Aortic stenosis. Questions and some answers

Estenosis aórtica. Interrogantes y algunas respuestas

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In 1968, Ross and Braunwald[1] published an article on the natural history of aortic stenosis (AS) that, in general, remains relevant today: the onset of symptoms indicates a reduced life expectancy **(Figure 1).** However, without questioning this assertion, three facts have substantially changed the scenario.

The first is related to the increase in life expectancy, which leads to a higher incidence of AS (new cases per year) and, consequently, a sustained increase in its prevalence. The etiology of AS is now predominantly a degenerative process equally affecting the entire cardiovascular system.
The second, also age-related, concerns myocardial adaptation to pressure overload, which necessarily differs between elderly and younger individuals.
Finally, the availability of aortic valve replacement (AVR) through a transcatheter procedure (TAVR) offers a lower-risk alternative to surgical replacement for intervention in elderly patients.
These factors, collectively, may modify the evolutionary course of AS, as illustrated in **Figure 1**, in two aspects:

- higher risk with less severe stenosis and ventricular dysfunction in presymptomatic disease;
- possibility of intervention in elderly patients with comorbidities that may contraindicate surgical procedures.

Recent literature aimed at analyzing these specific topics in detail has raised many questions and provided some answers, which are the focus of this article. Let us examine the following topics:

Do the current categories of AS severity—mild, moderate, and severe—reflect clinical practice?
No, because diagnostic protocols often include intermediate categories such as *mild-to-moderate AS* and *moderate-to-severe AS*, which account for 5% and 8% of all cases, respectively, according to a recent study that includes thousands of echocardiographic records[2]. This is likely due to imprecisions in valve area calculations or other reasons related to technical difficulties.

What are the prognostic determinants of AS?
Observational studies identify several factors influencing evolution. These can be grouped into three categories **(Figure 2):**

- AS severity;
- left ventricular ejection fraction (LVEF);
- comorbidities.

While all three affect prognosis regardless of AS severity, the absolute impact of two of them becomes more clinically significant in moderate AS and moderate-to-severe AS.

Are patients with severe AS, either symptomatic or with LVEF < 0.50, treated with AVR through surgery or TAVR as per the evidence and guidelines from scientific societies?
In severe AS with the aforementioned conditions, guidelines strongly recommend AVR. However, an observational study showed that despite a 45-% mortality rate over four years, only 61% of patients underwent intervention[2].

In that study, is it possible that the population who did not undergo intervention is a selected group at higher risk because AVR was reserved for individuals with fewer comorbidities?

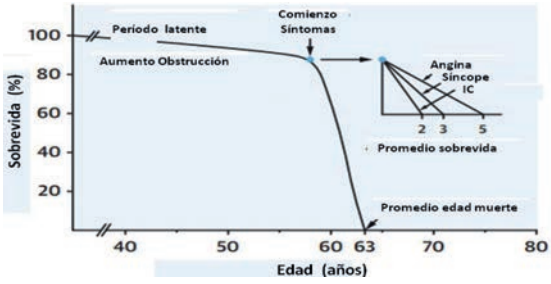

Figure 1. *Modified from Ross J. Jr., Braunwald E. Aortic stenosis. Circulation. 1968;38:61.*

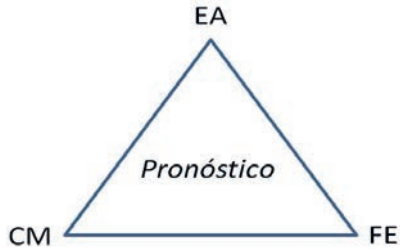

Figure 2. *Determinants of aortic valve disease evolution. AS: aortic stenosis. CM: comorbidities. LVEF: left ventricular ejection fraction.*

In that study[2], the population was adjusted using the inverse probability of treatment weighting (IPTW) statistical technique, resulting in a sample without differences in mortality compared to the original population. The authors concluded that the severe AS patients who did not undergo intervention are representative of the natural evolution of valve disease.

TABLE 1. Adjusted risk relationship between no AS and AS in patients with LVEF <0.50 (*) and independent of LVEF. (2): Reference no. 2. (5): Reference no. 5.

vs. no AS	HR (95%CI)
Moderate AS[5] (*)	1,32 (1,07-1,63)
Moderate to severe AS[2]	1,48 (1,33-1,65)
Moderate[2]	1,56 (1,42-1,71)

AS: aortic stenosis.

What could explain the low AVR rate?

- Possible reasons include, but are not limited to:
- patient refusal;
- comorbidities contraindicating the intervention;
- absence of symptoms.

In patients with severe AS who are asymptomatic and with LVEF >0.50, is it justified to withhold intervention?

Guidelines generally do not recommend AVR in asymptomatic patients without LV dysfunction[3,4]. As a matter of fact, several ongoing randomized controlled trials are evaluating the effect of AVR in this patient group. Some of these are

- the EASY-AS trial;
- the DANAVR study;
- the EVoLVeD trial.

Inclusion criteria for all three require LVEF >0.50, but the last two will include patients with "other indicators of LV dysfunction" or with myocardial fibrosis on MRI, respectively.

While guidelines generally do not recommend intervention in asymptomatic severe AS or AS without ventricular dysfunction, are there any exceptions to that rule?

Yes, AVR is potentially acceptable under the following conditions:

- peak velocity >5 m/s;
- LVEF <0.55 or <0.60, per American and European guidelines, as indicators of early ventricular dysfunction[3,4];
- rapid progression of the obstruction, as evidenced by a velocity increase of >0.3 m/s/year;
- reduced tolerance to exertion during a stress test.

In practice, asymptomatic patients with LVEF >0.50 often undergo AVR due to one or more of these indicators. In the real-world, however, other limiting factors, sometimes related to the healthcare system, may contribute to non-intervention.

In terms of prognosis, is moderate AS positioned between mild and severe AS?

In a study that only included patients with LVEF <0.50, the prognosis for moderate AS was similar to that for severe AS and significantly different from that of the population without valve disease (hazard ratio [HR] = 1.32 [1.07-1.63]) (sample adjusted by propensity score matching)[5]. In one of the previously mentioned studies[2] (the one with 595,120 echocardiographic records from 24 US sites for the assessment of aortic valve function, in which approximately 20% of patients had LVEF <0.50), the prognosis for moderate AS (34% over 4 years) and for moderate-to-severe AS (46% over 4 years) came close to that for severe AS (45% over 4 years).

What is the role of LVEF as a determinant of moderate AS prognosis?

While one study argues that LVEF <0.50 is a prognostic determinant[5], another trial[2] suggests that it is not, as the HR adjusted for mortality associated with LVEF <0.50 was significant (1.47 [1.37-1.58]) but did not surpass that for moderate-to-severe AS (1.48 [1.33-1.65]) or for moderate AS (1.56 [1.42-1.71]). In conclusion, LVEF is a partial determinant of moderate AS prognosis approaching that of severe AS.

Additionally, the aforementioned study showed that the number of days free from mortality or hospitalization in severe AS was surprisingly lower than in moderate AS. This finding was attributed to prompt resolution through intervention in the former and recurrent hospitalizations for decompensation in the latter[5].

Regarding comorbidities, the other determinant of evolution, what is their impact on moderate AS?

First, the prevalence of comorbidities increases linearly from the absence of AS to the highest severity levels, reaching a *plateau* starting from moderate AS. Thus, moderate and severe AS are equalized in terms of associated comorbidities[2].

Second, compared to the absence of valve disease, the adjusted HR for moderate AS was significantly higher than that for comorbidities, both with LVEF <0.50 (1.32 [1.07-1.63])[5] and independently of it (1.56 [1.42-1.71])[2] **(Figure 3)**.

Conclusion regarding moderate AS prognosis

The prognosis of moderate AS and that of moderate-to-severe AS are similar to the prognosis of severe AS. The latter is only partially conditioned by LVEF and associated comorbidities.

During its evolution, does moderate AS remain stable or progress in severity?

In general, it progresses. In the aforementioned trial involving patients with LVEF <0.50, 34% of cases initially classified as moderate AS underwent AVR. In 80% of cases, that was due to its progression to severe AS within approximately one year. In the remaining 20%, treatment was due to patients requiring other cardiovascular interventions[5]. This indicates that, once its classified as "moderate," AS progression clearly accelerates.

In moderate AS, is the "close monitoring" strategy always the best approach?

In the presence of symptoms resistant to pharmacological treatment, a low-risk intervention is increasingly favored, with the idea of eliminating a factor that is likely to limit the activity level and then assessing the subsequent evolution.
In cases of LVEF >0.50 without symptoms, an intervention is a distinctly controversial decision. However, two aspects should be considered.
Symptoms may be downplayed by the patient and sometimes also by the physician. Proposing AVR after a long time of what was until then a seemingly favorable evolution can be difficult and undesirable, thus leading to indefinite postponement. Additionally, minimal progression in severity or ventricular dysfunction may also be underestimated.
Under these circumstances, the current strategy is likely to remain alert to these scenarios, remembering that short-term prognosis may not be favorable in these cases and that the decision for AVR may come at a later time.

Moderate AS vs. low-flow, low-gradient AS

Severe AS with *low flow and low gradient* is diagnosed if the mean 20-40-mmHg gradient is associated with LVEF <0.50 or reduced stroke volume due to a small ventricular chamber resulting from wall hypertrophy.
In these cases, diagnosis is always challenging, requiring inotropic stimulation or calcium scoring to confirm the valve disease severity. However, even with these procedures, uncertainty often remains as to whether we are facing merely moderate AS. In these circumstances, the previously mentioned reserved moderate AS prognosis may warrant an intervention, to some extent.

Beyond the considerations above, are there any trials investigating the benefits of intervention in moderate AS?

The following randomized trials will assess the effect of AVR through endovascular implantation on moderate AS:

- TAVR UNLOAD;
- PROGRESS;
- EXPAND II.

These trials will include patients with ventricular dysfunction and symptoms attributable to valve disease. However, in the case of PROGRESS, signs of ventricular compromise in the absence of symptoms will also be considered.

Medical practice, which often challenges available recommendations and evidence, and the observational studies derived from it are both crucial in advancing medical knowledge. Randomized trials, which are unquestionably the highest level of evidence, may confirm new strategies—sometimes merely backing up what we are already implementing in our daily practice.

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