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Moderate aortic stenosis in the dysfunctional ventricle: should it be treated?

Edoardo Sciatti[1], Alice Calabrese[1], Vincenzo Duino[1], Salvatore D'isa[1], Luca Antonio Felice Di Odoardo[1], Emilia D'elia[1], and Michele Senni[1,2]*

[1]Cardiovascular Department, ASST Papa Giovanni XXIII, Bergamo; and [2]Milano-Bicocca University, Milan

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Moderate aortic stenosis is associated with a worse prognosis than milder degrees. Pathophysiologically, this condition in a dysfunctional ventricle could lead to a further mechanism of haemodynamic worsening, so its treatment should lead to clinical advantages for the patient. The low risk of complications associated with percutaneous correction of aortic valve disease (transcatheter aortic valve implantation) should also be considered, which would seem to favour an interventional approach even in the aforementioned condition. However, sparse data and small population studies make this approach still controversial. Three randomized controlled trials are underway to shed definitive light on the topic.

Aortic stenosis (AS) can cause or worsen the impact of heart failure (HF) through increased afterload, causing left ventricular hypertrophy and remodelling.[1] Current international guidelines recommend aortic valve replacement (AVR) in severe AS if it causes symptoms or left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) < 50%].[2,3] However, one of the most important gaps in knowledge remains the management and recommendations for moderate AS with HF,[4] also in light of the complex echocardiographic evaluation necessary to diagnose AS in the case of reduced LVEF.[2,3] In particular, international guidelines do not address the problem due to a lack of data (*Table 1*).[2,3,5,6]

Large registries have shown that patients with moderate AS have worse clinical outcomes than patients with less severe forms of AS.[7] In a cohort of ~240 000 patients undergoing echocardiogram, regardless of the presence of reduced LVEF, left ventricular diastolic dysfunction, and other comorbidities, moderate AS is associated with a 5-year mortality rate of 56%, which becomes 67% in the case of severe AS (and 19% in patients without AS).[7] In particular, a marked increase in all-cause mortality and cardiovascular death was observed in patients with at least moderate AS, after correction for the variables mentioned (*Figure 1*).[7] A recent systematic review of 12 134 patients with moderate AS (diagnosed echocardiographically or with cardiac catheterization), followed for an average of nearly 4 years, showed aggregate rates per 100 person-years of 9.0 events for all-cause mortality, 4.9 for cardiac mortality, 3.9 for HF, and 1.1 for sudden death.[8] Furthermore, the presence of symptoms or left ventricular systolic dysfunction was associated with a significant impact on the overall estimate of death from all causes.[8] These findings lead to the hypothesis that AVR could be useful in patients with moderate AS, particularly in those with symptoms and/or left ventricular systolic dysfunction. Finally, a recent analysis taken from a large contemporary and 'real-world' database has shown a progressive increase in mortality at a 4-year follow-up as the extent of AS increases, equal to 29.7% in mild-to-moderate AS and 33.5% in moderate AS. Of note, ~12% of patients had a history of heart failure with reduced ejection fraction (HFrEF) in this severity range.[9] Moreover, the same working group had already shown that mortality and adverse events at 2 years after AVR were proportional to the extent of cardiac damage present at baseline. The latter was classified into five stages according to the presence of echocardiographic alterations, both structural and functional, already known and validated

*Corresponding author. Email: msenni@asst-pg23.it

in the literature. In their analysis, the extent of cardiac damage represented a significant predictor of outcome and led the authors to hypothesize that early AVR intervention, before it can reach the state of severity and symptomaticity, could limit the extent of cardiac damage and improve not only cardiac function but also outcomes and prognosis.[10]

Currently, surgical AVR in the case of moderate AS should be considered in patients undergoing surgical coronary revascularization or surgery on the ascending aorta or another valve.[2,3] However, the low complication rates of percutaneous AVR [transcatheter aortic valve implantation (TAVI)] and lower in-hospital mortality rates compared with surgical AVR in patients with low, intermediate, and high operative risk raise the question of whether TAVR could be a viable option for patients with moderate AS. In particular, among patients with moderate AS and symptoms of HF with or without reduced LVEF or in those with only reduced LVEF (HFrEF) in whom there is no indication for coronary revascularization or surgery on the aortic root and ascending aorta, TAVR could relieve pressure overload of the compromised left ventricle and improve symptoms as well as left ventricular remodelling.

The prevalence of both AS and HF increases exponentially with advancing age, leading to a frequent coexistence of the two conditions in older age. Consistent data are available on the prognostic role of severe AS in patients with HF, and the benefit of TAVR for this condition has been demonstrated.[3] In contrast, data on patients with moderate AS and HF are scarce and derive from small observational studies.[11-13,15,16] Furthermore, the possible role of TAVR in this population is largely unexplored.[11,16]

In a cohort of 262 HFrEF patients with moderate AS (confirmed by ecodobutamine) compared with a matched group without AS, moderate AS was shown to be a strong independent predictor of hospitalization for HF and all-cause mortality [hazard ratio (HR) 2.34] and all-cause mortality only (HR 2.98) at an average follow-up of 2.9 years (*Figure 2*).[11] In the same study, 44 patients with moderate AS at baseline required AVR during follow-up. In this subgroup, TAVI, but not surgical AVR, was associated with a survival benefit; however, TAVR was performed in only 15 patients. Furthermore, patients who underwent AVR had worse baseline characteristics than other cohorts and could not be adequately compared. Finally, the treatment of HF was suboptimal and did not include new therapies such as angiotensin-neprilysin inhibitors (ARNi) and sodium-glucose cotransporter 2 inhibitors (SGLT2i).[11] Another recent study, which enrolled 952 patients with moderate AS matched with a comparable population without AS using propensity matching, documented similar results, showing a significantly higher mortality risk in patients with moderate AS (survival at 1, 2, 3, and 5 years: 80 ± 1% vs. 82 ± 0.7%, 70 ± 1.5% vs. 74 ± 0.8%, 62 ± 1.7% vs. 66 ± 0.9%, and 47 ± 2.4% vs. 52 ± 1.3%, respectively).[12] This also occurred independently of the LVEF. However, the prevalence of HF in this study was low (<10%) and patients who underwent AVR were excluded. Furthermore, some baseline differences between groups still remained after matching, leaving doubts regarding the possible independent prognostic role of moderate AS.[12] In contrast, a previous report including 107 patients with low-flow, low-gradient AS (divided into

Table 1 **Recommendations for heart failure with moderate aortic stenosis (in the absence of other cardiac surgical indications for surgery)**

	Europe	USA
Heart failure guidelines	Unmentioned problem[5]	The ongoing TAVR UNLOAD trial mentioned[6,14]
Valve guidelines	Unmentioned problem[5]	Unmentioned problem[2]

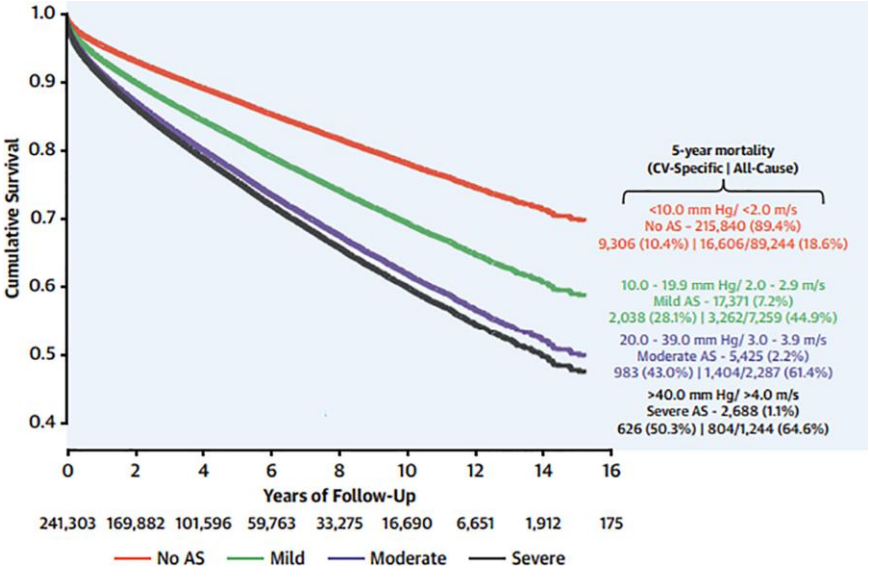

Figure 1 Long-term survival adjusted for severity of aortic stenosis. Adapted from Strange *et al.*[7]

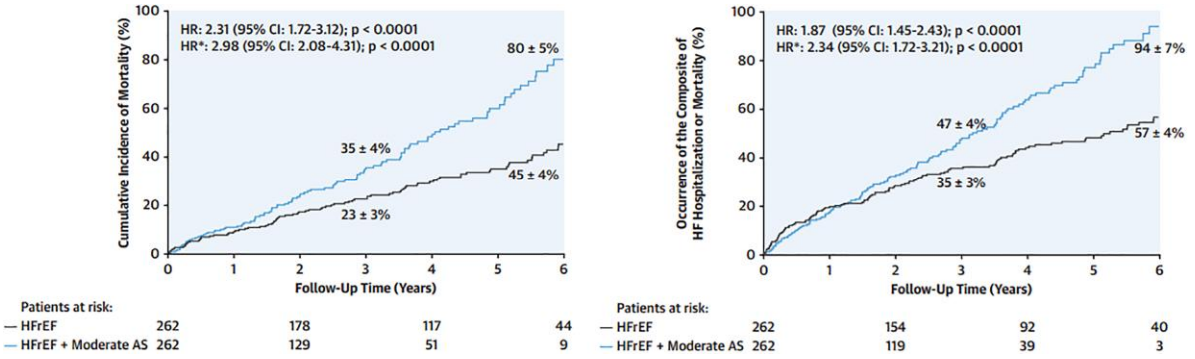

Figure 2 Cumulative incidence of adverse outcome in patients with heart failure with reduced ejection fraction with or without moderate aortic stenosis. Adapted from Jean *et al.*[11] Left: all-cause mortality. Right: hospitalization for heart failure or all-cause mortality. *Adjusted for age, sex, body mass index, diabetes, hypertension, previous myocardial infarction, dyslipidaemia, ischaemic heart disease, New York Heart Association functional classes III to IV, renal filtration rate, greater than mild aortic regurgitation, greater than mild mitral regurgitation, and left ventricular ejection fraction.

truly severe and moderate using echodobutamine test) and HFrEF demonstrated a significantly lower risk of death in patients with moderate AS compared with those with severe AS (HR 0.53).[13] Furthermore, a group of 28 patients with HFrEF and moderate AS was adequately matched to 28 patients with HFrEF without AS and no difference in the 5-year survival rate was documented.[13] On the contrary, a discriminating prognostic role in moderate AS is provided by the global longitudinal strain (GLS) evaluated with 2D speckle-tracking echocardiography: the work of Stassen *et al.* on 760 patients with moderate AS has demonstrated, even with the limitations related to the retrospective nature of the study, that, with the same LVEF (>50%), what discriminates the risk of events and the prognosis is the value of the GLS: in fact, patients with LVEF < 50% had a similar prognosis to those with LVEF > 50% but GLS < 16%.[14] In a recently published series, 1974 patients with moderate AS were correctly divided into 4 groups based on flow gradient patterns: concordant moderate AS [mean gradient (GM) > 20 mmHg], normal-flow, low-gradient AS [GM < 20 mmHg, stroke volume indexed (SVi) ≥ 35 mL/m^2, and LVEF ≥50%], low-flow, low-gradient 'paradoxical' AS (GM < 20 mmHg, SVi < 35 mL/m^2, and LVEF ≥ 50%), and 'classical' low-flow, low-gradient AS (GM < 20 mmHg and LVEF < 50%). On multivariate analysis, only 'paradoxical' (HR 1.458) and 'classic' moderate low-flow, low-gradient AS (HR 1.710) emerged as independent predictors of all-cause mortality, while concordant moderate AS and normal-flow, low-gradient AS did not.[15] Interestingly, patients with these patterns were also significantly older and had a higher prevalence of comorbidities.[15] Finally, the multinational ATLAS-TAVI registry enrolled 706 patients with low-gradient AS (both severe and moderate, differentiated by transthoracic echocardiogram and chest computed tomography) and LVEF < 50% compared with 470 similar patients on medical therapy.[16] After propensity score matching among patients with moderate AS, those undergoing TAVI compared with medical therapy showed greater 2-year survival for all causes (65.4% vs. 48.8%, $P \leq 0.004$) as well as cardiovascular (80.4% vs. 58.5%, $P \leq 0.004$). At the multivariate analysis regarding patients with moderate AS, TAVI was confirmed as an independent predictor of survival (HR 0.39). However, the failure to use ecodobutamine to correctly classify 'classic' moderate low-flow, low-gradient AS may have affected these results.[16]

Therefore, these data, in many ways dubious and sometimes conflicting, reinforce the need for randomized controlled trials comparing TAVR with medical therapy in patients with HF and non-severe AS. In this regard, three randomized studies are underway and will provide definitive data on the topic. The Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients With Advanced Heart Failure (TAVR UNLOAD; ClinicalTrials.gov: NCT02661451) study aims to enrol 300 patients with HF and moderate AS who will be randomized to TAVI using a balloon-expandable bioprosthesis vs. guideline-directed medical therapy.[17] Results are expected in 2024. The PROGRESS trial (Management of Moderate Aortic Stenosis by Clinical Surveillance or TAVR; ClinicalTrials.gov: NCT04889872) will randomize 750 patients with moderate AS and symptoms or cardiac damage to TAVI with a balloon-expandable bioprosthesis vs. medical therapy, while the Evolut EXPAND TAVR II Pivotal Trial (ClinicalTrials.gov: NCT05149755) will randomize 650 patients with symptomatic moderate AS to TAVR vs. clinical surveillance on medical therapy.

In addition to knowing the potential survival benefit of TAVR in patients with moderate AS, it will certainly be interesting to see whether TAVI is associated with a regression of the haemodynamic consequences of increased pressure overload. This hypothesis will be counterbalanced by the risk of pacemaker implantation and the presence of minor paravalvular leak. Although the concept of performing TAVI in moderate AS seems reasonable from a pathophysiological point of view, the results of these studies are needed to prove it. In fact, considering all the reported data as a whole, the independent prognostic role of moderate AS in HF remains unclear, with some conflicting results in the literature, partly also due to a not always adequate classification of valvular disease by means of variation in transaortic flow and LVEF. The number of patients enrolled in these studies was generally low, and the possible beneficial role of TAVR was only reported in a very small sample, clearly limiting conclusions for this population. However, it should be emphasized that

optimal medical treatment is generally underrepresented and will need to be implemented in future studies. Furthermore, timely treatment of comorbidities, which are usually observed in these patients, is crucial as they could independently act as causative factors for the ventriculo-valvular afterload observed in patients with AS. Finally, it is still controversial whether moderate AS may have a different impact in patients with HFrEF or with HF and preserved LVEF (HfpEF).

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Data availability

No new data were generated or analysed in support of this research.

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