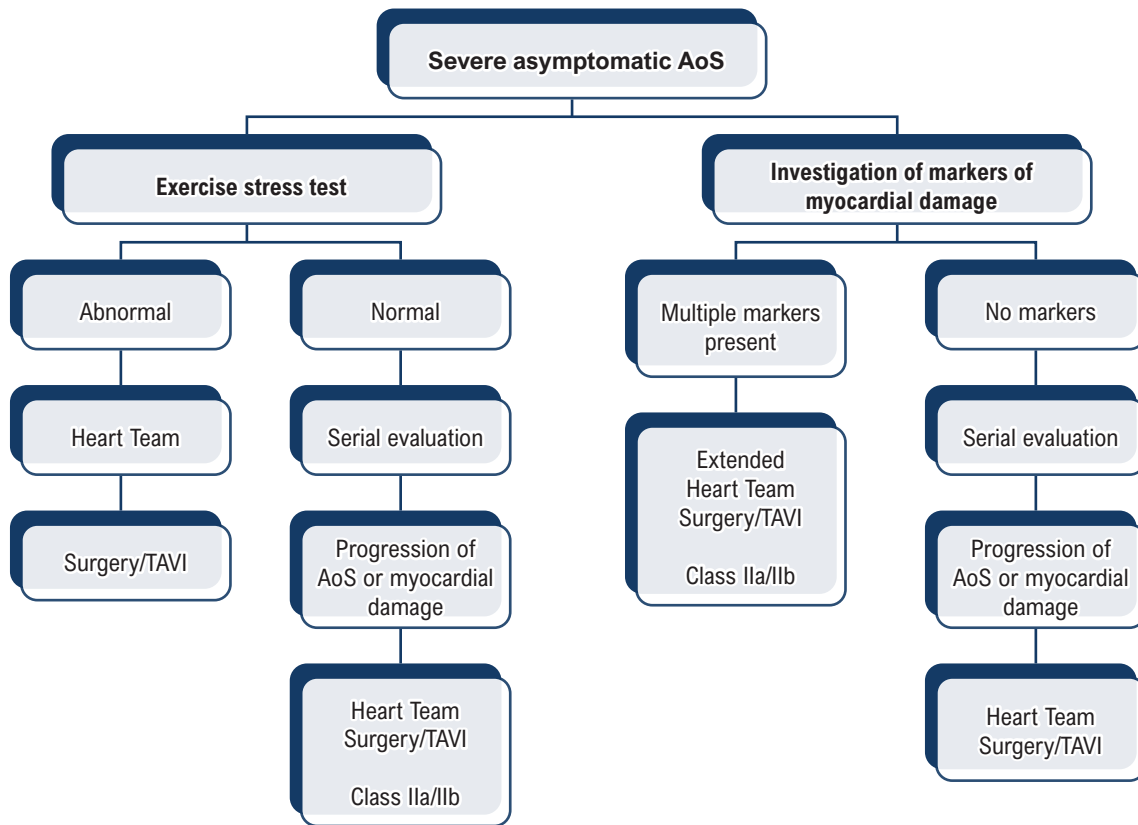


# Recognition of Clinical Stages and Myocardial Damage in Aortic Stenosis: Beyond Diagnosis – To Op or Not To Op

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**Central Illustration:** Recognition of Clinical Stages and Myocardial Damage in Aortic Stenosis: Beyond Diagnosis – To Op or Not To Op



Arq Bras Cardiol: Imagem cardiovasc. 2026;39(2):e20260054

Proposed flowchart for guiding the management of patients with severe aortic stenosis, differentiating between healthy and frail patients. AoS: aortic stenosis; TAVI: transcatheter aortic valve implantation.

## Keywords

Aortic Valve Stenosis; Echocardiography; Magnetic Resonance Imaging

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Manuscript received April 7, 2026, revised manuscript April 22, 2026, accepted April 22, 2026

Editor responsible for the review: Marcelo Tavares

**DOI:** <https://doi.org/10.36660/abcimg.20260054i>

## Abstract

Severe aortic stenosis is a progressive clinical entity that has historically developed alongside descriptions of pathological anatomy, cardiovascular semiology, heart surgery, and percutaneous cardiovascular interventions. Indication for valve replacement in patients with severe aortic stenosis is still based on symptom onset. With advances in surgical techniques, especially transcatheter implantation, the focus has shifted to identifying early markers of myocardial damage that may indicate irreversible myocardial injury. This review article seeks to provide a comprehensive analysis

of methods for identifying myocardial damage in patients with severe aortic stenosis, including clinical evaluation, electrocardiography (ECG), echocardiography, cardiac magnetic resonance imaging (CMR), and plasma biomarkers. It also discusses the staging of myocardial damage and the optimal timing for therapeutic intervention based on clinical, functional, and structural findings. Recent studies designed to address how to manage asymptomatic patients with aortic stenosis have yielded divergent results. Accordingly, the aim is to assist clinicians in deciding the optimal timing for valve replacement, taking individual patient characteristics into account.

## Introduction

Aortic stenosis is the most frequently surgically treated valvular heart disease in the current population.<sup>1</sup> The clinical entity has evolved concomitantly with descriptions of pathological anatomy, cardiovascular semiology, cardiac surgery, and, recently, percutaneous cardiovascular interventions.

In 1663, the French physician Lazare Rivière described the first anatomopathological finding of a stenotic aortic valve.<sup>1</sup> Subsequently, Giovanni Battista Morgagni and Jean-Nicolas Corvisar described an “ossified aortic valve” that did not allow the passage of relevant-sized structures. In 1819, Laënnec described ossified aortic stenosis as a valvular clinical entity with the currently recognized semiological characteristics.<sup>2</sup>

The twentieth century was characterized by detailed anatomopathological description, knowledge of the pathophysiology of the disease, and the development of surgical techniques with increasingly sophisticated prostheses, followed by the development of percutaneous interventions in the twenty-first century. It is currently possible to estimate the degree of progression of aortic stenosis based on echocardiographic epidemiological studies.<sup>3</sup>

Notwithstanding advances in knowledge of pathophysiology, the only current therapeutic option for calcified aortic valve stenosis remains valve replacement.<sup>4</sup> Current guidelines, including the Brazilian guideline, recommend that valve replacement be indicated in patients with severe aortic valve stenosis (peak Doppler velocity > 4.0 m/s, mean gradient > 40 mmHg, valve area < 1.0 cm<sup>2</sup>, or indexed valve area < 0.6 cm<sup>2</sup>/m<sup>2</sup>) who present with symptoms, or in patients with severe stenosis and reduced ejection fraction (< 50%).<sup>5</sup>

With the advent of transcatheter aortic valve implantation (TAVI), it has become possible to perform valve replacement in frail patients with high surgical risk, for whom surgical intervention would be prohibitive.<sup>6</sup> The enthusiasm stemming from the favorable results of percutaneous intervention and the development of new techniques for assessing myocardial damage has led to greater interest in identifying early markers of myocardial damage to indicate valve replacement.<sup>7</sup>

The central question that therefore follows is: Since percutaneous intervention has proven to be safe, why not indicate valve replacement in patients with severe calcified

stenosis before symptoms appear? Although the procedure is considered safe, it is not without risks. In some situations, it can worsen the clinical condition and quality of life, in addition to the fact that prosthesis durability has not been fully defined from an epidemiological point of view.<sup>8</sup> The mortality of asymptomatic patients under expectant management is less than 1% per year, much lower than that expected after surgical valve replacement. On the other hand, the durability of the new prostheses (valve prostheses) has not been tested.

Regarding expectant management, several studies have attempted to identify myocardial damage through electrocardiography (ECG), exercise stress testing, reduction in ejection fraction and myocardial strain by echocardiography, transvalvular gradient response to physical stress echocardiography, myocardial fibrosis and edema by cardiac magnetic resonance imaging (CMR), and plasma biomarkers such as B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP).<sup>9</sup>

In spite of all these advances, studies comparing expectant management with early intervention have not demonstrated benefits, and there are still challenges in defining the optimal timing for intervention.<sup>10</sup> The purpose of this article is to review the methods for identifying myocardial damage and suggest the most appropriate timing for valve replacement intervention, before irreversible myocardial damage occurs, as well as to propose designs for future studies.

## Epidemiological implications

Calcified aortic valve stenosis has a prevalence of 0.4% in the general population, increasing to 1.7% at age 65 and 3.4% at age 75; in other words, it increases significantly after 65 years of age.<sup>11</sup> Bicuspid aortic valve has a prevalence of 0.5% to 1.0% in the population and is responsible for approximately 50% of valve interventions, especially in younger patients.<sup>12</sup> Surgery for calcified aortic valve stenosis represents 47% of all valve surgeries performed.<sup>12</sup>

In spite of recent knowledge about the pathophysiology of calcified valve disease, to date there is no specific clinical treatment for this condition.<sup>13</sup> Symptom onset represents the defined threshold for the indication of valve replacement. From symptom onset, expectant management (without intervention) is associated with a 50% mortality rate within 2 years.<sup>14</sup>

## Pathophysiology

Calcified aortic valve disease shares the same pathophysiological mechanisms and risk factors as atherosclerotic disease. In the initial phase, the inflammatory process predominates, followed by the calcification phase.<sup>15</sup> More recently, the deposition of lipoproteins, such as apoA1, apoB, apoE and lipoprotein(a), has been highlighted, followed by inflammation, oxidative stress, osteogenic differentiation of interstitial cells, and subsequent calcification.<sup>15</sup>

Risk factors for the development of calcified valvular disease include bicuspid aortic valve, age, male sex, smoking, systemic arterial hypertension, dyslipidemia, obesity, metabolic syndrome, diabetes mellitus, elevated

lipoprotein(a), mediastinal radiotherapy, chemotherapy, and rheumatological diseases.<sup>15,16</sup> Regarding the risk of more rapid progression to severe aortic stenosis, the following stand out: advanced age, female sex, hemodynamic severity of the initial stenosis, degree of valve calcification, active smoking, uncontrolled systemic arterial hypertension, metabolic syndrome, hyperparathyroidism, chronic renal failure, and elevated lipoprotein(a).<sup>16</sup>

The advent of percutaneous intervention in patients with prohibitive surgical risk has opened a window of therapeutic opportunity for these patients. On the other hand, a trend has emerged to perform this type of procedure in situations where the cost-benefit should be carefully discussed in the context of a multidisciplinary Heart Team. The concept of an extended Heart Team includes the participation of nephrologists, geriatricians, neurologists, nutritionists, patients, and family members, especially for the population of frail patients with multiple morbidities.<sup>17</sup> Despite the lower risk compared to conventional surgery, studies in patients with high frailty have shown results that question the indiscriminate indication of early intervention.<sup>18</sup>

### Adaptation to pressure overload and myocardial damage

Following sustained pressure overload, an increase in myofibrillar content is observed, with a consequent increase in left ventricular mass. This increase in mass leads to a reduction in coronary microcirculation density and an increase in coronary vascular resistance. Coronary reserve is progressively reduced, initially only during exertion, and subsequently at rest as well.<sup>19</sup>

Consequently, the myocardium is subjected to repeated ischemia, initially manifesting as diastolic dysfunction.<sup>19</sup> With recurrent ischemia, fibrosis subsequently develops. Initially, this fibrosis is interstitial, diffuse, and reversible after valve replacement. In later stages, the fibrosis is substitutive, focal, and irreversible. Subsequently, changes in the functional geometry of the left ventricle occur, resulting in increased end-diastolic pressure. This increase is transmitted to pulmonary venous pressure, and symptoms of pulmonary congestion appear (dyspnea on exertion).<sup>19</sup> Ischemia may manifest with symptoms of angina. Impaired ejection flow, especially during exertion, is responsible for symptoms of pre-syncope and syncope, particularly during exertion.<sup>19</sup>

Once the mechanism of myocardial damage has been understood, it is imperative to use the available diagnostic tools in a rational and individualized manner. As previously mentioned, there is still no drug treatment for calcified aortic stenosis. Despite knowledge about the mechanisms of myocardial damage, we still do not fully understand the implications of early intervention before the onset of symptoms.<sup>19</sup>

### Identifying myocardial damage

#### Clinical evaluation

According to current guidelines, intervention in patients with severe aortic stenosis should be indicated

when symptoms appear.<sup>5</sup> Although the classic symptoms (dyspnea, angina, and syncope) have been well defined, their identification can be challenging in certain populations.

Patients with aortic stenosis secondary to bicuspid aortic valve are typically younger (approximately 20 years younger than those with degenerative aortic stenosis), physically active, and without significant comorbidities.<sup>20</sup> In these cases, in addition to clinical history and physical examination with the goal of identifying symptoms, an exercise stress test is recommended in order to identify functional limitations and reproducible symptoms.<sup>20</sup>

In contrast, patients with degenerative calcified aortic stenosis present a completely different clinical profile. They are elderly, often with orthopedic problems, chronic lung diseases, and cognitive impairment. In this scenario, it is very difficult to adequately identify symptoms of ischemia or congestion.<sup>21</sup>

Regardless of profile, asymptomatic patients with severe aortic stenosis should be monitored periodically every 3 to 6 months, with the expectation of identifying emerging symptoms or changes on ECG and echocardiography.<sup>5</sup>

### Electrocardiogram

ECG can provide important information related to left ventricular overload in the assessment of myocardial damage. An ECG with findings suggestive of left ventricular overload (left ventricular hypertrophy) in asymptomatic patients with severe aortic stenosis, estimated by the transvalvular gradient on echocardiography, represents a warning sign (yellow flag) that justifies intensified monitoring.<sup>22</sup> Studies of prognostic markers suggest that ventricular hypertrophy, identified by ECG, echocardiogram, or CMR, represents a worse outcome compared to patients without ventricular hypertrophy. The presence of arrhythmia, especially atrial fibrillation, can result from increased ventricular filling pressure secondary to diastolic dysfunction, followed by left atrial overload, and may indicate myocardial damage.

### Exercise stress test

Exercise stress tests play an important role in the evaluation of asymptomatic patients with severe aortic stenosis. This test can reveal typical symptoms (dyspnea disproportionate to exertion, precordial angina, or syncope) that were not detected at rest, in up to 30% of individuals considered asymptomatic, thus guiding the decision to intervene. In addition to symptoms, a hypotensive response to exertion, ischemia on ECG, or the appearance of malignant arrhythmias are also indicators of greater severity, with a relative risk more than 7 times higher compared to patients with normal results.<sup>23</sup>

### Echocardiography

Transthoracic echocardiography is the method of choice for evaluating aortic valve anatomy, quantifying stenosis severity, identifying associated valvular and diastolic dysfunction, estimating left ventricular filling pressures (E/e' ratio), estimating left ventricular ejection fraction, assessing

right ventricular function, and estimating pulmonary arterial pressure.<sup>24</sup> Although the traditional cutoff point for systolic dysfunction is an ejection fraction of 50%, values above this threshold, but with significant progressive decline (> 10%), may represent relevant myocardial damage and justify valve replacement, in a manner similar to patients with cancer undergoing chemotherapy.<sup>25</sup>

Very severe aortic stenosis ( $V_{max} > 5$  m/s) or progression of stenosis severity (> 0.3 m/s/year) is associated with onset of symptoms and worsening mortality in the first year.<sup>24</sup> The European guideline considers this condition a class IIa indication for intervention.

Serial evaluation with progressive reduction of ventricular function is particularly informative. For example, a patient with an initial ejection fraction of 68% who shows a progressive reduction to 60% demonstrates a decline greater than 10%, which may signify significant myocardial damage in progression.<sup>25</sup>

Valvulo-arterial impedance ( $Z_{va}$ ) represents a marker of myocardial damage, calculated as systolic blood pressure (SBP) plus mean transvalvular gradient (MG) divided by the stroke volume indexed by body surface area (SVI), as follows:  $Z_{va} = (SBP + MG) / SVI$ . Values greater than 4.5 have prognostic importance for indicating valve replacement.<sup>26</sup>

The left atrium undergoes enlargement proportionally to diastolic dysfunction, representing the chronic progression of atrial overload. Left atrial enlargement and elevated pulmonary artery systolic pressure represent signs of myocardial damage, as do right ventricular dysfunction and tricuspid regurgitation.<sup>27</sup>

Genereux et al. analyzed patients from the PARTNER 2 study, who were grouped and classified according to the presence or absence of cardiac damage detected by echocardiography before aortic valve replacement in the following manner: no extravalvular cardiac damage (stage 0), left ventricular damage (stage 1), left atrial or mitral valve damage (stage 2), pulmonary vasculature or tricuspid valve damage (stage 3), or right ventricular damage (stage 4). Among the 1,661 patients with echocardiographic data, 1-year mortality was 4.4% in stage 0, 9.2% in stage 1, 14.4% in stage 2, 21.3% in stage 3, and 24.5% in stage 4 ( $p$  for trend < 0.0001). The extent of cardiac damage was independently associated with higher mortality after aortic valve replacement (hazard ratio 1.46 for each stage increment, 95% confidence interval 1.27–1.67,  $p < 0.0001$ ). These results suggest that stages other than 0 and 1 demonstrate structural and functional changes in which symptoms were likely already present and which had prognostic importance. In this case as well, the sum of myocardial damage markers suggests that valve replacement before the onset of symptoms may be an acceptable approach, even though the results have been controversial to date.<sup>28</sup>

### Global longitudinal strain

Echocardiographic assessment may also include global longitudinal myocardial strain, which has been shown to be a more sensitive tool for identifying early systolic dysfunction.<sup>9</sup> Although the traditional cutoff points for strain in patients

with ventricular dysfunction and patients with aortic stenosis are –17% and –14%, respectively, progressive strain reduction can also be interpreted as evidence of progressive myocardial damage.<sup>9,29</sup> Studies have correlated reduced myocardial strain with the onset of symptoms. Reduced strain also has prognostic value after valve replacement.<sup>29</sup>

Atrial strain is an additional tool that can be used when equipment with this feature is available. Although the data are controversial, atrial strain can identify atrial dysfunction before remodeling and predict the onset of atrial fibrillation during the course of the disease and post-operatively<sup>30</sup> (Figure 1).

### Stress echocardiography

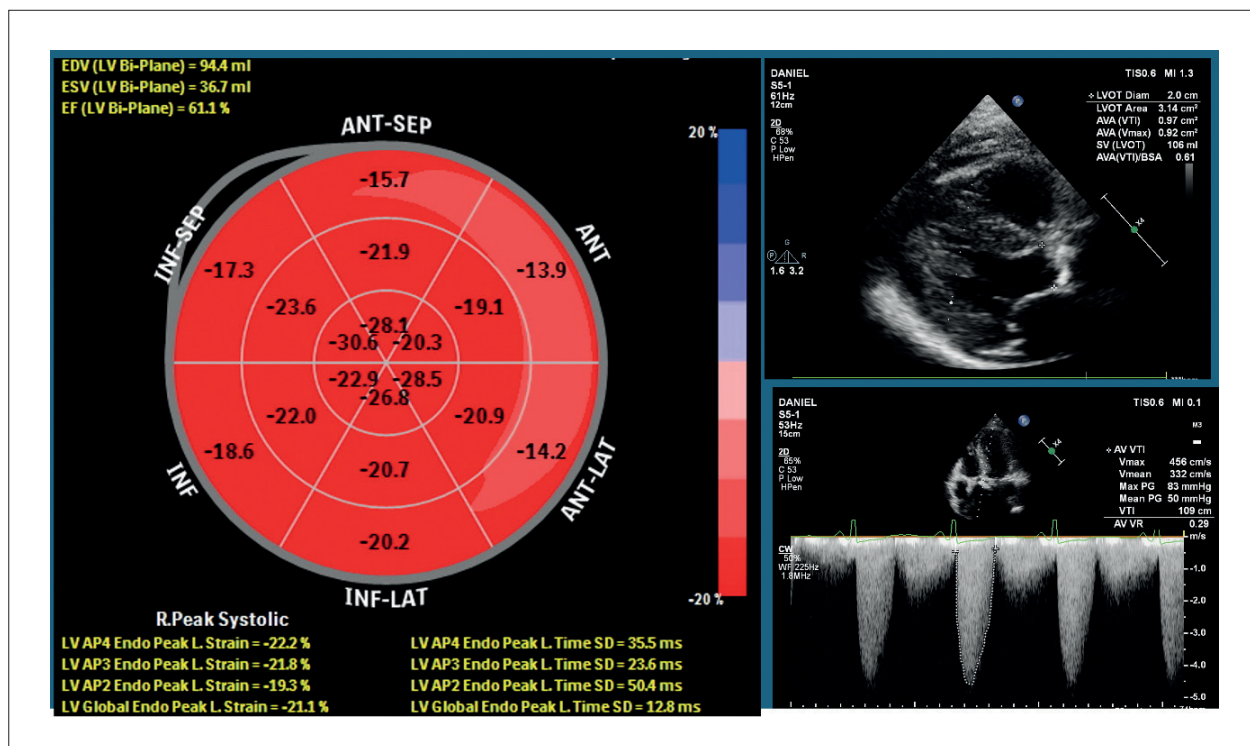
Although current guidelines do not recommend stress echocardiography as a tool for stratifying asymptomatic patients with severe aortic stenosis,<sup>5</sup> its use during physical or pharmacological stress (dobutamine) to assess the transvalvular gradient, electrocardiographic tracing, and ventricular functional response continues to be investigated.<sup>9</sup> Studies comparing patients with positive versus negative stress tests, subsequently undergoing valve intervention, show variability in results, without significant and consistent differences in long-term prognosis between groups.<sup>31</sup> Further studies are needed to define the role of stress echocardiography in the management of asymptomatic patients with severe aortic stenosis.

### Cardiac magnetic resonance imaging

CMR has emerged as an important non-invasive marker of myocardial damage in severe aortic stenosis.<sup>32</sup> In addition to assessing the severity of stenosis with results comparable to echocardiography, it is now possible, by means of native T1 mapping, to identify and quantify diffuse interstitial myocardial fibrosis lesions that may be partially reversible after valve replacement. Late gadolinium enhancement allows identification of focal fibrosis, which is usually irreversible, and it is an important indicator for early valve replacement.<sup>32,33</sup>

Some initial studies have suggested that anticipating valve replacement in patients with fibrotic changes detected by CMR could favorably modify the clinical and functional outcomes.<sup>34</sup> However, the recently published randomized EVOLVED study with 224 patients did not demonstrate benefits in anticipating valve replacement before the onset of symptoms, even in the presence of myocardial fibrosis detected by CMR.<sup>35</sup> Likewise, Myhr et al., comparing 42 symptomatic patients with 80 asymptomatic patients, showed that the presence of myocardial fibrosis identified by CMR with late enhancement did not demonstrate significant differences in relation to progression after valve replacement<sup>36</sup> (Figure 2; Video 1).

On the other hand, another recently published randomized study by Génereux et al. (EARLY TAVR), albeit with some methodological limitations, evaluated a significantly larger sample (901 patients), suggesting favorable results for early percutaneous intervention in asymptomatic patients with severe aortic stenosis.<sup>36</sup> Although their conclusions



**Figure 1** – Two-dimensional transthoracic echocardiography with color Doppler demonstrating severe aortic stenosis. Top right: Parasternal longitudinal view showing left ventricular hypertrophy and calcified aortic valve. Bottom right: Transvalvular velocity > 4.5 m/s and mean gradient = 50 mmHg. Left: Bull's eye map showing normal global longitudinal strain = 21.1%.

were favorable, mortality and prognosis were similar. The intervention reduced the outcome of hospitalization. A large part of these hospitalizations resulted from decompensation in the clinical follow-up group, in patients who underwent intervention in the subsequent 90 days. Similar results were found in the AVATAR study (Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis).<sup>37</sup>

### Plasma biomarkers

Elevated BNP and NT-proBNP levels are correlated with increased ventricular filling pressure and predict worse prognosis in severe aortic stenosis.<sup>38</sup> Elevated values may reflect myocardial damage with consequent diastolic dysfunction.<sup>38</sup> Similarly to other markers of myocardial damage, perhaps progressive worsening in serial evaluations, when associated with other markers, may indicate the need for early valve replacement.

Other biochemical markers have also shown prognostic value in surgical outcome during preoperative evaluation. High-sensitivity troponin T has important prognostic value. Elevations in troponin T, even slight ones, in patients with severe aortic stenosis correlate with worse clinical progression and a higher risk of adverse events.<sup>39</sup> This marker can identify structural cellular damage that is already present in the myocardium.<sup>39</sup> Osteopontin, a glycoprotein secreted by cells linked to inflammatory and remodeling processes, has been shown to be a marker of irreversible myocardial damage.

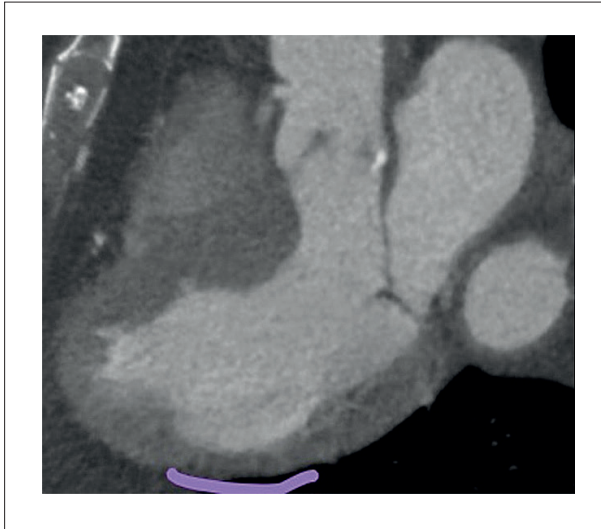
Studies have shown that osteopontin predicts adverse clinical outcomes in patients after treatment of severe aortic stenosis with TAVI.<sup>40</sup> Annexin A1, studied in pericardial fluid of patients with severe aortic stenosis, has been shown to be a marker of atrial fibrillation associated with aortic stenosis, representing a marker of atrial remodeling.<sup>41</sup> Plasma ACE2 activity has also been shown to be associated with severe myocardial fibrosis and to predict mortality in patients with aortic stenosis.<sup>42</sup> Elevated levels indicate pathological myocardial remodeling processes with the development of fibrosis.<sup>7</sup>

Although biomarkers can identify patients with worse prognosis, current guidelines still do not mention their role in decision-making.

### Discussion: When to intervene?

In spite of the multiple diagnostic tools available and the numerous published studies, the optimal timing to perform aortic valve replacement (to op) remains controversial and without absolute consensus (not to op).<sup>7</sup> In the real world, we have observed increasingly frequent indications for TAVI placement in patients under 65 years of age. Despite the safety of the procedure, long-term results have shown that mortality is higher in the percutaneous intervention group. The **Central Illustration** presents a proposed flowchart to guide the follow-up of asymptomatic patients with severe aortic stenosis.

Clinical experience suggests prudence and common sense in decision-making. In young, healthy, and asymptomatic patients with severe calcified aortic valve stenosis, close follow-up is recommended with consultations every 3 to 6 months, including:



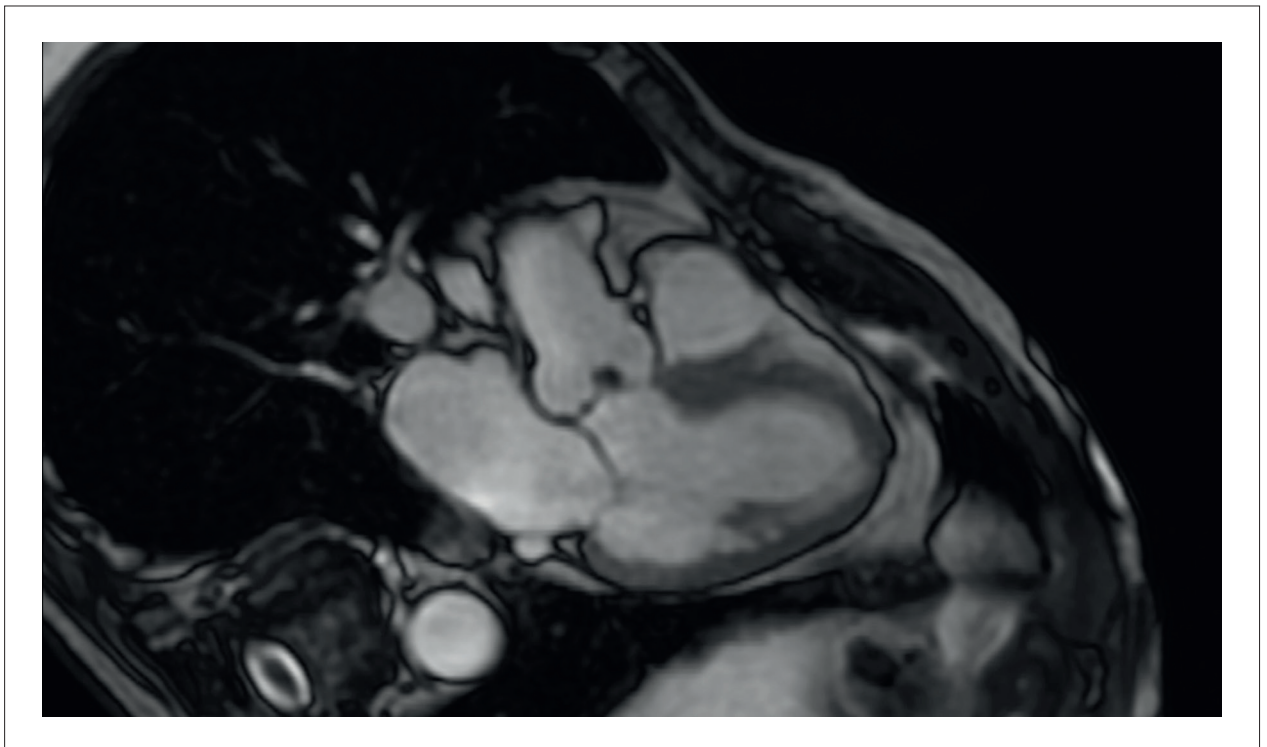
**Figure 2** – Cardiac magnetic resonance imaging in a patient with severe aortic stenosis. Late gadolinium enhancement demonstrates a pattern of focal subendocardial fibrosis. These changes represent evidence of irreversible structural myocardial damage (image kindly provided by Dr. Luiz Augusto Quaglia).

- Serial ECG
- Echocardiogram with evaluation of ejection fraction and myocardial strain
- Exercise stress test (if appropriate for the patient's clinical profile)
- Plasma biomarkers (BNP/NT-proBNP, high-sensitivity troponin T)
- CMR with T1 and T2 maps and late gadolinium enhancement (less frequently, in selected situations)

Progressive changes with worsening ventricular function, whether due to ejection fraction or myocardial strain, left atrial enlargement, stenosis progression, and signs of elevated pulmonary arterial pressure, coupled with an abnormal exercise stress test (whether due to ischemia, decreased pressure, or malignant arrhythmias), may represent grounds for recommending valve replacement.<sup>15</sup>

In elderly patients with frailty that poses difficulties in adequately assessing symptoms, in addition to the parameters listed above (with the exception of exercise stress test, which may be contraindicated), assessment should integrate the multidimensional concept of frailty (extended Heart Team) to assist in the decision between performing elective valve intervention or clinical management with rigorous follow-up.<sup>43</sup>

For all patients, the classification of myocardial damage proposed by Genereux et al., after evaluating the population



**Video 1** – Cardiac magnetic resonance imaging demonstrating severe aortic stenosis with myocardial structural remodeling and focal fibrosis. Courtesy of Dr. Luiz Augusto Quaglia. In: [http://abcimaging.org/supplementary-material/2026/3902/ABCImag-2026-0054\\_AR\\_Video\\_1.mp4](http://abcimaging.org/supplementary-material/2026/3902/ABCImag-2026-0054_AR_Video_1.mp4)

of the PARTNER study, can assist in identifying the initial stages of myocardial damage and justify the surgical indication described above. When applying the classification, it is important to bear in mind that all stages, except stage 0, are associated with a worse prognosis, justifying further monitoring and anticipation of intervention when appropriate.<sup>7</sup>

## Conclusion

Severe aortic stenosis poses a challenge in current clinical management, characterized by the technical possibility of safe percutaneous intervention, but without absolute clarity regarding the optimal timing. Advances in the pathophysiological understanding of the disease and the development of sophisticated diagnostic tools (strain echocardiography, CMR with tissue mapping, and specific biomarkers) allow for the identification of myocardial damage in progressive stages before the onset of symptoms. Although the pathophysiological rationale points to intervention based on the identification of myocardial damage markers, studies conducted to date have yielded controversial results. Characteristics of the disease's phenotypic expression, which influence ventricular remodeling, worsening diastolic and systolic function, atrial remodeling, and the reaction of the pulmonary microcirculation, can affect the timing of symptom onset. Well-designed studies with consistent results are needed to incorporate the intervention approach into the guidelines.

An individualized and risk-stratified approach is recommended, considering the patient's clinical profile (young versus elderly, frail versus healthy), the presence and progression of markers of structural and functional myocardial damage, associated comorbidities, and the patient's informed preferences. The decision regarding closer follow-up intervals versus elective intervention should be based on multidisciplinary discussion within the context of an extended Heart Team. In the elderly population, whether asymptomatic or symptomatic, in the presence of a phenotype of left ventricular hypertrophy, the possibility of amyloid disease should always be considered.

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## Acknowledgements

The author would like to thank the echocardiography and CMR teams who contributed to compilation of the clinical images presented in this manuscript.

## Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, writing of the manuscript and critical revision of the manuscript for intellectual content: Vasconcelos DF.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Sources of Funding

There were no external funding sources for this study.

## Study Association

This study is not associated with any thesis or dissertation work.

## Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

## Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

## Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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