Review Article on Novel Concepts in Cardiopulmonary and Structural Heart Disease

Mitral regurgitation after transcatheter aortic valve replacement

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Abstract: Patients undergoing transcatheter aortic valve replacement (TAVR) might have an associated significant MR that can potentially lead to left ventricular (LV) failure after procedure. Considering the specific alterations in the mitral valve in TAVR scenario and the widespread use of TAVR in recent years, it appears important to know and understand the anatomical, functional and clinical implications to develop adequate strategies for the future. Patients with severe mitral regurgitation (MR) have been generally excluded from randomized clinical trials, making poor the impact that associated MR can have on clinical outcomes after TAVR. Several factors must be considered whose presence influences the severity of MR. For example, the elevated prevalence of coronary disease with consequent ischemic MR may account for LV dilation observed at the end stage of aortic stenosis. Evidence randomized studies and registries suggests that the rate of concomitant moderate-to-severe MR in patients undergoing TAVR oscillates between 2% and 33%, and patients with moderate to severe MR may have hemodynamic frailty with clinical deterioration during mechanical intervention. Short- and long-term outcomes, including cardiac mortality, appear to be influenced by the existence of preoperative moderate-to-severe MR or by the postprocedural worsening of mild MR, generally due to adverse LV remodeling. The incidence and the prognostic effect of concomitant MR in patients undergoing TAVR requires specific attention as might trigger adjunctive strategy treatment which should be carefully evaluated in clinical trials.

Keywords: Mitral regurgitation (MR); mitral valve; transcatheter aortic valve; transcatheter aortic valve replacement (TAVR)

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Introduction

Conventional surgical aortic valve replacement (SAVR) remains one of the most common cardiac surgery operations performed worldwide. It has been shown to be the most effective treatment for several categories of patients affected by aortic valve disease (1). In presence of concomitant severe mitral regurgitation (MR), a double-valve operation is indicated according to international guidelines (2-4). Conversely, in case of moderate MR the choice of performing mitral valve surgery combined to SAVR should be carefully assessed, considering that a double valve operation carries increased operative mortality and morbidity (5,6). Clinical and echographic evidences showed that MR severity may decrease after isolated SAVR due to reduced systolic intraventricular pressure (7). However, in some cases (still anatomically to be determined) MR appears to worsen, thus requiring a second surgical treatment which implies a greater risk for frail patients (8).

In recent years, this surgical problem has been translated in the scenario of transcatheter aortic valve replacement (TAVR) considering that the key pathophysiologic mechanisms are similar. Patients undergoing TAVR might have an associated significant MR that can potentially lead to left ventricular (LV) failure after procedure (9). Another factor contributing to detrimental mitral valve functioning after TAVR, not present in SAVR, relies in the anatomical features of the mitro-aortic continuity. The mitral valve may be subject to changes in both geometry and structure that can potentially cause functional MR or accentuate the problems of a pathological mitral valve (10-17). Considering the specific alterations in the mitral valve in the setting of TAVR and the widespread use of TAVR in recent years (18), it appears important to know and understand the anatomical, functional and clinical implications to develop adequate strategies for the future.

Methods

A literature search using PubMed, EMBASE and Cochrane library was performed to evaluate clinical studies, observational studies and reports on mitral valve biomechanics after TAVR from inception to November 2019. Search strategy included the following keywords and their MeSH terms, in various combinations: transcatheter aortic valve, surgical implantation, transcatheter, transapical, transfemoral, percutaneous, aortic valve replacement/implantation/insertion, MR, mitral valve mechanics. References from retrieved results were checked for potential additional sources.

Results and discussion

Anatomical, functional and biomechanical implication

The mitral valve and subvalvular apparatus are composed of annulus, leaflets, chordae, papillary muscles, and LV wall. In the anterior and posterior leaflets of the valve, scallops A1, A2, and A3 and in P1, P2, and P3 can be distinguished. The continuity between the leaflets is ensured by the anterior and posterior commissures. The chordae tendinae are connected to the free edge of the leaflets creating a connection between the valve and the subvalvular apparatus. The subvalvular apparatus is composed antero-lateral and postero-medial papillary muscles that are embedded in the wall of the left ventricle. Chordae tendinae originate from the tips of the papillary muscles, and their anatomy and function ensure continence of the mitral valve that depends on the coordinated interaction of the valve with the subvalvular apparatus. From a biomechanical point of view, the MV can be divided into: anterior and posterior cantilever beams (the leaflets), the basements (the papillary muscles) and the pillars (chordae tendinae) (11,17). During the systole, the upper part of the LV chamber moves towards the lower base rotating around the interventricular septum, and the left fibrous trigone of the heart is subjected to a high mechanical stress. The aortic valve and the mitral valve are in close contact at the level of the left trigone, so that the anterior commissure of the mitral valve is significantly affected by mechanical modifications of the aortic root (11,17).

The biomechanics of the MV differs between the leaflets and the connective support. A linear inverse finite element technique was used to measure the properties of the MV anterior leaflet *in vivo*. The mechanical testing was performed by Stanford group in order to assess the stiffness of anterior leaflets, but these results are not in agreement with *ex-vivo* studies on explanted anterior leaflets placed in heart simulators, reporting circumferential and radial strains oscillating between 15% and 40%. *In-vitro* studies of mechanical testing underlined inadequacy of biomodelling of numerical studies on the MV apparatus. Recent biomechanics studies suggest that all the components of the MV are responsible of active contraction thus affecting MV functionality and self-influencing each component of the mechanism (19-24).

General considerations of mitral valve regurgitation in patients with TAVR

Patients with severe MR have been generally excluded from randomized clinical trials, making poor the impact that associated MR can have on clinical outcomes after TAVR (25-31). Mitral-valve pathology is characterized predominantly by organic etiology, documented in about 70% of studied patients (32). The patients who received the transcatheter valvular therapy for severe aortic valve stenosis are predominantly older with annular and/or leaflets calcification of MV (33,34). The prolapsing mitral valve, when documented, does not have excess leaflet tissue but shows fibroelastic deficiency indicating a myxomatous processes (1,34). A functional MR in ischemicnon ischemic cardiomyopathy may be highlighted in patients who received a TAVR (26,27,29,30). MV structure is normal and the gap in leaflet coaptation is determined only by LV remodeling. Echographic-based assessment shows normal leaflets with a restrictive movement, that is determined by tethering resulting in outward displacement of papillary muscles and worsening in sphericity of LV wall. Although these patients can have a regional LV wall motion abnormality with a preserved overall LV function; however various degrees of LV systolic dysfunction, geometric changes, or annular dilation can be revealed. Moreover, many elderly patients have severe target coronary lesion or clinical evidence of ischemic cardiomyopathy. The presence of LV remodeling in the population of patients with isolated compensated aortic stenosis is not generally linked to functional MR. However, several factors must be considered whose presence influences the grade of functional MR in these subjects. For example, the high prevalence of CAD with consequent ischemic MR may account for LV dilation observed in the late phase of aortic stenosis. Another factor that contributes to increased driving force through the regurgitation area is the marked increase in LV-to-left atrial pressure gradient observed in case of severe AS. Thus, the possibility of mixed etiologies must be taken into account in assessing the severity of the MR and its potential regression or worsening after TAVR. Patients with AS and concomitant MR may evidence an ERO that is less variable than in case of isolated AS, and this parameter should be systematically measured. Similarly, volume overload on the left ventricle imposes rigorous echographic detection as LV volume abnormalities have a role in MR etiology. Results from studies showing an EROA ≥0.2 cm^2 and a regurgitant volume ≥30 mL/beat have been associated with poorer outcomes in case of functional MR. When the range of regurgitant orifice area is between 0.2 and 0.4 cm^2 a more thorough echocardiographic evaluation of regurgitation severity is required with the use of additional parameters (2,3,7,35,36).

Clinical evidence

We are not aware of any randomized trials that have evaluated the outcomes of TAVR procedure in patients with significant MR, either treated percutaneously or with medical therapy alone. However, evidence from the RCT Partner and TAVR registries strongly suggests that the proportion of concomitant moderate-to-severe MR oscillates between 2% and 33% (27,29,30,37-45). In the Partner 3 study (30), moderate-to-severe MR was present in 1.3% (6 out of 477 patients) in TAVR group and in 3.2% (14 out of 437 patients) of SAVR group (P=0.045, data not shown), and this statistically significant baseline difference may account for worse results in the SAVR group. Worth noting, studies did not report systematically the grade of regurgitant volume and ERO for the assessment of MR and the effect on early and mid-term outcomes. One study, SOURCE (SAPIEN Aortic Bioprosthesis European Outcome) registry evaluated the rate of MR which reached 25.2%, but no data were reported about the severity of concomitant mitral valve disease. Incongruences are noticed concerning the rate and the grade of MR. Hence, some study reports the rate of grade ≥3/4 or severe MR that was estimated at 10% of all cohort. When the rate was grade ≥2/4 or moderate the incidence of MR increased up to 20% (37,39-42,44,45).

Data from the PARTNER trial showed an incidence of moderate-to-severe MR that range between 19.8% in the cohort A and 22.2% in the cohort B (39,40). One meta-analysis from PARTNER 1 cohorts A and B showed that 3.8% of patients had severe MR, although severe MR was an a priori exclusion criterion for enrollment (46). In a recent meta-analysis performing that included 8 studies involving 8,927 patients, none-mild MR was present in 77.8% and moderate-severe MR in 22.2% of the patients (47).

The number of studies that provided details on the etiology of MR in patients undergoing TAVR are poor (45,48-54). Although a vast majority of patients have an organic mitral valve disease a range between 30% and 50% among recipients of TAVR shows a functional MR that is likely to improve after mechanical intervention (33).

We had found a discrepancy in the studies that evaluate the impact of significant MR in early mortality (30-day mortality) after TAVR (46). To our knowledge, some studies reported an increase in early mortality (37) after TAVR whereas others do not notice this complication (44-46). Again, however, data from studies suggest for a discordance concerning severity of MR, highlighting both severe MR (37,44) or moderate to severe (43,46,53,55,56), that might partially account for the clinical differences.

A global weighted analysis of 8 studies showed that patients with moderate-to-severe MR had higher early mortality [odds ratio (OR) 1.49; 95% CI, 1.12 to 2.00, P=0.004]. However, the studies lack information regarding the nature of diseased mitral valve, functional or organic, not indicating which of it can affect early mortality.

Patients with moderate to severe MR may have hemodynamic frailty with clinical deterioration during mechanical intervention. However, increasing severity of hemodynamic status inflicts a volume overload on the LV that results in HF if sustained over time (57). In addition, pulmonary congestion and the resulting pulmonary hypertension can determine cardiogenic shock leading to poorer outcomes both in patients who received SAVR than in those who had TAVR (37,38,45,58,59). The high risk of decompensated heart failure may imply more hospitalization due to HF within the first months (45).

Evidence from several series strongly suggests that concomitant moderate-to-severe MR independently predicts mid-term mortality after TAVR. One study evaluated the effect of moderate to severe MR on mortality in 1,391 patients undergoing TAVR within 1 month; after excluding 30-day events, patients with significant MR undergoing TAVR had a worse survival rate [adjusted risk ratio 1.70; 95% confidence interval (CI), 1.19 to 2.42; P=0.003] (42).

In another study, 1,007 patients with moderate to severe MR and aortic stenosis were studied. During the follow-up period of 1 year, the MR was independently associated with a higher risk of death (HR 1.7; 95% CI, 1.2 to 3.4; P=0.01) (45).

In German and Italian registries, a significant increase of MR in patients who underwent TAVR was shown, similarly to other cardiac diseases (60). In contrast, in a report from the PARTNER trial (TAVR cohort) with 499 patients who received TAVR, there was no statistically significant difference in survival at 30 days between patients with moderate-to-severe MR (20.6% of the cohort) and those who had no or mild MR (3.9% *vs.* 6.1%, P=0.41) (46). A pooled analysis of 10 studies showed that patients with moderate-to-severe MR had higher late cumulative mortality (OR 1.44; 95% CI: 1.23 to 1.68, P<0.001).

The SWEDEHEART registry (61) included all TAVR patients in Sweden. Mild MR was observed in 82% of patients and moderate-to-severe MR in 18%. Baseline moderate-to-severe MR carried a higher mortality risk after 5 years (HR 1.29; 95% CI, 1.01–1.65, P=0.04). Notably, if pre-procedural moderate-to-severe MR improved to mild MR after TAVR, no excess mortality was observed (HR 1.09; 95% CI, 0.75–1.58, P=0.67). On the other hand, in case of persistence or worsening of MR after TAVR, 5-year mortality rates were increased (HR 1.97; 95% CI, 1.29–3.00, P=0.002). Factors associated with MR worsening were atrial fibrillation (OR 2.1; P=0.004), self-expanding valve (OR 3.8; P<0.001) and paravalvular leak (OR 4.3; P<0.001) (61).

Other studies indicate that post-procedural, but not pre-procedural moderate-to-severe MR was associated with mortality and adverse effects (62), and significant MR post TAVR resulted in adverse LV and right ventricular remodeling and poor hemodynamic suggesting an early treatment to reduce the clinical impact of MR after TAVR (62). Those results are supported by other studies (32,63-66) suggesting that intervention to treat persistent severe MR after TAVR should be discussed by the heart team. In fact, after stratification for MR after 30 days from TAVR, the 5-year cumulative incidence of adverse cardiac events (cardiovascular mortality and HF hospitalization) was 37.5%, 40.0%, and 58.2% in patients with mild, moderate, and severe MR, respectively (P<0.001). Compared to mild MR, severe HR carries a 5-fold increase in complications during mid-term follow-up (HR 4.83; 95% CI, 2.49–9.38, P<0.001).

The most recent analyses indicate that baseline MR grade ≥2 was connected with both early and late increased mortality rate (67). Patients who receive TAVR procedure are older with several comorbidities and a high-risk for frailty, hence severe MR with symptoms or with LV dysfunction or both should be observed until the resolution of the hemodynamic overload (57).

TAVR is associated with insignificant improvement in quality of life or functional capacity in one-fourth of patients (59,68,69). These results are not confirmed in others several studies in which an improvement in functional status was noticed (45,46,55,56). However, baseline differences such as the incidence of moderate-to-severe MR, as in the Partner 3 study, may account for different results.

One of the most common cause for poor functional response after TAVR is the severe baseline MR and organic nature is a worse condition (57). In patient with moderate to severe MR the poorer New York Heart Association class is not an accurate parameter for functional for the evaluation of functional improvement and it should not consider in combined end point of mortality and poor functional response (70,71). Clearly a further evaluation with the use of more objective and reliable tools is necessary to assess the real impact of MR after TAVR.

Clinical implication

Patients with significant MR should undergo transthoracic or transesophageal echocardiography (TTE/TEE) or computed tomography (CT) to evaluate the mechanism and severity of MR, LV size and function (32). Quantitative doppler assessments are advocated to establish the severity of MR mitral more accurately; parameters that indicate severe MR include a regurgitant volume >60 mL, a regurgitant fraction >50%, and an effective regurgitant orifice >40 mm. When severe aortic stenosis is combined to significant MR, we can observe various physiological change after aortic flow restoration resulting with a decreased MR severity (72). First, LV cavity pressure decreases dramatically after SAVR and, consequently, the trans-mitral pressure gradient may decrease, resulting in a reduction in MR in a large number of recipients of mechanical intervention. In patients who have functional MR this mechanism is not visible, and the reduction of the closing forces may determine a persistence of MR. Second, we can observe a decline of concentric myocardial hypertrophy related to a reduction in ventricular afterload that is frequent in patients who received mechanical intervention causing an improvement of mitral valve hemodynamics (73,74). Finally, a better improvement of reverse remodeling leads to restore an adequate geometry of LV causing an amelioration of functional MR related to a decrease of LV end-diastolic volume and mitral tethering forces (75). Clinical and echographic evidence might suggest a MR improvement after TAVR in case of functional etiology (45,51,53), but the identification of factors for potential improved LV reverse remodeling have a primary role in the evaluation of the likelihood of MR improvement after TAVR.

The use of CoreValve (Medtronic, Minneapolis, Minnesota) system, as documented in registries of TAVR, revealed that moderate-to-severe MR was an independent and effective predictor of late mortality (38,42,45). In patients in which the use of the CoreValve system was preferred (41,44), multivariable analysis failed to replicate the results of univariable analysis but an incidence of 50% was observed.

Data from registries reporting the use of balloon-expandable valves evidenced no impact on late mortality with a 100% of incidence (37,43,53,76). Conversely when evaluating the data from several report describing the use of self-expandable system, we found a higher rate of moderate-to-severe aortic regurgitation after TAVR (41,77-81), that could have a detrimental effect on LV remodeling and increase the exposure of patients with moderate to severe MR to adverse outcomes. Although difference in survival was detected when compare two systems of implant; however, a final word about which type of transcatheter heart valve therapy is optimal remains an objective for future studies.

Recently, a report that evaluate 1,110 patients has confirmed that significant MR is not uncommon in TAVR recipients and it was coupled with greater mortality both in hospital than 6-month follow-up clinical outcomes. By mean of a predictive model using multidetector CT that can evaluate the features of valvular and subvalvular mitral valve apparatus, the authors showed that in more than one-half of patients the degree of MR improves after TAVR. According to standardized imaging criteria, the authors concluded that at least 1 in 10 patients MR persists after TAVR and that they could benefit from percutaneous mitral procedures. The extreme solution considers the use of MitraClip after a dedicated pre-imaging evaluation (32).

Adverse effects

The most common cause of mechanic dysfunction of mitral valve is the altered post implant MV configuration. Predictors of mechanic dysfunction include associated MV abnormalities contributing to left ventricular outflow tract (LVOT) obstruction. Also, the role of a mechanic dysfunction of MV can be significant in case of anterior leaflet and chordae tendineae elongation with papillary muscles displacement (82-86). Each mechanism might individually or conjunctly contribute to the development of chordal slack, systolic anterior motion (SAM), or dynamic LVOT obstruction, eventually resulting in MR.

The role of mitral annular calcifications (MAC) has been recently evaluated by Okuno *et al*. (87). Authors concluded that isolated MAC has no effect on clinical outcomes following TAVR in patients with preserved MV function (adjusted HR 0.52; 95% CI, 0.21–1.33, P=0.173). However, patients with MV disease had an increased risk of death at 1 year irrespective of MAC (adjusted HR 1.97; 95% CI, 1.12–3.44, P=0.018 in case of MAC and significant MR). The role of MAC in patients undergoing TAVR with concomitant significant MR should be further investigated.

The experimental data from porcine biomechanical model of mitral valve were used in finite element studies of human MV to investigate the dynamic changes on the MV mechanical response during systole. Authors found that during systole the diseased MV bulged into the left atrium with the shape of a balloon, while the anterior leaflet of a normal MV remained in the LV. This phenomenon could be exacerbated significant MR post TAVR implant (21,22).

Areas of uncertainty

We are not aware of any RCT that have compared TAVR combined to Mitraclip procedure with TAVR alone for significant mitral-valve regurgitation and aortic stenosis, and it is not likely that this trial will be held before to determine with certainty safety and effectiveness of transcatheter mitral valve treatment using edge to edge procedure. Therefore, the current recommendation for percutaneous MV repair in the treatment of severe organic and functional MR is confined to handling of one valve (2).

It is unclear whether predictive biomodelling using 3D CT through finite element analysis (FEA) may give a contribute to the identification of patients who should undergo to double transcatheter valve therapy (10,11,17,88-92). Some investigators found evidences that a wrinkle process can induced tear in the mitral valve leaflet tissue leading for a progression of diseased MV in presence of degenerative MV disease (93,94) or the EROA may not change after successful TAVR (95).

The growing experience in the use of FEA research is required to develop predictive modelling performed through 3D imaging (10,11,17,96,97). Single and multi-center series involving a large number of patients may be useful to assess the indication to handling two valves by mean of transcatheter valve treatment using one of the validated risk-scoring algorithms (10,11,17,96,97). Intraoperative transesophageal echocardiography coupled with FEA investigation should be performed to provide anatomical and functional details for biomodelling assessment that would tailor the details of the operative procedure (10,11,17). This specific approach requires further evaluation for generalizability and cost-effectiveness and it is currently performed only in few specialized centers (10,11,17,96-99).

Conclusions

In recent years, the change in paradigm from surgical treatment to percutaneous options revealed the importance of comprehensively addressing all functionally and prognostically relevant factors in order to optimize treatment and improve long-term prognosis. The incidence and the prognostic impact of concomitant MR in patients undergoing TAVR requires specific attention as might trigger adjunctive strategy treatment which should be carefully evaluated in clinical trials.

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Footnote

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References

1. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. Nat Rev Cardiol 2011;8:162-72.
2. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252-89.
3. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). Eur

Heart J 2012;33:2451-96.
4. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-91.
5. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231-43.
6. Bonow RO, Brown AS, Gillam LD, et al. ACC/AATS/AHA/ASE/EACTS/HVS/SCA/SCAI/SCCT/SCMR/STS 2017 Appropriate use criteria for the treatment of patients with severe aortic stenosis. Eur J Cardiothorac Surg 2018;53:306-8y.
7. Bonow RO, Brown AS, Gillam LD, et al. ACC/AATS/AHA/ASE/EACTS/HVS/SCA/SCAI/SCCT/SCMR/STS 2017 Appropriate Use Criteria for the Treatment of Patients With Severe Aortic Stenosis: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Valve Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Soc Echocardiogr 2018;31:117-47.
8. Alghamdi AA, Elmistekawy EM, Singh SK, et al. Is concomitant surgery for moderate functional mitral regurgitation indicated during aortic valve replacement for aortic stenosis? A systematic review and evidence-based recommendations. J Card Surg 2010;25:182-7.
9. Rodés-Cabau J. Transcatheter aortic valve implantation: current and future approaches. Nat Rev Cardiol 2011;9:15-29.
10. Nappi F, Attias D, Avtaar Singh SS, et al. Finite element analysis applied to the transcatheter mitral valve therapy: Studying the present, imagining the future. J Thorac Cardiovasc Surg 2019;157:e149-51.
11. Nappi F, Carotenuto AR, Avtaar Singh SS, et al. Euler's Elastica-Based Biomechanics of the Papillary Muscle Approximation in Ischemic Mitral Valve Regurgitation: A Simple 2D Analytical Model. Materials (Basel) 2019. doi: 10.3390/ma12091518.
12. Nappi F, Spadaccio C, Fraldi M. Reply: Papillary Muscle Approximation Is an Anatomically Correct Repair for Ischemic Mitral Regurgitation. J Am Coll Cardiol 2016;68:1147-8.
13. Nappi F, Spadaccio C. Biomechanics of failed ischemic mitral valve repair: Discovering new frontiers. J Thorac Cardiovasc Surg 2017;154:832-3.
14. Nappi F, Santana O, Mihos CG. Geometric distortion of the mitral valve apparatus in ischemic mitral regurgitation: Should we really forfeit the opportunity for a complete repair? J Thorac Cardiovasc Surg 2019;158:e91-2.
15. Nappi F, Lusini M, Avtaar Singh SS, et al. Risk of Ischemic Mitral Regurgitation Recurrence After Combined Valvular and Subvalvular Repair. Ann Thorac Surg 2019;108:536-43.
16. Nappi F, Spadaccio C, Chello M, et al. Double row of overlapping sutures for downsizing annuloplasty decreases the risk of residual regurgitation in ischaemic mitral valve repair. Eur J Cardiothorac Surg 2016;49:1182-7.
17. Nappi F, Spadaccio C, Mihos CG, et al. Euler's elastica-based biomechanical assessment for neochordal insertion in the treatment of degenerative mitral valve repair. J Thorac Cardiovasc Surg 2018;155:603-5.
18. Stähli BE, Reinthaler M, Leistner DM, et al. Transcatheter Aortic Valve Replacement and Concomitant Mitral Regurgitation. Front Cardiovasc Med 2018;5:74.
19. Krishnamurthy G, Ennis DB, Itoh A, et al. Material properties of the ovine mitral valve anterior leaflet in vivo from inverse finite element analysis. Am J Physiol Heart Circ Physiol 2008;295:H1141-9.
20. Kunzelman KS, Cochran RP, Chuong C, et al. Finite element analysis of the mitral valve. J Heart Valve Dis 1993;2:326-40.
21. Prot V, Skallerud B. Contributions of prestrains, hyperelasticity, and muscle fiber activation on mitral valve systolic performance. Int J Numer Method Biomed Eng 2017. doi: 10.1002/cnm.2806.
22. Prot V, Skallerud B, Sommer G, et al. On modelling and analysis of healthy and pathological human mitral valves: two case studies. J Mech Behav Biomed Mater 2010;3:167-77.
23. Sacks MS, He Z, Baijens L, et al. Surface strains in the anterior leaflet of the functioning mitral valve. Ann Biomed Eng 2002;30:1281-90.
24. Jimenez JH, Liou SW, Padala M, et al. A saddle-shaped annulus reduces systolic strain on the central region of the mitral valve anterior leaflet. J Thorac Cardiovasc Surg 2007;134:1562-8.
25. Kapadia SR, Leon MB, Makkar RR, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2485-91.
26. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic

stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2477-84.
27. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2016;374:1609-20.
28. Auffret V, Lefevre T, Van Belle E, et al. Temporal Trends in Transcatheter Aortic Valve Replacement in France: FRANCE 2 to FRANCE TAVI. J Am Coll Cardiol 2017;70:42-55.
29. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2017;376:1321-31.
30. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med 2019;380:1695-705.
31. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790-8.
32. Cortés C, Amat-Santos IJ, Nombela-Franco L, et al. Mitral Regurgitation After Transcatheter Aortic Valve Replacement: Prognosis, Imaging Predictors, and Potential Management. JACC Cardiovasc Interv 2016;9:1603-14.
33. Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet 2009;373:1382-94.
34. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611-44.
35. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777-802.
36. Topilsky Y, Grigioni F, Enriquez-Sarano M. Quantitation of mitral regurgitation. Semin Thorac Cardiovasc Surg 2011;23:106-14.
37. Rodés-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol 2010;55:1080-90.
38. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation 2011;123:299-308.
39. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.
40. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.
41. Gilard M, Eltchaninoff H, Iung B, et al. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med 2012;366:1705-15.
42. Zahn R, Gerckens U, Linke A, et al. Predictors of one-year mortality after transcatheter aortic valve implantation for severe symptomatic aortic stenosis. Am J Cardiol 2013;112:272-9.
43. Di Mario C, Eltchaninoff H, Moat N, et al. The 2011-12 pilot European Sentinel Registry of Transcatheter Aortic Valve Implantation: in-hospital results in 4,571 patients. EuroIntervention 2013;8:1362-71.
44. Sabaté M, Canovas S, Garcia E, et al. In-hospital and mid-term predictors of mortality after transcatheter aortic valve implantation: data from the TAVI National Registry 2010-2011. Rev Esp Cardiol (Engl Ed) 2013;66:949-58.
45. Bedogni F, Latib A, De Marco F, et al. Interplay between mitral regurgitation and transcatheter aortic valve replacement with the CoreValve Revalving System: a multicenter registry. Circulation 2013;128:2145-53.
46. Barbanti M, Webb JG, Hahn RT, et al. Impact of preoperative moderate/severe mitral regurgitation on 2-year outcome after transcatheter and surgical aortic valve replacement: insight from the Placement of Aortic Transcatheter Valve (PARTNER) Trial Cohort A. Circulation 2013;128:2776-84.
47. Chakravarty T, Van Belle E, Jilaihawi H, et al. Meta-analysis of the impact of mitral regurgitation on outcomes after transcatheter aortic valve implantation. Am J Cardiol 2015;115:942-9.
48. Tzikas A, Piazza N, van Dalen BM, et al. Changes in mitral regurgitation after transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2010;75:43-9.
49. Durst R, Avelar E, McCarty D, et al. Outcome and improvement predictors of mitral regurgitation after transcatheter aortic valve implantation. J Heart Valve Dis 2011;20:272-81.
50. De Chiara B, Moreo A, De Marco F, et al. Influence of CoreValve ReValving System implantation on mitral valve function: an echocardiographic study in selected patients. Catheter Cardiovasc Interv 2011;78:638-44.
51. Samim M, Stella PR, Agostoni P, et al. Transcatheter aortic implantation of the Edwards-SAPIEN bioprosthesis: insights on early benefit of TAVI on mitral regurgitation. Int J Cardiol 2011;152:124-6.

52. Hekimian G, Detaint D, Messika-Zeitoun D, et al. Mitral regurgitation in patients referred for transcatheter aortic valve implantation using the Edwards Sapien prosthesis: mechanisms and early postprocedural changes. J Am Soc Echocardiogr 2012;25:160-5.
53. Toggweiler S, Boone RH, Rodes-Cabau J, et al. Transcatheter aortic valve replacement: outcomes of patients with moderate or severe mitral regurgitation. J Am Coll Cardiol 2012;59:2068-74.
54. Giordana F, Capriolo M, Frea S, et al. Impact of TAVI on mitral regurgitation: a prospective echocardiographic study. Echocardiography 2013;30:250-7.
55. D'Onofrio A, Gasparetto V, Napodano M, et al. Impact of preoperative mitral valve regurgitation on outcomes after transcatheter aortic valve implantation. Eur J Cardiothorac Surg 2012;41:1271-6; discussion 6-7.
56. Hutter A, Bleiziffer S, Richter V, et al. Transcatheter aortic valve implantation in patients with concomitant mitral and tricuspid regurgitation. Ann Thorac Surg 2013;95:77-84.
57. De Bonis M, Maisano F, La Canna G, et al. Treatment and management of mitral regurgitation. Nat Rev Cardiol 2011;9:133-46.
58. Melby SJ, Moon MR, Lindman BR, et al. Impact of pulmonary hypertension on outcomes after aortic valve replacement for aortic valve stenosis. J Thorac Cardiovasc Surg 2011;141:1424-30.
59. Gotzmann M, Pljakic A, Bojara W, et al. Transcatheter aortic valve implantation in patients with severe symptomatic aortic valve stenosis-predictors of mortality and poor treatment response. Am Heart J 2011;162:238-45.e1.
60. Grigioni F, Enriquez-Sarano M, Zehr KJ, et al. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103:1759-64.
61. Feldt K, De Palma R, Bjursten H, et al. Change in mitral regurgitation severity impacts survival after transcatheter aortic valve replacement. Int J Cardiol 2019;294:32-6.
62. Ben-Assa E, Biner S, Banai S, et al. Clinical impact of post procedural mitral regurgitation after transcatheter aortic valve replacement. Int J Cardiol 2020;299:215-21.
63. Abdelghani M, Abdel-Wahab M, Hemetsberger R, et al. Fate and long-term prognostic implications of mitral regurgitation in patients undergoing transcatheter aortic valve replacement. Int J Cardiol 2019;288:39-43.
64. Mavromatis K, Thourani VH, Stebbins A, et al. Transcatheter Aortic Valve Replacement in Patients With Aortic Stenosis and Mitral Regurgitation. Ann Thorac Surg 2017;104:1977-85.
65. O'Sullivan CJ, Tuller D, Zbinden R, et al. Impact of Mitral Regurgitation on Clinical Outcomes After Transcatheter Aortic Valve Implantation. Interv Cardiol 2016;11:54-8.
66. Takagi H, Umemoto T. Coexisting Mitral Regurgitation Impairs Survival After Transcatheter Aortic Valve Implantation. Ann Thorac Surg 2015;100:2270-6.
67. Muratori M, Fusini L, Tamborini G, et al. Mitral valve regurgitation in patients undergoing TAVI: Impact of severity and etiology on clinical outcome. Int J Cardiol 2020;299:228-34.
68. Bagur R, Rodes-Cabau J, Dumont E, et al. Performance-based functional assessment of patients undergoing transcatheter aortic valve implantation. Am Heart J 2011;161:726-34.
69. Reynolds MR, Magnuson EA, Wang K, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). J Am Coll Cardiol 2012;60:548-58.
70. Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J 2005;150:707-15.
71. Arnold SV, Spertus JA, Lei Y, et al. Use of the Kansas City Cardiomyopathy Questionnaire for monitoring health status in patients with aortic stenosis. Circ Heart Fail 2013;6:61-7.
72. Simpson IA, Valdes-Cruz LM, Sahn DJ, et al. Doppler color flow mapping of simulated in vitro regurgitant jets: evaluation of the effects of orifice size and hemodynamic variables. J Am Coll Cardiol 1989;13:1195-207.
73. Walther T, Falk V, Langebartels G, et al. Prospectively randomized evaluation of stentless versus conventional biological aortic valves: impact on early regression of left ventricular hypertrophy. Circulation 1999;100:II6-10.
74. Ikonomidis I, Tsoukas A, Parthenakis F, et al. Four year follow up of aortic valve replacement for isolated aortic stenosis: a link between reduction in pressure overload, regression of left ventricular hypertrophy, and diastolic function. Heart 2001;86:309-16.
75. Gotzmann M, Lindstaedt M, Bojara W, et al. Hemodynamic results and changes in myocardial function after transcatheter aortic valve implantation. Am Heart J 2010;159:926-32.
76. Rodés-Cabau J, Webb JG, Cheung A, et al. Long-term outcomes after transcatheter aortic valve implantation: insights on prognostic factors and valve durability from the Canadian multicenter experience. J Am Coll Cardiol 2012;60:1864-75.
77. Moat NE, Ludman P, de Belder MA, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol 2011;58:2130-8.

78. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol 2013;61:1585-95.
79. Nombela-Franco L, Ruel M, Radhakrishnan S, et al. Comparison of hemodynamic performance of self-expandable CoreValve versus balloon-expandable Edwards SAPIEN aortic valves inserted by catheter for aortic stenosis. Am J Cardiol 2013;111:1026-33.
80. Watanabe Y, Hayashida K, Yamamoto M, et al. Transfemoral aortic valve implantation in patients with an annulus dimension suitable for either the Edwards valve or the CoreValve. Am J Cardiol 2013;112:707-13.
81. Van Belle E, Juthier F, Susen S, et al. Postprocedural aortic regurgitation in balloon-expandable and self-expandable transcatheter aortic valve replacement procedures: analysis of predictors and impact on long-term mortality: insights from the FRANCE2 Registry. Circulation 2014;129:1415-27.
82. Kim DH, Handschumacher MD, Levine RA, et al. In vivo measurement of mitral leaflet surface area and subvalvular geometry in patients with asymmetrical septal hypertrophy: insights into the mechanism of outflow tract obstruction. Circulation 2010;122:1298-307.
83. Halpern DG, Swistel DG, Po JR, et al. Echocardiography before and after resect-plicate-release surgical myectomy for obstructive hypertrophic cardiomyopathy. J Am Soc Echocardiogr 2015;28:1318-28.
84. Hwang HJ, Choi EY, Kwan J, et al. Dynamic change of mitral apparatus as potential cause of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. Eur J Echocardiogr 2011;12:19-25.
85. Schoendube FA, Klues HG, Reith S, et al. Long-term clinical and echocardiographic follow-up after surgical correction of hypertrophic obstructive cardiomyopathy with extended myectomy and reconstruction of the subvalvular mitral apparatus. Circulation 1995;92:II122-7.
86. Kiriyama H, Kodera S, Ando J, et al. Worsening of Mitral Regurgitation by Balloon Aortic Valvuloplasty for Severe Aortic Stenosis. Int Heart J 2019;60:768-71.
87. Okuno T, Asami M, Khan F, et al. Does isolated mitral annular calcification in the absence of mitral valve disease affect clinical outcomes after transcatheter aortic valve replacement? Eur Heart J Cardiovasc Imaging 2020;21:522-32.
88. Khalighi AH, Rego BV, Drach A, et al. Development of a Functionally Equivalent Model of the Mitral Valve Chordae Tendineae Through Topology Optimization. Ann Biomed Eng 2019;47:60-74.
89. Kunzelman KS, Reimink MS, Cochran RP. Flexible versus rigid ring annuloplasty for mitral valve annular dilatation: a finite element model. J Heart Valve Dis 1998;7:108-16.
90. Kunzelman KS, Cochran RP. Mechanical properties of basal and marginal mitral valve chordae tendineae. ASAIO Trans 1990;36:M405-8.
91. He Z, Ritchie J, Grashow JS, et al. In vitro dynamic strain behavior of the mitral valve posterior leaflet. J Biomech Eng 2005;127:504-11.
92. Rego BV, Khalighi AH, Drach A, et al. A noninvasive method for the determination of in vivo mitral valve leaflet strains. Int J Numer Method Biomed Eng 2018;34:e3142.
93. Mohammadi H, Herzog W, Mequanint K. Micro-Finite Element Modeling of Wrinkle Formation for Cell Locomotion Applications. J Mech Med Biol 2013;13:1350019.
94. Mohammadi H, Bahramian F, Herzog W. A novel continuum model for the reduction of numerical errors of finite-element analysis. Proc Inst Mech Eng C J Mech Eng Sci 2011;225:817-25.
95. Thomas M, Schymik G, Walther T, et al. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: A European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2010;122:62-9.
96. Morganti S, Conti M, Aiello M, et al. Simulation of transcatheter aortic valve implantation through patient-specific finite element analysis: two clinical cases. J Biomech 2014;47:2547-55.
97. Morganti S, Brambilla N, Petronio AS, et al. Prediction of patient-specific post-operative outcomes of TAVI procedure: The impact of the positioning strategy on valve performance. J Biomech 2016;49:2513-9.
98. Nappi F, Spadaccio C, Sablayrolles JL. Pushing the Limits in Transcatheter Aortic Valve Replacement: High-Volume Center's Effect, Overconfidence, or Something Else? JACC Cardiovasc Interv 2016;9:2186-8.
99. Nappi F, Mazzocchi L, Avtaar Singh SS, et al. Complementary Role of the Computed Biomodelling through Finite Element Analysis and Computed Tomography for Diagnosis of Transcatheter Heart Valve Thrombosis. Biomed Res Int 2018;2018:1346308.

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