

Percutaneous Mitral Valve Repair: The Next Wave

A review of investigational mitral repair therapies, emphasizing device design and highlighting key clinical studies.

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Mitral regurgitation (MR) is the most common form of valvular heart disease in the United States.¹ The etiologies of MR can be related to primary degeneration of the mitral valve (DMR), functional mitral regurgitation (FMR) secondary to ischemic or nonischemic cardiomyopathy, or a combination of both. Nearly 2 million people are affected by FMR associated with congestive heart failure (CHF), and direct and indirect CHF health care costs are projected to reach \$70 billion by 2030.²⁻⁴ Current guidelines recommend surgical mitral valve repair or replacement (MVR) in patients with significant primary DMR.⁵ However, the overall benefit of mitral valve surgery for isolated severe FMR with persistent New York Heart Association (NYHA) class III or IV symptoms has not been as rigorously studied in randomized trials, hence the class IIb indication per the 2014 American College of Cardiology/American Heart Association valvular heart disease guidelines.⁵ Nearly 50% of patients with severe symptomatic MR are turned down for surgery due to older age, frailty, left ventricular dysfunction, and comorbid conditions.⁶

As a consequence of this untreated or undertreated population of MR patients, the medical device industry has seen explosive growth in the percutaneous and minimally invasive MVR device markets, with multitudes of startups and several innovative and exciting technologies making it to first-in-human testing and CE Mark approval. Due to challenges with transcatheter MVR platforms and the surgical mantra of “repair over replacement,” the device industry and investment pipeline have focused enormous investment and capital in mitral repair systems. The only US Food and Drug Administration (FDA)–approved, commercially available percutaneous mitral valve repair platform is the transcatheter mitral

leaflet edge-to-edge percutaneous repair MitraClip device (Abbott Vascular), which has been studied in randomized trials and registries. In Europe, several mitral valve repair systems have received CE Mark approval and are currently in commercial and registry use, including MitraClip, Mitralign (Mitralign, Inc.), Carillon (Cardiac Dimensions, Inc.), Cardioband (Edwards Lifesciences), and NeoChord DS1000 (NeoChord, Inc.).

In this article, we canvas some of the technologies in the next wave of mitral repair therapies, emphasizing device design and highlighting key clinical studies performed to date. All therapies discussed are minimally invasive percutaneous procedures with fluoroscopic and transesophageal echocardiographic (TEE) guidance. Table 1 lists the mitral repair therapies and their corresponding regulatory status.

DIRECT ANNULOPLASTY TECHNOLOGIES

Mitralign Percutaneous Annuloplasty System

The Mitralign percutaneous annuloplasty system is predicated on tissue plication of the mitral annulus using a transcatheter pledget delivery system with retrograde aortic access to the left ventricle and atrium (Figure 1). Typically, two pairs of pledgets are placed at opposite



Figure 1. The Mitralign percutaneous annuloplasty system.

Courtesy of Mitralign, Inc.

TABLE 1. MITRAL REPAIR TECHNOLOGIES AND REGULATORY STATUS*

Device	Manufacturer	Investigational?	CE Mark Approved?	FDA Approved?
AccuCinch	Ancora Heart, Inc.	Yes	No	No
Amend mitral valve repair annuloplasty ring	Valcare Medical	Yes	No	No
Arto system	MVRx, Inc.	Yes	No	No
Cardioband	Edwards Lifesciences	—	Yes	No
Carillon mitral contour system	Cardiac Dimensions, Inc.	—	Yes	No
Iris complete annuloplasty ring	Millipede, Inc.	Yes	No	No
MitraClip	Abbott Vascular	—	Yes	Yes
Mitralign	Mitralign, Inc.	—	Yes	No
NeoChord DS1000	NeoChord, Inc.	—	Yes	No
PASCAL mitral valve repair system	Edwards Lifesciences	Yes	No	No
TSD-5 device	Harpoon Medical, Inc.	Yes	No	No
VenTouch system	Mardil Medical	Yes	No	No

*As of July 2017.
Abbreviation: FDA, US Food and Drug Administration.

ends of the annulus to decrease the annulus circumference and in turn reduce the degree of functional regurgitation. The spacing as well as the number of pairs, can be adjusted.

The first-in-human (FIH) trial experience for the Mitralign system was reported by Nickenig and colleagues in 71 prospectively enrolled patients with moderate-to-severe FMR on stable medical therapy for heart failure.⁷ Device success was 70.4%, there were no deaths, and the rate of cardiac tamponade was 8.9%.⁷ At 30 days, the investigators reported an all-cause mortality and stroke rate of 4.4%, respectively, and a 0% rate of myocardial infarction (MI).⁷ At 6 months, all-cause mortality was 12.2%, and the rates of stroke and MI were 4.9% and 0%, respectively, with nonurgent MVR in 2.4% and mitral valve repair in 17.1% of patients.⁷ Six-month MR mean reduction of 1.3 grades was achieved in 50% of patients, with significant improvement in 6-minute walk tests and fewer patients with NYHA class III/VI symptoms (53.3%–23.3%).⁷ Average annular dimensions were reduced by approximately 3 mm anterior-posterior, 2 mm septal-lateral, and there was a 0.57-cm² reduction in mitral valve tenting area.⁷ Significant improvement was seen in remodeling, with reductions in left ventricular end-diastolic diameter, end-diastolic volume, and end-systolic volume.

The Mitralign system is CE Mark approved and available for commercial use in Europe. The Trialalign platform (Mitralign, Inc.) applies this similar concept to the tricuspid space.

Arto System

The Arto (arto in Latin means “to press together”) transcatheter annular reduction therapy system (MVRx, Inc.) is designed to address annular dilatation in symptomatic patients with FMR by reducing the mitral valve anterior-posterior dimension (APD) (Figure 2). This device requires placement of 12-F venous access sheaths in the right internal jugular vein and right common femoral vein, followed by wiring the great cardiac vein, to gain transseptal access to the left atrium. Magnet-tipped catheters are then placed in the great cardiac vein and the posterolateral aspect of the left atrial wall to facilitate puncture and formation of a veno-venous loop. An atrial septal anchor and a coronary sinus anchor are then placed and cinched together, which works to shorten the APD and decrease MR under echocardiographic guidance.

Initial 30-day results from 11 patients in the MAVERIC trial were published in 2015, with no reported adverse

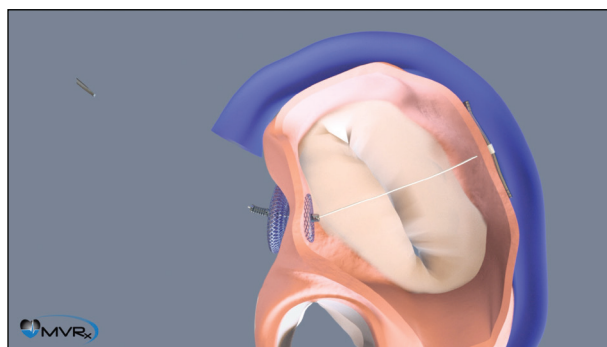


Figure 2. The Arto system.

Courtesy of MVRx, Inc.

procedural events; however, at 30 days, there was one case of pericardial effusion requiring a pericardial window and one asymptomatic device dislodgement.⁸ The investigators also reported reduction in the effective regurgitant orifice area from $30.3 \pm 11.1 \text{ mm}^2$ to $13.5 \pm 7.1 \text{ mm}^2$.⁸ Additionally, regurgitant volumes decreased from $45.4 \pm 15 \text{ mL}$ to $19.5 \pm 10.2 \text{ mL}$.⁸ Mitral annular APD was reduced from $45.0 \pm 3.3 \text{ mm}$ to $38.7 \pm 3.0 \text{ mm}$, which resulted in functional status improvements from 81.8% of patients in NYHA class III/VI at baseline to 54.6% in NYHA class I/II at 30-day follow-up.⁸

This device is currently being studied in the MAVERIC trial (NCT02302872), which is a multicenter, single-arm study that aims to enroll 45 patients with FMR of any etiology and NYHA class II to IV heart failure across 15 international centers.⁸ Key exclusion criteria include patients with hemodynamic instability, history of atrial septal defects (repaired or not), femoral or jugular veins unable to accommodate the catheter system, structural abnormality of the mitral valve, significant mitral annular calcium, and history of repaired patent foramen ovale or patent foramen ovale with clinical symptoms within 6 months of the procedure.⁸

Iris Complete Annuloplasty Ring

The Iris device (Millipede, Inc.) is a semirigid nitinol ring that is implanted in the mitral valve annulus. The ring consists of an edge design with a collar zone that allows the ring to be adjusted and tailored to the needs of the patient's annulus (Figure 3). The Iris system is implanted and manipulated on the atrial side, obviating concerns about left ventricular chordal interaction.

Initial data for this device were gained via direct atrial surgical access in animals, followed by FIH cases in three

patients who had temporary implants placed during the course of open heart surgery (implants were removed prior to further surgical repair); there were also four patients who had open surgical permanent implants that have remained stable up to 1 year later, with evidence of LV remodeling.

The Iris system was recently revised to be implanted via a transfemoral venous transcatheter route through transseptal access to the left atrial, and it is adjustable, repositionable, and retrievable until customized to its final position and dimension. In May 2017, two patients underwent successful implantation with the Iris device via transfemoral transseptal transcatheter access and were discharged within 48 hours. A trial to evaluate the Iris system outside of the United States (NCT02607527) is underway, with a goal of enrolling 10 patients. The primary endpoint is acute safety, defined as incidence of adverse events, with a secondary endpoint of 30-day efficacy. This device has tricuspid valve repair applications as well.

Amend Mitral Annuloplasty Ring

The Amend device (Valcare Medical) is a semirigid, D-shaped ring that emulates the current surgical annuloplasty ring standard (Figure 4). The implantation procedure utilizes transapical surgical access, and the device is



Courtesy of Valcare Medical.

Figure 4. The Amend mitral valve repair annuloplasty ring.

then advanced across the mitral valve to the atrial aspect. Once across the mitral valve, the ring is released from the delivery catheter, takes on a D-shape, and is aligned with the mitral valve plane. The ring is then secured to the posterior mitral annulus via a series of stabilizers. Once affixed, the posterior mitral annulus is pulled anteriorly to then affix the anterior rim of the ring, and anterior stabilizers are then deployed. Once the ring is fully secured to the mitral annulus, the anterior-posterior mitral annulus dimension is reduced, which aims to improve anterior-posterior leaflet coaptation and reduce the regurgitant orifice. Additional delivery system designs for the Amend device, such as the transfemoral transseptal route, are also being developed.

In November 2016, Valcare Medical announced its FIH experience, with successful device implantation in a patient at high surgical risk via transapical access at Sheba Medical Center in Israel. The Amend platform

Courtesy of Millipede, Inc.



Figure 3. The Iris complete annuloplasty ring.

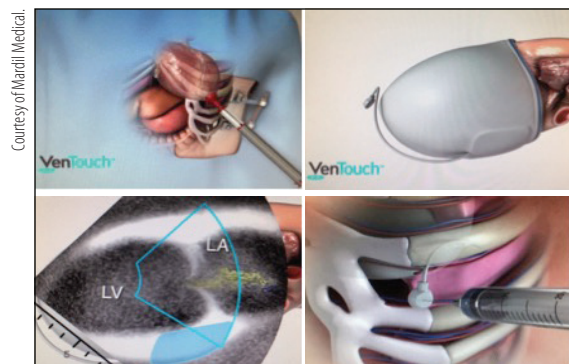


Figure 5. The VenTouch system.

may also lend itself to use as an anchor or landing zone for mitral valve-in-ring therapies for select patients in the future. There are currently no publicly reported trial data on this device.

VenTouch System

The VenTouch system (Mardil Medical) uses a ventricular reshaping strategy. The VenTouch device is an external sleeve that is deployed over the heart via surgical transapical access, with an inflatable saline pouch located on its inferoposterior aspect (Figure 5). The pouch is injected with saline, which extrinsically pushes the posterior aspect of the mitral valve annulus anteriorly and thus reduces the mitral annular APD and regurgitant orifice. The system is designed with a subcutaneous access port that can be manipulated in the future to increase or decrease the amount of saline in the bladder pouch, thereby customizing the degree of mitral annular reduction.

The system is currently being studied for human use. Per a presentation by Dr. Jai Raman at Heart Valve Society 2016, a multicenter trial is ongoing, with at least 30 patients enrolled.

BASAL VENTRICULOPLASTY TECHNOLOGIES

AccuCinch System

The AccuCinch system (Ancora Heart, Inc.) is a device and therapy for the treatment of FMR due to dilated cardiomyopathy of ischemic or nonischemic etiology (Figure 6). The device is designed to treat FMR and left ventricular remodeling with a less-invasive percutaneous procedure. The AccuCinch implant decreases the circumference of the posterior free wall of the dilated left ventricle, which reduces left ventricle wall stress by reducing the left ventricle radius, realigning the papillary muscles, reducing mitral valve tenting, and reducing the mitral valve annulus. These primary mechanisms facilitate subsequent secondary effects of reverse left ventricle remodeling and restoring proper

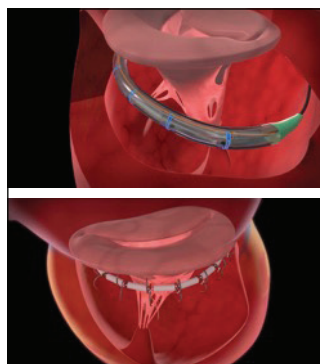


Figure 6. The AccuCinch device.

coaptation of the mitral valve leaflets, with a reduction of FMR.

The AccuCinch device is implanted in the sub-annular groove 10 to 20 mm below the mitral valve plane at the base of the left ventricle using a percutaneous transfemoral retrograde approach.

Several successful cases have been performed in humans. Currently, Ancora

Heart is sponsoring three clinical trials: a non-US early feasibility trial (NCT00800046), a non-US CE Mark approval study (NCT03183895), and a US early feasibility trial (NCT02806570). There are currently no published trial data on human use of this investigational device.

EDGE-TO-EDGE REPAIR TECHNOLOGIES

Pascal Mitral Valve Repair System

The Pascal mitral valve repair system (Edwards Lifesciences) was developed to improve upon previous surgical and transcatheter mitral valve repair therapies.

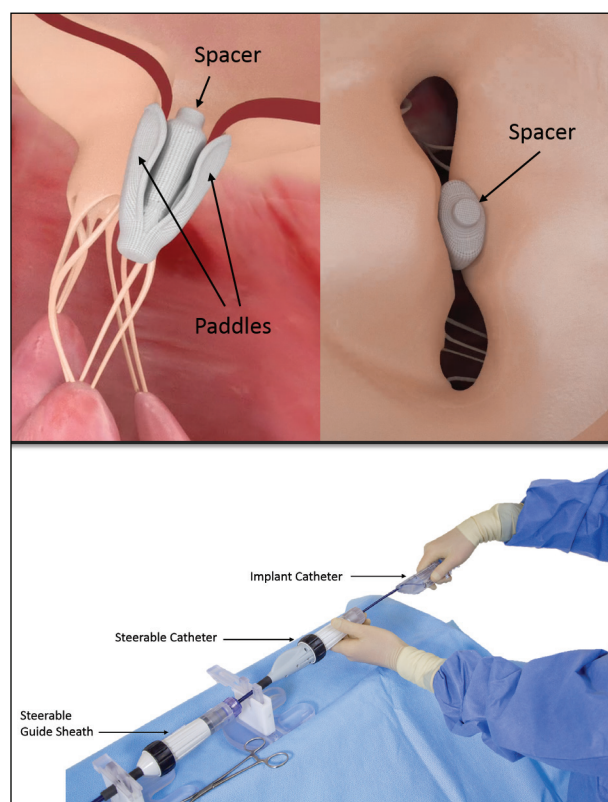


Figure 7. The Pascal mitral valve repair system.

The transcatheter repair device is aimed at interventional treatment of patients with MR who are currently not well-served by available therapies. The device implantation technique utilizes the transseptal access route. The Pascal device consists of two paddles for independent grasping of mitral leaflets to facilitate leaflet coaptation around a central spacer for reduction of MR (Figure 7). The paddle dimensions are tailored to accommodate the larger coaptation gaps akin to FMR patients. The device coaxiality and success is independent of septal puncture height.

Recently, Spargias and colleagues presented 30-day compassionate use results at the EuroPCR 2017 meeting. The investigators reported on 23 patients: mean age was 71 ± 15 years, 70% were men, average EuroScore II was $9.4\% \pm 7.9\%$, average left ventricular ejection fraction (LVEF) was $42\% \pm 14\%$, and 96% had NYHA class III/IV symptoms.⁹ Of the 23 patients, 52% had adjudicated FMR, 26% had degenerative MR, and 22% had mixed etiology.⁹ Technical success (as defined by the Mitral Valve Academic Research Consortium) was achieved in 96% of patients. There was 0% procedural mortality, 0% emergent conversion to open heart surgery, no patients required ASD closure, and average hospital length of stay was 4 days.⁹ At discharge, 77% of patients had MR grade 0 to 1, and the mean mitral valve gradient at discharge was 3 mm Hg.⁹ All-cause mortality at 30 days was 13%. There were no hospitalizations for heart failure, no reinterventions for mitral valve dysfunction, a 4% rate of transient ischemic cerebral attacks, and 0% rates of ischemic stroke, MI, and device thrombosis.⁹ At 30 days, 95% of the patients had MR grades ≤ 2 , and 95% of the patients were NYHA class I/II.

CHORDAL TECHNOLOGIES

NeoChord DS1000

The NeoChord DS1000 device (NeoChord, Inc.) is aimed at addressing DMR. The device is delivered via transapical access and consists of a high-translucency expanded polytetrafluoroethylene (ePTFE) synthetic fiber, which has a labeled indication for use as artificial chord for mitral valve repair. After transapical access, the delivery system crosses the valve and grasps the problematic leaflet; the grasp is confirmed via a leaflet grasp indicator console. The delivery system then pierces the leaflet, delivers the ePTFE chord, and then externalizes it; this is followed by loop knotting and pushing of the knot to the grasped leaflet. The artificial chord is thereby secured to the leaflet and then pulled and anchored to the myocardial apex site of entry for the desired reduction in regurgitant orifice (Figure 8).

This device design was first conceived in 2003, followed by animal studies in 2005, and a United



Courtesy of NeoChord, Inc.

Figure 8. The NeoChord DS1000 device.

States patent in 2006. The 2010 FIH non-United States TACT trial subsequently led to CE Mark approval in 2012. Results of the TACT trial were published by Seeburger and colleagues in 2014.¹⁰ Thirty patients at seven European centers underwent off-pump transapical implantation of the NeoChord DS1000 device. The average patient age was 63.5 years, average LVEF was 59%, 90% patients had MR grade 4, and 100% of patients had posterior mitral leaflet (PML) prolapse and PML chordal rupture or elongation.¹⁰ Major adverse events included one death due to postcardiotomy syndrome and sepsis, one minor stroke with no residual deficits at 30-day follow-up, and six patients required reoperation for failed repair.¹⁰ At 30 days, 17 of 30 patients had $\leq 2+$ MR.¹⁰ To date, > 450 patients have been treated with the NeoChord DS1000 device at centers outside the United States. A TACT Registry study is ongoing. Two-year follow-up data on 127 treated patients were presented at the 2016 European Association of Cardiothoracic Surgery in Barcelona, Spain.

In May 2016, NeoChord, Inc. announced that it had received investigational device exemption approval from the FDA, and in November 2016, the company noted that the first patient had been treated with the NeoChord DS1000 device in the United States as part of the prospective, multicenter, randomized RECHORD trial at Mount Sinai Health System in New York. The RECHORD trial is the United States FDA pivotal study, which aims to enroll 585 patients at 20 investigational sites.

TSD-5 Mitral Valve Repair Device

The TSD-5 mitral valve repair device (Harpoon Medical, Inc.) is an artificial chord-based system that consists of a preformed ePTFE knotted suture delivered via minimally invasive surgical transapical 12-F access (Figure 9). It is designed for patients with DMR. Based on fluoroscopic and TEE guidance, the device is advanced just below the

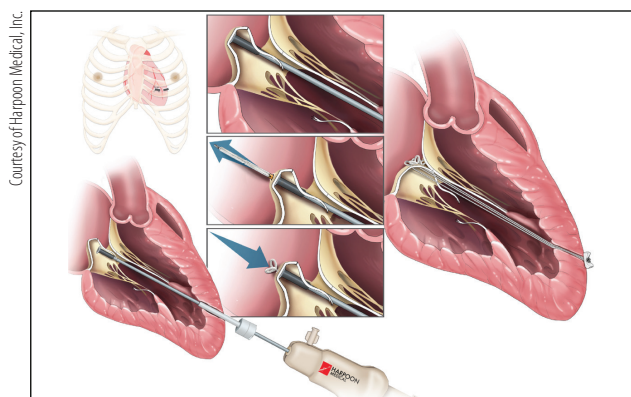


Figure 9. The TSD-5 device.

posterior mitral leaflet and positioned on the ventricular aspect of the leaflet with assistance from a stabilizer. This decreases the need to catch the prolapsing leaflet directly. Once the device position is confirmed on TEE, a needle is released by depressing the plunger on the delivery system, and the preformed ePTFE knot is released on the atrial aspect of the posterior leaflet. The device is then removed, and the ePTFE artificial chord remains. This process can be repeated multiple times to achieve the desired degree of posterior mitral leaflet tethering. At the conclusion of the artificial chord implantation procedure, the ideal chord length is confirmed under TEE guidance, and then the chords are secured to the exterior of the heart by a piece of Teflon (Chemours) felt material.

At the 2016 Transcatheter Cardiovascular Therapeutics meeting, Dr. James Gammie presented 1-year follow-up data from the initial 13 patients treated with the device.¹¹ The average patient age was 66 years, mean Society of Thoracic Surgeons score was 1.15, mean LVEF was 62%, and the average number of chords implanted was 3.7. In this initial 13-patient experience, there was 100% procedural success. At 30 days, all 13 patients had none-to-trace or mild residual MR, and there were no reports of 30-day or 1-year mortality, stroke, MI, or endocarditis or acute conversion to open heart surgery during the procedure. Two patients had reoperations for pericardial effusions on postoperative days 5 and 13, respectively. Two patients had reoperations for recurrent MR on postoperative days 72 and 231, respectively. One reoperation was due to detachment of the ePTFE chord to the apical pledget, and the other reoperation was due to rupture of a native anterior leaflet chord. Thirty-day results demonstrated statistically significant reduction in left ventricular end-diastolic dimension, left ventricular end-diastolic volume, left atrial volume, and mitral annular dimension.¹¹ At 1 year, four of the 13 patients had adjudicated moderate MR.¹¹ Currently, there is an ongoing CE Mark study (NCT02432196) taking place at 22 centers in five European nations.

SUMMARY

Many devices are well beyond the preclinical phase and available for mitral valve repair. Transcatheter mitral valve repair technologies show incredible promise to replicate many surgical techniques, such as leaflet edge-to-edge repair, annuloplasty, and use of artificial chords. The platforms are working their way through feasibility studies and onto larger head-to-head trials in patients with both DMR and FMR. At this point, device safety and efficacy are promising, and as the operator learning curve and device iterations progress, these will likely improve going forward. With this armament of options, the goal is within sight—the right therapy for the right patient at the right time. ■

- Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. *Lancet*. 2009;373:1382-1394.
- Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005-1011.
- Patel JB, Borgeson DD, Barnes ME, et al. Mitral regurgitation in patients with advanced systolic heart failure. *J Card Fail*. 2004;10:285-291.
- Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6:606-619.
- Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published erratum appears in *J Am Coll Cardiol*. 2014;63:2489]. *J Am Coll Cardiol*. 2014;63:e57-185.
- Mirabel M, Iung B, Baron G, et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J*. 2007;28:1358-1365.
- Nickenig G, Schueler R, Dager A, et al. Treatment of chronic functional mitral valve regurgitation with a percutaneous annuloplasty system. *J Am Coll Cardiol*. 2016;67:2927-2936.
- Rogers JH, Thomas M, Morice MC, et al. Treatment of heart failure with associated functional mitral regurgitation using the ARTO system: initial results of the first-in-human MAVERIC trial (Mitral Valve Repair Clinical Trial). *JACC Cardiovasc Interv*. 2015;8:1095-1104.
- Spargias K, Praz F, Chrysosheeris M, et al. The Edwards PASCAL transcatheter mitral valve repair system: 30-day compassionate use results. Presented at EuroPCR 2017; May 16-19, 2017; Paris, France.
- Seeburger J, Rinaldi M, Nielsen SL, et al. Off-pump transapical implantation of artificial neo-chordae to correct mitral regurgitation: the TACT trial (Transapical Artificial Chordae Tendinae) proof of concept. *J Am Coll Cardiol*. 2014;63:914-919.
- Gammie J. Beating heart mitral valve repair using a preformed ePTFE knot implantation device. Presented at Transcatheter Cardiovascular Therapeutics 2016; October 29–November 2, 2016; Washington, DC.

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