## EDITORIAL



## **Timing of Intervention in Aortic Stenosis**

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Current guidelines require that in patients with severe aortic stenosis, symptoms related to the valvular disease be present for consideration of transcatheter aortic-valve replacement (TAVR) or surgical aortic-valve replacement.<sup>1,2</sup> In the absence of symptoms, only very severe aortic stenosis is an indication (class IIa) for intervention.<sup>1-3</sup>

Kang et al.3 now report in the Journal the results of a trial involving patients with asymptomatic, very severe aortic stenosis who were randomly assigned to surgical aortic-valve replacement or conservative care (clinical follow-up and observation). Outcomes (death during or within 30 days after surgery [operative mortality] or death from cardiovascular causes; death from any cause; and hospitalization for heart failure) were significantly better among patients who underwent surgical aortic-valve replacement promptly (within approximately 2 months after randomization) than among those who were randomly assigned to the conservative-care group. These benefits started early and persisted over 8 years, and — impressively the number needed to treat to prevent one death from cardiovascular causes within 4 years was 20 patients.

It is remarkable that the operative mortality among patients in both the early-surgery group and the conservative-care group was zero, and this includes approximately 17% of the patients in the conservative-care group for whom urgent surgical aortic-valve replacement was indicated because of acute cardiac decompensation. The rather small number of deaths from any cause (5 in the early-surgery group and 15 in the conservative-care group) does constitute a limitation of the trial. Nonetheless, taken at face value, these results certainly confirm the unreliability of symptoms

as a guide to the timing of surgery in patients with aortic stenosis, especially in the elderly or when lifestyle adjustments or coexisting medical conditions limit activity or confound symptoms attributable to valvular disease.

However, in interpreting the trial results, it is important to take the patient population into account. First, the populations of patients in recent TAVR trials, as compared with the population in this trial, include patients who are typically approximately two decades older and have clinically significant coexisting medical conditions, and they do not include patients with congenital bicuspid valves. Furthermore, in the trial conducted by Kang et al., the patients had very severe aortic stenosis (defined as an aortic-valve area of ≤0.75 cm<sup>2</sup> with either a peak aortic jet velocity of ≥4.5 m per second or a mean transaortic gradient of ≥50 mm Hg), and many of these patients would have met the current class IIa criteria for intervention (according to data from Doppler echocardiography and symptoms during exercise testing or the presence of left ventricular systolic dysfunction).

So, although the trial by Kang et al. has certainly emphasized the challenge of ascertaining valve-related symptoms in the real world, direct extension of these results to patients with asymptomatic severe aortic stenosis cannot be made at this time. We will have to await the results of large, randomized studies of early TAVR in patients with asymptomatic severe aortic stenosis for further guidance. These studies include AVATAR (Aortic Valve Replacement versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis; Clinical Trials.gov number, NCT02436655), EVOLVED (Early Valve Replacement Guided by Biomarkers

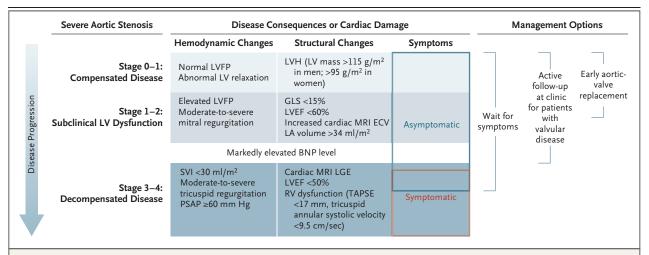


Figure 1. An Approach to Staging in Severe Aortic Stenosis.

The consequences of aortic stenosis are characterized by distinct intracardiac hemodynamics and structural abnormalities. The staging approach shown allows for assessment of the risk of aortic stenosis and influences the follow-up plan, timing of interventions, and indications for intervention. The active follow-up strategy involves scheduling frequent follow-up (typically every 3 to 6 months) and may include stress testing to assess for symptoms that may not otherwise be apparent. The timing of surgery (as indicated by the ranges covered by each management option) is likely to be later in the course of disease with the strategies of waiting for the development of symptoms and active follow-up. Markedly elevated levels of B-type natriuretic peptide (BNP) (3 times the upper limit of the normal range corrected for age and sex) typically occur with the development of decompensated disease. Extracellular volume (ECV) is measured with cardiac magnetic resonance imaging (MRI) T1 mapping to estimate diffuse fibrosis. Global longitudinal strain (GLS) is assessed by means of echocardiography. Late gadolinium enhancement (LGE) is used to evaluate replacement fibrosis. LA denotes left atrial, LV left ventricular, LVEF left ventricular ejection fraction, LVFP left ventricular filling pressure, LVH left ventricular hypertrophy, PSAP pulmonary-artery systolic pressure, RV right ventricular, TAPSE tricuspid annular plane systolic excursion, and SVI stroke volume index.

of LV Decompensation in Asymptomatic Patients with Severe AS; NCT03094143), ESTIMATE (Early Surgery for Patients with Asymptomatic Aortic Stenosis; NCT02627391), and EARLY TAVR (Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis; NCT03042104). Also, although the excellent surgical outcomes in this trial may speak to the surgical expertise of the centers involved, the findings cannot be extended confidently to centers with less expertise.

The trial by Kang et al. highlights another issue. Although surgical aortic-valve replacement was indicated for approximately 78% of the patients in the "wait and watch" conservative-care group, it is intriguing that 22% of the patients in this group never underwent surgery. Given that urgent surgical aortic-valve replacement was indicated in 17% of the patients and the time to surgery ranged from approximately 9 months to 4 years, this was a heterogeneous population of patients in whom the structural and functional abnormalities of the heart varied or in whom the valvular disease progressed at varied rates.<sup>5</sup> The

patients in the conservative-care group who did not undergo surgery may have been those who had less cardiac damage or in whom the disease progressed slowly.

This leads to the question of how best to assess risk among patients with aortic stenosis, formulate a follow-up plan, decide on the timing of intervention, and devise a management strategy. Given that there appears to be a continuous increase in risk starting at a mean aortic-valve gradient of approximately 20 mm Hg,6 staging aortic stenosis instead of classifying the valvular lesion only according to data from Doppler imaging appears to be the best approach. Staging the disease includes assessing structural abnormalities of the heart, considering other hemodynamic cardiac abnormalities, and assessing the biomarker profile.7-9 This multipronged method integrates assessment of risk-based disease severity and disease progression and permits the formulation of a follow-up and management plan for each patient with aortic stenosis. An approach to staging in severe aortic stenosis is shown in Figure. 1. In a time of rapidly evolving transcatheter-valve therapies, this framework of risk assessment in patients with aortic stenosis is perhaps best achieved in clinics that are dedicated to the care of patients with more than mild valvular disease to maximize the benefit of timely treatment.<sup>5</sup>

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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