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Transcatheter repair of tricuspid regurgitation with MitraClip☆

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ABSTRACT

Transcatheter therapy with the MitraClip system (Abbott Structural, Menlo Park, CA) is the most commonly used transcatheter therapy for patients with tricuspid regurgitation, with over 1000 cases performed worldwide. The procedure is an off-label approach that requires meticulous attention to anatomical features obtained via comprehensive echocardiography and, in some cases, using cardiac computed tomography. Herein, we describe patient selection, procedural performance, and clinical outcomes of this therapy.

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Significant tricuspid regurgitation (TR) is a highly prevalent and morbid condition that affects ~0.6% of the general population.[1] Transcatheter therapy for TR has received increasing attention due to the risk of surgery, which can be excessive in some patients.[2–4] Presently, the most common transcatheter approach for such patients is off-label use of the MitraClip system (Abbott Structural, Menlo Park, CA), with an estimated 1200 patient implants thus far. In this approach, the MitraClip system is used to permanently appose the tricuspid leaflets to recreate coaptation and reduce TR.[5–9] The procedure relies heavily on comprehensive transesophageal echocardiography (TEE) for planning and technical performance. Early reports have described feasibility, with pivotal trials in the U.S. currently under way.

Patient evaluation

As advised for valvular heart interventions, a complete heart team evaluation is performed, with close collaboration between cardiologists, interventionalists, and cardiac surgeons, and comprehensive imaging with both transthoracic echocardiography (TTE) and TEE. Key patient considerations for the treatment of TR with the MitraClip system are: a) symptoms of heart failure (HF) due to TR (i.e., New York Heart Association [NYHA] class ≥II); b) severe TR on echocardiography; c) preference of a non-surgical approach by the local heart team; d) patient imaging and anatomy conducive to transcatheter therapy; and e) informed consent from the patient for off-label treatment with the MitraClip system.[9] Patients with TR and the presence of a right ventricular (RV) pacemaker or defibrillator lead placement should be considered only when a) the lead is not the cause of significant TR; and b) the lead will not interfere with manipulation of the MitraClip system

Abbreviations and acronyms: CDS, clip device system; EROA, effective regurgitant orifice area; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; MR, mitral regurgitation; NYHA, New York Heart Association; RA, right atrium; RV, right ventricular or ventricle; SGD, steerable guide device; SLDA, single leaflet device attachment; TEE, transesophageal echocardiography; TR, tricuspid regurgitation; TVRS, tricuspid valve repair system.

☆ Conflict of interest statement: see page 492.

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in the cardiac chambers nor during leaflet grasping. In some instances, MitraClip can be performed when these two conditions are not met if TR reduction is possible through addressing other segments of the tricuspid valve, but this is generally not advised.

Echocardiography

When evaluating patients with TR for off-label use of MitraClip, it is important to note the anatomical boundaries of the device and the need for adequate leaflet insertion. When opened to 120°, the MitraClip NTR system is 17 mm wide, while the XTR system is 22 mm in width. Similar to the approach for patients with mitral regurgitation (MR), ideal leaflet insertion should be ≥6 mm for NTR, and ≥9 mm for XTR. Thus, the anatomical evaluation of suitability requires an examination of leaflet length, tethering or mobility, and gaps (Fig. 1). Overall, leaflet gaps ideally should be ≤7 mm for both NTR and for XTR, with enough flexibility to enable insertion and apposition with the MitraClip in place. The anatomical assessment is performed by examining the relationships between septal leaflet and the lateral leaflets (i.e., anterior and/or posterior segments). Implantation between the anterior and posterior leaflet segments is rarely beneficial. A common anatomic exclusion for the procedure is the presence of a severely restricted and small septal leaflet (Fig. 2). Certainly, patients with TR who do not have these anatomic features can be treated with MitraClip, though procedure success is lower and the risk of single leaflet device attachment (SLDA) is higher.

Severity of TR is determined conventionally via TTE while TEE is performed for the assessment of anatomical suitability. The RV inflow view with short axis imaging (typically 50°) at the mid-esophageal level is used to examine the location of the TR along the septal coaptation line, akin to a commissural view for MR procedures. Using this view, x-plane imaging is performed to assess the leaflet quality for grasping. It is important in this step to record the position of the cursor that was used for x-plane imaging, in order to inform the viewer as to whether the x-plane image represents anterior or posterior location along the septal leaflet coaptation plane (Fig. 1). Transgastric imaging of the tricuspid valve is then performed with an emphasis on examining the leaflet tips to measure gap width and location of the TR.

Assessments of pulmonary hypertension, size of the right-sided chambers and tricuspid annulus, and the presence of dysfunction are important for patient prognosis. However, leaflet anatomy is the key determinant of anatomic suitability for the procedure.

Transcatheter tricuspid valve repair

The procedure is performed with general anesthesia and TEE guidance (Fig. 3). Following femoral venous access, the steerable guide catheter (SGC) is introduced into the right atrium (RA) over a super stiff wire. The clip delivery system (CDS) is inserted into the guide catheter and typically "mis-keyed" by 90° counter-clockwise. The miss-key technique, which is the most commonly used approach, maximizes height of the device relative to the tricuspid annulus by allowing steering to be controlled by the "A" knob with negative deflection applied to the SGC.

The CDS is straddled in the SGC and placed into the RA with imaging in the bi-caval view to ensure no injury to the surrounding cardiac structures. In some instances, straddling in the superior vena cava may be required. Negative deflection on the SGC is maintained to preserve device height relative to the tricuspid annulus. The SGC is then rotated counter clockwise ~120°. The "A" knob on the CDS is used to steer the sleeve toward the tricuspid valve. Perpendicularity of the clip arms relative to the coaptation plane of the tricuspid valve in the area of TR is established on echocardiography. Anterior/superior vs. posterior/inferior movements occur from adjustment of the "A" knob and from advancement or retraction of the stabilizer. Rotation of the SGC leads to engagement of the lateral (counter-clockwise) or septal leaflets (clockwise). Initial establishment of the clip positioning is best performed with 3-dimensional imaging from the RA (i.e., surgeon's view), in which the septal leaflet is on the left side of the screen (Fig. 4).

The RV inflow view with x-plane imaging can then be used to confirm trajectory of the delivery catheter in orthogonal imaging planes. In some instances, there is excessive trajectory of the delivery catheter from the septal to lateral direction (i.e., "septal hugger"). The presence

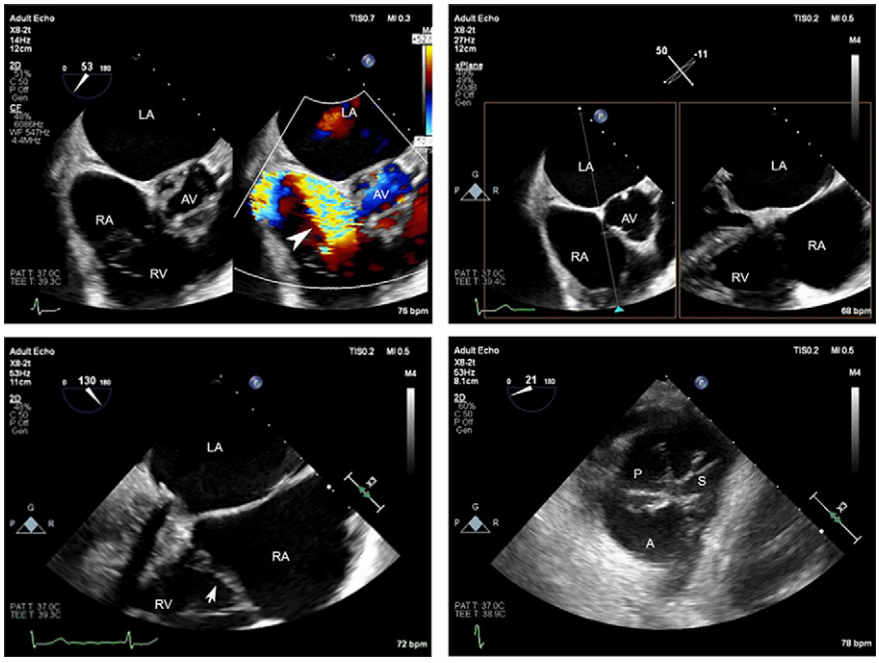

Fig. 1. Essential echocardiographic view for anatomic evaluation for transcatheter repair of tricuspid regurgitation with the MitraClip device. Top left, right ventricular inflow view with color compare imaging showing severe tricuspid regurgitation involving the anterior septal leaflets (arrowhead). Top right, an x-plane cursor is placed over the area of regurgitation, and the corresponding leaflets are identified. Bottom left, the anteroseptal leaflets are examined as the grasping view, with an examination of leaflet length, thickness, and gap width. Bottom right, a transgastric view is obtained to show ability to examine the tissue bridge and assist with leaflet insertion. Abbreviations: A, anterior leaflet; Av, aortic valve; LA, left atrium; P, posterior leaflet; RA, right atrium; RV, right ventricle; S, septal leaflet.

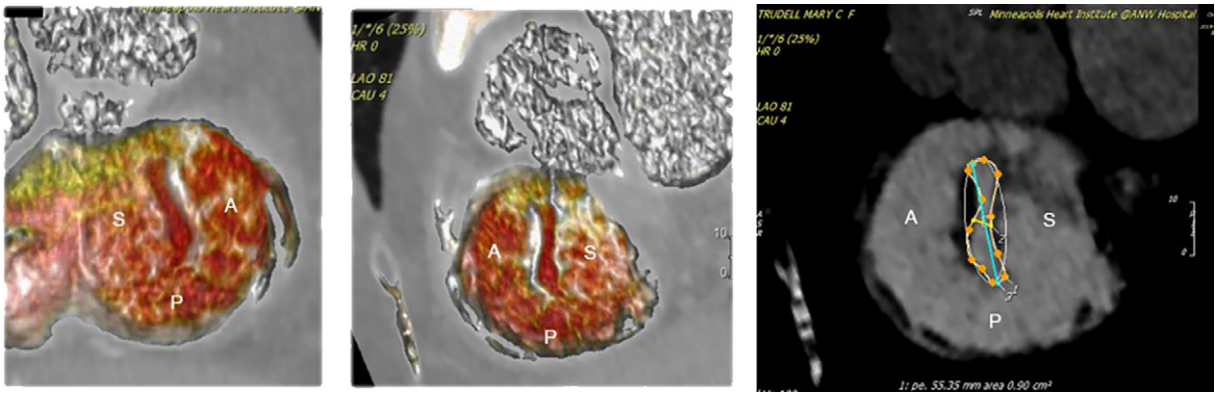

Fig. 2. Imaging of tricuspid leaflet gaps with cardiac computed tomography. Left, three-dimensional imaging from the surgeon's view. Middle, corresponding view from the right ventricle. Right, measurement of the regurgitant orifice area and leaflet gap width. Abbreviations: A, anterior leaflet; P, posterior leaflet; S, septal leaflet.

of a septal hugger can make simultaneous grasping of the septal and lateral leaflets very challenging, especially if the septal leaflet is restricted or small. For correction, one can advance the system to move superior/anterior, apply more "A" knob, followed by clockwise rotation of the SGC. Of note, for all maneuvers, adding "+" to the SGC will move the system inferiorly, but will also result in loss of height, which may already be low due to the sleeve curves of the off-label MitraClip device. Use of the "M" knob also is not beneficial for steering of the system.

The delivery catheter is advanced into the RV underneath the tricuspid valve leaflets. Transgastric imaging with short-axis views of the tricuspid valve is used to confirm clip arm orientation relative to the coaptation plane and, in some instances, can be used to view leaflet insertion prior to placement of the atrial frictional elements (i.e., "grippers"). Using a RV inflow view for grasping, the delivery catheter is retracted with adjustments to the septal and lateral directions performed with rotation of the SGC. Once the two leaflets are inserted into the clip arms, the grippers are lowered, followed by closure of the arms to 60°. Leaflet insertion is assessed on echocardiography in multiple planes, especially the transgastric imaging views. TTE and intracardiac echocardiography may be used to help confirm insertion. The clip arms are then fully closed, and assessment for reduction in TR and evidence of stenosis is performed. The clip may then be repositioned or removed, or decoupled from the delivery catheter for permanent placement. The system is removed from the patient followed by vascular closure with either sutures (i.e., "preclose" technique), a "figure-of-8" stitch, or manual compression.

Clinical outcomes

Thus far, transcatheter repair of TR with the MitraClip system has been performed predominantly via off-label use of the device, which was specifically designed for treatment of MR. This use commonly has been part of procedures with concomitant therapy of MR (i.e., "drive-by" TR therapy).

The first experience of off-label use with the MitraClip system for the treatment of TR was reported in 2016.[5,6] The patient was a 78-year old man who was admitted for recurrent decompensated right HF with severe NYHA Class III symptoms despite currently optimal HF therapy. Echocardiography showed moderate to severe left ventricular (LV) dysfunction, and severe secondary TR (an effective regurgitant orifice area [EROA] of 1.0 cm^2) due to annular dilatation and loss of leaflet coaptation. Considering the high risk of surgical tricuspid valve repair (EuroSCORE 45%), transfemoral percutaneous edge-to-edge repair for TR was attempted using the MitraClip system. Two clips were

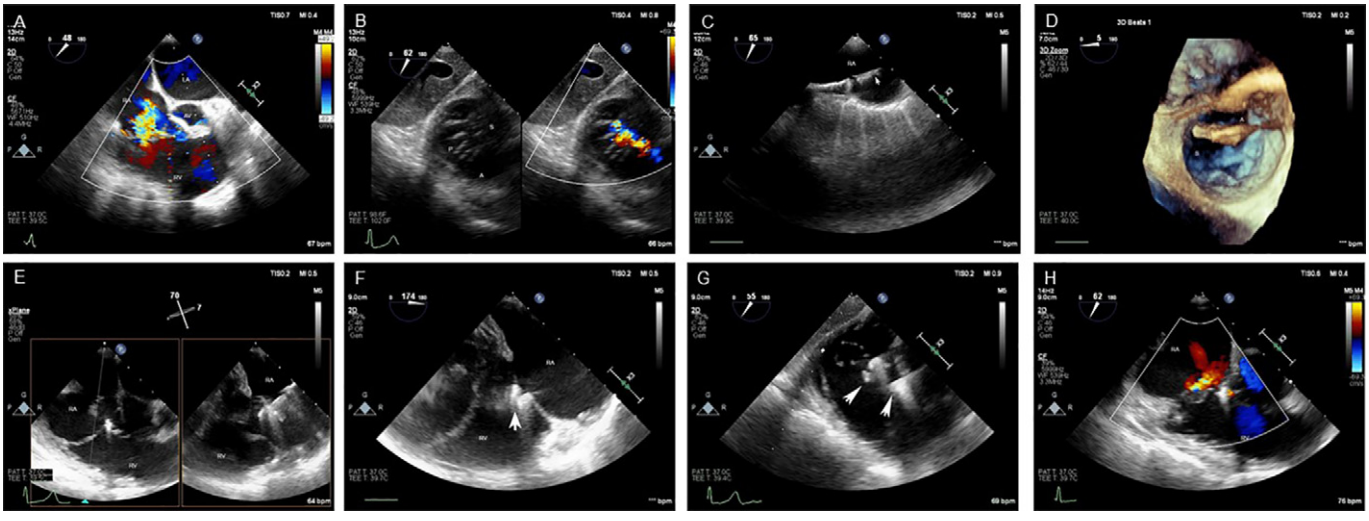

Fig. 3. Transcatheter repair of tricuspid regurgitation with the MitraClip device. A, Right ventricular inflow view shows severe tricuspid regurgitation (TR). B, Transgastric view with color compare imaging shows the TR. C, Following vascular access and placement of the steerable guide catheter, the clip delivery system (arrowhead) is inserted and straddled in the right atrium. D, Using 3-dimensional imaging, the clip is opened and aligned across the coaptation plane of the tricuspid valve. E, x-plane imaging shows the clip advanced from the right atrium to the right ventricle. F, Leaflet insertion is confirmed in multiple views of the clip (arrowhead). G, Transgastric view shows tissue bridges created by placement of two clips (arrowheads). H, Final right ventricular inflow view with color shows mild residual TR. Abbreviations: A, anterior leaflet; Av, aortic valve; LA, left atrium; P, posterior leaflet; RA, right atrium; RV, right ventricle; S, septal leaflet.

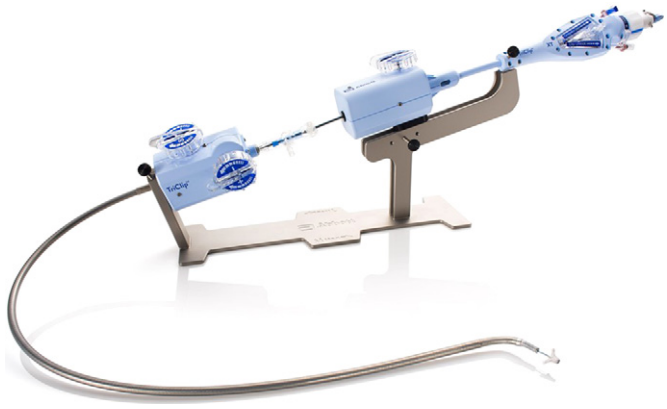

Fig. 4. The transcatheter tricuspid valve repair system (TVRS). Note that, contrary to the MitraClip system, the TVRS is composed of a steerable guide catheter with two knobs for steering, while the steerable sleeve has one knob for flexion/extension. The distal curve of the sleeve also has a shorter radius. These features enable movements with low heights relative to the tricuspid valve.

successfully placed in the anterior-septal and posterior-septal commissures of the tricuspid valve, leading to a significant reduction of EROA to 0.49 cm^2 and improvement of functional status at 40 days follow up post-intervention.[5]

In 2017, Nickenig et al reported a multicenter study of 64 patients.[8] Mean age was 77 years, and morbidities were common (EuroSCORE, 27.8 ± 16.7). Functional etiology was the predominant cause (88%), and 22 patients (34%) had concomitant MR therapy. Most patients had LV dysfunction (mean ejection fraction, 47 ± 14%) and impaired RV function (mean TAPSE, 16.9 ± 5.8 mm). Device implantation was successful in 97%. Clip placement was predominantly on the anterior and septal leaflets, whose location was treated in 78% of patients. Twenty-seven patients (42%) had more than one clip placed.

Overall, TR reduction by ≥1 grade occurred in 91%. There also were reductions in quantitative measures of TR severity, with improvements in EROA (0.9 ± 0.3 cm^2 vs. 0.4 ± 0.2; $p < 0.001$), vena contracta width (1.1 ± 0.5 cm vs. 0.6 ± 0.3 cm; $p = 0.001$), and regurgitant volume (57.2 ± 12.8 ml/beat vs. 30.8 ± 6.9 ml/beat; $p < 0.001$). Importantly, there were no intra-procedural deaths, strokes, device migrations, or conversions to cardiac surgery, though in-hospital mortality did occur in 3 patients (5%), including one patient who died of cardiogenic shock. In follow-up, clinical improvement in overall functional class was observed, with 63% being in NYHA III (none in class IV) vs. 93% in class III or IV at baseline. Improvements in echocardiographic parameters of TR severity were similar in analyses that excluded patients who had concomitant MR therapy.

The TriValve Registry reported one-year outcomes of edge-to-edge repair for severe TR.[10] In this study, 249 patients were treated at 14 centers in Europe and North America between June 2015 and June 2018. TR was reduced to grade 2 or less in 77% of patients, with concomitant therapy of MR performed in 52%. At one-year follow-up, wither was durability of TR reduction (72% with grade 2 or less) and favorable symptoms (class I or II in 69%). All-cause mortality at one year was 20%, and the rate of mortality and HF hospitalization was 25%. Worse outcomes were observed in those with large leaflet gaps, absence of TR in the central or anteroseptal area, kidney dysfunction, and atrial fibrillation.

Future therapy

The system has been redesigned for dedicated use in patients with TR as the Tricuspid Valve Repair System (TVRS, Abbott Structural, Menlo Park, CA). In this design iteration, the primary curve of the SGC has been displaced distally to maximize height to the tricuspid annulus. The sleeve curves have been rotated to match the direction of the SGC, with a flex knob used for steering toward the tricuspid valve (i.e., akin to the "a" knob function).

Results on the first 30 patients with 30-day follow-up who were treated as part of a CE Mark and U.S. Early Feasibility Study were presented at London Valves meeting in 2018. Mean age was 79 ± 8 years, with 57% women. There was a high prevalence of severe HF (NYHA III or IV, 76%) and atrial fibrillation (97%). Acute device success was 100%, with an average time of 71 ± 40 min. The mean number of clips per patient was 1.9, with the anterior-septal location utilized in 76%. As measured in an independent core echocardiographic laboratory, significant reductions in both vena contracta width (2.03 ± 0.64 vs. 1.30 ± 0.58; $p < 0.0001$) and PISA radius (1.05 ± 0.20 vs. 0.84 ± 0.24; $p < 0.0001$), as well as an increase in forward stroke volume (62.4 ± 17.3 vs. 70.4 ± 13.8; $p = 0.02$) occurred. SLDA occurred in two patients (~7%), with no mortality, embolization, or stroke. Notably, SLDA rates for MitraClip when used for the treatment of MR historically were 8–10%, and these rates have now decreased to 1–2% with improvements in patient selection, operator experience, and imaging guidance. Overall, there were significant improvements in functional class (NYHA III/IV, 20.7% vs. 75.9%; $p < 0.001$) and quality of life measured by Kansas City Cardiomyopathy Questionnaire (KCCQ score; mean change, 18.8; $p < 0.001$).

A pivotal clinical trial evaluating the effectiveness and safety of the TVRS system has been launched. The system in the pivotal trial has a new feature in which the A/P knob has been moved from the CDS to the SGC, in order to better address septal hugger scenarios. In addition to improvements made specifically for the treatment of TR, a new system will also employ both NTR and XTR versions. This study, the Clinical Trial to Evaluate Cardiovascular Outcomes in patients treated with the TVRS (TRILUMINATE), will enroll 450 patients at up to 80 sites in the U.S. and Canada. Key enrollment criteria are 1) severe or worse TR with ambulatory symptoms (NYHA II, III, or IVa); 2) intermediate or greater surgical risk; 3) stable, optimal medical therapy for HF; 4) anatomic suitability for treatment with the TVRS system. Key exclusion criteria are the presence of 1) severe pulmonary hypertension (i.e., pulmonary artery systolic pressure >70 mm Hg and pulmonary vascular resistance >4 Wood units); 2) severe mitral regurgitation or need for other valvular correction; 3) LV ejection fraction ≤20%; 4) pacemaker or defibrillator leads that would preclude clip placement; 5) tricuspid stenosis.

In the TRILUMINATE pivotal study, which was officially launched in September 2019, patients will enter a randomized arm and a non-randomized arm. In the former arm, patients are randomized 1:1 to either TVRS or medical therapy. Patients placed in the non-randomized arm are those in whom there is clinical belief that reduction in TR severity to moderate or less is unlikely. The primary endpoint of the randomized arm is a composite of mortality and tricuspid valve surgery, HF hospitalizations, and quality of life improvement assessed using the KCCQ, evaluated at 12 months in a hierarchical fashion. Secondary endpoints to be assessed after the first 350 randomized subjects that complete 12 month follow-up are 1) TR reduction to moderate or less at 30-day post procedure (superiority of device vs. control), 2) freedom from major adverse events at 30 days, 3) change in KCCQ at 12 months (superiority of device vs. control), and 4) change in 6 min walk distance at 12 months (superiority of device vs. control). At 24-month follow-up, secondary endpoints are 1) recurrent HF hospitalization (superiority of device vs. control) and 2) combination of all-cause mortality and need for tricuspid valve surgery or intervention (superiority of device vs. control). For the single arm, the primary endpoint is survival and quality of life improvement at 12 months compared to baseline.

Conclusions

Patients with symptomatic TR commonly are high-risk individuals, with recent population studies describing a mortality that approaches

9% per year. Approximately 20% of patients who have MR in need of correction with MitraClip will also have significant TR.[11,12] Thus, the ability to treat both lesions with the same femoral access with similar methods of leaflet apposition may be beneficial. Going forward, it could be expected that the impact on functional capacity might improve with expanding clinical experience, greater understanding of patient selection, refinement of procedure techniques, and use of the TVRS which has specific modifications for use in patients with TR. These dedicated methods are now being evaluated in pivotal clinical trials that include control arms, and may expand transcatheter therapy for TR, particularly for those who currently go untreated and have a poor prognosis.

Statement of conflict of interest

- Paul Sorajja, MD - consultant and speaker's bureau for Abbott Vascular, Medtronic, Boston Scientific, Edwards Lifesciences, Admedus, Gore; research support, Abbott Vascular, Medtronic, Boston Scientific, Edwards Lifesciences
- Richard Bae, MD - speaker's bureau for Abbott Vascular
- Yu Du, MD - none
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