle* is achieved. Device damage may occur.<br>**NOTE 1**: If Clip does not open smoothly, retract the Lock Lever farther, then repeat steps 2 – 5.<br>**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:<br>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.<br>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.<br>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.<br>D. Advance the Gripper Lever and repeat NOTE 2, Step C. Retract the Gripper Lever after Clip opens.<br>E. If the Clip is in the LA and free of tissue, release the DC Fastener, then release the Sleeve curves and repeat NOTE 2, Step C.<br>**WARNING:** Failure to release the DC Fastener before releasing Sleeve curves may result in device damage and/or embolization.<br>If the Clip does not open after performing all steps in NOTE 2, DO NOT use the device. |

| TERM | DEFINITION AND RELATED TECHNIQUE |
|---|---|
| *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.<br>2. Turn the Arm Positioner at least 1/2 turn in the “Close” direction.<br>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.<br>4. *Lock the Clip*. |
| *Raise the Grippers* | 1. Rotate the Gripper Lever outward.<br>2. Slowly retract the Gripper Lever (under fluoroscopic observation) until the mark on the lever is just exposed.<br>**NOTE:** If pulling beyond the mark is required, advance the Gripper Lever back to the mark once the Grippers are fully raised.<br>3. Rotate the Gripper Lever inward to engage the lever. |
| *Lower the Grippers* | 1. Rotate the Gripper Lever outward.<br>2. Fully advance the Gripper Lever.<br>3. Rotate the Gripper Lever inward to engage the lever. |
| *Clip Arm Angle* | • Angle between the inner edges of both Clip Arms.<br>• All *Clip Arm Angles* are measured using fluoroscopy with optimal view in plane of “V” (see Figure 6). |
| *Grasping Arm Angle* | A *Clip Arm Angle* of approximately 120 degrees.<br>**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.<br>• Under direct visualization, the Clip is fully closed when the Clip Covering contacts the DC.<br>• Under fluoroscopic observation, the Clip is fully closed when the inner edges of the Clip Arms are parallel.<br>**CAUTION:** Never close the Clip while the Lock Lever is in an unlocked state. Device damage may occur. |
| *Establish Final Arm Angle* | Pre-deployment *Clip Arm Angle* that reflects the *Clip Arm Angle* post-deployment.<br>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.<br>2. Confirm that the Clip is locked by observing slight Delivery Catheter shaft deflection using fluoroscopy.<br>**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*. |

## 18.0 PATIENT PREPARATION

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

18.2 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.

18.3 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.

18.4 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).

18.5 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.

18.6 Prepare the patient for invasive hemodynamic monitoring.

## 19.0 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.

**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.

**WARNING:** DO NOT remove the protective cover placed over the Clip. DO NOT handle the Clip directly; leave it in the protective cover to avoid potential contamination.

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

## 19.1 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 embolization.

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

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

**CAUTION:** DO NOT use if damage is detected.

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

19.1.4 Fill a basin with 1000 cc of heparinized saline.

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

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

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

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

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

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

19.1.5.6 De-air the Guide.

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

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

19.1.5.6.3 Close the Guide stopcock.

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

19.1.7 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.

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

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

19.1.9.1 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.

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

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

## 19.2 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 embolization.

**CAUTION:** 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. Device damage may occur.

**Guide Inspection**

19.2.1 Inspect all Guide parts to verify they are undamaged.

**CAUTION:** DO NOT use device if damage is detected.

19.2.2 To confirm proper tip deflection with “+” knob rotation:

19.2.2.1 Rotate the +/- Knob in the “+” direction until the Guide is curved to approximately 80 degrees.

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

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

19.2.2.4 Repeat steps 19.2.2.1 through 19.2.2.3.

19.2.3 To confirm proper tip deflection with “-” knob rotation:

19.2.3.1 Rotate the +/- Knob in the “-” direction until the Guide curve is substantially straightened.

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

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

19.2.3.4 Repeat steps 19.2.3.1 through 19.2.3.3.

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

## 19.3 Stabilizer Preparation

19.3.1 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.

## 19.4 Clip Delivery System Preparation

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

**CAUTION**: DO NOT use the device if damage is detected.

**Sleeve Preparation**

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

19.4.3 Remove the cap from the Clip Introducer.

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

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

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

19.4.7 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.

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

19.4.8.1 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.

19.4.8.2 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.

19.4.8.3 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.

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

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

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

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

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

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

19.4.15 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.

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

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

## 19.5 Clip Delivery System Functional Inspection

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

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

**CAUTION:** DO NOT use device if damage is detected.

**CAUTION:** 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. Device damage may occur.

**Sleeve Inspection**

**CAUTION:** DO NOT deflect the Sleeve more than 90 degrees during the inspections below.

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

19.5.2.1 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.

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

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

19.5.2.4 Repeat steps 19.5.2.1 through 19.5.2.3.

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

19.5.3.1 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.

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

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

19.5.3.4 Repeat steps 19.5.3.1 through 19.5.3.3.

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

19.5.4.1 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.

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

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

19.5.4.4 Repeat steps 19.5.4.1 through 19.5.4.3.

**Delivery Catheter and Clip Inspection**

**WARNING:** DO NOT handle the Clip directly, leave in the protective cover to avoid potential contamination.

**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*.

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

**CAUTION:** DO NOT use the device if damage is detected.

19.5.6 *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.

19.5.7 Unlock the Clip.

**WARNING:** Retracting the Lock Lever forcefully may result in the inability to lock or unlock the Clip.

19.5.8 *Invert the Clip Arms*.

**CAUTION:** DO NOT continue turning the Arm Positioner if resistance is felt; device damage may occur.

19.5.9 *Lock the Clip*.

19.5.10 Close the Clip to *Grasping Arm Angle*.

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

19.5.12 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.

19.5.13 Secure the DC Fastener with DC Handle fully advanced.

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

19.5.15 *Establish Final Arm Angle*.

19.5.16 Return the *Arm Positioner to Neutral*.

19.5.17 Unlock the Clip.

19.5.18 Open the Clip to *Grasping Arm Angle*.

19.5.19 *Lock the Clip*.

19.5.20 Return the *Arm Positioner to Neutral*.

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

19.5.22 Secure the DC Fastener.

19.5.23 Temporarily discontinue heparinized saline flushes.

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

19.5.24 Re-start heparinized saline flushes.

19.5.25 *Raise the Grippers*.

19.5.26 *Fully Close the Clip Arms*.

19.5.27 *Lower the Grippers*.

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

**CAUTION:** DO NOT compress the Clip Arms. Compressing the Clip Arms may result in inability to open the Clip.

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

19.5.30 Turn the *Arm Positioner to Neutral*.

**CAUTION:** 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.

**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.

## 20.0 ACCESS TO THE MITRAL VALVE

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

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

20.2 Heparinize the patient.

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

20.3 Carefully place a 260 cm super stiff 0.9mm (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.

## 21.0 STEERABLE GUIDE CATHETER INSERTION

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

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

**CAUTION:** 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.

21.1 Rotate the +/- Knob in the “-” direction until the Guide curve is substantially straightened.

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

21.3 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 to prevent patient injury.

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

21.5 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. Tissue injury may result.

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

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

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

21.9 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.

21.10 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 device damage.

21.11 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. Patient injury may result.

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

## 22.0 CLIP DELIVERY SYSTEM INSERTION

22.1 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. Patient injury may result.

22.2 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.

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

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

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

22.6 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.

**CAUTION:** DO NOT continue to advance the Clip Introducer if resistance is felt; the Guide Hemostasis Valve, Clip Introducer or the Clip may be damaged.

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

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

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

22.9 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.

22.10 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.

22.11 Position the Sleeve Handle in the Stabilizer slot.

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

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

## 23.0 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 patient injury.

**CAUTION:** DO NOT continue to rotate or manipulate any of the handle knobs if significant resistance is noted; device damage may occur.

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

23.2 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.

23.3 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.

**CAUTION:** DO NOT deflect the Sleeve tip more than 90 degrees as device damage may occur.

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

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

23.6 Adjust the MitraClip System position to maintain adequate height above the mitral valve in the LA.

**CAUTION:** Maintain the Clip above the leaflets until ready to grasp to minimize the risk of Clip entanglement in the chordal apparatus.

## 24.0 FINAL MITRACLIP SYSTEM POSITIONING

24.1 *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.

24.2 *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. Intervention may be required.

24.3 *Lock the Clip*.

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

24.4 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.

24.5 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.

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

**CAUTION:** 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.

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

## 25.0 GRASPING THE LEAFLETS AND VERIFYING THE GRASP

25.1 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.

**WARNING:** DO NOT make substantial Clip Arm orientation adjustment in the LV. Clip entanglement in sub-valvular apparatus may result in difficulty or inability to remove the Clip.

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

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

25.3 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.

25.4 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.

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

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

25.6 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.

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

25.6.1.1 *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.

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

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

25.6.2.1 *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.

## 26.0 CLOSING THE CLIP AND EVALUATING CLIP POSITION

26.1 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.

**CAUTION:** Closing the Clip too tightly may result in inability to deploy the Clip.

26.2 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.

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

26.2.2 Retract the inverted Clip into the LA.

26.2.3 Confirm both leaflets move freely.

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

## 27.0 MITRACLIP DEVICE PRE-DEPLOYMENT CLIP ASSESSMENT

27.1 Confirm DC Handle is secure.

**WARNING:** Failure to secure the DC Handle may result in leaflet injury or loss of leaflet insertion.

27.2 *Establish Final Arm Angle*.

**CAUTION:** DO NOT turn the Arm Positioner more than 1/2 turn in the "Open" direction once initial resistance is felt. Device damage may occur.

27.3 Turn the Arm Positioner to the "closed" side of the neutral position.

27.3.1 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.

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

27.5 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.

27.5.1 Confirm the Gripper Lever is fully advanced.

27.5.2 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.

27.5.3 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.

**CAUTION:** While Establishing Gripper Line Removability, ensure that both ends of the Gripper Line remain exposed.

**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. Intervention may be required.

27.5.3.1 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.

27.5.3.1.1 Hold both free ends of the Gripper Lines together and apply tension to maintain the Grippers in a raised position through Step 27.5.3.1.4.

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

27.5.3.1.3 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.

27.5.3.1.4 *Fully Close the Clip Arms.*

27.5.3.1.5 Continue to Section 30.2: MITRACLIP SYSTEM REMOVAL WITH CLIP ATTACHED to remove the Clip.

## 28.0 CLIP DEPLOYMENT

### 28.1 Deployment Step 1: Lock Line Removal

28.1.1 Remove the Lock Lever Cap and “O” ring. Unwrap the two ends of the Lock Line. Remove the plastic cover from the lines so that that no twists or knots are present.

28.1.2 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.

28.1.3 *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*.

28.1.4 Turn the *Arm Positioner to Neutral*.

### 28.2 Deployment Step 2: Delivery Catheter Shaft Detachment

28.2.1 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.

28.2.2 Turn the Actuator Knob of the DC approximately 8 turns counterclockwise.

If it is difficult to turn the Actuator Knob, confirm that the Arm Positioner moves freely.

**CAUTION:** Failure to stop turning the Actuator Knob when resistance is felt or turning the Actuator Knob in the clockwise direction may result in inability to deploy the Clip.

28.2.3 Release the DC Fastener then retract the Actuator Knob after it is fully unthreaded.

28.2.4 Confirm that the Release Pin groove is fully exposed.

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

28.2.6 Secure the DC Fastener.

28.2.7 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.

## 28.3 Deployment Step 3: Gripper Line Removal

28.3.1 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, removal may be impaired.

**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.

28.3.1.1 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.

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

28.3.1.3 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.

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

28.3.3 Secure the DC Fastener.

28.3.4 Confirm that the Clip position is stable.

28.3.5 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.

**28.4 If placing an additional Clip proceed to Section 29.0. If not placing an additional Clip proceed to section 30.0.**

## 29.0 ADDITIONAL MITRACLIP 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.

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

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

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

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

29.1.4 *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. Intervention may be required.

## 30.0 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 embolization.

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

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

### 30.1 MitraClip System Removal After Clip Deployment

#### 30.1.1 Removal of the CDS While Leaving the Guide in Place.

30.1.1.1 Release the DC Fastener.

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

30.1.1.3 Secure DC Fastener once Sleeve curves are released.

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

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

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

30.1.1.7 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.

30.1.1.8 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 embolization and/or user injury.

**WARNING:** DO NOT create a vacuum while removing the CDS from the Guide; air may enter the lumen of the Guide. Patient injury may result.

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

**30.1.2 Removal of the CDS and Guide simultaneously.**

30.1.2.1 Release the DC Fastener.

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

30.1.2.3 Secure the DC Fastener once Sleeve curves are released.

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

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

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

30.1.2.7 Remove the MitraClip System from the femoral vein, while providing hemostasis.

## 30.2 MitraClip System Removal with Clip Attached

**30.2.1 Removal of the CDS while leaving the Guide in place.**

30.2.1.1 Confirm Clip is locked.

30.2.1.2 *Fully Close the Clip Arms*.

**WARNING:** Failure to *Fully Close the Clip Arms* prior to retraction into the Guide may result in device damage, inability to remove the CDS and/or patient injury.

30.2.1.3 *Lower the Grippers*.

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

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

30.2.1.6 Secure the DC Fastener once Sleeve curves are released.

30.2.1.7 Straighten the Guide with the +/- Knob when the tip of the MitraClip 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 patient injury.

30.2.1.8 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 patient injury.

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

30.2.1.10 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.

30.2.1.11 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 embolization.

**WARNING:** DO NOT create a vacuum while removing the CDS from the Guide; air may enter the lumen of the Guide. Patient injury may result.

**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. Patient injury may result.

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

**30.2.2 Simultaneous removal of CDS and Guide.**

30.2.2.1 Confirm Clip is locked.

30.2.2.2 *Fully Close the Clip Arms*.

**WARNING:** Failure to *Fully Close the Clip Arms* prior to retraction into the Guide may result in device damage, inability to remove the CDS and/or patient injury.

30.2.2.3 *Lower the Grippers*.

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

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

30.2.2.6 Secure the DC Fastener once Sleeve curves are released.

30.2.2.7 Straighten the Guide with the +/- Knob when the tip of the MitraClip 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 patient injury.

30.2.2.8 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 patient injury.

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

30.2.2.10 Remove the MitraClip System from the femoral vein, while providing hemostasis.

## 31.0 PATENTS AND TRADEMARKS

This device and its use are covered by one or more of the following US patents: 7,736,388; 7,682,369; 7,666,204; 7,655,015; 7,608,091; 7,604,646; 7,563,267; 7,464,712; 7,288,097; 7,226,467; 7,048,754; 6,770,083; 6,752,813; 6,629,534; 6,461,366; 6,269,819. Additional US and OUS patents pending.

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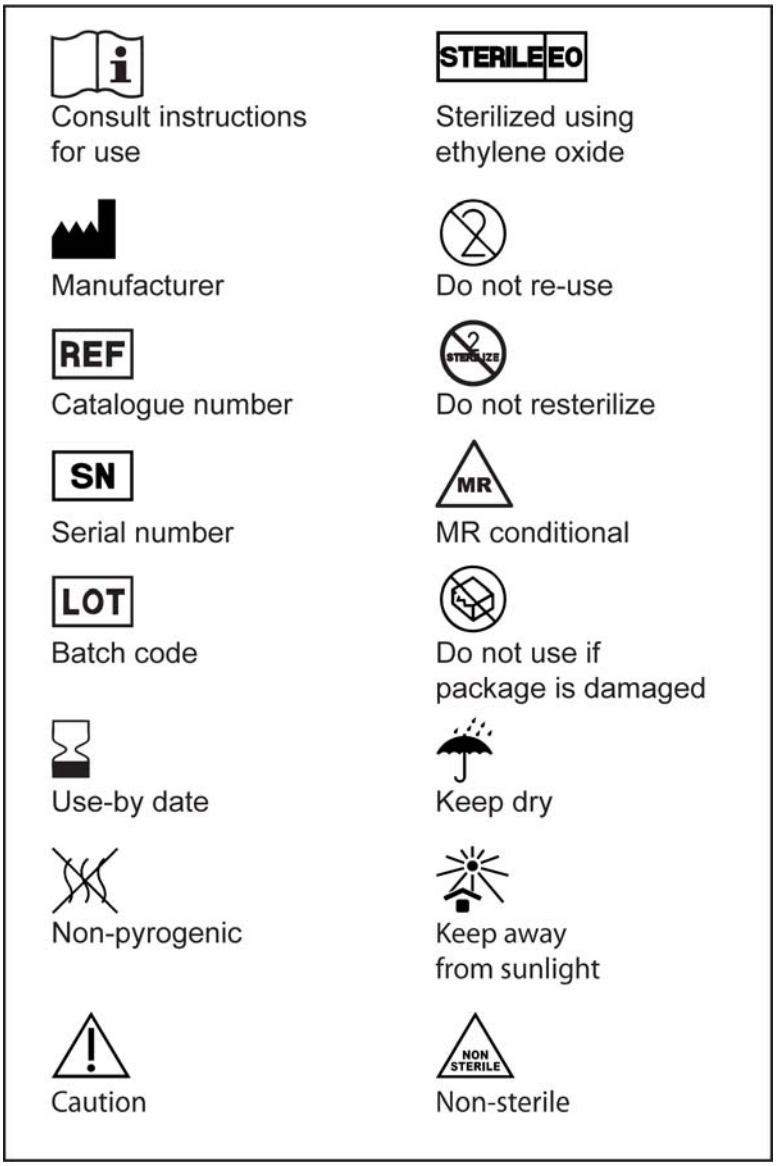
**GRAPHICAL SYMBOLS FOR MEDICAL DEVICE LABELING**

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