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Commentary: In the eye of the beholder

Dawn S. Hui, MD

This edition of the *Journal* presents a meta-analysis of studies comparing conservative management with early surgery for asymptomatic severe aortic stenosis (AS).¹ The principal finding was an association of early surgery with reduction in all-cause and cardiovascular mortality. Over the last several decades, growing evidence on this topic has produced similar results. This may suggest consideration of a change in the guidelines (Figure 1).² However, a deeper analysis is needed before considering this step.

One must first examine the consistency of definitions. What constitutes “asymptomatic” has evolved, with recognition that advanced age, self-regulation of activity, and comorbidities may render patient-reported history insufficient. In the contemporary era, objective criteria should supplement subjective reports, and these are incorporated in the guideline recommendations. Similarly, the multi-society Appropriate Use Criteria consider stress test positivity “a surrogate for symptomatic AS,” making valve intervention “Appropriate regardless of surgical risk” and medical management “Rarely Appropriate.”³ Viewed through this lens, it is unclear whether all studies hewed to this approach. Selective exercise testing was performed in the 2020 randomized trial of very severe AS, with positive tests considered symptomatic,⁴ but the same group in 2010 expressed reticence toward exercise testing due to safety concerns.⁵ Bohbot and colleagues⁶ used exercise testing in 64%, Campo and colleagues⁷ in <30%, and the remainder of the studies in the meta-analysis did not discuss the role of exercise testing. Thus, whether patients would be classified as asymptomatic may vary between studies and contemporary practice. A uniform, guideline-directed approach is needed in future trials.

Dawn S. Hui, MD

CENTRAL MESSAGE

Studies in a meta-analysis of asymptomatic severe AS have wide variation in classifications of disease and management.

Another definition to be examined is that of “conservative management.” The more colloquial “watchful waiting” implies close monitoring for symptoms, with surgery reserved for the case of symptom development. However, several studies reported continued nonoperative management of patients despite symptom development. Here again, there is variability in inclusion criteria. Some restricted analysis to “potential surgical candidates” (without commenting on risk),^{4,5,7} one included only low surgical risk patients (European System for Cardiac Operative Risk Evaluation $\leq 4\%$),⁶ and one included patients “ineligible for surgery” in the conservative management arm.⁸ Further confounding the problem is that 2 studies^{9,10} did not appear to have stratified by any sort of intentional management strategy from the outset. Rather, patients were retrospectively stratified by whether they underwent aortic valve replacement. In observational studies of asymptomatic AS, this could be considered analogous to the difference in intention-to-treat analysis and as-treated analysis.

Management strategy was often described as being at the physicians’ discernment, or in contemporary literature as a shared decision of the patient and Heart Team.^{4,5} Scrutiny of this variable reveals a rather mixed bag. Campo and colleagues reported that 49% of patients undergoing early surgery did so for treatment of concomitant cardiac disease, whereas in other studies concomitant disease cases were excluded and patients who received early surgery had more severe AS, suggesting that the decision was primarily driven by the potential for valve disease progression.

From the Department of Cardiothoracic Surgery, University of Texas Health Science Center at San Antonio, San Antonio, Tex.

Disclosures: The author reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication July 12, 2020; revisions received July 12, 2020; accepted for publication July 14, 2020; available ahead of print July 18, 2020.

Address for reprints: Dawn S. Hui, MD, 7703 Floyd Curl Dr, Suite 211L, San Antonio, TX 78229 (E-mail: huid@uthscsa.edu).

J Thorac Cardiovasc Surg 2022;163:1786-8

0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2020.07.046>

Recommendations	COR	LOE
AVR is recommended for asymptomatic patients with severe AS (stage C2) and LVEF < 50%	I	B
AVR is indicated for patients with severe AS (stage C or D) when undergoing other cardiac surgery	I	B
AVR is reasonable for asymptomatic patients with very severe AS (stage C1, aortic velocity ≥ 5.0 m/s) and low surgical risk	IIa	B
AVR is reasonable in asymptomatic patients (stage C1) with severe AS and decreased exercise tolerance or an exercise fall in BP	IIa	B
AVR may be considered for asymptomatic patients with severe AS (stage C1) and rapid disease progression and low surgical risk	IIb	C

FIGURE 1. Multi-society guidelines for treatment of asymptomatic severe aortic stenosis. Adapted from Nishimura and colleagues,² 2014 AHA/ACC guideline for the management of patients with valvular heart disease. *COR*, Class of Recommendation; *LOE*, Level of Evidence; *AVR*, aortic valve replacement; *AS*, aortic stenosis; *LVEF*, left ventricular ejection fraction; *BP*, blood pressure.

Proposed prognostic parameters have included peak aortic jet velocity, rate of progression, valve calcification, and left ventricular mass in excess of the expected predicted value.^{11,12} This was confirmed by several studies in the meta-analysis, with significant correlations of echo parameters to cardiac death in the conservative management arm.^{5,8} These confounders would not have been adjusted for in the sensitivity analyses performed by Yokoyama and colleagues, and thus the potential for selection bias remains significant.

Reflecting on the reasons for poorer outcomes, there are several possibilities. If and when patients in the conservative strategy go on to surgery, they may experience greater operative mortality or poorer late clinical outcomes, due to worsening left ventricular hypertrophy and fibrosis during the waiting period. A recent registry study demonstrated that acute heart failure was associated with poorer outcomes in both surgical aortic valve replacement and transcatheter aortic valve replacement,¹³ and Taniguchi and colleagues⁸ found a greater operative mortality in the conservative arm (3.7% vs 1.2%, $P = .03$), although this was not reported in other studies that compared this metric.^{4,6,7} A more concerning possibility is that symptom development may go unrecognized, or that such patients may reject or be rejected for surgery at a later date. Brown and colleagues¹⁴ demonstrated that the absence of aortic valve replacement in asymptomatic patients with severe AS was the strongest independent predictor of late mortality. In the 3 studies reporting on continued nonoperative management for symptom development, the incidence was 22% (13 of 59) in the study with “potential candidates,”⁵ 46% (17 of 37) in the older study that did not specify surgical candidacy,¹⁵ and up to 51% in the study that included

surgery-ineligible patients. As discussed previously, the variation in inclusion criteria make it difficult to ascertain to what degree this plays a role in late outcomes.

Thus, interpreting the study of Yokoyama and colleagues requires attention to the variation of definitions and decision-making among the various studies. One may contend that this allows for assessment of real-world practices, which may be valuable in building an evidence basis. A need for a randomized trial of asymptomatic severe AS still exists. The ongoing Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis (AVATAR) trial¹⁶ may meet this need. In the meantime, we should remain clear-eyed about what is in the eye of the beholder with regards to “watchful waiting” of “asymptomatic” patients.

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Commentary: Early surgery versus conservative management of asymptomatic severe aortic stenosis: Is it time to rethink the guidelines?

Oliver J. Liakopoulos, MD

The debate about the optimal management of asymptomatic severe aortic stenosis (AS) is ongoing. Current European and US guidelines recommend surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement only in symptomatic patients with severe AS (class I).^{1,2} In the absence of symptoms and severe AS, only SAVR is currently indicated in the presence of an impaired left ventricular dysfunction (left ventricular ejection fraction <50%; class I) or abnormal exercise test

Oliver J. Liakopoulos, MD

CENTRAL MESSAGE

This systematic review with meta-analysis demonstrates the benefit of early surgery for asymptomatic patients with severe AS in terms of reduced all-cause and cardiovascular mortality.

From the Department of Cardiac Surgery, Kerckhoff Clinic, Campus Kerckhoff, University of Gießen, Bad Nauheim, Germany.

Disclosures: The author reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication Aug 16, 2020; revisions received Aug 16, 2020; accepted for publication Aug 17, 2020; available ahead of print Aug 20, 2020.

Address for reprints: Oliver J. Liakopoulos, MD, Department of Cardiac Surgery, Kerckhoff Clinic, Campus Kerckhoff, University of Gießen, Benekestr. 2-8, 61231 Bad Nauheim, Germany (E-mail: o.liakopoulos@kerckhoff-klinik.de).

J Thorac Cardiovasc Surg 2022;163:1788-9

0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2020.08.047>

result (class I). If none of these 2 criteria are fulfilled, SAVR is downgraded to a class IIa recommendation mainly for asymptomatic patients with very severe AS.

Current evidence is scarce with only a few observational studies showing improved survival with early aortic valve replacement in asymptomatic patients with AS compared to watchful waiting.³⁻⁵ However, important evidence was recently provided by the results of the multicentric RECOVERY trial that randomly assigned in a 1:1 ratio