Current Diagnosis and Therapeutic Approach of Functional Mitral Regurgitation

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ABSTRACT

Functional mitral regurgitation is characterized by normal structures of the mitral valve and chordae tendinea, but the regurgitation occurs due to geometric changes in the left atrium and left ventricle. This condition can contribute to heart failure progression and lead to a poor prognosis. Functional mitral regurgitation is found in approximately one-third of patients with heart failure with a decreased ejection fraction. Echocardiography is the primary work-up for assessing the anatomy and function of the left ventricle, mitral valve, and severity of functional mitral regurgitation. Additionally, for the latter, an integrated qualitative and quantitative assessment is essential to determine the optimal therapeutic strategy. According to the current guidelines, medical therapy remains the main treatment for functional mitral regurgitation. Yet, transcatheter intervention is a safe and effective treatment option in selected patients. While the effect of surgery on improving mortality in patients with functional mitral regurgitation is not established yet, recent guidelines recommend considering surgery for patients who have undergone coronary artery bypass surgery or other cardiac procedures.

Keywords: *functional mitral regurgitation, diagnosis, management.*

INTRODUCTION

According to the 2017 American Society of Echocardiography (ASE) guidelines, mitral regurgitation is classified into two categories according to its etiology, namely organic (primary) and functional (secondary) mitral regurgitation. The latter is characterized by the regurgitation resulting from the imbalance between leaflet closure and tethering, caused by geometric changes in the left ventricle and left atrium, despite having normal structures of the mitral valve and chordae tendinea. Functional mitral regurgitation is divided into two subtypes: primarily due to left ventricle remodeling and primarily due to left atrial dilatation (i.e., atrial functional mitral regurgitation).[1]

Moderate to severe mitral regurgitation affects approximately one-third of patients with heart failure and contributes to clinical deterioration, symptom progression, and poor outcomes. A community-based study found that of all mitral regurgitation, one-third was of organic cause, one-third was of functional cause primarily due to left ventricular remodeling, and the rest was of functional cause primarily due to left atrial dilatation.[2] Organic mitral regurgitation is seen commonly in young patients, whereas functional mitral regurgitation with predominantly atrial remodeling occurs in older patients. Functional mitral regurgitation with predominantly left ventricular remodeling can be found in patients of all ages.[3]

PATHOPHYSIOLOGY

In functional mitral regurgitation, a complex interplay between annulus dilatation, papillary muscle displacement with increased systolic leaflet tethering, and left ventricular remodeling leads to incomplete mitral valve closure. Global left ventricular enlargement or scarring can cause the papillary muscles to move posteriorly and apically, resulting in mitral regurgitation. Additionally, as a saddle-shaped annulus is important for maintaining normal valvular forces, loss of the shape/flat annulus can result in increased leaflet stress with chronic mitral regurgitation. Subsequently, this condition can increase mitral leaflet area and left ventricular remodeling, which may lead to severe mitral regurgitation.[2,3]

Primary left ventricular myocardial disorders due to ischemic heart disease affect papillary muscle displacement, leaflet tethering, annulus remodeling, and left ventricle dilatation. Adaptive leaflet growth is often inadequate, sometimes accompanied by maladaptive leaflet thickening and fibrosis, leading to impaired leaflet coaptation. Dynamic factors related to left ventricular preload (such as hydration status and medications) and afterload (such as blood pressure, exercise, and drugs) affect the severity of secondary mitral regurgitation. Progressive left ventricular dilatation increases secondary mitral regurgitation, leading to higher regurgitation fraction and decreased forwarding flow, which further dilates the left ventricle.[2,3]

DIAGNOSTIC APPROACH

Echocardiography remains the main diagnostic tool for functional mitral regurgitation. It evaluates systolic and diastolic function, the morphology of the mitral annulus and mitral valve, left atrial size, and right ventricle function. Moreover, integrated qualitative and quantitative assessments are applied to evaluate the severity of mitral regurgitation. The algorithm of mitral regurgitation grading based on quantitative and qualitative assessments according to the ASE guidelines is shown in **Figure 1**.[1,4]

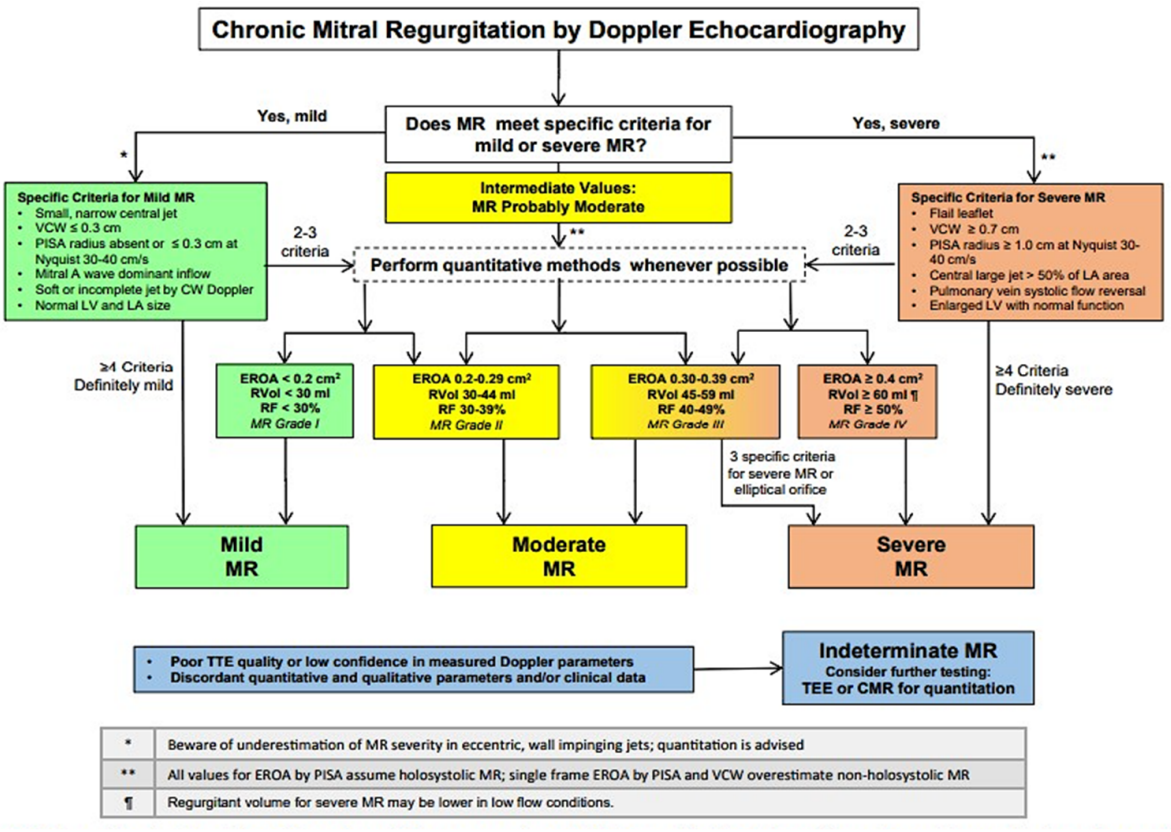

Figure 1. Algorithm of mitral regurgitation severity grading using integration of multiple parameters[1]

Thoroughly identifying the mechanism of mitral regurgitation using 3-dimensional (3D) transesophageal echocardiography (TEE) and transthoracic echocardiography (TTE) is important for determining the optimal therapeutic strategy. The severity of secondary mitral regurgitation is assessed using an integrated multiparameter approach. Two-dimension (2D) TTE is limited in assessing functional mitral regurgitation, and 3D imaging is preferable whenever possible. Notably, functional mitral regurgitation is a dynamic phenomenon, and hence, its severity can vary significantly depending on loading conditions. Assessments should be performed under stable clinical conditions (e.g., controlled blood pressure, optimal medical therapy), and interpreted cautiously in patients with decompensated conditions (e.g., fluid overload, inotropic support).[4]

Quantitative assessment is highly operator-dependent and has limited reproducibility. Particularly, the assessment is inaccurate when an elliptical regurgitant orifice (which is often found in functional mitral regurgitation) or multiple jets are present. Thus, quantitative assessment is often insufficient for establishing accurate diagnoses in daily clinical practice. To reduce the risk of measurement error, it is important to assess various parameters, such as vena contracta, pulmonary vein systolic reversal, proximal isovelocity surface area (PISA) radius, effective regurgitation orifice area (EROA), and regurgitation volume which includes 3D assessment (vena contracta area) if there is still uncertainty about the diagnosis.[5,6]

In functional mitral regurgitation, the mitral regurgitation is nonholosystolic. This condition may overestimate the EROA calculation. However, based on 3D echocardiography, the vena contracta area in functional mitral regurgitation is more elliptical with non-hemispheric PISA, unlike primary mitral regurgitation, which has circular and hemispherical PISA. This can lead to an underestimation of EROA. Consequently, the calculation of EROA on functional mitral regurgitation can be underestimated or overestimated.[4,5]

On the other hand, 3D vena contracta may overestimate EROA due to the blooming color Doppler effect, the inclusion of low-velocity signal in tracing, and non-planar/flat orifices. Magnetic resonance imaging (MRI), 3D echocardiography, and exercise echocardiography can be useful to identify patients with severe mitral regurgitation when 2D echocardiography is inconclusive. MRI is considered the gold standard for quantifying ventricular size, function, ventricular remodeling, and myocardial characteristics. MRI can also estimate regurgitant volume and fraction by calculating the difference between left ventricular stroke volume and flow forward volume in the aorta. The 3D echocardiography can directly measure the vena contracta without being affected by the shape of the orifice or the number of jets. [4] Exercise echocardiography can assess the hemodynamic response and the severity of regurgitation after exercise.[4,5]

PROGNOSIS

Vast literature has shown mitral regurgitation as an independent predictor of clinical heart failure and major adverse cardiac events after acute myocardial infarction or in patients with left ventricular dysfunction. A study also demonstrated significant functional mitral regurgitation in 50% of patients after myocardial infarction. Moreover, compared to all other consequences of myocardial infarction combined, functional mitral regurgitation is associated with higher mortality and complications. Further, in patients with chronic heart failure, those with functional mitral regurgitation have more hospitalization and poorer long-term prognosis than those without significant functional mitral regurgitation. [3] Additionally, while the incidence of heart failure is high in all subtypes of mitral regurgitation, the incidence is generally higher in functional mitral regurgitation, especially the cases with primarily left ventricular remodeling. The mortality rate is increasing with age among patients with functional mitral regurgitation.[3]

TREATMENTS

Optimizing guidelines-directed medical therapy (GDMT) is an important step in managing

moderate or severe symptomatic functional mitral regurgitation. Heart failure medications such as angiotensin receptor-neprilysin inhibitor (ARNI), angiotensin-converting enzymes inhibitor (ACEI), angiotensin receptor blocker (ARB), beta blocker, sodium-glucose cotransporter-2 (SGLT2) inhibitors (SGLT2), and mineralocorticoid receptor antagonist (MRA) are mandatory treatment in patients with heart failure unless contraindicated or not tolerated. These medications need to be titrated to the recommended or maximum dose tolerated. The medications reduce left ventricular dysfunction and remodeling. In the Pharmacological Reduction of Functional Ischemic Mitral Regurgitation (PRIME) study in patients with heart failure and functional mitral regurgitation, sacubitril valsartan significantly reduced EROA and regurgitant volume at one year of follow-up with standard medical therapy.[3,5]

Cardiac resynchronization therapy (CRT) can improve global left ventricular function, reduce left ventricular remodeling, and restore papillary muscle synchronization in patients with a prolonged QRS duration. Therefore, CRT can improve functional mitral regurgitation by increasing mitral valve closure forces and reducing leaflet tethering both during rest and exercise. Large Randomized Controlled Trials (RCTs) have shown short-term and long-term improvement of mitral regurgitation (assumed to be secondary in most patients) as a result of reverse remodeling after CRT implantation, despite the mild improvement (i.e., 20-35% reduction of regurgitation identified by different quantification methods). After coronary artery bypass graft (CABG) alone, mitral regurgitation improves in about 50% of patients. Data on the effect of percutaneous coronary intervention (PCI) on functional mitral regurgitation are limited.[3]

Because functional mitral regurgitation is primarily a problem with the left ventricle rather than the valve itself, current therapeutic strategies focus on addressing left ventricular abnormalities. However, functional mitral regurgitation may play a role in left ventricular remodeling by increasing volume overload. In addition to GDMT, mechanical correction has been suggested to improve symptoms and prognosis.[3]

Transcatheter Intervention

Two recent RCTs, the Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR) trial and the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial, have evaluated the safety and efficacy of MitraClip implantation in patients with symptomatic heart failure and moderate-severe functional mitral regurgitation who were on optimal medical therapy. Nevertheless, the findings from the studies were contradictory. In the MITRA-FR trial, MitraClip implantation, in comparison to GDMT alone, had no impact on the primary outcome of all-cause mortality or heart failure hospitalization at 12 months follow-up. In the COAPT trial, MitraClip implantation

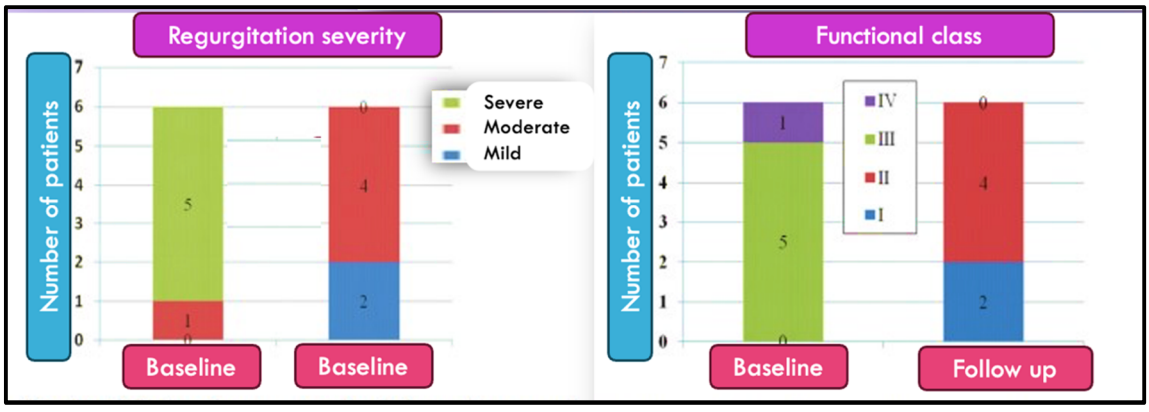

Figure 2. Comparison of regurgitation severity and functional class before and after MitraClip implantation in Indonesia[7]

significantly improved the primary outcome of hospitalization for heart failure, mortality, symptoms, quality of life, and the need for implantation of a left ventricular assist device (LVAD) or heart transplantation.[5,6] Despite the conflicting findings, both the MITRA-FR trial and COAPT trial indicated that transcatheter edge-to-edge repair (TEER) using the MitraClip is a safe procedure that may effectively reduce functional mitral regurgitation. The COAPT trial demonstrated the efficacy of transcatheter edge-to-edge repair using a clip device in patients with symptomatic functional mitral regurgitation who did not respond to medical therapy and met the study inclusion criteria. More studies are needed to determine which patients will benefit most from this procedure.[5,6]

In Indonesia, a study at Harapan Kita Heart Hospital of six patients undergoing MitraClip implantation showed good clinical outcomes

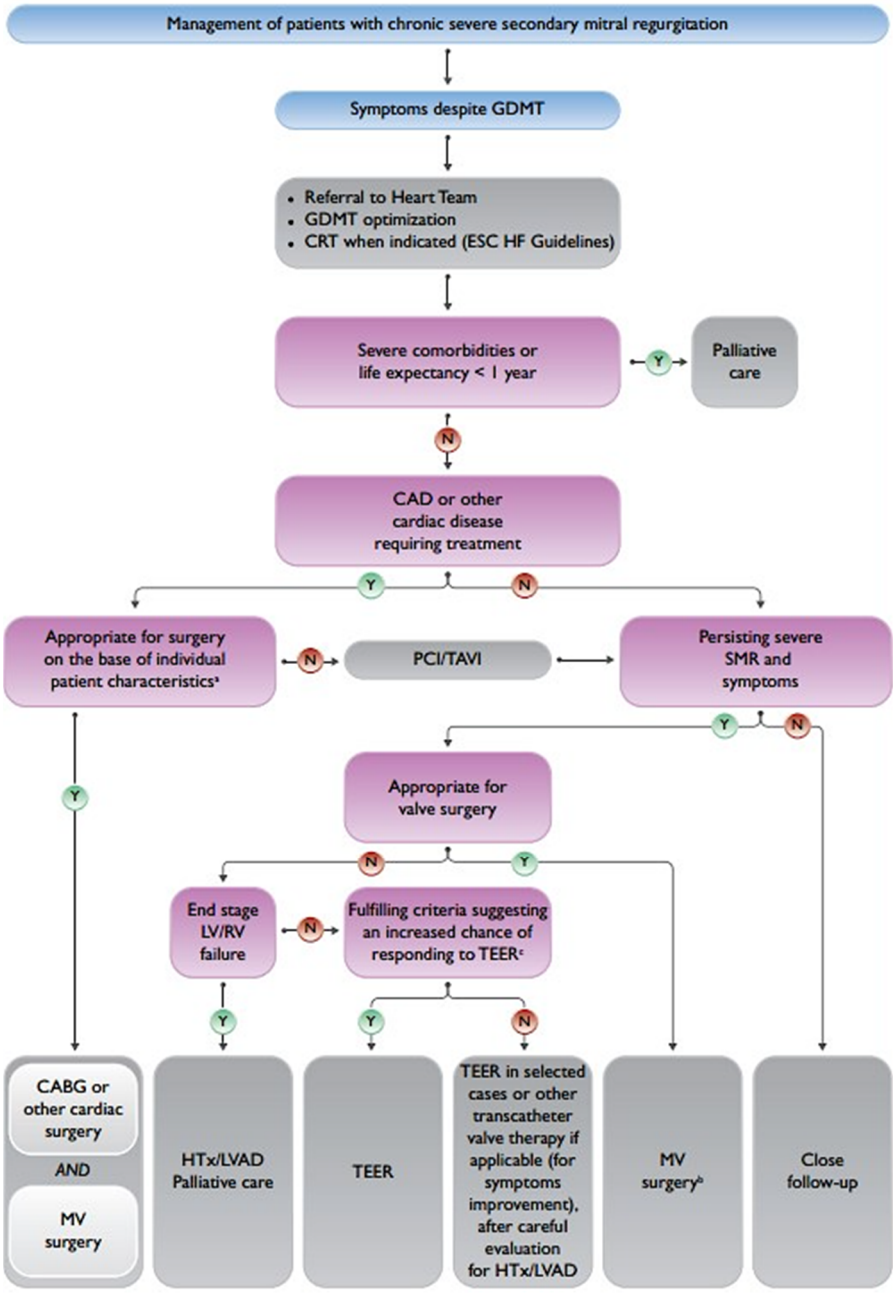

Figure 3. Management of patients with chronic severe secondary mitral regurgitation based on the 2021 ESC guidelines[5]

with improvements in mitral regurgitation and functional status. No complications were observed. The study suggests that transcatheter edge-to-edge repair is a safe and effective procedure for the management of mitral regurgitation in Indonesia.[7]

Surgical Intervention

Evidence supporting surgery for functional mitral regurgitation is yet limited. There is no evidence that surgery for secondary mitral regurgitation improves survival yet, whereas a direct comparison between surgery and optimal medication has not been performed. Based on the 2021 European Society of Cardiology (ESC) guidelines, mitral valve surgery is recommended in patients with severe functional mitral regurgitation undergoing CABG or other cardiac surgery (class I).[5,6]

Based on the 2020 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, mitral valve surgery is recommended with the level of evidence 2A in patients with severe functional mitral regurgitation (stages C and D) who also undergo CABG. In addition, valve surgery can be considered with the level of evidence 2B in severe functional mitral regurgitation with atrial annulus dilatation, preserved EF ≥ 50% with

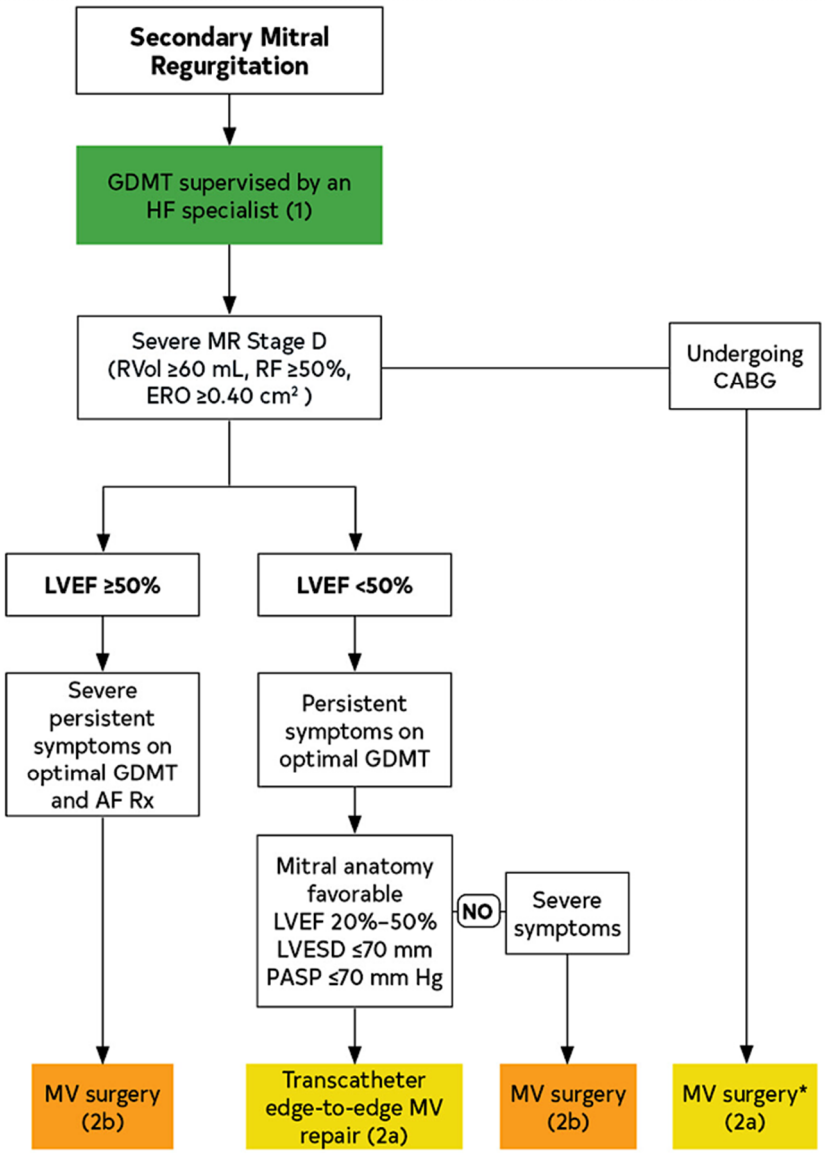

Figure 4. Management of patients with chronic severe secondary mitral regurgitation based on the 2020 ACC/AHA guidelines[6]

persistent severe symptoms (NYHA III or IV) despite optimal GDMT, and severe functional mitral regurgitation with reduced EF <50%, persistent severe symptoms (NYHA III or IV) despite optimal GDMT.[5,6]

Repairing with ring annuloplasty has a lower risk of morbidity and mortality. However, it has an increased risk of mitral stenosis and a high recurrence rate of mitral regurgitation. Mitral valve replacement with chordal sparing offers a longer duration of correction and better ventricular remodeling. Nevertheless, it has an increased risk of thromboembolism, endocarditis, and valve structural degeneration.[8] According to the study, no difference in left ventricular reverse remodeling and survival between repair and valve replacement was observed at a 2-year follow-up in patients with severe ischemic mitral regurgitation. Nonetheless, repair is associated with a higher recurrence rate of moderate or severe mitral regurgitation, leading to a higher incidence of heart failure and rehospitalization. The durability of repair depends on the regression and progression of left ventricular dilatation. If the heart continues to dilate, the repair is less durable.[8]

CONCLUSION

Optimal medications and device-based treatment are important in the management of functional mitral regurgitation. Chronic severe functional mitral regurgitation has a poor prognosis. Its management is complex, and for each patient, a multidisciplinary heart team is required to determine the optimal intervention, whether transcatheter or surgery.

CONFLICT OF INTEREST

There are no potential conflicts of interest.

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