Medical management of symptomatic severe aortic stenosis in patients non-eligible for transcatheter aortic valve implantation

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1 Transcatheter aortic valve implantation in symptomatic severe aortic stenosis: where do we stand?

Aortic stenosis occurs in 2%–9% of patients over the age of 65, the most common cause being degenerative.[1,2] The preferred treatment in symptomatic severe aortic stenosis (SAS) is surgical aortic valve replacement (SAVR), but in the elderly, the surgical risk can be greater than the benefit.[3] Since Alain Criblier performed the first percutaneous transcatheter aortic valve implantation (TAVI) in 2004, many studies have demonstrated that this technique is non–inferior to SAVR and superior to medical therapy in inoperable patients with symptomatic SAS.[6] TAVI is a great progress in the management of SAS because it is safer than SAVR in the elderly, in whom symptomatic SAS is very frequent. According to the current guidelines, this is a class I recommendation of treatment in patients with symptomatic SAS who are not suitable for SAVR, as assessed by the Heart Team.[3,5] At the same time, there are some situations in which TAVI is difficult to perform: any unfavorable vascular access to the aorta, size of the aortic annulus out of range for TAVI, short distance between the coronary ostia and aortic valve annulus, degree and pattern of calcification unfavorable to TAVI, bicuspid aortic valve, aortic or left ventricular thrombosis, suspicion of aortic valve endocarditis, aneurysm of the ascending aorta, concomitant severe mitral valve and severe tricuspid valve disease, and coronary artery disease requiring coronary revascularization by coronary artery by-pass grafting. In these situations, the indication is to perform SAVR, but in most cases, the surgical risk is very high.[1]

Even in patients with an established TAVI indication, in real life there is a high rate of delayed TAVI interventions, as shown in IMPULSE (Improve Outcomes in Aortic Stenosis) enhanced registry, which included 2171 participants with symptomatic SAS from 9 European countries of mean age 77.9 years, with 48% female.[6] 24.8% of these patients did not receive TAVI or SAVR intervention within three months after the indication was made according to the recent guidelines.[3]

At the same time, in some patients even minimally invasive interventional therapy can be harmful and the only possible therapy for symptomatic SAS remains palliative medical care.[2,5] Such patients have comorbidities, dementia, frailty, less than 1-year anticipated life expectancy (Table 1), and their mortality risk related to the intervention is high.[2]

In a study including 3,687 patients with SAS, Hermiller, et al.[7] showed that the 30-day and one-year mortality after TAVI increases in the following conditions: age over 85, Charlson comorbidity index score higher than 5, home oxygen use, serum albumin level less than 3.3 g/dL, falls in the last 6 months before TAVI, STS-PROM (the Society of Thoracic Surgeons Predicted Risk of Mortality) score higher than 7%, residence in an assisted living facility. High-risk patients had a one-year mortality rate of 36.6% compared to 12.3 % in the low-risk group.[7,8]

2 What can the medical team do for elderly patients no longer suitable for TAVI?

There is no specific medical treatment for symptomatic SAS in this situation. The drugs used for heart failure, arrhythmia, ischemic heart disease, and other comorbidities are the same as in other patients. Still, many precautions need to be taken due to hemodynamic instability in such patients.
Table 1. Contraindications of the interventional therapy in severe symptomatic aortic stenosis.[2]

| Patients with comorbidities which seem to influence their health status more than SAS, anticipated life expectancy less than one year, STS-PROM 8%–15% or more than 15% |
|---|
| Patients with moderate or severe dementia (minimally oriented), symptoms described by the family and not verbalized by the patients, STS-PROM 8%–15% |
| Patients with malignancy and life expectancy less than one year, STS-PROM 8% |

SAS: severe aortic stenosis; STS-PROM: Society of Thoracic Surgery Predicted Risk of Mortality.

### 2.1 General measures

The medical management of patients with symptomatic SAS begins with some lifestyle changes and general care: (1) patients should limit their physical activity, in case they do not already have a sedentary lifestyle because of frailty or comorbidities; (2) sodium intake should be restricted to 2 g/day; (3) doctors should review patients’ current medication to avoid hypotension and dehydration, knowing the patient is “afterload fixed and preload dependent”;[3] (4) hyperhydration should be avoided because of the risk of acute heart failure; (5) according to recent guidelines, endocarditis prophylaxis is indicated only in patients with a previous history of infectious endocarditis[5] and (6) patients should be evaluated for coronary heart disease and should receive appropriate medication.

### 2.2 Medical treatment

A crucial aspect regarding the medical treatment of symptomatic SAS is that almost all cardiovascular drugs should be used with caution due to the possibility of iatrogenic hypotension and syncope.

#### 2.2.1 Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin 2 receptor blockers (ARB)

ACEI and ARB are very useful in the treatment of arterial hypertension and systolic heart failure in the general population. Still, their use in patients with SAS should be carefully monitored because of the risk of hypotension and syncope. However, there is experimental and clinical evidence that ACEI and ARB prevent the hemodynamic impairment of aortic stenosis.[10] Nevertheless, most of these studies included patients with moderate aortic stenosis and normal left ventricular ejection fraction (LVEF). SCOPE AS (Symptomatic Cardiac Obstruction-Pilot Study of Enalapril in Aortic Stenosis) trial included 56 patients with SAS (aortic valve area < 0.75 cm², mean aortic gradient > 50 mmHg, or aortic valve Doppler jet velocity > 4.5 m/s), angina or heart failure NYHA functional class ≥ III/IV. Patients received Enalapril 2.5 mg bid titrated up to 10 mg bid.[11] After a 4-week follow-up, there was a statistically significant improvement of the 6-min walk distance and Borg dyspnoea scale versus baseline, without any significant adverse events. Dalsgaard, et al.[12] studied 22 patients with SAS (aortic valve area (AVA) < 1 cm²) without symptoms at rest and treated with Trandolapril up to 2 mg/day (maximally tolerated dose) versus 22 patients in the placebo group. After three days of treatment, they noted a significant decrease in systolic blood pressure and an increase in systemic arterial compliance in the Trandolapril group versus control. None of the treated patients experienced hypotension. The RIAS (Ramipril in Aortic Stenosis) trial randomized 100 patients with asymptomatic moderate or severe aortic stenosis and LVEF more than 50% to either Ramipril 10 mg/day for 1 year or placebo and showed that Ramipril leads to a delay in the progression of the aortic stenosis and also to an improvement of left ventricular hypertrophy (LVH). In this study, the mean aortic valve area was 1.2 cm² and 79% of the patients had moderate aortic stenosis.[13]

ARBs appear to be effective in reducing left ventricular mass and slowing the progression of calcification of the aortic valve. Again, there are few studies, and they included patients with moderate aortic stenosis. Dahl, et al.[14] studied 114 patients with symptomatic SAS (AVA < 1 cm²) and LVEF ≥ 40%, randomized after aortic valve replacement to Candesartan up to 32 mg/day or conventional therapy for one year. Mortality and hospitalization did not differ between groups, but there was a significant improvement of echocardiographic parameters (left ventricular mass index and left atrial volume index) in the active treatment group. Helske-Suihko, et al.[15] studied 51 patients with SAS referred for aortic valve replacement. Twenty five patients were treated with Candesartan up to 16 mg/day for 164 ± 67 days versus 26 patients with placebo for 151 ± 72 days. There were no statistically significant differences between the two groups according to changes in the 6-min walk test, left ventricular mass index, N-terminal fragment of brain natriuretic peptide, or the occurrence of adverse events.

At the same time, ACEI or ARBs administered for a minimum of 6 months after TAVI in 1,215 patients included in the OCEAN-TAVI (Optimized CathEter vAlvular iNtervention) registry reduced LVH and all-cause mortality.[16]
2.2.2 Calcium channel blockers

Calcium channel blockers should be used with caution because of the risk of hypotension and aggravation of heart failure. Saeeda et al.,[17] in a retrospective analysis of 314 patients aged 65 ± 12 years with moderate or severe asymptomatic aortic stenosis, reported the evolution of patients on calcium channel blockers indicated for arterial hypertension. Patients on calcium channel blockers compared to those not on this drug had a 7-fold increased hazard ratio for all-cause mortality and significantly lower event-free interval (20.5% vs. 5.6 %, P < 0.001), independent of age, diabetes, left ventricular ejection fraction, and aortic valve area. Nifedipine should be avoided or used with very much caution because of the risk of hypotension and induced coronary hypoperfusion.[18,19]

2.2.3 Diuretics

Diuretics must be used with caution because patients with SAS are preload-dependent, and they can develop a low cardiac output and arterial hypotension with peripheral hypoperfusion.[19]

2.2.4 Beta-blockers

Beta-blockers are difficult to manage in patients with SAS because of the risk of negative inotropic effect in the presence of left ventricular outflow tract obstruction.[18,20] They are not indicated in symptomatic SAS with heart failure but can be used in low doses in patients with atrial fibrillation for rate control or in hypertension.[18] However, some studies reported more promising data.

Hansson, et al.[21] showed that in a group of 40 patients with moderate-severe asymptomatic aortic stenosis (AVA: 0.5 ± 0.1 cm²/m²; peak gradient 53 ± 19 mmHg), Metoprolol 100 ± 53 mg/day versus placebo for 22 weeks reduces valvulo-arterial impedance, myocardial oxygen consumption, aortic peak and mean gradient, as well as heart rate and increases systolic ejection time. Thus, the study suggests a favorable hemodynamic profile of beta-blocker use in moderate-severe aortic stenosis.

Rossi, et al.[22] evaluated the treatment with beta-blockers in a retrospective analysis of 113 subjects with symptomatic SAS who did not undergo surgery and demonstrated a 62% reduction in all-cause mortality. Other studies consider less severe aortic stenosis. From 1873 patients with asymptomatic mild-moderate aortic stenosis and preserved LVEF included in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study, 932 (50%) received beta-blockers and demonstrated a lower risk of all-cause mortality, cardiovascular death and sudden cardiac death during 4.3 ± 0.9 years of follow-up.[23]

The association of moderate-severe aortic regurgitation is a contraindication for the treatment with beta-blockers, which can aggravate aortic regurgitation by prolonging ventricular diastole.[18,23]

2.2.5 Digoxin

Digoxin is indicated for rate control in concomitant atrial fibrillation.[18] There are no randomized trial data about survival rates in patients with symptomatic SAS treated with digoxin.

2.2.6 Aldosterone receptor antagonist eplerenone

Eplerenone was studied in 33 patients with asymptomatic moderate-severe aortic stenosis and LVEF higher than 50% versus 32 controls, followed up for 15-25 months. There were no significant differences between groups regarding the left ventricular mass index and left ventricular end-systolic volume index.[24]

2.2.7 Nitrate derivatives

Nitrate derivatives are not recommended in patients with SAS as long-term therapy but can be used in decompensated states with proper hemodynamic monitoring.[10,18] Twenty five patients with SAS, heart failure, low cardiac index (≤ 2.2 L/min per m²) and LVEF ≤ 35% were admitted to an intensive care unit and treated with intravenous nitroprusside, titrated to achieve a mean arterial pressure between 60 and 70 mmHg. Nitroprusside significantly increased the cardiac index and right ventricular stroke volume and decreased the mean arterial pressure, systemic vascular resistance, and pulmonary vascular resistance at 6 and 24 h compared with baseline, without causing any clinically significant hypotension.[25]

2.2.8 Statins

Statins are not useful to improve the evolution of aortic stenosis according to randomized trials such as SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression)[26] and TASS (Tyrolean Aortic Stenosis and Lipid Lowering Trial, Impact on Regression)[27]—trials with atorvastatin, SEAS (Simvastatin and Ezetimibe in Aortic Stenosis)[28]—trial with simvastatin, PROCAS (Effects of rosuvastatin on progression of stenosis in adult patients with congenital aortic stenosis)[29] and ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin)[30]—trials with rosuvastatin, despite some promising results in observational studies on aortic calcification rate.[31] At this moment, statins are not used in aortic stenosis, except for the coexistence of other indications.

Experimental studies showed that phosphodiesterase type
ischemia. \[18\]

decreased diastolic ventricular filling, and also myocardial tachycardia, with subsequently reduced cardiac output by the setting of acute heart failure because they may induce 2.2.9 Positive inotropic agents

Positive inotropic agents should be used with caution in the setting of acute heart failure because they may induce tachycardia, with subsequently reduced cardiac output by decreased diastolic ventricular filling, and also myocardial ischemia.\[18\]

2.3 Emergency balloon aortic dilatation

Emergency balloon aortic dilatation can be performed instead of TAVI, but preferably as a bridge therapy before TAVI. Bongiovanni, et al.\[33\] investigated 118 patients who underwent emergency balloon aortic dilatation followed by elective TAVI and 23 patients who underwent emergency TAVI in case of cardiogenic shock and in case of need for cardiac resuscitation or mechanical ventilation. The immediate mortality in the TAVI group was 8.7% and in the balloon aortic dilatation group 20.3%, without any statistically significant difference (\(P = 0.19\)). Also, there was no statistically significant difference between the two groups according to the 30-day mortality: 23.8% in the TAVI group, 33% in the balloon aortic dilatation group (\(P = 0.4\)).

3 Common clinical scenarios

3.1 Arterial hypertension

Concomitant arterial hypertension must be treated with the usual drug classes, but with careful titration of doses and rigorous blood pressure monitoring. Calcium channel blockers, especially nifedipine, must be used with caution, if ever.\[18\]

3.2 Atrial fibrillation

25% of the patients develop atrial fibrillation, which worsens heart failure.\[3\] Therefore, every effort must be made to restore sinus rhythm by antiarrhythmics like amiodarone or electrical cardioversion. Unfortunately, successful long-term cardioversion is uncommon in SAS patients. Rate control may be obtained with beta-blockers or digitals. Chronic anticoagulation is decided according to the CHA2DS2-VASc and HAS BLED scores.

3.3 Chronic heart failure

Patients may be treated with low doses of diuretics, ACEI or ARB, with cautious dose increases. Beta-blockers must be used very carefully or even avoided.\[18\]

3.4 Acute decompensated heart failure

Positive inotropic agents, vasodilators like nitroprusside, emergency balloon aortic dilatation, and emergency TAVI can be tried in such clinical scenarios. However, the improvement of the hemodynamic state is very difficult to achieve.\[18\] Balloon aortic dilatation can be useful, but acute complications like myocardial infarction, stroke, acute aortic regurgitation can occur in 10%–20% cases, and progressive restenosis can appear in 6–12 months.\[34\] Therefore balloon aortic dilatation is indicated, especially as bridging to TAVI or SAVR.

Significant coronary artery disease is present in 40% to 75% of patients with symptomatic SAS and indication of TAVI or SAVR and requires concomitant coronary artery by-pass grafting (CABG), but often the interventional risks are too high.\[35\] There are no randomized trials regarding the results of the concomitant CABG and TAVI or SAVR and some studies report higher 30-day mortality after TAVI or SAVR in patients with severe coronary artery disease.\[36\]

The PCI has fewer complications but it often is not viable because of the severity of the coronary artery disease. In patients who are not eligible for coronary revascularization, the medical treatment should be used with caution due to the risk of hypotension and aggravation of coronary hypoperfusion. In this regard, it is better to limit chronic administration of nitrates and calcium channel blockers and to use low doses of beta-blockers. Antiaggregant and anticoagulant therapy should be used according to the guidelines while taking into account the comorbidities of the patient.

3.5 Low-flow low-gradient aortic stenosis

Despite a different hemodynamic profile, there are no therapeutic differences between low-flow low-gradient, paradoxical low-flow low-gradient, and high gradient aortic stenosis. The practical problem is to accurately establish the severity of the aortic stenosis and the degree of left ventricular flow reserve. Patients with low-flow low-gradient aortic stenosis and no left ventricular flow reserve had better outcomes with TAVI than with medical treatment but were often treated conservatively because of comorbidities and frailty.\[37\] Palliative care and end of life decision should be discussed with the patients and their families.

In conclusion, medical treatment in patients with symptomatic SAS who, for various reasons, cannot undergo the recommended aortic valve replacement is a difficult decision, and the outcomes are inferior to invasive procedures.

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