Supplement to

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Cardiac Interventions TODAY

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DESIGN EVOLUTION OF THE MITRACLIP™ DEVICE

Adding years to life, and life to years…

Learn more about the life-saving MitraClip device, benefiting select patients with Primary and Secondary MR for over 20 years in clinical studies.

20 YEARS MitraClip™ Transcatheter Edge-to-Edge Repair

See Important Safety Information referenced within.

DESIGN EVOLUTION OF THE MITRACLIP™ DEVICE

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Important Safety Information is included at the end of this publication.

Introduction

Transcatheter edge-to-edge repair (TEER) treatment of mitral regurgitation (MR) was first conceived in the late 1990s based on a novel edge-to-edge surgical repair technique pioneered by Professor Ottavio Alfieri. In 1998, interventional cardiologist Fred St. Goar, after learning of Prof. Alfieri's unique surgical approach, proposed the concept of catheter-delivered mitral valve (MV) repair to the Silicon Valley med-tech incubator, The Foundry. After some basic proof-of-concept work and intellectual property diligence, they founded a startup, Evalve, Inc., in the fall of 1999. Although initial TEER device concepts were focused on installing sutures into opposing valve leaflets[1] or stapling the leaflets together using a catheter,[2] Evalve's early prototyping and testing efforts led to the insight that an implantable Clip (without the need to puncture through leaflets) would be a safer and more effective approach. Working with innovative physician collaborators, Evalve's engineering team built and tested a variety of early device concepts, finally arriving at the first Clip-based TEER technology, known today as the MitraClip™ system (Abbott). Evalve continued the early development of the MitraClip platform through its first-in-human implantation in 2003 and subsequently achieved CE Mark approval in Europe in 2008.[3,4] Evalve was acquired by Abbott Laboratories in 2009.[5] Abbott continued to develop and mature the MitraClip TEER technology and therapy, supporting the approval of the MitraClip system by the United States FDA in 2013.[6]

A REVOLUTION IN TRANSCATHETER MV REPAIR

With a 20-year history, the MitraClip device has defined TEER therapy for treating regurgitant MVs and was the first and only transcatheter valve repair option available for its first 10 years. The MitraClip therapy has been studied extensively with the largest body of clinical data across any transcatheter MV repair therapy, spanning more than 20 trials evaluating more than 80,000 patients with over 3,200 articles published.[7]

"When we first proposed the concept of catheter-based mitral valve repair 25 years ago, we were cautiously optimistic that it would have significant clinical value. After we performed the initial clinical TEER case in 2003 and witnessed the remarkable reduction in mitral regurgitation, our confidence grew, but we had no idea that it would be such an extraordinary game changer."

–Frederick St. Goar, MD

In real-world use, MitraClip therapy has now been used to treat more than 200,000 patients across the world in more than 75 countries with an excellent safety profile and favorable outcomes in terms of reduction in MR, improved heart failure prognosis, and improved patient quality of life.[8] As will be described in this supplement, steadily improving outcomes have been made possible through the addition of key design features in each MitraClip device generation, along with a continual partnership with highly skilled imagers and implanters who use MitraClip devices to improve the lives of patients in the clinical setting (Figure 1). ■

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ONGOING COMMITMENT TO INNOVATION

GEN 5 AND FUTURE GENERATIONS

FUTURE

Continuous clinical data driven:
- EXPAND G4
- EXPANDed
- RESHAPE
- REPAIR MR
- Other TEER RCTs

GEN 4 (G4)

2023

COAPT 5 YRS OUTCOMES

EXPANDED
EXPAND + EXPAND G4
2205 Patients

2020

EXPAND-G4 STUDY
Observational Study
Core Lab
2020–2022
1164 Patients
Study Ongoing

REPAIR MR
Observational Study
Multi-Center RCT – IDE Trial
Enrollment Ongoing
500 Patients

MITRACLIP RUSSIA
Single-Arm Study
2020
16 Patients

MITRACLIP KOREA PMS
Post-Market Surveillance
Enrollment Ongoing
600 Patients/4 Yrs

MITRACLIP CHINA PMS
Post-Market Surveillance
Enrollment Ongoing
50–100 Patients

MITRACLIP INDIA PMS
Post-Market Surveillance
2020–2022
90 Patients

GEN 3 (NTR/XTR)

MITRACLIP FDA APPROVAL FOR SMR

2019

MITRACLIP PAS
Secondary MR
Commercial Registry
2019–2020
5000 Patients
Study Ongoing

2018

EXPAND STUDY
Observational Study
Core Lab/CEC Adjudication
2018–2019
1041 Patients

MITRACLIP JAPAN PMS
Post-Market Surveillance
2018–2019
500 Patients

GEN 2 (NT)

MITRACLIP JAPAN MINISTRY OF HEALTH, LABOUR, AND WELFARE (MHLW) APPROVAL

2017

COAPT CAS
Continued Access
2017–2019
162 Patients

GEN 1

2015

MATTERHORN*
RCT, SMR
Enrollment Ongoing
210 Patients

MITRACLIP HEALTH CANADA APPROVAL

2014

MITRA-FR*
RCT
2014-2017
304 Patients

RESHAPE-HF2*
RCT, SMR
Enrollment Ongoing
650 Patients

MITRACLIP FDA APPROVAL FOR PMR

2013

COAPT™
RCT
2013–2017
617 Patients

2009

EVEREST II REALISM
Continued Access
2009–2014
965 Patients

MITRACLIP™ PAS
Prohibitive Risk Primary MR Commercial Registry
2013–2016
1998 Patients

MITRACLIP CE MARK APPROVAL

2008

ACCESS EUROPE
Single-Arm Study
2009–2012
567 Patients

2007

MITRACLIP™ FIRST IN HUMAN

EVEREST II HIGH RISK STUDY
Single-Arm Study
2007–2008
78 Patients

2005

EVEREST II
RCT
2005–2008
279 Patients

2003

EVEREST I
Feasibility Study
2003–2006
55 Patients

Note: Asterisk indicates Investigator Sponsored Study. Data on file at Abbott.

Figure 1. The evolution of MitraClip™ technologies and associated clinical studies.

Background: A Surgical Foundation for the MitraClip™ Device

The adaptation of a surgical technique to safely provide benefits to more patients.

Dr. Ottavio Alfieri performed the first surgical edge-to-edge mitral valve (MV) repair procedure in Milan in 1991.[1,2] This surgical technique has since been used in thousands of patients to correct mitral regurgitation (MR).[3] Dr. Alfieri's edge-to-edge repair technique is broadly usable to treat a wide range of valve disease states, including both primary (also termed organic or degenerative) and secondary (also called functional) MR etiologies.[4] The attractiveness of Dr. Alfieri's edge-to-edge valve repair technique is its simplicity, as it involves only a single modification to the native valve anatomy. Specifically, a row of sutures is placed by the surgeon to attach the free edge of a diseased leaflet to the corresponding edge of the opposing leaflet of the MV.[5] The sutures are installed directly in the lesion location on the valve leaflets—where the regurgitant jet is observed—to reestablish effective leaflet coaptation. In Figure 1, a MV is converted from a regurgitant state to a repaired double orifice valve with fully eliminated or a significantly reduced residual MR. The hemodynamic consequences of the double orifice configuration have been studied extensively and found to introduce minimal risk of stenosis. The hemodynamics of a repaired double orifice valve and a native single orifice valve have been found to be similar when the total orifice area(s) are equivalent.[6] In either valve configuration, a global mitral valve area greater than 2.5 cm^2 is associated with minimal gradients with a threshold of 1.5 cm^2 being used as a guideline to avoid symptoms.[7] When compared to other repair techniques, the Alfieri edge-to-edge repair is simpler, more reproducible, and achieves more predictable results and has been found to be more durable than other repair techniques by a large meta-analysis.[8]

Surgical edge-to-edge valve repair (Figure 1D) is simple and versatile and has been applied successfully to treat diverse pathologies, being agnostic to the underlying mechanism of regurgitation. Although surgery is appropriate for low-risk patients, many older patients with comorbidities cannot tolerate surgery and require less invasive options.[9,10] To treat these patients, the MitraClip™ device (Abbott) was designed to adapt the elegant versatility of surgical edge-to-edge repair into a minimally invasive procedure. Transcatheter edge-to-edge repair (TEER) with the MitraClip device provides effective MR reduction and has multiple advantages including:

Being safer than surgery. The minimally invasive transcatheter MitraClip procedure involves only a small incision in the groin to obtain transfemoral venous catheter access to the MV and avoids the need for cardiopulmonary bypass, thus making the procedure

"I was inspired by a rare congenital defect I observed, a double orifice mitral valve that still functioned sufficiently. This gave me confidence that an edge-to-edge repair could be a solution for diseased valves. What I found was that the technique was surprisingly simple and extremely effective."

– Ottavio Alfieri, MD

"The techniques we developed for the Alfieri stitch all apply to the MitraClip device today—the importance of the leaflet length, the symmetry of the valve, the use of deep leaflet suturing in DMR and short leaflet suturing in FMR—so while we say 20 years today, it's really more like 30 years that we have been building upon these principles for repairing the mitral valve."

– Francesco Maisano, MD

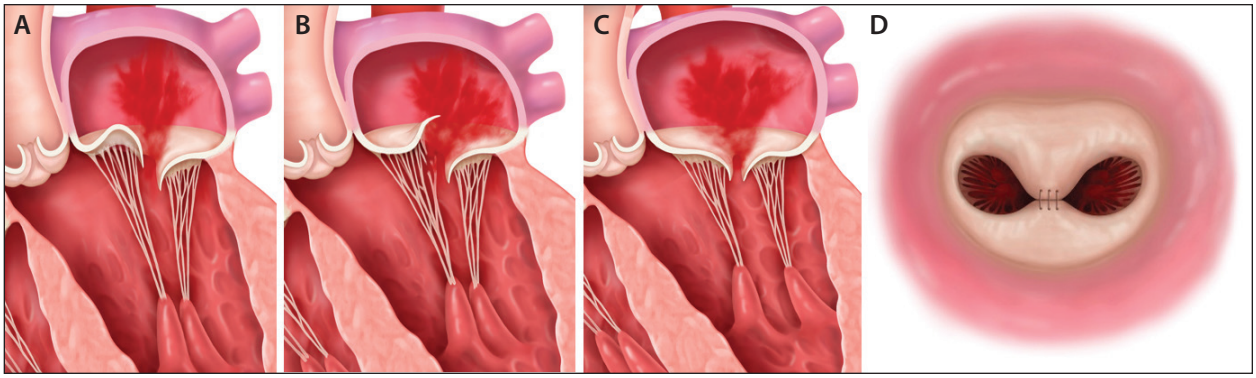

Figure 1. MR etiologies and surgical repair. Primary MR due to prolapse (A), primary MR due to flail (B), secondary MR (C), and MV with a surgically repaired double orifice (D).

much safer for select patients who are unable to tolerate invasive cardiac surgery procedures.[9,10] Additionally, transcatheter procedures allow patients to have a shorter length of hospital stay with better discharge characteristics as compared to surgery.[11]

Enabling immediate feedback on hemodynamic performance. Clearly visualizable under echocardiography and designed with the ability to grasp and re-grasp as needed, the MitraClip therapy allows for real-time assessment of the device, the MV, and the impact of the therapy on hemodynamics of the heart.

Providing real-time optimization. In addition to the immediate effect observed on MV function, the repositionable and retrievable catheter-based design of the MitraClip device ensures a safe and controlled repair. Using imaging feedback, the implanter can safely release, reposition, and re-grasp leaflets to achieve an optimal result. If needed, the implanter may also remove the Clip entirely to abort the procedure.

Stabilizing the valve leaflets and annulus. Optimal edge-to-edge MV surgical repair includes both improving leaflet coaptation and supporting the valve annulus.[12] The MitraClip device is designed to accomplish both of these important functions with controllable and lockable rigid metal arms that (1) stabilize the leaflet-to-leaflet coaptation zone to ensure sustained MR reduction and (2) interrupt or reverse annular dilatation, which is a characteristic of MV disease progression.[2] This second function of the MitraClip device provides a distinct benefit over suture-based surgical repairs and conveys how MitraClip device implantation provides a sustained reduction in MR years after implantation while ensuring a stable device-tissue interface with an optimal healing response.[13]

With these advantages, the MitraClip device was adopted as the first transcatheter valve repair option and established the field of transcatheter valve repair. With over 2 decades of learning, collaboration with physicians, and innovative device development, MitraClip therapy has continued to build upon the above advantages realized in the original design solution. As will be described throughout this supplement, each product generation is a balance of *maintaining what worked well and striving for what could be*. Each generation is the result of careful and intentional design and thoughtful analysis of the vast clinical experience built with the MitraClip therapy. ■

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Design, Development, and Clinical Experience of Four MitraClip™ Device Generations

The impact of 20 years of innovation, from early concept to present day.

The First-Generation MitraClip™ Device

EARLY CLIP DESIGN EVOLUTION

A series of published textbook chapters chronicle the early development of the first-generation MitraClip™ device (Abbott) and the imaging-guided approach to Clip-based mitral valve (MV) repair in a beating heart.[1,2] As detailed in these cited chapters, the first catheter-based device prototypes created at Evalve, Inc., were designed to replicate the surgical Alfieri stitch. These early prototypes included nitinol arms (made of looped wire) that contacted the MV leaflets, while pledgeted sutures were delivered into the leaflets through hollow needles housed within a catheter. The concept of puncturing through leaflet tissue introduced risks that were cleverly avoided with a key observation—that the supporting arms themselves could be used to bring the leaflets into coaptation without the use of any sutures. With this key insight, the Clip concept was born.

Although flexible nitinol arms were a hopeful design and material concept, their instability made grasping leaflets difficult. Chronic motion between the deployed flexing nitinol arms and the grasped leaflet tissue was associated with unstable and incomplete healing in chronic animal studies. Therefore, a more stable and robust tissue-to-tissue apposition structure was needed to provide a more steady and favorable healing response, and nitinol arms were abandoned in favor of stable grasping arms made of Elgiloy® (Elgiloy Specialty Metals).[2,3] The evolution of initial concepts from the initial suture delivery approach, to flexible arms (uncovered and covered), and finally to a Clip design with stable controllable arms is shown in Figure 1.

This suture-free, stable clipping approach was an attractive option as it allowed the user to grasp and release leaflets with precision and control. In addition, the small size and

"The ability to precisely control the Arm angle of the MitraClip device provides a way to reduce the risk of high gradients or stenosis in patients with a relatively small mitral valve area. We can slowly open the arms and judge the balance of reducing MR versus the risk of iatrogenic stenosis and have found angles up to 30° of opening to be safe."

– Paul Sorajja, MD

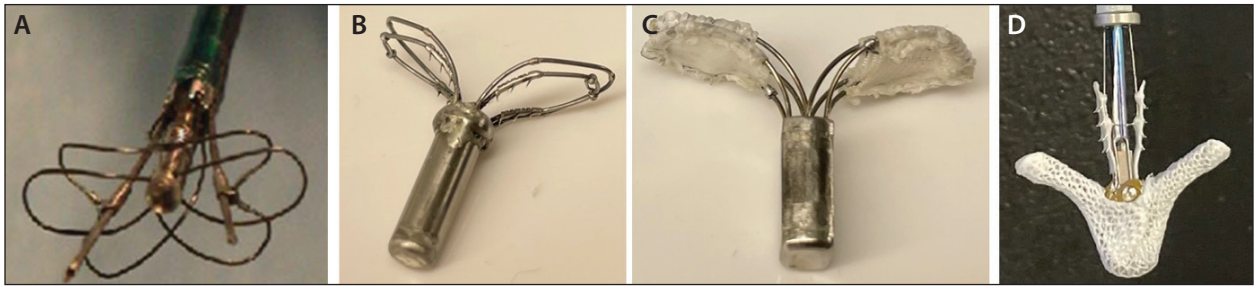

Figure 1. Evolution of MitraClip™ implant from initial suture delivery concept (A), flexible nitinol loop implant (uncovered) (B), nitinol loop implant with covered arms and grippers (C), to covered clip with rigid stable arms (D).

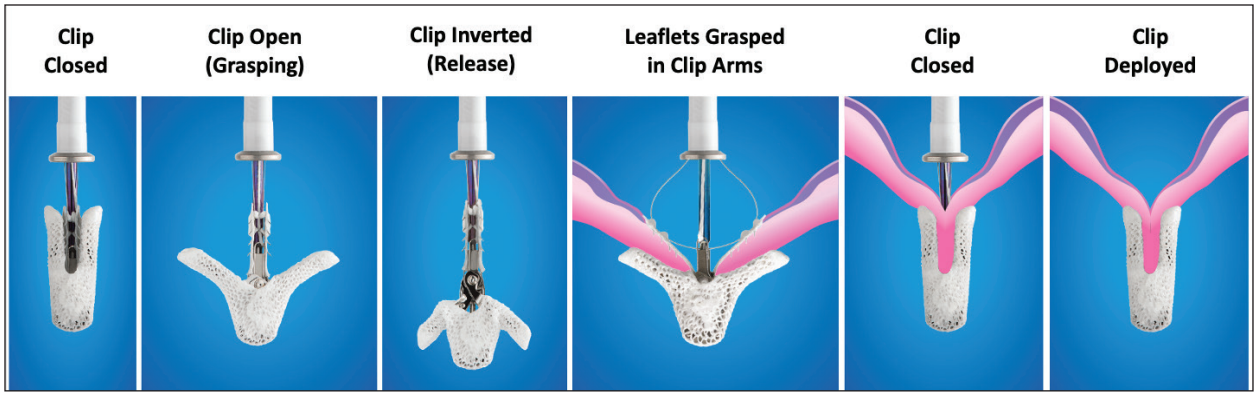

Figure 2. Clip arm angle configurations of the MitraClip™ device.

covered Elgiloy® construction of the MitraClip device ensure it is echo friendly. This enables visualization of the device and its interaction with the native anatomy, which is instrumental to the success of the MitraClip procedure. Other technologies with less echo-friendly devices have proven unsuccessful due to poor visualization of the leaflet and device.[4] The atraumatic Clip design also allowed users to reposition a Clip multiple times if needed, without causing any punctures to the leaflets. Additionally, the Clip design enabled the user to tailor the repair by controlling the amount of Clip closure to maximize the amount of mitral regurgitation (MR) reduction while optimizing the resultant MV gradient.[5] These combined design characteristics ensured that Clips provide robust long-term MR reduction, stable leaflet coaptation throughout the cardiac cycle, and a transmitral pressure gradient that remains consistently low over time.[6]

THE MITRACLIP DEVICE DESIGN: OPTIMIZED FOR TRANSCATHETER MV REPAIR

The MitraClip device design and operation were defined to optimize the MV repair procedure with controllable clip arms, a gripper designed to be atraumatic when capturing the leaflets, and a delivery system designed specifically for precise and optimal treatment of the MV.

Controlled and Stable Clip Arm Closure

Although some of the first transcatheter edge-to-edge repair (TEER) prototypes employed a pair of opposing nitinol loops to coapt the MV leaflets, this design approach and material choice proved to be suboptimal. The flexibility of the nitinol loops meant they were unstable during leaflet grasping, which limited the user's ability to accurately position a Clip when repairing moving leaflets in a beating heart environment. Additionally, nitinol structures incur alternating strains when bending or flexing during each cardiac cycle, which can increase the risk of eventual device fatigue failure.[7] This concern caused the engineering team to question whether nitinol material could withstand the long-term cyclic fatigue loading conditions after implantation.

Considering the need for a more stable and robust tissue-to-tissue apposition, the nitinol loop system evolved into a Clip device with rigid, stable grasping arms.[1,2] The flexural rigidity of the Clip arms is an important design characteristic that is critical for coaptation of the MV leaflets during and after the MitraClip procedure. Both the Clip arm material choice and structural design provide rigidity, which enables the device to stabilize moving leaflets when grasping and capturing them within the Clip during the procedure in a beating heart. After the procedure, the rigid Clip arms support the tissue and the gripper inside the Clip and ensure long-term coaptation between the leaflets, providing a steady and favorable healing response and stable pressure gradients.[1,6,8]

The precise and controlled opening and closure of the Clip arms was a main priority for the MitraClip device (Figure 2), as stable closure of the arms provides ease of grasping the leaflets, enables controlled leaflet coaptation, promotes an optimal tissue healing response between the stabilized leaflets, and encourages reverse remodeling of the MV annulus.[1,2] The long-term stability of the Clip and tissue-to-tissue interface ensures that a stable tissue bridge forms between the leaflets,[8] and a polyester Clip cover was added to further aid in providing a predictable healing response in both primary and secondary valvular disease.

Based on early learnings from the initial MitraClip clinical trial (EVEREST I), the Clip-locking mechanism was redesigned to provide the user even greater control when closing the Clip, enabling the Clip to be locked at any chosen angle < 90°.[2] This unique design provides the user the ability to control the amount of Clip closure to maximize the amount of MR reduction while optimizing the resultant MV gradient.[5]

Device material selection is also critical to ensure any repair is biocompatible, durable, and promotes favorable remodeling of the MV and cardiac chambers. The MitraClip device's arms and load-bearing metallic struc-

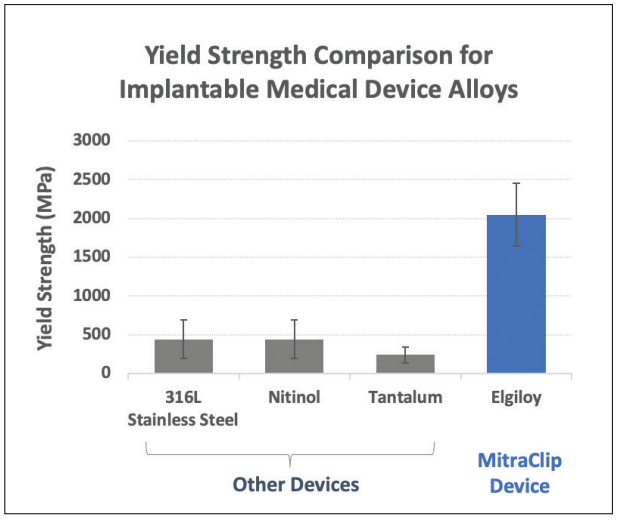

Figure 3. Yield strength comparison for typical MitraClip™ device alloys as reported by Thierry et al where error bars represent minimum and maximum reported values.[9]

ture is made of a high-strength super-alloy called Elgiloy. This alloy is significantly more durable than other medical device alloys like nitinol, stainless steel, and tantalum (Figure 3) and provides excellent corrosion and fatigue resistance.[9,10] Elgiloy's high strength enables the metallic load-bearing Clip components to be made with a minimized thickness and surface area to promote faster healing and earlier tissue encapsulation around the device after implantation. In addition, the high strength and fatigue resistance of Elgiloy ensures that the long-term structural integrity of the implant is maintained for many years after deployment. As described previously,[2] locked Clips are tested at Abbott for 600 million worst-case simulated cardiac loading cycles (equivalent to 15 years) to ensure

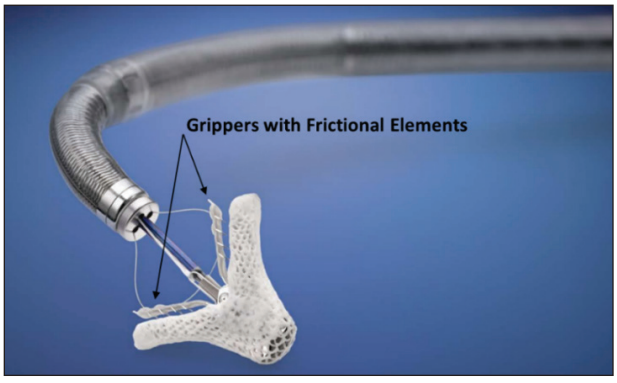

Figure 4. The first-generation MitraClip™ device with grippers and FEs distributed along the length of the grippers, which prevents the leaflets from slipping out of the Clip arms during Clip closure and maintains the Clip's long-term attachment to both MV leaflets.

they remain free of fractures and stay closed to support the valve repair long after deployment. The stable closure of the rigid Elgiloy Clip arms also provides a beneficial and stabilizing effect on the valve annulus.

Grippers Designed to Safely Secure and Release Leaflets

The first-generation MitraClip device design includes a pair of Elgiloy arms that can be precisely opened or closed by the user, providing stability and control when grasping leaflets to optimize the procedure. The rigid Elgiloy arms stabilize the leaflets from their ventricular surface during leaflet grasping. The more flexible grippers are then lowered by the user onto the atrial surface of the grasped leaflets to capture them within the Clip arms. The gripper is designed with rows of pointed features called frictional elements (FEs) that gently secure, but do not perforate, leaflets within the Clip arms during the beating-heart procedure.[2] As shown in Figures 4 and 5, FEs are distributed along the entire length of the grippers, which ensures leaflets do not slip out as the user closes the Clip. The FEs positioned at the inner part of each gripper are critical for ensuring the device retains the maximum amount of leaflet possible within the closed Clip, which maximizes leaflet coaptation and the amount of MR reduction achieved. After a Clip is deployed, the gripper FEs permanently maintain the Clip's long-term attachment to both leaflets, ensuring MR reduction is sustained for years after deployment.

Many different gripper prototype designs were built and tested during the development of the MitraClip device. The final gripper design for the first-generation MitraClip device was made of Elgiloy and is shown in Figure 4. Gripper designs in subsequent device generations (MitraClip NT, MitraClip NTR/XTR, MitraClip G4) are made of nitinol but employ the same FE lengths and spacing as the first-generation MitraClip gripper design. In all generations, the flexible gripper component is supported by the rigid Elgiloy Clip arms when the Clip is closed and implanted. All MitraClip gripper designs incorporate the following key design features:

Optimized FE length for security and safety. As shown in Figure 5, gripper FEs are designed to be long enough to sufficiently secure tissue while being short enough to never penetrate through even the thinnest central belly regions of MV leaflets, which can be as thin as 0.7 mm.[1,11] This short FE length is particularly important when capturing frail or diseased leaflets as puncturing the leaflet could lead to perforation and tears. With this FE design, leaflets can safely and repeatably be secured and captured (and released and recaptured) by the grippers without being perforated or damaged.[3]

Evenly spaced FEs for distributing the force on the leaflet. Pairs of gripper FEs are spaced evenly in a row

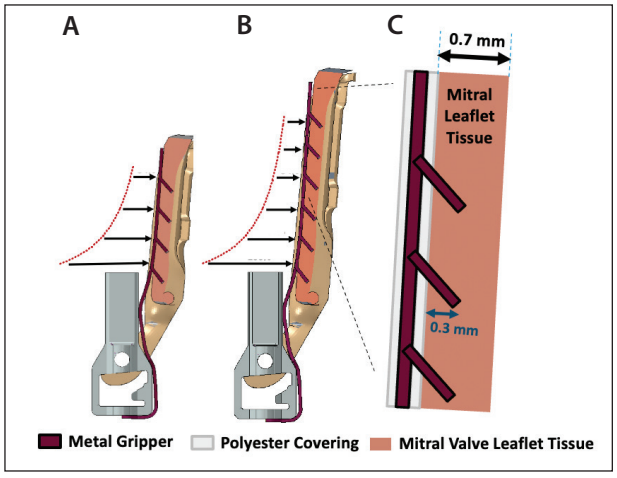

Figure 5. Gripper force distribution shown for one side of the Clip for NT/NTR/NTW Clip size (A) and XTR/XT/XTW Clip size (B) with FE engagement into mitral leaflet tissue (C) with a minimum reported mitral leaflet thickness of 0.7 mm shown per Sahasakul et al.[11]

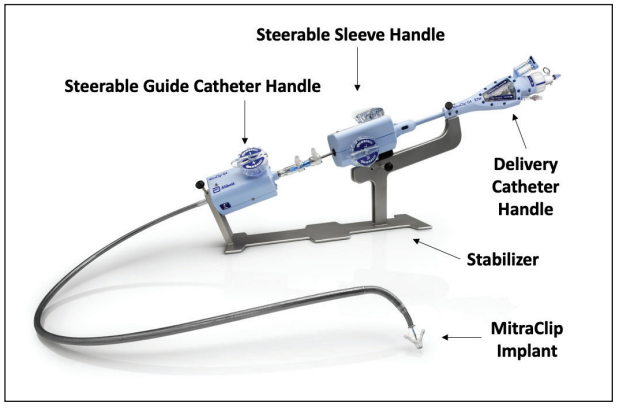

Figure 6. The MitraClip™ System including the Delivery Catheter, Steerable Sleeve, and Implant that comprise the Clip Delivery System (CDS) as well as the Steerable Guide Catheter (SGC) and Stabilizer.

along the entire gripper length. This design ensures that the force applied to leaflets by the gripper is distributed along the entire inserted leaflet length that is supported within the Clip arm. This force-distributing design (Figure 5) prevents stress concentration from occurring at any single spot of the leaflets, which helps to prevent damage to the leaflets. The gripper design applies the highest force at the innermost part of the Clip to the leaflet's closing edge—where the leaflet is the thickest and most robust. The gripper force is lowest at the tip of the gripper, which ensures the gentlest force is applied where the gripper engages with the thinner belly region of the leaflet.[3,11] Most importantly, in addition to being safe, this force-distributing design has the added benefit of maximizing the amount of leaflet captured and brought into coaptation by the Clip—the overall goal of any TEER procedure.

Intentional FE placement and angle for reliable tissue securement and disengagement. Gripper FEs are short and angled inward to gently secure leaflets when the user closes the Clip arms. FEs are placed along the entire length of the gripper so that the entire length of leaflet inserted during grasping is retained in the Clip during device closure, without any slippage.[2,3] The angled design of the FEs (Figure 5) also provides safe and easy release of leaflets if the grippers are raised, the Clip is opened and inverted, and then retracted into the atrium. This design choice balances the need to adequately secure and coapt leaflets, while allowing for safe and atraumatic disengagement from the leaflets.

Designed with a thin metallic structure for optimal healing response. The gripper structure was intentionally designed to be thin (about 0.1 mm) to avoid injury to the leaflets during the MitraClip procedure. The thin design of the gripper also limits the amount of metal present between the coapted leaflets, minimizing any obstruction to healing and tissue bridge formation between the coapted leaflets.[3] Similar to the Clip covering described previously, the gripper component includes a polyester covering to facilitate a safe and stable healing response and ingrowth after Clip implantation. Studies have demonstrated that tissue growth steadily occurs between the FEs and around the gripper as a tissue bridge forms as early as 30 days, with eventual complete device encapsulation as early as 90 days.[8]

Catheter controls and curves planes designed to efficiently position a Clip on the MV. The first-generation MitraClip system was a low-profile, multi-catheter system specifically designed to enable access to the MV (Figure 6). The catheters were designed to provide the user with the ability to accurately steer and navigate three-dimensional space in medial-lateral, anterior-posterior, and superior-inferior directions (Figure 7), while maintaining an optimal trajectory toward the MV.

This mitral-specific, dedicated catheter design was possible due to unique curves and a "key" and "keyway" system within the catheters. This unique alignment feature is critical to the efficiency of the MitraClip procedure. It enhances the overall system rotational stability and makes the device more predictable to use without the need for iterative steering adjustments during Clip positioning. The key feature also optimizes the insertion position of the Clip to be closer to the nominal position of most human MVs, which enables even faster and easier Clip positioning with even fewer steering adjustments needed at the beginning of the procedure.[2] This

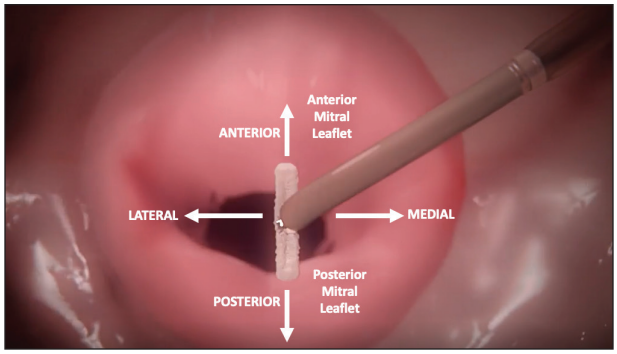

Figure 7. CDS steering in the medial-lateral direction and anterior-posterior direction.

keyed MV-specific curving system design was further optimized based on experiences in the EVEREST I feasibility trial, and the effectiveness of the final system design was further demonstrated in the EVEREST II trial with high procedural success rates in treating both primary and secondary MV disease. These curves and their controls have been used successfully in treating a broad range of anatomies across more than 2,000 studied patients in more recent product generations.[12]

Beyond the design improvements, procedural efficiencies were developed including the definition of "situational steering" to enable Clip implantation in a wide range of anatomies—particularly in patients where only a low transeptal puncture height was possible. The MitraClip device's dedicated steering system allowed for anatomies with puncture heights as low as 2.49 cm to be treated effectively further demonstrating the ability for the MitraClip system to treat a broad range of anatomies with stability and control.[3] This capability has since proven to be particularly useful in certain geographies and within patients with small MVs and left atria.[3,13]

EARLY CLINICAL EXPERIENCE WITH THE MITRACLIP DEVICE

Multiple trials were initiated to study the safety and efficacy of MitraClip device implantation in patients with moderate to severe MR (≥ grade 3). These included an early feasibility study (EVEREST I, 2003),[14,15] a randomized pivotal study comparing MitraClip device treatment to surgery (EVEREST II RCT, 2005), and a study comparing MitraClip device treatment in patients with high surgical risk (EVEREST II HRR, 2007).[16,17] Additional continued access studies (REALISM and REALISM HR, 2009) further evaluated procedural safety of treatment with the MitraClip device as important complements to the RCT.[18] The clinical evidence from the EVEREST II HRR and REALISM HR, along with supportive safety data from EVEREST II RCT, led to the 2013 approval of the MitraClip System in the United States for patients with primary MR (PMR) with prohibitive surgical risk.[17,18] These trial results for this first-ever TEER device indicated that leaflet grasping with the MitraClip device was repeatable, obtaining MR reduction was feasible and durable with follow up through 5 years, and that the device safely provided sustained clinical benefits with minimal adverse events.[14-18] Taken together, these trials laid the foundation for the unparalleled outcomes that the MitraClip device would achieve in future trials like COAPT and with future device generations.

"The discovery of the initial MitraClip concept was really by chance, but the field of medicine, the MitraClip device design, and the clinical evidence we have today have been intentionally built into something amazing."
– Francesco Maisano, MD

In 2012, Abbott commenced a trial in heart failure (HF) patients with symptomatic secondary (functional) MR (SMR) despite optimal medical management, the Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for Extremely High Surgical Risk Patients RCT (COAPT™ RCT) with follow-up through 5 years. This was a groundbreaking trial in that MR reduction was shown to be beneficial in HF patients with severe secondary MR. The trial demonstrated that MitraClip device implantation in this patient group was associated with significantly lower rates of all hospitalizations, hospitalizations for cardiovascular causes, and hospitalizations for HF during the 5-year follow-up. The COAPT trial resulted in an expanded United States indication in 2019 for the treatment of symptomatic, moderate to severe or severe SMR (MR ≥ grade 3 per American Society of Echocardiography criteria) in patients with a left ventricular (LV) ejection fraction ≥ 20% and ≤ 50%, and a LV end-systolic dimension ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated guideline-directed medical therapy (GDMT), as determined by a multidisciplinary heart team experienced in the evaluation and treatment of HF and MV disease. Similarly, the study demonstrated that treatment with the MitraClip device was associated with lower all-cause mortality, cardiovascular mortality, and HF-related mortality at 5 years, predominantly notable during the first 2 years after randomization. Treatment with the MitraClip device in these patients was safe, with no device-specific complications occurring after 30 days.[6,19]

After a series of successful trials and regulatory approvals, the MitraClip system became the leading transcatheter MV repair solution in the world and was commercialized

across a growing number of medical centers and geographies. The dedication of a growing community of clinicians pioneering the MitraClip TEER therapy prompted updates to the guidelines used around the world for evaluating valvular disease and valvular repair with TEER. A growing base of device users provided feedback to Abbott, which led to some notable design changes to improve the performance of the first-generation MitraClip product. Between 2011 and 2014, the locking mechanism component tolerances were updated to improve the reliability of locking and unlocking the Clip. The Clip deployment mechanism design was also changed from an S-shaped lock (S-Lock) attachment to an L-shaped lock (L-Lock) attachment to facilitate reliable device detachment from the delivery catheter.[20] As a final enhancement of the first-generation system, a one-way clutch was incorporated into the device handle to ensure the user always rotates the mandrel in the correct direction to unthread the Clip delivery system's (CDS's) connection to the Clip during device deployment.[21] These important design updates improved the ease of use of the system, ensuring safe and effective outcomes could be accomplished more efficiently. ■

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The Second-Generation MitraClip™ Device: MitraClip NT

MITRACLIP NT: NITINOL GRIPPER FOR IMPROVED LEAFLET CAPTURE WITH IMPROVED STEERING

As the MitraClip therapy grew commercially in Europe and the United States and expanded into other geographies, Abbott surveyed physicians to determine how to further improve the ease of use and effectiveness of the first-generation MitraClip device. As users began to treat increasingly complex anatomies, improved leaflet capture was identified as a goal for the next product generation. In addition, improved steering responsiveness and accuracy were also identified as areas for improvement. To incorporate these improvements, a second-generation MitraClip system was developed and commercialized in 2016 as the MitraClip™ NT product. The MitraClip NT device offered users a new nitinol gripper design that enabled improved leaflet capture and steering capability.

"The nitinol Grippers in the MitraClip NT device better captured leaflets when compared to first-generation MitraClip device, allowing leaflets to be captured at wider grasping angles while preventing leaflets from slipping out of the Clip. With this new design, leaflet capture was more frequently successful on the first attempt with MitraClip NT, which greatly impacted the success of the procedure."

– Ralph Stephan von Bardeleben, MD

In the MitraClip NT device design, the gripper material was changed from Elgiloy to super-elastic nitinol, and the gripper hinge design was updated to optimize

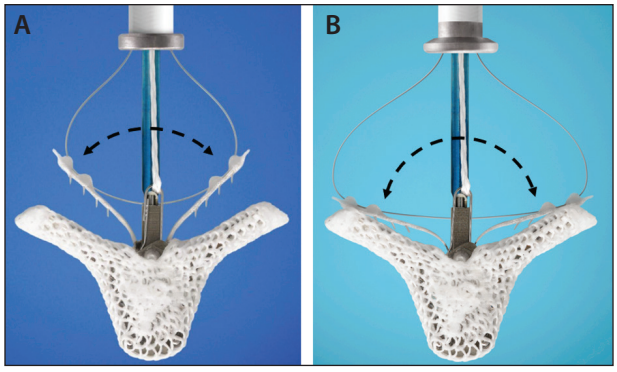

Figure 8. Gripper drop angle differences between the first-generation MitraClip™ Elgiloy gripper lowered to 85° (A) and the second-generation MitraClip™ NT nitinol gripper lowered to 120° (B).

how leaflets were captured by the gripper. As shown in Figure 8, the gripper design change in MitraClip NT allowed the grippers to drop fully onto the Clip arms, which ensured better leaflet capture within the Clip. This new nitinol gripper design, with FEs designed for deep leaflet insertion, greatly reduced the chance for leaflets to slip out of the Clip during leaflet capture or during subsequent closure of the Clip arms.

Bench tests were developed at Abbott to evaluate the capture efficiency of the MitraClip NT design under various anatomic challenge conditions (mimicking both primary and secondary MV disease) and the benefit of the new nitinol gripper design was clearly demonstrated. Leaflet tissue was more fully captured within the Clip arms with the MitraClip NT device and better retained within the Clip.[1] In simulated use testing, fewer grasping attempts were needed to successfully capture leaflets with the MitraClip NT device when compared to MitraClip across a wide range of scenarios, and the benefit of the MitraClip NT gripper design was especially significant in challenging anatomic scenarios including large leaflet prolapse or flail heights and cases with large coaptation gaps.

In addition to the new nitinol gripper design, the steerable sleeve was redesigned for the MitraClip NT device to increase the stability and responsiveness of the CDS. The compressive stability of the sleeve was enhanced, and steering cables within the catheter were updated to improve articulation and responsiveness of the system's steering.[2] These changes made the NT sleeve even more predictable during use, allowing users to more effectively steer and position Clips onto the MV of their patients. ■

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The Third-Generation MitraClip™ Device: MitraClip™ NTR/XTR

MITRACLIP NTR/XTR: IMPROVED LEAFLET GRASPING AND SYSTEM STABILITY

MitraClip NT device provided a significant improvement in leaflet capture over the first-generation MitraClip device, but larger leaflet gaps and longer redundant leaflets were still challenging to efficiently treat. Large flail widths and flail gaps were also identified as independent predictors of recurrent MR and reintervention.[1,2] Thus, Abbott focused its efforts on increasing the amount of leaflet grasped while improving device stability and trajectory during grasping. Abbott incorporated these improvements in the third-generation device—MitraClip NTR/XTR system—in 2018, which added a new longer-arm Clip size (XTR) and introduced delivery catheter shaft stability improvements. The benefits of these features were evaluated in the EXPAND Post Market Clinical Follow-up (PMCF) study, which was initiated for the MitraClip XTR device as a condition of regulatory approval for the MitraClip NTR/XTR system. EXPAND enrolled 1,041 patients (50.5% PMR and 49.5% SMR) who underwent mitral TEER according to regional guidelines and indications with follow-up at 1-year postprocedure. Relative to prior device generation trials results,[3,4] EXPAND observed improved postprocedural MR severity (89% MR ≤ 1+ in EXPAND relative to 55% MR ≤ 1+ in EVEREST II HRR

"I've been implanting MitraClip for over 10 years and I can always be confident that I can safely perform the procedure without harming the patient, even when treating the sickest patients with cardiogenic shock and those with very poor ventricular function. Without question, I have found there is no technique or device out there that is safer than MitraClip."

– Anita Asgar, MD

and REALISM registries) and reduced median procedure times (46 min in EXPAND vs 112 min in REALISM). In addition, an extremely low rate of adverse events was reported, and quality-of-life improvement was demonstrated per Kansas City Cardiomyopathy Questionnaire. Functional capacity per New York Heart Association functional class was also measured and observed an improvement relative to previously reported outcomes after treatment with previous device generations.

Following his comprehensive assessment within the EXPAND Study, **Dr. Federico M. Asch** noted that "registries for newer-generation devices (and device sizes), such as EXPAND, are demonstrating effective treatment in more patients who are identified as proper candidates for the TEER therapy. There is more opportunity for treatment and less anatomic restrictions."

KEY DESIGN FEATURES STUDIED IN EXPAND

Longer Arm Clip Size to Efficiently and Safely Treat a Broad Range of Anatomies

The added MitraClip XTR Clip size was developed with 3-mm-longer Clip arms to help implanters more easily repair valve pathologies with severe prolapse and larger coaptation gaps. This longer Clip arm length increased the grasping width of the Clip from 17 to 22 mm (Figure 9). This small but very meaningful change meant that users could achieve more leaflet coaptation with fewer capture attempts and achieve greater MR reduction with a single Clip.[5] In addition to the Clip arm length increase in the XTR Clip, the nitinol gripper was also lengthened, increasing the number of FE rows from four to six. The MitraClip XTR Clip size allowed for over 1 cm of coapted leaflet length mimicking the suture depths reported in surgical edge-to-edge tissue approximation.[6,7]

The engineering of the new longer MitraClip XTR Clip size (Figure 9) was extensive and included the following tests to evaluate the impact of longer Clip arms on leaflet capture performance, hemodynamic performance, and leaflet integrity.

Improved leaflet capture performance. Abbott's engineering teams confirmed that MitraClip XTR's longer Clip arms enabled more efficient leaflet capture in a range of bench models. In simulated-use testing scenarios, fewer grasping attempts were needed to successfully capture leaflets with the MitraClip XTR device when compared to the MitraClip NT device, with more FEs being engaged into the tissue during simulated use.[5] The addition of the MitraClip XTR Clip size demonstrated clear benefits in the EXPAND trial, as implanters more efficiently treated patients with reduced procedure times and with a reduced number of Clips implanted compared to prior trials. The increased amount of leaflet coaptation achievable when adding the MitraClip XTR Clip size also correlated with improved MR severity after Clip implantation with 89% of patients having MR ≤ 1+ after discharge.[3,4]

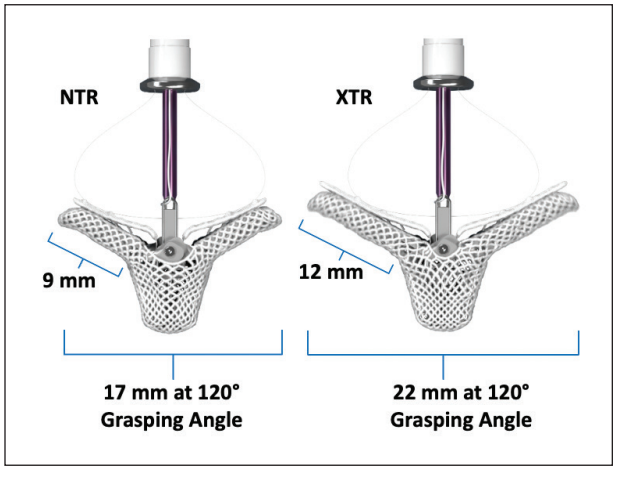

Figure 9. The third-generation MitraClip™ device with increased grasping width options with NTR and XTR Clip sizes.

Effective hemodynamic performance. The XTR Clip size achieved 44% more coaptation area when compared to MitraClip NT, enabling 11% more MR reduction with a single Clip.[5] Furthermore, the XTR Clip size did not increase the risk of mitral stenosis. Computational modeling and bench flow models were employed to confirm that the added longer MitraClip arm size would not increase the risk of an elevated transmitral gradient (a measure of mitral stenosis). Even when deploying in a small valve model (4 cm^2), the highest measured transvalvular gradient for the XTR Clip size was found to be 3.24 mm Hg,[5] which falls well within the mean pressure guideline limit of 5 mm Hg.[8] This finding was confirmed in the EXPAND trial, where the addition of the XTR Clip size contributed to improved MR reduction and was not associated with elevated gradients, being especially useful and effective in cases with smaller annular dimensions in primary disease.[9]

Leaflet integrity. The goal of TEER is to restore coaptation while maintaining leaflet integrity, and the MitraClip XTR device has consistently demonstrated it is safe on leaflets. Leaflet tension applied by the MitraClip XTR device was characterized experimentally with diseased, cadaveric leaflet tissue obtained from human donors with HF. The force experienced by leaf-

lets during Clip closure was measured under worst case conditions and found to be well below the force threshold at which leaflets begin to tear. Specifically, the tissue tear force was determined to be 3.76 times higher than the tensile force applied by the MitraClip XTR device during Clip closure.[5] This test result is in alignment with the EXPAND study, where the adjudicated rate of leaflet tear or perforation was found to be extremely low at 0.4%.[10]

As EXPAND was an all-comers study, patients with complex anatomies were treated if the heart team assessed the patient as suitable for TEER. A total of 18% of subjects were deemed to have a complex MV anatomy by the central echocardiographic core laboratory (ECL). The newly added longer Clip size, XTR, was used more frequently than NTR. At least one XTR Clip was used for treatment of 64% PMR patients, whereas 59% of SMR patients were treated with at least one NTR Clip. The average number of Clips implanted per patient was 1.5, which was lower than the Clip rate of previous generations. Anatomic complexity was similar between patients treated with the two Clip sizes, although subjects treated with XTR had larger prolapse gaps, larger flail gaps, larger annular and ventricular dimensions, greater baseline MR grade, and larger coaptation depth compared with subjects with NTR.[11]

The reduction in MR following treatment with NTR/XTR was maintained during follow-up with 84.5% and 93% of patients with PMR and SMR achieving an MR grade of 1+ at 1 year. The use of the new MitraClip XTR Clip size was found to be especially useful and effective in the treatment of severe primary valve disease.[5] This finding agrees with the historical surgical practice of employing longer suture bites in edge-to-edge surgical repair in cases with more leaflet redundancy (such as Barlow disease) and more severe leaflet prolapse.[6,7]

Improved Delivery Catheter Shaft for Precision and Control

The delivery catheter shaft was redesigned for the MitraClip NTR/XTR device to improve the shaft's rotational stability and to ensure a straighter trajectory when advancing a Clip across the MV.[5] This design change replaced the five metallic helical lumens in the original delivery catheter shaft design with a 5-lumen solid polymer core.[12] The new shaft core material and its processing were selected to optimize the shaft flexural (bending) stability, and an internal compression coil was included in the design to maintain the straight trajectory of the shaft when advancing a Clip across the valve. In addition, an outer metallic braid design was included and optimized to provide rotational stability and more precise torque control of the Clip when the user rotates the device handle.

"The goal is not to just get leaflets in the clip… You must be perpendicular to the line of coaptation so that you're able to grasp the leaflets evenly in such a way that you don't distort the anatomy of the valve. The DC shaft stability of the MitraClip NTR/XTR and in G4 devices helps to ensure this is possible and can be done efficiently."

– Anita Asgar, MD

The new NTR/XTR delivery catheter shaft design was combined with an improved lock line made of ultra-high molecular weight polyethylene having both increased creep resistance and optimized force transmission to the implant. With these enhancements, this more robust NTR/XTR system could now be used with the Clip being unlocked during the majority of the procedure. This meant fewer unlocking and relocking steps were needed during the procedure, which enabled a significant reduction in procedure time. Successful Clip implantation rate in the EXPAND study was 98.9%, and the acute procedural success defined as Clip implantation with MR ≤ 2+ was 96% with a low median device time of only 46 minutes.[11]

SUMMARY

The combination of a more precise delivery catheter and the added utility of the XTR Clip size option meant users could position, grasp, and deploy the Clip more efficiently. Users reported the advantages of the third-generation system, discussing shorter procedure times with successful Clip positioning on the first grasp in the majority of cases (56.5%).[13] The improved stability of the delivery catheter enabled users to more easily treat pathologies with large dynamic gaps between the leaflets[5] and delivery catheter extension length was increased to enable users to achieve procedural success with a system that was now more forgiving to a high transseptal puncture location and in very dilated atria.[5,13] ■

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The Fourth-Generation MitraClip™ Device: MitraClip™ G4

MITRACLIP G4: FOUR CLIP SIZES, CONTROLLED GRIPPER ACTUATION, AND AUTOMATIC GRIPPER LINE DETACHMENT

With the MitraClip NTR/XTR platform, procedure volumes increased as users were able to treat more challenging valve pathologies. Having two available Clip sizes allowed users to choose the best Clip for each case, with longer Clip arms being favored for larger gaps and/or longer leaflet lengths. Even with the longer Clip arms, users still frequently needed to implant multiple Clips (1.5 Clips were implanted on average in EXPAND) to fully treat wide regurgitant jets. It was noted that grasping leaflets in the most challenging cases could be further improved. These insights led to multiple design enhancements that would be included in the fourth generation product, the MitraClip G4 system.

Similar to the EXPAND postmarket study, the EXPAND G4 PMCF study was initiated to generate global contemporary evidence with the fourth-generation MitraClip G4 system and understand the clinical impact of use of the new features.[1] The EXPAND G4 trial enrolled 1,164 patients (PMR and SMR) who underwent mitral TEER according to regional guidelines/indications in the United States, Europe, Canada, and Japan and allowed users to make use of the following design features.

Wider arm Clip sizes allow for tailored patient-specific treatment. To help implanters achieve better outcomes in repairing wide regurgitant jets with fewer Clips, two new wider Clip arm designs were introduced as part of the MitraClip G4 family of devices, which increased the width of the NT and XT Clip arms from 4 to 6 mm. As shown in Figure 10, the added NTW and XTW Clip sizes were now 50% wider than the NT and XT Clips, respectively. The widest portion of the new NTW and XTW Clip arms is intentionally located in the region where the leaflets coapt and where the tissue is well secured by grippers. This efficient change in arm geometry maximizes MR reduction with a minimal increase in the implant size (Figure 11). The Clips are designed to be placed immediately adjacent to one another without interference to maximize reduction of MR and optimize MV gradients. With the MitraClip G4 system, four Clip sizes are now available to the user to tailor valve repair to the specific valve lesion being treated.

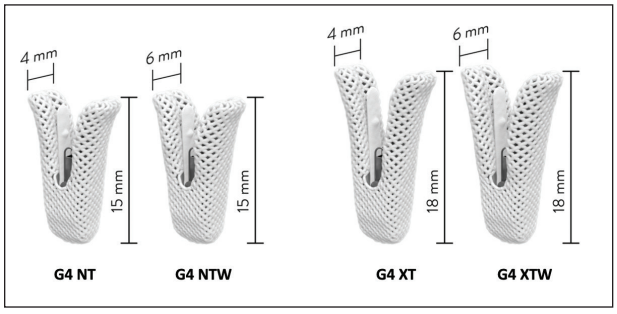

Figure 10. Four MitraClip™ fourth-generation Clip sizes with width and length dimensions shown for each Clip size.

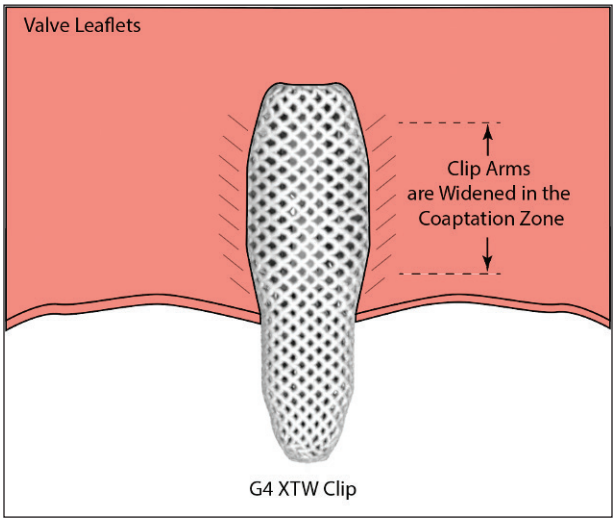

Figure 11. MitraClip™ G4 arm design is widened in the coaptation zone where tissue is secured by gripper FEs.

Small changes, big impact. A regurgitant flow model was used to quantify the differences in effectiveness

"What Abbott has done to change and improve the design of the MitraClip system is very important, because small changes in a device can actually make large differences overall. The continual improvements are why the MitraClip device is the first and most widely used transcatheter treatment option for select patients with degenerative and functional mitral regurgitation."

– Saibal Kar, MD

"Having four Clip sizes allows different leaflet lengths, lesion locations, and valve areas to be treated more optimally. These different clip sizes can be chosen to effectively reduce mitral height in patients with severe prolapse, and, for patients with FMR, match the orientation and shape needed to restore leaflet coaptation. The CGA capability is particularly important for optimizing leaflet insertion, whereby we can focus on getting the leaflets deep in the arms to restore coaptation."

– Paul Sorajja, MD

between Clip sizes, and the wider NTW and XTW Clip sizes were both found to reduce MR approximately 21% more than the NT and XT Clip sizes, respectively (Figure 12).[2] In EXPAND G4, MR was significantly reduced at 30 days compared to baseline (98% achieved MR ≤ 2+ and 91% MR ≤ 1+; $P < .0001$). In addition, computational modeling and benchtop forward flow testing in a simulated MV were used to evaluate the potential risk of mitral stenosis, and the largest device size (XTW) was found to pose a minimal risk.[2] EXPAND G4 demonstrated that contemporary use of the fourth-generation NTW and XTW implants in appropriately selected patients, despite having wider Clip arms, did not increase the MV gradient postprocedure at 30 days (ECL-assessed) compared with the standard arm width (4 ± 2 mm Hg for NTW, 3.5 ± 1.7 mm Hg for XTW, and 3.8 ± 1.9 mm Hg for all Clip types). The composite major adverse event rate was 2.7%, and the all-cause death rate was the lowest ever reported at 1.3% at 30 days.[1]

Expanding the toolbox for the most tailored repair to date. Within the EXPAND G4 Study, an average of 1.4 Clips were implanted per subject, which was lower than the 1.5 Clips per subject in the prior EXPAND study. Sixty-five percent of the patients enrolled were successfully treated with one Clip, 31% with two Clips, and the remaining 4% with three or more Clips. Overall, 14 different Clip combinations were applied, from which 11 included a wide Clip. When Clip usage is compared across geographic regions, the benefit of four Clip sizes as tailored to patient anatomy is clearly observed

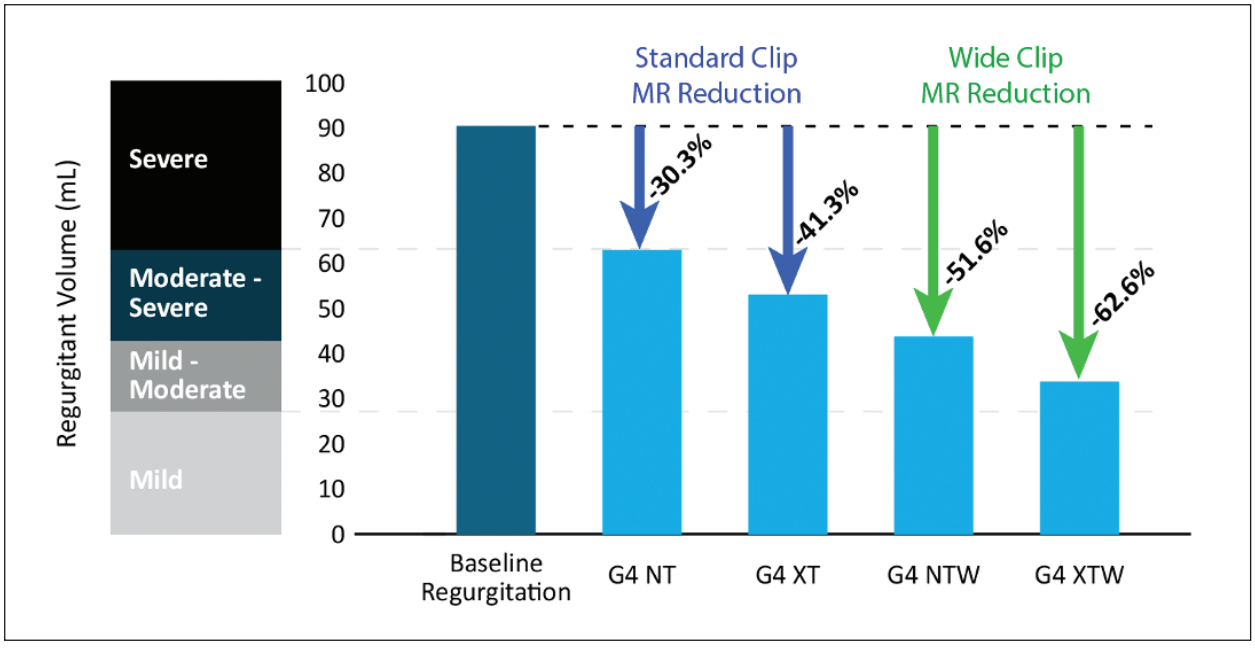

Figure 12. Regurgitant flow test results for standard and wide G4 Clip sizes.

"I think MitraClip G4 was a real game changer... I now understand how 4 Clip sizes can really help me tailor the therapy to treat the individual patient and their anatomy in a much more efficient and effective way."
– Anita Asgar, MD

"The latest device iteration for the MitraClip system with wider and longer clip arms and independent grasping broadened our treatment options for patients with "routine" MR but especially also for those with more challenging anatomies."

"Besides proven effectiveness, the safety of a MitraClip procedure is extremely appealing. In all studies and registries, periprocedural rates of serious adverse events are in the low single-digit percentage range."
– Georg Nickenig, MD

(Figure 13). Specifically, the NT Clip size was frequently used with other previously implanted Clips to optimize a repair while minimizing any impact to the gradient. In addition, this smallest Clip size (NT) was used more frequently in the Asia Pacific region (19% of PMR cases) where valve anatomies tend to be smaller.[3] Because the MitraClip design incorporates arms with appropriate flexural rigidity and controlled arm angle closure, the use of different Clip sizes provides predictable results for the user in terms of MR reduction and mitral gradient, despite varying patient anatomies. This is evident in Figure 13, which indicates users select any of the four Clip sizes during the MitraClip TEER procedure to optimize the repair.[4]

Controlled gripper actuation (CGA) to optimize leaflet capture. To improve the user's ability to obtain full leaflet capture, the MitraClip G4 system added independent leaflet capture capability (Figure 14). This new feature gave users the ability to capture leaflets independently or simultaneously and provided a tool to optimize leaflet insertion on one side of the Clip without jeopardizing the leaflet captured on the other side of the Clip. In some anatomies, it has also been found useful to perform the initial grasp independently. With independent grasping, users can capture the optimal amount of leaflet in the clip, thus maximizing leaflet coaptation and MR reduction.

CGA provides users added flexibility when operating the grippers. CGA has resulted in significant ease of use improvements, especially in challenging cases that were tested by device users in benchtop ex vivo beating heart models. Different pathologies, like large coaptation gaps, were simulated, and CGA was shown to be effective at achieving increased levels of leaflet insertion with fewer capture attempts.[2] After repeated grasping and capture cycles, all leaflet tissue was judged to be free of damage by a certified surgeon.[2] In real-world use, independent leaflet capture was shown to be safe and effective at capturing leaflets in the EXPAND G4 study, with independent leaflet capture being employed in nearly one-quarter of cases. With its independent leaflet capture capability, the use of the MitraClip G4 device in EXPAND G4 resulted in a lower rate (1.1%) of single

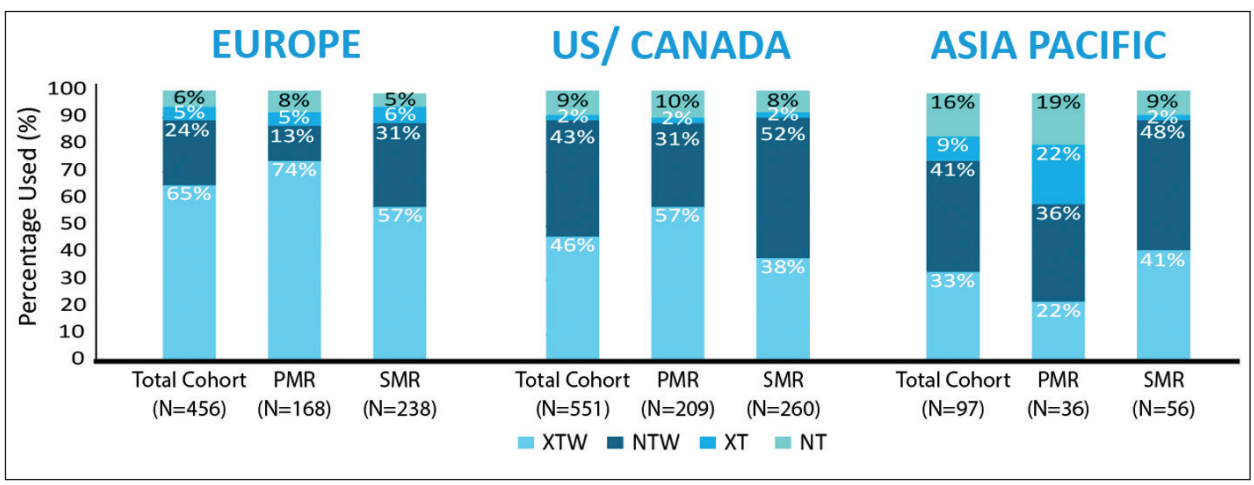

Figure 13. MitraClip™ G4 Clip size usage across different geographies in EXPAND G4.[4]

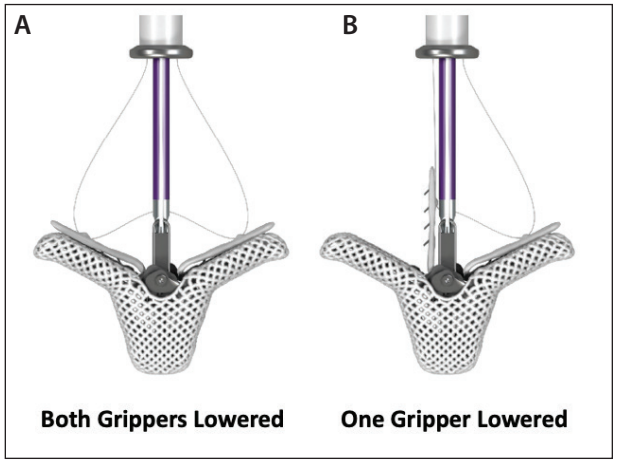

Figure 14. MitraClip™ G4 independent leaflet capture functionality allows the user to lower both grippers simultaneously (A) or lower one gripper at a time (B).

leaflet device attachment (SLDA) when compared with the already low rate previously reported (1.7%) for the prior MitraClip NTR/XTR device generation in EXPAND, and the use of the wider G4 XTW Clip size was associated with zero cases of leaflet injury.[1,8,9]

Automatic gripper line detachment. In the first three MitraClip device generations, the user was required to remove the continuous gripper line after rotating the actuator mandrel to unthread and detach the Clip from the delivery catheter as part of the Clip deployment procedure. With the CGA design change in the MitraClip G4 system, the gripper line removal step was eliminated from the procedure. The two gripper lines automatically disengage from the L-Lock as the user rotates the actuator to unthread the Clip. The user then raises the gripper levers to retract the gripper lines away from the Clip and the Clip fully deploys as the user retracts the delivery catheter.

In EXPAND G4, implantation and acute procedural success rates were 98% and 96%, respectively, with a median procedure time of 77 minutes and a median device time of 35 minutes. This is the shortest device time to date when compared to historical MitraClip clinical studies (Figure 15).[1,5]

SUMMARY

The combination of design features included in the fourth-generation MitraClip system were intended to work together to improve the versatility and efficiency of the MitraClip procedure. The addition of two wider Clip sizes now provided physicians a family of four Clip sizes to choose from to optimize MR reduction when treating different valve sizes, leaflet lengths, and regurgitant jet widths. Leaflet grasping and capture was made easier with the added ability to operate the grippers independently, and the deployment procedure was streamlined to reduce the steps the user was asked to perform. The device preparation procedure was simplified, and additionally, channels were added to the soft tip of the steerable guide catheter to enable left atrial pressure monitoring during the procedure. The benefits of these G4 features have been measured and demonstrated in the EXPAND G4 postmarket study and described in the literature for clinical scenarios with valve anatomic complexity.[10] Even with faster procedure times and fewer Clips per case, greater MR reduction at 30 days was achieved in EXPAND G4 compared to EXPAND (paired analysis of patients with baseline MR ≥ 3+ shows reduction to ≤ 1+ in 89.0% vs 83.0% of patients; $P = .02$). Importantly, almost one-third of the patient population treated achieved MR reduction to

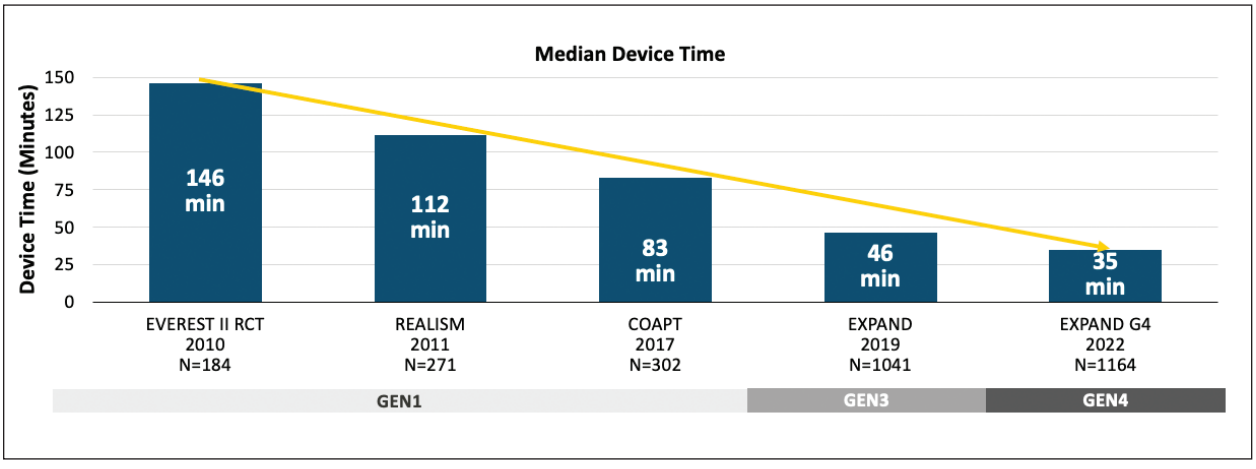

Figure 15. Reduction in device times across historical MitraClip™ device clinical studies demonstrates improved procedural efficiency and the shorter device times with newer device generations.[1,5-8]

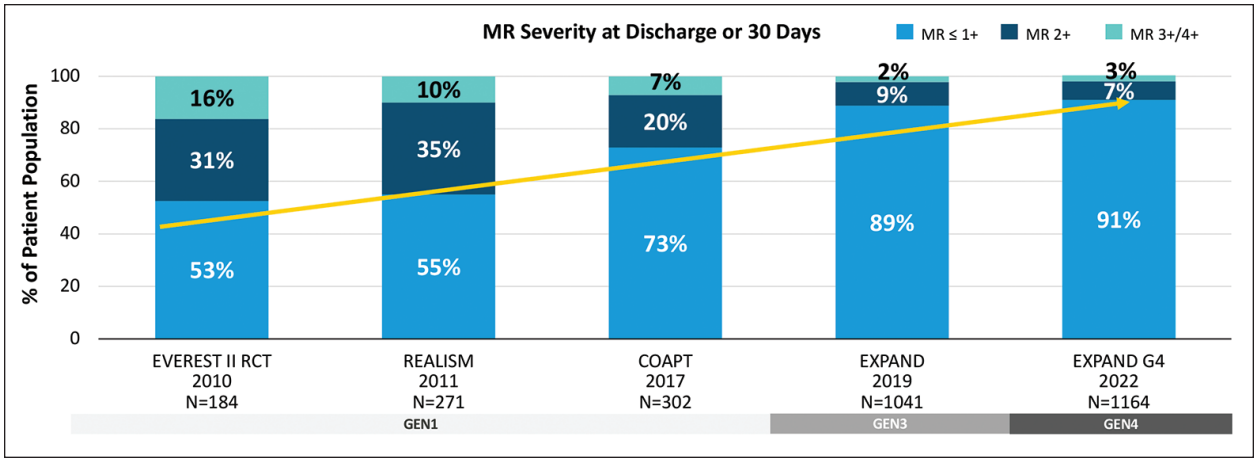

Figure 16. Clinical studies demonstrate improved MR reduction with the latest generations of the MitraClip™ device, including the highest MR reduction in TEER to date with 91% of patients achieving MR ≤ 1+.[1,5-8]

none/trace (29.0% vs 19.0% in EXPAND; $P < .001$). This greater MR reduction with the MitraClip G4 system, as compared with historical MitraClip clinical studies (Figure 16),[1,5-8] may be attributed to the additional wider Clip sizes that provide increased coaptation, the use of four Clip sizes to tailor a repair to each anatomy, and the added ability for users to optimize leaflet capture. In nearly one-quarter of the cases in EXPAND G4 (23.6%), users independently captured leaflets either to further optimize leaflet capture after a first simultaneous capture attempt (19.0% of cases) or when independently capturing leaflets (4.6% of cases).[1] ■

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Therapeutic Benefits of TEER With the MitraClip™ Device

Setting the bar for transcatheter mitral valve repair with unparalleled outcomes.

The continual design evolution over four generations of MitraClip™ (Abbott) products has established the foundation of transcatheter edge-to-edge repair (TEER) therapy and set a bar to which other emerging repair devices and methodologies are compared. MitraClip devices are intentionally designed to repair a regurgitant valve by restoring leaflet coaptation while also providing a second important benefit of applying a stabilizing effect on the valve annulus. Together, these mechanisms reduce mitral regurgitation (MR) while favorably improving the long-term function of the mitral valve (MV) and left ventricle. The design features of MitraClip TEER systems have evolved to improve the amount of MR reduction achieved (Figure 1) and further enhanced the effectiveness of the beneficial mechanisms as described in this article.

"Despite the fact that patients with symptomatic severe secondary MR suffer from high morbidity and mortality rates, additional options with guideline-directed medical therapy are limited and surgery is not possible. In these patients, the MitraClip TEER procedure provides a disruptive therapy as impressively shown in the COAPT trial."
– Georg Nickenig, MD

LEAFLET CAPTURE AND RESTORED COAPTATION

MitraClip devices enable the user to restore leaflet coaptation during cardiac systole. With each generation, MitraClip devices have increased the amount of leaflet that can be captured and coapted through a wider grasping angle and improved gripper (NT), longer Clip arms (MitraClip XTR), independent leaflet capture functionality (G4), and wider Clip arms (G4 NTW and XTW Clip sizes). Importantly, even with the introduction of new larger Clip sizes, smaller Clip sizes continue to be used at significant rates. In all device generations, the gripper design secures leaflets deep inside the Clip arms with rows of frictional elements distributed along the full length of the gripper. As shown in Figure 2, the entire length of leaflet inserted in a G4 XTW Clip during leaflet grasping (at an arm angle of 120°) is maintained within the Clip arm during the closure of a Clip. When measuring leaflet insertion with simulated leaflets made of a range of materials (such as foam and silicone) and of different thicknesses (up to approximately 3-mm thick), leaflet insertion during grasping was found to be the same as after closure. The position of the gripper frictional element rows (along the entire gripper length and particularly the innermost rows) secure leaflets in place and prevent any slippage or loss of leaflet insertion during Clip closure. This design ensures that the full amount of

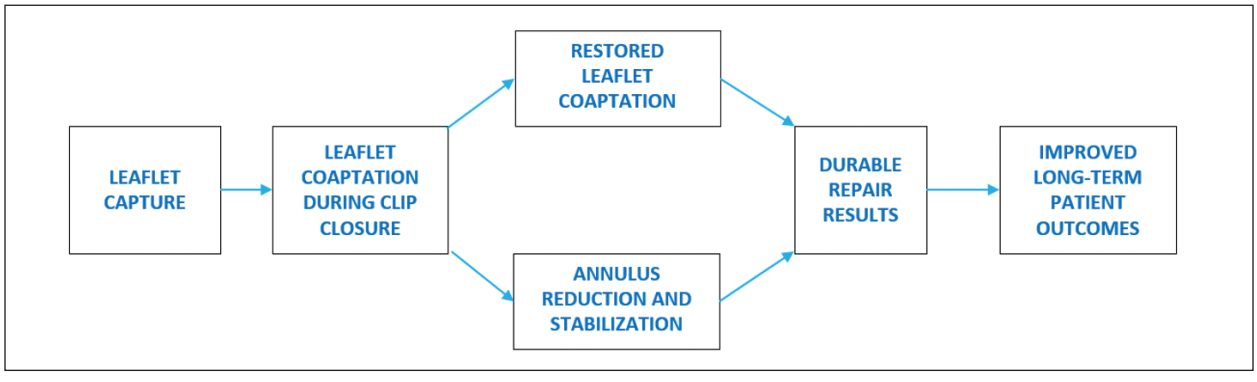

Figure 1. Therapeutic benefits of MitraClip™ TEER.

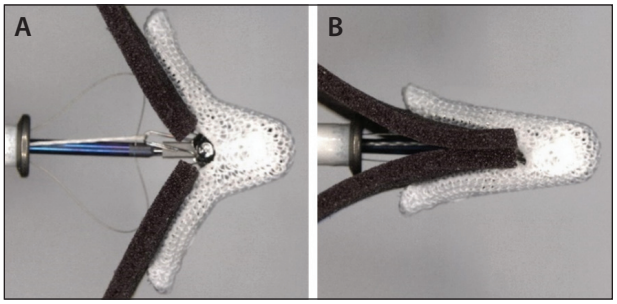

Figure 2. Leaflet insertion and coaptation with simulated (foam) leaflets after grasping (A) and Clip closure (B).

leaflet inserted is retained, which maximizes the restored coaptation after the Clip is closed onto leaflets.

ANNULUS REDUCTION AND STABILIZATION

In chronic MV disease, the MV annulus tends to enlarge and flatten as heart failure (HF) progresses to a worsened state.[1,2] This pathologic change to the valve anatomy is interrupted and reversed by the implantation of MitraClip device(s), which restores long-term coaptation and provides an annulus cinching effect. This annulus cinching effect of MitraClip device implantation was first described in 2012 by Feldman and St. Goar based upon observations in the EVEREST trial[3] and has since been further described in subsequent studies (Table 1).[4-14] This annulus remodeling effect is more prominently observed in secondary MR (SMR) disease; however, some studies listed in Table 1 have also demonstrated annulus reduction in primary MR (PMR), particularly when PMR sample size was large or when the XTR device was evaluated.[4,5] The study time frames encompass large sets of patients and include follow-up out to 1 year, thus indicating that the effects of annular reduction and related MR reduction are maintained over time, and no studies reported any adverse trends in mean gradient. As noted in several studies (Table 1), annulus changes were observed directly after Clip implantation including reduction in valve annulus area, reduction in the anterior-posterior (AP) diameter, increase in ellipticity, and partial restoration of the saddle-shape of the valve annulus. These observations illustrate the sustained annuloplasty effect of the MitraClip device and highlight the importance of implant material choice. Unlike more flexible materials like nitinol and polymeric sutures, the MitraClip device's unique locking mechanism and Elgiloy® (Elgiloy Specialty Metals) arm design stabilizes the annulus and results in restored leaflet-to-leaflet coaptation throughout the cardiac cycle.[15,16]

As shown in Figure 3,[4,15] dynamic annular measurements obtained throughout the entire cardiac cycle indicate that Clip implantation provides constant support and stability to the annulus during both systole (when the valve seals during ventricular contraction) and diastole (when the valve dynamically enlarges to support filling of the ventricle).[15] The amount of AP reduction achieved during a MitraClip procedure has been found to correlate with the amount of MR reduction achieved during TEER therapy, which supports the importance of this annulus remodeling effect on cardiac hemodynamics.[4,8,11] Studies listed in Table 1 also concluded that AP reduction correlates with improved New York Heart Association (NYHA) functional class and 6-minute walk tests scores, which provide measures of HF and quality of life.[9,11] Finally, studies incorporating the recently available longer (MitraClip XTR) and wider arms (MitraClip G4) have indicated an increased remodeling

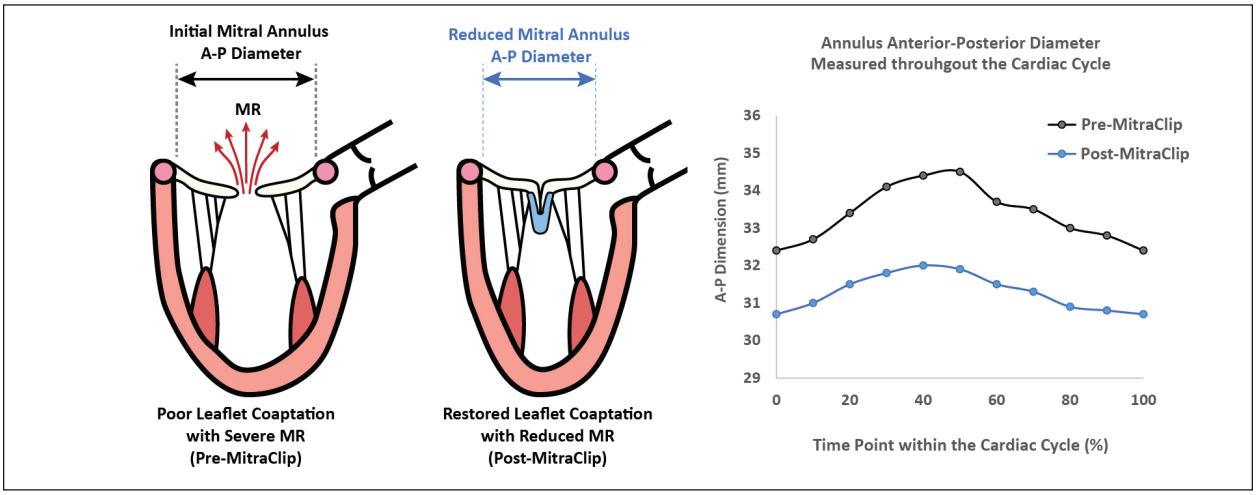

Illustration adapted from Patzelt J, et al. Improved mitral valve coaptation and reduced mitral valve annular size after percutaneous mitral valve repair (PMVR) using the MitraClip system. Eur Heart J Cardiovasc Imaging. 2018;19:785–791. Plot adapted from Noack T, et al. Changes in dynamic mitral valve geometry during percutaneous edge-edge mitral valve repair with the MitraClip system. J Echocardiogr. 2019;17:84–94.

Figure 3. Illustration of MV AP diameter reduction due to MitraClip™ implantation (left) alongside AP diameter difference plotted throughout the cardiac cycle (right). Note that the black line indicates AP diameter prior to Clip implantation and the blue line indicates AP diameter after Clip implantation.

TABLE 1. STUDIES CHARACTERIZING MITRAL VALVE ANNULUS REMODELING AFTER MITRACLIP™ IMPLANTATION

Author (Year)	Patients Studied	Follow-Up	Statistically Significant Findings After Clip Implantation ($P \leq .05$)
Schmidt et al (2013)[6]	n = 14 PMR; n = 41 SMR	Acute	Reduction in AP diameter, annulus and tenting area in SMR
Schueler et al (2013)[7]	n = 36 PMR; n = 71 SMR	6 mo	Reduction of AP diameter and annulus area in SMR; acute AP diameter reduction associated with improved functional outcomes at 6-mo follow-up in SMR
Hidalgo et al (2016)[8]	n = 30 SMR	Acute	Reduction of AP diameter in SMR; AP reduction associated with ROA reduction
Schueler et al (2016)[9]	n = 24 PMR; n = 60 SMR	1 y	Reduction of AP diameter and annulus area in SMR; annulus changes remained significantly reduced at 1-y follow-up and correlated with sustained MR reduction and improved 6MWT
Al Amril et al (2016)[10]	n = 42 SMR	3 mo	Annulus becomes more elliptical post–Clip implantation
Herbrand et al (2017)[11]	n = 45 SMR	6 mo	Greater AP diameter reduction after Clip implantation was associated with more favorable improvements in NYHA heart failure classification, quality of life, and 6MWT results
Patzelt et al (2017)[4]	n = 77 PMR; n = 106 SMR	6.7 mo	Immediate reduction of AP diameter in both SMR and PMR; residual MR was inversely correlated with MV AP reduction; AP diameter reduced further at 6.7-mo follow-up
Mantegazza et al (2018)[12]	n = 38 PMR; n = 42 SMR	6 mo	Reduction in MV area, circumference, AP diameter, MV flatness (nonplanar angle), and sphericity index
Garcia et al (2019)[13]	n = 10 PMR; n = 38 SMR	6 mo	Greater reduction in MV AP diameter in SMR vs PMR; reduction in MV AP diameter correlated with grasped leaflet length; AP diameter reduction correlated with lower probability of MR recurrence
Tusa et al (2021)[5]	n = 26 PMR; n = 33 SMR	Acute	Reduction of AP diameter and saddle shape recovery in SMR; significant improvement in saddle index with XTR in SMR and DMR
Alperi et al (2023)[14]	n = 40 SMR (G1-G3); n = 76 SMR (G4)	1 y	Greater reduction in AP diameter, annulus area, and annulus perimeter for G4 vs earlier devices; no MR recurrence at 1 year for G4 vs 12.4% for G1-G3

Abbreviations: 6MWT, 6-minute walk test; AP, anterior-posterior; DMR, degenerative mitral regurgitation; G1, generation one; G3, generation three; G4, generation four; MR, mitral regurgitation; MV, mitral valve; NYHA, New York Heart Association; PMR, primary mitral valve regurgitation; ROA, regurgitant orifice area; SMR, secondary mitral valve regurgitation.

effect on the annulus. This finding suggests that the longer and wider stable Clip arm designs in the MitraClip G4 product support the annulus to a greater extent than the smaller first-generation Clip size.[5,14] These studies also support that the MitraClip G4 system allows users to select among four Clip sizes to better tailor and optimize the overall repair by achieving better long-term MR reduction and greater annulus remodeling benefits while maintaining acceptable MV gradients that remain stable over time.[14,17]

VENTRICULAR REMODELING

In secondary MV disease, the left ventricle becomes progressively more spherical and enlarges as HF progresses.[18] As demonstrated in the COAPT™ RCT, patients with severe SMR treated with MitraClip and guideline-directed medical therapy (GDMT; device group) had significant reductions in left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) over 2 years when compared to patients in the control group treated with GDMT alone.[19] These data are plotted in Figure 4,[19] indicating that Clip implantation can produce immediate reduction in LVEDV and significantly slows down the progression of ventricular enlargement at time points out to 2 years. As indicated by the difference between the curves, the benefit of MitraClip device implantation over the control group increases over time.

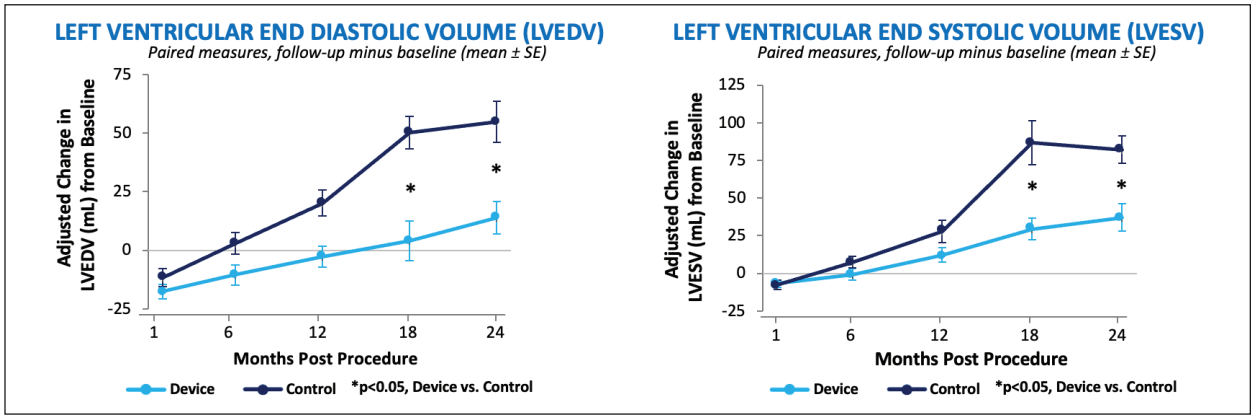

Figure 4. Two-year LVEDV and LVESV data from the COAPT study comparing MitraClip™ plus GDMT (device group) and GDMT alone (control group).[19]

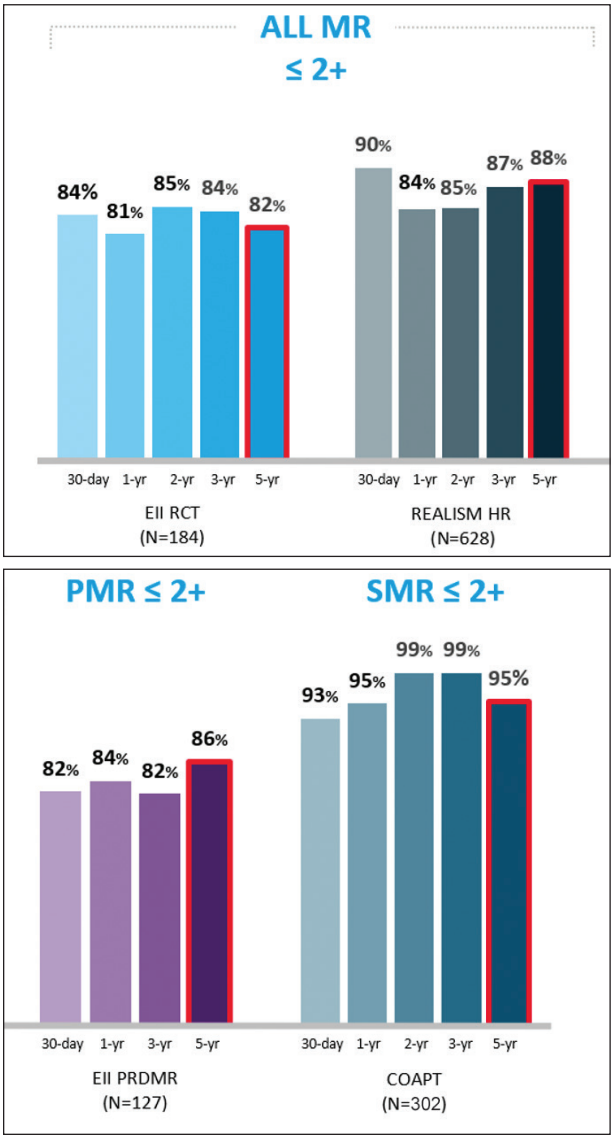

Figure 5. Percentage of patients with MR of ≤ 2+ at follow-up time points out to 5 years after MitraClip™ device implantation for all MR, primary MR, and secondary MR disease states.[16,21,22]

DURABLE MR REDUCTION AND LONG-TERM QUALITY-OF-LIFE IMPROVEMENT

The most profound difference made by the MitraClip therapy is the impact it has had on peoples' lives. Since the first Clip was implanted some 20 years ago, more than 200,000 patients and their families have benefited from the MitraClip TEER therapy in real-world clinical practice. As demonstrated in recent larger contemporary studies, EXPAND and EXPAND G4, patients treated with MitraClip devices implanted feel better—experiencing significant improvements in NYHA functional class and quality of life (as measured per Kansas City Cardiomyopathy Questionnaire [KCCQ] score) with these improvements being maintained through 30 days and 1 year after MitraClip implantation. EXPAND reported NYHA functional class I or II in 80.1% at 30 days and 80.3 % at 1 year, and KCCQ scores of 67.0 at 30 days and 70.2 at 1 year.[20] Even at 5 years, MR reduction is sustained across multiple studies in PMR and SMR populations with previous generation devices (Figure 5),[16,21,22] and as reported in the COAPT trial, symptomatic status per NYHA class was improved throughout follow-up and consistent reductions in the risks of death and hospitalization for HF were observed.[17] Throughout all MitraClip device generations and all the clinical evidence, the outcomes are abundantly clear: patients feel significantly better in the days and years after treatment with MitraClip TEER therapy.[23] ■

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Conclusion: Closing the Gap, Opening Options

A bright future for the MitraClip™ therapy.

The MitraClip™ technology (Abbott) has a 20-year history of enabling minimally invasive transcatheter edge-to-edge repair (TEER) treatment of patients with mitral regurgitation (MR). Although the MitraClip device restores leaflet coaptation in a way that seemingly mimics the surgical Alfieri stitch, the Clip's unique mechanism of action accomplishes more than a simple suture. With its locking mechanism, grippers, and Clip arms, the MitraClip device reduces the mitral valve (MV) annulus anterior-posterior (AP) dimension and interrupts its progressive enlargement. The unique annulus stabilization effect of the MitraClip device provides long-term MR reduction, promoting improved heart failure prognosis for years after device implantation. Finally, the dedicated delivery system design, made specifically for optimal MV access, enables procedure efficiency and predictability.

All four generations of MitraClip device designs have been robustly engineered and optimized with feedback from clinicians. The progressive enhancements to the device design—from introducing four Clip sizes, to adding independent leaflet capture, and enhanced steering precision and control—were based on user input on how new features could steadily improve patient clinical outcomes, broaden the range of treatable patient anatomies, reduce procedure times, and allow physicians to tailor the therapy to each patient for more optimal results. The 20 years of continual efforts and partnership with the physician community—including heart teams, interventional cardiologists, cardiac surgeons, and hospital administration staff—have established a level of care for patients that is unprecedented and paves the way for future device generations that could enable even better patient outcomes. In parallel, the MitraClip therapy has generated the largest body of clinical data in the TEER space with over 20 years of clinical studies evaluating the treatment of more than 80,000 patients. These studies spanning across each MitraClip device generation have demonstrated Abbott's ongoing commitment to innovation and to achieving improved outcomes for patients with MR. The data generated have further characterized the impact of MitraClip implantation on the MV annulus and left ventricle, providing insights on how the MitraClip device, with its stable locked Clip arms, safely supports the structures of the heart in a way that slows the progression of heart failure.

"Over the last 20 years, we have shaped the results of this revolutionary treatment of MR with the MitraClip device, especially for patients who had no other great options. And now, this therapy is being adapted and evaluated for the treatment of tricuspid regurgitation, opening even more possibilities."

"The best part of the journey was to see the outcome in patients, to see people who were suffering, some who were almost dying, and to see them back at life with minimal symptoms was the most dramatic thing. In fact, putting it very simply, the MitraClip therapy has added life to years and years to life."

–Saibal Kar, MD

Moving forward, the MitraClip therapy is being studied in new, expanded patient populations. The REPAIR MR (Percutaneous MitraClip Device or Surgical Mitral Valve Repair in Patients with PrImaRy Mitral Regurgitation who are Candidates for Surgery) trial (NCT04198870 clinicaltrials.gov) will evaluate the safety and effectiveness of TEER with the MitraClip device in patients with primary MR who are at moderate surgical risk and are candidates for surgical MV repair. The trial will generate contemporary clinical evidence comparing the MitraClip device and surgical MV repair.

Beyond the treatment of additional patient populations, the MitraClip system is a platform technology that can be leveraged to develop products for treating other valvular diseases such as tricuspid regurgitation. Elements of the technology can be used to develop future delivery systems for transcatheter MV and tricuspid valve replacement, chordal repair, and annuloplasty therapies. If the last 20 years and the more than 200,000 patients treated worldwide are any reflection of what's to come, the next 20 years look bright for the MitraClip therapy and the field of cardiovascular therapeutics. ■

The testimonials do not provide any indication, guide, warranty, or guarantee as to the response a patient may have to the treatment or effectiveness of the product or therapy in discussion. Opinions about the treatment discussed can and do vary, are specific to the individual, and might not be representative of others.

Physician Disclosures

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Rx Only

Important Safety Information

MITRACLIP™ CLIP DELIVERY SYSTEM

Indications for Use
The MitraClip™ G4 System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.

The MitraClip™ G4 System, when used with maximally tolerated guideline-directed medical therapy (GDMT), is indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria) in patients with a left ventricular ejection fraction (LVEF) ≥ 20% and ≤ 50%, and a left ventricular end systolic dimension (LVESD) ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease.

Contraindications
The MitraClip G4 System is contraindicated in patients with the following conditions: Patients who cannot tolerate, including allergy or hypersensitivity to, procedural anticoagulation or post procedural anti-platelet regime; Patients with known hypersensitivity to clip components (nickel / titanium, cobalt, chromium, polyester), or with contrast sensitivity; Active endocarditis of the mitral valve; Rheumatic mitral valve disease; Evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus.

Potential Complications and Adverse Events
The following ANTICIPATED EVENTS have been identified as possible complications of the MitraClip G4 procedure: Allergic reactions or hypersensitivity to latex, contrast agent, anaesthesia, device materials (nickel / titanium, cobalt, chromium, polyester), and drug reactions to anticoagulation, or antiplatelet drugs, Vascular access complications which may require transfusion or vessel repair including: wound dehiscence, catheter site reactions, Bleeding (including ecchymosis, oozing, hematoma, hemorrhage, retroperitoneal hemorrhage), Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation / rupture, vascular occlusion, Emboli (air thrombotic material, implant, device component); Peripheral Nerve Injury; Lymphatic complications; Pericardial complications which may require additional intervention, including: Pericardial effuse on, Cardiac tamponade, Pericarditis; Cardiac complications which may require additional interventions or emergency cardiac surgery, including: Cardiac perforation, Atrial septal defect; Mitral valve complications, which may complicate or prevent later surgical repair, including: Chordal entanglement / rupture, Single Leaflet Device Attachment (SLDA), Thrombosis, Dislodgement of previously implanted devices, Tissue damage, Mitral valve stenosis, Persistent or residual mitral regurgitation, Endocarditis; Cardiac arrhythmias (including conduction disorders, atrial arrhythmias, ventricular arrhythmias); Cardiac ischemic conditions (including myocardial infarction, myocardial ischemia, and unstable / stable angina); Venous thromboembolism (including deep vein thrombosis, pulmonary embolism, post procedure pulmonary embolism); Stroke / Cerebrovascular accident (CVA) and Transient Ischemic Attack (TIA); System organ failure: Cardio-respiratory arrest, Worsening heart failure, Pulmonary congestion, Respiratory dysfunction / failure / atelectasis, Renal insufficiency or failure, Shock (including cardiogenic and anaphylactic); Blood cell disorders (including coagulopathy, hemolysis, and Heparin Induced Thrombocytopenia (HIT)); Hypotension / hypertension; Infection including: Urinary Tract Infection (UTI), Pneumonia, Septicemia; Nausea / vomiting; Chest pain; Dyspnea; Edema; Fever or hyperthermia; Pain; Death; Fluoroscopy, Transesophageal echocardiogram (TEE) and Transthoracic echocardiogram (TTE) -related complications: Skin injury or tissue changes due to exposure to ionizing radiation, Esophageal irritation; Esophageal perforation, Gastrointestinal bleeding.

CAUTION: Product(s) intended for use by or under the direction of a physician. Prior to use, reference to the Instructions for Use, inside the product carton (when available) or at eifu.abbottvascular.com or at medical.abbott/manuals for more detailed information on Indications, Contraindications, Warnings, Precautions and Adverse Events.

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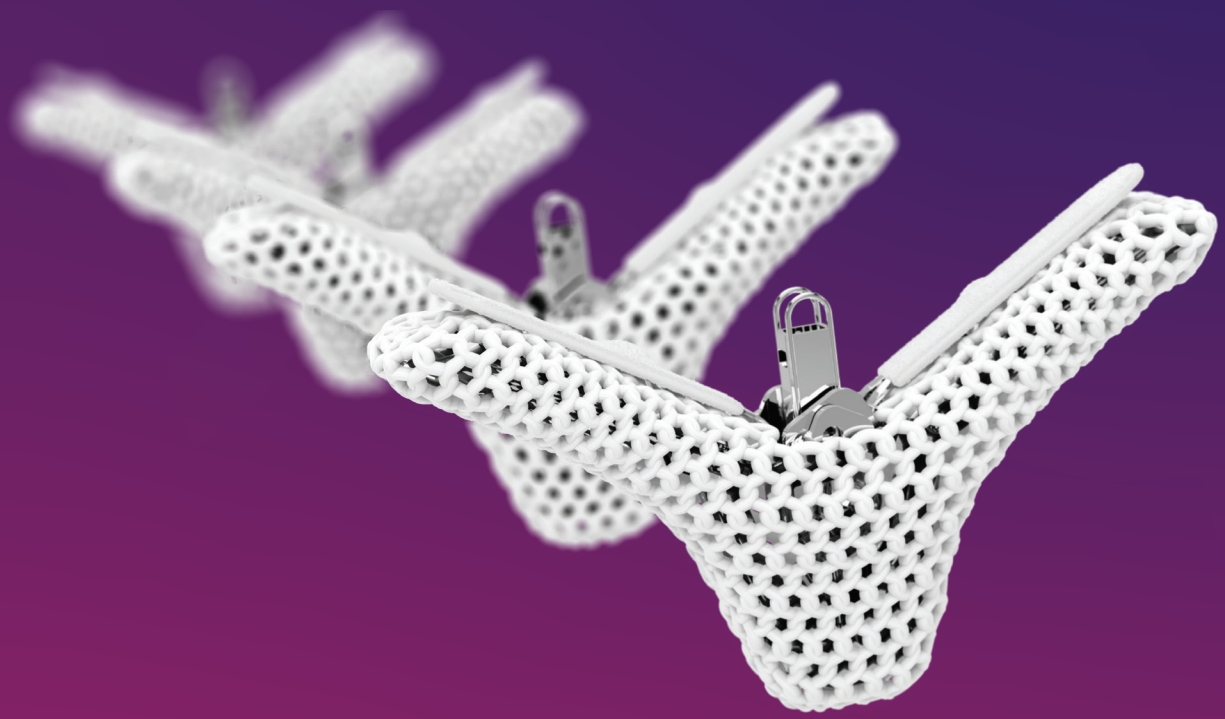
Closing the Gap Opening Options



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See Important Safety Information referenced within.