

Incidental Moderate Mitral Regurgitation in Patients Undergoing Aortic Valve Replacement for Aortic Stenosis: Review of Guidelines and Current Evidence

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Recent evidence has shown that moderate mitral regurgitation is common and clinically relevant in patients presenting for surgical and transcatheter aortic valve replacement for aortic stenosis. Prospective multicenter clinical trials are now indicated to resolve the clinical equipoise about whether or not mitral valve intervention also is indicated at the time of aortic valve intervention. Advances in three-dimensional transesophageal echocardiography, transcatheter mitral interventions, and surgical aortic valve replacement, including the advent of sutureless valves, likely will expand the therapeutic possibilities for moderate mitral regurgitation in the

setting of aortic valve interventions for severe aortic stenosis.

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IN CONTEMPORARY CARDIOVASCULAR PRACTICE, aortic valve replacement (AVR) for calcific aortic stenosis (AS) in adults is common.¹⁻³ Multiple studies in the past 20 years have reported the significant prevalence of mitral regurgitation (MR) in patients with AS scheduled for AVR.³⁻¹⁰ This prevalence of incidental MR in severe AS has varied from approximately 10% to 70% depending on the selected study inclusion criteria, including the chosen echocardiographic definitions for MR.³⁻¹⁰ Furthermore, these studies frequently have addressed the clinically important question for this incidental MR in the setting of AVR: Does it adversely affect clinical outcome?

The perioperative decision as to whether or not to surgically treat the MR concomitantly has depended largely on its severity, patient comorbidity, and technical complexity of the mitral intervention. The reluctance to intervene stems in part from the significantly increased perioperative mortality risk from a second valve intervention at the time of AVR.^{11,12} Current guidelines recommend that mitral intervention is indicated when the MR is severe.¹³ The question of whether moderate MR affects clinical outcome after AVR remains unanswered, despite multiple studies over the past 20 years.³⁻¹⁰ Consequently, a clear recommendation for the management of moderate MR in this setting has not been forthcoming in valvular heart disease guidelines.¹³ The purpose of this expert review is to summarize the recent evidence related to this clinically important question as a guide for perioperative decision-making.

SEVERE AORTIC STENOSIS WITH MODERATE MITRAL REGURGITATION

A recent systematic review (N = 2,113; 13 nonrandomized studies; 1990-2009) documented a 12.7% incidence of moderate MR in adults undergoing AVR for AS.¹⁴ The

echocardiographic criteria for moderate MR included a regurgitant jet area equal to 20% to 40% of the left atrial area, a vena contracta width of 0.30 to 0.69 cm, a regurgitant volume of 30 to 59 mL/beat, a regurgitant fraction of 30% to 49%, and/or a regurgitant orifice area of 0.20 to 0.39 cm².¹⁴ After isolated AVR, there was a trend toward improvement in the moderate MR, although the overall study quality was suboptimal. Significant factors associated with progression of the MR after AVR included left ventricular dysfunction, structural mitral valve abnormalities, left atrial enlargement, and atrial fibrillation.¹⁴ There was no clear outcome effect of moderate MR on mortality after AVR in this setting. The investigators concluded that the pooled current evidence was insufficient to support a clinical recommendation for routine surgical correction of moderate MR at the time of AVR.¹⁴ The importance, however, of organic mitral valve disease in this setting must be considered: Rheumatic and myxomatous etiologies for

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moderate MR at the time of AVR for AS are likely to progress significantly over time, and strong consideration should be given to their concomitant correction.^{14,15}

A second larger systematic review and meta-analysis (N = 3,053 patients: 17 studies, 1990-2010) reported that, although moderate MR may improve after AVR for AS, its persistence was associated significantly with higher mortality at 30 days, 3 years, 5 years, and 10 years (p < 0.05 for all groups).¹⁶ Based on this larger analysis, the investigators concluded that surgical intervention was reasonable for moderate MR at the time of AVR for AS.¹⁶

Despite these 2 recent systematic reviews, clinical interest in the fate and best management of moderate MR after AVR remains intense because it is a common perioperative scenario and the cumulative evidence suggests possible outcome improvement from surgical mitral correction. Ongoing studies have been undertaken in an effort to resolve this clinical equipoise. A recent single-center trial (N = 255; mean age 67 ± 11.7 years, 63.5% male; 1999-2009) demonstrated a 36.8% incidence of mitral valve surgery at the time of AVR for AS.¹⁷ In this clinical trial, the perioperative mortality was 0.3%, with mitral repair comprising 96% of mitral procedures. Mitral intervention at the time of AVR significantly improved the severity of MR (82.3% v 67.4%; p = 0.011).¹⁷ Independent predictors for late mortality included persistent MR (hazard ratio (HR) 4.90; 95% confidence interval (CI) 1.92-12.60; p = 0.001), chronic renal failure (HR 3.01; 95% CI 1.22-7.40; p = 0.0016), persistent atrial fibrillation (HR 2.74; 95% CI 1.24-6.06; p = 0.013), previous stroke (HR 3.25; 95% CI 1.04-10.10; p = 0.041), and coronary artery disease (HR 2.97; 95% CI 1.32-6.70; p = 0.009). Independent predictors for persistent MR at hospital discharge included no mitral surgery (odds ratio (OR) 2.81; 95% CI 1.16-20.30; p = 0.009), prolonged inotropic support (OR 1.34; 95% CI 0.20-2.83; p = 0.012), and aortic root enlargement (OR 1.53; 95% CI 0.13-3.11; p = 0.006). Independent predictors for MR at medium-term to long-term follow-up included degree of MR at discharge (OR 1.92; 95% CI 1.19-3.09; p = 0.007) and atrial fibrillation (OR 2.65; 95% CI 1.02-6.88; p = 0.044).¹⁷ The investigators concluded that, although persistent moderate MR after AVR significantly decreased long-term survival, mitral intervention significantly improved the resolution of moderate MR in this setting. Furthermore, they suggested that patients in atrial fibrillation should not only have mitral repair but also an ablation procedure, given the adverse outcome effects of atrial fibrillation in this setting.¹⁷

The fate of MR after AVR was further evaluated in a large single-center trial (N = 462; 2010-2011).¹⁸ The incidence of at least mild MR was 62.5%. Despite the relief of the left ventricular outflow obstruction after AVR, the degree of improvement in MR was modest, with an average improvement of 0.24 degrees per patient.¹⁸ In the setting of moderate MR, the degree of improvement was 0.54 degrees per patient.¹⁸ A detailed linear regression analysis found that there was no relationship between the reduction in MR and the preoperative gradient across the aortic valve. The investigators concluded that prospective randomized clinical trials are indicated to assess the outcome effects of surgical intervention for moderate MR at the time of AVR for AS.¹⁸

The natural history of moderate MR in a patient undergoing aortic root replacement also was evaluated recently in a large

single-center analysis (N = 104; 2000-2011).¹⁹ In this trial cohort of patients undergoing aortic root replacement, 70% underwent mitral repair and 30% received no mitral repair. The average clinical follow-up in this trial was 6.5 years.¹⁹ Mitral intervention in this setting resulted in significantly greater improvement in MR (p < 0.001) that persisted beyond 6 months (p = 0.002). Furthermore, mitral intervention significantly increased the likelihood that the MR would improve at least one full grade postoperatively (100% v 70%; p = 0.001) and beyond 6 months' follow-up (90% v 61%; p = 0.006).¹⁹ Mitral repair, however, did not significantly improve long-term survival, freedom from moderate or greater MR, or mitral reinterventions.¹⁹ The investigators concluded that mitral repair combined with aortic root replacement is reasonable and that it should be considered strongly for moderate MR in the setting of aortic root replacement.¹⁹

The outcome significance of moderate MR in the setting of AS also was demonstrated in a detailed analysis of patients with AS undergoing noncardiac surgery.²⁰ The presence of AS significantly increased the risk of perioperative mortality (2.1% v 1.0%; p = 0.036) and myocardial infarction (3.0% v 1.1%; p = 0.001). Multivariate logistic regression analysis found the following independent predictors of perioperative mortality and/or myocardial infarction as a composite trial endpoint: Moderate or greater MR (OR 9.8; 95% CI 3.1-20.4), high-risk surgery (OR 7.3; 95% CI 2.6-20.6), symptomatic severe AS (OR 2.7; 95% CI 1.1-7.5), and coexisting coronary artery disease (OR 2.7; 1.1-6.2).²⁰ Although the investigators concluded that prospective trials should explore the outcome benefits of aortic valve intervention for AS in high-risk patients before noncardiac surgery, moderate MR as an independent predictor of adverse outcome in this setting would be a marker of high risk for this group of prospective randomized trials.²⁰

The cumulative evidence suggests that moderate MR in the setting of severe AS is common and clinically important, because it likely adversely affects downstream outcomes after both cardiac and noncardiac surgery, as has been the case for moderate MR in the setting of patients undergoing coronary artery bypass grafting.²¹ At this stage, large randomized trials should be undertaken to resolve the clinical equipoise about whether or not moderate MR requires surgical intervention at the time of AVR for AS. A detailed recent search of major trial registries has failed to find any such registered clinical trials in progress (search last conducted November 1, 2013, including www.controlled-trials.com and www.clinicaltrials.gov). Given the burst of clinical interest in this question, it is likely that these trials will begin in the near future, as has been the case for moderate MR in the setting of coronary artery surgery.²¹ The prospective trials also should consider addressing the question of whether mitral valve repair or replacement is indicated in this setting, because this question also remains controversial, as illustrated by a recent clinical trial.²²

MODERATE MITRAL REGURGITATION AND TRANSCATHETER AORTIC VALVE REPLACEMENT

Transcatheter aortic valve replacement (TAVR) has become a mainstream therapy for severe aortic stenosis in patients with high perioperative risk.^{23,24} Although TAVR is now in its second decade, with more than 50,000 procedures performed

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