LITERATURE HIGHLIGHTS

Study Endpoint Finds Early TAVR Superior to Clinical Surveillance for Asymptomatic, Severe Aortic Stenosis

With Hemal Gada, MD

In a cohort of patients with asymptomatic, severe aortic stenosis (AS), Généreux et al found that early transcatheter aortic valve replacement (TAVR) was superior to clinical surveillance in reducing the primary composite endpoint of death, stroke, and unplanned hospitalization due to cardiovascular causes. The results were published in *The New England Journal of Medicine*.[1]

The EARLY TAVR trial is a prospective, multicenter, open-label, randomized controlled trial designed to evaluate TAVR with the Sapien 3 or Sapien 3 Ultra balloon-expandable valve (Edwards Lifesciences) as compared with guideline-directed clinical surveillance.[2]

Patients aged ≥ 65 years with asymptomatic, severe AS and suitable anatomy for transfemoral TAVR were randomized 1:1 to either TAVR or clinical surveillance. All randomized patients were part of the intention-to-treat population.

The primary endpoint was a composite of any-cause death, stroke, or unplanned hospitalization for cardiovascular causes. Secondary endpoints included favorable outcome at 2 years (Kansas City Cardiomyopathy Questionnaire [KCCQ] score of ≥ 75 points that had not decreased > 10 points from baseline); a composite of left ventricular (LV) and left atrial health at 2 years; change in LV ejection fraction (LVEF) from baseline to 2 years; new-onset atrial fibrillation; and a composite of death or disabling stroke.

Edwards Lifesciences funded the trial, participated in site selection, oversaw data collection and monitoring, and performed statistical analyses. Endpoints and outcomes were adjudicated by an independent clinical events committee, which was not blinded to treatment group assignments.

KEY FINDINGS

- An early TAVR strategy was superior to clinical surveillance in reducing the primary composite endpoint.
- Favorable outcome at 2 years, as measured by the KCCQ score, and integrated measures of LV and left atrial health were better in TAVR versus clinical surveillance patients.
- 95.2% of living clinical surveillance patients eventually underwent aortic valve replacement during follow-up.

Of 1,578 patients screened from March 2017 to December 2021, 901 were randomized at 75 sites in the United States and Canada (445 to TAVR and 446 to clinical surveillance; mean age, 75.8 years; 30.9% women; mean Society of Thoracic Surgeons Predicted Risk of Mortality score, 1.8%; 83.6% considered low surgical risk). AS severity was similar between groups, mean LVEF was 67.4%, and mean KCCQ score was 92.7 in both groups.

Median follow-up was 3.8 years, with data available for analysis for 97.1% and 97.5% in the TAVR and clinical surveillance groups, respectively. The primary composite endpoint occurred in 26.8% (122 patients) in the TAVR group

versus 45.3% (202 patients) in the clinical surveillance group (hazard ratio, 0.50; 95% CI, 0.40-0.63; $P < .001$).

For the secondary endpoints, 86.6% of patients in the TAVR group had a favorable outcome at 2 years as determined by KCCQ score versus 68.0% in the clinical surveillance group ($P < .001$), and 48.1% in the TAVR group had integrated measures of LV and left atrial health versus 35.9% in the clinical surveillance group ($P = .001$). Change in LVEF, new-onset atrial fibrillation, and composite of death or disabling stroke were similar between groups.

During follow-up, 87% (388/446) of patients in the clinical surveillance group, or 95.2% of at-risk patients, underwent aortic valve replacement (median time from randomization to conversion to aortic valve replacement, 11.1 months; interquartile range, 5.0-19.7 months). Procedure-related adverse events were not different between the clinical surveillance group converted to aortic valve replacement and those in the TAVR group.

The investigators noted some study limitations, including that the members of the independent clinical events committee were unblinded to treatment assignments, the patient population was mainly White and at low surgical risk with suitable anatomy, and only one device was used in this trial and thus findings cannot be applied to other valves.

The study demonstrated superiority of early TAVR over clinical surveillance for the primary composite endpoint. Clinical surveillance was associated with a decrease in quality of life as measured by the KCCQ and worsening LV and left atrial function, highlighting that progression of AS is unpredictable. Long-term follow-up is ongoing, noted the investigators.

1. Généreux P, Schwartz A, Oldemeyer JB, et al. Transcatheter aortic valve replacement for asymptomatic severe aortic stenosis. N Engl J Med. 2025;392:217-227. doi: 10.1056/NEJMoa2405880
2. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021;77:e25-e197. doi: 10.1016/j.jacc.2020.11.018

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Study coauthor Hemal Gada, MD, expands on the study's findings and their implications for practice.

How do these findings apply to real-world practice? Should screening and monitoring efforts for AS be augmented to identify patients who might benefit from TAVR sooner?

This trial taught us that it's a good idea to get ahead with these patients and consider some additional testing to shed light on any symptoms. For this trial, we had to demonstrate lack of symptoms and used a treadmill test, which I would characterize as a historically underutilized assessment for this condition. Over 40% of patients who consented for this study were excluded for randomization, and many of these patients had a positive treadmill test. This highlighted the importance of performance metrics and electrocardiographic and hemodynamic findings that should be used to objectively define symptom status. My advice to physicians who are taking their patient's word for their "asymptomatic" status—I wouldn't do that. Do the treadmill test; it's worthwhile to obtain these results to objectively assess the presence or absence of symptoms or worrisome signs because that definitely makes a difference for a patient.

Although not statistically significant, you noted that an unexpected finding was that strokes occurred more frequently in the clinical surveillance group than the TAVR group (6.7% vs 4.2%). What might explain this finding, and should this be further investigated in future studies?

It's hard to say. I think that given the really high crossover rate, or aortic valve replacement conversion, upwards of 70% at 2 years, it's tough for us to drill down into these statistics and discern any kind of clinically meaningful evidence that strokes would be potentially attributed to some mechanism for one arm versus another.

Among the living clinical surveillance patients, over 95% underwent aortic valve replacement at 5 years. What is the main takeaway from this finding, and how should it impact initial discussion and decision-making surrounding TAVR for those presenting with asymptomatic, severe AS?

I think this is one of the limitations of this study. Obviously, there was no sham control group, and the preponderance of patients who enrolled in this trial wanted to receive TAVR. They were well-educated, knew that they were asymptomatic, had likely done the treadmill test, and ostensibly, at least in our practice, were geared up to hopefully

undergo TAVR but did not meet any kind of commercial indication for it. For patients who were then randomized into the clinical surveillance arm, it may have been difficult for them to stomach that. It is curious that we found that high level of crossover in a short period of follow-up, with almost half the patients in the study crossing over from the clinical surveillance arm at 1 year. What this does is heighten our focus on ensuring that we provide thoughtful, shared decision-making with these patients, we objectively assess them with the treadmill stress test, and we then avail them of their options should they be symptomatic or have worrisome signs from that evaluation. Those were my takeaways, given that the unplanned hospitalization rate and not mortality drove the primary endpoint, and the hospitalization for an aortic valve replacement within 6 months after randomization itself counted toward the primary endpoint in the clinical surveillance arm. This 6-month time point really defined the delta between the two arms as it relates to the primary endpoint.

In your own practice, how do you select appropriate patients for early TAVR consideration?

I think that a lot of this revolves around the treadmill test, and I would say that having a good stress lab with a cardiologist who oversees these studies and does not stop the test prematurely is essential. A lot of these folks are older, but they still need to get to a certain level of exertional capacity to truly determine if TAVR could be pursued, whether that's getting to an 80% maximal predicted heart rate goal or the 60% age-predicted metabolic equivalent goal. This is something that our cardiologists should be doing when they're subjecting these patients to stress tests; do not stop the test prematurely because they think the patient did well enough or they're complaining of nonspecific fatigue. That objective level of evidence from the treadmill test is so important. I'm hopeful that we utilize this form of metric-based evaluation going forward as we select who would potentially benefit from having a TAVR when the patient's current quality of life is not seemingly being trammeled. I think the treadmill is an essential tool to identify folks who are going to be in trouble down the road. ■

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