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EDITORIAL COMMENT

What Is the Cost of a "Watchful Waiting" Strategy in Asymptomatic Severe Aortic Stenosis?

Ole De Backer, MD, PhD, Arif Khokhar, BM BCh, MA

Managing patients with asymptomatic severe aortic stenosis (AS) is an emerging clinical conundrum. Prolonged exposure to increased afterload can lead to gradual deterioration of cardiovascular (CV) health, with significant prognostic implications.[1] This subclinical damage may progress silently and, in some cases, result in sudden and unpredictable clinical decline, which in the extreme may lead to sudden cardiac death. Recent evidence suggests that early aortic valve replacement (AVR) in these asymptomatic patients could potentially prevent this (sub)clinical deterioration.[2-4] However, treating asymptomatic patients with procedures that carry inherent risks and uncertain lifetime management considerations remains a controversial topic.

In this context, the EARLY TAVR (Evaluation of TAVR Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis) trial, a pivotal randomized controlled trial, provides critical insights.[5] It enrolled 909 patients with stress test-confirmed asymptomatic severe AS who were randomized to undergo early transcatheter AVR (TAVR) or to a clinical surveillance strategy. In the intention-to-treat analysis, early TAVR significantly reduced the composite primary endpoint of death, stroke, and unplanned CV hospitalization. Notably, in the surveillance group, 87% of patients eventually received AVR, referred to as delayed AVR, at a median follow-up of 3.8 years.

In this issue of *JACC: Cardiovascular Interventions,* Généreux et al[6] present a prespecified analysis from the EARLY TAVR trial, comparing outcomes between patients who underwent early TAVR (n = 444) and those who underwent delayed AVR (n = 388) in the surveillance group. At 2 years postprocedure, patients in the delayed AVR cohort experienced a higher incidence of death, stroke, and heart failure hospitalization (10.6% vs 6.8%; HR: 0.61; $P = 0.045$). Uniquely, the study stratified patients undergoing delayed AVR into 2 phenotypes on the basis of clinical presentation and preprocedural echocardiography: acute valve syndrome (AVS) and progressive valve syndrome (PVS). Interestingly, patients presenting with AVS (40%) were generally older, had higher rates of atrial fibrillation and diabetes, and were less able to perform treadmill testing compared with the PVS group (60%). At 2-year follow-up, patients presenting with AVS who underwent delayed AVR had a markedly higher composite risk for death, stroke, or heart failure hospitalization compared with those treated with early TAVR (14.9% vs 6.8%; HR: 2.37; $P = 0.003$), driven mainly by a higher stroke rate (8.3% vs 2.7%; HR: 3.11; $P = 0.007$). Conversely, no significant differences were observed between early TAVR and delayed AVR in the PVS subgroup. Multivariate analyses identified predictors of AVS development at baseline, including inability to perform treadmill testing, diabetes, elevated N-terminal pro-B-type natriuretic peptide levels, and increased left atrial volume index.[6]

A notable limitation of the EARLY TAVR trial is its open-label design, which may have contributed to a surge in early unplanned CV hospitalizations because of patients' developing symptoms in the surveillance group. Consequently, about one-half of the patients in the clinical surveillance group transitioned to delayed AVR within the first year, mostly because of

From The Heart Center, Rigshospitalet, Copenhagen, Denmark.
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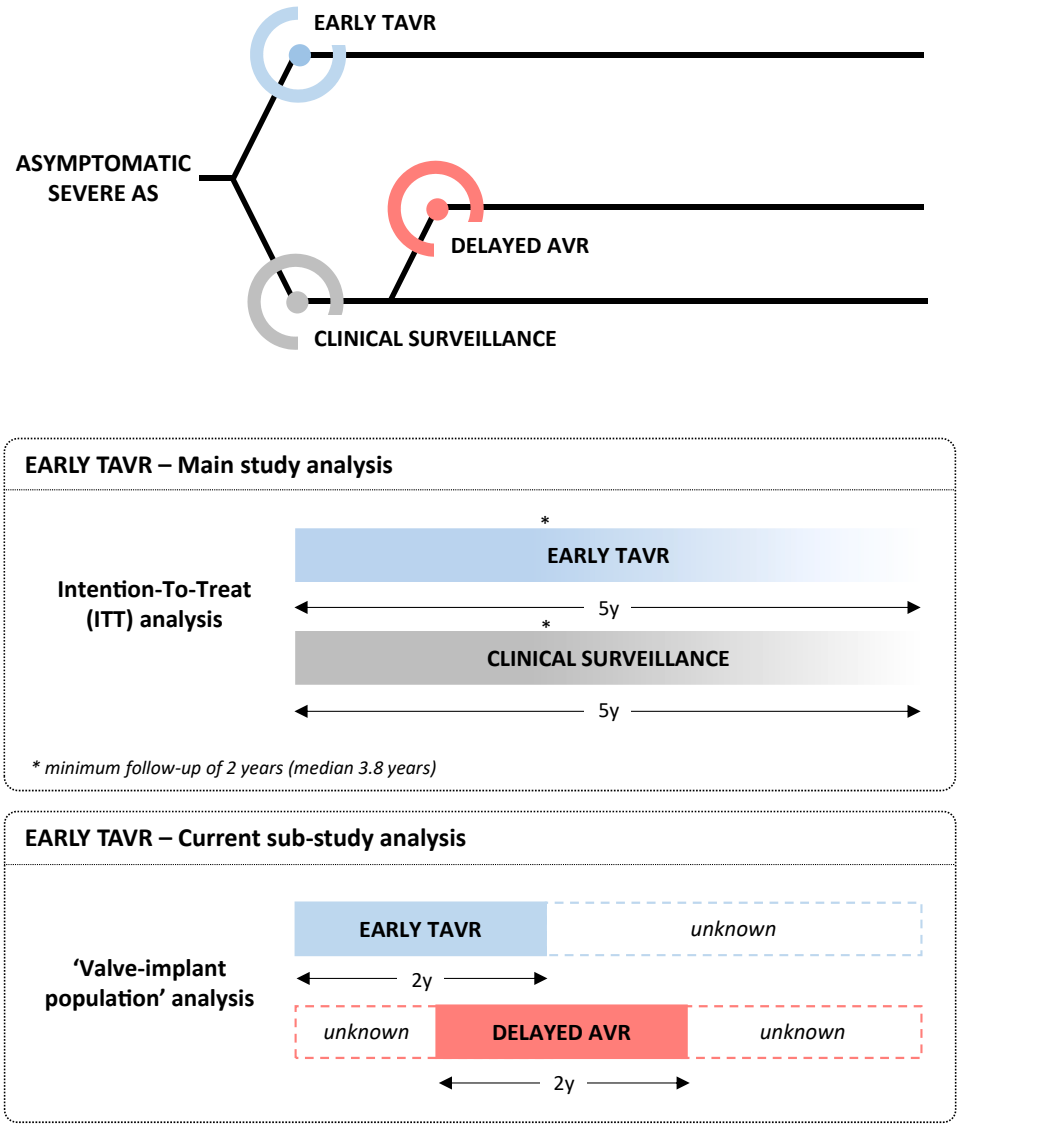
FIGURE 1 Comparison of the Intention-to-Treat and Valve Implant Analyses From the EARLY TAVR Trial



AS = aortic stenosis; AVR = aortic valve replacement; EARLY TAVR = Evaluation of TAVR Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis; ITT = intention-to-treat; TAVR = transcatheter aortic valve replacement.

the onset of symptoms. This effectively means that in the present substudy by Généreux et al,[6] the comparison between early TAVR and delayed AVR reflects a comparison between the treatment of asymptomatic and symptomatic severe AS patients, albeit with different time frames. Early TAVR was performed shortly after randomization, whereas delayed AVR was performed following the onset of symptoms. The period before symptom onset in the delayed AVR group is not accounted for, which limits definitive conclusions (Figure 1). A more comprehensive long-term analysis, following all patients from randomization to a predefined endpoint, would better clarify whether early intervention offers advantages or if delaying AVR until symptoms appear remains a suitable approach.

Nonetheless, this study offers valuable insights. It is the first to directly compare the clinical profiles, underlying myocardial damage, and outcomes of asymptomatic vs symptomatic severe AS patients undergoing TAVR, with both groups being well matched initially. The classification of symptomatic

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severe AS patients into AVS and PVS phenotypes is a novel approach, analogous to acute and chronic coronary syndromes, and captures the unpredictable natural evolution of severe AS. The finding that nearly 40% of patients managed conservatively progressed to AVS within a relatively short interval underscores the risks associated with a "watchful waiting" approach.

This evidence emphasizes the concept that once a patient progresses to "echocardiographically confirmed" severe AS, they enter an unpredictable and vulnerable phase, during which silent progression can eventually lead to sudden deterioration. In case of asymptomatic severe AS, the conventional "watchful waiting" strategy may be harmful for certain patients at risk for rapid decline. This presents a 2-fold challenge. First, identifying which patients are at increased risk for acute deterioration and who may benefit from earlier intervention. Second, determining the optimal "golden moment" for intervention in patients with moderate to severe AS; balancing the concerns of lifetime management and valve durability with early intervention, against the risks for worsening cardiac damage and suboptimal longer term outcomes with delayed intervention.

To date, numerous attempts to pinpoint at-risk individuals using biomarkers, echocardiography, or myocardial tissue analysis with cardiac magnetic resonance imaging have produced mixed results.[7,8] Future strategies that combine biomarkers, multimodal imaging, and machine learning techniques may prove to be more promising. Ongoing randomized controlled trials, such as EASY-AS (Early Valve Replacement in Severe Asymptomatic Aortic Stenosis Study; NCT04204915), DANAVR (Danish National Randomized Study on Early Aortic Valve Replacement in Patients With Asymptomatic Severe Aortic Stenosis; NCT03972644), and the Evolut™ EXPAND TAVR II Pivotal Trial (NCT05149755), are expected to shed further light on this issue. Until then, the traditional teaching of Braunwald—that AVR should be planned only when symptoms develop—should be re-evaluated. Instead, the contemporary approach advocated by Généreux et al[6] instructs us to worry even when severe AS patients are asymptomatic. The key question of exactly when to worry remains to be solved.

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ADDRESS FOR CORRESPONDENCE: Dr Ole De Backer, The Heart Center, Rigshospitalet, Inge Lehmanns Vej 7, Copenhagen 2100, Denmark. E-mail: ole.debacker@gmail.com.

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