Chapter

Perspective Chapter: Moderate Aortic Stenosis and Heart Failure With Reduced Ejection Fraction; Early Replacement or Conservative Treatment?

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Abstract

Aortic stenosis (AS) is the most common valve lesion among the continuously aging population with serious effect on the left ventricular ejection fraction (LVEF). If left untreated, it is associated with serious complications such as heart failure (HF), pulmonary hypertension, thromboembolic events, and even sudden death. Early diagnosis and treatment is of outmost importance to avoid the above complications but also to maintain the patient's normal heart function. Echocardiography is the key examination that assesses the severity of the stenosis, valve calcification, left ventricular (LV) function, and wall thickness. Also new imaging methods such as cardiac computed tomography (CT) and cardiac magnetic resonance imaging (MRI) help in assessing the severity of aortic valve stenosis when echocardiography has limitations. Based on the categorization of the severity of the stenosis, its treatment is determined. Although things are clear in cases of asymptomatic disease and severe stenosis, this is not the case in moderate disease. Experts and clinical trials do not define clearly which cases can be treated conservatively and which need surgical or transcatheter intervention. The purpose of this article is to gather all the latest data on the treatment of moderate aortic stenosis, especially in patients with heart failure and low ejection fraction.

Keywords: moderate aortic stenosis, heart failure, reduced ejection fraction, early replacement, conservative treatment

1. Introduction

Aortic stenosis (AS) is the most common valvular disease in developed countries, and its prevalence on the population is constantly increasing [1, 2]. Calcific "degenerative" AS of trileaflet valve is the most common etiology of AS. It is characterized by progressive thickening, fibrosis, chronic inflammation, lipoprotein deposition, and calcification of the outflow, resulting in inadequate cardiac output, decreased exercise

capacity, progressive heart failure, myocardial remodeling response, left ventricular (LV) fibrosis, arrhythmias, and death [3]. Other important causes are congenital valve abnormalities which are usually accompanied by marked calcium deposition as well as rheumatic fever. As previously mentioned, aortic stenosis is a degenerative disease that is largely associated with vascular calcification, so conditions such as chronic kidney disease or clinical entities with abnormal calcium metabolism or increased vascular calcification, such as Paget disease, are associated with its development, especially in younger patients. The guidelines for the treatment of patients with moderate aortic stenosis in order to avoid its complications are not fully defined. Data from studies and experts are hesitant whether a quick replacement of the pathological valve or conservative treatment and monitoring is the best option [4]. According to the guidelines from the American and European Heart Association, moderate aortic stenosis is defined by echocardiography with the presence of aortic valve area (AVA) >1.0 and ≤ 1.5 cm^2 and an average gradient of >20 to <39 mmHg [5, 6]. Although, patients with moderate AS may not experience symptoms such as dyspnea or reduced exercise tolerance, there is evidence that the prognosis is not as benign as previously reported [7]. The physicians should be aware that in several cases, moderate AS can lead to significant obstruction of left ventricular outflow track in many different ways, slowly evolving into heart failure with reduced ejection fraction (HFrEF).

2. Current ESC Guidelines on moderate aortic stenosis

Current guidelines recommend aortic valve intervention when the level of stenosis is severe and the patients have symptoms that are attributed to the severity of the disease. Such is also the recommendation for asymptomatic patients suffering from severe aortic stenosis and reduced LV ejection fraction (LVEF) that is associated specifically with the level of stenosis. Advances in the field of invasive heart valve replacement, through transcatheter bioprosthesis implantation, have enabled patients with severe aortic stenosis, who are at high risk for surgery, to be able to repair the defective valve. Therefore, taking into account the rapid development in the field of invasive cardiology, it is very likely that in the future patients with a lesser degree of valve, stenosis will be advised to proceed into early valve replacement. Already according to the latest guidelines, patients with moderate aortic stenosis and the coexistence of other pathology that requires cardiac surgery, such as coronary artery bypass graft (CABG), should simultaneously replace the defective aortic valve [6].

3. Progression of aortic stenosis

It is important to distinguish the difference between the anatomical and clinical progression of the aortic stenosis. While severe aortic valve stenosis has been extensively studied and treatment is specific, in the case of moderate disease, the field remains gray and unclear. Anatomical progression is considered a constant fact, and although age is considered the main factor in the progression of the disease, significant differences are found between the population, which indicates that there are other aggravating factors. Past studies have demonstrated that moderate aortic stenosis is associated with a substantial increase in mortality from both noncardiac and cardiac causes. A huge registry from Australia that followed up patients with aortic stenosis showed that patients with moderate aortic stenosis had poor survival

rates, specifically a 5-year mortality rate up to 56%, almost the same with patients with severe aortic stenosis [8]. The fact that clinicians classify patients based on numerical criteria, which is practical and efficient, sometimes leads them not to see each patient individually and in relation to their comorbidities and their individual medical memory. Hence, a patient can have a prognosis similar to severe aortic stenosis, but the measurements on echocardiography indicate moderate stenosis. Most of our patients do not suffer only from aortic stenosis, but also from other comorbidities that can impact negatively the LVEF, such as in individuals with previous myocardial infarction. So the main problem that a physician should take into consideration is if in cases of moderate aortic stenosis, the patient's left ventricular with reduced ejection fraction has the ability to manage the afterload effectively. These issues concern the medical community, especially whether coexisting heart disease and beyond can affect the essential function of the valve, the left ventricle and consequently systemic circulation. Dweck et al. showed that aortic valve narrowing imposes increased afterload and wall stress on the left ventricle. As a result, a hypertrophic response of the heart is stimulated, which initially restores wall stress and maintains cardiac performance through the progress of heart remodeling. However, this process ultimately becomes decompensated and consequently the LV cannot handle the afterload with the appearance then of all known complications of this procedure [9]. These patients with moderate aortic stenosis, in association with left ventricle hypertrophy and finally decompensation, are those with the poorest prognosis and higher mortality rates [10].

4. Aortic stenosis and left ventricle dysfunction

What is going on, however, in cases with moderate aortic stenosis with reduced LV ejection fraction? In daily practice, patients with moderate aortic stenosis have no indication of valve replacement unless cardiac surgery is needed for other reasons (i.e. coronary artery bypass grafting, ascending aorta). There is a gap in guidelines for this particular category of patients, the majority of which are symptomatic. Recently, they have been published many randomized clinical trials that support that patients with moderate aortic stenosis and reduced ejection fraction is not benign as believed. Van Gils et al. with a retrospective study from four large academic instutitions between 2010 and 2015 analyzed echocardiogrpahic and clinical data from patients with moderate AS and systolic dysfunction. Moderate AS was defined as aortic valve area between 1.0 and 1.5 cm^2 and LV systolic dysfunction defined as LV ejection fraction <50%. The primary end point was a composite of all-cause death, aortic valve replacement (AVR), and heart failure (HF) hospitalization. The conclusion of the study was that patients with concomitant moderate AS and LV systolic dysfunction are at high risk for major adverse cardiac and cerebral events [11]. Another retrospective study from the Duke echocardiographic database demonstrated that patients who had moderate aortic stenosis and left ventricle dysfunction and underwent aortic valve replacement had mortality benefit compared with patients received medical therapy only [12]. Also a recent study from Ito et al. showed that in patients with moderate AS, low LVEF and volume index were at increased risk of mortality [13]. Another question that we always have to answer are the symptoms of the patients. Are the symptoms correlated with aortic stenosis or are from different causes? From registries even in patients with severe aortic stenosis, the symptoms are not specific. So it is not always easy to define the severity of a stenosis based on the symptoms patients describe. We highlight the presence of

symptoms because the guidelines recommend aortic valve replacement when the aortic stenosis is severe and symptomatic. But how sure are we that a patient with moderate aortic stenosis and systolic dysfunction of the left ventricle has no symptoms from the narrowed valve on itself? Also Castano et al. showed with a prospective study of elderly patients who underwent transcatheter aortic valve replacement (TAVR) that 16% percent of them had transthyretin cardiac amyloidosis (ATTR-CA). This is important because these patients had a thicker interventricular septum (1.3 vs. 1.1 cm, P = 0.007), higher left ventricular (LV) mass index (130 vs. 98 g/m2, P = 0.002), and lower stroke volume. So when these patients have even moderate aortic stenosis, the symptoms may be exacerbated and we should think earlier intervention [14]. Another factor that contributes in increased afterload and decreased LV function is reduced systemic arterial compliance (SAC). In patients with aortic stenosis, reduced systemic arterial compliance coexists with a serious impact on LV function as a randomized controlled trial of 208 consecutive patients with moderate and severe aortic stenosis showed. This observation should be taken into consideration when examining such patients, because it may impact significantly on both diagnostic evaluation and ensuing clinical conduct [15]. As an example, a patient with uncontrolled arterial blood pressure and moderate aortic stenosis in many cases is equivalent to severe aortic stenosis due to the increased afterload. Approximately 10% of patients with aortic stenosis have reduced left ventricle ejection fraction (HFrEF). A retrospective study from Jean G. et al. included 262 patients with moderate aortic stenosis and HFrEF (LVEF<50%) and 262 patients with HFrEF and no AS. The populations of the two groups were well balanced. In patients with HFrEF, moderate AS is independently correlated with a threefold increase in mortality. AVR, and mainly transcatheter AVR during follow-up, was related with better survival in patients with HFrEF and moderate AS. These findings support the fact that early transcatheter AVR may improve outcomes of patients with HFrEF and moderate AS [16].

5. Assessment of the left ventricle

Left ventricle dysfunction is a strong prognostic marker for adverse events, and in patients without symptoms with both impaired LVEF and severe aortic stenosis, aortic valve replacement has a Class I indication. However, LVEF remains normal until the disease is well advanced. Systolic long-axis function may be affected even in the presence of a normal ejection fraction, in patients with aortic stenosis. Kjetil Steine et al. with a small RCT of 53 patients with asymptomatic moderate aortic stenosis have impaired LV systolic function as measured by reduced peak systolic tissue velocity and strain. Augmented LV filling pressure measured by E/E' sep and impaired LV relaxation measured by reduced E' sep also indicate diastolic dysfunction in these patients [17]. Hence, aortic valve stenosis is often combined with impaired systolic function, a parameter that should not be neglected in clinical examination of a patient. Left ventricle global longitudinal strain (GLS) is an important echocardiographic factor for aortic valve stenosis estimation. A meta-analysis from Julien Magne et al. among 1067 patients with significant AS and LVEF >50% were analyzed. The median GLS was 16,2% and the best cutoff value identified was GLS of 14,7%. The risk of death in patients with GLS < 14,7% was multiplied by >2,5. This meta-analysis demonstrates that LVGLS is associated with reduced survival even in asymptomatic patients with significant AS and normal LVEF, impaired. These data emphasize that for management and risk stratification of this specific population, the potential

usefulness of LVGLS is considered [18]. Another retrospective study including 287 patients with moderate aortic stenosis (mean aortic valve area was 1,25cm^2), preserved ejection fraction, and median GLS – 15,2% demonstrated that impaired GLS in patients with moderate aortic stenosis is associated with higher mortality rates even among those who undergo aortic valve replacement [19]. So including longitudinal global strain in evaluation of patients with aortic stenosis seems to be of major importance. Early pressure unloading of the left ventricle with an early intervention would result in better outcomes and regression of diffuse fibrosis. All these data come from retrospective studies, so randomized clinical trials may delineate the efficiency and necessity of early interventions in moderate aortic valve stenosis. Another tool that nowadays is being used more and more in the evaluation of the severity of aortic stenosis is cardiac computed tomography (CT). Especially via cardiac CT, we can calculate the calcium score of the valve. Sex-specific CT-aortic valve calcification (AVC) thresholds (women 1377 Agatston unit and men 2062 Agatston unit) accurately identify severe AS and provide powerful prognostic information. These findings support their integration into routine clinical practice [20]. A prospective study from Boulif et al. with 266 consecutive patients with moderate to severe AS who underwent multidetector row computed tomography (MDCT) to measure aortic valve calcium load and a comprehensive echocardiographic examination to assess AS severity resulted that MDCT-derived AVC load correlated well with valve weight and hemodynamic indices of AS severity [21]. In the current guidelines, cardiac CT which calculates aortic valve calcium is recommended, and in the next few years more modalities from computed tomography will be used for aortic stenosis severity evaluation. Cardiac Magnetic resonance imaging (MRI) is used broadly in everyday clinical practice. It is necessary to locate myocyte hypertrophy and mainly myocardial fibrosis expressed on many different ways (diffuse interstitial fibrosis, as well as partly disease-specific patterns of fibrosis, described as compact or 'focal', perimyseal, perivascular, plexiform, or patchy). Everett et al. with a small study of 67 patients with aortic stenosis (43% mild, 34% moderate, and 23% severe aortic stenosis) showed that myocyte hypertrophy and myocardial fibrosis progressed rapidly but are reversible after aortic valve replacement. On the other hand, mid late gadolinium enhancement (LGE) accumulates rapidly but is irreversible after AVR. So, taking into account the adverse prognosis of midwall LGE, early AVR when for first time LGE identified should be considered [22]. The association of myocardial fibrosis and long-term survival was studied by Azevedo et al. with a small prospective study of 54 patients. These people with severe aortic valve disease and indication for aortic valve replacement were prospectively enrolled between May 2001 and May 2003 and were examined with contrast-enhanced magnetic resonance imaging (ce–MRI). The larger the amount of fibrosis, the worse the long-term survival rates after aortic valve replacement [23]. The findings of these studies may be indicative that the quantification of the amount of fibrosis is a useful tool in the assessment of such patients and the choice of the time of intervention.

6. Mixed aortic valve disease

Mixed aortic valve disease (MAVD) is the coexistence of aortic stenosis (AS) and aortic regurgitation (AR). Although many studies have established well the isolated aortic stenosis or aortic regurgitation, there are not sufficient data about the prognosis and impact of mixed aortic valve disease. The remodeling of the myocardium in

mixed aortic valve disease is not well studied but is hypothesized that MAVD leads to increased left ventricle diameters of intermediate severity compared to that seen in isolated aortic regurgitation or aortic stenosis as well as increased relative wall thickness, resulting in larger indexed left ventricular mass than each lesion separately [24].

There are very few data for the management of MAVD. A retrospective study by Egbe et al. gathered 213 patients with moderate to severe aortic disease and found that in the group of patients with mixed disease, they had more side effects compared to those with isolated severe AS. In addition, it was indicated that peak aortic velocity and severe MAVD (either severe AS or severe AR component) at presentation are predictors of adverse events [25]. They did not establish the optimal time for surgical intervention; however, this data suggests that patients with moderate MAVD should be monitored as patients with isolated severe aortic stenosis. Moreover, an observational cohort study of 862 patients with preserved left ventricular ejection fraction and at least moderate aortic regurgitation and moderate aortic stenosis showed that MAVD has a significant effect on those individuals who are at high risk of all-cause mortality, a risk that was sustained even after AVR [26, 27].

7. When should we intervene?

There is a growing number of data that support that an early intervention in moderate aortic valve stenosis might be beneficial. A retrospective study from Moon et al. and the echocardiography database of Seoul National University Hospital (SNUH) compared those who underwent early surgical AVR (within 2 years of index echocardiography) at the stage of moderate AS versus those who were followed medically without AVR at the outpatient clinic. Among 255 patients with moderate AS, 37 received early AVR and 218 patients were treated conservatively and had specific follow-up (medical therapy observation group). Using multivariate Cox-proportional hazard regression adjusting for age, sex, comorbidities, and laboratory data, early AVR at the stage of moderate AS significantly reduced the risk mortality risk. However, a prospective randomized trial is needed in order to confirm those findings [28]. Data from the prospective TOPAS study which included 481 patients with low flow and low gradient aortic stenosis has indicated a beneficial impact through early intervention in both classic and paradoxical low flow low gradient aortic stenosis. This benefit seems to extend also to the subgroup population with pseudo-severe AS (moderate AS). These findings suggest that TAVR using femoral access might be the best strategy in these patients [29]. Future results from the TAVR UNLOAD trial, an international, multicenter, randomized, open-label, clinical trial comparing the efficacy and safety of TAVR with the Edwards SAPIEN 3 Transcatheter Heart Valve in addition to optimal heart failure therapy (OHFT) versus optimal heart failure treatment alone in patients with moderate AS (defined by a mean trans-aortic gradient ≥20 mmHg and < 40 mmHg, and an aortic valve area > 1.0 cm2 and ≤ 1.5 cm2 at rest or after dobutamine stress) are highly anticipated. A total of 600 patients will be randomized in a 1:1 trial design, and the aim of this trial is to test the hypothesis that TAVR in addition to optimal heart failure treatment improves clinical outcomes in patients with moderate aortic stenosis and heart failure with reduced ejection fraction [30]. Another retrospective study from Delesalle G et al. included 508 patients with moderate aortic stenosis (aortic valve area between 1 and 1.5 cm^2; mean SD aortic valve area, 1.2 cm^2) and preserved left ventricle ejection fraction compared to control. The results showed that patients

with moderate aortic stenosis have an increased mortality risk compared to general population, and that was mainly associated with their comorbidities. Consequently, those patients should be managed in an overall manner assessing all potential cardiovascular risk factors and their impact on the patient's survival. Additionally patients with moderate AS with an aortic valve area close to 1 cm^2 should be followed up closely, because an aortic valve replacement performed at the stage of severe AS in patients with an indication for surgery is associated with improved survival (Delesalle et al) [4].

8. Discussion

In order to summarize the latest data about moderate aortic stenosis and impaired left ventricle ejection fraction, we should have in mind properly all these that were referred above. Firstly, moderate aortic stenosis is not so benign as previous believed. As we see, the quantification of the severity of aortic stenosis is not always so simple. In one-fourth of the patients with aortic stenosis, the measurements with echocardiography are discordant (i.e. low flow – low gradient), so we must use all the modalities that are available today (transthoracic echocardiogram (TTE), transoesophageal echocardiogram (TOE), CT, and MRI) to determine the severity of stenosis. Also, we must always correlate the symptoms and be careful with the clinical history of our patients. Maybe the symptoms are extracardiac and other time the symptoms are not described by the patients until an exercise test is performed.

Then we should always have in mind the extra-aortic findings, the LVEF, and their consequences on patients symptoms and overall progression of disease. An impaired LVEF whether or not the patients has symptoms prompts an investigation into the etiology of the LV dysfunction. When there is no other reason for the impaired LVEF that can be fixed other than moderate AS, we should have a low threshold for recommending transcatheter or surgical aortic valve replacement. If LVEF is normal and the patient has symptoms, then try to treat comorbidities at first or perform cardiac MRI or LVGLS for early detection of replacement fibrosis, which as said before is a bad prognostic factor and in occasions can lead patients to early aortic valve intervention.

The strict adherence to guidelines and numbers often leads to a counterproductive effect as shown by Chan et al. in the PRIMID-AS trial. With this prospective, observational, multicenter study of asymptomatic moderate-to-severe AS in the United Kingdom, the investigators wanted to evaluate its influence on management decisions in asymptomatic patients with moderate-to-severe AS. Of the 174 patients, 45% classified as severe AS were reclassified as moderate AS. Both the severe and reclassified groups had a higher risk compared with moderate AS with the reclassified group demonstrating an intermediate risk [31]. This study demonstrates that moderate AS is still in gray area where multi-modality imaging and exercising testing are essential to personalize each patient and make decision about risk stratification and early intervention.

As we can see, moderate aortic stenosis has a high morbidity and mortality rate and there is evidence that these patients could have benefit from early intervention. The current data that we are collecting are from small retrospective studies mainly that limit our evidence. New randomized clinical trials are required in order to emphasize that moderate aortic stenosis under certain circumstances is not so benign and early intervention should be in every physician's mind (**Figure 1**).

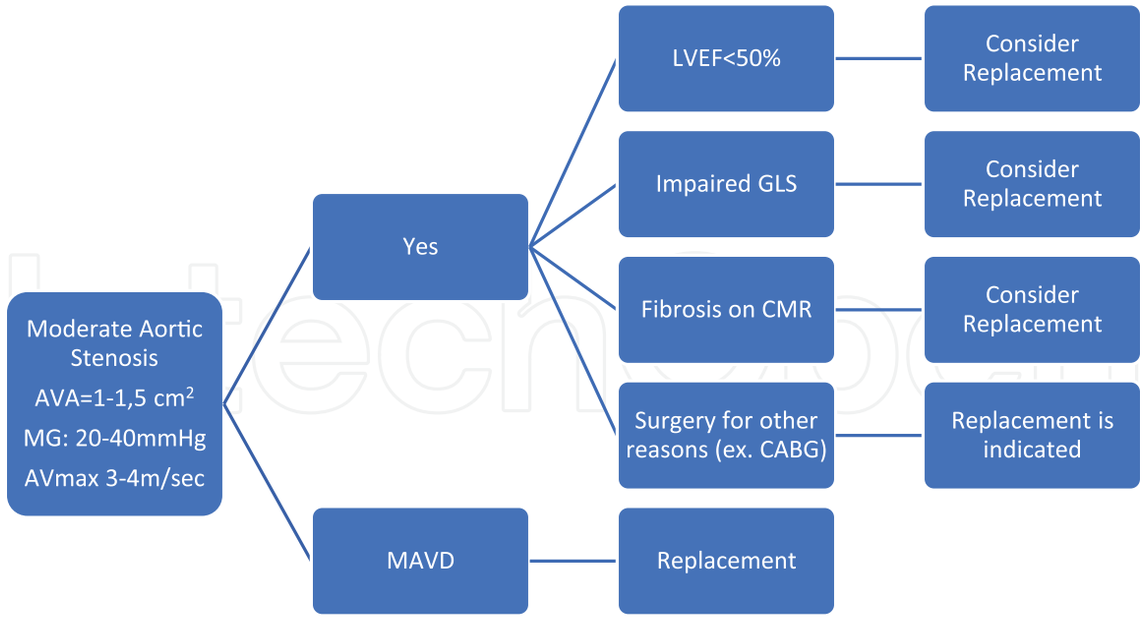

Figure 1.
Summarized algorithm for the management of patients with moderate aortic stenosis based on the provided data.

Abbreviations

ATTR-CA	Transthyretin cardiac amyloidosis
AR	Aortic regurgitation
AS	Aortic stenosis
AVA	Aortic valve area
AVC	Aortic valve calcification
AVR	Aortic valve replacement
CABG	Coronary artery bypass graft
CMR	Cardiovascular magnetic resonance
CT	Computed tomography
GLS	Global longitudinal strain
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
EF	Ejection fraction
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVGLS	Left ventricular global longitudinal strain
MAVD	Mixed aortic valve disease
MDCT	Multidetector row computed tomography
MRI	Magnetic resonance imaging
OHFT	Optimal heart failure therapy
RCT(s)	Randomized controlled trial(s)
SNUH	Seoul National University Hospital
TAVR	Transcatheter aortic valve replacement
TOE	Transoesophageal echocardiogram
TTE	Transthoracic echocardiogram

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