Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 24, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.02.573

STATE-OF-THE-ART PAPERS

Significant Mitral Regurgitation Left Untreated at the Time of Aortic Valve Replacement

A Comprehensive Review of a Frequent Entity in the Transcatheter Aortic Valve Replacement Era

Luis Nombela-Franco, MD,*† Henrique Barbosa Ribeiro, MD,* Marina Urena, MD,* Ricardo Allende, MD,* Ignacio Amat-Santos, MD,* Robert DeLarochellière, MD,* Eric Dumont, MD,* Daniel Doyle, MD,* Hugo DeLarochellière, MS,* Jerôme Laflamme, MS,* Louis Laflamme, MS,* Eulogio García, MD,† Carlos Macaya, MD, PhD,† Pilar Jiménez-Quevedo, MD,† Mélanie Côté, MSc,* Sebastien Bergeron, MD,* Jonathan Beaudoin, MD,* Philippe Pibarot, PhD,* Josep Rodés-Cabau, MD*

Quebec City, Quebec, Canada; and Madrid, Spain

Significant mitral regurgitation (MR) is frequent in patients with severe aortic stenosis (AS). In these cases, concomitant mitral valve repair or replacement is usually performed at the time of surgical aortic valve replacement (SAVR). Transcatheter aortic valve replacement (TAVR) has recently been considered as an alternative for patients at high or prohibitive surgical risk. However, concomitant significant MR in this setting is typically left untreated. Moderate to severe MR after aortic valve replacement is therefore a relevant entity in the TAVR era. The purpose of this review is to present the current knowledge on the clinical impact and post-procedural evolution of concomitant significant MR in patients with severe AS who have undergone aortic valve replacement (SAVR and TAVR). This information could contribute to improving both the clinical decision-making process in and management of this challenging group of patients. (J Am Coll Cardiol 2014;63:2643–58) © 2014 by the American College of Cardiology Foundation

Aortic stenosis (AS) is the most prevalent valvular heart disease referred for treatment, and it is frequently associated with concomitant mitral regurgitation (MR) (1). Surgical aortic valve replacement (SAVR) is the standard treatment for symptomatic severe AS, and there is a general consensus that in the presence of severe MR, a double-valve operation is indicated (2,3). If MR is moderate, the decision of whether to perform a mitral intervention at the time of SAVR has to be carefully evaluated, given that a double-valve operation is associated with increased operative mortality (4,5). Although MR severity may decrease after isolated SAVR, it may not improve or even worsen in a substantial proportion of patients, and a subsequent mitral valve procedure is associated with increased operative risk in such cases (6).

Transcatheter aortic valve replacement (TAVR) has recently emerged as an alternative to SAVR or medical treatment for patients at high or prohibitive surgical risk, respectively (7). Concomitant significant MR in this setting is typically left untreated. The persistence of moderate to severe MR after TAVR is therefore a relatively new and important entity. The objective of this systematic review is to present the current state of knowledge on the prevalence, clinical impact, and evolution of concomitant significant MR in patients with severe AS who have undergone aortic valve replacement (AVR) (SAVR and TAVR). For this purpose, a literature search using PubMed, EMBASE, the Cochrane Library, and Internet-based sources of information on clinical trials (ClinicalTrials, tctmd, and theheart) was performed from November 2002 to September 2013 using "surgical, transcatheter, percutaneous, transfemoral, transapical aortic valve implantation, replacement and/or insertion, and mitral regurgitation and/or insufficiency" as subject headings.

Mitral Regurgitation Etiology, Mechanisms, and Assessment

There are multiple causes of MR, and a specific cause might induce regurgitation by different mechanisms

From the *Quebec Heart & Lung Institute, Quebec City, Quebec, Canada; and the †Cardiovascular Institute, Hospital Clínico San Carlos, Universidad Complutense, Madrid, Spain. Dr. Nombela-Franco has received funding via a research grant from the Fundación Mutua Madrileña, Spain. Dr. B. Ribeiro is supported by a research PhD grant from "CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico–Brasil." Dr. Amat-Santos is supported by a grant (beca Rio Ortega) from the Instituto de Salud Carlos III, Madrid, Spain. Dr. Pibarot holds the Canada Research Chair in Valvular Heart Diseases, Canadian Institutes of Health Research, Ottawa, Ontario, Canada. Dr. Rodés-Cabau is a consultant for Edwards Lifesciences Inc. and St-Jude Medical. Dr. Dumont is a consultant for Edwards Lifesciences Inc. Dr. Pibarot has received a research grant from Edwards Lifesciences for the Echocardiography Core Laboratory. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received November 2, 2013; revised manuscript received February 18, 2014, accepted February 25, 2014.

Abbreviations and Acronyms

AS = aortic stenosis
AVR = aortic valve replacement
CI = confidence interval
HR = hazard ratio
LV = left ventricle
MR = mitral regurgitation
OR = odds ratio
SAVR = surgical aortic valve replacement
STS = Society of Thoracic Surgeons
TAVR = transcatheter aortic valve replacement

(Online Table 1). The mechanisms of MR are usually classified as organic (valve structurally abnormal) or functional (mitral valve is structurally normal, and the leaflet coaptation deficit is determined by ventricular remodeling) (8). The most common cause of organic MR is degenerative MR from myxomatous processes, or particularly in the elderly, calcification of the mitral apparatus. The most common cause of functional MR is ischemic cardiomyopathy, where the normal leaflets have a restricted motion, driven by tethering because of outward displacement of the left ventricular (LV) walls and papillary muscles. LV wall motion abnormalities may be focal, with a preserved ejection fraction, or global with various degrees of LV systolic dysfunction, geometry changes, and annular dilation. The variable combination of these factors involved in functional MR genesis can explain the heterogeneous response in MR evolution after a given intervention. In addition, a combination of MR etiologies can be seen in many elderly patients with coronary artery disease or cardiomyopathy. Although the concentric LV remodeling seen in isolated compensated AS is not typically associated with functional MR, various factors can influence the presence and severity of functional MR in this population, including the high prevalence of coronary artery disease with subsequent ischemic MR, the LV dilation seen in end-stage AS, and/or with associated aortic regurgitation. The marked increase in the LV-left atrial pressure gradient associated with severe AS can also contribute to increase the driving force through the regurgitant orifice area. Hence, the possibility of mixed etiologies has to be taken into consideration when evaluating MR severity and its potential regression after AVR.

The echocardiographic evaluation of the severity of MR is complex, and the integration of various echocardiographic methods, including quantitative measurements, is recommended in clinical practice (Online Table 2) (2,3,9). An effective regurgitant orifice is less variable compared with regurgitant volume in the presence of increased afterload, and it should therefore be systematically measured in cases of AS with concomitant MR. In addition, the parameters and the prognostic implication of a similar degree of volume overload vary depending on the MR etiology and the underlying LV substrate (Online Table 2) (10,11). In particular, an effective regurgitant orifice area $\geq$0.2 cm^2 and a regurgitant volume $\geq$30 ml/beat have been associated with poorer outcomes in the context of functional ischemic MR (11), but functional MR with a regurgitant orifice area between 0.2 and 0.4 cm^2 can be graded as severe in the presence of other echocardiographic signs of regurgitation severity.

SAVR in the Presence of Significant MR

Most surgical studies to date have focused on single valve disease; data on multivalve disease are scarce (12). The European and American guidelines on the management of valvular heart disease do not provide specific recommendations for the management of multivalvular disease (2,3). There is a general consensus that a double-valve intervention should be performed in the presence of severe MR, especially in cases of organic etiology. However, the surgical management of moderate to severe functional MR in the setting of severe AS remains controversial.

Double mitral and aortic valve surgeries have been associated with a higher mortality rate compared with isolated SAVR (4,5,13–15). In the Euro Heart Survey on Valvular Heart Disease, perioperative mortality in patients with multivalve surgery was 6.5% compared with 2.7% for isolated SAVR and 4.3% for SAVR combined with coronary artery bypass grafting (4). The latest report of the Society of Thoracic Surgeons (STS) showed a rate of 3.5% for double-valve surgery in the past decade (5). Although the ratio of double-valve interventions/SAVR has decreased slightly in the last few years, the total number of double-valve procedures has constantly increased over the last decade (Online Fig. 1). The perioperative mortality after mitral-aortic valve replacement ranged from 8.2% to as much as 11%, whereas the mortality rate after isolated SAVR was between 2.3% and 3.5% (5).

The decision to intervene in MR in the setting of severe AS depends on the severity and the etiology of MR. Although no series of patients with severe MR left untreated at the time of SAVR have been reported, and a higher perioperative mortality has been associated with double-valve interventions, combined aortic and mitral valve surgery seems to be justified in the presence of severe MR (either functional or organic) (12). Although retrospective studies have suggested better outcomes with MR repair versus replacement for ischemic MR (16), this has not been confirmed in a recent randomized trial (17). The use of mitral valve repair techniques is preferred for organic MR, when feasible, due to lower perioperative mortality, improved survival, and better preservation of post-operative LV function (3). However, mitral valve repair options may be very limited in the presence of rheumatic lesions, severe valve prolapse, or extensive leaflet or annulus calcification (18). When repair is not possible, mitral valve replacement with preservation of the subvalvular apparatus is recommended. However, valve replacement can be difficult and of high risk in the presence of severe annular calcification, and this may be a further incentive not to intervene on the mitral valve in such cases.

There is still some controversy regarding the optimal surgical strategy when significant MR is less than severe. Although data about moderate organic MR left untreated at the time of SAVR is very limited (19,20), most investigators support a double-valve operation (21). Barreiro et al. (19)

reported a higher cumulative mortality in patients with moderate MR (severe MR was excluded) in a series of 63% of patients with organic MR. In the PARTNER (Placement of Aortic Transcatheter Valve) trial, 59 of the 299 patients who underwent isolated SAVR had more than mild MR (moderate: 90.5%, severe: 9.5%; no data on MR etiology available). There was a trend toward a higher 30-day mortality in patients with significant (moderate or severe) MR (13.6% vs. 7.1%; $p = 0.10$), and the mortality rate at 2-year follow-up was also higher in this group (49.1% vs. 27.9%; $p < 0.01$) (20). Furthermore, moderate or severe MR was an independent predictor of 2-year mortality in the multivariate analysis (hazard ratio [HR]: 1.77; 95% confidence interval [CI]: 1.17 to 2.68) (22).

In patients with moderate MR of functional origin who underwent SAVR, the debate of whether or not to perform mitral intervention continues (21,23). Some investigators support a conservative approach in such cases (24–27), but others suggest a double-valve intervention because of the lack of improvement in MR severity in approximately one-half of the patients after isolated SAVR and the negative impact of concomitant MR on early and late mortality (28–31) (Table 1). Although 2 case-matched studies (26,27), and more recently, Takeda et al. (31) showed no impact of significant MR on mortality after SAVR, other studies (28–30) reported an increase in perioperative complications and/or mortality in the presence of significant MR. The variability in the design and inclusion criteria among studies may partially explain these contrasting results. Patients with functional severe MR were included in some studies (11,12,14,20,27–29), but not in others (26,30,31), and some studies included patients with nonsignificant (trivial or mild) MR in the concomitant MR group (30). Coutinho et al. (32) evaluated the impact of mitral intervention in patients with functional moderate MR on survival in the setting of SAVR. Although late mortality was not influenced by the decision of MR intervention, patients who underwent combined mitral and aortic surgery experienced more pronounced reverse LV remodeling and less congestive heart failure symptoms (New York Heart Association functional [NYHA] functional classes III to IV). More importantly, the lack of improvement in MR severity over time was associated with late mortality in multivariate analysis (HR: 4.90, 95% CI: 1.92 to 12.60; $p = 0.001$).

Table 1 Impact of Significant Mitral Regurgitation on Mortality in Patients Undergoing Isolated Surgical Aortic Valve Replacement

First Author, Year (Ref. #)	N	Etiology	Grade of MR	Early Mortality	p Value	Follow-Up (yrs)	Cumulative Survival	p Value	Multivariate Analysis HR (95% CI)
Absil, 2003* (26)	116	FMR 100%				3.2 ± 2.4			
	58		0–1	3.5%	0.67	(8)	60.9%	0.10	NA
	58		2–3†	7.0%			55.0%		
Moazani, 2004 (28)	107	FMR 100%				5			
	72		1–2 (trivial–mild)				89.1%	0.04	
	35		3–4 (moderate–severe)				71.4%		
Barreiro, 2005 (19)	408	FMR 37.1%				10			
	338		No/mild	3.8%	0.21		40.1%	0.04	1.43 (1.03–1.98)
	70		Moderate†	7.1%			14.6%		
Ruel, 2006 (29)	706	FMR 100%				5.4 ± 3.2			
	630		0–1	NA		(10)			
	76		≥2	NA			2.7 (1.5–4.7)		1.8 (0.9–3.4)
			≥2 + RF‡					0.02	2.7 (1.4–5.4)§
Caballero-Borrego, 2008 (30)	572	FMR 100%				NA			
	419		No MR	5.6%	0.02		NA		
	153		Non-severe MR†	10.5%			NA		
Wan, 2009* (27)	182	FMR 100%				10			
	91		0–1	NA			43.4%	0.33	NA
	91		≥2	NA			48.3%		
Takeda, 2010 (31)	193					3.3 ± 0.5			
	134		No/trivial (0–1)	2.9%	0.60	(10)	90.3%	0.49	NA
	59		Mild/moderate (2–3)†	1.7%			88.0%		
Partner A, 2012 (20)	299	NA				2			
	240		None/mild	7.1%	0.09		28.1%	0.04	1.77 (1.17–2.68)
	59		Moderate/severe	13.6%			49.8%		
Coutinho, 2013 (32)	255	FMR 100%				10			
	161	B	>2 Untreated	0.0%	0.19		66.6%	0.44	NA
	94	>2 with surgical treatment		1.1%			76.7%		

Values are n, %, or mean ± SD. *Case-matched study. †Grade 4 or severe mitral regurgitation (MR) excluded. ‡One of the following risk factors: left atrial size >5 cm, low preoperative aortic gradient (peak <60 or mean <40 mm Hg) or atrial fibrillation. §Incidence of the composite endpoint, including heart failure symptoms, heart failure death, and mitral valve surgery.

CI = confidence interval; FMR = functional mitral regurgitation; HR = hazard ratio; NA = not applicable/available; RF = risk factor.

Incidence and Etiology of MR in Patients Who Underwent TAVR

The prevalence and severity of MR in patients included in several TAVR registries and the PARTNER trial are shown in Figure 1 (33–41). The rate of concomitant moderate to severe MR in this population ranges between 2% and 33%. Of note, quantitative methods, such as regurgitant volume and effective regurgitant orifice for the assessment of MR, were not systematically used. Some studies, such as the SOURCE (SAPIEN Aortic Bioprosthesis European Outcome) registry, reported the rate (25.2%), but not the severity of concomitant mitral valve disease (42). Also, although the severity of MR was classified in 4 grades (from 1 to 4) in some studies, others used a 3 grade classification (mild, moderate, and severe). Overall, the rate of ≥3/4 or severe MR was systematically <10% (33,35–38,40,41). However, if patients with ≥2/4 or ≥moderate MR were included, the incidence increased up to approximately 20%. The PARTNER trial reported an incidence of moderate to severe MR of 19.8% and 22.2% in cohorts A and B, respectively (35,36). In a recent analysis, severe MR was present in 3.8% of TAVR patients (from cohorts A and B together) after evaluation from a central echocardiography core laboratory, even when severe MR was a pre-specified exclusion criterion in the trial (20).

Only a few studies have provided data on the etiology of MR in patients who have undergone TAVR (Fig. 2) (41,43–49). Although organic MR is usually more frequent than functional MR in the general population (8), functional MR accounts for approximately 50% of patients with MR in patients who have undergone TAVR. This may be related to a patient selection bias secondary to the belief that functional, but not organic, MR is likely to improve after TAVR. As previously mentioned, no study to date has reported the incidence of mixed MR etiologies, which are probably very frequent among TAVR candidates. Also, future studies will have to standardize MR evaluation and severity according to the mechanism and determine its implications after TAVR.

Impact of Significant MR on Acute Mortality After TAVR

The results of studies evaluating the impact of significant MR on in-hospital or 30-day mortality after TAVR are summarized in Table 2 (33,39–41,48,50,51). Some studies suggested an increase in early mortality after TAVR (33,39–41,48), and others failed to demonstrate this association (20,50,51). Importantly, although some studies (33,40) included severe MR only, others (20,39,48,50,51) included moderate or severe MR in the significant MR

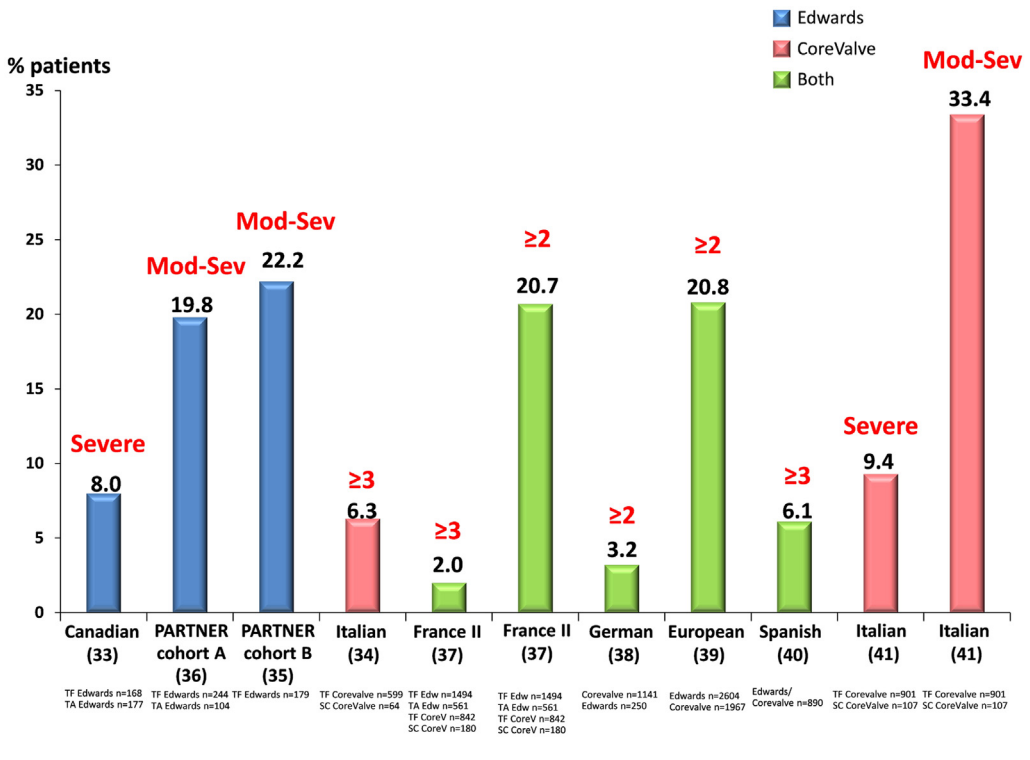

Figure 1 Incidence of Significant Mitral Regurgitation in Patients Undergoing Transcatheter Aortic Valve Replacement

Incidence of moderate to severe mitral regurgitation across the national TAVR registries and the PARTNER trial. SC= subclavian; TA = transapical; TAVR = transcatheter aortic valve replacement; TF = transfemoral.

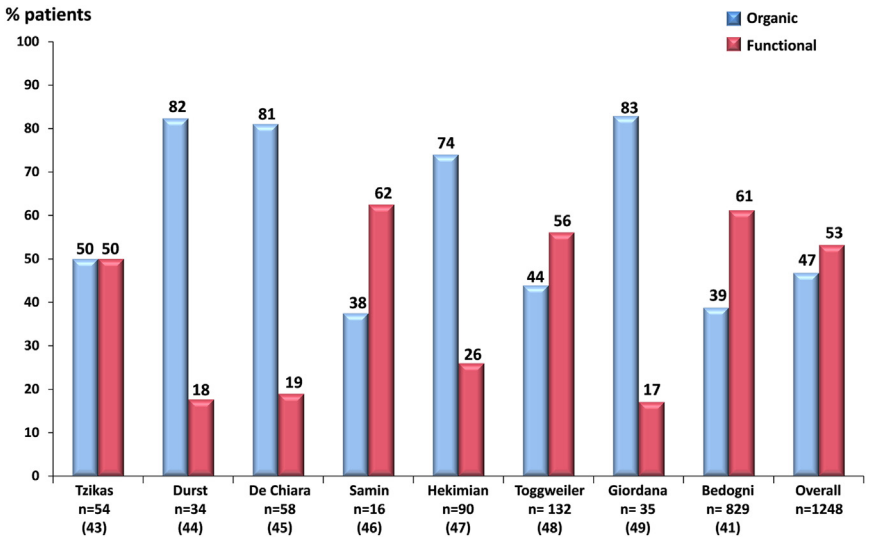

Figure 2 **Etiology of Mitral Regurgitation in Patients Undergoing Transcatheter Aortic Valve Replacement**

Percentage of patients with organic and functional mitral regurgitation across transcatheter aortic valve replacement studies.

group. This might partially explain differences in the acute clinical impact of MR among studies. A global weighted analysis with the published data revealed that patients with significant (moderate or severe) MR experienced higher early mortality (odds ratio [OR]: 1.49, 95% CI: 1.12 to 2.00; p = 0.004; heterogeneity test = 0.006) (Table 2). However, no studies to date reported the mortality rate according to the MR etiology (functional or organic). Whether this increase in early mortality depends on MR etiology has to be determined in future studies.

The presence of significant MR may increase patients' vulnerability with regard to periprocedural hemodynamic changes and/or complications. Any complication leading to hemodynamic instability may rapidly decompensate the hemodynamic status of the patient, leading to a refractory heart failure and cardiogenic shock. Caballero-Borrego et al. (30) showed that concomitant MR before SAVR was associated with a higher rate of low output during the immediate post-operative period. Significant MR has also been associated with an early risk of decompensated heart failure and mortality after cardiac and noncardiac surgery (32,52,53). In accordance with these data, those patients with severe MR in the Italian TAVR registry experienced more hospitalization due to heart failure within the first month (41). Thus, patients with MR constitute a population with poorer hemodynamic reserve. A meticulous fluid balance and afterload reduction are essential, especially during the immediate post-operative period. In addition, MR often leads to pulmonary hypertension, which, in turn, has been associated with poorer outcomes after cardiac surgery and TAVR (34,41,54–56).

Impact of Significant MR on Late Mortality After TAVR

Several studies have identified the presence of concomitant moderate-to-severe MR as an independent predictor of mid-term mortality after TAVR (Table 2). The German and the Italian TAVR registries showed that the presence of moderate or ≥2 MR was a strong predictor of 1-year mortality, and this prognostic value persisted after a landmark analysis at 1 month (excluding 30-day events) (38,41). In addition, both registries found an incremental risk associated with increasing grades of MR severity, similar to other cardiac diseases (11,57). Furthermore, the Italian registry reported an increased risk in cardiac mortality in patients with ≥moderate MR. The FRANCE 2 and the Spanish TAVR registries also found an association between significant MR and mortality at 1-year follow-up in the univariate analysis, but only a trend toward higher mortality after adjustment for other confounding variables in the multivariate analysis (40,58). Unlike these results, patients with moderate to severe MR included in the PARTNER trial (TAVR cohort) had similar mortality rates compared with the patients with no or mild MR (20). Weighted analysis with all the studies revealed a higher cumulative mortality in patients with significant MR (OR: 1.44, 95% CI: 1.23 to 1.68; p <0.001; heterogeneity test = 0.019) (Table 2).

The presence of MR has been identified as a prognostic marker in the setting of acute coronary syndromes (59–61), surgical (62) and percutaneous coronary interventions (63), chronic heart failure (57,64,65), and cardiomyopathies (66).

Table 2 Impact of Moderate to Severe Mitral Regurgitation in Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement

First Author, Year (Ref. #)	N	Grade of MR	Univariate Analysis OR/HR (95% CI)	Multivariate Analysis OR/HR (95% CI)
In-hospital or 30-day mortality				
Rodés-Cabau, 2010 (33)	339	Severe: 27 (8.0%)	2.40 (1.04–5.56), p = 0.049	3.01 (1.09–8.24), p = 0.033
Toggweiler, 2012 (48)	451	≥Moderate: 132 (29.3%)	2.04 (1.11–3.74), p = 0.02	2.10 (1.12–3.94), p = 0.02
D'Onofrio, 2012 (50)	176	≥2: 43 (24.4%)	9.3% vs. 3%, p = 0.10	—
Hutter, 2013 (51)	268	≥Moderate: 60 (22.4%)	13.3% vs. 9.6%, p = NA	—
Di Mario, 2013 (39)†	4,571	≥2: (20.8%)	—	1.45 (1.08–1.93), p = 0.010*
Sabaté, 2013 (40)	890	≥3: 55 (6.2%)	3.28 (1.87–5.76), p = 0.001	4.12 (1.99–8.5), p = 0.001*
Bedogni, 2013 (41)	1,007	Moderate: 243 (24.1%) Severe: 94 (9.3%)	11% vs. 9% vs. 5%, p = 0.006	2.2 (1.78–3.28), p = 0.001 1.9 (1.1–3.3) p = 0.02
Barbanti, 2013 (20)	499	≥Moderate: 103 (20.6%)	3.9% vs. 6.1% p = 0.41	—
Overall (weighted analysis)	3,956		1.49 (1.12–2.00) p = 0.004‡	
Late (>30-day) mortality				
Rodés-Cabau, 2010 (33)	339	Severe: 27 (8.0%)	—	10.7% vs. 7.2%, p = 0.447
Toggweiler, 2012 (48)	451	≥Moderate: 132 (29.3%)	0.94 (0.58–1.51), p = 0.80	0.82 (0.50–1.34), p = 0.42
Zhan, 2013 (38)	1,391	≥2: 42 (3.2%)	—	1.70 (1.19–2.42), p = 0.003§
Bedogni, 2013 (41)	1,007	Moderate: 243 (24.1%) Severe: 94 (9.3%)	17% vs.12% vs. 10%, p = 0.01	1.7 (1.2–3.41), p = 0.001 1.4 (1.2–2.2), p = 0.03
Late cumulative mortality				
Leon, 2010 (35)	171	≥Moderate: 38 (22.2%)	23.7% vs. 32.3%, p = 0.307	—
Tamburino, 2011 (34)†	663	3–4: 42 (6.3%)	35.7% vs. 15.9%, p = 0.001	4.62 (1.66–12.87), p = 0.003
Smith, 2011 (36)	334	≥Moderate: 66 (19.8%)	24.2% vs. 24.6%, p = 0.948	—
D'Onofrio, 2012 (50)	176	≥2: 43 (24.4%)	22% vs. 25%, p = 0.21	—
Van Belle, 2012 (58)	3,195	0: 1183 (37.0%) 1: 1351 (42.3%) ≥2: 661 (20.7%)	24% vs. 20.1% vs. 15.8%, p = 0.002	1.16 (0.94–1.42), 1.09 (0.85–1.40), p = 0.39
Zhan, 2013 (38)	1,391	≥2: 42 (3.2%)	5.7% vs. 2.5%, p = 0.009	1.57 (1.22–2.02), p = 0.001
Hutter, 2013 (51)	268	Moderate and severe: 60 (22.4%)	30.2% vs 21.2%, p = 0.068	—
Sabaté, 2013 (40)	890	≥3: 55 (6.2%)	2.63 (1.58–4.36), p = 0.001	1.67 (0.94–2.96), p = 0.09
Bedogni, 2013 (41)	1,007	Moderate: 243 (24.1%) Severe: 94 (9.3%)	25% vs. 20% vs. 15%, p = 0.02	2.9 (2.5–3.8), p = 0.001
Overall (weighted analysis)	6,734		1.44 (1.23–1.68) p <0.001‖	

Values are n and %, unless otherwise indicated. *In hospital mortality. †Excluded from the weighted analysis due to repetitive patients from other series. ‡Heterogeneity test = 0.006. §Late mortality (discharge to 1 year). ‖Heterogeneity test = 0.019.
OR = odds ratio; other abbreviations as in Table 1.

It is therefore not surprising that the presence of ≥moderate MR has been found to have an impact on long-term mortality in patients who have undergone TAVR, commonly an elderly population with several comorbidities and a high-risk profile. In the presence of significant MR, volume overload continues and maintains LV remodeling, even after pressure overload correction with TAVR. Prolonged hemodynamic overload ultimately leads to heart failure, which, in turn, translates into poorer outcomes (67). Interestingly, registries of TAVR predominantly using the CoreValve (Medtronic, Minneapolis, Minnesota) system showed that significant MR was an independent and powerful predictor of late mortality (34,38,41), whereas only a univariate (but not multivariate) association was observed in registries with approximately 50% use of the CoreValve system (37,40). No impact on late mortality was observed in

the studies with a 100% use of balloon-expandable valves (20,33,48,55). Several studies showed a higher rate of moderate to severe aortic regurgitation after TAVR with the CoreValve system (37,68–72), which, in turn, could adversely affect LV remodeling and increase patients' vulnerability in the presence of significant MR. However, whether the type of transcatheter heart valve has an influence on the impact of significant MR in TAVR patients will have to be confirmed in future studies.

A careful assessment of baseline patient characteristics, the repercussion of all degrees and etiologies of MR on LV geometry and remodeling, and the determination of the precise causes of death (cardiovascular vs. noncardiovascular) in such patients are needed to confirm the nature and real impact of concomitant MR in patients undergoing TAVR. In addition, whether or not survival directly correlates with improvement in MR severity after TAVR remains unclear. Finally, future studies will have to elucidate the prognostic value of significant MR according to its etiology (organic vs. functional).

Impact of Significant MR on Functional Status After TAVR

About one-fourth of patients experience no improvement in their quality of life and/or functional capacity after TAVR (56,73,74). Among other factors, Gotzmann et al. (56) found that severe baseline MR was an independent predictor of poor functional response after TAVR, particularly in patients with organic MR. However, other studies in the TAVR field have reported an improvement in functional status similar to that of the nonsignificant MR group (20,41,50,51,75). These data, however, must be interpreted with caution due to the possibility of a survival bias (only patients who survived had a functional status evaluation). The combined endpoint of mortality and poor functional response to the treatment may have been higher among patients with significant MR. In addition, NYHA class has been shown to be inaccurate for the evaluation of functional improvement and had a poor correlation with other functional capacity status or quality-of-life tests in heart failure patients (76,77). Further evaluation of functional capacity with more objective and reliable methods is therefore needed to determine the real impact of MR after TAVR.

Changes in MR After AVR (SAVR and TAVR)

The severity of MR results from the complex interaction among the causal mechanism, the effective regurgitant orifice area, its dynamic behavior during the cardiac cycle, and the magnitude of the systolic pressure gradient between the LV and the left atrium (78). In patients with severe AS and concomitant significant MR, several physiological changes occur after aortic flow restoration, which, in turn, could contribute to reducing MR severity (Fig. 3). LV cavity pressure drops very early after AVR, and consequently, the transmitral pressure gradient may decrease, resulting in a

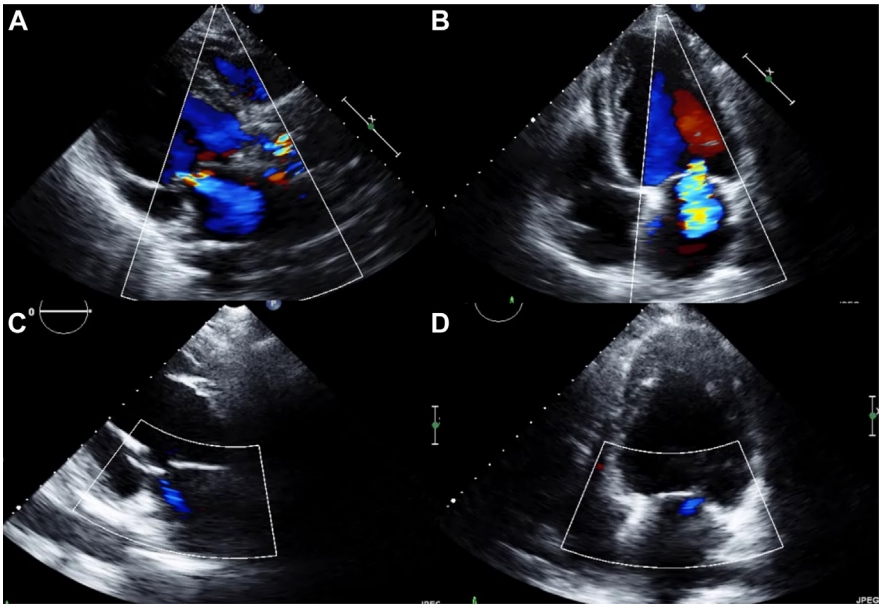

Figure 3 **Transthoracic Echocardiographic Images of Mitral Regurgitation Pre- and Post-Transcatheter Aortic Valve Replacement (Patient with Functional Mitral Regurgitation)**

Example of mitral regurgitation improvement after transcatheter aortic valve replacement as assessed by transthoracic echocardiography in parasternal and 4-chamber views. **(A and B)** Pre-transcatheter aortic valve replacement. **(C and D)** Twelve months post-transcatheter aortic valve replacement.

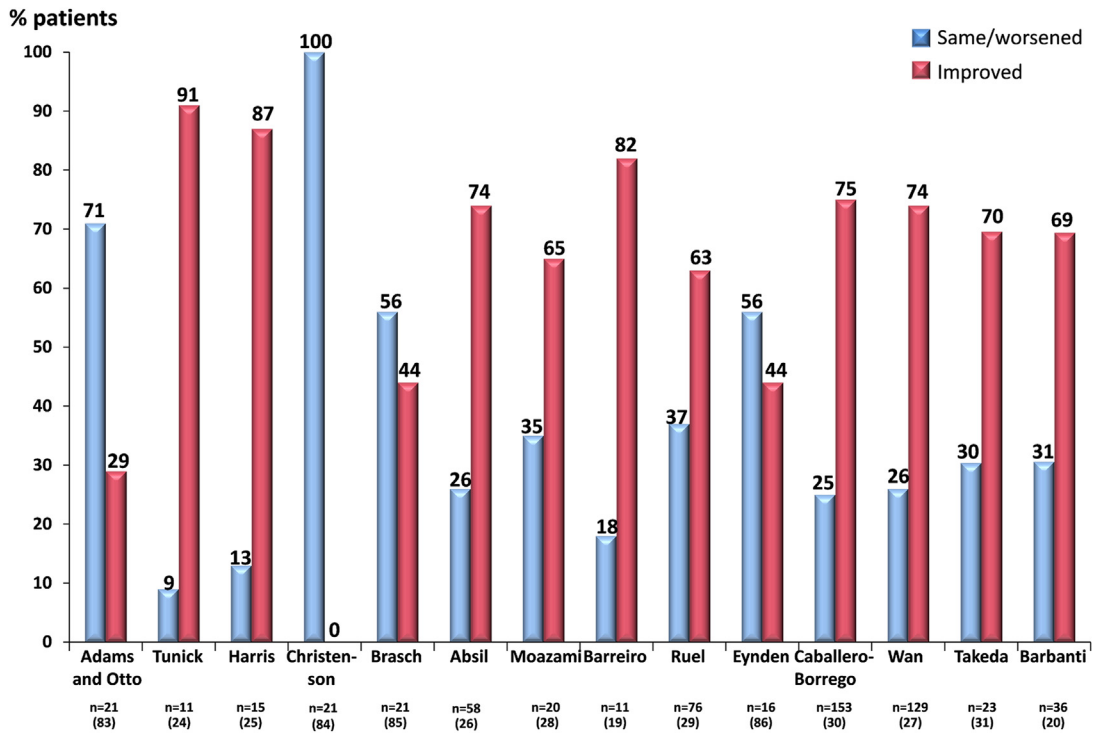

Figure 4 **Changes in Moderate Mitral Regurgitation (Functional Etiology) After Surgical Aortic Valve Replacement**

Percentage of patients with improvement or unchanged mitral regurgitation after surgical aortic valve replacement.

reduction in MR in most patients. However, in some patients with functional MR, the decrease in the transmitral gradient may lead to reduction in the mitral valve closing forces, and therefore, persistence of MR. In the late post-operative period, a regression of concentric myocardial hypertrophy due to a decrease in ventricular afterload has been described after SAVR (79,80) and TAVR (81), and this, in turn, can influence mitral valve hemodynamics. In addition, a reverse remodeling effect leading to changes in LV shape and geometry may also contribute to improving functional MR due to a reduction in LV end-diastolic volume and mitral tethering forces. Although this mechanism has been described in the early perioperative period after SAVR (82), it is more likely to play a role in the long-term improvement of MR.

A decrease in functional MR severity is common after isolated SAVR (24–27,30,31). However, some studies have shown that concomitant MR may not improve in up to one-half of the patients or even increase after SAVR (6,83–86) (Fig. 4). In accordance with these results, MR severity improvement after TAVR has been described in several studies using both self- and balloon-expandable transcatheter heart valves (Table 3; Fig. 5). However, although some degree of improvement in MR was observed in a significant number of patients in all studies, MR severity remained unchanged or even worsened in at least half of the patients in most studies (20,42–51,87–89). Importantly, some studies reported the changes, including all grades of MR severity (from none to severe) (43–47,81,88), and others focused only on patients with moderate to severe MR (20,48–51). Of note, the parameters for MR evaluation varied across the studies, and this may partially explain the discrepancies among studies in MR changes after SAVR and TAVR (9,90).

The factors that have been associated with MR improvement after AVR (SAVR and TAVR) are listed in Table 4. The presence of LV dysfunction and MR of functional origin have been associated with greater improvements in MR severity after SAVR (6). In accordance with these data, the presence of functional MR has been identified as 1 important factor that determines MR improvement after TAVR (41,46,48). The presence of a poorer LV ejection fraction and larger ventricular diameters have also been associated with greater improvements in MR (20,42,43,47). This suggests that identifying a potential for LV reverse remodeling may be the key when evaluating the likelihood of MR improvement after AVR. In contrast, in the presence of degenerated and calcified mitral valve disease, the regurgitant orifice area may remain unchanged after successful TAVR (42) (Fig. 6). However, no data exist about

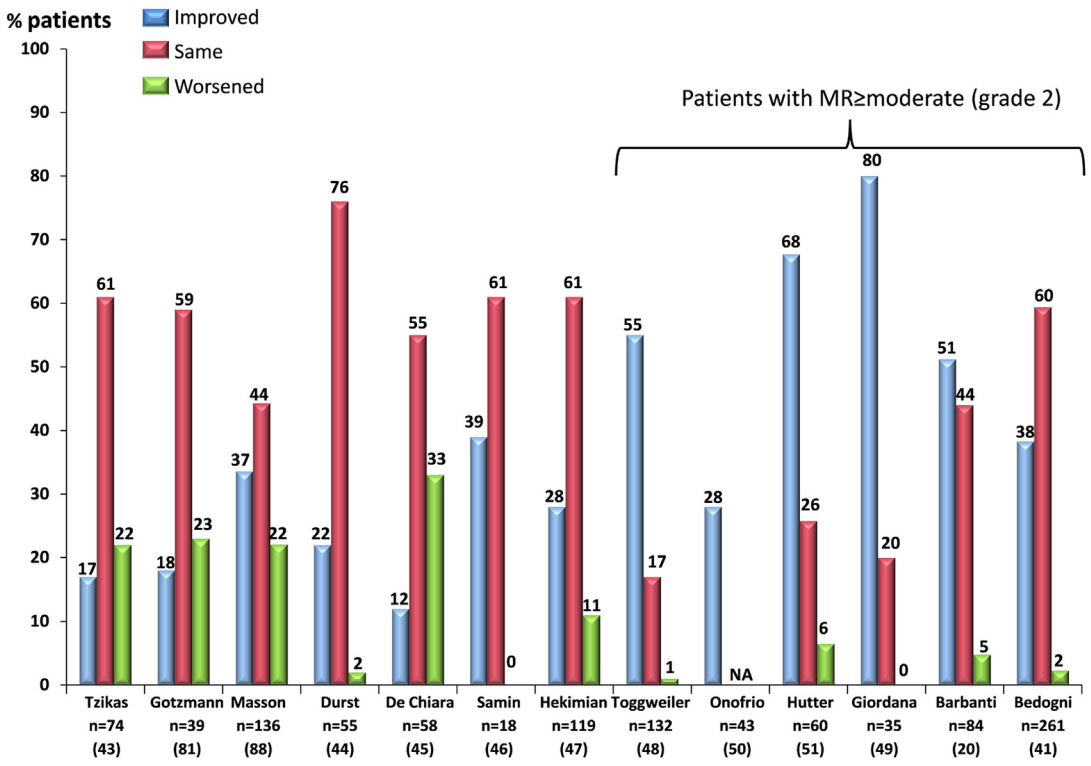

Figure 5 **Changes in Mitral Regurgitation After Transcatheter Aortic Valve Replacement**

Percentage of patients with improvement, unchanged or worsened mitral regurgitation (MR) after transcatheter aortic valve replacement.

MR changes in patients with mixed (functional and organic) mitral valve disease. Chronic atrial fibrillation, pulmonary hypertension, and a larger atrial size have been identified as predictive factors of the lack of MR improvement after SAVR (25,29,30,91,92) and TAVR (41,48). These factors may reflect more advanced MR and/or LV disease and a lower likelihood of improvement after AS release. In addition, a lesser degree of MR improvement with the use of the self-expandable CoreValve system compared with the balloon-expandable Edwards valve (Edwards Lifesciences, Irvine, California) has been suggested (49,93). Several factors could be related to this hypothesis, such as the higher incidence of new pacemaker implantation, left bundle branch block, and residual aortic regurgitation with the CoreValve system (37,69,94,95). LV ventricular dyssynchrony observed during right ventricular pacing and/or in the presence of left bundle branch block may also adversely affect MR (96,97). Importantly, it has been suggested that residual aortic regurgitation may negatively influence MR improvement in SAVR (91) and TAVR (98). Although a deeper implantation of the CoreValve with a potential interaction of the stent frame and the anterior mitral leaflet was initially described (45), this has not been confirmed by other studies (41). A higher transvalvular gradient preprocedure has also been identified as an independent predictor of MR improvement after SAVR and TAVR (29,48), which is probably secondary to a greater reduction in the systolic atrioventricular gradient after AS release and greater regression of LV hypertrophy and remodeling. In this regard, the presence of prosthesis–patient mismatch (i.e., residual AS) has been shown to be associated with lesser regression of concomitant MR after SAVR (99,100). Interestingly, TAVR has been associated with a lower incidence of prosthesis–patient mismatch compared with SAVR (101), and future studies will have to evaluate whether this translates into differences in MR improvement compared with SAVR.

Although the observational nature and the heterogeneity of the current literature limits drawing definite conclusions, it appears that concomitant significant MR improves in approximately 50% of patients after TAVR, especially in cases with MR of functional etiology. More detailed pathophysiological data on the effects of TAVR on MR are needed to better identify the predictors of improvement and/or worsening, and to clarify the potential benefit of improvement with longer clinical follow-up.

Percutaneous Treatment of MR After TAVR

Percutaneous mitral valve repair simulating the surgical "edge-to-edge" technique with the Mitraclip device (Abbot Vascular, Abbot Park, Illinois) has been shown to be

Table 3 Changes in Mitral Regurgitation Severity After Transcatheter Aortic Valve Replacement

First Author, Year (Ref. #)	Valve Type	Baseline		Discharge		Follow-Up			Global Changes in MR Grade	% Improved	% Worsened
		n	MR, Etiology	n	MR	n	MR	Days			
Webb, 2007 (87)	ES	50	None/trivial: 26% Mild: 26% Moderate: 32% Severe: 16%	42	None/trivial:31% Mild: 36% Moderate: 24% Severe: 9%	29	None/trivial:14% Mild: 62% Moderate: 21% Severe: 3%	180	Median grade 2 to grade 1 ($p = 0.01$)	—	—
Tzikas, 2010 (43)	CV	74	None: 24% Mild: 57% Moderate: 18% Severe: 1% FMR = 50%	71	None: 28% Mild: 53% Moderate: 18% Severe: 1%	46	None: 22% Mild: 59% Moderate: 17% Severe: 2%		Pre to discharge: 1.91 to 1.89 Pre to follow-up 1.91 to 1.98, $p = 0.89$	17.4%*	21.7%*
Osten, 2010 (89)	ES	46	24%	41	9%	14	<9%	365	—	—	—
Gotzmann, 2010 (81)	CV	39	None: 12.8% Mild: 38.5% Moderate: 38.5% Severe: 10.2%	39	None: 7.7% Mild: 43.6% Moderate: 38.5% Severe: 10.2%	39	None: 12.8% Mild: 43.6% Moderate: 33.3% Severe: 10.2%	180	Pre to discharge: 1.46 to 1.51, $p = 0.160$ Pre to follow-up 1.46 to 1.41, $p = 0.160$	18%†	23%†
Masson, 2010 (88)	ES	136	≤2: 55.9 ≥3: 44.1		—	113	0–2: 69.0% 3: 24.8% 4: 6.2%	30	—	33.6%†	22.1%†
Durst, 2011 (44)	ES	55 (34)	≤Mild: 36.4% Mild–Moderate: 47% Moderate: 47% Severe: 6% FMR = 18%	28	≤Mild: 36 Mild–Moderate: 46% Moderate: 14% Severe: 4%	26	≤Mild: 31 Mild–Moderate: 50% Moderate: 15% Severe: 4%	180	VC Pre to discharge: 0.5 ± 0.2 to 0.3 ± 0.2, $p < 0.001$ VC Pre to follow-up: 0.5 ± 0.2 to 0.3 ± 0.2, $p < 0.001$	22%*‡	6.4%§
De Chiara, 2011 (45)	CV	58	≤+1: 72.4% +2: 22.4% +3: 3.5% +4: 1.7% FMR = 19%		—	58	≤+1: 69.0% +2: 17.2% +3: 12.1% +4: 1.7%	234	Pre to follow-up 1.34 to 1.48, $p = 0.086$	12%*	33%*
Samin, 2011 (46)	ES	18	≤ +1: 33.3% +2: 33.3% +3: 27.8% +4: 5.6% FMR = 62%	18	≤+1: 50.0% +2: 22.2% +3: 27.8% +4: 0%	18	≤+1: 50.0% +2: 38.9% +3: 11.1% +4: 0%	30	Pre to discharge: 2.1 ± 0.9 to 1.5 ± 1.1, $p = NA$ Pre to follow-up 2.1 ± 0.9 to 1.4 ± 0.9 $p < 0.05$	39%† (if MR ≥2, 58%)	0%†
Hekimian, 2012 (47)	ES	119	0: 24.4% +1:43.7% +2: 28.6% +3: 2.5% +4: 0.8% FMR = 26%	99	0: 31.3% +1: 44.4% +2: 23.2% +3: 1.0% +4: 0%	60	0: 36.7% +1: 41.7% +2: 18.3% +3: 3.3% +4: 0%	30	Pre to 7 day: 1.2 ± 0.8 to 0.9 ± 0.8, $p < 0.01$ 7 to 30 day: 0.9 ± 0.8 to 0.9 ± 0.8, $p = 0.182$	28%†	11%†
Toggweiler, 2012 (48)	ES	451 (132)	≤Mild: 70.7% Moderate: 67.4% Severe: 32.6% FMR = 56%	123	≤Mild: 57.7% Moderate: 27.7% Severe: 14.6%	94	≤Mild: 64.9% Moderate: 26.6% Severe: 8.5%	365	Pre to discharge: 2.3 ± 0.4 to 1.6 ± 0.7, $p < 0.01$ Pre to follow-up: 2.3 ± 0.4 to 1.4 ± 0.6, $p < 0.01$	54.6%*	0.7%*

Continued on the next page

Table 3 Continued

First Author, Year (Ref. #)	Valve Type	Baseline		Discharge		Follow-Up			Global Changes in MR Grade	% Improved	% Worsened
		n	MR, Etiology	n	MR	n	MR	Days			
D'Onofrio, 2012 (50)	Both	176	0: 19.9% +1: 55.7% +2: 17.0% +3: 6.8% +4: 0.6%	—		—		312	—	6.8%* (if MR ≥2, 28%)	6.8%* (if MR ≤1, 9%)
Hutter, 2013 (51)	Both	268 (60)	≤Mild: 77.6% ≥Moderate:22.4%	—		31		180	—	67.7%	6.5%
Giordana, 2013 (49)	Both	35	≥2: 100% +2: 60.0% +3: 28.6% +4: 11.4% FMR = 17%	—		35	0: 11.4% +1: 54.3% +2: 22.9% +3: 11.4% +4: 0%	90	Pre to follow-up: 2.5 ± 0.7 to 1.4 ± 1.1, p <0.001	80%†	0%†
Bedogni, 2013 (41)	CV	1,007	None/mild: 66.5% Moderate: 24.1% Severe: 9.3% FMR = 61%	—		829	None/mild: 70.9% Moderate: 23.9% Severe: 5.2%	365		13.0%* (if MR ≥ moderate, 38.3%)	6.4% (if MR ≤ mild, 8.3%)
Barbanti, 2013 (20)	ES	331 (65)	≤Mild: 80.4% ≥Moderate:19.6%	—		52	—	30		57.7%†	5.8†

Values are n, %, or mean ± SD. *At follow-up. †At discharge or 30 days. ‡Defined as reduction ≥30% of the vena contracta. §Patients with MR ≤1 or ≤mild.
CV = CoreValve; ES = Edwards Sapien; VC = vena contracta; other abbreviations as in Table 1.

associated with favorable results compared with medical therapy in patients with symptomatic severe MR who are deemed inoperable or at high surgical risk (102,103). The EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) trial demonstrated the safety of the technique with a very low complication rate (104). Patients who undergo TAVR and who remain symptomatic due to significant MR could potentially benefit from a staged percutaneous procedure to treat MR. The feasibility of implanting a Mitraclip device after TAVR with the Edwards and CoreValve systems was first described in 2011 (105,106). In both cases, the aortic prosthesis did not influence Mitraclip implantation. However, there are a lack of data on the clinical benefits associated with this procedure in the TAVR population. Only 2 series with a limited number of patients showed contrary results in mortality rate and changes in functional class in the follow-up (107,108). Although Rudolph et al. (107) reported a 36% mortality rate at 7-month follow-up, Kische et al. (108) showed a significant improvement in functional status after a percutaneous mitral repair procedure in 12 patients with persistent severe MR after TAVR at 6-month follow-up.

Currently, experience with percutaneous mitral valve repair after TAVR is scarce, but it seems to be technically feasible and may be a therapeutic option in the future for nonresponder patients. In contrast to the increased risk associated with a second stage surgery, previous TAVR does not seem to increase the risk of a subsequent percutaneous mitral intervention. However, careful patient evaluation and selection is crucial to better identify those who will derive the greatest benefit from percutaneous mitral repair.

Management of Concomitant Moderate to Severe MR in Patients With Severe AS

The management of patients with severe AS and concomitant MR is challenging. The decision to intervene in both valves requires a careful evaluation of the patient's comorbidities and MR etiology and severity by quantitative echocardiographic methods. Thus, the decision-making process should be based in the assessment of operative risk, MR severity, and likelihood of MR improvement after isolated AVR (Fig. 7). In patients with low or intermediate surgical risk and moderate to severe MR, appropriate patient selection is crucial to identify patients in whom MR will not improve or even progress after SAVR. In those patients with a low likelihood to improve, the increased risk of a double-valve procedure may be justified (assuming an operative mortality of 6% to 10%). In patients with high surgical risk in whom SAVR and TAVR are both an option, identification of factors associated with improvement may predispose to one or the other treatment. Patients with a high likelihood of a decrease in MR after the intervention might be inclined to undergo TAVR, thus avoiding the increased risk of double-valve intervention, whereas a combined SAVR with mitral repair and/or replacement would be

Table 4 Predictive Factors Associated With Improvement in Mitral Regurgitation Severity After Aortic Valve Replacement (Surgical Aortic Valve Replacement and Transcatheter Aortic Valve Replacement)

Factors	Procedure (Ref. #)	OR/HR in Multivariate Analysis (Ref. #)
MR etiology (functional vs. organic)	SAVR (19,31,86) TAVR (41,46,48)	HR: 2.6 (1.8–3.1) p <0.01 (41) HR: 2.6 (1.1–5.9) p = 0.02 (48)
Absence of pulmonary hypertension	SAVR (30) TAVR (41,48)	OR: 3.0 (1.0–10.0) p = 0.05 (30) HR: 2.9 (2.7–3.3) p <0.01 (41) HR: 2.7 (1.1–6.6) p = 0.03 (48)
Absence of atrial fibrillation	SAVR (29,92) TAVR (41,48)	p = 0.03 (90) HR: 2.0 (1.9–2.5) p <0.01 (41) HR: 2.5 (1.2–5.5) p = 0.02 (48)
LVEF (low vs. normal) and LV diameters	SAVR (27) TAVR (20,42,43,47)	OR: 1.1 (1.0–1.1) p = 0.01(27) OR: 5.4 (1.2–23.4) p = 0.02* (20)
Mean gradient	SAVR (29) TAVR (48)	HR: 2.7 (1.2–6.2) p = 0.02 (48)
Residual aortic regurgitation	SAVR (91) TAVR (97)	p = 0.01 (91)
Increase left atrial size	SAVR (25,29,91)	p = 0.03* (25) p <0.01 (91)
Presence of coronary artery disease or previous myocardial infarction	SAVR (28,30,84)	OR: 5.0 (1.4–18.4) p = 0.01 (28) OR: 3.7 (1.1–13.0) p = 0.04 (30)
Prosthesis patient mismatch	SAVR (98)	
Absence of mitral annular calcification with restriction	TAVR (44)	17% vs. 61%, p = 0.05* (44)
Valve type (ES vs. CV)	TAVR (49)	Greater improvement with ES* (49)
Deeper implantation CV	TAVR (45)	9.4 vs. 7.6 mm p = 0.02* (45) Not found in (41)

*Univariate analysis.

LV = left ventricular; LVEF = left ventricular ejection fraction; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; other abbreviations as in Tables 1 to 3.

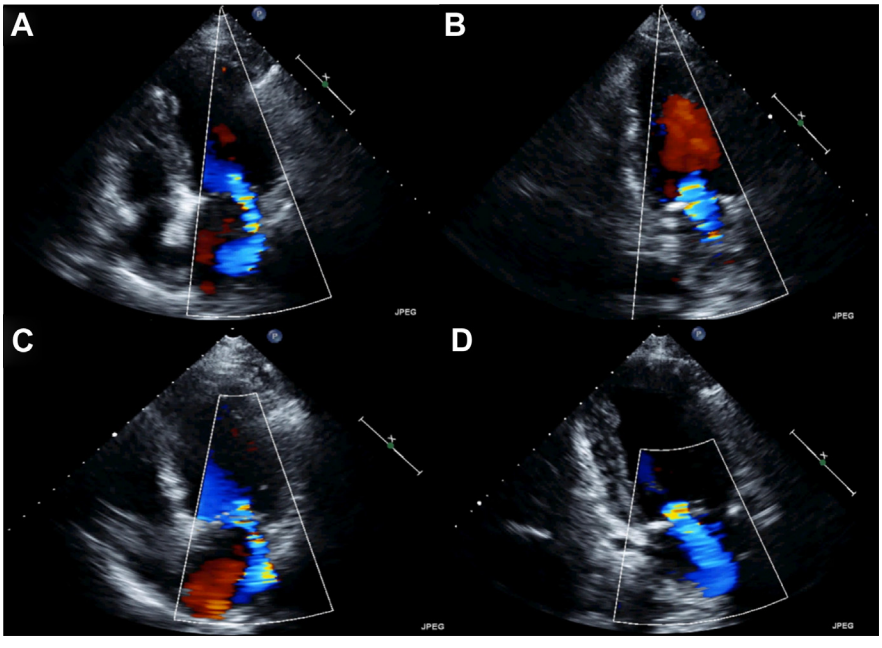

Figure 6 Transthoracic Echocardiographic Images of Mitral Regurgitation Pre- and Post-Transcatheter Aortic Valve Replacement (Patient With Organic Mitral Regurgitation)

Example showing the lack of change in mitral regurgitation severity after transcatheter aortic valve replacement as assessed by transthoracic echocardiography in 4- and 2-chamber views. **(A and B)** Pre-transcatheter aortic valve replacement. **(C and D)** Six months after transcatheter aortic valve replacement.

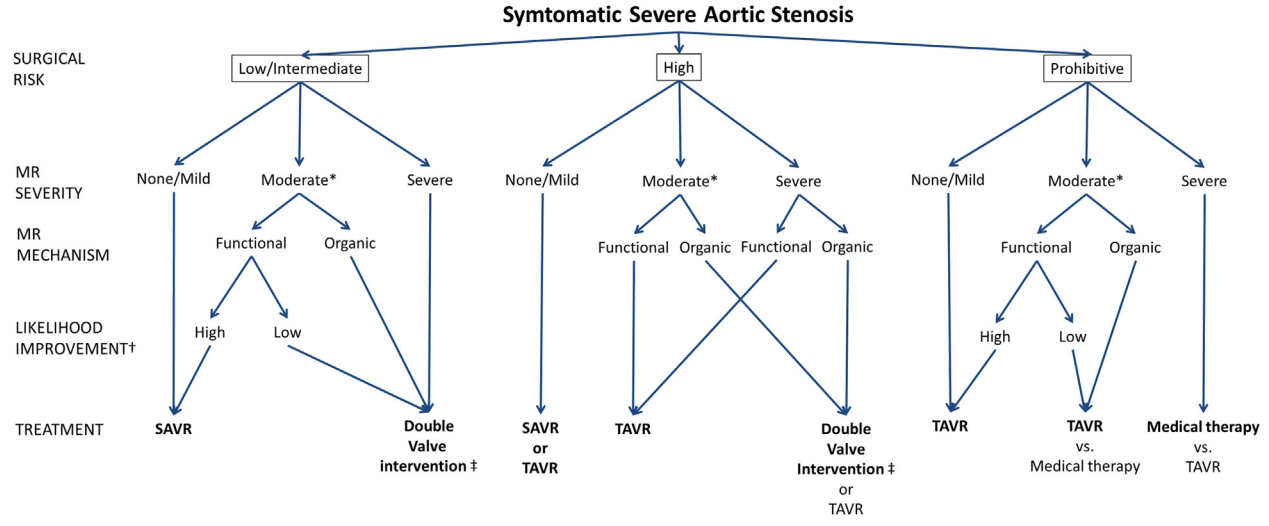

Figure 7 Decisional Algorithm for Management of Patients With Severe Aortic Stenosis and Concomitant Mitral Regurgitation

*Quantitative echocardiography evaluation to differentiate between moderate and severe mitral regurgitation (MR). †Most frequent factors associated with improvement: absence of atrial fibrillation or pulmonary hypertension, normal atrial size. ‡Assuming perioperative mortality of 6% to 10%. Several of the recommendations proposed in this algorithm are based on limited data and will need to be further validated by future studies. SAVR = surgical aortic valve replacement; other abbreviations as in Figure 1.

better in patients with a low likelihood of MR improvement after TAVR. In patients with very high or prohibitive surgical risk, TAVR is the first option, assuming an increase mortality risk determined by the presence of moderate to severe MR. However, if MR severity is deemed to be unchanged or worsened after TAVR, medical treatment should be considered as an additional option.

Conclusions

Concomitant significant MR left untreated at the time of AVR is an important and frequent entity in the TAVR era. Moderate to severe MR is common (approximately 20%) in patients undergoing TAVR, and it has been associated with higher early and late mortality. Given the limitations (publications bias and lack of standardized studies) of the current literature, the nature of this association, as a cause or as a marker of worse prognosis, has not been yet determined. MR severity improves in approximately 50% of the patients after TAVR, especially in those with LV dysfunction and functional MR. However, future studies with centralized core laboratories should standardize the evaluation of MR severity and mechanism to better determine the main predictors of MR improvement and its impact on mortality. Identifying the patients with the highest and lowest likelihood for MR improvement is of utmost importance in the clinical decision-making process, especially in moderate to high risk but still operable patients who might benefit from a double (aortic and mitral) surgical therapy. A second staged percutaneous approach for mitral valve repair with the Mitraclip device may be an additional option in cases with persistent severe symptomatic MR after TAVR. However, more data on the efficacy and safety of Mitraclip implantation in patients who have undergone TAVR is needed.

Acknowledgment

The authors thank Serge Simard, MSc, from the Quebec Heart and Lung Institute for his help with the statistical analyses.

Reprints requests and correspondence: Dr. Josep Rodés-Cabau, Quebec Heart & Lung Institute, 2725 Chemin Ste-Foy, Quebec City, G1V 4G5 Quebec, Canada. E-mail: josep.rodes@criucpq.ulaval.ca.

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Key Words: aortic stenosis ■ mitral regurgitation ■ percutaneous therapy ■ transcatheter aortic valve implantation.

APPENDIX

For supplemental tables and a figure, please see the online version of this article.