Mitral Regurgitation in Transcatheter Aortic Valve Replacement
The Complexity of Multivalvular Disease
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Transcatheter aortic valve replacement (TAVR) has emerged as an alternative treatment for patients with symptomatic aortic stenosis (AS) who are at an unacceptably high risk for conventional surgical aortic valve replacement (AVR).1,2 Approximately 60,000 patients worldwide have undergone TAVR in the 11 years since it was introduced.3 Although good procedural success and favorable clinical outcomes have been reported,4,5 issues remain regarding the best patient selection for the procedure. Risk calculators commonly used to estimate the risk of valvular surgery, such as the logistic EuroSCORE and the Society of Thoracic Surgeons model, are not considered accurate in patients undergoing TAVR because they do not account for all clinical characteristics that may significantly affect procedural and postprocedural mortality. The current selection criteria are based on those used in randomized trials, and, in conjunction with the clinical evaluation, echocardiography is a mainstay in the assessment of candidates for this procedure. Beyond the clinical and anatomic exclusion criteria, severe pulmonary hypertension with right ventricular dysfunction, very severe left ventricular (LV) systolic dysfunction (ejection fraction <20%), and severe mitral regurgitation (MR) are among the echocardiographic indications.6 Moreover, each of the commercially available prosthesis manufacturers presents its own recommendations for the procedure, with the CoreValve being more restrictive with respect to concomitant valvular disease.

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Nevertheless, the criteria for patient selection are still open to debate and are not considered binding. As a consequence, patients found in TAVR registries often have characteristics that go beyond the recommended criteria, and this procedure is being considered in a wider array of patients with off-label indications. TAVR in patients with significant MR is one example, and several large series have reported up to 48% of patients with moderate or severe MR.7,8 Nevertheless, until recently, the prognostic impact of MR among patients undergoing TAVR was unknown, and conflicting results have been reported.9

Previous studies have shown that patients with moderate or severe MR undergoing TAVR exhibit a worse baseline clinical profile, including advanced age, higher EuroSCORE and Society of Thoracic Surgeons scores, higher prevalence of atrial fibrillation, and previous myocardial infarction. On echocardiography, they have lower LV ejection fraction, larger LV volumes, smaller aortic valve area, and higher systolic pulmonary pressure.8,10,11 In this issue of Circulation, Bedogni et al12 highlight the prognostic significance of MR in patients undergoing TAVR. This study included 1007 consecutive patients from the Italian nationwide registry, 33.4% with moderate/severe MR, treated with the third-generation 18-Fr CRS CoreValve Revalving System device. As with previous studies, patients with moderate or severe MR had higher logistic EuroSCORE and Society of Thoracic Surgeons scores, higher rate of New York Heart Association class 3 to 4, and higher frequency of pulmonary hypertension and atrial fibrillation, and those with severe MR had lower mean estimated glomerular filtration rate compared with patients with mild baseline MR. At 1 month and 1 year after TAVR, the cardiac mortality rates in patients with moderate/severe MR were significantly higher compared with those with none to mild MR. At 1 year, they observed a stepwise increase in the risk of mortality across the MR groups (none to mild, 10%; moderate, 12%; severe 17%), but the difference between patients with moderate/severe MR was not statistically significant. Most patients presented with functional MR, and a substantial percentage demonstrated MR improvement (47% with severe MR and 35% with moderate MR) at 1 year, whereas MR severity worsened in only 8.4%. However, in this registry, the improvement in MR severity was not associated with a beneficial effect on survival. Importantly, severe pulmonary hypertension and atrial fibrillation were more frequently found among patients whose MR severity worsened and were also independent predictors of mortality.12

Other registries and observational studies have previously reported similar findings concerning the effect of MR on mortality among patients undergoing TAVR. Toggweiler et al,8 using the Edwards SAPIEN valve, reported a doubling of mortality at 1 month after TAVR among patients with moderate/severe MR compared with mild or less MR. Nevertheless, those patients had similar mortality rates at 1 year. In addition, the Canadian13 and the Italian CoreValve registries have reported a higher frequency of severe MR among patients who died at 30 and 69 days after the procedure, respectively.14 The German registry recently showed that, among 1385 patients undergoing TAVR, 33.8% presented with MR ≥ grade 2. These patients had high procedural success but lower survival
rates at 30 days and 1 year, although the improvement in quality of life at 30 days was similar in both groups.\textsuperscript{11} There is limited information regarding the effect of TAVR on MR, but, after aortic valve gradient relief, the immediate decrease in afterload and LV pressure would be expected to result in improvement in MR. Moreover, the longer-term effects of TAVR may, similarly to AVR, lead to regression of hypertrophy or reversal of LV dilation, improving ventricular geometry with resultant reduction in MR severity over time. However, functional MR can be a maladaptive consequence of AS, and it is found in patients with greater LV dilation and worse LV function\textsuperscript{15} and thus is a marker of LV disease that reflects underlying LV dysfunction. In this study, patients with AS and severe MR presented with higher end-diastolic LV volumes, but LV ejection fraction was not significantly different in patients with varying degrees of MR severity. Considering that MR enhances LV ejection fraction, which may mask subclinical myocardial dysfunction, the similarity of LV ejection fraction between patients with moderate/severe MR and those with mild MR might indicate the absence of myocardial functional compensation in the former group. This may help explain the higher mortality and hospitalization rates for heart failure of patients with moderate/severe MR, despite MR improvement. Additional insights into LV myocardial contractility and function in patients with AS and MR referred to TAVR might be obtained with strain analysis, which is a less load-dependent measure of cardiac function than ejection fraction.

Parallels can be drawn with surgical AVR, because MR is recognized as an independent risk factor influencing long-term survival in elderly patients undergoing AVR,\textsuperscript{16} and concomitant MR surgery is selectively considered in symptomatic patients undergoing AVR. Mitral valve (MV) repair has been associated with improved late survival in patients with double valve disease, including the elderly and those with depressed LV function; however, simultaneous replacement of the aortic valve and MV significantly increases surgical morbidity and mortality. Thus, echocardiographic MV morphologic evaluation is critical for the assessment of mechanism and reparability. MR improvement after AVR is more likely in patients with lesser degrees of MR or in the presence of normal MV morphology, because it usually reflects the functional nature of MR. In patients with myxomatous, calcific, and ischemic MR, the decrease in MR severity should not be expected.\textsuperscript{16} In contrast to surgical AVR, concurrent MV repair has not been an option for patients undergoing TAVR. However, bivalvular transcatheter treatment of concomitant AS and MR has been reported previously from a very experienced center,\textsuperscript{9} using TAVR and mitral clip in a single session. Additional studies showing efficacy and safety of bivalvular transcatheter treatments are needed for future recommendations.

The effect of TAVR on the degree of MR may be different depending on the type of prosthesis used. It has been suggested that the effects of the 2 commercially available transcatheter valves could differ because of the potential for increased risk of MV anterior leaflet restriction or secondary chordae disruption by the longer CoreValve prosthesis.\textsuperscript{17} In the current study, CoreValve MV function impairment was ruled out, because the low implant had no effect on MR.

If left untreated, patients with severe AS and concomitant moderate/severe MR have a very poor prognosis. Although patients with moderate/severe MR undergoing TAVR have higher overall morbidity and mortality compared with those with lower degrees of MR, the benefit of TAVR may indeed be higher in this group. The randomized trials PARTNER A and B suggested that patients with MR may experience an even greater benefit from TAVR compared with both medical management and surgical AVR.\textsuperscript{1,7} In the PARTNER 1B trial, MR was a marker of higher TAVR procedural mortality but also of greater procedural benefit compared with medical management. Likewise, in the PARTNER 1A study, patients with MR had a lower risk with TAVR than with surgical AVR (24.2% versus 35%).\textsuperscript{2}

Nevertheless, the PARTNER trial was not designed to determine whether patients with more substantial MR would benefit from TAVR. Even with the best attempts to minimize confounding, registries and observational studies have limited ability to determine the potential benefit of this intervention in clinical practice and only provide incentive for designing properly powered trials. Considering the high prevalence of MR and the frequency of events in patients undergoing TAVR with significant MR, additional trials to determine whether patients with moderate to severe MR will benefit from TAVR are certainly warranted to support the best medical decision.

Sources of Funding
Dr Gonçalves receives funds from Portuguese Foundation for Science and Technology Grant HMSP-ICS/007/2012.

Disclosures
None.

References


KEY WORDS: Editorials ■ aortic stenosis ■ mitral valve insufficiency ■ percutaneous aortic valve replacement
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Circulation. 2013;128:2101-2103; originally published online October 2, 2013; doi: 10.1161/CIRCULATIONAHA.113.006196
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/128/19/2101

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