OPINION ARTICLE

Aortic Stenosis and Transcatheter Aortic Valve Replacement: A Real or Illusory Shift in the Landscape?

Estenosis aórtica y reemplazo valvular endovascular: cambio del escenario, ¿real o ficticio?

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Two recently reported clinical trials aimed to address clinically relevant questions.

Their conceptual foundations were as follows:

a) The increase in afterload caused by aortic stenosis (AS), even moderate, may worsen left ventricular function. In symptomatic patients, transcatheter aortic valve replacement (TAVR) improves the quality of life and the long-term prognosis.
b) Asymptomatic severe AS without a current indication for TAVR tends to progress over a short period of time. In asymptomatic patients, TAVR prevents the onset of symptoms and potential deterioration of ventricular function, allowing the procedure to be performed in better clinical condition.

TAVR UNLOAD trial (1)

Objective

To estimate the probable superiority of TAVR in symptomatic patients with moderate AS and reduced ventricular function in relation to the conservative surveillance strategy and eventual intervention in case of progression to severe AS.

Design

Multicenter (66 centers in the United States, the Netherlands and Austria), controlled (open-label) and randomized study with assignment to TAVR or control arms.

Inclusion criteria

Moderate AS: valve area 1-1.5 cm2. If valve area ≤1 cm2 and suspected low-flow low-gradient at rest, dobutamine stress Doppler echocardiography is used to define the actual area.

Left ventricular ejection fraction (LVEF): 20% to 50%.

Symptoms: functional class (FC) II to IV.

Endpoint

Hierarchical combined endpoint of all-cause death, disabling stroke, heart-failure hospitalization, change from baseline on the Kansas City Cardiomyopathy Questionnaire (to assess patient's quality of life).

Statistics

Win Ratio (WR) with hierarchical endpoint according to the previous order.

Original sample size: 600 patients. There was an extension of the follow-up period due to the study low recruitment rate, which started in January 2017 and ended in December 2022.

Number of patients: 178; 89 in the TAVR arm and 89 in the control arm.

Mean follow-up: 23 months.

Baseline characteristics

Age: 77.4 ± 7.2 years; 20.8% women; Society of Thoracic Surgeons (STS) score: 4.4 ± 3.4; functional class (FC): 95% II/III; coronary artery disease: 76%; implantable cardioverter defibrillator (ICD): 62%; previous stroke: 9%; peripheral vascular disease: 22%; previous heart failure hospitalization: 45%; atrial fibrillation: 25%; frailty: 27%; Kansas score: 55.8 ± 23.1; aortic valve area: 1.2 ± 0.2cm^2; mean transaortic gradient: 21.9 ± 6.8 mmHg; LVEF: 39 ± 9.6%.

Crossover: 43% of the control arm crossed over to the TAVR arm due to progression from moderate to severe AS.

Results

This study did not demonstrate the superiority of TAVR over the control:

- No difference in the primary endpoint: WR 1.31 (95% CI 0.81-1.88), not significant.
- Significant difference in favor of TAVR over the

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Kansas score.
- No difference in mortality, major vascular events, stroke, hospitalization, and other outcomes.
- Feasibility of the procedure and a low complication rate.

Questions raised from the TAVR UNLOAD trial

a) Could the population characteristics have affected the result?

The high rate of associated comorbidities may suggest that the additional prognostic burden arising from the moderate AS is less significant. In symptomatic patients with moderate AS and reduced ventricular function, but a lower burden of comorbidities, the result is likely to differ.

b) What is the methodological question?

Lack of power: high false-negative rate, close to 70%, due to the small sample size.

Change in methodology: as a result, the follow-up period was extended, and due to the low enrollment rate, the statistical analysis was ultimately performed with the available data.

High crossover rate from the control group to the TAVR group

Although the WR is a validated methodology in multiple clinical trials, time-to-event analysis (Cox model) is the standard design in follow-up studies.

c) Why was there such a low enrollment rate?

There are several possible reasons:

The COVID-19 pandemic (although the study inclusion period extended beyond the pandemic itself).

Lack of an adequate referral strategy from low-to-high complexity centers within the study network (as suggested by the authors).

Perhaps for general practitioners, the objective of the study did not raise a clinically valid question, either because this was not appropriate to perform the TAVR, or, conversely, because the it was fully justified.

d) Does the symptomatic improvement reflected by the Kansas score alone justify the superiority of the procedure?

Although data is objective, it has less value because this was an open-label study, which limits the conclusions that can be drawn from it. Moreover, 43% of patients in the control group crossed over to the TAVR arm.

e) Why was crossover to the TAVR are not included in the combined endpoint?

It would not have substantially changed the results: in the control group, the rates of all-cause mortality, stroke and hospitalization were influenced by the patients who ultimately underwent TAVR. Furthermore, the indication for intervention was probably considered a more subjective criterion than the assessment of the functional status using the Kansas score.

f) How can the results of the TAVR UNLOAD trial be translated into clinical practice?

A logical conclusion would be to wait for the results of trials providing solid evidence without methodological flaws. However, from a strictly personal perspective, the clinical approach to managing symptomatic patients with moderate AS and reduced LVEF is unlikely to change. We will return to this point later.

EARLY TAVR trial (2)

Objective

To evaluate whether TAVR is superior to a conservative strategy (clinical surveillance) in patients with asymptomatic severe AS and preserved ventricular function.

Design

Multicenter (75 centers in the United States and Canada), controlled (open-label) and randomized study with assignment to TAVR or control arms.

Inclusion criteria

Age >65 years old.
Severe AS suitable for transfemoral TAVR.
LVEF >50%.
Absence of symptoms (assessed via exercise stress test in more than 90% of cases).

Endpoint

Combined endpoint of all-cause death, stroke, cardiovascular hospitalization (including crossover to TAVR in the control arm).

Statistics

Time to first event (Kaplan Meier, Cox model).

Original sample size: 900 patients. No changes to the original protocol

Number of patients: 901, 455 in the TAVR arm and 466 in the control arm, who were recruited from March 2017 to December 2021.

Mean follow-up: 3.8 years.

Baseline characteristics

Age: 76 ± 6 years; STS score 1.8; 30.9% women; coronary artery disease: 27%; previous stroke: 4.3%; peripheral vascular disease: 6%; possibility of performing exercise stress test: 90%; atrial fibrillation: 15%; aortic valve area: 0.85 ± 0.20 cm2; mean transaortic gradient: 47 ±10 mmHg; LVEF: 67.4 ± 6.6%.

Crossover: No crossover (the procedure in the control arm was included as part of the endpoint).

Results

The TAVR arm was superior to the conservative strategy control (Table 1).
- Significant reduction in the endpoint.
- No difference in mortality or stroke.
- Significant difference in unplanned hospitalization (motivated by the procedure in the control arm).
- 71% of control patients underwent the procedure at 24 months, one third of them due to advanced or severe symptoms.

QUESTIONS RAISED FROM THE EARLY TAVR TRIAL

a) Are there any methodological issues as in the TAVR UNLOAD trial?

Clearly not. As above noted, there was no crossover in the control arm, as the need to undergo TAVR in this arm was a component of the endpoint.

b) If the inclusion criterion was >65 years, why was the mean age 76 years and 95% of patients aged between 70 and 82 years?

This is striking. It is likely that younger patients were not referred because treating physicians usually recommend valve replacement in young patients with severe AS, even if they are asymptomatic.

c) Does the population included in this study differ from that of the TAVR UNLOAD trial?

The difference is evident in terms of comorbidities.

If prognosis is considered as the algebraic sum of the AS severity and the burden of comorbidities, in the TAVR UNLOAD trial it leaned more toward the associated diseases, whereas in the EARLY TAVR trial, it leaned more toward the valve disease itself.

In this study, all-cause mortality was 8.5% over a 47-month follow-up compared to 19% over an average 23-month follow-up in the TAVR UNLOAD trial.

d) How can the results of the study be translated into clinical practice?

The difference in favor of TAVR was driven by the high rate of intervention-related hospitalizations in the control group (86% at 3 years).

In a broader context, this was an open-label trial, in which the decision to perform the procedure was left to the physician's discretion, which, in the absence of differences in mortality, becomes a factor to be considered.

e) Therefore, is it feasible to wait and perform the procedure only upon the onset of symptoms?

In theory, based on the study results, it is feasible to wait, which could be defined as "watchful surveillance" with eventual intervention depending on progression. However, is this a usual strategy in everyday clinical practice? Probably. But in any case, the EARLY TAVR trial merely reinforces a common behavior, even if it is not always explicitly stated.

OVERALL CONCLUSION

It is highly likely that neither study will substantially alter the clinical approach followed in most high-complexity centers. Several factors support this conclusion.

In the presence of symptoms, a mean transvalvular gradient of 20 to 40 mmHg and associated comorbidities, the question often arises as to whether this represents true moderate AS or severe AS with low-flow low-gradient. Although different assessment criteria may be used (dobutamine stress Doppler echocardiography, calcium score, stroke volume), reaching a differential diagnosis is usually challenging.

The second issue concerns whether the symptoms are attributable to the valve disease or to associated comorbidities or, even better, in what proportion both conditions are involved.

Therefore, it is clear that, in the presence of symptoms, both aspects create a favorable scenario for TAVR to be considered a strong option, particularly when procedural risk is low.

A similar situation occurs in asymptomatic severe AS, where close and strict clinical surveillance is inherently challenging for several reasons. The progression of severity may be insidious, and its assessment is often complex due to the inherent variability of the assessment method. Moreover, the frequency of follow-up visits and the progressive limitation of physical activity on medical advice, may negatively impact the patient's lifestyle. In this context, such factors may become more limiting than those experienced after the procedure itself. Of course, a sine qua non condition is that the procedure must be a low-risk.

Although valve replacement for asymptomatic severe AS is not typically advocated at round tables, conferences or expert meetings, the proportion of patients managed with watchful waiting strategy alone may be minimal: when procedural risk is low, TAVR is often proposed at the slightest suspicion of symptoms –sometimes loosely related to the valve disease.

The above considerations are supported by evidence from the literature.

In the TAVR UNLOAD trial, at two years, 32% of patients in the control arm were hospitalized for heart failure. In addition, 43% underwent TAVR. By comparison, only 15% were hospitalized or underwent TAVR over two years in an observational study of patients with moderate AS and ventricular dysfunction. (3)

Similarly, in the EARLY TAVR trial, the likelihood of hospitalization leading to crossover to TAVR in the control arm was 71% at two years, significantly higher than that reported in an observational study by the Mayo Clinic (622 patients with asymptomatic severe AS), where only 33% developed symptoms or underwent the procedure. (4)

Taken together, these findings suggest that, in these trials, disease progression in the control arm was interrupted by the procedure in a much higher proportion than previously observed in observational studies. This may have influenced the results of the TAVR UNLOAD and EARLY TAVR trials.

It worth noting that in both studies, TAVR proved to be very safe –with no intraprocedural mortality and a low rate of serious complications– even in the higher-risk TAVR UNLOAD population. This is a key aspect, as physicians must consider procedural risk when making clinical decisions. The findings of both studies rely on the availability of a highly safe procedure. If the procedure risks were higher, the results and conclusions would likely differ significantly.

Another relevant aspect, particularly in the EARLY TAVR trial, is the relative safety of the close clinical surveillance strategy. Patients did not experience

Table 1. Primary endpoints of EARLY TAVR trial. Modified from (2)

Primary Endpoint	TAVR	Control	HR (95% CI)	p-value
Combined (%)	122 (26.8)	202 (45.3)	0.50 (0.40-0.63)	<0.001
Death (%)	38 (8.4)	41 (9.2)	0.93 (0.60-1.44)	-
Stroke (%)	19 (4.2)	30 (6.7)	0.62 (0.35-1.10)	-
Unplanned CV hospitalization (%)	95 (20.9)	186 (41.7)	0.43 (0.33-0.55)	-

CV, cardiovascular; HR, hazard ratio; 95% CI, 95% confidence interval; TAVR, transcatheter aortic valve replacement.

serious events; the main "consequences" were clinical progression, unscheduled hospitalizations or some deterioration in echocardiographic parameters. In other words, if access to a very low-risk TAVR is not available, the strategy of close clinical surveillance seems to be a good option –provided it includes frequent clinical follow-up visits, echocardiographic assessments and regular stress testing.

It is possible that, in the medium term, clinical practice guidelines will include this procedure in these patients as a Class IIa recommendation, provided that both the patient's risk profile and the center's outcomes ensure a very high probability of success in percutaneous implantation, with a very low rate of complications.

In conclusion, regardless of the results of both studies, it is likely that a significant proportion of symptomatic patients with moderate AS and ventricular dysfunction will continue to be referred for TAVR, just as occurs in cases of severe AS –even in the absence of symptoms. Those who choose clinical surveillance should implement it systematically and according to protocol in order to identify potential patients who may experience disease progression.

Conflicts of interest

None declared.
(See authors' conflict of interests forms on the web/Additional material).

Ethical considerations

Not applicable.

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