



## Debate. Asymptomatic severe aortic stenosis: when should we intervene? The clinician's perspective

*A debate. Estenosis aórtica grave asintomática, ¿es el momento de actuar? Perspectiva del clínico*

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**QUESTION:** Can the prevalence of asymptomatic aortic stenosis and its various degrees of severity be estimated in the general population?

**ANSWER:** Although estimates can be made, they undoubtedly underestimate the true prevalence of asymptomatic aortic stenosis (AS). What we know is that, according to the 2017 European Cardiovascular Disease Statistics, over 6 million new cases of cardiovascular disease are diagnosed each year in Europe, with over 50 million prevalent cases (a 30% increase since 2000). In Spain, this amounts to over 250 000 new cases of cardiovascular disease diagnosed each year, and over 4 million prevalent cases.

If we focus on valvular heart disease, according to the latest Euro Heart Survey, AS is still the most widely diagnosed (41%) and frequently treated (45% of all procedures performed) severe valvular heart disease in the hospital setting. Undoubtedly, AS represents the highest burden of valvular heart disease among patients overall, and is even more significant among older adults. In the Olmsted County registry,<sup>1</sup> the prevalence of AS was 0.5% (4.6% in patients older than 75 years, a rate very similar to that of the AGES-Reykjavík trial,<sup>2</sup> where the prevalence of severe AS in patients older than 70 years was 4.3%.)

If we look at asymptomatic patients, data on the true prevalence are available but they are drawn from indirect sources. Spain has played a major role in our ability to estimate the prevalence in these patients. In the registry of Ferreira et al.<sup>3</sup> the prevalences of sclerosis was 45.5% and that of stenosis was 3%. More recently, a study conducted by our group<sup>4,5</sup> in vaccination centers found undetected aortic sclerosis in 53.4% of the patients and undetected AS in and 4.2%.

Therefore, based on the population prevalence data obtained and the current and projected composition of the Spanish population for the next 40 years, it is estimated that 470 000 Spaniards currently have undiagnosed AS. If the expectations for population growth and distribution of Spain's National Statistics Institute are met, and if

the proportion of diagnosed or treated cases vs undetected cases doesn't change, the number of people with undiagnosed AS would be close to 1 million by 2060. If we assume that 10% of all undetected cases of AS are severe, we're talking about nearly 100 000 cases of undiagnosed severe AS and, therefore, not followed-up or potentially treated. Let's not forget that, currently, nearly 4500 cases of severe AS are treated each year, which helps put the problem in perspective.

**Q.:** How should patients with severe AS who remain asymptomatic be approached from a diagnostic standpoint?

**A.:** First, it is essential to make sure that a patient with severe AS is truly asymptomatic. The key is to delve deep into the patient's past medical history and have an expert review the EKG performed. If stenosis is genuinely severe and asymptomatic, there are data that will eventually lead us to start early treatment. We should remember to assess the presence of ventricular dysfunction, symptom onset during exercise, a fall in blood pressure on exertion, marked elevations of brain natriuretic peptide levels, very extensive coronary artery calcification, and rapid reduction in aortic area during disease progression; these are clear indications that we need to act quickly. This is much more important with today's well-established, low-risk percutaneous techniques. We should remember that, with the rapid advancement of the technique since the introduction of transcatheter aortic valve implantation (TAVI), practices that we never thought to question, such as waiting for symptom onset or starting treatment before progression to severe disease, may have become outdated.

I think that the best time to treat asymptomatic patients with severe AS is when they develop left ventricular decompensation. Data such as brain natriuretic peptide levels, the EKG strain pattern, T<sub>1</sub> mapping, and delayed enhancement on magnetic resonance imaging help identify high mortality risk in these patients. Therefore, stratifying heart damage adds additional prognostic value to the traditional clinical risk factors for predicting survival in asymptomatic AS.

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Ongoing trials<sup>6,7</sup> may lead us to consider earlier interventions even in asymptomatic patients.

**Q.:** What relevant evidence could support the use of aortic valve replacement in a case of truly asymptomatic severe aortic stenosis?

**A.:** There is evidence from patients who underwent surgery that supports the idea of treating asymptomatic patients. The AVATAR trial<sup>8</sup> demonstrated that, in asymptomatic patients with severe AS, early surgery reduced the composite primary endpoint of all-cause mortality, acute myocardial infarction, stroke, and heart failure-related admissions compared with conservative treatment.

The EARLY TAVR trial (NCT03042104) will examine the safety and efficacy profile of TAVI with the SAPIEN 3 or SAPIEN 3 Ultra valves vs clinical follow-up in asymptomatic patients with severe AS. The aim of this trial is to compare outcomes between patients undergoing valve replacement early in the disease and those undergoing clinical surveillance.

However, given the natural progression of AS and the low morbidity and mortality of TAVI, the idea of treating AS at an earlier stage of the disease has been suggested. The recent VALVENOR trial<sup>9</sup> demonstrated that, compared with the general population, patients with moderate symptomatic AS had more cardiovascular mortality than those with mild AS (although still lower than that of patients with severe AS). In this regard, the PROGRESS (NCT04889872), TAVR UNLOAD (NCT02661451), and landmark EXPAND TAVR II trials (NCT05149755) assess TAVI vs clinical surveillance in symptomatic patients with moderate AS. While cautious optimism is warranted, it's important to acknowledge certain potential limitations. Also, we must be aware that preventing valve degeneration is an important area of current research and that replacing the native valve with a prosthetic valve is not a permanent solution to the problem. Additionally, as we treat progressively younger patients, it is important to understand the anatomical limitations imposed by the need for future valve-in-valve procedures and the durability of the valves.

**Q.:** How does your center currently manage these patients?

**A.:** It's obvious that our center has radically changed the diagnosis, follow-up, and treatment of these patients since we set up the Valve Clinic (2 clinical cardiologists and 1 heart valve clinical nurse specialist) 7 years ago. Diagnoses are reached following a standardized protocol and always with the same echocardiography machine, which is configured to only perform valve EKGs. This guarantees acceptable variability and standardization. Once the clinical cardiologist has decided that a patient needs treatment, we stay in close contact with other professionals specialized in the management of this type of patient. This undoubtedly enhances the quality of care. Data are reported to the hospital annually and are then published, including all possible complications and outcomes. Surgeons also

present data on their surgically-treated patients on a yearly basis. We're lucky to have excellent clinical cardiologists, operators, and surgeons at Hospital Ramón y Cajal with broad experience in the management of patients with valvular heart disease and with published data that can be audited.

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## STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

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