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**GREAT DEBATE**
*Valvular heart disease*

# Great debate: all patients with asymptomatic severe aortic stenosis need valve replacement

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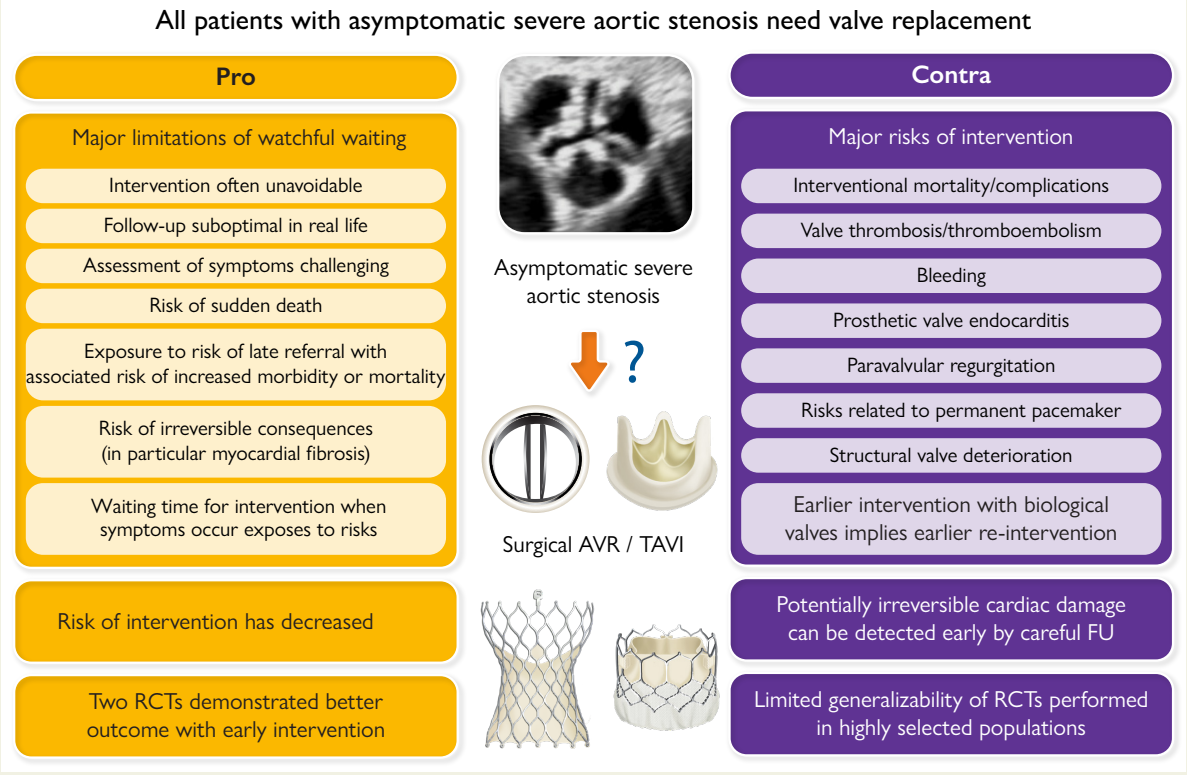
## Graphical Abstract




AVR = aortic valve replacement, TAVI = transcatheter aortic valve implantation, FU = follow-up, RCT = randomized controlled trial.

**Keywords** Aortic stenosis • Early intervention • Watchful waiting

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# Introduction

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Aortic stenosis (AS) has become a significant health burden affecting 2%–6% of the population older than 65 years.[1–3] A recent study[4] estimated for 2017 globally 12.6 million patients with calcific AS—the most common etiology of AS—causing 102 700 deaths and a rapid increase in prevalence is observed with the aging population, particularly in Europe and North America.[4,5] Since calcific AS can easily be detected by echocardiography at a very early stage—when no or only mild hemodynamic consequences are present—develops slowly, and is an active process sharing pathophysiologic similarities with atherosclerosis,[6] there is hope to find medical treatment that interferes with its progression. Unfortunately, all attempts to develop effective medical treatment over the last decades—in particular addressing cholesterol lowering and statin therapy[7] but also other innovative approaches[8,9]—were so far unsuccessful and the only treatment option currently remains aortic valve replacement (AVR) by a prosthetic valve when the stenosis has become severe. While studies reported a relatively good outcome for asymptomatic severe AS,[10,11] the prognosis becomes dismal as soon as the patients develop symptoms.[12,13] AVR has been shown to dramatically improve symptoms and survival at this stage of the disease.[13,14] Therefore, the strong indication for AVR in symptomatic severe AS is generally accepted.[15,16] Whether and when to intervene in asymptomatic severe AS to improve outcome remains, however, controversial.[15–17] In a recent survey, asymptomatic patients accounted for 19% of patients with severe AS[18] and 17% of patients with severe high gradient AS[19] referred to the participating centers, but the percentage in the general population must be expected to be much higher. Thus, the question of how to manage these patients is of critical importance. The potential rationale for intervening in asymptomatic severe valvular heart disease has recently been summarized.[17] Arguments include in particular the risk of life-threatening events and irreversible end-organ damage as well as practical limitations of a watchful waiting strategy in guaranteeing optimal timing of intervention.[17]

The potential benefits of intervening in an asymptomatic patient must, however, be weighed against the operative/catheter interventional risk and the long-term risks associated with a valve substitute.[15–17]

Over the years, a number of predictors of worse outcome in asymptomatic AS have been identified.[15] These include clinical characteristics such as older age, atherosclerotic risk factors, and echocardiographic parameters such as degree of valve calcification, peak velocity and its progression,[11,20] ejection fraction, increase in mean gradient > 20 mmHg with exercise,[21,22] severe left ventricular hypertrophy,[23] indexed stroke volume,[24] left atrial volume,[25] left ventricular global longitudinal strain,[26–28] pulmonary hypertension,[29–33] and abnormal biomarker levels (natriuretic peptides, troponin, and fetuin-A).[34–37] While these risk factors could be demonstrated to predict event-free survival, it must be kept in mind that in most studies, the predominating event was the development of symptoms requiring intervention. It still remains to be shown whether, in the presence of such risk factors, patients benefit indeed from early intervention when they are still asymptomatic.

Based on observational data, current guidelines recommend by expert consensus rather than by strong evidence to intervene in the following groups of asymptomatic patients with severe AS[15] (the references cited after each recommendation are the ones provided in the guideline document to support the respective recommendation):

- Patients with systolic left ventricular dysfunction defined by ejection fraction <50% when no other causes are present (IB)[38–40]
- When exercise testing reveals symptoms attributable to AS (IC)

They recommend that intervention should be considered in the following patient groups:

- Patients with systolic left ventricular dysfunction defined by ejection fraction <55% when no other causes are present (IIaB)[38,41,42]
- Patients with a sustained fall in blood pressure > 20 mmHg during exercise testing (IIaC)
- Patients with ejection fraction >55% and a normal exercise test who are at low procedural risk and present with one of the following parameters (IIaB):
  - Mean gradient ≥ 60 mmHg or peak velocity >5 m/s[38,43]
  - Severe valve calcification and peak velocity progression ≥0.3 m/s/year[11,44,45]
  - B-type natriuretic peptide levels >3 × age- and sex-corrected normal range confirmed by repeated measurements and without other explanations[34,35]

Current guidelines admit, however, that the management of patients with asymptomatic AS (including a normal exercise test) and normal left ventricular function remains controversial. Decision-making requires careful weighing of risk and benefit. In this regard, the fact that catheter interventional treatment of AS is rapidly evolving and recent data demonstrate that the risk of both, surgical AVR and transcatheter aortic valve implantation (TAVI) have markedly decreased over the years[46] has an obvious impact as this may change the threshold to intervene in asymptomatic patients when weighing risk vs. potential benefit. On the other hand, the complexity of long-term planning considering the consequences for later re-interventions, access to coronary arteries after TAVI, and other aspects have been recognized.[47] New important data including randomized controlled trials comparing watchful waiting vs. early surgery in asymptomatic AS have also been provided.[48] Thus, it appears timely to revisit the pro and cons of whether all patients with asymptomatic severe AS need a valve replacement.

## Declarations

### Disclosure of Interest

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# Pro

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The consequence of restricted indications for intervention in asymptomatic patients with severe aortic stenosis (AS) is that the majority of patients are managed according to the so-called "watchful waiting" strategy, i.e. waiting for symptom onset. However, the rationale supporting the safety of watchful waiting is challenged in clinical practice by a number of considerations derived from observational findings and recent trials.

## Watchful waiting strategy in practice

### Intervention is often unavoidable

Cardiac events, most often symptom onset requiring an intervention, will occur in as many as 80% of asymptomatic patients with severe AS within 3 years and in more than 20% within one year.[1] The likelihood of remaining asymptomatic further decreases with AS severity and is very low among the subset of patients classified as very severe AS for whom an intervention is now recommended.[2]

### Follow-up is suboptimal in real life

Close follow-up is thus needed, at least twice a year to detect symptom onset. However, the watchful waiting strategy relies on two major principles that are often unsatisfactory in clinical practice: first, the patient immediately reports the occurrence of symptoms (patient compliance), and, second, a close follow-up could always be achieved (optimal follow-up). Thus, it has been shown that a third of asymptomatic patients with known severe AS are followed less than once a year and experience higher mortality.[3] Although patients are informed to promptly report any change in symptoms, this is frequently not done in clinical practice.

### Assessment of symptoms is challenging in the AS population

Symptoms are subjective and may develop insidiously and patients adapt to symptoms, which accounts for an underestimation of symptoms by both patients and practitioners.[4] Since AS frequently occurs in the elderly, impaired functional capacity may be attributed to ageing and/or comorbidities. Difficulties in symptom interpretation highlight the usefulness of exercise testing for an objective evaluation of exercise tolerance. However, in the recent valvular heart disease (VHD) II survey which included 2152 patients referred to the hospital for severe AS, stress tests were used in only 6% of asymptomatic patients with severe AS.[5] Although exercise testing is now recommended in guidelines for asymptomatic severe AS, it was not performed more frequently in VHD II than in the Euro Heart Survey in 2001. In addition, in the elderly AS population, a stress test may not be feasible in a significant proportion of patients.

### Risk of sudden death

Sudden death rates are low in asymptomatic patients but higher than in the general population, and this very low risk of mortality is generally achieved in patients having strict follow-up in the context of heart valve clinics.[6] Although the rate of sudden death is low in true-asymptomatic patients, it significantly raises in those who developed symptoms during follow-up, especially if not reported and/or not recognized as shown in the RECOVERY trial.[7]

### Delaying intervention exposes to the risk of late referral with associated increased mortality and morbidity risk

A recent meta-analysis has shown that the risk of death under conservative management is high, that deaths are mostly of cardiac cause, and that sudden death only accounts for a part of it.[8] The VHD II survey attests to the late referral of patients with severe AS. More than a third of patients with severe AS were referred to hospital in outpatient clinics or in hospitalization in NYHA class III or IV and 16% had been hospitalized for heart failure during the preceding year.[5] These findings combine patients with undiagnosed AS and patients with known AS but in whom symptom onset has not been interpreted in due time. Late referral is also observed in patients followed in dedicated heart valve clinics. In a series of 103 asymptomatic patients

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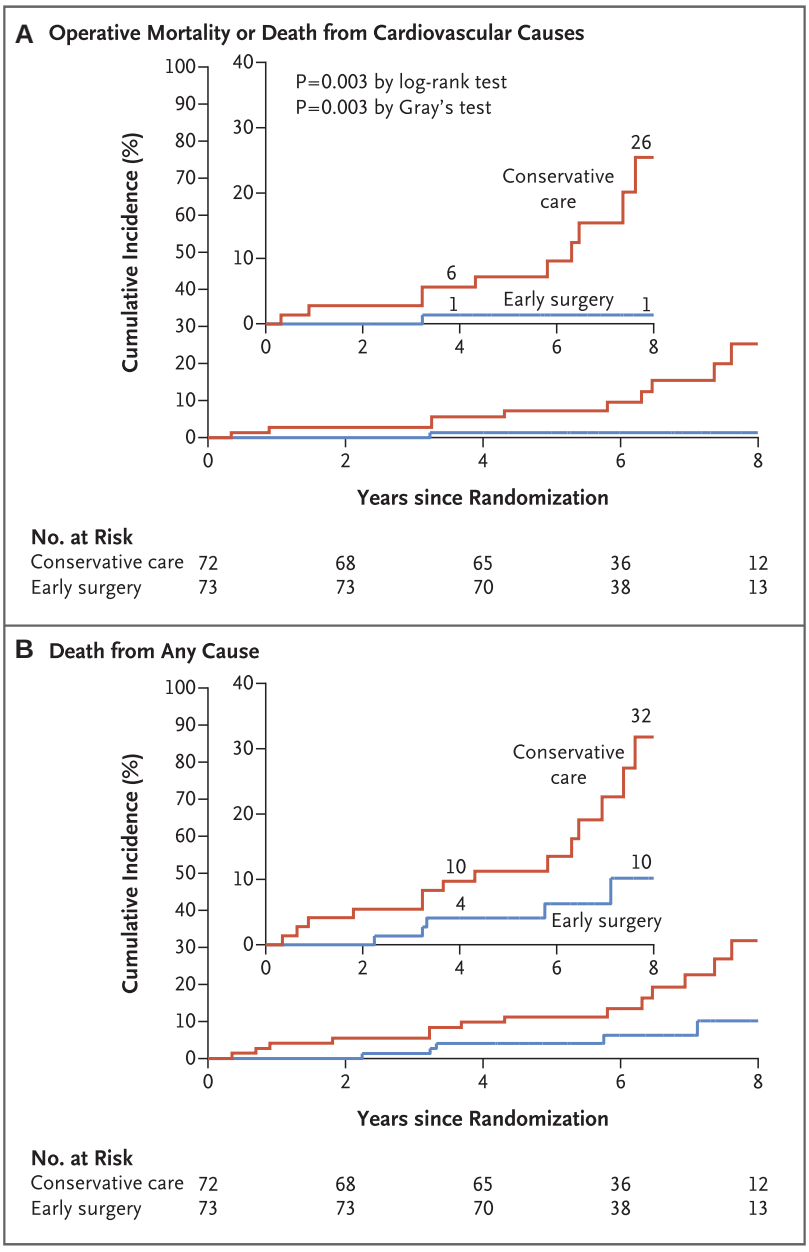


**Figure 1** Comparison of incidence rates of the primary endpoint of all-cause mortality and major adverse cardiac events between early surgery and conservative treatment in the randomized RECOVERY trial. Reproduced with permission from Kang *et al.*[7].

aged ≥ 70 years with severe AS who were followed every 6 months in a heart valve clinic, an indication of aortic valve replacement occurred in 82 of them during a mean follow-up of only 19 months and 32 patients had severe symptoms at the time of aortic valve replacement, as defined by NYHA class ≥ III or CCS class ≥ 3.[9] A total of 30 patients had impaired mobility due to comorbidities and this contributed probably to defer the identification of symptom onset. Severe symptoms or prior heart failure are associated with an increased risk of early morbidity and mortality after surgical AVR or TAVI, as compared with interventions performed in patients with few or no symptoms.[10–12] Indications for intervention based only on the severity of AS appear as an effective approach to reduce late referral by avoiding delays in the interpretation of symptom onset.

## Risk of irreversible consequences

Advanced left ventricular remodelling due to AS may compromise the quality of late results of aortic valve intervention. In contrast to ejection fraction, strain analysis detects subtle impairment of left ventricular function, and abnormal strain rate is associated with decreased event-free survival.[13] Left ventricular remodelling in AS is also related to the presence of ventricular fibrosis which has an incremental negative prognostic value.[14,15] Beyond the left ventricle, more than half of asymptomatic patients with moderate-to-severe AS present markers of left atrial or mitral valve damage, pulmonary hypertension, or right heart failure which are associated with impaired outcome.[16] Not all these features are direct consequences of AS; however, it is likely that they would be less frequent if intervention is performed early.

## Waiting time and increased mortality

Excessive time delays in the identification of symptom onset and inherent late referral cumulate with time delays on the waiting list for intervention, which are associated with an increased risk of hospitalizations for heart failure and death before intervention.[17,18]

## Risk of intervention is now lower

The last decade has seen a marked decrease in the operative mortality and morbidity, in particular with transcatheter valve interventions in the elderly population. The risk of intervention increases with age and severity of the clinical presentation and the watchful waiting strategy is therefore intrinsically associated with an increased operative mortality.

# Association between early intervention and outcome

## Observational series

These have been used to compare the strategies of early intervention and watchful waiting. Their interpretation is hampered by inherent sources of bias which affect the comparability of therapeutic groups. Large series allow for adjusting on potential confounders, and this approach was used in the CURRENT AS registry which included 1808 consecutive asymptomatic patients with severe AS, of whom 291 underwent early AVR and 1517 were managed conservatively.[19] In a comparison of two propensity-matched subgroups of 291 patients, there was a significant decrease in the incidence of hospitalization for heart failure and, more importantly, of all-cause mortality in asymptomatic patients who underwent early surgery as compared with conservative management.

## Randomized controlled trials

Randomized trials are the only valid method to compare therapeutic strategies without bias due to measured and unmeasured confounders, although one should not forget their limitations due to open-label (and not double-blind) design and, as for all clinical trials, concerns on the generalizability of the findings. Two randomized trials comparing surgical AVR in asymptomatic patients with severe AS with a conventional conservative strategy have been published over the last two years, formally proving the benefit of an early intervention. The first randomized trial (RECOVERY) was conducted in four Korean centres and randomized 73 patients to early surgery and 72 patients to conservative strategy.[7] Inclusion criteria corresponded to a more severe degree of AS than usual criteria and were defined by valve area $\leq 0.75$ cm$^2$ and ($V_{max} \geq 4.5$ m/s or mean gradient $\geq 50$ mmHg). The absence of symptoms was based on case history and exercise testing was performed only in case of doubtful symptoms. The mean age was 64 years, and the mean EuroSCORE II was 0.9%. Outcome according to the primary endpoint of operative mortality or post-operative cardiovascular mortality was markedly better after early surgery as compared with conservative management [hazard ratio (HR) 0.09; 95% confidence interval (CI) 0.01–0.67] (*Figure 1*). The benefit of early surgery was also consistent across the different secondary endpoints, even for all-cause mortality (HR 0.33; 95% CI 0.12–0.90).

More recently, the AVATAR trial included patients with commonly used definitions of severe aortic stenosis (valve area $\leq 1.0$ cm$^2$ and $V_{max} \geq 4.0$ m/s or mean gradient $\geq 40$ mmHg).[20] Exercise testing was mandatory to confirm the absence of symptoms, thereby corresponding to current guidelines. The mean age was 67 years, and the mean STS score was 1.7%; 78 patients were randomized to early surgery, and 79 patients to conservative strategy. The incidence of the primary endpoint combining all-cause death or major adverse cardiac events was significantly reduced in the early surgery group as compared with

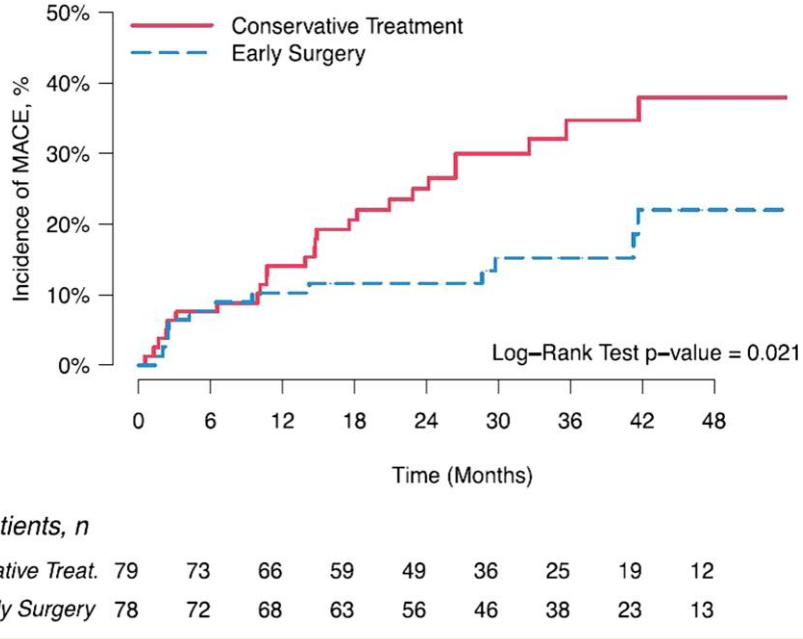


**Figure 2** Comparison of incidence rates of the primary endpoint of all-cause mortality and major adverse cardiac events between early surgery and conservative treatment in the randomized AVATAR trial. Reproduced with permission from Banovic *et al.*[20].

conservative management (HR 0.46; 95% CI 0.23–0.90, $P = 0.02$) (*Figure 2*). Although not reaching statistical significance, the trend for all-cause mortality (HR 0.56; 95% CI 0.24–1.27, $P = 0.16$) and heart failure hospitalization were also in favour of the early surgery group (HR 0.32; 95% CI 0.08–1.19, $P = 0.075$). The absence of difference in cardiovascular mortality may seem paradoxical. However, of the 16 deaths which occurred in the conservative strategy group, four were caused by pneumonia, including three due to COVID-19. Severe AS may have contributed to worse outcome and highlighted the difficulties related to an accurate identification of the cause of death.

A meta-analysis combing 10 observational series (two prospective and eight retrospective) and the two randomized trials included 4130 patients and showed a significant association between early surgery and significantly lower all-cause mortality as compared with conservative management (pooled odds ratio 0.40; 95% CI 0.35–0.45, $P < 0.01$).[8] The restriction of the analysis to the two randomized trials showed also a lower all-cause mortality after early surgery (pooled odds ratio 0.45; 95% CI 0.25–0.82, $P < 0.01$) with no heterogeneity. Ongoing randomized controlled trials comparing the watchful waiting strategy and an early intervention using either surgical AVR or TAVI will formally demonstrate the superiority of one strategy vs. the other.

# Implications on AS detection

Early intervention in asymptomatic patients as soon as AS becomes severe will require an increased awareness towards the diagnosis of AS. The underdiagnosis of heart valve disease in the community was first reported by Nkomo *et al.* in 2006[21] and confirmed more recently in the OxVALVE study.[22] In the OxVALVE cohort, systematic echocardiographic screening in the general practice of patients aged ≥ 65 years detected a prevalence of 6.4% of undiagnosed moderate or severe valvular disease (0.7% for AS), higher than the 4.9% prevalence of previously diagnosed valvular disease of the same severity.[22]

# Conclusion

In conclusion, although the watchful waiting strategy seems sound, its routine implementation is hampered by different issues, in particular, the considerable underuse of exercise testing and the frequent delay in the identification of symptom onset. This contributes to late referral, thereby compromising the safety and quality of the results of the valvular intervention. The results of the two recent randomized trials now provide evidence that early surgical aortic valve replacement in asymptomatic patients with severe AS is a valuable alternative to watchful waiting.

# Declarations

## Disclosure of Interest

Dr. Iung has nothing to declare. Dr. Messika-Zeitoun received a research grant from Edwards Lifesciences.

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# Contra

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Aortic stenosis (AS) is the most frequent valvular heart disease.[1] Both European and American guidelines recommend aortic valve replacement (AVR) (Class I or IIa) in patients with severe AS exhibiting symptoms and/or left ventricular ejection fraction (LVEF) < 50%.[2,3] However, for asymptomatic patients with severe AS and preserved LVEF, the management and, in particular, the timing of intervention remains highly controversial and challenging and is still based on a relatively lower level of evidence.

## What are the current guideline recommendations for the management of asymptomatic severe AS?

Current guidelines recommend that asymptomatic patients with severe AS be followed closely in a heart valve clinic and be referred to a comprehensive heart valve center for confirmation of the indication of AVR and the selection of the type of AVR: i.e. surgical AVR (SAVR) with a mechanical or bioprosthetic valve or transcatheter aortic valve implantation (TAVI) with a balloon-expandable or self-expanding valve.[2,3] This should be a shared decision-making process with particular emphasis on patient preferences. Until now, AVR is not recommended for all patients with asymptomatic severe AS. Indeed, according to the guidelines, AVR is indicated (Class I) if the patient has a LVEF <50% or an indication for another cardiac surgery (Class I) or if symptoms can be demonstrated on exercise testing. However, specifically in such cases, the patient should not be considered as truly asymptomatic. Furthermore, AVR (SAVR or TAVI) may be considered (Class IIa) in the presence of specific risk markers (*Table 1*). Several studies[4–10] lend support to this recommendation of early AVR in the presence of these risk markers. Nevertheless, these studies are only observational and cannot lead to a high level of evidence. In addition, these studies also show that the majority of asymptomatic patients with severe AS do not present with any of these risk markers and can be safely managed with conservative management.

In light of the current evidence,[9,11] we believe that early 'prophylactic' AVR strategy, i.e. in patients without current indication according to most recent guidelines, should not be applied to all asymptomatic patients but should be individualized by taking into account the patient's risk profile and personal preferences (*Figure 3*) and by addressing the four following key questions: (i) Is the patient really asymptomatic?; (ii) is the stenosis really severe?; (iii) does the risk of conservative management exceed the risk of early AVR?; (iv) does the proven durability of the prosthetic valve match the expected life expectancy of the patient?

## Is the patient really asymptomatic?

Many patients with asymptomatic severe AS may have progressively reduced their level of activity to avoid symptoms or may deny or not report their symptoms. This issue is more important in older vs. younger patients and in women vs. men.[12] An exercise test is recommended to unmask symptoms and identify true asymptomatic patients.[11,13] Regrettably, only a minority (6.1%) of asymptomatic patients are submitted to an exercise test as shown in the EURObservational VHD II survey.[14] Previous studies reported that at least one-third of patients claiming to be asymptomatic and submitted to an exercise test actually develop exercise-limiting symptoms.[15] These falsely asymptomatic patients have an increased risk of adverse events in the short term and have a Class I indication for AVR according to current guidelines. Das *et al.* reported that the positive predictive value of exercise testing was good (79%) in patients younger than 70 years but only 57% for the older population.[15] These findings underline the limitations of exercise test in the elderly population and provide an argument for the utilization of other tools to identify the asymptomatic patients who are at higher risk for adverse events and who may benefit from early AVR.

## Is aortic stenosis really severe?

AS is considered severe when peak aortic velocity is ≥4 m/s, mean transvalvular pressure gradient is ≥40 mmHg, and aortic valve area (AVA) is <1.0 $cm^2$ (or <0.6 $cm^2/m^2$). However, AVA may be underestimated and thus AS severity may be overestimated because of the underestimation of left ventricular outflow tract diameter by echocardiography, which is squared in the continuity equation. Furthermore, Doppler echocardiography may overestimate pressure gradient and thus AS severity because of the pressure recovery phenomenon. Peak aortic jet velocity and pressure gradients and thus severity may also be underestimated if meticulous multiwindow interrogation with continuous-wave Doppler is not performed. Indeed, the exclusion of non-apical windows may result in the misclassification of AS severity in a significant proportion of patients. Hence, in asymptomatic patients with apparently severe AS, it is first essential to rule out measurements errors and to use additional parameters of AS severity to confirm the presence of true severe AS, particularly in patients with discordant grading at echocardiography (i.e. severe AVA but non-severe gradient). These parameters include Doppler velocity index < 0.25 to corroborate AVA, energy loss index < 0.55 $cm^2/m^2$ to account for pressure recovery, and computed tomography aortic valve calcium score >1200 AU in women and >2000 AU in men to assess the anatomic severity of AS.

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**Table 1 Indications for intervention in asymptomatic severe AS according to European guidelines**

| Criteria | Class of indication and LOE | Comments |
|---|---|---|
| LVEF <50% | I, B | Applicable to very few (<2%) asymptomatic patients with severe AS and no CAD |
| Symptoms during exercise | I, C | If not, patients should be considered as truly asymptomatic |
| LVEF <55%[a] | IIa, B | Recommendation only based on retrospective studies |
| Sustained fall in blood pressure >20 mmHg during exercise | IIa, C | Despite being supported by pathophysiologic mechanisms, limited data are available. Recommendation requiring further investigation |
| LVEF >55% and:<br>Very severe AS (mean gradient ≥60 mmHg or $V_{max}$ >5 m/s)<br>- Severe valve calcification and $V_{max}$ progression ≥0.3 m/s/year<br>- Elevated BNP levels (>three-fold higher than age- and sex-corrected normal range) | IIa, B | – Supported by strong evidence but true asymptomatic patients rarely have very severe AS.<br>- CT is the gold standard for aortic calcium score measurement. $V_{max}$ progression is limited by measurement inter- intra-variability that may exceed the proposed cut-off.<br>- Need to be cautiously interpreted in the context of patients with comorbidities |

[a] < 60% in US guidelines when a progressive decrease in LVEF is observed in at least three serial imaging studies.
LOE, level of evidence; LVEF, left ventricular ejection fraction; AS, aortic stenosis; CAD, coronary artery disease; BNP, brain natriuretic peptide; CT, computed tomography.

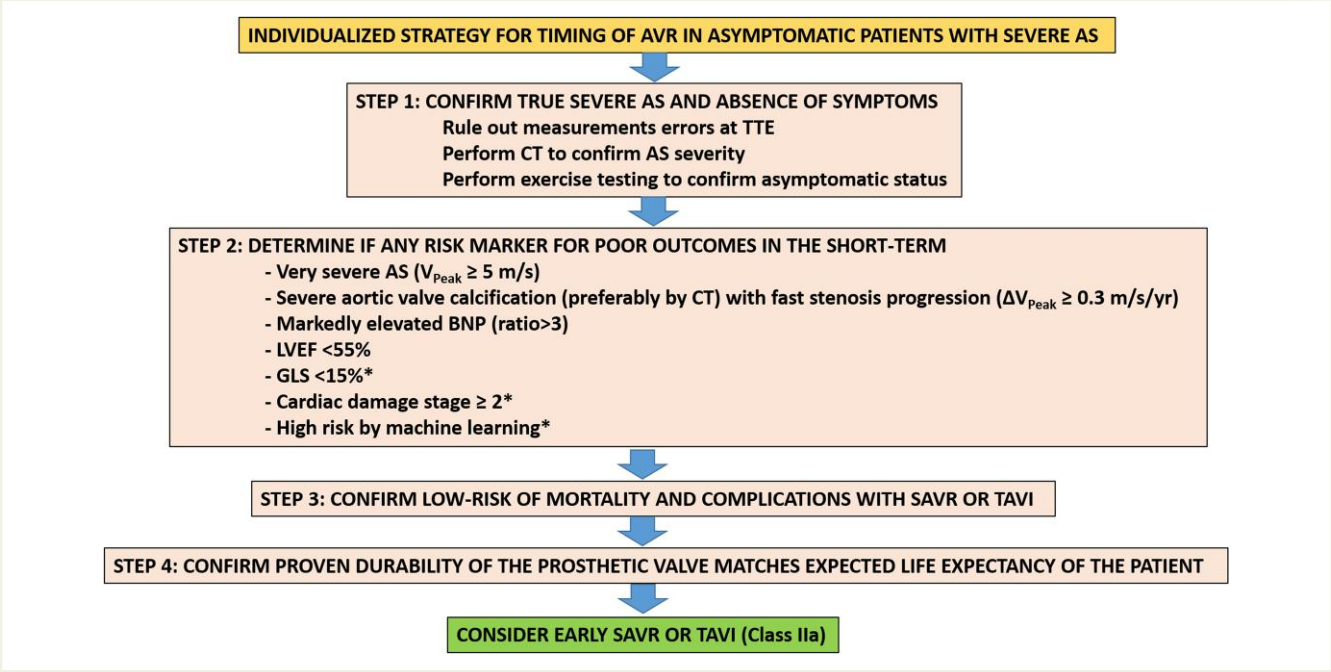


**Figure 3** Individualized strategy for the management of asymptomatic severe aortic stenosis. *These are risk markers that are not presented in the guidelines and that will thus require further validation to be adopted in clinical practice. AVR, aortic valve replacement; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; $V_{Peak}$, peak aortic jet velocity; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

## Does the risk of conservative management exceed the risk of early AVR?

AVR consists in replacing a severe native aortic valve disease with another hopefully milder disease, which is the prosthetic valve. Early intervention is associated with a substantial risk of procedural mortality and complications including bleeding, coronary obstruction and myocardial infarction, stroke, permanent pacemaker implantation, and non-structural valve dysfunction (paravalvular regurgitation and prosthesis-patient mismatch). Furthermore, an earlier intervention will expose the patients, sooner in their life, to the long-term risk of complications related to the prosthetic valve including valve thrombosis,

**Table 2 Summary of the design and results of the ongoing randomized trials in asymptomatic severe aortic stenosis**

| Trial | Location | Design | *n* | Primary outcome | Main inclusion criteria | Main non-inclusion criteria | Sponsor | Comments |
|---|---|---|---|---|---|---|---|---|
| Early TAVR—evaluation of TAVR compared to surveillance for patients with asymptomatic severe aortic stenosis. https://clinicaltrials.gov/ct2/show/study/NCT03042104 | US and Canada | Randomized (TAVR vs. clinical surveillance). Open label | 901 | 2-year combined all-cause death, all stroke, and unplanned cardiovascular hospitalization. | ≥ 65 years old. Severe asymptomatic AS. LVEF ≥50%. Low risk (STS score ≤10). | >3 + mitral and/or aortic regurgitation. Patients unsuitable for TAVI. | Edwards lifesciences | Patients with class IIa indication can be randomized. Highly selected patients. Estimated primary completion date March 2024 |
| EVOLVED—early valve replacement guided by biomarkers of LV decompensation in asymptomatic patients with severe AS. https://clinicaltrials.gov/ct2/show/study/NCT03094143 | UK | Randomized (4 arms according to results of cardiac MRI: mid-wall fibrosis or not). Open label. | 400 | Composite of all-cause mortality or unplanned AS-related hospitalization (mean follow-up of 2.75 years). | Severe asymptomatic AS. | LVEF <50%. Severe aortic or mitral regurgitation. Mild mitral stenosis. Coexistent hypertrophic cardiomyopathy or cardiac amyloidosis. Advanced renal impairment. | Academic | Patients with class IIa indication can be randomized. Randomization based on MRI results and not echocardiography. Patients with mid-wall fibrosis despite LVEF >50% will be randomized in no intervention group whereas their prognosis is already known to be reduced in absence of intervention. |
| EASY-AS—the early valve replacement in severe asymptomatic aortic stenosis study https://clinicaltrials.gov/ct2/show/NCT04204915 | UK, Australia and NZ | Randomized (surgery vs. expectant management). Open label. | 2844 | 3-year combined measure of cardiovascular death and hospitalization for heart failure | Severe asymptomatic AS. | Additional severe valvular heart disease. LVEF <50%. Other pre-inclusion cardiac surgery. Co-morbid condition that, in the opinion of the treating cardiologist, limits life expectancy to <2 years | Academic | Patients with class IIa indication can be randomized. No TAVI in the intervention arm. |

thromboembolism, haemolysis, structural valve deterioration, valve failure, valve-related reintervention, or death. Furthermore, the risk of sudden cardiac death in asymptomatic patients with severe AS is low (<1% per year) and is actually lower than the risk of operative mortality with SAVR. When considering early AVR in a true asymptomatic patient, it is important to emphasize that AVR has no or minimal potential to improve the patient because he or she is not suffering from any symptom or side effect of the disease prior to AVR. In this context, it is crucial to not deteriorate the symptomatic status and quality of life of the patient with the intervention and to avoid any complication. Hence, early AVR can only be considered in these patients if the risk of procedural mortality and complications is very low.

Adopting a delayed intervention strategy in asymptomatic patients with severe AS may lead to the development of more advanced and potentially irreversible damage and dysfunction of the left ventricle and other cardiac chambers. Using a multi-echocardiographic parameter integrative approach for staging extra-valvular cardiac damage, Tastet *et al.* reported that 61% of patients with asymptomatic severe AS have advanced cardiac damage (i.e. Stage ≥ 2) and these patients display a higher risk of mortality in the short-term and may thus benefit from early intervention.[7] However, in a substantial proportion of these patients, the advanced cardiac damage was likely not related to the AS *per se* but to other comorbidities, therefore undermining the potential benefit of early AVR in these patients. Moreover, close to 40% of the patients in this series were in Stage 0 or 1 (left ventricular damage only), and these patients harbored an excellent mid-term outcome with the management strategy currently recommended in the guidelines, i.e. intervention when symptoms or left ventricular systolic dysfunction develop or when one of the risk markers mentioned above occur.

## Does the proven durability of the bioprosthetic valve match the expected life expectancy of the patient?

When selecting a type of AVR and valve substitute, it is essential to match the proven durability of the prosthetic valve vs. the expected life expectancy in order to reduce the risk of reintervention and ensuing complications.[16] Asymptomatic patients with severe AS are generally younger and have longer life expectancy and considering early AVR in these patients inherently raises the requirements in terms of long-term durability of the prosthetic valve. Hence, in most of these patients, the prosthetic valve should have a minimum durability of at least 10, if not 15, years. Few SAVR valves and no TAVI valves have such proven long-term durability, thus further limiting the consideration of early AVR in all asymptomatic patients with severe AS.

## Current randomized trials of early AVR vs. conservative management in asymptomatic severe AS

Two small controlled randomized trials have been published until now. Kang et al. randomized 145 patients to early SAVR (within 2 months) vs. conservative management.[17] The primary endpoint, which was the composite of death within 30 days or cardiovascular death during the entire follow-up, occurred in only one patient in the early surgery group vs. 11 of 72 (15.2%) patients in the conservative group. In this group, the incidence of sudden death was 4% at 4 years and 14% at 8 years. There was no operative mortality in both the surgical group and the conservative group (17% submitted to surgery because of acute decompensation). Such outstanding results may be difficult to achieve in real-life practice and in all cardiac surgery centers. There are severe other limitations to this study. First, it included predominantly young patients (average: 64 years) with bicuspid valve disease, and all of them had very severe AS (peak aortic jet velocity > 5 m/s). Furthermore, several patients who developed symptoms did not undergo AVR and were thus not treated according to the guidelines.

The second trial, AVATAR (aortic valve replacement vs. conservative treatment in asymptomatic severe aortic stenosis), randomized 157 patients (mean age 67 years; severe AS using the classical criteria; normal left ventricular function and negative exercise test) SAVR vs. conservative management.[18] The incidence of the primary endpoint, i.e. the composite of all-cause death, acute myocardial infarction, stroke, and unplanned hospitalization for heart failure, was lower in the SAVR vs. conservative management group (hazard ratio 0.46), and operative mortality in the SAVR arm was 1.4%. The sample size was, however, small, and although this was a multicenter trial, 73% of patients were recruited in one center. The study was prematurely stopped because of early superiority in the SAVR arm. There was no difference in cardiovascular death: 9.54% in the early SAVR group vs. 9.09% in the conservative group. The event curves diverged only after 18 months for both all-cause death and heart failure and the indications for delayed surgery in the conservative group were symptom onset (60%), AS progression (16%), and a decrease in LVEF (4%), which can all be identified during appropriate close (every 6 months) follow-up.

These two trials are interesting but do not provide any definitive answer regarding the timing of intervention in asymptomatic severe AS. We must wait for the results of large controlled trials (*Table 2*), such as ESTIMATE (early surgery for patients with asymptomatic aortic stenosis—NCT02627391), early TAVR (evaluation of trans-catheter aortic valve replacement compared to surveillance for patients with asymptomatic severe aortic stenosis—NCT03042104), EVOLVED (early valve replacement guided by biomarkers of left ventricular decompensation in patients with asymptomatic severe aortic stenosis—NCT03094143), and EASY-AS (early valve replacement in severe, asymptomatic aortic stenosis study—NCT04204915). These trials plan to include 360, 901, 1000, and 2844 patients, respectively.

The use of TAVI rather than SAVR in some of these trials may reduce the risk of short-term complications, but there are not yet any large studies on the potential benefits and more importantly the long-term valve durability and outcomes of TAVI in asymptomatic patients with severe AS.

In the event that these trials are positive and demonstrate the superiority of early AVR over conservative management, this would not necessarily imply that the results of these trials apply to all asymptomatic patients with severe AS and that early AVR is the best option for all patients.

## Individualized strategy rather than early AVR for all asymptomatic patients with severe AS

The incidence of severe AS is expected to increase markedly in the next decades due to the aging of the population and rise of the prevalence of

cardiometabolic risk factors involved in the initiation and progression of AS.[19] Furthermore, AS is currently under-detected and under-diagnosed[20,21] and the anticipated improvement in screening due to the implementation of digital tools and artificial intelligence may also contribute to the rise in the prevalence of asymptomatic severe AS. In the last 10 years, the number of AS-related interventions (mainly TAVI) has grown exponentially in both the US[22] and European countries.[23]

Currently, these issues may exceed the capacity of interventional cardiology and cardiovascular surgery departments to treat all patients with TAVI or SAVR. As a consequence, the waiting lists for AVR may increase. In the future, the diminished incidence of coronary artery disease due to better prevention may allow the healthcare systems to re-allocate more resources to structural heart diseases. Furthermore, TAVI happened to be futile in a substantial number of patients.[24–26] And finally, it is estimated that about one-third of patients with symptomatic severe AS and Class I indication for AVR ultimately do not receive SAVR or TAVI because of various reasons. Hence, expanding AVR indication to all patients with asymptomatic severe AS may be questionable from both an ethical and healthcare resource standpoint.

Given that current evidence as well as current guidelines do not support the application of an early AVR strategy for all asymptomatic patients with severe AS and the results of the ongoing trials will likely not refute this statement, we would strongly favor the adoption of an individualized strategy including the following steps (*Figure 3*): **Step 1:** Confirm that the patient has true severe AS and is really asymptomatic. **Step 2:** Determine if the patients have any risk marker included in the guidelines (i.e. very severe AS, severe aortic valve calcification with fast stenosis progression, markedly elevated B-type natriuretic peptide, LVEF <55%) as well as other emerging risk markers (i.e. cardiac damage stage ≥ 2; global longitudinal strain <15%, etc.) pending further validation.[7,27] In the future, machine learning algorithm using clinical, imaging, and/or blood biomarker data may help to identify the patients who are at higher risk of poor outcomes in the short term and who may thus benefit from earlier intervention.[28] **Step 3:** Ascertain that the patient has a low risk for mortality and procedural complications with SAVR or TAVI. **Step 4:** Ascertain that the proven durability of the prosthetic valve selected for early AVR matches or exceeds the expected life expectancy of the patient.

If the patients do not meet the criteria described in these four steps, they should probably be managed conservatively. However, this conservative management should not be a passive, i.e. 'wait for symptoms' strategy but rather an active clinical surveillance with regular (every 3 to 6 months) clinical, echocardiographic, and blood biomarkers follow-up, ideally conducted in the context of a dedicated heart valve clinic.[4,10,29]

In conclusion, early AVR is likely not the optimal strategy for all patients with asymptomatic severe AS. We rather advocate for an individualized strategy that would determine the best management for the given patient according to his or her risk profile, preferences, and life expectancy.

# Declarations

## Disclosure of Interest

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