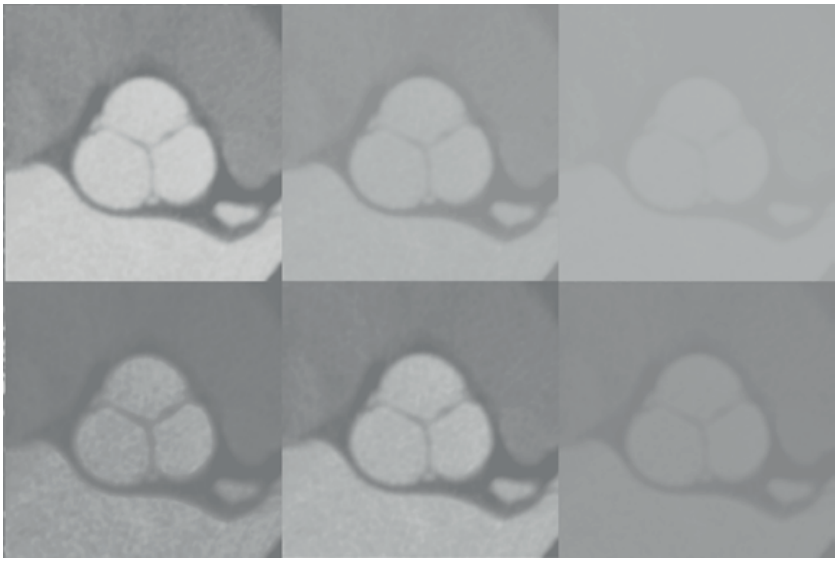
Diagnosis and management of left valvular heart disease with advanced echocardiography and cardiac computed tomography

Kamperidis, V.

CHAPTER 3

Diagnosis and management of aortic valve stenosis in patients with heart failure



Vasileios Kamperidis MD, PhD1,2; Victoria Delgado MD, PhD1; Nicolas M van Mieghem, MD, PhD3; Arie-Pieter Kappetein, MD, PhD;4 Martin B Leon, MD5; Jeroen J Bax MD, PhD1

Eur J Heart Fail 2016;18(5):469-81

Abstract

Aortic stenosis (AS) is the most frequent degenerative valvular heart disease in Western countries and its prevalence increases parallel to the ageing process of the population. Heart failure (HF) may be present in up to a quarter of patients with severe AS posing diagnostic and management challenges. The present article reviews the prevalence of HF in severe AS patients, discusses the diagnostic challenges and the advances in multimodality imaging to identify the patients that may benefit from surgical or transcatheter aortic valve replacement and summarizes the current evidence on management for this group of patients.

Keywords

Aortic stenosis;
Heart failure;
Stress echocardiography;
Multi-detector computed tomography;
Transcatheter aortic valve replacement

INTRODUCTION

Aortic stenosis (AS) is the most frequent degenerative valvular heart disease in Western countries and its prevalence increases with the ageing of the population.[1, 2] While the development of symptoms (angina, syncope or dyspnea) demarks an inflexion point in the survival of the patients with AS, the correlation between severity of AS and onset of symptoms is poor and depends largely on the hypertrophic response of the left ventricle (LV) to the pressure overload.[3] LV hypertrophy is a compensatory mechanism to restore wall stress and maintain cardiac output under increasing pressure afterload caused by the stenotic valve. However, progressive cardiomyocyte death and consequent fibrosis that accompany LV hypertrophy may lead to the development of LV dysfunction and heart failure (HF) symptoms. The onset of symptoms is not the only determinant of the timing for intervention in severe AS. Reduction of LV ejection fraction (LVEF) <50% even in asymptomatic patients with severe AS is also considered as class I indication (level of evidence B) for aortic valve replacement.[4, 5] However, the co-existence of severe AS, reduced LVEF and HF is complex and poses diagnostic and clinical decision-making dilemmas.

In HF patients with low LVEF, aortic valve area (AVA) ≤1.0cm^2 and low mean transaortic pressure gradient (<40mmHg) frequently co-exist challenging the diagnosis of severe AS.[6] In this circumstance, differentiation between true severe AS and pseudosevere AS is mandatory. In true severe AS, the compensatory mechanism of LV hypertrophy is exhausted with cardiomyocyte death and myocardial fibrosis that lead to reduced LVEF and low stroke volume and transaortic gradient. This entity is known as "classical" low-flow low-gradient severe AS. In contrast, in pseudosevere AS, reduced LVEF is caused by a primary dysfunction of the myocardium leading to reduced stroke volume, reduced opening forces of the valve and underestimation of AVA.

Besides the "classical" low-flow low-gradient severe AS, another circumstance characterized by inconsistent grading of severe AS is the "paradoxical" low-flow low-gradient severe AS, where LVEF is preserved (≥50%) and the reason of low-flow and consequently low-gradient AS is other than systolic HF. This condition is characterized by a small LV chamber size due to pronounced concentric remodeling in response to increased global afterload and reduced systemic arterial compliance which cause impaired LV mechanics (despite preserved LVEF) and diastolic filling.[6]

The decision making for patients with severe AS, reduced LVEF and HF is an important clinical dilemma. Currently the therapeutic options are conservative medical treatment, surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI).[4, 5] Data from randomized clinical trials and observational registries have provided important evidence on the benefits and risks of SAVR versus TAVI.[7, 8] However, there remain areas of uncertainty in the treatment of patients with severe AS and HF (i.e. patients with LVEF<30%, treatment options for patients with pseudosevere AS and patients with preserved LVEF and inconsistently graded severe AS).

The present review article provides an overview of current literature on the prevalence of HF (defined as reduced LVEF) in patients with severe AS, focusing on the diagnostic challenges and the various therapeutic options.

PREVALENCE OF HF IN SEVERE AS PATIENTS

In AS the left ventricle responds to the increased pressure load with adaptive concentric wall hypertrophy that maintains wall stress and LVEF. However, at this point, LV diastolic filling and LV longitudinal shortening are already impaired.[3, 9] In more advanced stages of AS, the pressure overload cannot be counterbalanced by the LV hypertrophy leading to reduced LVEF and HF symptoms and poor outcomes.[3, 9]

The prevalence of HF among severe AS patients varies largely based on the definition of HF (i.e. LVEF<50%, presence of symptoms) and the characteristics of patients included in the studies (Figure 1).[7, 10-13] In a large retrospective series of 9940 patients with severe AS, the prevalence of symptomatic LV dysfunction (LVEF<50%) was 24% whereas the prevalence of asymptomatic LV dysfunction was 0.4%.[10] In addition, in a retrospective population-level epidemiological study of hospitalized care in Scotland, among 13 200 patients diagnosed with AS (mean age 76±11 years old, 47% male), 25.1% were admitted with concomitant HF and 10.5% had at least one episode of previous HF hospitalization.[14] This prevalence was higher in a retrospective study including 453 patients with severe AS (mean age 75±13 years old, 48% male) who were conservatively treated during 1.5 years of follow-up: 35% of patients had an LVEF<40%.[11]

Reduced LVEF is associated with increased operative mortality risk and up to 30% of the patients with severe AS and reduced LVEF were deemed inoperable according to the EuroHeart Survey.[15] The advent of TAVI has changed the management of patients with severe AS and data from randomized clinical trials and registries on TAVI may provide more information on the prevalence of HF in severe AS patients. For example, among the 971 patients with severe AS included in the Placement of Aortic Transcatheter Valve (PARTNER) trial cohorts A and B, 23% had LVEF<50%.[7] In the US CoreValve trial, which randomized 795 patients with severe AS and high operative risk to TAVI or SAVR, 19% of patients reported NYHA functional class IV HF symptoms while the prevalence of LVEF<50% was not reported.[16] These randomized clinical trials excluded patients with LVEF<20% and, therefore may not represent the real-world patients treated with TAVI. In the the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry, including 7710 patients treated with TAVI, the prevalence of LVEF<30% was 7%.[13] Similar prevalence has been reported across several European registries of patients with severe AS treated with SAVR or TAVI.[12, 17-20] The largest European registry so far is the German Aortic Valve Registry (GARY) including 15 964 patients treated with TAVI;[12] in this registry the prevalence of LVEF<30% was 9.5%.

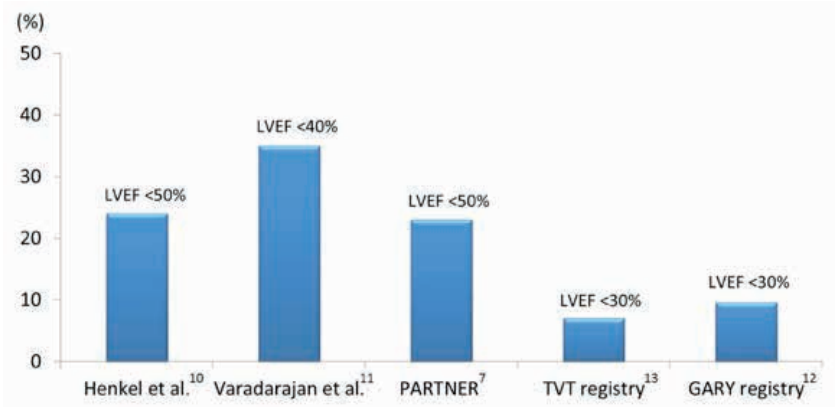


Figure 1. Prevalence of heart failure based on left ventricular ejection fraction (LVEF) in patients with severe aortic stenosis.

Besides failure of LV concentric hypertrophic remodeling to match the increased pressure overload, concomitant underlying coronary artery disease (CAD) is an important cause of HF in AS patients and has important therapeutic and prognostic implications.[21] Calcific AS and CAD share common pathophysiologic mechanisms and therefore frequently coexist.[22] In patients undergoing SAVR, coronary artery bypass grafting was performed in >50% of patients aged over 70 years.[23] In a recent observational analysis comparing 2286 patients with severe AS undergoing SAVR and coronary artery bypass grafting versus 1637 patients undergoing isolated SAVR, the short- and long-term prognosis of the former group was worse (survival rates at respective 30 days and 10 years: 97.6% versus 98.7% and 43% versus 59%).[24] The study showed that the increased mortality of patients undergoing combined SAVR and coronary artery bypass grafting was associated with the effects of pre-existing ischemic myocardial damage and co-morbidities. Therefore, evaluation of the presence of significant coronary artery disease and its consequences on LV performance is relevant for appropriate timing of SAVR.

In the randomized clinical trials on TAVI, the reported prevalence of coronary artery disease ranged between 74-76%[7, 16] whereas this prevalence is lower in the TAVI registries ranging from 31% to 69%.[12, 13, 17, 18, 20] In this specific group of patients, management of concomitant significant coronary artery disease remains controversial. In elderly patients, complete revascularization in patients undergoing TAVI seems less paramount.[25, 26] However, similarly to surgical series, some observational studies have suggested that the presence of myocardial ischemic damage (myocardial scar) is associated with worse outcome after TAVI.[27, 28]

DIAGNOSTIC CHALLENGES IN PATIENTS WITH SEVERE AS AND HF

In patients with reduced LVEF, inconsistently graded severe AS (tight AVA with low transvalvular gradients/velocity) can be observed in 5-10% of patients with severe AS posing a diagnostic dilemma.[29, 30] Differentiation between true severe AS and pseudosevere AS is crucial to decide the most appropriate management (aortic valve replacement or medical treatment, respectively).

True severe AS versus pseudosevere AS

The outcome of patients with low flow low gradient severe AS and reduced LVEF is dismal under medical therapy but the operative mortality is high and therefore accurate assessment of the AS grade and the severity of LV myocardial damage is crucial to select the appropriate treatment.[29, 30] Calculation of AVA in this subgroup of patients is challenging since it is directly proportional to the cardiac output. Therefore, increasing the cardiac output (improving myocardial contractility and increasing stroke volume) with intravenous administration of dobutamine may help to assess the AVA in different flow status and differentiate between fix severe AS and pseudosevere AS.[31, 32] During intravenous administration of dobutamine at 5mcg/kg/min increase every 3-5 minutes until a maximum doses of 20 mcg/kg/min, the mean transvalvular gradient and the stroke volume are measured keeping constant the LV outflow tract diameter. The AVA is then calculated by continuity equation. An increase in ≥20% in wall motion score and in ≥20% in stroke volume relative to baseline define LV contractile[32] and flow reserve,[31] respectively. In true severe AS, LV wall motion score, stroke volume and transvalvular gradients increase (>30 mmHg) at low dose dobutamine whereas AVA remains fixed (≤1.0 cm^2). In contrast, in pseudosevere AS, the improvement in LV contractility and stroke volume leads to an increase in AVA (>1.0 cm^2 or absolute increase >0.3 cm^2) while the transvalvular gradients remain low.

Assessment of AS severity in patients without LV contractile or flow reserve

However, one third of the patients with low flow low gradient severe AS and reduced LVEF may not show LV contractile or flow reserve during dobutamine stress echocardiography.[31, 32] In this situation, definition of the severity of AS remains difficult. Several series have demonstrated that these patients have the highest operative mortality and the worst prognosis if medically treated.[31, 33] The lack of LV contractile or flow reserve can be due to increased afterload that blunts the myocardial response to dobutamine, the presence of significant coronary artery disease that reduces myocardial blood flow or the presence of extensive myocardial scar. To overcome the limitations of dobutamine stress echocardiography, several additional echocardiographic variables and imaging techniques have been proposed to identify patients with true severe AS.[34, 35]

In the multicenter Truly or Pseudo-Severe Aortic Stenosis (TOPAS) study, including 46 patients with low flow low gradient severe AS (AVA≤1.2 cm^2 or indexed AVA≤0.6 cm^2/m^2, mean gradient <40 mmHg and LVEF≤40%), the accuracy of the projected AVA to differentiate between true severe AS

and pseudosevere AS was investigated.[34] Twenty-three patients underwent SAVR and the severity of the AS was assessed by the surgeon. The projected AVA is defined as the AVA calculated at standardized flow rate (250 ml/s which corresponds to the normal flow rate observed in patients with severe AS and normal LVEF) using the formula: $AVA_{proj}=AVA_{rest} + VC \times (250-Q_{rest})$, where the AVA_{rest} is the AVA at baseline, Q_{rest} is the mean transvalvular flow rate and VC is the valve compliance which corresponds to the slope of the relationship between AVA and flow and represents the rate of change in AVA in relation to the flow during stress. A cut-off value of indexed $AVA_{proj} \leq 0.55$ cm^2/m^2 correctly classified true severe AS in 91% of patients who underwent SAVR.[34] In contrast, the percentage of correct classification of patients with true severe AS reduced to 71%, 65% and 61% when an increase in mean transvalvular gradient >30 mmHg, and AVA at peak stress <1.0 cm^2 or an increase in AVA <0.3 cm^2 were applied (Figure 2). With larger number of included patients (n=142, 52 patients undergoing SAVR), the investigators of the TOPAS study could confirm and extend these results.[36] However, this technique remains inaccurate in patients with increase in mean transvalvular flow rate <15%.[36]

Furthermore, simple evaluation of the aortic valve morphology and amount of calcifications causing restriction of the aortic cusps suggest the presence of severe AS. Computed tomography permits accurate evaluation of the aortic valve calcification burden (Figure 3). Using this imaging modality, Cueff et al. demonstrated in 49 patients with severe AS and LVEF≤40% (20 of them with an AVA<1cm^2 and mean transvalvular gradient≤40 mmHg) that an aortic valve calcification burden of 1651 AU or more identified the patients with true severe AS with an sensitivity, specificity, negative and positive predictive value of 95%, 89%, 80% and 97%, respectively.[35]

Imaging modalities for risk stratification.

Despite a significant reduction in operative mortality from 20% to 10% in the last years,[33] accurate risk stratification of patients with severe AS and reduced LVEF remains challenging. Patients with true severe AS, regardless the presence or absence of LV contractile and flow reserve during dobutamine stress echocardiography, have better prognosis when treated surgically rather than medically [31, 37] whereas patients with pseudosevere AS have better prognosis when medically treated.[38] Therefore, the definition of the severity of AS is the first step in risk stratification of patients with low flow low gradient severe AS and reduced LVEF. The presence of LV contractile or flow reserve has been associated with better prognosis in patients undergoing SAVR.[31] In a multicenter study including 136 patients with low flow low gradient severe AS and reduced LVEF, patients with LV flow reserve defined by an increase in LV stroke volume of ≥20% had lower perioperative mortality compared with patients without LV flow reserve (5% versus 32%, p=0.0002).[31] The presence of LV flow reserve was associated with better perioperative survival (odds ratio 0.091, 95% confidence interval 0.023-0.38; p=0.001) and long-term prognosis (hazard ratio 0.4, 95% confidence interval 0.23-0.69; p=0.001).[31] However, a subsequent study showed that in terms of LVEF recovery, patients with LV flow reserve had similar improvement in LVEF after SAVR as compared to patients without flow reserve.[39] Furthermore, data from the French multicenter registry demonstrated that in patients with

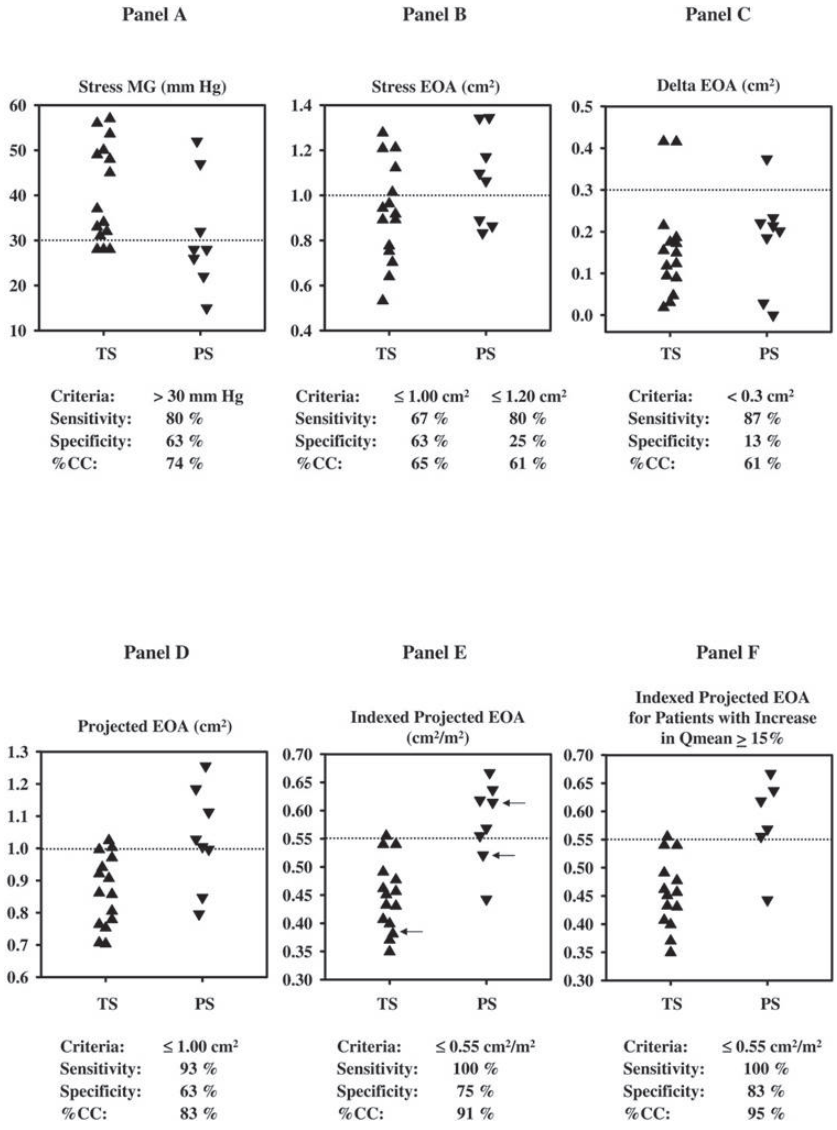


Figure 2. Low dose dobutamine stress echocardiography to differentiate true severe (TS) from pseudosevere (PS) aortic stenosis. The panels indicate the individual data of several echocardiographic parameters across each aortic stenosis category. The percentage of correctly classified true severe or pseudosevere AS was higher using the indexed projected aortic valve area. The arrows in E indicate the 3 patients who had <15% increase in mean flow rate with dobutamine stress. Reproduced with permission from Blais et al.[34]

Abbreviations:
CC: correct classification;
EOA: effective orifice area;
MG: mean gradient;
PS: pseudosevere;
Qmean: mean flow rate;
TS: true severe.

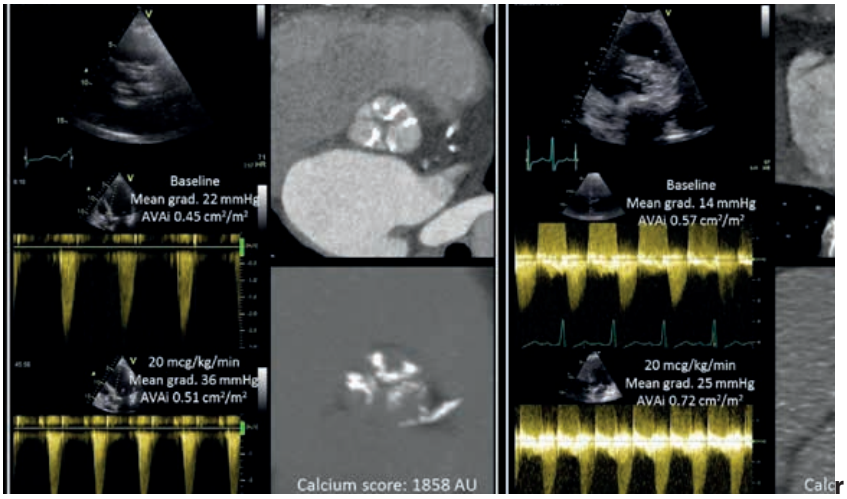


Figure 3. Aortic valve calcification burden assessed with computed tomography to differentiate between true and pseudosevere aortic stenosis. The left panel shows the example of an 85 year old patient with severe aortic stenosis and reduced left ventricular ejection fraction. During low dose dobutamine stress echocardiography, the mean gradient increased to 36 mmHg and the aortic valve area (AVA) remained <0.6 cm^2/m^2. On computed tomography, the calcium score of the valve was 1858 AU (above the cut-off value proposed to define severe AS; see main text). The right panel shows the example of a 79 year old woman with severe aortic stenosis and reduced left ventricular ejection fraction. During low dose dobutamine stress echocardiography, the AVA increased >0.6cm^2/m^2 suggesting the diagnosis of pseudosevere AS. On computed tomography, the calcium score of the aortic valve was below the proposed cut-off value).

low flow low gradient severe AS and reduced LVEF (n=81) and no LV flow reserve on dobutamine stress echocardiography, the long-term prognosis was better after SAVR compared with medical treatment.[37] Therefore, in this specific group of patients other factors should be considered to decide whether SAVR may be a safe and feasible therapeutic option.

Assessment of LV systolic function with conventional echocardiographic parameters such as LVEF or stroke volume in patients with low flow low gradient severe AS and reduced LVEF has several limitations since these parameters are highly influenced by LV geometry and preload conditions. The advent of novel echocardiographic techniques such as speckle tracking echocardiography has permitted detection of early myocardial damage in the left ventricle, and have proven good correlations with extent of myocardial scar assessed with LGE-MRI.[40, 41] By evaluating active myocardial deformation of the LV, speckle tracking echocardiography has shown that patients with aortic stenosis have impaired multidirectional deformation that may improve after SAVR (Figure 4).[42, 43] Particularly in the group of patients with low flow low gradient severe AS, investigators from the TOPAS study demonstrated the prognostic value of LV longitudinal strain in 47 patients (16 of them undergoing SAVR).[44] Peak longitudinal strain (rate) was measured at rest and following peak dose dobutamine infusion. Although peak longitudinal strain did not change (from -7.56±2.34% to -7.41±2.89%, p=0.7), peak longitudinal strain rate improved significantly at peak stress suggesting an improvement in LV contractility (from -0.38±0.12 s^{-1} to -0.53±0.18 s^{-1}, p<0.001). Peak stress longitudinal strain rate had incremental prognostic value over the STS-

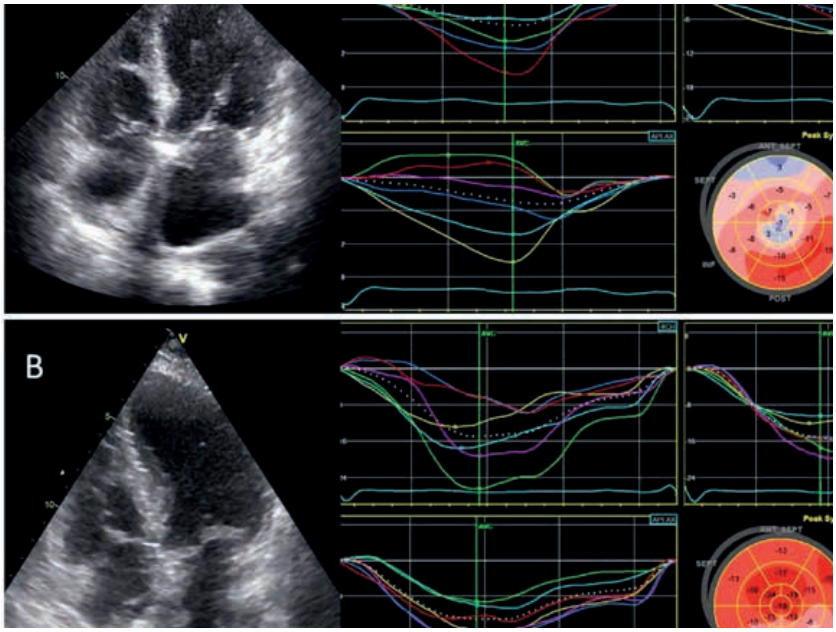


Figure 4. Improvement in left ventricular systolic function after transcatheter aortic valve implantation in an 83 year old female with severe aortic stenosis. Panel A shows the baseline left ventricular systolic function measured with conventional transthoracic echocardiography (LVEF 31%) and speckle tracking echocardiography (global longitudinal strain -5.9%). At 6 months follow-up, LVEF normalized and global longitudinal strain improved to -14.6% (panel B).

PROM (Society of Thoracic Surgeons Predicted Risk of Mortality score) and NT-proBNP (area under the curve 0.89, p=0.034).[44] In a subsequent sub-analysis of the TOPAS trial, including 202 patients with low gradient severe AS and LVEF≤40%, global LV longitudinal strain at rest and at peak stress was independently associated with outcome: a value of global LV longitudinal strain at rest of -9% or higher (indicating more impaired LV shortening) was associated with a two-fold increased mortality risk after correction for age, coronary artery disease, AVA_{proj} and type of treatment (SAVR versus medical treatment).[45] In addition, the lack of LV contractile reserve during dobutamine stress echocardiography (defined by a global LV longitudinal strain value at stress of -10% or higher) had incremental prognostic value over rest global LV longitudinal strain.

The underlying LV substrate is characterized by increasing amounts of myocardial fibrosis, which explains the impaired LV myocardial deformation and lack of LV contractile or flow reserve.[40, 46] The increased afterload imposed by the stenotic valve and associated factors such as hypertension and increased valvulo-arterial impedance lead to development of LV hypertrophy, which may eventually lead to HF if aortic stenosis (and arterial hypertension) is left untreated. This transition is characterized by increased apoptosis and fibrosis (scar) formation. The patterns of replacement fibrosis (scar) in AS patients assessed with late gadolinium contrast-enhanced magnetic resonance imaging (LGE-MRI) can be divided in midwall fibrosis and infarct-like fibrosis (subendocardial or transmural)(Figure 5).[47] In patients with low gradient severe AS, Herrmann et al showed that the amount of replacement

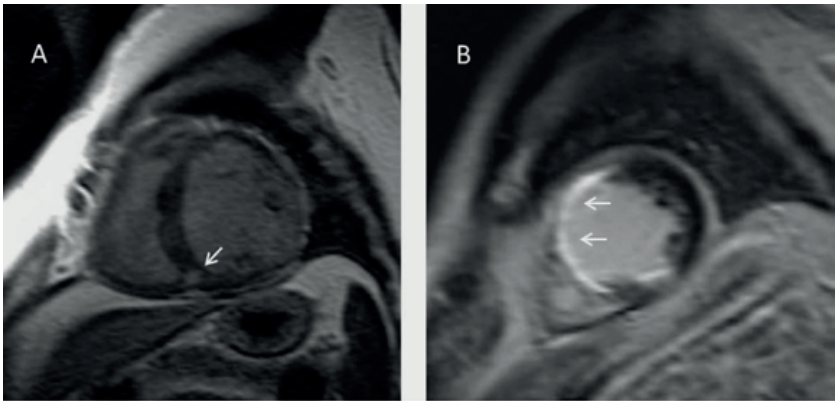


Figure 5. Late gadolinium contrast-enhanced magnetic resonance imaging in aortic stenosis. Panel A shows midwall focal fibrosis at the junction between the right and the left ventricle (arrow). Panel B shows infarct-like myocardial fibrosis with transmural hyperenhacement of the septum (arrows).

fibrosis (scar) was significantly larger compared with patients with high gradient severe AS, and was associated with more impaired LV longitudinal shortening.[46] In 143 patients with at least moderate AS undergoing LG-MRI, the presence of myocardial scar was observed in 64% (38% midwall scar; 28% infarct-like scar).[47] The presence of midwall and infarct-like scar was associated with 8- and 6-fold increase in all-cause mortality, respectively. On multivariate analysis, lower LVEF (HR: 0.96, 95% CI 0.94-0.99; p=0.009) and midwall fibrosis (HR: 5.35, 95% CI 1.16-24.56; p=0.003) were independently associated with all-cause mortality. In patients undergoing SAVR, the presence of LGE was also shown independently associated with worse postoperative mortality (HR:2.8, 95% CI 1.3-6.9; p=0.025).[28]

However, LGE identifies only regional differences in macroscopic replacement fibrosis (scar) and does not detect diffuse interstitial fibrosis, which is the predominant form of fibrosis at earlier stages of AS. MRI T1 mapping techniques have allowed quantifying this interstitial diffuse fibrosis (which can be considered as a precursor of HF). Flett et al applied

T1 mapping in patients with severe AS, and demonstrated that diffuse myocardial fibrosis correlated with clinical symptoms and LV systolic function parameters.[48] Six months after SAVR, LV mass reduced but the amount of diffuse myocardial fibrosis remained unchanged suggesting that regression in LV hypertrophy occurred due to reduction in cell volume rather than regression in diffuse fibrosis.

These studies demonstrate the clinical value of advanced assessment of LV function (beyond LVEF) using strain (rate) imaging or advanced anatomical imaging using MRI T1 mapping to assess myocardial tissue characteristics (fibrosis). These functional and anatomical imaging techniques may help to understand the outcome after SAVR, TAVI and medical treatment of patients with severe AS and reduced LVEF.

Aortic valve replacement is the definitive treatment of severe calcific AS. Recent registries have shown significant declines in 30-day mortality risks after SAVR (from 0.83 in 1992-1994 to 0.64 in 2007-2009).[49] The operative mortality rates for isolated SAVR in patients aged <70 years are 1-3% whereas for older patients the mortality rates range between 4-8%.[4] One of the factors independently associated with increased operative mortality is the presence of HF and reduced LVEF.[11, 50, 51] In a contemporary observational analysis including 114,135 patients aged ≥65 years old who underwent isolated aortic valve replacement, the presence of HF was associated with increased operative mortality and worse long-term survival.[50] In addition, longer duration of HF symptoms before aortic valve replacement was significantly associated with worse outcome.[50] Therefore, management of patients with severe AS and HF requires careful weighing of the operative risks and the clinical benefits.

Medical treatment and percutaneous balloon valvuloplasty may be appropriate therapeutic bridges to definitive aortic valve replacement in specific circumstances such as patients with hemodynamic instability. Indication for SAVR or TAVI relies on Heart Team discussion evaluating the individual's operative risk, frailty and comorbidities as well as the technical suitability for TAVI. Finally, patients with pseudosevere AS represent a specific subgroup with better outcomes under medical therapy than patients with true severe low flow low gradient AS and comparable survival to that of HF patients without AS.[38]

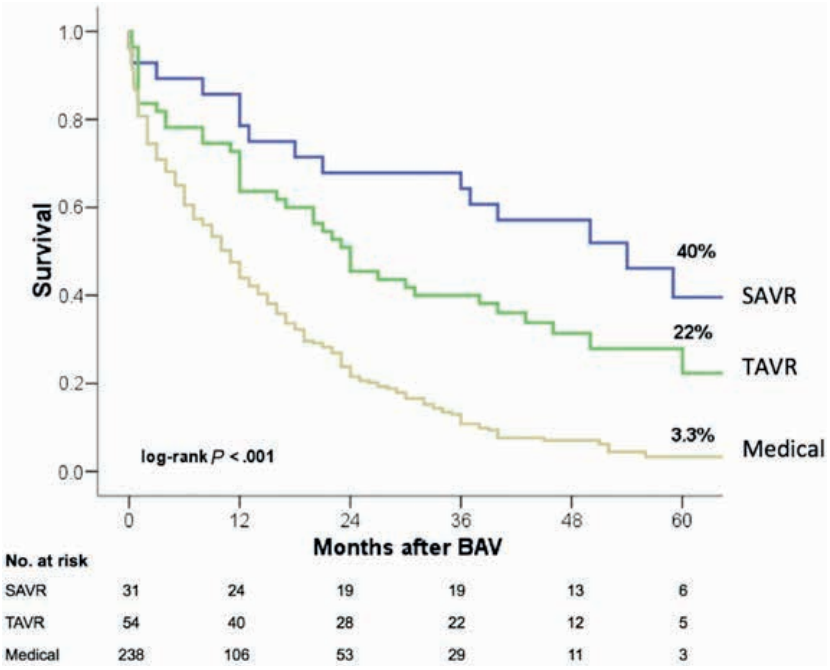


Figure 6. Long-term survival of patients with severe aortic stenosis undergoing balloon aortic valvuloplasty. Reproduced with permission from Eltchaninoff et al. Am Heart J. 2014;167(2):235-40.[54]

Severe AS and decompensated HF.

This high risk situation urges prompt hemodynamic stabilization that cannot be delayed by the screening process to decide suitability for SAVR or TAVI. Few studies have reported on the role of medical treatment in critically ill patients with severe AS and LV systolic dysfunction.[52, 53] Although vasodilators are traditionally contraindicated in this group of patients, small studies have demonstrated that nitroprusside and levosimendan can improve cardiac output and stabilize the hemodynamic condition allowing later referral to SAVR.[52, 53] Of note, patients with hypotension (mean arterial systolic pressure <60 mmHg) or under inotropic treatment were excluded from these trials[52, 53] and therefore, such a therapeutic option would not be indicated in those specific patients. More experience has accumulated with the use of percutaneous balloon aortic valvuloplasty as alternative to inotropic treatment.[54] This technique permits decreases in mean transaortic pressure gradient >50% and improvement in AVA >1.0cm^2 in 80% of the patients. Reductions of the arterial sheaths and development of vascular closure devices have improved the safety of this procedure with significant decreases in vascular complication rates. In 323 patients with severe AS and high operative risk (logistic EuroSCORE 28.7±12.5%) who underwent balloon aortic valvuloplasty, the rate of major inhospital complications was 6.8% and inhospital mortality was 2.5%.[54] After this treatment, 65% of patients continued medical treatment while the remaining patients were bridged to SAVR or TAVI. Single balloon aortic valvuloplasty was associated with worse outcome compared with SAVR and TAVI (Figure 6).

Severe AS and stable compensated HF.

In patients with low flow low gradient severe AS and reduced LVEF and presence of contractile/flow reserve, current guidelines recommend SAVR.[4] Studies comparing the outcomes of SAVR versus medical treatment of patients with classical low flow low gradient severe AS demonstrated that SAVR was associated with better survival at follow-up.[29, 55] Similar results have been reported for patients with classical low flow low gradient severe AS without contractile/flow reserve on dobutamine stress echocardiography.[37] In addition, SAVR was associated with improvement in LVEF at follow-up in patients with classical low flow low gradient severe AS independently of the presence of contractile/flow reserve.[39] The French multicentre study including 66 patients with classical low flow low gradient severe AS (46 with contractile/flow reserve and 20 patients without) showed that after SAVR the increment in LVEF was comparable between patients with and without contractile/flow reserve (19±10% versus 17±11%, p=0.54).[39] The advent of TAVI has altered the management of such high-risk patients. The Placement of Aortic Transcatheter Valves (PARTNER) trial included a large cohort of patients with severe AS who were randomized to TAVI or medical treatment (including balloon aortic valvuloplasty) for patients with contraindications for SAVR (cohort B) and to TAVI or SAVR for patients with increased surgical risk (cohort A).[56, 57] The prevalence of classical low flow low gradient severe AS was 15% (n=147). Low flow status was associated with increased 2-year mortality compared with normal flow status (for both cohorts) (47.1% versus 33.7%; hazard ratio 1.58, 95% confidence interval 1.28-1.95; p<0.001).[7] However, the presence of reduced LVEF (<50%) was not associated with further increase in mortality. Compared with medical treatment, TAVI was associated with significant reductions in 2-year mortality of patients

with classical low flow low gradient severe AS (80% versus 47.1%, p=0.04) whereas there were no differences between SAVR and TAVI (37.1% versus 42.9%, p=0.5).[7] In addition, subanalysis of the PARTNER cohort A showed that SAVR and TAVI lead to comparable improvements in LVEF at follow-up (from 38.0±8.0% to 50.1±10.8% and from 35.7±8.5% to 48.6±11.3%, respectively). Importantly, right ventricular pacing or induction of left bundle branch block (LBBB) after TAVI have been associated with lack of improvement in LV systolic function.[58, 59] Recent series including 3726 patients treated with TAVI showed that, after a mean follow-up of 22 months, 15% and 5.6% of deaths were caused by advanced HF and sudden cardiac, respectively.[60] LVEF≤40% was independently associated with death from advanced HF and sudden cardiac death whereas persistent LBBB following TAVI was associated with increased risk of sudden cardiac death. These findings have important clinical implications and fuel the discussion on the use of cardiac resynchronization therapy with or without defibrillator capabilities in these patients.

Pseudosevere AS.

In this subgroup of patients, optimal medical treatment provides similar survival than that of patients with HF and normal aortic valve function.[38] Cardiac resynchronization therapy, an established HF therapy indicated in patients who remain symptomatic despite optimal medical treatment, reduced LVEF and wide QRS,[61] may be one of the therapies underutilized in this specific group of patients. A recent analysis including 88 patients with classical low flow low gradient severe AS showed that the prevalence of QRS duration ≥130 ms was 56%. [62] In addition, QRS duration was strongly associated with worse outcome (hazard ratio 2.20, 95% confidence interval 1.15-4.24; P = 0.027). Whether treatment with cardiac resynchronization therapy would have resulted in better outcomes remains unknown.

FUTURE DIRECTIONS

Severe AS and HF are common conditions that may coincide having important clinical and prognostic implications. The development of TAVI has shifted the attention to this subgroup of patients who were considered inoperable a decade ago. However, there are still uncertainties regarding the treatment of specific subgroups of patients with severe AS and HF. For example, patients with LVEF<20% have been excluded from recent randomized trials on TAVI.[16, 56, 57] Currently few case reports have shown the safety and feasibility of performing TAVI under extracorporeal membrane oxygenation. Whether patients with such reduced LVEF may benefit from TAVI remains to be elucidated. Probably, accurate assessment of the LV structure and function using late gadolinium contrast enhanced MRI may help to identify the patients with limited amount of scar that can lead to functional recovery after TAVI and better prognosis.[28] Another question is the role of cardiac resynchronization therapy in these patients. Upgrade of right ventricular pacing to cardiac resynchronization therapy or implantation of cardiac resynchronization therapy in patients with LBBB prior or after TAVI may further improve LVEF and improve the prognosis. Finally, afterload reduction with medical therapy is the mainstay of HF therapy. Bearing in mind the increasing prevalence of HF and degenerative AS along with the ageing of the population, additional afterload reduction by TAVI on top of established HF therapy seems an attractive new concept. The Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with ADvanced heart failure (TAVR UNLOAD) is a newly designed international randomized trial to assess whether TAVI on top of optimized HF therapy affects the composite hierarchical endpoint of all-cause death, disabling stroke, hospitalization for HF or aortic valve disease and change in quality of life in patients with HF and proven moderate AS. Additional randomized clinical studies are needed to better define the management of HF patients with aortic stenosis.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006 September 16;368(9540):1005-11.

2. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003 July;24(13):1231-43.

3. Carabello BA, Paulus WJ. Aortic stenosis. *Lancet* 2009 March 14;373(9667):956-66.

4. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De BM, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012 October;33(19):2451-96.

5. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, III, Thomas JD. 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 Practice Guidelines. *J Am Coll Cardiol* 2014 June 10;63(22):e57-185.

6. Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. *J Am Coll Cardiol* 2012 November 6;60(19):1845-53.

7. Herrmann HC, Pibarot P, Hueter I, Gertz ZM, Stewart WJ, Kapadia S, Tuzcu EM, Babaliaros V, Thourani V, Szeto WY, Bavaria JE, Kodali S, Hahn RT, Williams M, Miller DC, Douglas PS, Leon MB. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. *Circulation* 2013 June 11;127(23):2316-26.

8. Clavel MA, Webb JG, Rodes-Cabau J, Masson JB, Dumont E, De LR, Doyle D, Bergeron S, Baumgartner H, Burwash IG, Dumesnil JG, Mundigler G, Moss R, Kempny A, Bagur R, Bergler-Klein J, Gurvitch R, Mathieu P, Pibarot P. Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction. *Circulation* 2010 November 9;122(19):1928-36.

9. Pibarot P, Dumesnil JG. Improving assessment of aortic stenosis. *J Am Coll Cardiol* 2012 July 17;60(3):169-80.

10. Henkel DM, Malouf JF, Connolly HM, Michelena HI, Sarano ME, Schaff HV, Scott CG, Pellikka PA. Asymptomatic left ventricular systolic dysfunction in patients with severe aortic stenosis: characteristics and outcomes. *J Am Coll Cardiol* 2012 December 4;60(22):2325-9.

11. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis. *Ann Thorac Surg* 2006 December;82(6):2111-5.

12. Walther T, Hamm CW, Schuler G, Berkowitsch A, Kotting J, Mangner N, Mudra H, Beckmann A, Cremer J, Welz A, Lange R, Kuck KH, Mohr FW, Mollmann H. Perioperative Results and Complications in 15,964 Transcatheter Aortic Valve Replacements: Prospective Data From the GARY Registry. *J Am Coll Cardiol* 2015 May 26;65(20):2173-80.

13. Mack MJ, Brennan JM, Brindis R, Carroll J, Edwards F, Grover F, Shahian D, Tuzcu EM, Peterson ED, Rumsfeld JS, Hewitt K, Shewan C, Michaels J, Christensen B, Christian A, O'Brien S, Holmes D. Outcomes following transcatheter aortic valve replacement in the United States. *JAMA* 2013 November 20;310(19):2069-77.

14. Berry C, Lloyd SM, Wang Y, Macdonald A, Ford I. The changing course of aortic valve disease in Scotland: temporal trends in hospitalizations and mortality and prognostic importance of aortic stenosis. *Eur Heart J* 2013 June;34(21):1538-47.

15. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, Gohlke-Barwolf C, Boersma E, Ravaud P, Vahanian A. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J* 2005 December;26(24):2714-20.

16. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Jr., Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014 May 8;370(19):1790-8.

17. Amabile N, Agostini H, Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Laskar M, Caussin C. Impact of low preprocedural transvalvular gradient on cardiovascular mortality following TAVI: an analysis from the FRANCE 2 registry. *EuroIntervention* 2014 November;10(7):842-9.

18. O'Sullivan CJ, Stortecky S, Heg D, Pilgrim T, Hosek N, Buellesfeld L, Khattab AA, Nietlispach F, Moschovitis A, Zanchin T, Meier B, Windecker S, Wenaweser P. Clinical outcomes of patients with low-flow, low-gradient, severe aortic stenosis and either preserved or reduced ejection fraction undergoing transcatheter aortic valve implantation. *Eur Heart J* 2013 November;34(44):3437-50.

19. Ludman PF, Moat N, de Belder MA, Blackman DJ, Duncan A, Banya W, MacCarthy PA, Cunningham D, Wendler O, Marlee D, Hildick-Smith D, Young CP, Kovac J, Uren NG, Spyt T, Trivedi U, Howell J, Gray H. Transcatheter aortic valve implantation in the United Kingdom: temporal trends, predictors of outcome, and 6-year follow-up: a report from the UK Transcatheter Aortic Valve Implantation (TAVI) Registry, 2007 to 2012. *Circulation* 2015 March 31;131(13):1181-90.

20. Onorati F, D'Errigo P, Barbanti M, Rosato S, Covello RD, Maraschini A, Ranucci M, Santoro G, Tamburino C, Grossi C, Santini F, Menicanti L, Seccareccia F. Different impact of sex on baseline characteristics and major periprocedural outcomes of transcatheter and surgical aortic valve interventions: Results of the multicenter Italian OBSERVANT Registry. *J Thorac Cardiovasc Surg* 2014 May;147(5):1529-39.

21. Paradis JM, Fried J, Nazif T, Kirtane A, Harjai K, Khalique O, Grubb K, George I, Hahn R, Williams M, Leon MB, Kodali S. Aortic stenosis and coronary artery disease: what do we know? What don't we know? A comprehensive review of the literature with proposed treatment algorithms. *Eur Heart J* 2014 August 14;35(31):2069-82.

22. Vahanian A, Otto CM. Risk stratification of patients with aortic stenosis. *Eur Heart J* 2010 February;31(4):416-23.

23. Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol* 2000 March 1;35(3):747-56.

24. Beach JM, Mihaljevic T, Svensson LG, Rajeswaran J, Marwick T, Griffin B, Johnston DR, Sabik JF, III, Blackstone EH. Coronary artery disease and outcomes of aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol* 2013 February 26;61(8):837-48.

25. Van Mieghem NM, van der Boon RM, Faqiri E, Diletti R, Schultz C, van Geuns RJ, Serruys PW, Kappetein AP, van Domburg RT, de Jaegere PP. Complete revascularization is not a prerequisite for success in current transcatheter aortic valve implantation practice. *JACC Cardiovasc Interv* 2013 August;6(8):867-75.

26. Girerd N, Magne J, Rabilloud M, Charbonneau E, Mohamadi S, Pibarot P, Voisine P, Baillot R, Doyle D, Dumont E, Dagenais F, Mathieu P. The impact of complete revascularization on long-term survival is strongly dependent on age. *Ann Thorac Surg* 2012 October;94(4):1166-72.

27. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the

myocardium. *J Am Coll Cardiol* 2012 November 6;60(19):1854-63.

28. Barone-Rochette G, Pierard S, De Meester de RC, Seldrum S, Melchior J, Maes F, Pouleur AC, Vancraeynest D, Pasquet A, Vanoverschelde JL, Gerber BL. Prognostic significance of LGE by CMR in aortic stenosis patients undergoing valve replacement. *J Am Coll Cardiol* 2014 July 15;64(2):144-54.

29. Connolly HM, Oh JK, Schaff HV, Roger VL, Osborn SL, Hodge DO, Tajik AJ. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction:result of aortic valve replacement in 52 patients. *Circulation* 2000 April 25;101(16):1940-6.

30. Kulik A, Burwash IG, Kapila V, Mesana TG, Ruel M. Long-term outcomes after valve replacement for low-gradient aortic stenosis: impact of prosthesis-patient mismatch. *Circulation* 2006 July 4;114(1 Suppl):I553-I558.

31. Monin JL, Quere JP, Monchi M, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Tribouilloy C, Gueret P. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation* 2003 July 22;108(3):319-24.

32. deFilippi CR, Willett DL, Brickner ME, Appleton CP, Yancy CW, Eichhorn EJ, Grayburn PA. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. *Am J Cardiol* 1995 January 15;75(2):191-4.

33. Levy F, Laurent M, Monin JL, Maillet JM, Pasquet A, Le TT, Petit-Eisenmann H, Gori M, Jobic Y, Bauer F, Chauvel C, Leguerrier A, Tribouilloy C. Aortic valve replacement for low-flow/low-gradient aortic stenosis operative risk stratification and long-term outcome: a European multicenter study. *J Am Coll Cardiol* 2008 April 15;51(15):1466-72.

34. Blais C, Burwash IG, Mundigler G, Dumesnil JG, Loho N, Rader F, Baumgartner H, Beanlands RS, Chayer B, Kadem L, Garcia D, Durand LG, Pibarot P. Projected valve area at normal flow rate improves the assessment of stenosis severity in patients with low-flow, low-gradient aortic stenosis: the multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study. *Circulation* 2006 February 7;113(5):711-21.

35. Cueff C, Serfaty JM, Cimadevilla C, Laissy JP, Himbert D, Tubach F, Duval X, Iung B, Enriquez-Sarano M, Vahanian A, Messika-Zeitoun D. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. *Heart* 2011 May;97(9):721-6.

36. Clavel MA, Burwash IG, Mundigler G, Dumesnil JG, Baumgartner H, Bergler-Klein J, Senechal M, Mathieu P, Couture C, Beanlands R, Pibarot P. Validation of conventional and simplified methods to calculate projected valve area at normal flow rate in patients with low flow, low gradient aortic stenosis: the multicenter TOPAS (True or Pseudo Severe Aortic Stenosis) study. *J Am Soc Echocardiogr* 2010 April;23(4):380-6.

37. Tribouilloy C, Levy F, Rusinaru D, Gueret P, Petit-Eisenmann H, Baleynaud S, Jobic Y, Adams C, Lelong B, Pasquet A, Chauvel C, Metz D, Quere JP, Monin JL. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. *J Am Coll Cardiol* 2009 May 19;53(20):1865-73.

38. Fougeres E, Tribouilloy C, Monchi M, Petit-Eisenmann H, Baleynaud S, Pasquet A, Chauvel C, Metz D, Adams C, Rusinaru D, Gueret P, Monin JL. Outcomes of pseudo-severe aortic stenosis under conservative treatment. *Eur Heart J* 2012 October;33(19):2426-33.

39. Quere JP, Monin JL, Levy F, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Gueret P, Tribouilloy C. Influence of preoperative left ventricular contractile reserve on postoperative ejection fraction in low-gradient aortic stenosis. *Circulation* 2006 April 11;113(14):1738-44.

40. Hoffmann R, Altiok E, Friedman Z, Becker M, Frick M. Myocardial deformation imaging by two-dimensional speckle-tracking echocardiography in comparison to late gadolinium

enhancement cardiac magnetic resonance for analysis of myocardial fibrosis in severe aortic stenosis. *Am J Cardiol* 2014 October 1;114(7):1083-8.

41. Weidemann F, Herrmann S, Stork S, Niemann M, Frantz S, Lange V, Beer M, Gattenlohner S, Voelker W, Ertl G, Strotmann JM. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. *Circulation* 2009 August 18;120(7):577-84.

42. Ng AC, Tran dT, Allman C, Vidaic J, Leung DY. Prognostic implications of left ventricular dyssynchrony early after non-ST elevation myocardial infarction without congestive heart failure. *Eur Heart J* 2010 February;31(3):298-308.

43. Delgado V, Tops LF, van Bommel RJ, van der Kley F, Marsan NA, Klautz RJ, Versteegh MI, Holman ER, Schalij MJ, Bax JJ. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. *Eur Heart J* 2009 December;30(24):3037-47.

44. Bartko PE, Heinze G, Graf S, Clavel MA, Khorsand A, Bergler-Klein J, Burwash IG, Dumesnil JG, Senechal M, Baumgartner H, Rosenhek R, Pibarot P, Mundigler G. Two-dimensional strain for the assessment of left ventricular function in low flow-low gradient aortic stenosis, relationship to hemodynamics, and outcome: a substudy of the multicenter TOPAS study. *Circ Cardiovasc Imaging* 2013 March 1;6(2):268-76.

45. Dahou A, Bartko PE, Capoulade R, Clavel MA, Mundigler G, Grondin SL, Bergler-Klein J, Burwash I, Dumesnil JG, Senechal M, O'Connor K, Baumgartner H, Pibarot P. Usefulness of global left ventricular longitudinal strain for risk stratification in low ejection fraction, low-gradient aortic stenosis: results from the multicenter True or Pseudo-Severe Aortic Stenosis study. *Circ Cardiovasc Imaging* 2015 March;8(3):e002117.

46. Herrmann S, Stork S, Niemann M, Lange V, Strotmann JM, Frantz S, Beer M, Gattenlohner S, Voelker W, Ertl G, Weidemann F. Low-gradient aortic valve stenosis myocardial fibrosis and its influence on function and outcome. *J Am Coll Cardiol* 2011 July 19;58(4):402-12.

47. Dweck MR, Joshi S, Murigu T, Alpendurada F, Jabbour A, Melina G, Banya W, Gulati A, Roussin I, Raza S, Prasad NA, Wage R, Quarto C, Angeloni E, Refice S, Sheppard M, Cook SA, Kilner PJ, Pennell DJ, Newby DE, Mohiaddin RH, Pepper J, Prasad SK. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. *J Am Coll Cardiol* 2011 September 13;58(12):1271-9.

48. Flett AS, Sado DM, Quarta G, Mirabel M, Pellerin D, Herrey AS, Hausenloy DJ, Ariti C, Yap J, Kolvekar S, Taylor AM, Moon JC. Diffuse myocardial fibrosis in severe aortic stenosis: an equilibrium contrast cardiovascular magnetic resonance study. *Eur Heart J Cardiovasc Imaging* 2012 October;13(10):819-26.

49. Martinsson A, Li X, Andersson C, Nilsson J, Smith JG, Sundquist K. Temporal trends in the incidence and prognosis of aortic stenosis: a nationwide study of the Swedish population. *Circulation* 2015 March 17;131(11):988-94.

50. Vassileva CM, Telila T, Markwell S, Hazelrigg S. Magnitude of negative impact of preoperative heart failure on mortality during aortic valve replacement in the medicare population. *Ann Thorac Surg* 2015 May;99(5):1503-10.

51. Romero J, Chavez P, Goodman-Meza D, Holmes AA, Ostfeld RJ, Manheimer ED, Siegel RM, Lupercio F, Shulman EH, Liakos M, Garcia MJ, Spevack DM. Outcomes in patients with various forms of aortic stenosis including those with low-flow low-gradient normal and low ejection fraction. *Am J Cardiol* 2014 October 1;114(7):1069-74.

52. Khot UN, Novaro GM, Popovic ZB, Mills RM, Thomas JD, Tuzcu EM, Hammer D, Nissen SE, Francis GS. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. *N Engl J Med* 2003 May 1;348(18):1756-63.

53. Garcia-Gonzalez MJ, Jorge-Perez P, Jimenez-Sosa A, Barragan AA, Lacalzada Almeida JB, Ferrer Hita JJ. Levosimendan improves hemodynamic status in critically ill patients with severe aortic stenosis and left ventricular dysfunction: an interventional study. *Cardiovasc Ther* 2015 May 8.

54. Eltchaninoff H, Durand E, Borz B, Furuta A, Bejar K, Canville A, Farhat A, Fraccaro C, Godin M, Tron C, Sakhuja R, Cribier A. Balloon aortic valvuloplasty in the era of transcatheter aortic valve replacement: acute and long-term outcomes. *Am Heart J* 2014 February;167(2):235-40.

55. Pereira JJ, Lauer MS, Bashir M, Afridi I, Blackstone EH, Stewart WJ, McCarthy PM, Thomas JD, Asher CR. Survival after aortic valve replacement for severe aortic stenosis with low transvalvular gradients and severe left ventricular dysfunction. *J Am Coll Cardiol* 2002 April 17;39(8):1356-63.

56. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010 October 21;363(17):1597-607.

57. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011 June 9;364(23):2187-98.

58. Nazif TM, Williams MR, Hahn RT, Kapadia S, Babaliaros V, Rodes-Cabau J, Szeto WY, Jilaihawi H, Fearon WF, Dvir D, Dewey TM, Makkar RR, Xu K, Dizon JM, Smith CR, Leon MB, Kodali SK. Clinical implications of new-onset left bundle branch block after transcatheter aortic valve replacement: analysis of the PARTNER experience. *Eur Heart J* 2014 June 21;35(24):1599-607.

59. Biner S, Michowitz Y, Leshem-Rubinow E, Topilsky Y, Ben-Assa E, Shimiaie J, Banai S, Keren G, Steinvil A, Finkelstein A. Hemodynamic impact and outcome of permanent pacemaker implantation following transcatheter aortic valve implantation. *Am J Cardiol* 2014 January 1;113(1):132-7.

60. Urena M, Webb JG, Eltchaninoff H, Munoz-Garcia AJ, Bouleti C, Tamburino C, Nombela-Franco L, Nietlispach F, Moris C, Ruel M, Dager AE, Serra V, Cheema AN, Amat-Santos IJ, de Brito FS, Lemos PA, Abizaid A, Sarmento-Leite R, Ribeiro HB, Dumont E, Barbanti M, Durand E, Alonso Briales JH, Himbert D, Vahanian A, Imme S, Garcia E, Maisano F, del VR, Benitez LM, Garcia del BB, Gutierrez H, Perin MA, Siqueira D, Bernardi G, Philippon F, Rodes-Cabau J. Late cardiac death in patients undergoing transcatheter aortic valve replacement: incidence and predictors of advanced heart failure and sudden cardiac death. *J Am Coll Cardiol* 2015 February 10;65(5):437-48.

61. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013 August;34(29):2281-329.

62. Sebag FA, Lellouche N, Chaachoui N, Dubois-Rande JL, Gueret P, Monin JL. Prevalence and clinical impact of QRS duration in patients with low-flow/low-gradient aortic stenosis due to left ventricular systolic dysfunction. *Eur J Heart Fail* 2014 June;16(6):639-47.