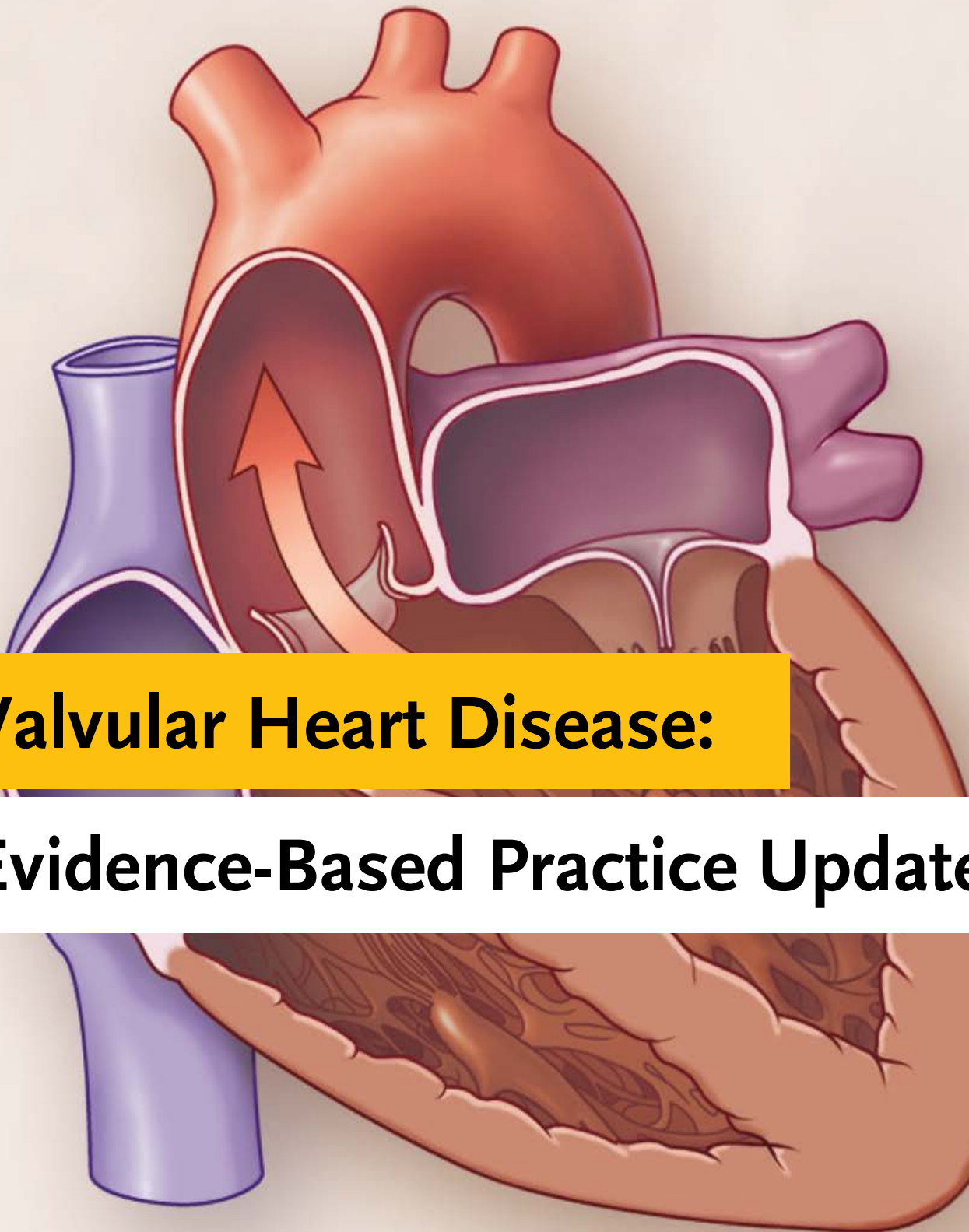




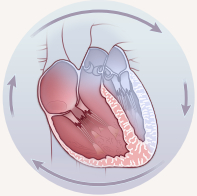
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Valvular Heart Disease:

Evidence-Based Practice Update

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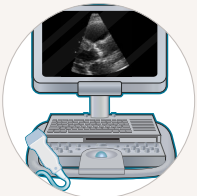
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REVIEW ARTICLE

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Tricuspid Regurgitation

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THE TRICUSPID VALVE, OFTEN REFERRED TO AS THE FORGOTTEN VALVE, has generated intense interest because of converging factors that make diagnosis and management of tricuspid regurgitation uniquely challenging. Historically, the tricuspid valve was considered to be a passive structure, on the systemic venous side of the heart, without clinically significant function. Surgeons believed that mitral-valve disease was the true culprit and that tricuspid regurgitation was a secondary finding that would resolve after surgical treatment of the primary mitral disease process. Because tricuspid regurgitation is most frequently diagnosed in patients with coexisting conditions, many clinicians have viewed it as an innocent bystander to the more consequential diseases of the left heart and pulmonary vasculature. In the absence of left heart disease, the clinical signs and symptoms of severe tricuspid regurgitation, such as edema, fatigue, and exercise intolerance, are often mistaken for normal signs and symptoms of aging, leading to delays in diagnosis and treatment. Natural history studies highlight the need for early diagnosis; survival is progressively shorter with the increasing severity of tricuspid regurgitation, even after adjustment for coexisting conditions.¹⁻⁴ Gaps in our understanding of the tricuspid-valve disease process, diagnostic challenges, and uncertainty about the appropriate timing of interventions have contributed to the high mortality among medically treated patients,^{4,5} as well as nonmedically treated patients,^{6,7} with severe tricuspid regurgitation.

ANATOMY

Insight into the anatomical relationship between the tricuspid-valve apparatus and the right atrium, right ventricle, and pulmonary vasculature provides the basis for our current understanding of the pathophysiology of tricuspid regurgitation. The tricuspid valve is the largest valve in the heart and typically has three leaflets of unequal size. However, the number of leaflets may vary in healthy persons, with the most common variant consisting of two posterior leaflets.^{8,9} Thinner than mitral-valve leaflets, the tricuspid-valve leaflets are supported by chordae attached to a major anterior papillary muscle along the lateral wall of the midright ventricle, as well as one or more smaller posterior papillary muscles.¹⁰ The anterior papillary muscle supplies chordae to the anterior and posterior leaflets along their line of coaptation, whereas the posterior papillary muscles supply chordae to the posterior leaflet (or leaflets) and the posterior segment of the septal leaflet. The chordal attachments arising either from small septal papillary muscles or directly from the septum are unique to the tricuspid valve and support the anterior segment of the septal leaflet and the adjacent segments of the anterior or posterior leaflet. Given the complex chordal arcades and their attachment sites, the tricuspid valve is sensitive to changes in the position and function of the free wall of the right ventricle, as well as the interventricular septum.

The tricuspid annulus has very little fibrous tissue or collagen. Adipose tissue fills the inter-ventricular space between the right atrium and ventricle on the anterosuperior and inferior sides but not on the septal side.¹¹ There are sex-related differences in the histologic features of the annulus. Males have more myocardial cells and elastic fibers than do females,¹² and females have a larger annulus, even after correction for heart or body weight.^{12,13} The normal annulus is saddle-shaped and dynamic, larger in early diastole and during atrial systole,¹³ which allows for large flow volumes under low pressure. Given the large size of the tricuspid valve, benchtop modeling suggests that only 40% annular dilatation may result in clinically significant tricuspid regurgitation, whereas this was seen at 75% annular dilatation in mitral-valve studies.¹⁴

The right coronary artery and the atrioventricular node are adjacent to the annulus and are important anatomical considerations for surgical or transcatheter interventions. The right coronary artery lies within the atrioventricular groove along nearly the entire anterior and posterior annulus, with the separation narrowing to less than 3 mm inferiorly, placing the vessel at risk for injury with devices that anchor in the annulus.¹⁵ The atrioventricular node and the bundle of His cross the septal leaflet attachment 3 to 5 mm from the antero-septal commissure, and injury to the node may result in heart block.

CLINICAL PRESENTATION

Patients with severe tricuspid regurgitation present with signs and symptoms of chronic right heart failure, including systemic fluid retention, leading to elevated jugular venous pressure, peripheral edema, and ascites; reduced intestinal absorption and anasarca; decreased cardiac reserve, resulting in exercise intolerance, dyspnea, and poor functional capacity; and decreased cardiac output, with progressive end-organ damage caused by a combination of end-organ venous congestion and underperfusion.¹⁶ End-stage disease is associated with cachexia resulting from poor absorption of nutrients, as well as a systemic proinflammatory state. The signs and symptoms of reduced cardiac output may also be mistaken for left heart failure, further delaying

a timely diagnosis of tricuspid regurgitation. Although many signs and symptoms of severe tricuspid regurgitation may initially be responsive to diuretics, reduced cardiac output, as well as other neurohormonal changes, may result in liver disease (the cardiohepatic syndrome) and kidney disease (the cardiorenal syndrome).^{16,17} The cardiohepatic syndrome not only increases the risk of bleeding in patients with tricuspid regurgitation but is also a strong independent predictor of death or hospitalization for heart failure within 1 year after transcatheter tricuspid-valve therapy.¹⁸

Atrial arrhythmias — in particular, atrial fibrillation — are common in patients with tricuspid regurgitation and occur in both incident and progressive valvular disease.¹⁹ Atrial fibrillation has been associated with left and right atrial dilatation, annular dilatation, and atrioventricular valvular regurgitation,²⁰ and rhythm control is associated with a reduction in tricuspid regurgitation.^{21,22} In patients with normal left ventricular function, atrial fibrillation may result in greater tricuspid annular dilatation than mitral annular dilatation.²³ Patients with heart failure and a preserved ejection fraction, with or without atrial fibrillation, also have a high prevalence of prognostically important tricuspid regurgitation resulting from dilatation of the annulus and right atrium.^{24,25}

EPIDEMIOLOGY

As with other valvular heart diseases, the prevalence of tricuspid regurgitation increases with age.²⁶⁻³⁰ Although clinically significant valvular disease is diagnosed more frequently in men than in women,²⁸ the overall prevalence of clinically significant tricuspid regurgitation may be up to four times as high among women.²⁶ Female sex is an independent predictor of the severity and progression of tricuspid regurgitation.^{4,19,31} Although the basis for these differences is unknown, the higher female prevalence of heart failure with a preserved ejection fraction^{32,33} and atrial fibrillation³⁴ may play a part. Besides older age, female sex, and atrial fibrillation, other clinical predictors of severe and progressive tricuspid regurgitation include elevated pulmonary-artery systolic pressure and increased left atrial size, which suggests that both pre- and postcap-

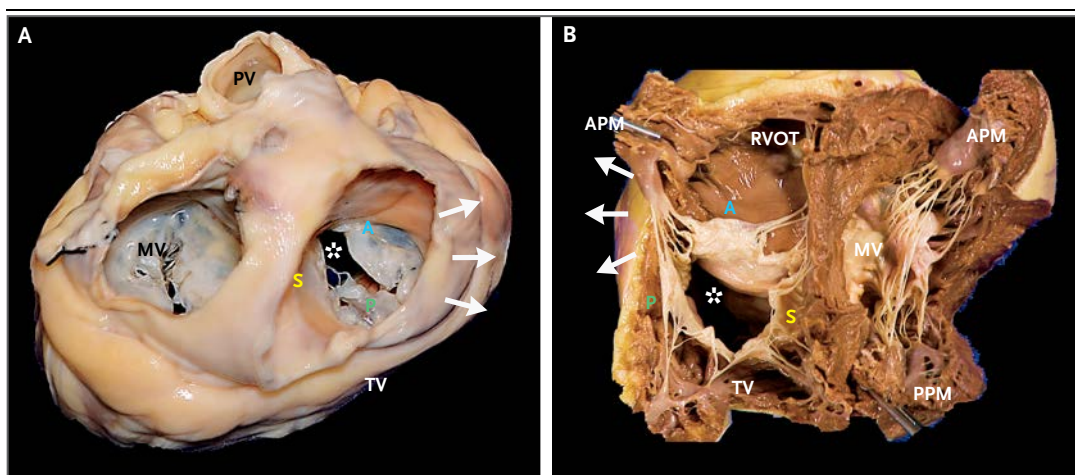


Figure 1. Anatomy of the Tricuspid Valve (TV).

As seen from the atrial aspect (Panel A), the valve has a D-shaped annulus, with the septal leaflet (S) adjacent to the interatrial and interventricular septum, the anterior leaflet (A) posterior to the aorta and pulmonic valve (PV), and the posterior leaflet (P) closest to the diaphragm. In this pathological specimen, the lateral annulus is dilated (arrows), resulting in a large leaflet coaptation gap (asterisk). The subvalvular complex is seen from the ventricular aspect (Panel B), with direct chordae from the septum to the septal and anterior leaflets and a large anterior papillary muscle (APM) supplying chordae to both the anterior and posterior leaflets. Displacement of the APM, caused by dilatation of the mid-to-apical right ventricular free wall (arrows) or a change in the position of the septum, will result in tethering of TV leaflets and a coaptation gap. MV denotes mitral valve, PPM posterior papillary muscle, and RVOT right ventricular outflow tract. Photographs courtesy of Dmitry Levin.

illary pulmonary hypertension contribute to this process.¹⁹

In two studies of patients with tricuspid regurgitation, medical management of severe disease was associated with 1-year mortality rates of 42% and 36%, respectively.^{4,5} As compared with persons who had mild or no tricuspid regurgitation, those with moderate or severe regurgitation had a long-term risk of death from any cause that was increased by a factor of 2.0 to 3.2, after adjustment for age and sex.⁴ Even mild tricuspid regurgitation was associated with a nearly 30% increase in all-cause, long-term mortality.⁴ A recent study of outcomes for aortic, mitral, and tricuspid-valve disease showed that all-cause mortality was higher for tricuspid regurgitation (hazard ratio, 2.74; 95% confidence interval [CI], 2.24 to 3.37) than for aortic-valve disease (hazard ratio, 1.62; 95% CI, 1.44 to 1.82) or mitral-valve disease (hazard ratio, 1.25; 95% CI, 1.09 to 1.44).²⁹

Morphologic predictors of progressive tricuspid regurgitation depend on the primary cardiovascular disease process. For patients with pulmonary arterial hypertension, predictors include right ventricular enlargement, increased right ven-

tricular sphericity, tricuspid annular dilatation, and increased tricuspid leaflet tenting area.³⁵ For patients with atrial fibrillation, the presence of tricuspid-valve tethering, increased left atrial volume, increased tricuspid annular diameter, and right ventricular remodeling predict severe tricuspid regurgitation.³⁶ Rapid progression to severe tricuspid regurgitation has been independently associated with all-cause mortality, and predictors of rapid progression include the presence of pacemaker or defibrillator leads, mild tricuspid regurgitation (vs. none), tricuspid annular dilatation, and any valvular heart surgery without concomitant tricuspid-valve surgery.³¹ In patients who have undergone mitral-valve surgery, the progression of tricuspid regurgitation is associated with clinical adverse events.³⁷

CAUSES AND CLASSIFICATION

The atrioventricular valves promote the transit of blood into the ventricles during diastole and prevent regurgitation during systole. Functioning under lower pressures, the right heart ejects the same stroke volume as the high-pressure left heart but in the presence of a closed mitral valve,

thus relying on the compliance of the pulmonary vasculature and left atrium. The large tricuspid-valve apparatus is particularly suited to optimizing diastolic filling of the right ventricle (Fig. 1), with the dynamic motion of the lateral annulus during ventricular relaxation (from the apex toward the base) allowing passive transfer of right atrial blood volume into the right ventricle. Changes in leaflet structure and annular size and dynamics, as well as changes in right ventricular support structures or function, can disrupt tricuspid-valve function.

The traditional subdivision of tricuspid regurgitation into primary leaflet disorders and secondary (nonleaflet) disorders has been refined with the current classification scheme, reflecting a more comprehensive understanding of different mechanisms of tricuspid regurgitation^{38,39} and their associated outcomes.^{40,41} Secondary tricuspid regurgitation has been subdivided into atrial secondary tricuspid regurgitation and ventricular secondary tricuspid regurgitation, and tricuspid regurgitation associated with a lead from a cardiac implantable electronic device is now a distinct category, separate from primary causes (Fig. 2).

PRIMARY TRICUSPID REGURGITATION

Primary tricuspid regurgitation occurs as a result of intrinsic valve disease and is attributable to congenital anomalies, infective endocarditis, rheumatic disease, carcinoid heart disease, toxic effects of chemicals, tumors, blunt trauma, or myxomatous degeneration. Congenital tricuspid regurgitation includes Ebstein's anomaly, tricuspid atresia, and the presence of a cleft valve typically associated with an atrioventricular canal defect, all of which are rare. An initial presentation of Ebstein's anomaly in adulthood is common and is frequently accompanied by atrial arrhythmias; however, biventricular failure and ventricular arrhythmias are associated with reduced survival.⁴²

The incidence of tricuspid-valve endocarditis in the United States is increasing in parallel with increases in intravenous drug use, antibiotic resistance, and use of cardiac implantable electronic devices.⁴³ The use of AngioVac-assisted vegetation debulking is also increasing,⁴⁴ and a recent meta-analysis of 44 studies that included 301 patients undergoing this procedure showed that the vegetation size was reduced by more

than 50% in 89.2% of the patients.⁴⁵ Although valvectomy may be associated with higher operative mortality,⁴⁶ a meta-analysis of surgical management of infective tricuspid-valve endocarditis showed no significant difference in short-term outcomes between valvectomy and surgical valve replacement.⁴⁷ Nonetheless, valvectomy remains a controversial management strategy but may be an acceptable bridge to definitive surgery.⁴⁸ There is probably no difference in outcomes between repair and replacement, although repair is associated with a lower risk of a need for a permanent pacemaker.⁴⁹

Thickening and restriction of tricuspid leaflet motion are commonly seen with rheumatic or carcinoid tricuspid-valve disease. Concomitant surgical management of rheumatic tricuspid regurgitation at the time of mitral-valve surgery reduces the progression of tricuspid regurgitation if the baseline disease is mild,⁵⁰ with an improvement in long-term survival when the baseline disease is moderate or severe (hazard ratio for death, 0.44; 95% CI, 0.23 to 0.87).⁵¹ Carcinoid heart disease, which occurs in 20 to 50% of patients with the carcinoid syndrome, is due to fibrosis and endocardial thickening of the heart valves, probably as the result of chronic exposure of valve tissue to high levels of serotonin. Valve replacement for tricuspid regurgitation due to carcinoid heart disease may be challenging because of the systemic effects of the carcinoid syndrome, especially in patients with impaired hepatic function. The short-term mortality associated with valve replacement may be lower with earlier intervention and with careful preoperative planning.⁵²

Other causes of primary tricuspid regurgitation include traumatic rupture of the tricuspid-valve apparatus from blunt chest trauma, a rare condition that may go undiagnosed until the chronic effects of volume overload result in symptoms of right heart failure.^{53,54} The overall prevalence of tricuspid regurgitation after heart transplantation is approximately 20% but is highest in the first month after transplantation and decreases over time. There are multiple causes of tricuspid regurgitation in the transplanted heart. However, late tricuspid regurgitation in the recipient of a heart transplant is predominantly related to cardiac allograft vasculopathy and endomyocardial biopsy procedures.⁵⁵

Causative Disease Process	Mechanism	Examples
Primary tricuspid regurgitation (5–10% of cases)		
	Congenital anomaly	Apical displacement (e.g., Ebstein's anomaly) or leaflet defect (e.g., AV canal or tricuspid hypoplasia)
	Infection	Endocarditis
	Infiltrative process	Leaflet infiltration (due to tumor, carcinoid, or drugs) or fibrosis (due to rheumatic disease or radiation-related valvulopathy)
	Degenerative disease	Prolapse or flail leaflet
	Trauma or iatrogenic cause	Leaflet avulsion or damage (from trauma, biopsy, or lead extraction)

Figure 2. Classification of Tricuspid Regurgitation (TR) According to Cause and Presenting Abnormalities.

AV denotes atrioventricular, CIED cardiovascular implantable electronic device, CTEPH chronic thromboembolic pulmonary hypertension, HFpEF heart failure with preserved ejection fraction, HFrEF heart failure with reduced ejection fraction, IAS interatrial septum, LAD left anterior descending artery, LVH left ventricular hypertrophy, MRI magnetic resonance imaging, PAH pulmonary arterial hypertension, PH pulmonary hypertension, PM papillary muscle, RA right atrial, RV right ventricular, 3D SAX three-dimensional short-axis view, TA tricuspid annular, TEE transesophageal echocardiography, and TTE transthoracic echocardiography.

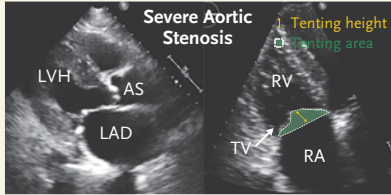
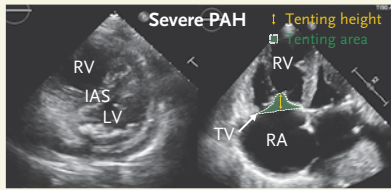
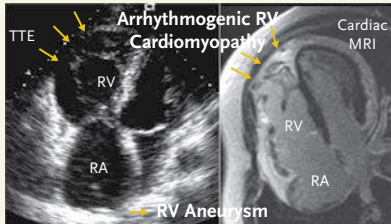
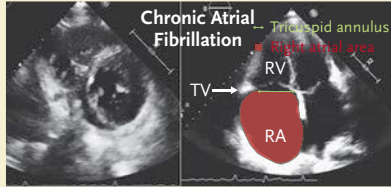
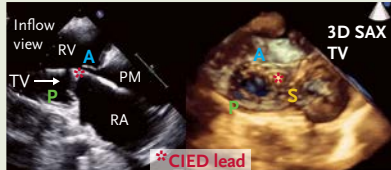
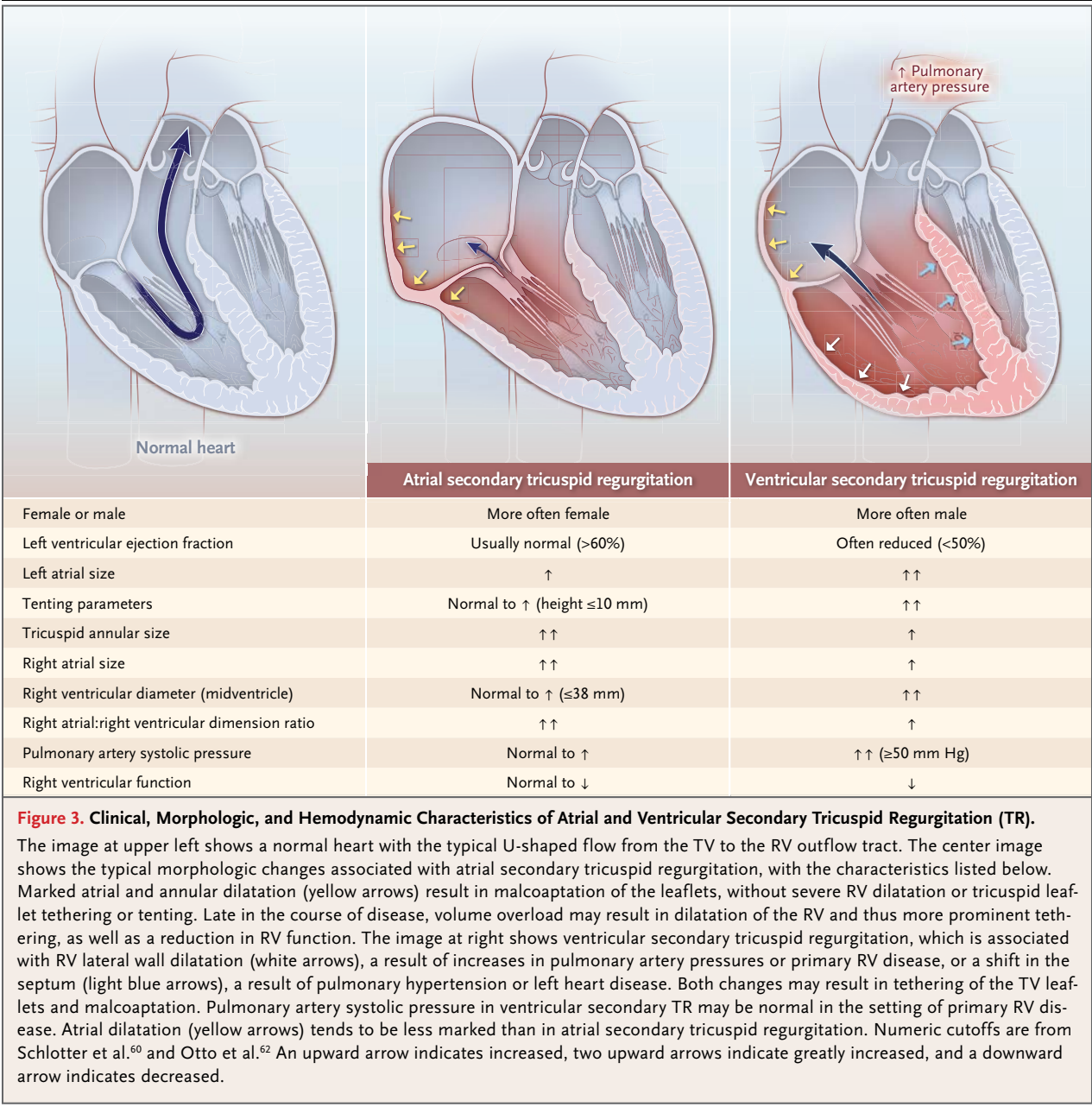
Causative Disease Process	Mechanism	Examples
Secondary tricuspid regurgitation (approximately 80% of cases)		
Ventricular secondary tricuspid regurgitation	Postcapillary PH due to left ventricular disease (HFpEF or HFrEF) or left valvular disease	
	Precapillary PH due to primary pulmonary arterial disease (e.g., PAH, chronic lung disease, or CTEPH)	
	Primary RV dysfunction or remodeling (due to RV infarct or RV cardiomyopathy)	
Atrial secondary tricuspid regurgitation	RA or TA dilatation (related to age, atrial fibrillation, or HFpEF)	
CIED-related tricuspid regurgitation (approximately 10–15% of cases)		
Lead-related tricuspid regurgitation	Causative: leaflet impingement, perforation, or valvular or subvalvular adhesions or restriction	
	Incidental: presence of CIED without interference in valvular apparatus	

Figure 2. (Continued.)

SECONDARY TRICUSPID REGURGITATION

In patients with secondary tricuspid regurgitation, the intrinsic structure of the leaflets appears normal, but there can be abnormalities of

the right atrium, tricuspid annulus, or right ventricle that result in leaflet malcoaptation (Fig. 3). Atrial abnormalities are seen in 10 to 25% of patients with secondary tricuspid regur-



gitation.⁵⁶⁻⁵⁸ Atrial secondary tricuspid regurgitation is characterized by normal-appearing leaflets that fail to coapt in the presence of marked annular and atrial dilatation. The leaflets exhibit minimal tethering or tenting, and the right ventricular structure and function are typically normal.^{56,59-61} Atrial secondary tricuspid regurgitation is associated with the presence of atrial fibrillation, a normal left ventricular ejection fraction, minimal elevation of pulmonary-artery

pressures, and the absence of left-side valve disease.⁶² Long-standing atrial secondary tricuspid regurgitation may also be associated with progressive right ventricular dilatation and may have a mixed morphologic appearance, with tethering of the leaflets. Patients with ventricular secondary tricuspid regurgitation have dilatation of the right ventricle (mainly the midventricular free wall), leading to apical displacement of the papillary muscles

and tethering of the leaflets.^{56,59,63} Right ventricular dilatation and dysfunction are most frequently due to remodeling in the context of elevated pulmonary-artery pressures resulting from precapillary or postcapillary pulmonary hypertension. However, ventricular secondary tricuspid regurgitation may also be attributable to other causes of right ventricular remodeling, including primary cardiomyopathies with right ventricular involvement, right ventricular ischemia, and infarction and arrhythmias.⁶⁴ In addition, left ventricular dilatation or dysfunction or concomitant left-side valvular disease may be present, contributing to septal abnormalities that may affect septal leaflet tethering and coaptation.

Discriminating atrial tricuspid regurgitation from the ventricular forms has prognostic and treatment implications.^{56,65-67} Patients with ventricular secondary tricuspid regurgitation (and either pulmonary arterial hypertension or left heart disease) have higher mortality than patients with atrial secondary tricuspid regurgitation or primary disease.⁶⁸ In a study involving 211 patients with secondary tricuspid regurgitation, the ventricular form was associated with a risk of death or hospitalization for heart failure that was 2.7 times (95% CI, 1.3 to 5.7) the risk with the atrial form. Outcomes were predicted on the basis of the severity of tricuspid regurgitation in the group of patients with atrial secondary tricuspid regurgitation and on the basis of both the severity of tricuspid regurgitation and right ventricular function in those with ventricular secondary tricuspid regurgitation.⁵⁶ A large retrospective registry study supports these findings.⁶⁹ Risk scores for medically treated and surgically treated patients (see the Supplementary Appendix, available with the full text of this article at NEJM.org) require further validation.

TRICUSPID REGURGITATION ASSOCIATED WITH AN IMPLANTABLE ELECTRONIC DEVICE

Although tricuspid regurgitation associated with cardiac implantable electronic devices was once categorized as a primary form of tricuspid regurgitation, it has features of both primary and secondary tricuspid regurgitation.⁷⁰⁻⁷² However, implantable electronic device–induced tricuspid regurgitation has distinct epidemiologic features and management and therapeutic options. The diagnosis can be made noninvasively with the use of advanced imaging techniques such as

three-dimensional echocardiography⁷¹ and computed tomography (CT),⁷³ although in most studies, electronic device interference with valve function has been assumed in patients with worsening tricuspid regurgitation.^{74,75} Device leads can interfere with any component of the tricuspid-valve apparatus.⁷¹

The proportion of patients with tricuspid regurgitation related to or mediated by a cardiac implantable electronic device is expected to increase because of the aging of the population, an increasing number of device implantations, and device complications requiring lead extraction.^{31,76,77} Approximately 25 to 29% of patients with permanent pacemakers have tricuspid regurgitation,⁷⁸ and the cardiac implantable electronic device is thought to be the cause of tricuspid regurgitation in 7 to 45% of patients.⁷¹ In one study, moderate-to-severe tricuspid regurgitation occurred in 27% of patients after implantation of a cardiac implantable electronic device and was associated with an increased number of hospitalizations for heart failure.⁷⁴ However, not all cardiac implantable electronic devices cause tricuspid regurgitation; it may instead be an incidental finding. In one study, up to 60% of cases of worsened tricuspid regurgitation after implantation of a cardiac implantable electronic device were of another origin, such as atrial fibrillation or previous open-heart surgery.⁷⁹ If tricuspid regurgitation is caused by the cardiac implantable electronic device, lead removal performed in a timely fashion may prevent the development of severe right ventricular dilatation and dysfunction,⁸⁰ but removal results in worsening of tricuspid regurgitation in approximately 10% of patients, with injury to the valve in approximately 3%.⁸¹

DIAGNOSIS

Echocardiography remains the primary imaging technique for identifying the cause, morphologic features, and severity of tricuspid regurgitation, with the recognition that cardiac magnetic resonance imaging (MRI) and cardiac CT have expanding roles, particularly for patients who are being considered for transcatheter therapies.³⁹

Echocardiography guidelines recommend a multiparametric approach to assess tricuspid regurgitation, with the use of a three-grade scheme (mild [1+], moderate [2+], and severe

[3+]) to describe the degree of regurgitation.^{39,82} However, patients presenting for catheter-based interventions frequently present late in the disease process, and an extended grading scheme (severe [3+], massive [4+], and torrential [5+]) was developed to more precisely describe the severity of tricuspid regurgitation in such patients (Table S1 in the Supplementary Appendix).⁸³ Data from early trials of transcatheter therapy for tricuspid regurgitation that used this grading scheme showed that even improvement limited to a single grade reduction was associated with short-term improvement in functioning and quality of life.^{84,85} An additional study has shown that the extended severity of tricuspid regurgitation grades are associated with worse outcomes.⁸⁶ In light of these results, the European Society of Cardiology⁷⁷ and European Association of Cardiovascular Imaging³⁹ guidelines suggest use of the five-grade scheme to subcategorize patients referred for transcatheter intervention. Color Doppler imaging is not recommended as the primary method for assessing the severity of tricuspid regurgitation, given the lower pressures of the right heart and the potential to underestimate severity. When mild tricuspid regurgitation is seen on color Doppler imaging, patients should undergo a comprehensive, multiparametric, and multimodal echocardiographic assessment.^{39,77}

Cardiac MRI is considered the reference standard for assessing right ventricular chamber size and volumes and can be used to quantify the severity of tricuspid regurgitation.^{39,82,87} A regurgitant volume of at least 45 ml or a regurgitant fraction of at least 50% may identify patients at highest risk for death.⁸⁷ In general, cardiac MRI is indicated when the echocardiographic assessment is suboptimal or there is discordance between the echocardiographic grading of tricuspid regurgitation and the patient's clinical presentation. A comprehensive cardiac MRI study also quantitates cardiac remodeling (both atrial and ventricular) and provides insights into the mechanism of tricuspid regurgitation. Alternatively, three-dimensional echocardiography may be useful for assessing right ventricular and tricuspid annular dimensions.^{59,88} Cardiac CT may also confirm chamber remodeling, with planimetric assessment of the anatomical orifice area in determining the severity of tricuspid regurgitation still investigational. In addition, CT has become a

standard imaging technique for assessment of the tricuspid valve and right heart in patients who are candidates for transcatheter device therapies.³⁸

THERAPY

MEDICAL AND RHYTHM MANAGEMENT

In the absence of robust evidence, guideline-directed medical therapy for tricuspid regurgitation is currently limited to diuretics and the treatment of underlying causes of secondary tricuspid regurgitation, both of which are class IIa recommendations.^{39,62,77,89} Although congestive symptoms associated with tricuspid regurgitation can respond initially to diuretics, unresponsiveness may develop as a result of neurohormonal activation (i.e., up-regulation of the renin–angiotensin–aldosterone system axis), an increased volume of diuretic distribution, visceral edema causing impaired drug absorption and tubular drug delivery, and rebound sodium absorption in the hypertrophied distal renal nephrons.¹⁶ In patients with tricuspid regurgitation who are being treated for heart failure, diuretic resistance is associated with a worse prognosis,⁹⁰ and stage D right heart failure, defined as refractory right heart failure at rest,¹⁷ is associated with an increased risk of death.⁹¹ A stepwise approach to diuretic management is suggested, with loop diuretics initially used to reduce volume load and thereby reduce pulmonary pressures (i.e., right ventricular afterload) and mineralocorticoid antagonists in natriuretic doses added to reduce decongestion in patients with more advanced disease.

Medical treatment of secondary tricuspid regurgitation requires a comprehensive evaluation of the type and severity of pulmonary hypertension, assessment of left ventricular function, and consideration of rhythm control for atrial fibrillation.^{62,77} Current management of pulmonary arterial hypertension requires an understanding of the underlying arterial disease and directed therapy to promote pulmonary vasodilatation or reduce pulmonary vasoconstriction.⁹² Because of the poor prognosis for patients with tricuspid regurgitation and precapillary pulmonary hypertension, recent European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines for managing pulmonary hypertension give a class I recommendation for right heart catheterization in patients who have

severe tricuspid regurgitation with or without left heart disease, before surgical or catheter-based valve interventions are performed.⁹² Medical treatment of pulmonary arterial hypertension is associated with right ventricular reverse remodeling and reversal of tricuspid annular dilatation, tricuspid-valve tenting, and regression of tricuspid regurgitation, with improved clinical outcomes.³⁵

Guideline-directed medical management of heart failure affects clinical outcomes and should be instituted.⁹³ There are few studies that assess the direct effect of first-line therapeutics for left heart failure on tricuspid regurgitation. In one study of cardiac resynchronization therapy,⁹⁴ approximately 41% of patients had a reduction in the severity of tricuspid regurgitation after undergoing cardiac resynchronization therapy for left heart failure, and this improvement was associated with improved clinical outcomes. Severe tricuspid regurgitation at follow-up after cardiac resynchronization therapy was independently associated with all-cause mortality. Other studies have shown that guideline-directed medical treatment of left heart failure may lead to changes in left heart hemodynamics that could reduce tricuspid regurgitation — specifically, a reduction in mitral regurgitation and improvements in left ventricular systolic and diastolic function.⁹³

Reduction of mitral regurgitation with the use of transcatheter devices has also been associated with an improvement in tricuspid regurgitation. In a study of mitral transcatheter edge-to-edge repair (TEER) for severe secondary mitral regurgitation, more than one third of patients had a reduction in tricuspid regurgitation soon after the intervention.⁹⁵ This improvement was associated with reduced heart failure symptoms and lower mortality, as compared with unchanged or worsened tricuspid regurgitation. Tricuspid regurgitation of 2+ or less, regardless of the baseline grade, was independently associated with a 42% reduction in the relative risk of long-term death from any cause.

Atrial fibrillation is a common clinical feature in patients with atrial secondary tricuspid regurgitation.^{20,24,60} Active restoration of sinus rhythm through cardioversion or ablation results in a reduction in both right and left atrial volumes, leading to improvement in tricuspid regurgitation.^{21,22}

SURGICAL MANAGEMENT

The late presentation of patients with severe symptomatic tricuspid regurgitation is largely responsible for the 10 to 12% in-hospital mortality associated with isolated surgical tricuspid-valve replacement.^{6,7} Guidelines give a class I level of recommendation for surgical treatment of severe tricuspid regurgitation at the time of left heart surgery.⁶² Management of severe, symptomatic secondary tricuspid regurgitation remains controversial, in part because of the heterogeneous patient population, the delay in diagnosis resulting from a late clinical presentation, and the absence of appropriate risk scores (see the discussion in the Supplementary Appendix and Fig. S1). The guidelines give a class IIa recommendation for isolated tricuspid-valve surgery for symptomatic, severe primary tricuspid regurgitation or symptomatic, severe secondary tricuspid regurgitation in patients in whom medical therapy has failed and who have no pulmonary hypertension or left heart disease. Given the high mortality rate associated with reoperation, guidelines give a class IIb recommendation for tricuspid-valve surgery in patients with symptomatic, severe tricuspid regurgitation and prior left-sided valve surgery in the absence of severe pulmonary hypertension or right ventricular systolic dysfunction. A class IIb recommendation is also given for surgical intervention in patients with severe, asymptomatic primary tricuspid regurgitation and progressive right ventricular dilatation or dysfunction.

The new classification of atrial and ventricular secondary tricuspid regurgitation based on valvular and ventricular morphologic features is supported by the differences in surgical annuloplasty outcomes.³⁸ Although surgical repair with an annuloplasty ring is the preferred procedure, recurrent tricuspid regurgitation is seen more frequently in patients with marked tethering of the leaflets and right ventricular dysfunction — features of ventricular secondary tricuspid regurgitation — prompting surgeons to replace valves in these patients.^{62,77} Given the association of tricuspid-valve tethering and right ventricular remodeling with disease that is chronic and severe, adjusted outcomes for repair and replacement therapies do not appear to differ substantially, although the outcomes are more favorable with valve replacement in patients with a tricuspid annular diameter larger than 44 mm.⁹⁶

Table 1. Current Transcatheter Devices.

Strategy	Ideal Anatomy
Annuloplasty (direct and indirect) devices	Annular dilatation as primary mechanism of tricuspid regurgitation) Mild tethering (tenting height <0.76 cm, tenting area <1.63 cm ² , and three-dimensional tenting volume <2.3 ml) Central jet location Sufficient landing zone for anchoring
Leaflet coaptation devices	Small septolateral gap ≤7 mm Anteroseptal jet location Confined prolapse or flail region if degenerative disease Trileaflet morphology
Heterotopic valve implantation (in inferior vena cava or both inferior and superior venae cavae)	Appropriate caval diameters or intercaval distances No other direct valve treatment option Preserved right ventricular function Reversal of flow in hepatic vein due to tricuspid regurgitation
Orthotopic valve replacement	Previous surgical repair or bioprosthetic valve replacement Leaflet thickening or shortening (rheumatic cause, carcinoid) feasible depending on anchoring Incidental or causative cardiac implantable electronic device feasible depending on anchoring Any leaflet morphology

TRANSCATHETER MANAGEMENT

Transcatheter solutions are being pursued aggressively as lower-risk interventions in higher-risk patients with tricuspid regurgitation (Table 1). Leveraging the success of the TEER devices for mitral regurgitation, proceduralists began using the commercially available mitral-valve devices to treat tricuspid regurgitation. Given the wide availability of this device, tricuspid TEER currently remains the most common transcatheter therapy around the world.³⁸

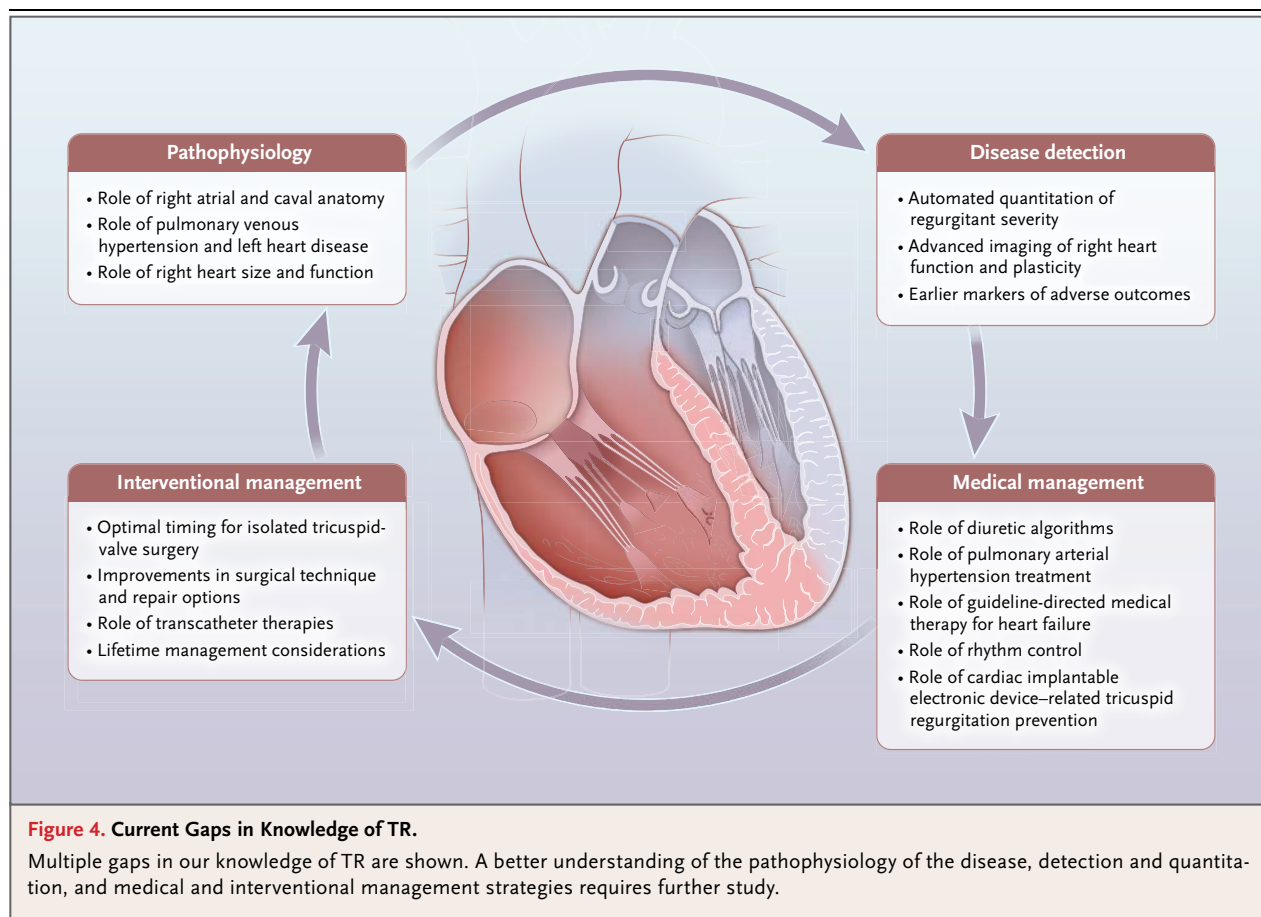
The multinational TriValve Registry was developed to better understand the characteristics of patients undergoing transcatheter interventions and the treatment outcomes.⁹⁷ In a study of registry data, the average age (±SD) of the patients was 76±9 years and 60.4% were women. More than one third of the patients had previously undergone left heart surgery (in most cases, valve surgery), and 79.0% were in permanent atrial fibrillation. Peripheral edema was observed in 81.0% of the patients, and 27.3% had ascites, despite the maximal tolerated diuretic therapy. A total of 56.6% of the patients had been hospitalized in the preceding 6 months

for right ventricular heart failure. The baseline median N-terminal pro-B-type natriuretic peptide level was 2253 pg per milliliter (interquartile range, 1416 to 5252), and nearly all the patients were being treated with a diuretic. These clinical characteristics have been consistent among patients treated with a transcatheter tricuspid valve.⁹⁸

When patients in the registry were propensity-matched with a medically treated cohort, transcatheter tricuspid-valve intervention was associated with a lower incidence (±SD) of the composite end point of death and rehospitalization (32±4% vs. 49±3%), as well as a lower incidence of the individual outcomes of death (23±3% vs. 36±3%) and rehospitalization (26±3% vs. 47±3%).⁵ A meta-analysis that included 21 transcatheter device studies showed an overall mortality of 5% (95% CI, 4 to 8) at 30 days, and an analysis of 6 studies showed an overall mortality of 25% (95% CI, 12 to 45) at 1 year.⁹⁸ Outcomes were improved for patients in whom the procedure was successful, with success defined as a reduction in the tricuspid regurgitation grade to 2+ or less, as compared with those in whom the procedure failed (odds ratio, 0.42; 95% CI, 0.27 to 0.66).⁹⁸

Predictors of short- and long-term outcomes after transcatheter interventions remain ill defined, in part because of the wide range of coexisting conditions in patients who undergo these procedures, as well as the range of pathophysiological and morphologic features that define the anatomical restrictions for specific device therapies. As with surgical repair, isolated transcatheter annuloplasty devices may be most useful primarily in patients who have annular dilatation without marked leaflet tethering. The success of the TEER devices has been studied most extensively, with the location of the regurgitant jet, leaflet coaptation gap, extent of pacemaker lead impingement, complexity of leaflet structure, and chordal density identified as the major determinants of success.³⁸ These limitations may result in reduced efficacy of the device. TEER devices can reduce tricuspid regurgitation to moderate or less in 80 to 85% of patients and to mild or less in only 30 to 50% of patients.

Early feasibility studies suggested that the class of device with the greatest efficacy in reducing tricuspid regurgitation is the orthotopic



tricuspid-valve replacement, which reduces tricuspid regurgitation to mild or less in more than 90% of patients; mortality at 1 year may be lower with this intervention than 1-year mortality in natural history studies of severe tricuspid regurgitation and in recent meta-analyses of mainly repair devices.⁹⁹ Elimination of tricuspid regurgitation, however, is associated with an increase in effective afterload to the right ventricle and unmasking of mechanical dysfunction, which may limit the hemodynamic benefits of this device. Despite reductions in right ventricular function, however, improvements in forward stroke volume can be seen.¹⁰⁰

Device therapy continues to evolve, and both early feasibility studies and randomized, controlled trials of transcatheter devices as compared with medical therapy will help define the appropriate treatment, patient population, and management approach. These trials should help fill the current gaps in our understanding of optimal medical therapy and anatomical limita-

tions of specific devices, as well as the efficacy of the devices and their impact on outcomes. Understanding the role of left ventricular dysfunction, pulmonary arterial hypertension, right ventricular dysfunction, and concomitant valvular heart disease, as well as renal and hepatic dysfunction, will also help inform physicians about treatment options.

The marked improvements in functioning and quality of life that patients with severe, symptomatic tricuspid regurgitation had in early device feasibility trials^{84,85} contributed to the justification for the Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System Pivotal (TRILUMINATE Pivotal) to use a novel hierarchical end point of three outcomes: death from any cause or tricuspid-valve surgery, hospitalization for heart failure, and an improvement in quality of life as measured with a patient-reported outcomes instrument.¹⁰¹ After 1 year of follow-up, the incidence of death or tricuspid-valve surgery and

the rate of hospitalization for heart failure did not differ significantly between the device and medical therapy groups; however, the trial met the primary end point because of significant improvements in the quality-of-life measure (win ratio, 1.48; 95% CI, 1.06 to 2.13; $P=0.02$). The results of this trial have highlighted gaps in our understanding of TEER in patients with severe tricuspid regurgitation: what are the benefits of device therapy, who are the patients who may benefit from it, and how can we predict a good outcome? As both device and surgical therapies continue to evolve, and optimal medical management is better defined, the answers to these questions are likely to be forthcoming.

CONCLUSIONS AND FUTURE DIRECTIONS

The grim natural history of tricuspid regurgitation has stimulated the search for a better understanding of the pathophysiology of the disease, early detection, optimal medical management, and ideal interventional timing and technique. Our understanding of clinical outcomes for patients with tricuspid regurgitation continues to expand, with the most recent large observational study suggesting that even mild tricuspid-valve disease is associated with reduced long-term survival.⁴ Recognition of the complexity of tricuspid-valve disease has led to a better

classification scheme, which is supported by studies showing differences in patient outcomes that are associated with the refined disease categories.⁵⁶ Finally, there has been rapid growth in the development of less invasive transcatheter options for disease management as a means of overcoming the reported poor outcomes of isolated tricuspid-valve surgery.³⁸

The pitfalls of current algorithms for detecting tricuspid-valve disease have necessitated the adoption of new methods for quantitation and grading of tricuspid regurgitation and have fostered an appreciation of the role of the right heart and pulmonary vasculature. Because of our nascent understanding of the pathophysiology, detection, and medical management of tricuspid regurgitation, patients are sent for surgical intervention late in the disease process, thereby increasing the risk of adverse outcomes. In this new era of transcatheter therapeutics, the number of devices to treat tricuspid regurgitation is rapidly increasing. Several knowledge gaps, however, impede our management of severe, symptomatic tricuspid regurgitation (Fig. 4). Improvement in outcomes will rely heavily on early recognition of tricuspid regurgitation by clinicians and referral to a level 1 comprehensive valve center, which has the medical, surgical, and interventional expertise to evaluate and manage this complex disease.⁶²

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Secondary Mitral Regurgitation

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors’ clinical recommendations.

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A 75-year-old man presents with dyspnea and fatigue that occur with less than moderate physical activity. He had an ST-segment elevation myocardial infarction involving the inferior and posterior segments of the left ventricle 10 years ago, and since then the left ventricular ejection fraction (LVEF) has decreased from 40% to 25%, accompanied by increasing mitral regurgitation. An implantable cardioverter–defibrillator (ICD) was placed for primary prevention 6 months ago. His medications include metoprolol succinate, spironolactone, and torsemide. How would you further evaluate and treat this patient?

THE CLINICAL PROBLEM

MITRAL REGURGITATION DERIVES FROM ANATOMICAL OR FUNCTIONAL impairment of one or more components of the mitral apparatus that are necessary for normal valve function, including the left ventricle, papillary muscles, chordae tendineae, leaflets, and annulus.¹ The two broad categories of mitral regurgitation are primary (or degenerative) mitral regurgitation, which is most commonly caused by leaflet prolapse or flail, and secondary (or functional) mitral regurgitation. Primary mitral regurgitation is a disease of the valve (or chordae), and secondary mitral regurgitation is a disease of the left ventricle or left atrium.



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of this article
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In the United States, mitral regurgitation is the most common cause of moderate-to-severe valvular heart disease among adults older than 55 years of age.² In a cross-sectional cohort study involving persons older than 65 years of age, the prevalence of moderate-to-severe mitral regurgitation detected on transthoracic echocardiography was 2.3%.³ In another study,⁴ moderate-to-severe mitral regurgitation was identified in 0.59% of 29,390 adults residing in Olmsted County, Minnesota. The mitral regurgitation was classified as secondary in 65% of the cases, of which 60% were attributed to left ventricular remodeling or dysfunction and the remainder were attributed to atrial fibrillation or flutter or to idiopathic annular dilation.⁵

The severity of secondary mitral regurgitation may vary dynamically as a function of left ventricular loading conditions, heart rhythm, conduction system disease, and myocardial ischemia. Ischemic mitral regurgitation is a type of secondary mitral regurgitation that occurs after myocardial infarction. Several studies have shown high risks of illness and death from cardiovascular disease among patients with symptomatic heart failure, reduced left ventricular systolic function,

KEY CLINICAL POINTS

SECONDARY MITRAL REGURGITATION

- Mitral regurgitation can be broadly classified into two different categories — primary and secondary mitral regurgitation. The evaluation, treatment, and prognosis in patients with these conditions differ. Primary mitral regurgitation is usually caused by leaflet abnormalities (prolapse), whereas secondary mitral regurgitation results from abnormal left ventricular size, shape, or function.
- Transthoracic echocardiography is the most frequently used test to determine the cause, mechanism, and severity of mitral regurgitation.
- Guideline-directed medical therapy is the first-line approach in the treatment of patients who have heart failure with secondary mitral regurgitation and a reduced left ventricular ejection fraction (LVEF). Surgical or transcatheter intervention should be undertaken only after the patient has received the maximal dose of medical therapy without adverse effects.
- Surgical treatment of secondary mitral regurgitation consists of downsized annuloplasty repair or replacement. Surgery has not been shown to improve long-term survival among these patients.
- In one of two randomized trials of transcatheter edge-to-edge repair (TEER) involving patients with secondary mitral regurgitation and a reduced LVEF, guideline-directed medical therapy plus TEER significantly decreased the incidence of hospitalization for heart failure or death from any cause at 2 years.
- The concept of differentiating mitral regurgitation as proportionate or disproportionate has been proposed to explain the benefit of TEER for secondary mitral regurgitation. Prospective validation of this concept is needed.

and moderate or greater degrees of ischemic mitral regurgitation.⁶⁻⁸ Secondary mitral regurgitation is associated with lower event-free survival than primary mitral regurgitation of similar magnitude. Adverse outcomes with secondary mitral regurgitation can occur in association with smaller regurgitant volumes than are observed in patients with remodeled primary mitral regurgitation. Whether secondary mitral regurgitation is simply a marker of poor outcomes due to left ventricular dysfunction or whether it contributes independently to the long-term prognosis in these patients is uncertain.

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

The clinical recognition of secondary mitral regurgitation begins with detection and characterization of a systolic heart murmur that is considered within the context of the patient's history, symptoms at presentation, and other evidence of an underlying cardiac condition (e.g., abnormalities on electrocardiography or chest radiography). Although the murmur can be difficult to detect, bedside maneuvers to increase left ventricular afterload may increase its intensity.

The identification of the cause, mechanism, severity, and consequences of mitral regurgitation relies primarily on performance of trans-

thoracic echocardiography with assessment of the morphologic characteristics and motion of the mitral-valve leaflets, size and calcification of the annulus, left ventricular and left atrial volumes, global and regional left ventricular systolic function, pulmonary-vein flow, pulmonary-artery pressures, right ventricular function, and the presence of tricuspid regurgitation (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org; and Fig. 1).⁹ The nature of secondary mitral regurgitation is dynamic, so the patient's blood pressure and heart rate and rhythm should be recorded. Transthoracic echocardiography often reveals more mitral regurgitation than can be detected on physical examination.

CLASSIFICATION AND ASSESSMENT

The Carpentier classification,¹⁰ which categorizes mitral regurgitation on the basis of normal, excessive, or restrictive leaflet mobility, can be useful for clinical categorization and surgical planning (Fig. S1). In Carpentier type IIIB disease, which is the main focus of this article, mitral regurgitation is attributable to restricted mitral-valve leaflet motion during systole in patients with an ischemic or nonischemic (dilated) cardiomyopathy. In patients with ischemic mitral regurgitation, the mitral-valve leaflets are also thickened and fibrotic, with reduced lengthening.¹¹ Mitral

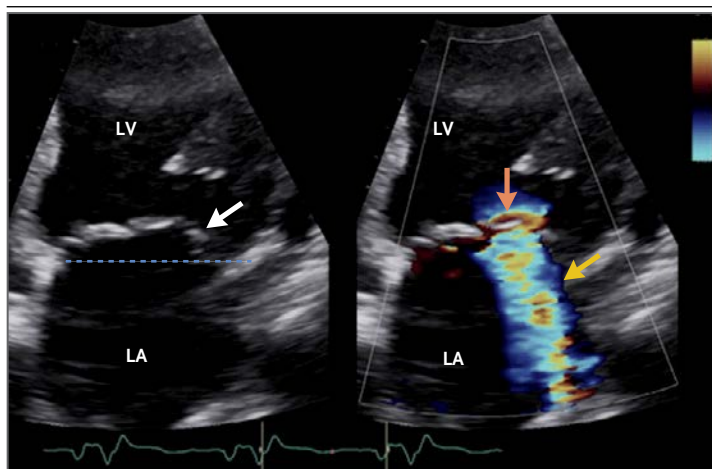


Figure 1. Secondary Mitral Regurgitation on Transthoracic Echocardiography.

An enlarged apical four-chamber view without color Doppler (left side) and with color Doppler (right side) is shown. On the left side, the posterior mitral-valve leaflet (white arrow) is tethered, and there is tenting of both leaflets above the valve plane (dashed blue line) during systole. The left ventricle (LV) and left atrium (LA) are enlarged. On the right side, there is an eccentric jet of mitral regurgitation (yellow arrow) directed posteriorly and laterally into an enlarged LA with an area of accelerated flow convergence at its cap (orange arrow). The mitral regurgitation was severe according to multiple criteria.

regurgitation occurs most often as a consequence of adverse left ventricular remodeling with papillary muscle displacement, leaflet tethering, reduced mitral-valve closing forces, annular dilation, and failure of leaflet coaptation. In some patients with ischemic mitral regurgitation, however, the left ventricle is not substantially remodeled. With atrial functional mitral regurgitation (Carpentier type I), mitral-valve leaflet motion is normal and the mitral regurgitation is due to left atrium and annular enlargement with insufficient leaflet lengthening, as occurs in some patients with chronic persistent atrial fibrillation.¹²

The severity of mitral regurgitation should be measured objectively. However, quantitative assessment of secondary mitral regurgitation is difficult because of geometric assumptions and technical challenges.¹³ In patients with ischemic mitral regurgitation, measurement may be inaccurate because of the eccentric nature of the jet and the crescentic shape of the regurgitant orifice.^{13,14} Professional societies have published various thresholds for the classification of severe mitral regurgitation. The American College of Cardiology–American Heart Association (ACC–

AHA) guidelines define severe secondary mitral regurgitation on the basis of an effective regurgitant orifice area of at least 0.4 cm² and a regurgitant volume of 60 ml or more (the same thresholds as those applied to primary mitral regurgitation).^{15,16} In contrast, the guidelines of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery use lower cutoff points (effective regurgitant orifice area ≥ 0.2 cm² and regurgitant volume ≥ 30 ml)¹⁷; these cutoff points are based on data on the natural history of this condition that link these lower values with poor outcomes. The American Society of Echocardiography guidelines¹⁴ caution that secondary mitral regurgitation may be severe even with an effective regurgitant orifice area of 0.3 cm² or more because of limitations in the technique used to measure it. One echocardiographic finding in isolation cannot define the severity of mitral regurgitation, and thus an integrative approach is needed.

ADDITIONAL TESTING

When assessment of the anatomy and function of the mitral valve by means of transthoracic echocardiography is not adequate, transesophageal echocardiography and cardiac magnetic resonance imaging (MRI) can provide more specific anatomical and hemodynamic detail.¹⁴ Because the patient has to be sedated during transesophageal echocardiography, the performance of this test can result in favorably altered left ventricular loading conditions and reduced severity of secondary mitral regurgitation. Thus, observations made on transthoracic echocardiography while the patient is awake should be used in clinical decision making. Cardiac MRI can provide accurate measurement of left ventricular volumes, detect areas of myocardial scarring, and assess for regional ischemia. Exercise transthoracic echocardiography may be useful when there are discrepancies between the clinical findings and data from other noninvasive testing. Cardiac catheterization with hemodynamic assessment, coronary angiography, and left ventriculography has a role in selected patients, particularly those with known or suspected coronary artery disease.⁹

MEDICAL THERAPY OR DEVICES

Recommendations regarding the treatment of secondary mitral regurgitation are based on multi-

ple variables, including the type (ventricular or atrial), severity, and hemodynamic consequences of secondary mitral regurgitation; coexisting conditions; and the experience and expertise of the multidisciplinary team providing care. Guideline-directed medical therapy (Table S2) is the first-line approach in patients who have heart failure with a reduced LVEF and secondary mitral regurgitation, and it is provided preferably with the supervision of a heart failure specialist. Randomized trials involving patients who have heart failure with a reduced ejection fraction (some of whom had secondary mitral regurgitation) have shown functional and survival benefits of beta-blockers, inhibitors of the renin-angiotensin-aldosterone system, angiotensin receptor-neprilysin inhibitors, and sodium-glucose cotransporter 2 inhibitors.¹⁸⁻²¹ Stepped therapy with these agents and others is implemented over a period of weeks to months. Both carvedilol²² and sacubitril-valsartan²³ have been shown to reduce the degree of secondary mitral regurgitation.

Cardiac resynchronization therapy can improve left ventricular function, decrease left ventricle size, and reduce the magnitude of mitral regurgitation in selected patients who have heart failure with a reduced ejection fraction and left bundle-branch block, particularly when the QRS duration exceeds 150 msec.^{24,25} In patients with atrial functional mitral regurgitation due to atrial fibrillation, restoration and maintenance of sinus rhythm can reduce the left atrium size, the mitral annular dimensions, and the degree of mitral regurgitation.²⁶ Attention to the principles of secondary prevention of coronary artery disease events (including lipid management) and reduction in the risk of sudden death (with an ICD) and stroke (with anticoagulation for atrial fibrillation) is important.

SURGERY

In contrast to primary mitral regurgitation, for which valve repair is indicated when symptoms develop or when certain thresholds for left ventricle size, function, or both are met,¹⁴⁻¹⁶ surgical or transcatheter intervention for secondary mitral regurgitation should be pursued only in patients with persistent symptoms and residual moderately severe or severe mitral regurgitation despite an adequate 3-month trial of guideline-directed medical therapy.⁹ Surgery for secondary mitral

regurgitation consists chiefly of either repair with a downsized annuloplasty ring or valve replacement with chordal sparing. In patients with ischemic mitral regurgitation, coronary-artery bypass grafting (CABG) is performed when appropriate. Surgical ablation for atrial fibrillation, amputation of the left atrial appendage, and other valve surgery is undertaken when indicated.

Although a case series showed improvement in left ventricular function and shape in patients with dilated cardiomyopathy and secondary mitral regurgitation with insertion of a downsized annuloplasty ring,²⁷ a subsequent propensity-matched cohort study from the same institution showed that survival was not longer among patients who underwent repair than among those who received medical therapy.²⁸ Data from randomized trials comparing mitral-valve surgery with medical therapy or transcatheter therapy in patients with ischemic mitral regurgitation are lacking. In a randomized trial comparing mitral-valve repair with chordal-sparing mitral-valve replacement in 251 patients with severe ischemic mitral regurgitation (mean effective regurgitant orifice area, 0.4 cm²), those assigned to mitral-valve replacement had a lower incidence of moderate-to-severe mitral regurgitation after surgery, fewer serious adverse events related to heart failure, and fewer readmissions for cardiovascular causes at 2 years, although there was no significant difference in survival at 2 years.²⁹ Thus, in contrast to severe primary mitral regurgitation (for which valve repair is preferred over replacement), valve replacement may be preferred for treatment of severe ischemic mitral regurgitation. In another randomized trial involving patients with moderate ischemic mitral regurgitation (mean effective regurgitant orifice area, 0.2 cm²), there was no difference between mitral-valve repair plus CABG and CABG alone with respect to the magnitude of left ventricular reverse remodeling, and survival was not longer with mitral-valve repair plus CABG than with CABG alone.³⁰

TRANSCATHETER REPAIR OR REPLACEMENT

In transcatheter intervention for mitral regurgitation, the use of a clip (MitraClip, Abbot Vascular) to create an edge-to-edge approximation of the midportion of the mitral-valve leaflets results in a double-orifice mitral valve (Fig. 2,

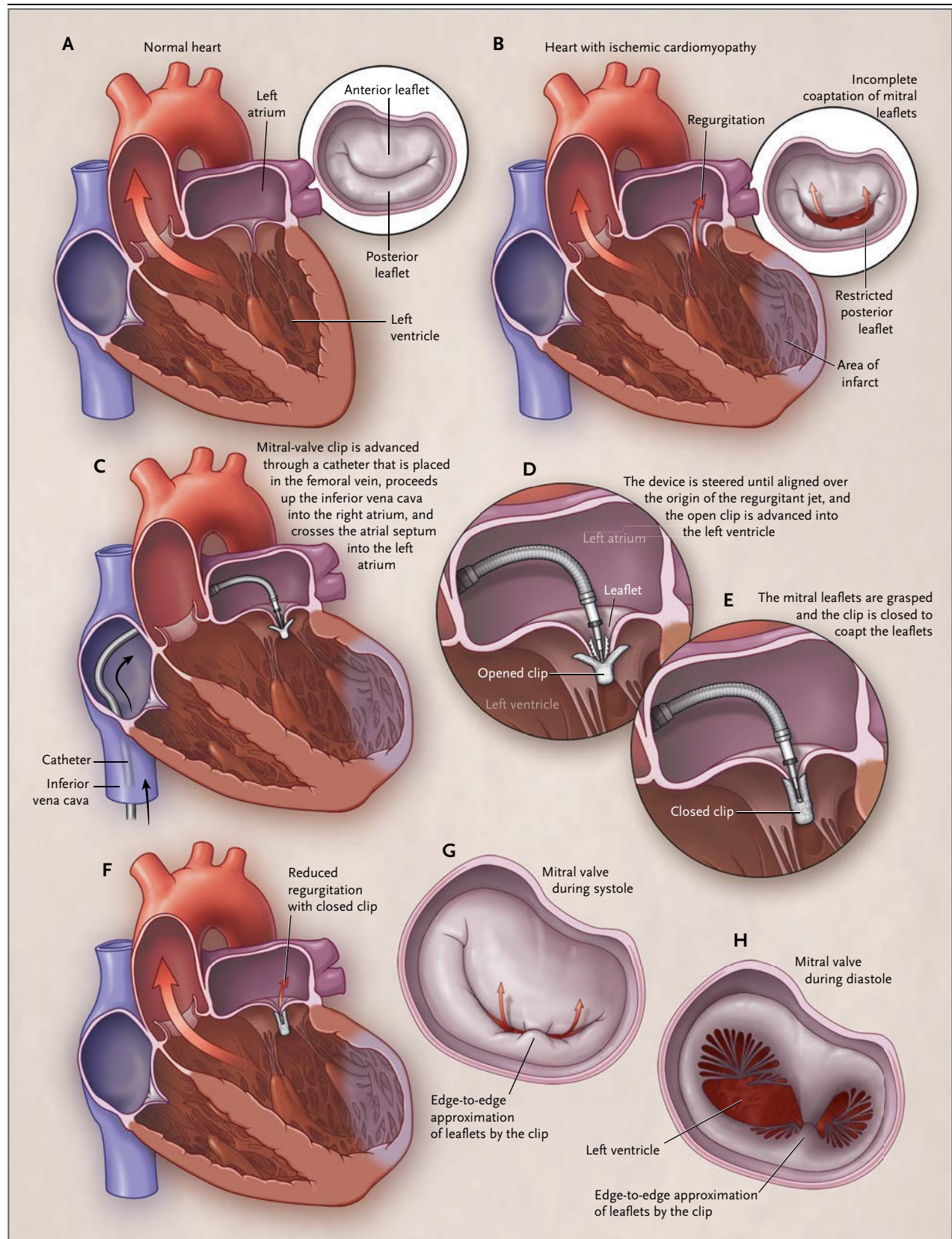


Figure 2 (facing page). Transcatheter Intervention for Mitral Regurgitation.

As shown in A (upper left), in the normal heart, the mitral valve is competent and systolic flow is directed out of the aorta. As shown in B, the left ventricle remodels after myocardial infarction with displacement of the papillary muscles and restricted movement of the posterior mitral-valve leaflet, resulting in mitral regurgitation. As shown in C, a catheter containing the mitral-valve clip device is threaded up the inferior vena cava into the right atrium, across the interatrial septum, into the left atrium, and across the mitral-valve leaflets. This procedure is performed with transesophageal and fluoroscopic guidance. As shown in D and E, the device is positioned to grasp the mitral-valve leaflets and clip them together in the region of the jet of mitral regurgitation. As shown in F and G, edge-to-edge clipping results in a decrease in the magnitude of mitral regurgitation. Placement of the clip results in the creation of a double-orifice mitral valve. The view in H is from the left atrial side of the valve, looking down into the left ventricle. In this example, the clip has been placed across the middle scallops of the anterior and posterior leaflets, creating a ridge of tissue that separates the two orifices.

Video 1, and Video 2). The favorable outcomes in both randomized and observational studies resulted in the 2013 Food and Drug Administration (FDA) approval of the clip for the treatment of patients with primary mitral regurgitation who are at high risk for surgery-related complications or death.³¹

Subsequently, the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial randomly assigned 614 patients with secondary mitral regurgitation (approximately 60% of whom had ischemic cardiomyopathy) and symptomatic heart failure with a reduced LVEF to either transcatheter edge-to-edge repair (TEER) plus guideline-directed medical therapy or guideline-directed medical therapy alone.³² The addition of TEER to medical therapy resulted in significantly fewer hospitalizations for heart failure and improved survival at 2 years, with a low incidence of device-related complications.

A second randomized trial that used the same device, the Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trial, involved 304 patients. The 1-year³³ and 2-year³⁴ follow-up results of that trial showed no significant differences between patients who received guideline-directed

medical therapy plus TEER and those who received guideline-directed medical therapy alone with respect to a composite outcome of death from any cause or unplanned hospitalization for heart failure. Possible reasons proposed for these discordant results include differences between the trial sample sizes and in end points, as well as differences in the severity of baseline mitral regurgitation, baseline left ventricle size, rigor of medical therapy, degree and durability of the reduction in mitral regurgitation, and operator experience.³⁵ Another proposed explanation is that the benefits of TEER in patients with secondary mitral regurgitation may depend on the relationship between the left ventricle size and the severity of mitral regurgitation.³⁶ These benefits are greater when the degree of mitral regurgitation exceeds — or is disproportionate to — that which would be expected for the size of the ventricle alone. Such disproportionate mitral regurgitation was more common in patients in the COAPT trial, who had more mitral regurgitation and smaller ventricles than patients in the MITRA-FR trial. Although a COAPT substudy of echocardiographic findings showed consistent benefits of TEER across numerous baseline echocardiographic measures,³⁷ a post hoc analysis involving a small subgroup of patients in the COAPT trial who more closely resembled patients in the MITRA-FR trial and who had mitral regurgitation that was considered to be proportionate to the degree of left ventricular dilatation did not show a benefit with TEER.³⁸

Patient selection for TEER is a nuanced process and must involve consideration of numerous clinical, imaging, and hemodynamic variables.^{39,40} In patients with secondary mitral regurgitation, important transesophageal echocardiographic findings to predict the feasibility of TEER include leaflet coaptation depth, coaptation length, grasping zone distance between leaflets, and the presence, extent, and distribution of calcification.⁹ The FDA approved the MitraClip device in March 2019 for use in patients with secondary mitral regurgitation who meet the inclusion criteria of the COAPT trial. These criteria are symptomatic heart failure with an ejection fraction of 20 to 50% and moderate-to-severe or severe mitral regurgitation despite guideline-directed medical therapy (plus cardiac resynchronization therapy, if indicated), a left



Videos showing transcatheter repair are available at [NEJM.org](https://www.nejm.org)

Table 1. 2017 Guidelines for Intervention in Patients with Chronic Severe Secondary Mitral Regurgitation.***American College of Cardiology–American Heart Association**

Class IIa recommendation

Mitral-valve surgery is reasonable for patients with chronic severe secondary mitral regurgitation who are undergoing CABG or aortic-valve replacement. (Level of evidence: C)

It is reasonable to choose chordal-sparing mitral-valve replacement over repair with a downsized annuloplasty ring if the operation is considered for severely symptomatic patients with chronic severe ischemic mitral regurgitation and persistent symptoms despite the use of maximal doses of guideline-directed medical therapy without adverse effects. (Level of evidence: B)

Class IIb recommendation

Mitral-valve repair or replacement may be considered for severely symptomatic patients with chronic severe secondary mitral regurgitation who have persistent symptoms despite the use of maximal doses of guideline-directed medical therapy without adverse effects. (Level of evidence: B)

European Society of Cardiology and the European Association for Cardio-Thoracic Surgery

Class I recommendation

Surgery is indicated in patients with severe secondary mitral regurgitation who are undergoing CABG and who have an LVEF >30%. (Level of evidence: C)

Class IIa recommendation

Surgery should be considered in symptomatic patients with severe secondary mitral regurgitation and an LVEF <30% who have an indication for revascularization and evidence of myocardial viability. (Level of evidence: C)

Class IIb recommendation

When revascularization is not indicated, surgery may be considered in patients with severe secondary mitral regurgitation and an LVEF >30% who remain symptomatic despite the use of maximal doses of medical therapy without adverse effects (and cardiac resynchronization therapy if indicated) and have a low risk of surgery-related complications or death. (Level of evidence: C)

When revascularization is not indicated and the risk of surgery-related complications or death is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and an LVEF >30% who remain symptomatic despite the use of maximal doses of medical therapy without adverse effects (and cardiac resynchronization therapy, if indicated) and who are found to have suitable valve morphologic characteristics on echocardiography, if the heart team thinks there is a reasonable chance for clinical improvement. (Level of evidence: C)

In patients with severe secondary mitral regurgitation and an LVEF <30% who remain symptomatic despite the use of maximal doses of medical therapy without adverse effects (and cardiac resynchronization therapy if indicated) and who have no option for revascularization, the heart team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a left ventricular assist device or heart transplantation according to individual patient characteristics. (Level of evidence: C)

* The class of recommendation indicates the strength of the recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. In general, a class I recommendation indicates that the intervention is indicated or useful and should be performed. A class IIa recommendation implies that the intervention is reasonable and can be effective, whereas a class IIb recommendation implies that the usefulness or effectiveness of the intervention is less certain. The guidelines differ with respect to methods and language, although the recommendations are directionally concordant. The level of evidence rates the quality of scientific evidence that supports the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources. Level B evidence may derive from randomized trials, observational studies, and registries, and it is considered to be of moderate quality. Level C evidence relies on limited data, expert opinion, or both. These guideline recommendations reflect the strength of the evidence base in existence in 2017. CABG denotes coronary-artery bypass grafting, and LVEF left ventricular ejection fraction.

ventricular end-systolic dimension of less than 7.0 cm, and a pulmonary-artery systolic pressure of less than 70 mm Hg.

Other transcatheter approaches to repair secondary mitral regurgitation include devices that target the mitral-valve leaflets or reduce the size

of the dilated annulus. Devices for mitral-valve replacement are also under investigation.⁴¹ Early studies have focused on feasibility, device performance, safety, and short-term efficacy in patients with a high or prohibitive risk of surgery-related complications or death.

GUIDELINES

International practice guidelines for the care of patients with valvular heart disease were most recently updated in 2017, before the publication of the results of the COAPT and MITRA-FR trials in 2018, and these guidelines were conservative in their recommendations regarding surgery for secondary mitral regurgitation (Table 1).^{16,17} Mitral-valve surgery was recommended¹⁶ or considered to be reasonable¹⁷ for patients with severe secondary mitral regurgitation who are undergoing CABG. The guidelines noted that isolated mitral-valve surgery could be considered for severe secondary mitral regurgitation in selected patients with severe symptoms despite the use of maximal doses of guideline-directed medical therapy without adverse effects. The surgical approach was not rigorously specified, although the ACC–AHA guidelines stated that it is reasonable to choose replacement in preference to repair with a downsized annuloplasty ring for patients with severe ischemic mitral regurgitation.¹⁶

The 2017 guidelines of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery also suggested a possible role for TEER in the treatment of severe secondary mitral regurgitation in patients who have heart failure with a reduced ejection fraction and persistent symptoms despite the use of maximal doses of guideline-directed medical therapy without adverse effects. Both guidelines are currently undergoing revision. The present article differs from the current guidelines¹⁵⁻¹⁷ by taking into account the results of the COAPT and MITRA-FR trials.

AREAS OF UNCERTAINTY

The disparate results of the COAPT and MITRA-FR trials have confused the clinical community. A third trial (A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation [RESHAPE-HF2]) (ClinicalTrials.gov number, NCT02444338) of the same device in similar patients is currently recruiting patients and is designed to provide additional data to guide the appropriate use of TEER in patients with secondary mitral regurgitation.

Currently, more than 380 U.S. centers offer TEER for mitral regurgitation (www.sts.org/registries-research-center/stsacc-tvt-registry). Whether they can reproduce the rigor applied in the COAPT trial to achieve similar results in a real-world setting is uncertain. Regulatory criteria for approval of new transcatheter repair and replacement devices need to be developed. Prospective validation of the concept of differentiating secondary mitral regurgitation as proportionate or disproportionate to guide patient selection for mitral-valve intervention is needed.^{35,38-40,42}

Despite clear recommendations for guideline-directed medical therapy, treatment is often not sufficient, and mortality among patients who have heart failure with a reduced ejection fraction and secondary mitral regurgitation remains high (e.g., 29% at 2 years in the device group of the COAPT trial); effective strategies are needed to improve guideline adherence.^{43,44} Given the results of the COAPT trial, the role of surgery in the management of secondary mitral regurgitation has become less clear for patients in whom there is no other primary indication for operation, such as severe coronary artery disease, for which CABG would be preferred over percutaneous coronary intervention.

CONCLUSIONS AND RECOMMENDATIONS

In the patient described in the vignette, the cause, mechanism, and severity of mitral regurgitation should be evaluated by means of transthoracic echocardiography, and an assessment of myocardial ischemia and viability should be performed. The first-line approach should be to initiate a regimen for heart failure that includes a low dose of an angiotensin-converting-enzyme inhibitor (or an angiotensin-receptor blocker), adjusted with attention to the patient's blood pressure, renal function, and potassium level, followed by an attempt to switch to an angiotensin receptor–neprilysin inhibitor. Efforts should be made to administer the doses of medications that have been shown to be useful in randomized heart failure trials. Cardiac resynchronization therapy should be considered if indicated.⁴⁵

If severe heart failure symptoms persist after the use of maximal doses of guideline-directed medical therapy without adverse effects for

3 months, TEER can be considered if the patient meets the inclusion criteria of the COAPT trial noted above and transesophageal echocardiographic assessment of the leaflet structure and motion indicates that this is feasible. We would consult with a multidisciplinary team that includes a heart failure specialist, an echocardiog-

rapher, an interventionalist, and a surgeon to seek a consensus recommendation regarding the best treatment strategy, and we would pursue a shared decision-making process with the patient and his family.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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RESEARCH SUMMARY

Transcatheter Repair for Patients with Tricuspid Regurgitation

Sorajja P et al. DOI: 10.1056/NEJMoa2300525

CLINICAL PROBLEM

For patients with severe tricuspid regurgitation, transcatheter edge-to-edge repair (TEER) has emerged as a safe and potentially effective treatment option. This percutaneous, transvenous procedure deploys one or more clips to hold the tricuspid-valve leaflets together, thereby reducing regurgitation without the need for cardiac surgery. However, the clinical benefit of tricuspid TEER as compared with medical therapy alone is uncertain.

CLINICAL TRIAL

Design: An international, open-label, randomized, controlled trial evaluated the effectiveness and safety of TEER as compared with medical therapy alone in patients with severe, symptomatic tricuspid regurgitation who were at intermediate or greater surgical risk.

Intervention: 350 patients were assigned to either TEER or medical therapy (control). The primary end point was a hierarchical composite that included death from any cause or tricuspid-valve surgery; hospitalization for heart failure; and an improvement in quality of life as measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ) (≥ 15 -point improvement at 1 year).

RESULTS

Effectiveness: During 1 year of follow-up, the primary outcome favored the TEER group over the control group. The difference between the groups was largely attributable to a significantly greater mean improvement in the quality-of-life score in the TEER group.

Safety: 98% of patients who underwent TEER were free from major adverse events at 30 days, a finding that exceeded the performance goal of the trial (90%).

LIMITATIONS AND REMAINING QUESTIONS

- The open-label nature of the trial could have introduced bias into the interpretation of clinical outcomes.
- The trial was conducted during the Covid-19 pandemic, which could have affected outcomes.
- The results may not apply to patients with hemodynamic or anatomical findings that do not meet the entry criteria used in the trial.

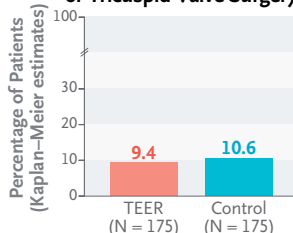
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Primary End Point

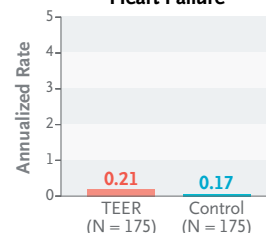
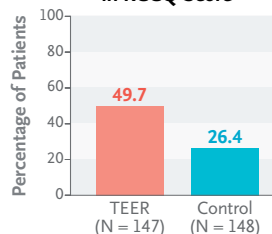
Win ratio, 1.48 (95% CI, 1.06–2.13); $P = 0.02$

	TEER Group (N = 175)	Control Group (N = 175)
Hierarchical composite — no. of wins	11,348	7643

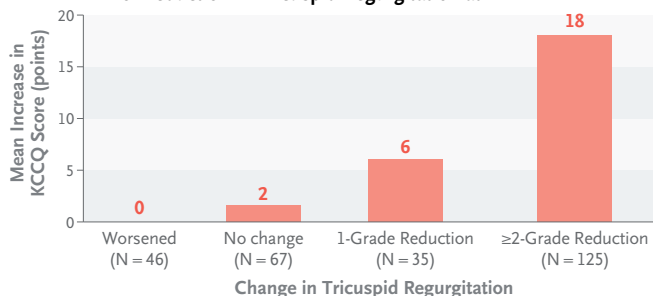
Death from Any Cause or Tricuspid-Valve Surgery



Hospitalization for Heart Failure

 ≥ 15 -Point Improvement in KCCQ Score

Change in Quality of Life According to Magnitude of Reduction in Tricuspid Regurgitation at 1 Yr



CONCLUSIONS

In patients with symptomatic, severe tricuspid regurgitation, TEER was safe and was associated with a greater improvement in quality of life than medical therapy alone.

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EDITORIALS



Transcatheter Therapy for Tricuspid Regurgitation — First Act

Mathias Orban, M.D., and Steffen Massberg, M.D.

Severe tricuspid regurgitation is associated with impaired quality of life and poor survival.¹ The condition is managed medically with diuretic agents; surgery is of limited use, since many patients have a variety of coexisting conditions that increase surgical risk. Current U.S. and European society guidelines recommend tricuspid-valve surgery primarily in conjunction with left heart surgery or in symptomatic patients with severe tricuspid regurgitation and right ventricular dilatation who do not have severe right ventricular dysfunction.^{2,3} Whether the available treatment options improve the prognosis of patients with severe isolated tricuspid regurgitation has not been addressed specifically in randomized trials. As a result, large numbers of patients with severe tricuspid regurgitation are undertreated.⁴

Isolated severe tricuspid regurgitation has become a therapeutic target for percutaneous approaches, especially for high-risk patients in whom tricuspid regurgitation persists despite treatment of the underlying cause (e.g., left heart disease). Tricuspid transcatheter edge-to-edge repair (TEER) has been the most widely investigated intervention for severe isolated tricuspid regurgitation.⁵ Retrospective registry studies and prospective single-group studies have shown that tricuspid TEER reduces tricuspid regurgitation, alleviates symptoms, reduces neurohumoral activation, and induces reverse remodeling of the right heart.⁶ However, a head-to-head comparison with medical management has been limited to retrospective propensity-matched studies.⁷

The Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System Pivotal (TRILUMINATE Pivotal), the results of which are presented by Sorajja and colleagues in this issue of the *Journal*, is a randomized evaluation of the safety and effective-

ness of tricuspid TEER as compared with medical therapy alone.⁸ The results for the primary end point of the trial — a hierarchical composite that included death from any cause or tricuspid valve surgery, hospitalization for heart failure, and an improvement in quality of life as assessed with a structured questionnaire — favored tricuspid TEER over medical therapy alone at 1 year after randomization (win ratio, 1.48; 95% confidence interval, 1.06 to 2.13). This finding was driven by an improvement in quality of life, a major therapeutic goal for patients with severe symptomatic tricuspid regurgitation. Although bias cannot be ruled out because of the open-label design, the finding of improved quality of life is consistent with previous, nonrandomized studies of tricuspid TEER.⁶ The extent of reduction in tricuspid regurgitation was also correlated with improvements in quality-of-life scores in the TEER group. There were important additional findings: TEER was safe in vulnerable patients, and the procedure was effective — 87.0% of the patients in the TEER group had moderate or less tricuspid regurgitation at 30 days, as compared with only 4.8% of the patients in the control group. These results were stable at 1 year.

Contrary to expectations, the trial did not show differences in the incidence of death or hospitalization for heart failure at 1 year. This suggests that tricuspid regurgitation is a phenotypic manifestation of the coexisting conditions in affected patients and that its correction has no effect on prognosis, which is determined by the underlying diseases. Conversely, the results may also indicate that patient selection in the trial did not allow for detection of differences between the groups. Thus, several important aspects must be considered when interpreting the findings of this trial.

First, the enrolled patients were less severely ill than those in previous studies.^{6,9} This observation is supported by the higher percentage of patients in New York Heart Association class II, as well as by the low percentage of patients who had been hospitalized for heart failure in the year preceding randomization. The level of health in this trial population may be explained by the fact that the trial excluded patients who were receiving dialysis or who had severe pulmonary hypertension, which could represent up to 50% of the patients treated with tricuspid TEER in previous registries.⁹ The patients enrolled in TRILUMINATE Pivotal also had a mean left ventricular ejection fraction of 59%. This implies that patients with heart failure with reduced ejection fraction, a major cause of secondary tricuspid regurgitation, were underrepresented in the trial. Therefore, death and hospitalization for heart failure occurred less frequently than had been predicted when the trial was designed. It remains unknown whether a population with a higher-risk profile and associated higher event rates would derive a prognostic benefit from tricuspid TEER as compared with medical therapy alone.

Second, catheter-based treatment of the tricuspid valve is highly demanding because of the complex and variable anatomy as well as the challenges in echocardiographic visualization. Against this background, the percentages of patients with single-leaflet device attachment (7%) or severe or greater residual tricuspid regurgitation at 30 days (13%) in the TEER group are not surprising. Randomized clinical trials of transcatheter tricuspid-valve replacement, a procedure that typically results in complete abolition of tricuspid regurgitation, may clarify whether complete reduction of tricuspid regurgitation translates into an improvement of prognosis.

Third, this trial was conducted during the Covid-19 pandemic, which may have had an effect on the incidence of hospitalization for heart failure; a preference for outpatient care over inpatient care during the pandemic could have affected rehospitalization rates.¹⁰ Fourth, there was a greater reduction in the daily diuretic dose in the TEER group. Thus, it is not known whether a more stringent continuation of diuretics in the TEER group would have resulted in fewer hospitalizations for heart failure during follow-up. Fifth, the follow-up period of 1 year might

have been too short to detect effects of tricuspid TEER on mortality or on hospitalizations for heart failure in this patient population. Other trials of tricuspid TEER are under way (TRICI-HF [ClinicalTrials.gov number, NCT04634266] and TRI-FR [NCT04646811]); with sufficient follow-up, the combined results of these trials may inform us about the potential prognostic effects of tricuspid TEER in general and about the subgroups of patients that derive the greatest benefit from this procedure.

TRILUMINATE Pivotal is an important first step in establishing tricuspid TEER as a new treatment strategy for patients with severe tricuspid regurgitation, but more studies are needed to identify the patient population that will benefit most from this new catheter-based treatment option.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From Medizinische Klinik und Poliklinik I, Klinikum der Universität München, Ludwig Maximilian University of Munich (M.O., S.M.), and DZHK (German Center for Cardiovascular Research), Partner Site Munich Heart Alliance (S.M.) — both in Munich, Germany.

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The NEW ENGLAND JOURNAL of MEDICINE

Early TAVR for Asymptomatic Severe Aortic Stenosis

A PLAIN LANGUAGE SUMMARY

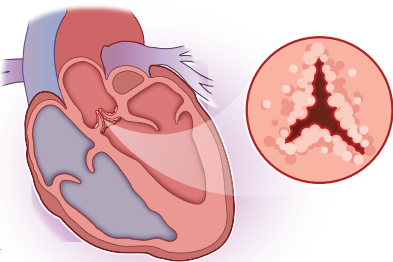
Based on the NEJM publication: Transcatheter Aortic-Valve Replacement for Asymptomatic Severe Aortic Stenosis by P. Généreux et al. (published October 28, 2024)

In this trial, researchers assessed whether early transcatheter aortic-valve replacement (TAVR) would lead to better outcomes than clinical surveillance in patients with asymptomatic severe aortic stenosis.

Aortic stenosis affects more than 3% of adults 65 years of age or older.

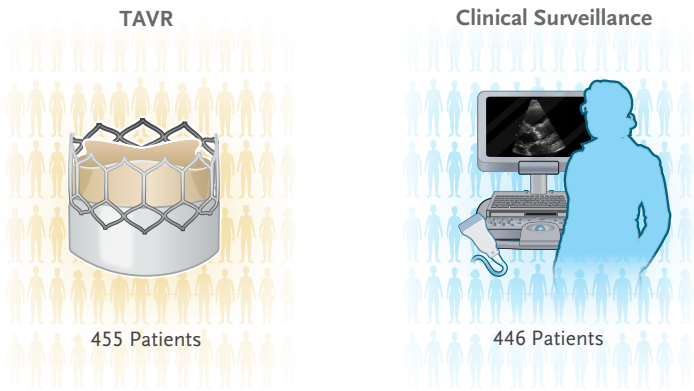
WHY WAS THE TRIAL DONE?

Current guidelines for patients with asymptomatic severe aortic stenosis and preserved left ventricular ejection fraction recommend clinical and echocardiographic follow-up every 6 to 12 months. Some evidence suggests a benefit of early surgical aortic-valve replacement in these patients, but data from randomized trials of TAVR are lacking.

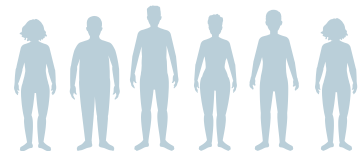


HOW WAS THE TRIAL CONDUCTED?

Adults who had asymptomatic severe aortic stenosis with indications for clinical surveillance were randomly assigned to undergo either early TAVR with transfemoral placement of a balloon-expandable valve or clinical surveillance according to American College of Cardiology and American Heart Association guidelines. The primary end point was a composite of death from any cause, stroke, or unplanned hospitalization for cardiovascular causes.



PATIENTS



WHO 901 adults
65 years of age or older; mean, 76 years
Men: 69%; Women: 31%

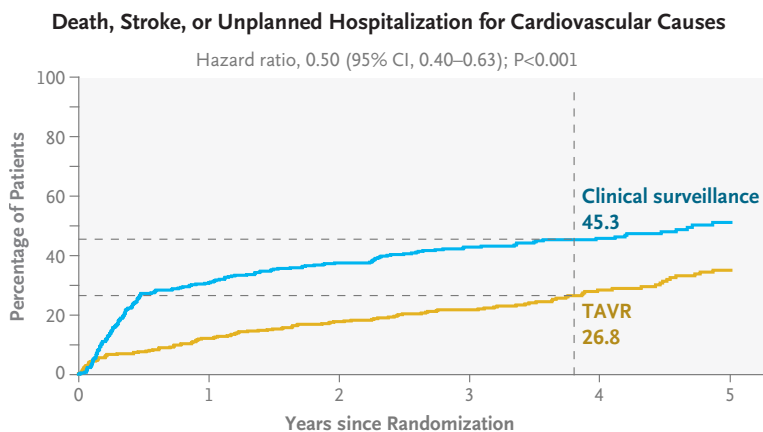
CLINICAL STATUS Asymptomatic severe aortic stenosis
Anatomy suitable for transfemoral TAVR
Society of Thoracic Surgeons Predicted Risk of Mortality score of 10% or lower (scores range from 0 to 100%, with higher scores indicating higher risk) and a left ventricular ejection fraction of 50% or higher

TRIAL DESIGN

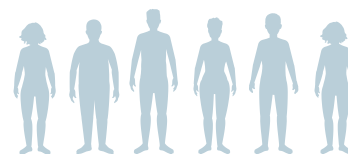
- OPEN-LABEL
- RANDOMIZED
- CONTROLLED
- LOCATION: 75 CENTERS IN THE UNITED STATES AND CANADA

RESULTS

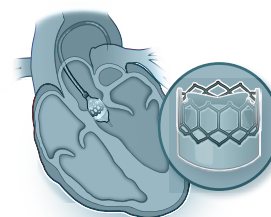
During a median follow-up of 3.8 years, the incidence of death from any cause, stroke, or unplanned hospitalization for cardiovascular causes was significantly lower in the TAVR group than in the clinical surveillance group.



Death from any cause occurred in 8.4% of the patients in the TAVR group and 9.2% of those in the clinical surveillance group, stroke in 4.2% and 6.7%, respectively, and unplanned hospitalization for cardiovascular causes in 20.9% and 41.7%.

VALVE REPLACEMENT IN THE CLINICAL SURVEILLANCE GROUP

87% of patients assigned to clinical surveillance underwent aortic-valve replacement during follow-up; the median time from randomization to valve replacement was 11.1 months.

**LIMITATIONS AND REMAINING QUESTIONS**

- Members of the independent committee that adjudicated end points were aware of the treatment assignments.
- The results apply only to the trial population, which included mainly patients at low surgical risk who were at least 65 years of age and had characteristics suitable for transfemoral TAVR.
- The findings cannot be extrapolated to TAVR performed with valves other than the balloon-expandable valve used in this trial.

CONCLUSIONS

In patients with asymptomatic severe aortic stenosis, early TAVR resulted in a lower risk of death from any cause, stroke, or unplanned hospitalization for cardiovascular causes than guideline-recommended clinical surveillance.

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT03042104

Trial funding: Edwards Lifesciences

Full citation: Généreux P, Schwartz A, Oldemeyer JB, et al. Transcatheter aortic-valve replacement for asymptomatic severe aortic stenosis. *N Engl J Med* 2025;392:217-27. DOI: 10.1056/NEJMoa2405880.

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EDITORIALS



Asymptomatic Severe Aortic-Valve Stenosis — To Wait or Not to Wait

Stefan Blankenberg, M.D.

Aortic-valve stenosis is an increasingly common clinical condition in the aging population. Population studies indicate a prevalence of up to 2.5% even among persons younger than 75 years of age, with a prevalence of up to 8% in those 75 years of age or older, with large geographic differences between low-income and high-income countries.¹⁻³ Severe aortic-valve stenosis is associated with increased mortality, and valve replacement has emerged as the only effective treatment. Consequently, treatment of aortic-valve stenosis has become one of the most common surgical or interventional procedures in the past several years. The severity of aortic-valve stenosis is typically determined by hemodynamic variables, anatomical orifice dimensions, and, most important, clinical symptoms. In particular, when aortic-valve stenosis just crosses the hemodynamic and anatomical threshold for being categorized as severe, patient-reported symptoms provide sensitive evidence of disease prognosis. As in many clinical conditions, determining the optimal timing for intervention remains a challenge. Balancing the competing priorities of careful clinical decision making and societal responsibility is essential.

The EARLY TAVR trial reported by Généreux et al.⁴ in this issue of the *Journal* addresses this critical issue. Among patients without any clinical symptoms related to aortic-valve stenosis but who met anatomical and functional criteria for having a severe form of the disease, the composite end point of death, stroke, or unplanned hospitalization for cardiovascular causes at 1 year occurred in 26.8% of patients who were randomly assigned to undergo transcatheter aortic-valve replacement (TAVR) with a balloon-expandable prosthesis, as

compared with 45.3% of those assigned to conservative management with clinical surveillance. The authors conclude that a strategy of early treatment of asymptomatic severe aortic-valve stenosis was superior to clinical surveillance in reducing the incidence of death, stroke, or unplanned hospitalization for cardiovascular causes.

Do these observations justify a paradigm shift in how we approach decisions about conservative or interventional treatment of asymptomatic severe aortic-valve stenosis? If so, is the choice of transcatheter-based intervention appropriate for younger patients, given their higher life expectancy and the lack of sufficient long-term outcome data beyond 10 years for transcatheter-based strategies?

At the completion of the present trial, 95% of the surveillance group had undergone an intervention after 5 years; nearly 50% of patients had converted to aortic-valve replacement by 1 year and more than 25% even after 6 months. The incidence of conversion was driven by the occurrence of progressive or advanced, acute clinical symptoms. Notably, during the course of the trial, the incidence of death and stroke appeared to be similar in the two groups, and the primary end point was driven by unplanned hospitalizations for cardiovascular causes. Although the authors conclude that “a strategy of early TAVR was superior to clinical surveillance in reducing the incidence of death, stroke, or unplanned hospitalization for cardiovascular causes,” it could also be argued that awaiting clinical symptoms remains justified. The incidence of death and stroke was not substantially higher in the surveillance group than in the TAVR group, and ventricular function

was not adversely affected. In younger patients, additional considerations include the risk of permanent pacemaker implantation and valve deterioration. Although these risks have been reduced with advancing technology, they remain critical factors when weighing conservative against interventional treatment strategies in patients with potentially decades of life expectancy.

Another important consideration is how well the trial population reflects daily clinical practice. Patients with anatomical characteristics that were unsuitable for specific transcatheter valves — such as specific annulus sizes, challenging iliofemoral anatomy, or left ventricular outflow tract calcifications — were excluded. These conditions are not uncommon in clinical settings. Therefore, industry-independent treatment strategy trials such as UK TAVI,⁵ NOTION,^{6,7} or DEDICATE⁸ are essential to capture the broader patient spectrum encountered in daily practice. These trials address heterogeneous patient populations and ensure that their findings are generalizable to real-world scenarios. To support these efforts, access to clinical-trial databases should be made available also for industry-sponsored trials. This complies with institutional-review-board and data-protection rules. By the merging of individual-level patient data, important medical questions can be addressed with sufficient statistical power, and sponsors should be encouraged to facilitate these scientific endeavors as successfully done for other important treatment strategies.⁹

Although the EARLY TAVR trial provides compelling data that may shift the paradigm in managing asymptomatic severe aortic-valve stenosis, further studies are essential to delineate the subgroups of patients who would derive the most benefit from early intervention. This approach

will ensure that the promise of TAVR is realized without compromising patient safety or resource allocation.

Expanding early or preemptive interventional treatment to all asymptomatic patients who might formally meet hemodynamic and anatomical criteria may be premature. For now, awaiting symptoms remains a justifiable strategy.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Department of Cardiology and the Center for Population Health Innovation, University Heart and Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, and German Center for Cardiovascular Research (DZHK) Partner Site Hamburg-Kiel-Lübeck — both in Hamburg, Germany.

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The NEW ENGLAND JOURNAL of MEDICINE

Transcatheter or Surgical Aortic-Valve Replacement at 7 Years

A Research Summary based on Leon MB et al. | 10.1056/NEJMoa2509766 | Published on October 27, 2025

WHY WAS THE TRIAL DONE?

Among low-risk patients with severe, symptomatic aortic stenosis, transcatheter aortic-valve replacement (TAVR) and surgical aortic-valve replacement showed similar outcomes at 5 years in a randomized trial. Longer-term assessment of clinical outcomes and valve durability are needed.

HOW WAS THE TRIAL CONDUCTED?

Patients with severe, symptomatic aortic stenosis and low surgical risk were randomly assigned to undergo transfemoral TAVR or surgery. The trial had two primary end points, assessed at 7 years: the first was a nonhierarchical composite of death, stroke, or rehospitalization related to the procedure, the valve, or heart failure; the second was a hierarchical composite of death, disabling stroke, nondisabling stroke, and the number of rehospitalization days related to the procedure, the valve, or heart failure, analyzed with the win ratio method.

TRIAL DESIGN

- Prospective
- Randomized
- Open-label
- Location: 71 clinical sites

RESULTS

At 7 years of follow-up, the incidence of death, stroke, or rehospitalization related to the procedure, the valve, or heart failure and the incidence of death, disabling stroke, nondisabling stroke, and the number of rehospitalization days did not differ significantly with TAVR or surgery. The percentage of patients with bioprosthetic valve failure appeared to be similar in the two groups.

LIMITATIONS AND REMAINING QUESTIONS

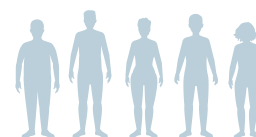
- The trial excluded patients with anatomical or clinical factors that precluded transfemoral access or increased the risk of complications associated with TAVR or surgery.
- A disproportionate percentage of patients in the surgery group withdrew from the trial, which may have biased findings.
- Long-term follow-up assessments in older patients with multiple coexisting conditions are subject to the influences of events that are unrelated to TAVR or surgery.

CONCLUSIONS

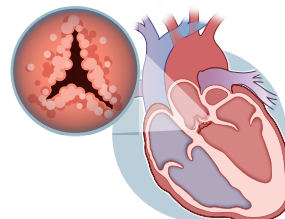
Among low-risk patients with severe, symptomatic aortic stenosis who had undergone either TAVR or surgery, no significant differences with respect to two primary composite end points involving death, stroke, and rehospitalization were observed at 7 years.

Patients

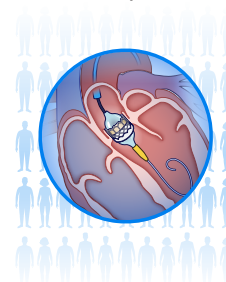
- 1000 adults
- Mean age, 73 years
- Men: 69%; Women: 31%



Aortic stenosis

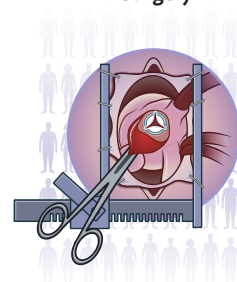


TAVR



N = 496

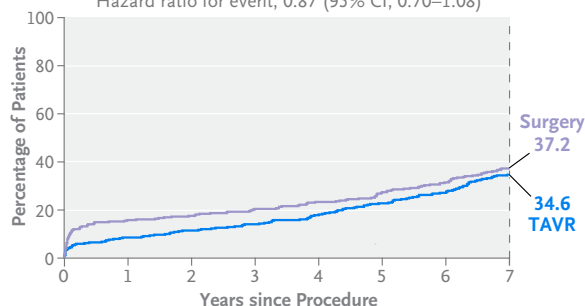
Surgery



N = 454

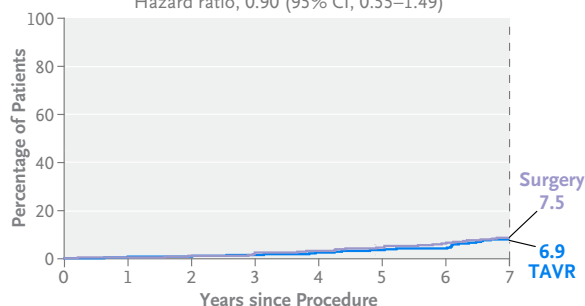
Death, Stroke, or Rehospitalization

Hazard ratio for event, 0.87 (95% CI, 0.70–1.08)



Bioprosthetic Valve Failure

Hazard ratio, 0.90 (95% CI, 0.55–1.49)



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The NEW ENGLAND JOURNAL of MEDICINE

Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis

A Research Summary based on Kang D-H et al. | 10.1056/NEJMoa2511920 | Published on March 26, 2026

WHY WAS THE TRIAL DONE?

Although guidelines have traditionally recommended watchful waiting in the treatment of asymptomatic patients with severe aortic stenosis, trial data have shown a 4-year survival benefit of early surgical aortic-valve replacement. Given the risks associated with the procedure and with prosthetic valves, longer-term data are needed to confirm whether the benefit of early surgery is sustained.

HOW WAS THE TRIAL CONDUCTED?

Asymptomatic patients with very severe aortic stenosis were randomly assigned to undergo early surgery or receive conservative care. (Very severe aortic stenosis was defined as an aortic-valve area of ≤ 0.75 cm² with a peak aortic jet velocity of ≥ 4.5 m per second or a mean transaortic gradient of ≥ 50 mm Hg.) The primary end point was a composite of operative mortality (death during or within 30 days after surgery) or death from cardiovascular causes during 10 years of follow-up.

TRIAL DESIGN

- Randomized
- Location: 4 centers in Seoul, South Korea
- Open-label

RESULTS

Patients undergoing early surgery had a significantly lower incidence of operative mortality or death from cardiovascular causes than those receiving conservative care.

LIMITATIONS AND REMAINING QUESTIONS

- The trial definition of very severe aortic stenosis could influence the risk-benefit ratio for early surgery, because the risks of sudden cardiac death and of myocardial damage due to pressure overload during watchful waiting increase according to the severity of aortic stenosis.
- Owing to the open-label trial design, nonfatal outcomes could have been influenced by ascertainment bias.
- The trial addressed early surgical aortic-valve replacement only; whether transcatheter aortic-valve replacement would have similar long-term results is unclear.

CONCLUSIONS

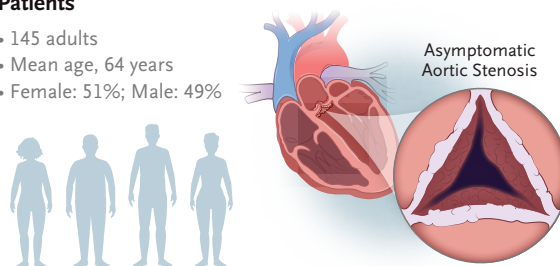
Among patients with asymptomatic very severe aortic stenosis, early surgery led to a lower risk of a composite end point of operative mortality or death from cardiovascular causes than conservative care at 10 years.



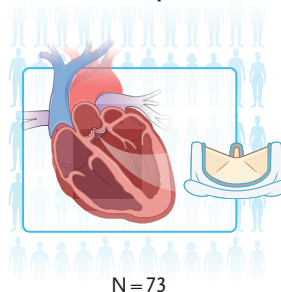
A Quick Take is available at
NEJM.org

Patients

- 145 adults
- Mean age, 64 years
- Female: 51%; Male: 49%

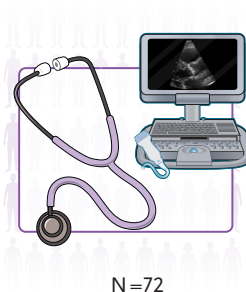


Early Surgical Aortic-Valve Replacement



N = 73

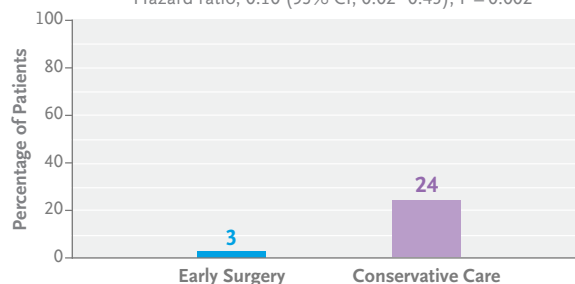
Conservative Care



N = 72

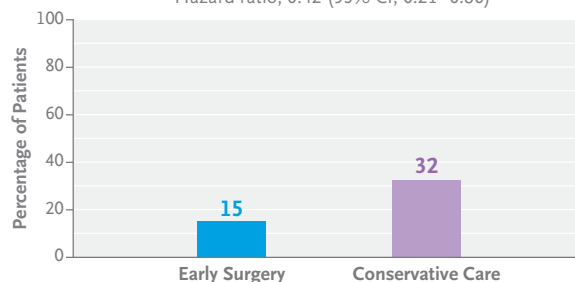
Operative Mortality or Death from Cardiovascular Causes

Hazard ratio, 0.10 (95% CI, 0.02–0.43); P = 0.002



Death from Any Cause

Hazard ratio, 0.42 (95% CI, 0.21–0.86)



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CLINICAL DECISIONS

INTERACTIVE AT NEJM.ORG

Transcatheter or Surgical Aortic-Valve Replacement in Asymptomatic Severe Aortic Stenosis

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options as assigned. Readers can participate in forming community opinion by choosing one of the options.

CASE VIGNETTE

A Woman with Asymptomatic Severe Aortic Stenosis

Christos P. Kotanidis, M.D., D.Phil.¹

A 72-year-old woman is referred to your clinic for evaluation of severe aortic stenosis. Her primary care physician had heard a murmur on physical examination and had ordered a transthoracic echocardiogram. The echocardiogram showed a mean pressure gradient of 42 mm Hg across the aortic valve, an aortic valve area of 0.9 cm², and a left ventricular ejection fraction of 44%. Her medical history is notable for hypertension, which is managed with ramipril at a dose of 2.5 mg once daily. She does not have diabetes mellitus or lung disease. She does not smoke or consume alcohol, and her body-mass index (the weight in kilograms divided by the square of the height in meters) is 28. She is a retired teacher and maintains an active lifestyle, walking 2 to 3 miles three times a week. She reports no chest pain, exertional dyspnea, or fatigue and has no history of syncope.

On physical examination, her heart rate is 75 beats per minute and regular, blood pressure is 120/75 mm Hg, respiratory rate is 16 breaths per minute, and oxygen saturation is 98% while she is breathing ambient air. Heart auscultation reveals a systolic ejection murmur best heard at the right upper sternal border, radiating to the

carotids, a finding consistent with aortic stenosis. Lung auscultation is clear, and there is no peripheral edema. You decide to perform a stress test, and the results are negative for myocardial ischemia. She is considered to be at low surgical risk on the basis of her Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) and the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) scores.

You conclude that the patient should undergo aortic-valve replacement, and you must decide whether to recommend transcatheter aortic-valve replacement (TAVR) or surgical aortic-valve replacement (SAVR).

TREATMENT OPTIONS

Which one of the following approaches would you take for this patient? Base your choice on the literature, your own experience, published guidelines, and other information.

1. Recommend TAVR.
2. Recommend SAVR.

To aid in your decision making, we asked two experts in the field to summarize the evidence in favor of approaches assigned by the editors. Given your knowledge of the patient and the points made by the experts, which approach would you choose?

¹Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom.

OPTION 1

Recommend TAVR

Hélène Eltchaninoff, M.D.¹

To aid in the decision making, the first step is to confirm the severity of aortic stenosis. This

patient presents with a typical pattern of high-gradient aortic stenosis on transthoracic echocardiography. In this case, the aortic stenosis can be assumed to be severe irrespective of the left ventricular ejection fraction and flow conditions. The second step is to assess for the

presence of symptoms. The patient describes walking 2 to 3 miles three times a week and reports no typical symptoms of severe aortic stenosis. In accordance with current guidelines,¹ a stress test was performed, and it confirmed the absence of symptoms.

Although the patient is asymptomatic, characteristics other than symptoms could guide the decision toward aortic-valve replacement and are well described in current guidelines.¹ Specifically, a left ventricular ejection fraction of less than 50% (class I B indication) or a left ventricular ejection fraction of less than 55% (class IIa B indication) — without another cause of left ventricular dysfunction — favors early aortic-valve replacement. The patient in the vignette has a left ventricular ejection fraction of 44%, and even though we cannot confirm at this stage the absence of another cause of left ventricular dysfunction, such as ischemic cardiomyopathy, the abnormal left ventricular function is clearly an indication to intervene.

Recently, the results of the multicenter, randomized EARLY TAVR trial were published; this trial compared TAVR with clinical surveillance in asymptomatic patients with severe aortic stenosis and a negative stress test but did not compare TAVR with surgery in that population.² Once the decision for intervention is made, the choice between transcatheter and surgical intervention must be decided by the heart team, primarily with consideration of the operative risk. At 72 years of age and with low STS and EuroSCORE II scores, this patient is considered to be at low surgical risk. Two large randomized trials in a low-risk population — the Placement of Aortic Transcatheter Valves (PARTNER) 3³ and Evolut Surgical Replacement and Transcatheter Aortic Valve Implantation in Low Risk Patients (Evolut Low Risk) trials⁴ — showed noninferiority of TAVR to surgery in patients with severe symptomatic aortic stenosis. However, women were underrepresented (<40% of the population) in these trials, which highlighted the need for a dedicated randomized trial in women. The randomized Research in Women All Comers with Aortic Stenosis (RHEIA) trial addressed this gap and showed the noninferiority and superiority of TAVR with a balloon-expandable device over surgery in symptomatic women (mean age, 72 years) with respect to the composite end point of

death, stroke, or valve-related, procedure-related, or heart-failure-related rehospitalization at 1 year; the between-group difference was driven primarily by a reduction in rehospitalization with TAVR.⁵ In addition, an important piece of missing information from the vignette is the patient's wishes, since shared decision making is a cornerstone of informed treatment choice, as indicated in recent guidelines.¹

Given this patient's clinical presentation, TAVR may represent the most suitable option. It is a less-invasive procedure associated with faster recovery and shorter hospital stay, allowing for a quicker return to daily activities — factors that are particularly relevant for an active woman of this age. Unless the patient has contraindications to transfemoral TAVR, has anatomical features that increase the risk associated with the TAVR procedure (e.g., low coronary-artery take-off [a short distance between the aortic annulus and the coronary artery ostia] or shallow sinuses of Valsalva), or has other conditions that necessitate a combined surgical procedure (e.g., an aortic aneurysm, severely calcified bicuspid valve, or complex coronary artery disease), this patient should be referred for TAVR.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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OPTION 2

Recommend SAVR

Elaine E. Tseng, M.D.,^{1,2} and
Vinod H. Thourani, M.D.³

The 72-year-old woman in the vignette has severe aortic stenosis, a condition for which symptoms typically drive the decision for treatment. Although she is asymptomatic, her depressed ejection fraction is a class I indication for aortic-valve replacement. Because she is at low surgical risk, her aortic-valve replacement can be surgical (SAVR) or transcatheter (TAVR). Decision making regarding SAVR or TAVR in low-risk patients depends heavily on age and anatomy; society guidelines differ in their recommendations.^{1,6} In the United States, for patients between 65 and 80 years of age, transfemoral TAVR is considered a valid alternative to SAVR after shared decision

making that balances expected longevity and valve durability.⁶ In Europe, for patients 70 years of age or older with tricuspid aortic stenosis and suitable anatomy, TAVR is the recommendation in updated guidelines, whereas in all remaining candidates for bioprostheses, SAVR or TAVR is recommended according to heart team assessment.¹ The reason for this lack of consensus is the absence of data on outcomes of TAVR beyond 10 years in low-risk and younger populations.

Two pivotal randomized, controlled clinical trials comparing TAVR and SAVR have included low-risk patients with symptomatic aortic stenosis and a mean age similar to the age of the patient described here.^{7,8} At the 7-year follow-up, the PARTNER 3 trial showed that the incidence of death from any cause, stroke, or rehospitalization (the composite primary end point) was similar with TAVR and SAVR, with elimination of the benefit of TAVR over SAVR that had been observed at the 1-year follow-up. The incidence of death from any cause after 3 years was consistently greater in the group that had undergone TAVR than in the group that had undergone SAVR, but further follow-up is required to determine whether this difference becomes statistically significant. Similarly, the incidence of death or disabling stroke by 7 years was greater with TAVR than with SAVR (hazard ratio, 1.31; 95% confidence interval [CI], 0.96 to 1.78). Increased rates of stroke and death after 2 to 3 years may be due to TAVR leaflet crimping before implantation or to a lack of washout jets in the aortic root, leading to thrombus. Although valve durability appeared to be similar in the two groups at 7 years, the incidence of clinically significant valve thrombosis was greater in the TAVR group than in the SAVR group (hazard ratio, 5.70; 95% CI, 1.29 to 25.25).⁷ In the Evolut Low Risk trial, the incidence of death or disabling stroke (the composite primary end point) at 5 years did not differ between the TAVR and SAVR groups.⁸ It is important to note that neither trial truly compared isolated SAVR with TAVR, because approximately one fifth of patients in the SAVR group in each trial underwent concomitant procedures, which increases the short-term risk of death.⁹

The benefits of surgery are long-term. In the United States, the 72-year-old woman described

in the vignette would be expected to live an additional 15 years.⁶ Among patients with the same STS-PROM score as this woman, the expected 8-year survival after isolated SAVR is 85 to 91%.⁹ Thus, lifetime management is warranted. The durability of TAVR at 10 years is currently unknown. Engineering simulations predict TAVR durability of only 8 years, whereas SAVR durability in patients 70 years of age or older has been shown to be outstanding, with freedom from structural valve degeneration or reoperation of at least 98% at 15 to 20 years.^{10,11} TAVR durability predictions come from engineering simulations similar to those performed for bridges or airplanes that undergo fatigue analysis by computational modeling to predict failure.

Key technical considerations include feasibility of transfemoral vascular access, sizing of the aortic annulus and aortic root, bicuspid versus tricuspid aortic stenosis, coronary ostial heights, and calcification — nuances that underscore the importance of the heart team in considering a SAVR-first as compared with a TAVR-first approach. Finally, avoidance of patient-prosthesis mismatch is essential for lifetime care of the woman in the vignette, who has a body-mass index of 28, because patient-prosthesis mismatch leads to decreased survival after surgery. A small annulus may be suitable for TAVR now but not necessarily for a later TAVR-in-TAVR procedure (a procedure in which a new TAVR valve is placed inside a failing first TAVR valve). Mortality associated with surgical TAVR explantation is 12 to 15%.⁹ For the 72-year-old patient described here, minimally invasive SAVR with annular enlargement if needed would provide a durable long-lasting solution and would preserve, if necessary, the option for TAVR-in-SAVR implantation in the future when she is older and unlikely to be a candidate for surgery.

In summary, this woman has the potential to live many more years. Although midterm outcomes of TAVR and SAVR are similar, SAVR offers outstanding long-term durability and survival, whereas long-term outcomes with TAVR are unknown. A heart team evaluation of a TAVR-first as compared with a SAVR-first approach is essential for lifetime management and shared decision making with the patient.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 25-2025: A 93-Year-Old Woman with Dyspnea and Fatigue

Suzanne V. Arnold, M.D., M.H.A.,^{1,2} Leigh H. Simmons, M.D.,^{3,4}Andrea C. Furlani, M.D.,^{5,6} and Nathanael Tran, M.D.^{3,4}

PRESENTATION OF CASE

Dr. Leigh H. Simmons: A 93-year-old woman was evaluated by her primary care physician because of dyspnea.

The patient had been in her usual state of health, which included being independent with respect to activities of daily living and participating in light exercise daily, until 1 month before the current presentation, when dyspnea developed.

Seven years before the current presentation, echocardiography was performed to assess a systolic murmur that radiated to the carotid arteries, and aortic stenosis was diagnosed. Five years before the current presentation, osteoarthritis that had been refractory to treatment resulted in total knee replacement; while the patient was hospitalized, arrhythmia was detected on telemetry and atrial fibrillation was diagnosed. During that hospitalization, repeat echocardiography was performed.

Dr. Nathanael Tran: Transthoracic echocardiography showed stable aortic stenosis, with a mean aortic-valve gradient of 18 mm Hg (<20 is mild), a peak aortic velocity of 2.8 m per second (<3.0 is mild), and an aortic-valve area of 1.5 cm² (>1.5 is mild) (Fig. 1 and Video 1).

Dr. Simmons: Anticoagulant therapy was not started at that time. However, 15 months before the current presentation, atrial flutter developed and treatment with apixaban and metoprolol was started. Echocardiography was performed.

Dr. Tran: Transthoracic echocardiography showed progression of aortic stenosis, with a mean gradient of 23 mm Hg, a peak velocity of 3.0 m per second, and an aortic-valve area of 0.9 cm².

Dr. Simmons: At the current presentation, the patient reported that the onset of dyspnea had been gradual and had progressed steadily during the past month. She stated that she had previously maintained a regular schedule of physical activity that had included dancing and daily walks but that the shortness of breath now prevented her from participating in these activities. She had no chest pain, palpitations, weight gain, leg swelling, or orthopnea, and she did not awaken at night with shortness of breath. She reported no melena or blood in the stool.

Author affiliations are listed at the end of the article.

N Engl J Med 2025;393:1017-24.

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Videos showing transthoracic echocardiography are available at NEJM.org



Figure 1. Transthoracic Echocardiogram Obtained 5 Years before the Current Presentation.

A parasternal short-axis view of the aortic valve shows mild aortic stenosis. The mean aortic-valve gradient is 18 mm Hg (<20 is mild), the peak aortic velocity is 2.8 m per second (<3.0 is mild), and the aortic-valve area is 1.5 cm² (>1.5 is mild).

Additional medical history included stage 3a chronic kidney disease, type 2 diabetes mellitus, sensorineural hearing loss in both ears (for which she used hearing aids), Hashimoto's thyroiditis, vitamin B₁₂ deficiency, obstructive sleep apnea, and depression. Granulomatosis with polyangiitis was diagnosed 17 years before the current presentation and had been treated with cyclophosphamide, followed by azathioprine and low-dose prednisone, which had led to remission; treatment with azathioprine was stopped 9 years before the current presentation, and low-dose prednisone therapy was continued. The most recent screening colonoscopy was performed when the patient was 78 years of age (15 years before the current presentation), and no polyps were seen. Other surgical history included hysterectomy and total replacement of one knee at 85 years of age and the other at 88 years of age.

Other medications included aspirin, calcium carbonate, vitamin D, vitamin B₁₂, citalopram, glipizide, and levothyroxine. The patient had no known adverse reactions to medications. Approximately 2.5 years before the current presentation, she had moved to an assisted-living facility after the death of her husband. She was a lifelong non-smoker and did not drink alcohol or use illicit drugs.

On examination, the temporal temperature was 36.2°C, the blood pressure 123/62 mm Hg,

the pulse 61 beats per minute, the respiratory rate 12 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 23.2. She appeared mildly fatigued but was in good spirits. The jugular venous pressure was estimated at 5 cm of water. The heart rhythm was regular, with normal heart sounds, and S2 was normal. A grade 4/6 systolic murmur that did not obscure the second heart sound was noted. The lungs were clear on auscultation. The skin was not pale. She had no leg edema. An electrocardiogram (ECG) showed sinus rhythm. Imaging studies were obtained.

Dr. Andrea C. Furlani: Chest radiography (Fig. 2) showed a normal cardiomeastinal silhouette and no pulmonary edema, along with pleuroparenchymal scarring in the lung apices with upper-lung volume loss — a finding that was unchanged from that seen on computed tomography (CT) that had been performed in the remote past. In addition, the radiograph showed coronary and aortic-valve calcifications.

Dr. Simmons: Diagnostic tests were performed, and management decisions were made.

DIFFERENTIAL DIAGNOSIS

Dr. Suzanne V. Arnold: I am aware of the final diagnosis in this case. This 93-year-old woman with moderate aortic stenosis and paroxysmal atrial fibrillation and flutter presented with dyspnea that had progressed over the course of 1 month. Slowly progressive dyspnea is a common presenting symptom that may be caused by cardiac or noncardiac processes.

CARDIAC CAUSES OF DYSPNEA

Progressive stable angina manifesting as exertional dyspnea is a possible diagnosis in this patient's case, and nonspecific symptoms of coronary ischemia are common in older women. Atrial arrhythmias can cause progressive dyspnea but would generally need to be persistent to account for this patient's symptoms. It is important to note that atrial flutter with adequate heart-rate control — or even atrial fibrillation — can be missed on physical examination, particularly when heart rates are slow and irregularity is more difficult to ascertain. However, this patient's ECG showed sinus rhythm.

Sick sinus syndrome with chronotropic incompetence leading to an abnormally slow heart rate should be considered in this older woman.¹ Frequent premature ventricular contractions (>15%

of total heartbeats), even in the context of a normal ejection fraction, can also cause exertional intolerance but would be unlikely in this patient who had no evidence of ectopy on examination or ECG. In patients in whom chronotropic incompetence or frequent premature ventricular contractions are suspected, short-term continuous rhythm monitoring can be useful.

Heart failure and valvular disease can also cause subacute dyspnea. The absence of signs of hypervolemia on examination of this patient makes heart failure an unlikely diagnosis, although a low-flow state can cause dyspnea in the absence of overt hypervolemia. In older patients, age-related hypertrophic obstructive cardiomyopathy, infiltrative cardiomyopathy, mitral stenosis due to mitral annular calcification, degenerative mitral regurgitation, tricuspid regurgitation, and aortic stenosis are all relatively common causes of subacute dyspnea. Atrial dilatation and resultant functional mitral or tricuspid regurgitation should be considered in this patient with atrial arrhythmias. It is important to note that, in this patient, the presence of a murmur associated with severe tricuspid regurgitation could easily be obscured by the murmur associated with her aortic stenosis. Progression of aortic stenosis is a probable diagnosis in this patient. However, preservation of the second heart sound on cardiac auscultation makes progression to severe aortic stenosis unlikely.

NONCARDIAC CAUSES OF DYSPNEA

Interstitial lung disease, pleural effusion, or hiatal hernia can cause dyspnea. The normal chest radiograph in this patient makes these pulmonary causes of dyspnea unlikely. In patients with chronic kidney disease, such as this patient, acute kidney injury can cause dyspnea, either through hypervolemia or metabolic acidosis. Anemia, neuromuscular disorders, and hyperthyroidism can lead to exercise intolerance that is often described by patients as dyspnea. Furthermore, these systemic symptoms of stress can lead other cardiac conditions to become symptomatic. For example, chronic coronary disease, cardiomyopathy, or valvular disease may not be symptomatic unless a patient has increased systemic stress from another condition such as sepsis or anemia.

At this point in the patient's clinical course, progression of aortic stenosis would be my lead-

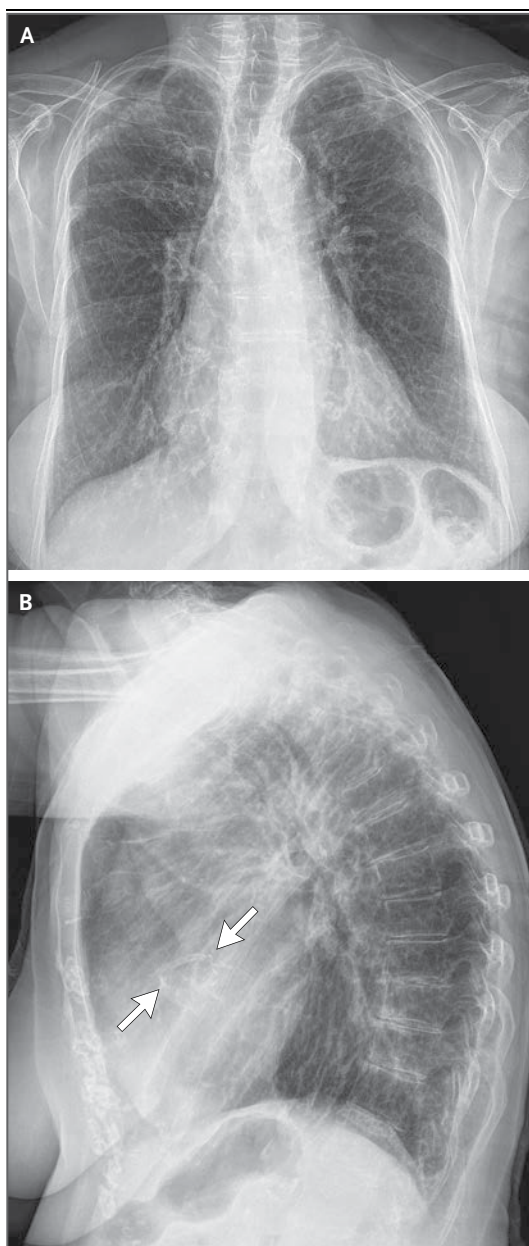


Figure 2. Chest Radiographs.

A frontal radiograph of the chest (Panel A) shows a normal cardiac silhouette without pulmonary edema. Stable pleuroparenchymal scarring is present in the lung apices. Coronary and aortic-valve calcifications are seen on a lateral radiograph (Panel B, arrows).

ing diagnosis. If basic laboratory testing ruled out noncardiac causes of dyspnea, I would obtain an echocardiogram to evaluate the degree of aortic stenosis.

DR. SUZANNE V. ARNOLD'S
DIAGNOSIS

Aortic stenosis.

DIAGNOSTIC TESTING

Dr. Simmons: A complete blood count was performed, and the level of hemoglobin was 7.7 g per deciliter (reference range, 12.0 to 16.0), which had decreased from a level of 10.6 g per deciliter obtained 2 months earlier. The remainder of the complete blood count was normal. The blood levels of iron and ferritin were normal, and the reticulocyte count was 1.1% (reference range, 0.5 to 2.0); the corrected reticulocyte count was 0.8% (reference range, 0.5 to 2.0), and the reticulocyte production index was 0.4 (reference value, >3.0). When the patient was asked again about stool color, she reported that her stools had occasionally been dark. Treatment with apixaban and aspirin was stopped. One unit of packed red cells was transfused. After transfusion, the blood level of hemoglobin increased to 9.0 g per deciliter and dyspnea resolved.

A diagnosis of slow gastrointestinal bleeding due to Heyde's syndrome (the triad of aortic stenosis, gastrointestinal bleeding, and acquired von Willebrand's disease) was considered. Further evaluation by means of esophagogastroduodenoscopy and colonoscopy was discussed, but the patient's preference was to avoid these procedures unless absolutely necessary. Treatment with apixaban was resumed, but aspirin was not restarted. Echocardiography was repeated.

Dr. Tran: Transthoracic echocardiography revealed moderate-to-severe aortic stenosis; the mean gradient had increased to 32 mm Hg, the peak velocity was 3.6 m per second, and the aortic-valve area was 0.6 cm².

Dr. Simmons: The blood level of hemoglobin remained stable on monthly checks, and dyspnea did not recur.

Dr. Tran: Nine months later, transthoracic echocardiography revealed severe aortic stenosis; the mean gradient had further increased to 39 mm Hg, the peak velocity was 4.1 m per second, and

the aortic-valve area was 0.5 cm² (Fig. 3 and Video 2).

Dr. Simmons: The patient was referred to the cardiology clinic affiliated with this hospital, and management decisions were made.

DISCUSSION OF MANAGEMENT

Dr. Arnold: Shared decision making with regard to the management of aortic stenosis in this patient begins with an understanding of multiple factors. These include the expected progression of aortic stenosis over time, the challenges in defining the severity of aortic stenosis, the way in which transcatheter aortic-valve replacement (TAVR) has increased the available options for intervention, and this particular patient's preferences, values, and goals of care.

PROGRESSION OF AORTIC STENOSIS

Most cardiac conditions involve varying patterns of progression over time. For example, a patient with dilated cardiomyopathy may have stable disease for many years without a decline in ejection fraction. In these patients, the severity of mitral regurgitation may remain moderate or even severe without the need for intervention.² In contrast, aortic stenosis will reliably progress from moderate to severe and then further progress to symptomatic disease. On average, in patients with aortic stenosis, the mean gradient increases by 4.1 mm Hg per year (with greater increases seen as aortic stenosis progresses), and the aortic-

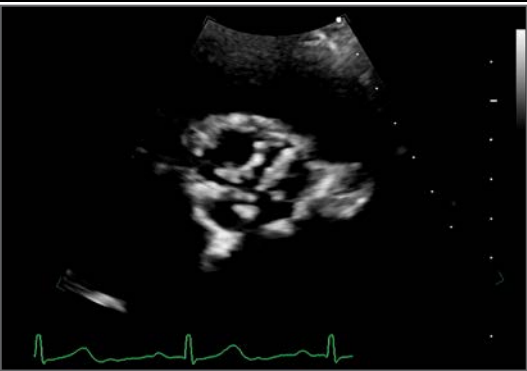


Figure 3. Transthoracic Echocardiogram Obtained 9 Months after the Current Presentation.

A parasternal short-axis view of the aortic valve shows severe aortic stenosis. The mean gradient has increased to 39 mm Hg, the peak velocity is 4.1 m per second, and the aortic-valve area is 0.5 cm².

valve area decreases by 0.08 cm² per year.³ Historical data suggest that it takes 2 to 5 years for aortic stenosis to progress from asymptomatic severe disease to symptomatic severe disease,⁴ but more recent data suggest that the true time to progression may be shorter. The results of a recent trial involving patients with asymptomatic severe aortic stenosis who had been randomly assigned to undergo either clinical surveillance or early intervention with TAVR showed that the median time from randomization to conversion to the intervention was only 11.1 months among patients in the surveillance group.⁵ Within 2 years after randomization, approximately 70% of these patients had progressively worsening symptoms and underwent TAVR.⁵

The predictable and fairly rapid progression from asymptomatic severe aortic stenosis to symptomatic severe aortic stenosis may support a strategy of treating patients earlier in the disease process. Severe aortic stenosis may cause upstream cardiac damage (e.g., ventricular fibrosis, atrial enlargement, pulmonary hypertension, or right ventricular dysfunction), and earlier intervention before the secondary effects of aortic stenosis occur may contribute to improved clinical and health-status outcomes after TAVR.^{6,7} However, a strategy of careful surveillance in asymptomatic patients is still reasonable given the current evidence.

CHALLENGES IN DIAGNOSING SEVERE AORTIC STENOSIS

Aortic stenosis is defined as severe when the peak velocity is 4 m per second or greater, the mean gradient is 40 mm Hg or greater, or the aortic-valve area is 1.0 cm² or less (or ≤ 0.6 cm² per square meter of body-surface area). However, it is common for a patient to meet some but not all the criteria for a severity classification, and additional data such as the dimensionless velocity index, the stroke volume index, and the detection of aortic-valve calcification on CT must be considered. The occurrence of errors in the measurement of certain variables is also possible and is especially common when the left ventricular outflow-tract area is measured. Paradoxical low-flow, low-gradient severe aortic stenosis is another consideration when evaluating for severe aortic stenosis, particularly in older women with small left ventricular cavities or restrictive ventricular filling. This condition results in a low

stroke volume despite a normal ejection fraction, which can affect the capacity to generate high gradients across a stenotic aortic valve.

In this patient, the aortic-valve area met the criterion of 1.0 cm² or less on an echocardiogram that had been obtained 15 months before the current presentation, although the mean gradient and peak velocity were in the moderate range. Nonetheless, given that the aortic stenosis was asymptomatic during this time, a plan of careful surveillance was appropriate. However, it is important to recognize that categorizing the severity of aortic stenosis may be challenging in patients with inconsistent measurements. In older patients with vague symptoms, careful consideration of supporting data and evaluation for measurement errors is needed to avoid the possibility of missing hemodynamically and prognostically important severe aortic stenosis.

CHANGES IN OPTIONS FOR INTERVENTION

Since the introduction of TAVR, the total annual number of aortic-valve interventions performed in the United States has doubled, with a decrease in the annual surgical volume of approximately 45%, indicating that the use of TAVR has led to a substantial increase in the number of patients undergoing intervention.^{8,9} Among patients older than 80 years of age, the annual number of surgical aortic-valve replacements has decreased by 96% from 2012 to 2022⁹ because these patients are almost exclusively choosing between TAVR and medical management. Although the long-term outcomes in older patients are similar with TAVR and surgical aortic-valve replacement, the difference in short-term recovery between these approaches has markedly changed the discussion as to whether an older person wants to undergo surgical intervention or receive medical management.

When TAVR was first approved in the United States in 2011, the median length of stay in the hospital after the procedure was 7 days and 50% of patients had a poor outcome at 1 year (30% had died and 20% had a persistently poor quality of life).¹⁰ Since the introduction of TAVR, there has been marked improvement, with the median length of stay after TAVR having decreased to 1 day, although variability is seen with older age, coexisting conditions, the vascular access site, the urgency of the procedure, and complications affecting the length of hospital stay.⁸

Short-term mortality and major complications are also relatively low with TAVR (30-day mortality, <4%; incidence of stroke, <2%; incidence of major bleeding, <3%), and most patients have clinically significant improvement in health status within a month after the procedure.⁸ Given the relatively short recovery time, combined with the low risk of major complications, few patients are considered to be inappropriate candidates for TAVR on the basis of age or coexisting conditions. As such, it is becoming less common for patients to choose medical management in the context of symptomatic severe aortic stenosis. However, it is still important to engage with the patient in shared decision making regarding all alternative treatment methods, including palliative care.

APPROACH TO MANAGEMENT

In patients with symptomatic severe aortic stenosis, aortic-valve replacement is a class I indication to prolong survival and improve health status, with TAVR being the preferred treatment for patients older than 80 years of age (on the basis of U.S. guidelines⁴) or older than 75 years of age (on the basis of European guidelines¹¹). This patient was symptomatic when hemodynamic stress from anemia was present, but she had minimal symptoms after red-cell transfusion. Given her history of symptoms during a time of increased hemodynamic stress, proceeding with TAVR was a possible option. Another option was to wait until symptoms recurred in the absence of additional stressors and then proceed to TAVR. A third option was to wait until symptoms developed and then pursue medical management with palliative care and eventually hospice. Although TAVR has greatly expanded the pool of patients who are willing and able to undergo intervention, many patients instead still elect to manage symptoms when they develop.

SHARED DECISION MAKING

When engaging in shared decision making with a patient with respect to the decision to pursue TAVR as opposed to medical management, it is important to ascertain the patient’s goals of care, values, and preferences. Although TAVR will often prolong survival, this outcome may not be the patient’s primary goal of treatment, given that many patients prioritize improvement in quality

of life and reduction of symptoms over prolonged survival.

It is also important to ensure that the patient understands the expected progression of disease and what the anticipated trajectory would be with each treatment option, including requirements for additional diagnostic procedures and follow-up appointments, potential complications, and expected recovery time. Although TAVR can be a very effective tool to improve quality of life for a patient with symptoms due to aortic stenosis, it involves both diagnostic and therapeutic procedures that take time and are associated with risks.

Ultimately, we must actively listen to patients, work to understand their values and goals, help them understand the trade-offs and potential consequences of their choices, and then support these decisions as best we can. Patients should not feel abandoned if they choose medical management over invasive interventions. Access to effective palliative care services is critical, since progression of symptoms is expected but can be anticipated and well managed.

FOLLOW-UP

Dr. Simmons: I referred the patient to a cardiologist, and I counseled her that she would be discussing management options for aortic stenosis. I assumed that she would be offered TAVR and expected that she would choose to proceed with that option. The patient met with the cardiologist three times over the course of a year and carefully discussed her options. The patient ultimately decided that she did not wish to undergo the extensive testing that would be required to be considered for aortic-valve replacement. She indicated that when she becomes more symptomatic with aortic stenosis, she would like to enroll in hospice care and cited her husband’s positive experience with hospice as one of the reasons she was choosing this path. She has chosen to have no further monitoring of her aortic stenosis.

Approximately 1.5 years after the current presentation, the patient continues to feel well and engages in her usual activities, including dancing, without dyspnea or substantial fatigue. She continues to receive apixaban therapy for stroke prevention. The complete blood count has been

checked every 2 to 3 months, and anemia has not recurred.

PATIENT PERSPECTIVE

The Patient: When I had started feeling short of breath, I didn’t expect that it would lead to the discovery of a serious heart-valve problem. I’ve had atrial fibrillation and a heart murmur for years, but it was still surprising to learn that I had severe aortic stenosis.

At 93 years of age, as I deliberated the option of valve replacement, which would have had risks, I saw the choice as being between treatment and an end-of-life decision. Without valve replacement, my projected life span would be 2 years. The risks of the procedure — like stroke or other complications — just didn’t feel worth it to me. I decided to forgo treatment based on my understanding of human life as impermanent, my advanced age, and gratitude for the fullness of life — a loving family; close friends; community; opportunities in education, social justice, and advocacy work; housing in a continuing-life-care community; and excellent health care. Additional factors that entered into my decision making were being a child of immigrant parents and helping them navigate medical systems; the strength, fearlessness, and practical sense of my mother; my studies in Eastern religions; my teaching and practice of Hatha yoga for nearly 30 years; my loving church community; and the influence of Erik Erikson’s human developmental theory of eight life stages, including the last one in which creativity, generativity, legacy-building, and social connection are called for.

My cardiologist recommended valve replacement and spoke about it favorably, but she always made sure to remind me that it was my choice. I felt respected and supported throughout. I’m still doing yoga, taking walks, and going to dance class. I don’t feel out of breath anymore, and I’m grateful for that. Looking back, I have no regrets. This decision reflects my values, and I’m thankful for the care I’ve received and for the freedom to make the choice that felt right for me.

On a practical level, I suggest that attention be paid to a patient’s ability to hear. At times during my medical visits, I struggled to hear what doctors were saying and didn’t fully under-

stand my diagnosis until my son joined me for a visit about my heart condition and could hear the conversation better. To ensure a patient’s understanding, I suggest that the physician provide a written summary of the diagnosis and recommendations at the end of the visit. Lastly, another very practical consideration is for the physician to speak slowly and deliberately.

FINAL DIAGNOSIS

Aortic stenosis.

CASE RECORDS EDITORS’ NOTE — LESSONS LEARNED

Dr. Simmons: In reflecting on this patient’s care, I think about the importance of allowing the proper time for deliberation when decisions are not clinically urgent, as well as the importance of clinicians being open to hearing patients’ perspectives on what treatments are right for them. I was certain that this patient would want to proceed with TAVR; after all, she had chosen total knee replacement twice, at the ages of 85 and 88 years. She had been very satisfied with her decisions to have surgery. However, our duty as her physicians went beyond diagnosing the aortic stenosis. In order to make the best recommendation for management, we first had to ascertain the patient’s preference. When she told me she did not want to proceed with TAVR, I had to adjust my own expectations about a successful management outcome for her aortic-valve disease. I came to understand her perspective on the burden and the risk of the preparatory testing and procedures that would be required before undergoing TAVR.

The work of coming together with our patients on a shared decision requires training, time, and tools to support both clinicians and patients.¹² I hope this patient’s story will serve to promote shared decision making that is individualized for patients across the spectrum of clinical care.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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