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Scientific editorial

Moderate aortic stenosis: The next frontier of transcatheter aortic valve implantation?

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1. Abbreviations

AS	aortic stenosis
AVR	aortic valve replacement
HFrEF	heart failure with reduced ejection fraction
LV	left ventricular
LVEF	left ventricular ejection fraction
TAVI	transcatheter aortic valve implantation
TAVR	transcatheter aortic valve replacement

2. Background

Aortic stenosis (AS) is the most common valvular heart disease, leading to surgery or transcatheter intervention in developed countries, and its prevalence is increasing due to aging of the population [1]. The negative impact of severe AS on clinical outcomes and survival has been well established for several decades. However, there is a growing body of evidence suggesting that moderate AS is not benign and is associated with an increased risk of adverse outcomes and reduced survival [2].

Aortic valve replacement (AVR), whether by surgical intervention or transcatheter aortic valve implantation (TAVI), is currently the only treatment available for AS. Current guidelines [3,4] recommend AVR (Class I indication) for patients with severe symptomatic AS or those with left ventricular ejection fraction (LVEF) < 50% in the absence of symptoms. For moderate AS, AVR is recommended (Class IIb indication) only in patients undergoing a coronary artery bypass graft or intervention on the ascending aorta or another valve [3,4]. This recommendation is mainly driven by the risk of a redo surgery in the short term, because of progression to severe AS.

3. Moderate AS is not benign

Several observational studies have reported that moderate AS is associated with a considerable risk of adverse cardiovascular events, including death and rehospitalization for congestive heart failure [5]. Strange et al. reported, in a very large observational nationwide registry including patients with severe AS ($n = 6383$), moderate AS ($n = 3315$) and mild AS ($n = 16129$), that the 5-year mortality rate for patients with moderate AS was similar to that for patients with severe AS (56% and 67%, respectively), after adjustment for left ventricular (LV) systolic dysfunction [6]. This negative impact of moderate AS on outcomes may be related to progression to severe AS during the 5 years of follow-up. However, moderate AS also had an impact on short-term survival, suggesting a direct effect of moderate AS on outcomes. Furthermore, the impact of moderate AS appears to be more pronounced in patients with evidence of cardiac damage, and in those with systolic heart failure. In a population of 305 patients with both moderate AS and LV systolic dysfunction (mean LVEF = 38 ± 9%), van Gils et al. showed that the rate of the

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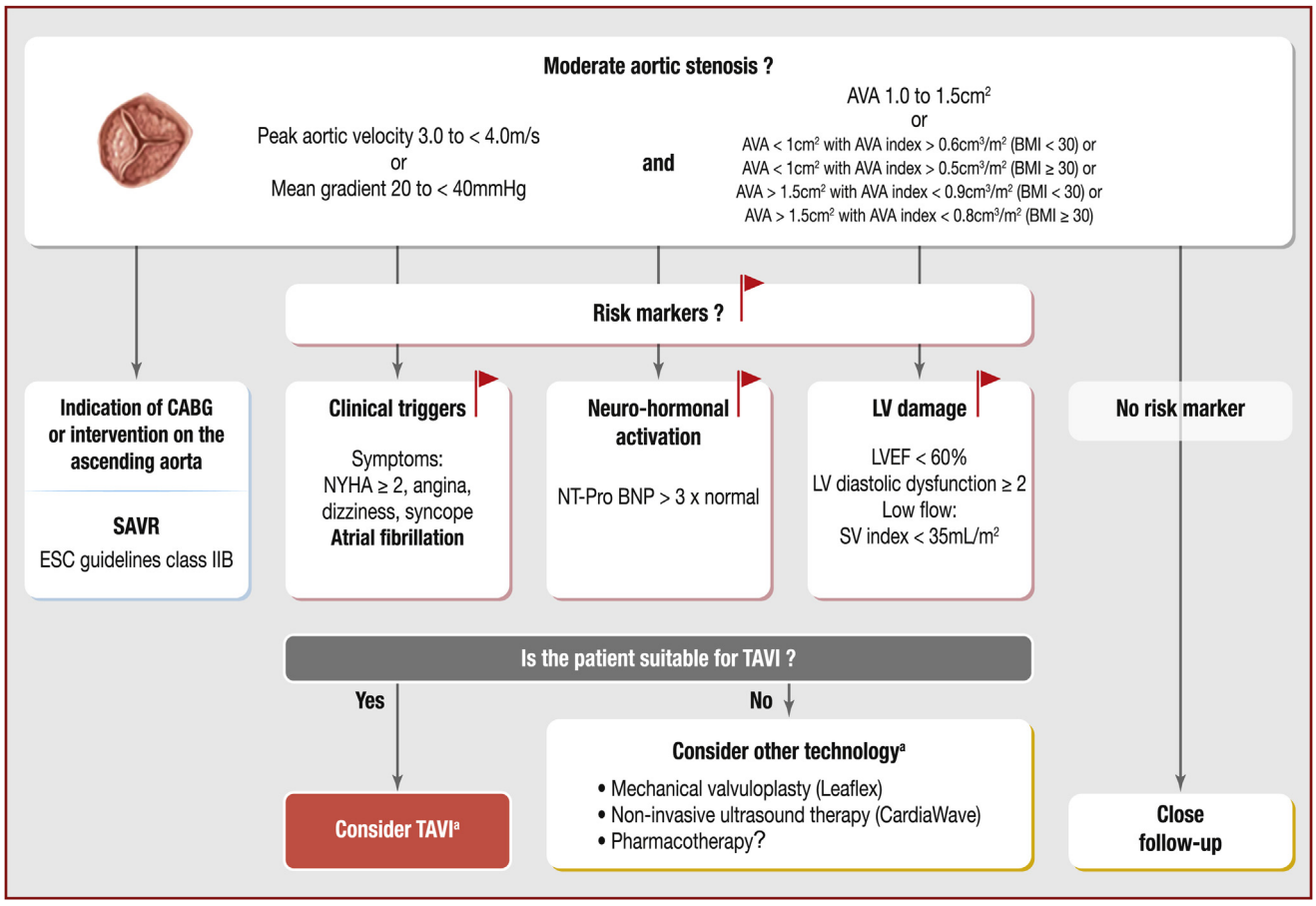

Fig. 1. Proposed management of moderate aortic stenosis in the present and in the future. AVA: aortic valve area; BMI: body mass index; CABG: coronary artery bypass graft; ESC: European Society of Cardiology; LV: left ventricular; LVEF: left ventricular ejection fraction; NT-ProBNP: N-terminal prohormone of B natriuretic peptide; NYHA: New York Heart Association: SAVR: surgical aortic valve replacement; SV: stroke volume; TAVI: transcatheter aortic valve implantation. [a] Not recommended in both European and USA guidelines. Under investigation.

composite endpoint of death or heart failure hospitalization was high (46% at 4 years) [7]. These findings suggest that moderate AS may be well tolerated by a patient with good LV systolic function, but poorly tolerated by a patient with a failing ventricle. However, it remained unclear whether moderate AS was a bystander or a causal factor of adverse outcomes.

To address this issue, Jean et al. matched 262 patients with both moderate AS and heart failure with reduced ejection fraction (HFrEF) (LVEF < 50%) with 262 patients with HFrEF and no AS [8]. Moderate AS was associated with a 3-fold increased risk of mortality and an increased risk of the composite endpoint of heart failure hospitalization and mortality. Furthermore, AVR was associated with a marked reduction in this mortality excess observed in patients with HFrEF and moderate AS. In a large study that included 709 patients with low-gradient AS and reduced LVEF, Ludwig et al. recently reported that even those identified as having non-severe (i.e. moderate) AS on dobutamine stress echocardiography had a major survival benefit with transcatheter aortic valve replacement (TAVR) [9].

Taken all together, these findings support the concept that moderate AS is not benign, and may have a direct impact on outcomes, especially in patients with evidence of cardiac damage or heart failure (Fig. 1). In the absence of drug therapy to halt the progression of AS, one solution would be to intervene earlier in the course of the disease, i.e. before the onset of symptoms and/or cardiac damage/dysfunction, provided that the timing for intervention is based on robust prospective randomized controlled trials.

4. The role of TAVI in the treatment of moderate AS

TAVI was initially validated and applied clinically for the treatment of patients with symptomatic severe AS and extreme/high, intermediate and, more recently, low surgical risk. However, the less invasive nature of TAVI has paved the way for the consideration of AVR in other populations with no Class I indication for AVR in the guidelines, including moderate AS. Several randomized trials are currently investigating the benefit of TAVR versus clinical surveillance in selected at-risk patients with moderate AS: TAVR UNLOAD, PROGRESS and EVOLUT EXPAND TAVR II.

The TAVR UNLOAD (Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients with ADvanced Heart Failure; ClinicalTrials.gov identifier: NCT02661451) study is a prospective randomized open-label trial that aims to determine the safety and efficacy of transfemoral TAVR with the SAPIEN 3 valve (Edwards Lifesciences, Irvine, CA, USA) in patients with systolic heart failure (i.e. LVEF < 50% at rest) and moderate AS, compared with optimized heart failure therapy. The primary endpoint of this trial is a hierarchical endpoint of all-cause death, disabling stroke, heart failure hospitalization and change in health status, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), at 1 year. Recruitment for this trial was completed recently.

The PROGRESS Trial (ClinicalTrials.gov identifier: NCT04889872) is a prospective randomized open-label trial that aims to establish the safety and effectiveness of early transfemoral TAVI with a SAPIEN 3 or SAPIEN 3 Ultra valve (Edwards

Lifesciences, Irvine, CA, USA) in patients with symptomatic moderate AS or those without symptoms, but with evidence of cardiac damage and dysfunction. The primary endpoint is the composite of death, stroke and unplanned cardiovascular hospitalization at 2 years. The study is ongoing, and is still recruiting for an estimated enrolment of 750 patients.

The EVOLUT EXPAND TAVR II study (ClinicalTrials.gov identifier: NCT05149755) is a multicentre international prospective randomized study where at-risk patients with moderate AS will be randomized to either TAVI with the Evolut PRO+ TAVR System or the Evolut FX System (Medtronic, Minneapolis, MN, USA) and guideline-directed management versus guideline-directed management alone. The primary endpoints are: (1) a composite of all-cause mortality, all stroke, life-threatening or fatal bleeding, acute kidney injury, hospitalization as a result of a device- or procedure-related complication or valve dysfunction requiring reintervention at 30 days; and (2) a composite of all-cause mortality, heart failure hospitalization or event or medical instability leading to AVR or aortic valve reintervention at 2 years. The study is ongoing, with an estimated enrolment of 650 patients.

5. Other "prosthetic implant-free" technologies for the treatment of moderate AS

AVR, whether surgical or transcatheter, carries an inevitable and substantial risk of prosthetic valve-related complications, including valve thrombosis, endocarditis and, ultimately, structural valve degeneration and failure. Hence, early TAVI may not be the optimal solution for all patients, particularly those at risk with moderate AS. Performing an early TAVI in such patients, with a long life expectancy may expose them to the risk of structural valve degeneration and failure, and thus to the risk of one or more reinterventions [10]. Reintervention is associated with a substantial risk of morbidity and mortality.

There is, therefore, a potential role for novel minimally invasive technologies to treat AS, but without implanting a prosthetic valve (Fig. 1). For example, the Leaflex Performer (Pi-Cardia, Rehovot, Israel) is a transcatheter technology that consists of performing a valve repair by creating scoring lines at the aortic surface of the aortic valve. These scoring lines allow cutting of the calcium bridges, thereby reducing the stiffness of the aortic valve leaflets and improving valve opening. This novel technology may significantly reduce the severity of AS, without leaving any device or foreign material in situ. Furthermore, given that this is a minimally invasive "device implant-free" procedure, it can be repeated in case of restenosis during follow-up. So far, this technology has been tested in patients with severe AS, but it could also be envisioned for patients with moderate AS in the future (Fig. 1).

Cardiawave (Paris, France) has developed another cutting-edge technology (Valvosoft), which consists of image-guided non-invasive ultrasound therapy. Valvosoft delivers focused high-intensity ultrasound to perform a remote and remodelling effect on the aortic valve leaflets. By delivering focused and high-intensity ultrasound to different areas of the valve, microscopic cavitation bubbles implode in contact with the leaflet, creating local shockwaves that fracture calcification and therefore improve leaflet mobility [11].

These novel "prosthetic implant-free" technologies are promising for the future treatment of moderate AS, and could represent both alternative and complementary approaches to TAVI in this context. These technologies could also be useful to postpone or even avoid the implantation of a prosthetic valve when used at an earlier stage of the disease.

Finally, several pharmacotherapies are currently under development and validation to slow or halt the progression of AS, and may therefore have a future role in the treatment of moderate and even mild AS [12].

6. Conclusions

Moderate AS has a detrimental impact on outcomes, especially in patients with symptoms and/or cardiac damage/dysfunction. Several randomized trials are ongoing to determine whether early TAVI improves clinical outcomes compared with standard of care, i.e. clinical surveillance and optimized medical therapy. Novel prosthetic implant-free technologies are emerging, and may offer an alternative or adjuvant therapy to TAVI for the future treatment of moderate AS.

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Disclosure of interest

The authors declare that they have no competing interest.

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