Treatment in patients with severe asymptomatic aortic stenosis: is it best not to wait?

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New insights into the natural history and pathophysiology of patients with aortic stenosis (AS), coupled with the dramatic evolution of transcatheter aortic valve implantation (TAVI), are fuelling intense interest in the management of asymptomatic patients with severe AS. This patient presenting for elective intervention poses a unique challenge. These patients are not traditionally offered surgical aortic valve replacement or TAVI given their lack of symptoms; however, they are at increased risk given the severity of their AS. Furthermore, clinical experience has shown that symptoms can be challenging to ascertain in many sedentary, deconditioned, and/or elderly patients. In addition, evolving data based on imaging and biomarker evidence of adverse ventricular remodelling, hypertrophy, inflammation, or fibrosis may radically transform existing clinical decision paradigms. However, management of asymptomatic severe AS is otherwise controversial and the decision to intervene requires careful assessment of the benefits and risks in an individual patient. Further randomized trials [EARLY TAVI (NCT03042104), AVATAR (NCT02436655), EVOLVED (NCT03094143)] will help determine future recommendations.

Introduction

Aortic stenosis (AS) is the most common heart valve lesion and affects 2-5% of older adults. Regardless AS progression is highly unpredictable and the risk of sudden death in patients with severe AS without classic symptoms has been estimated between 1 and 3% for year.

Stratification and recommendations for aortic valve replacement (AVR) in patients presenting with AS relies on two criteria: the first one concerns the diagnosis of severe stenosis based on echocardiographic criteria, including $V_{\text{max}}$, mean gradient, and aortic valve area (AVA) or aortic valve area index; the second one interests the presence or the absence of symptoms related to AS. Additional diagnostic and prognostic parameters could be surgical risk scores (e.g. the Society of Thoracic Surgeons [STS] Predicted Risk of Mortality Score) and the presence of comorbidities (e.g. frailty, chronic obstructive pulmonary disease, renal failure).

According to new ESC guidelines intervention is recommended in asymptomatic patients with severe AS and systolic LV dysfunction (LVEF < 50%) without another cause and in those who are asymptomatic during normal activities but develop symptoms during exercise testing. In the absence of adverse prognostic features, watchful waiting has generally been recommended with prompt intervention at symptom onset (Table 1). Asymptomatic patients and medical carers need careful education, with emphasis on the importance of regular follow-up and prompt reporting of symptoms. Those with severe AS should be followed up every six months (at least) to allow earliest symptom detection (Figure 1).

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The role of echocardiography

Echocardiography is the most used imaging modality for the assessment and treatment of asymptomatic patients with AS. Among different criteria, peak aortic-jet velocity ($V_{\text{max}}$) represents a robust prognostic parameter in relation to long-term clinical outcomes. In the HAVEC (Heart Valve Clinic International Database) registry, 1375 asymptomatic patients with AS, either undergone AVR or not, have shown a higher rate of all-cause mortality, when peak velocity >5 m/s. Furthermore, the rate of symptom development or mortality have been significantly influenced by the progression of stenosis, as reflected by the increasing aortic-jet velocity peak >0.3 m/s/year.

**LV function, remodelling, and strain**

AS is related to increased afterload that could lead to ventricular remodelling and enlargement. Left ventricular ejection fraction (LVEF) is used as the main criteria to select asymptomatic patients for AVR. However, the LVEF is often normal during the first phase thanks to compensatory mechanisms. In this setting, left ventricular global longitudinal strain (LVGLS), measured with the speckle tracking analysis, has appeared to be a promising parameter for detecting early LV dysfunction as supported and confirmed in the recent PROPSERO study that has been associated an impaired GLS with a significant rate of major adverse cardiovascular events (MACE), all-cause mortality, and AVR in 1512 asymptomatic patients compared with the normal GLS group. The prognostic role of impaired GLS in patients with significant AS and preserved EF has been still uncertain but evidence has been accumulating.

**Exercise testing**

Exercise stress testing can unmask symptoms or abnormal blood pressure response and, when positive, it is associated with an increased risk of death or adverse events. However, interpreting exercise test results is a challenge and more objective parameters are necessary. Stress echocardiography can help to make a diagnosis and stratify patients. Particularly, an increase in mean aortic pressure gradient by $\geq 18-20$ mmHg and a decrease or a small increase in LV ejection fraction during exercise represent powerful predictors of poor outcome. The current guidelines do not recommend exercise echocardiography in asymptomatic patients with AS, and its role in patient management requires further investigation.

**Left atrial size and pulmonary hypertension**

In the echocardiographic assessment, the other two measures influenced patient prognosis. Left atrial size, which increases with worsening diastolic dysfunction, is associated with cardiac events and pulmonary hypertension (PHT) is related to a poor prognosis and a higher mortality rate after AVR. PHT is often associated with symptoms and it can be useless for clinical decisions. The role of exercise PHT as a predictor of the occurrence of resting PHT during the follow-up, development of symptoms, and/or outcome in various cardiac diseases has been explored, as reported by Magne et al.

**Novel staging classification, CMR, and EVOLVED Trial**

A new staging classification is needed taking into account extra-valvular cardiac damage to avoid that irreversible end-organ damage, particularly of the myocardium and pulmonary vasculature, may develop during the asymptomatic phase which results in increased mortality and morbidity even after successful intervention.

An anatomic and functional cardiac staging classification was described for a subgroup of patients with severe AS undergoing AVR in PARTNER 2 trial. The patients were pooled and classified in different stages according to the presence or the absence of cardiac damage as detected by pre-AVR (Table 2).
Management and treatment in patients with severe asymptomatic aortic stenosis

ASYMPTOMATIC SEVERE AORTIC STENOSIS (AS)

Table 2  Novel staging classification of cardiac damage

| Cardiac damage classification                   |
|------------------------------------------------|
| Stage 0  | No extra-valvular cardiac damage             |
| Stage 1  | LV damage                                    |
| Stage 2  | Left atrial or mitral valve damage           |
| Stage 3  | Pulmonary vasculature or tricuspid valve damage |
| Stage 4  | Right ventricular damage                     |

At 1-year, all-cause death and cardiac death significantly increased with each stage of worsening cardiac damage. Furthermore, after multivariable analysis and when tested in multiple models, the stage of cardiac damage was shown to be significantly associated with 1-year death, with an adjusted mortality hazard ratio of 1.45 with each increase in stage, even after adjusting for frailty and STS score.\(^5\) The limitations of this classification are that: it was derived in symptomatic patients at intermediate surgical risk, the components of each stage are not specific for AS alone, and higher stages could reflect the effect of cumulative cardiac and non-cardiac comorbidities as coronary artery disease (CAD), hypertension, atrial fibrillation, and chronic lung disease that contribute to poor outcomes after AVR. The physiopathological processes driving LV decompensation and the transition from hypertrophy (adaptive remodelling) to heart failure (maladaptive remodelling) are progressive myocyte death and myocardial fibrosis. Myocardial fibrosis is detectable with the use of CMR, in particular with LGE technique. A midwall pattern of LGE is observed that can be differentiated from the subendocardial or transmural pattern of ischaemic cardiomyopathy and from global or patchy subendocardial pattern of amyloidosis (Figure 2).

Once it first develops, further midwall LGE accumulates rapidly in the ventricle and is irreversible even after AVR.\(^10\) As a consequence, the myocardial scarring that patients develop while waiting for AVR persists into the long term, potentially governing myocardial health and adverse events well beyond valve intervention. Midwall LGE has been confirmed as a powerful long-term prognostic marker in a dose-dependent manner in several independent studies.\(^11-14\)

These assumptions are the basis of EVOLVED trial, a multicentre, randomized controlled trial investigating a novel approach to identify both the high-risk patients who will benefit most from early valve intervention and the asymptomatic patients with a healthy myocardium in whom major heart intervention can be safely delayed. Furthermore, it will investigate whether this personalized medicine approach can optimize the timing of AVR, improve long-term patient outcomes, and therefore justify the costs of this stratified biomarker/imaging approach. Asymptomatic patients with severe AS will initially be screened for LV decompensation by using hsTnI...

Figure 1  Management and treatment in patients with severe asymptomatic AS. Management of patients with asymptomatic severe AS: although left ventricular ejection fraction and verification of asymptomatic status with exercise testing remain the key points for diagnosis and evaluation of AS, there are several established indices of disease severity as well as traditional and novel indices of risk. Novel indices of risk are now being tested in randomized controlled trials to determine if early AVR results in better outcomes than traditional clinical surveillance until onset of symptoms. EF, left ventricular ejection fraction; RCTs, randomized controlled trials; AVR, aortic valve replacement; BNP, B-type natriuretic peptide; BP, blood pressure; HT, hypertension; LVH, left ventricular hypertrophy; EARLY TAVR, evaluation of transcatheter aortic valve replacement compared to surveillance for patients with asymptomatic severe AS; EVOLVED, the early valve replacement guided by biomarkers of LV decompensation in asymptomatic patients with severe AS.
and electrocardiography. Those patients with a normal level (<6 ng/L) marker will be considered to have healthy myocardium and continue to undergo routine clinical follow-up. Patients with an elevated troponin level or an electrocardiographic strain pattern will proceed to CMR. Patients in whom midwall LGE is identified will then be randomized to receive either early TAVI/SAVR or the standard watchful waiting approach. The primary endpoint is a composite of all-cause death or unplanned AS-related hospital admission. The results are expected for October 2024.

**Blood biomarkers and early TAVR**

Blood biomarkers offer additional information that might clarify patient risk and optimize recommendations regarding the timing of AVR.

According to new ESC guidelines, natriuretic peptides predict symptom-free survival in normal and low-flow severe AS. They can be used to arbitrate the source of symptoms in patients with multiple potential causes and identify those with high-risk asymptomatic AS who may benefit from early intervention. In particular, N-terminal B-type natriuretic peptide (NT-proBNP) independently predicts postoperative outcome about survival, symptomatic status and left ventricular function.  

In addition in patients with AS, plasma high-sensitivity troponin I concentration is associated with advanced hypertrophy and replacement myocardial fibrosis as well as AVR or cardiovascular death. Finally, serum levels of the calcification inhibitor fetuin-A are associated with the progression of aortic valve calcification and major clinical adverse events, independent of the renal function and inflammation.

Nevertheless, the most likely utility for biomarkers in optimizing the timing of SAVR or TAVI is to identify patients with progressively maladaptive hypertrophic remodelling and subclinical dysfunction that place them at risk for LV impairment and heart failure after AVR if intervention is delayed until the development of symptoms or overt evidence of LV systolic function.

However, further investigation is needed to show an adverse association between increased levels of certain biomarkers and clinical outcomes before they can be incorporated into the clinical management of patients with asymptomatic AS.

The lack of robust data to support guideline recommendations for asymptomatic patients has led to the conception of the EARLY TAVI trial. This trial is a prospective, randomized controlled, multicentre study which will evaluate the safety and effectiveness of the Edwards SAPIEN 3 Ultra Transcatheter Heart Valve compared with clinical surveillance in asymptomatic patients (≥65 years of age) with severe, calcific AS and LVEF ≥50%. The primary endpoint at two years is a composite of all-cause death, all stroke, and unplanned cardiovascular hospitalization. To complement the EARLY TAVR trial, the pre-defined biomarker sub-study (with blood collected in both randomization arms, at baseline, and pre- and post-TAVI) will provide meaningful biological insight to evaluate the potential benefit of a biomarker-driven early intervention strategy. The results of the EARLY TAVR trial have the potential to substantially influence the future management paradigms for patients with severe asymptomatic AS.
The RECOVERY and AVATAR Trial

Indications for early SAVR in asymptomatic patients with severe AS and normal left ventricular function remain debated. The RECOVERY18 (The Randomized Comparison of Early Surgery vs. Conventional Treatment in Very Severe Aortic Stenosis) and the AVATAR19 (Aortic Valve Replacement vs. Conservative Treatment in Asymptomatic Severe Aortic Stenosis) trials, that randomized asymptomatic patients with severe AS and normal LVEF to early surgery or to conservative care, have demonstrated a significantly lower incidence of primary composite endpoint in the early surgery group. The ongoing EARLY TAVR (Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis) (NCT03042104) trial might give more information, enrolling patients with asymptomatic severe AS.

Comparing with RECOVERY and AVATAR trials, patients will be probably older (≥65 years) with the same inclusion echocardiographic criteria (severe AS and LVEF ≥ 50%), an STS < 10 and a negative exercise testing that will be performed only if patients can, such as in the RECOVERY trial.

Conclusion

New methods of risk stratification for asymptomatic patients with AS are emerging. Echocardiography will continue to be the clinical workhorse for initial diagnosis and routine re-evaluation. However, echocardiography is also expanding its diagnostic horizons, principally through advances in strain imaging. The coupling of these newer echocardiographic modalities with advanced CMR imaging of myocardial fibrosis and the use of multiple serum biomarkers hold promise for the earlier identification of patients with AS who can be treated effectively before the onset of irreversible structural and functional myocardial changes that would otherwise impair long-term outcomes. Pending the results of the ongoing trials, tailored treatment for each patient, through a multidisciplinary (echo-cardiograph, radiologist, interventional cardiologist) and multiparametric evaluation, is the winning strategy for the best benefit of the patient.

Conflict of interest: None declared.

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