JACC: ADVANCES VOL. 3, NO. 3, 2024

ORIGINAL RESEARCH

VALVULAR HEART DISEASE

Quantifying the Survival Loss Linked to Late Therapeutic Indication in High-Gradient Severe Aortic Stenosis

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ABSTRACT

BACKGROUND International guidelines recommend aortic valve replacement (AVR) as Class I triggers in high-gradient severe aortic stenosis (HGSAS) patients with symptoms and/or left ventricular ejection fraction (LVEF) <50%. The association between waiting for these triggers and postoperative survival penalty is poorly studied.

OBJECTIVES The purpose of this study was to examine the impact of guideline-based Class I triggers on long-term postoperative survival in HGSAS patients.

METHODS 2,030 patients operated for HGSAS were included and classified as follows: no Class I triggers (no symptoms and LVEF >50%, n = 853), symptoms with LVEF >50% (n = 965), or LVEF <50% regardless of symptoms (n = 212). Survival was compared after matching (inverse probability weighting) for clinical differences. Restricted mean survival time was analyzed to quantify lifetime loss.

RESULTS Ten-year survival was better without any Class I trigger than with symptoms or LVEF <50% (67.1% ± 3% vs 56.4% ± 3% vs 53.1% ± 7%, respectively, $P < 0.001$). Adjusted death risks increased significantly in operated patients with symptoms (HR: 1.45 [95% CI: 1.15-1.82]) or LVEF <50% (HR: 1.47 [95% CI: 1.05-2.06]) than in those without Class I triggers. Performing AVR with LVEF >60% produced similar outcomes to that of the general population, whereas operated patients with LVEF <60% was associated with a 10-year postoperative survival penalty. Furthermore, according to restricted mean survival time analyses, operating on symptomatic patients or with LVEF <60% led to 8.3- and 11.4-month survival losses, respectively, after 10 years, compared with operated asymptomatic patients with a LVEF >60%.

CONCLUSIONS Guideline-based Class I triggers for AVR in HGSAS have profound consequences on long-term post-operative survival, suggesting that HGSAS patients should undergo AVR before trigger onset. Operating on patients with LVEF <60% is already associated with a 10-year postoperative survival penalty questioning the need for an EF threshold recommending AVR in HGSAS patients. (JACC Adv 2024;3:100830) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.100830

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AS = aortic valve stenosis

AVA = aortic valve area

AVR = aortic valve replacement

CAD = coronary artery disease

ESC/EACTS = European Society of Cardiology/European Association for Cardio-Thoracic Surgery

HGSAS = high-gradient severe aortic stenosis

IPW = inverse probability weighting

LV = left ventricular

LVEF = left ventricular ejection fraction

RMST = restricted mean survival time

SAS = severe aortic valve stenosis

Aortic valve stenosis (AS) affects 5% of adults >65 years old and is associated with a high mortality burden if not timely treated.[1] Due to the aging population and inherent progressive disease pattern, an increasing number of patients require aortic valve replacement (AVR).[2] Indeed, without effective pharmaceutical treatment, AVR is the only intervention that can alter the patient's prognosis.[3] Severe AS (SAS) in its typical form, that is, high-gradient severe AS (HGSAS), is defined as an aortic valve area (AVA) <1 cm^2 or an indexed AVA <0.6 cm^2/m^2 and a mean transvalvular gradient ≥40 mmHg or a peak jet velocity ≥4 m/s. Currently, the American Heart Association/American College of Cardiology and European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines recommend AVR as Class I trigger for HGSAS if symptoms or a left ventricular ejection fraction (LVEF) <50% are present.[4,5] However, defining symptom presence can be challenging in patients who are sedentary, deconditioned, elderly, or in denial.[6] As a result, ESC/EACTS guidelines strongly recommend exercise testing to reveal hidden symptoms in asymptomatic SAS patients. Nevertheless, performing exercise tests in asymptomatic patients is rarely practiced (in <10% of eligible patients).[7] LV function warrants valve replacement when impaired in SAS. However, LVEF becomes impaired late in the disease course. Furthermore, long-term survival of patients with LVEF <50% and SAS is poor despite AVR and regardless of symptoms.[8,9] In addition, recent magnetic resonance imaging-based studies have demonstrated that left ventricle structural and functional abnormalities may be common despite an LVEF >50%.[10,11] This could explain the reduced postoperative survival of patients with an LVEF of 50 to 60% compared with those with an LVEF >60%.[8,9,12,13] As a result, the ESC/EACTS guidelines recommend AVR in asymptomatic patients with LVEF <55% as a Class IIa indication.[5]

Yet, the optimal intervention timing in asymptomatic HGSAS patients and preserved LVEF is under debate. Since AVR ideally aims to restore patient life expectancy to that of the same age healthy population, a watchful waiting strategy raises the question of the intrinsic risks of referring patients too late, with potential consequences regarding late postoperative survival. In this work, we sought to explore the impact of guideline-based Class I triggers on late postoperative survival rates in HGSAS patients. Therefore, we analyzed patients from the BEL-F-ASt (Belgian-French-Aortic Stenosis) registry, a multicenter international outcome registry pertaining to AS in routine practice. We investigated whether waiting for Class I triggers occurrence before operating on HGSAS patients would be associated with a late postoperative survival penalty.

METHODS

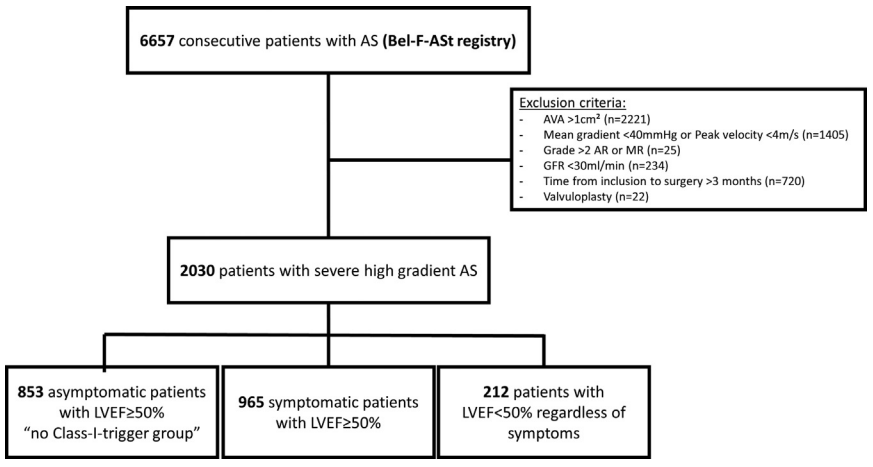
STUDY POPULATION AND DESIGN. Patients aged >18 years old diagnosed with at least mild AS in the echocardiography laboratories of 2 French (Amiens and Lille) and 1 Belgian (Brussels) tertiary hospitals between 2000 and 2020 were prospectively enrolled in the BEL-F-ASt registry (**Figure 1**). Enrolled patients underwent AVR within 3 months of the index echocardiography. AVR was surgical in 87.9% of patients and percutaneous in 12.1%. Coronary artery disease (CAD) was defined as the presence of a documented acute coronary syndrome history and previously confirmed by coronary angiography or coronary revascularization history. Symptoms were validated by each patient's personal cardiologist. Patients were retrospectively classified into 3 groups: no Class I trigger: asymptomatic with LVEF ≥50% (n = 853); symptomatic: dyspnea or/and angina or/and syncope with LVEF ≥50% (n = 965); and LV dysfunction presence: LVEF <50% regardless of symptoms (n = 212). The study was conducted in agreement with the institutional policies and the revised Helsinki Declaration.

ECHOCARDIOGRAPHY. All patients underwent a comprehensive ultrasound examination including 2-dimensional echocardiography and Doppler examinations. Multiple transducer positions were systematically used to record maximal instantaneous and mean pressure gradients across the aortic valve. AVA was calculated by the continuity equation. In patients

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received September 25, 2023; revised manuscript received November 17, 2023, accepted December 5, 2023.

FIGURE 1 Flow Chart Illustrating Case Selection and Classification



AR = aortic valve regurgitation; AS = aortic valve stenosis; AVA = aortic valve area; GFR = glomerular filtration rate; LVEF = left ventricle ejection fraction; MR = mitral regurgitation.

with atrial fibrillation (AF), 5 consecutive beats were systematically averaged. LV volumes and LVEF were calculated by using the biplane Simpson method.

FOLLOW-UP AND OUTCOMES. Selected patients underwent AVR within 3 months of the index assessment. AVR indication was decided by the cardiology team and the patient's physician. Clinical follow-up data were obtained by patient interview and telephone calls to physicians, patients, or their relatives if necessary. The surgery day was the first follow-up day and patients were censored at the time of last medical contact. The primary endpoint was overall postoperative mortality at 10 years.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD or median (IQR), depending on distribution normality, and categorical data as numbers (percentages). Baseline continuous data differences among the groups were explored using 1-way analysis of variance (normally distributed data) or Kruskal-Wallis test (nonnormally distributed data). Pearson's chi-square test was used for categorical variables. Outcomes (all-cause mortality at 10 years) were displayed using the Kaplan-Meier method and compared between the 3 groups (no Class I trigger vs symptoms + LVEF >50% vs LVEF <50%) using 2-sided log-rank test. The observed survival of the no Class I trigger subgroup was compared using log-rank test with the expected survival of the general population which was similar in age and sex and provided by the World Health Organization database. A Cox proportional hazard survival model was built to determine the independent outcome-associated factors. For this purpose, a preliminary model was built from which Class I triggers (ie, symptoms and LVEF <50%) were excluded. The ability of these Class I triggers to improve the prediction of death by this preliminary model was tested and 4 different models were created. The proportional hazards assumption was confirmed using statistics and graphs based on Schoenfeld residuals. The model fit was evaluated with martingale and Cox-Snell residuals. The relationship between LVEF and the 10-year postoperative mortality risk was analyzed using a penalized smoothing spline. HR values were calculated for each LVEF cutoff using a multivariate Cox regression. The maximum of the log-rank statistics was then calculated for LVEF thresholds (<50%, <55%, and <60%). An inverse probability weighting (IPW) analysis was performed to balance the baseline characteristics among groups with weighting to compare outcomes and further explore the prognostic value of the LVEF threshold. The inverse propensity score was calculated using the variables identified as independent mortality predictors in the multivariate analysis and additional echocardiographic confounders. These variables were used to estimate case weights using a multinomial logistic regression model to predict the inverse probability of having symptoms or LV dysfunction.

TABLE 1 Clinical and Echocardiographic Characteristics of Patients With Severe Aortic Stenosis According to the Trigger Group

	All (N = 2,030)	(1) No Class I Trigger (n = 853, 42%)	(2) Symptoms and LVEF >50% (n = 965, 47.5%)	(3) LVEF <50% (n = 212, 10.5%)	*P* Value			
					Overall	(1) vs (2)	(1) vs (3)	(2) vs (3)
Clinical characteristics								
Age, y	76 ± 9	75 ± 10	76 ± 9	77 ± 8	<0.001	0.002	0.001	0.240
Male	53%	54%	49%	64%	<0.001	0.022	0.019	<0.001
BSA, m^2	1.88 ± 0.21	1.88 ± 0.21	1.88 ± 0.21	1.89 ± 0.21	0.652	0.989	0.633	0.682
NYHA functional class >II	34%	0%	60%	52%	<0.001	<0.001	<0.001	0.005
Angina pectoris	25%	0%	48%	23%	<0.001	<0.001	<0.001	<0.001
Syncope	11%	0%	21%	8%	<0.001	<0.001	<0.001	<0.001
Diabetes	25%	24%	27%	21%	0.161	0.323	0.323	0.274
Hypertension	70%	68%	73%	65%	0.008	0.024	0.450	0.024
CAD	52%	45%	57%	52%	<0.001	<0.001	0.113	0.215
AF	19%	17%	20%	26%	0.014	0.163	0.015	0.093
GFR, mL/m^2	63 (48-81)	66 (50-85)	62 (48-79)	57 (46-76)	<0.001	0.018	<0.001	0.018
Charlson index	4 (3-6)	4 (3-5)	4 (3-5)	5 (3-6)	<0.001	0.040	<0.001	<0.001
EuroSCORE II	1.91 (1.26-3.06)	1.65 (1.03-2.43)	1.99 (1.33-3.25)	3.09 (2.16-5.08)	<0.001	<0.001	<0.001	<0.001
Echocardiographic parameters								
AVA, cm^2	0.66 ± 0.16	0.67 ± 0.16	0.66 ± 0.16	0.59 ± 0.15	<0.001	0.482	<0.001	<0.001
PG, mm Hg	90.6 ± 22.7	91.0 ± 22.1	91.1 ± 23.4	86.2 ± 21.4	0.015	0.988	0.019	0.013
MG, mm Hg	57.2 ± 14.7	57.5 ± 14.5	57.3 ± 14.8	55.1 ± 14.3	0.084	0.933	0.073	0.113
LVEDD, mm	48 ± 7	47 ± 7	47 ± 7	53 ± 7	<0.001	0.983	<0.001	<0.001
LVESD, mm	30 ± 8	29 ± 7	29 ± 7	41 ± 9	<0.001	0.491	<0.001	<0.001
LVEF, %	63 ± 11	65 ± 8	65 ± 8	40 ± 7	<0.001	0.991	<0.001	<0.001
iSV, mL/m^2	40 ± 10	41 ± 10	41 ± 10	35 ± 8	<0.001	0.198	<0.001	<0.001
sPAP, mm Hg	33 ± 11	32 ± 11	33 ± 11	39 ± 13	<0.001	0.620	<0.001	<0.001
AR grade 2	5.3%	4.1%	5.3%	9.9%	0.003	0.283	0.004	0.026
MR grade 2	3.8%	2%	3.9%	10%	<0.001	0.023	<0.001	<0.001
TR grade >1	3%	2.6%	2.8%	6.1%	0.022	0.887	0.040	0.040

Values are mean ± SD, %, or median (IQR). The comparison test for LVEF is shown for illustrative purposes because LVEF is part of the independent variable.

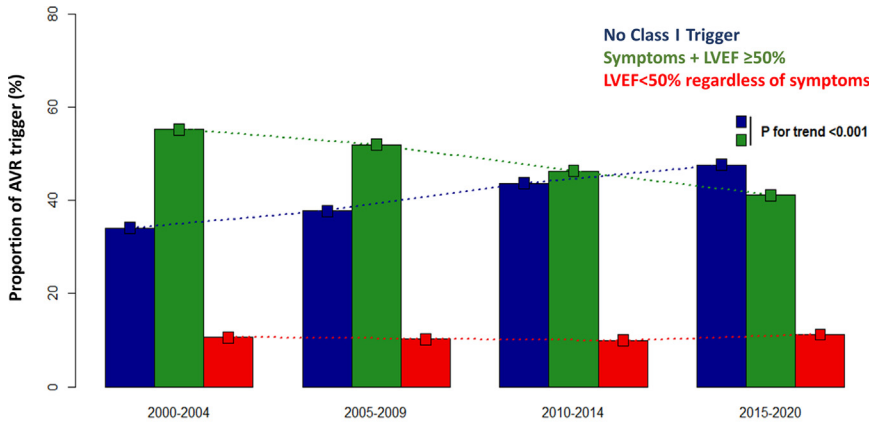
AF = atrial fibrillation; AR = aortic regurgitation; AVA = aortic valve area; BSA = body surface area; CAD = coronary artery disease; GFR = glomerular filtration rate; iSV = indexed stroke volume; LVEDD = left ventricle end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricle end-systolic diameter; MG = transaortic mean pressure gradient; MR = mitral regurgitation; PG = transaortic peak pressure gradient; sPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

Cox proportional hazard regression models were adjusted for IPW to clarify the impact of symptoms and LV dysfunction on survival. Finally, the survival penalty was quantified according to AVR indication using restricted mean survival time (RMST) analysis at the truncated time point of 10 years. This method compares the mean survival time of each group in a pairwise analysis by subtracting the area under the survival curve to a specific time point. This analysis does not require a proportional hazard assumption, taking into account censored observations. RMST analysis was performed by integrating an adjusted Kaplan-Meier estimator with IPW. Statistical analyses were conducted using RStudio 1.4.1106. A *P* value of <0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. The population comprised 2,030 patients among which 853 (42%) underwent AVR without meeting a Class I trigger, 965 (47.5%) while presenting symptoms and having an LVEF ≥50%, and 212 (10.5%) with an LVEF <50%, regardless of symptoms. Their demographic, clinical, and echocardiographic characteristics are summarized in Table 1. Patients who underwent AVR without meeting a Class I trigger were younger and had a lower CAD and AF prevalence compared with those with symptoms or LV dysfunction. They also had better renal function and less comorbidities as well. Patients with LVEF <50% presented fewer symptoms compared with those included based on their symptomatic status. As anticipated, they had lower AVAs, transaortic peak velocities and lower stroke volumes, and higher systolic pulmonary pressures. There was no difference in CAD or AF prevalence between symptomatic patients with LVEF ≥50% and those with LVEF <50%. Notably, the operated patient proportion varied over time, whether they met a Class I trigger or not. During patient enrollment (2000-2020), the symptomatic operated patient percentage decreased, whereas the asymptomatic

FIGURE 2 Temporal Evolution of the Operated HGSAS Patient Proportion Meeting a Class I Trigger or Not



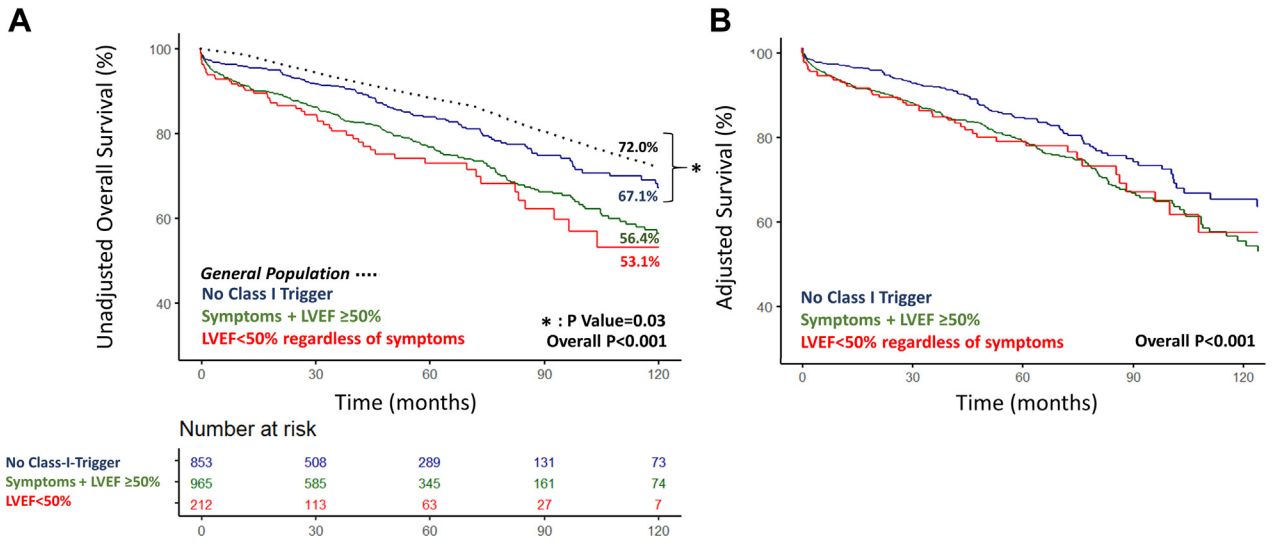
The symptomatic patient proportion who underwent surgery (green) significantly decreased over time, while patients with LVEF <50% (red) at the time of surgery remained stable. AVR = aortic valve replacement; HGSAS = high-gradient severe aortic stenosis; LVEF = left ventricle ejection fraction.

operated patient proportion increased, suggesting that interventions were initiated earlier over time. However, the proportion of operated patients with an LVEF <50% remained stable over time (Figure 2). Indications for AVR in patients without Class I trigger are showed in Supplemental Table 1.

POSTOPERATIVE SURVIVAL ACCORDING TO CLASS I TRIGGERS. During a median follow-up of 40 months (IQR: 17-74 months), 405 (20%) deaths were recorded, of which 52 (2.5%) occurred within the first 30 days after AVR. There was no difference in perioperative mortality among the groups ($P = 0.37$). Overall perioperative mortality decreased between the first and second recruitment decade (3.9% vs 1.7%, $P = 0.005$). The 10-year postoperative survival rate was better in patients without Class I trigger than in those with symptoms or LVEF <50% (67.1% ± 3% vs 56.4% ± 3% vs 53.1% ± 7%, respectively, $P < 0.001$). However, patients who underwent AVR without meeting Class I triggers did not achieve the anticipated survival rates compared with the age- and sex-matched general population (67.1% vs 72.0%, $P = 0.03$) (Figure 3A). Then, a basal multivariate Cox model was built with 5 covariates (age, diabetes, CAD, renal function, and AVA). By adding the Class I triggers to this model, symptom presence and/or LV dysfunction remained associated with increased mortality (Table 2). Different models were built. In model 1, symptoms (HR: 1.46, 95% CI: 1.17-1.81, $P < 0.001$) and LVEF expressed as a continuous variable (HR: 0.95, 95% CI: 0.91-0.99), $P = 0.019$) added significant strength in predicting death risks. Furthermore, when presenting LVEF as a categorical variable and when considering patients without Class I trigger as the reference group (model 2) (Table 2), the mortality relative risk increased with an adjusted HR: 1.45 (95% CI: 1.15-1.82, $P = 0.002$) in the symptomatic group and with an adjusted HR: 1.47 (95% CI: 1.05-2.06, $P = 0.024$) in the LVEF <50% group (Figure 3B).

PROGNOSTIC IMPACT OF LVEF THRESHOLD. To explore the prognostic impact of LVEF thresholds, we built a multivariate Cox model using a 55% EF and a 60% EF cutoff (model 3 and model 4, respectively) (Table 2). With an LVEF <55% and when considering patients without Class I trigger as the reference group, the mortality relative risk increased with an adjusted HR: 1.50 (95% CI: 1.17-1.92, $P = 0.001$) in the symptomatic group with LVEF >55% and with an adjusted HR: 1.92 (95% CI: 1.44-2.55, $P < 0.001$) in the LVEF <55% group. Similarly, with an LVEF <60% and when considering patients without Class I trigger as the reference group, the mortality relative risk already increased with an adjusted HR: 1.60 (95% CI: 1.21-2.11, $P < 0.001$) in the symptomatic group with LVEF >60% and with an adjusted HR: 2.00 (95% CI: 1.52-2.65, $P < 0.001$) in the LVEF <60% group. Therefore, we used these different LVEF thresholds (ie, <55% and <60%) to redefine our groups (Supplemental Tables 2 and 3). As observed in

FIGURE 3 10-Year Postoperative Survival Curves of High-Gradient Severe Aortic Stenosis Patients According to the Guideline Trigger Group



Graphs comparing unadjusted (A) and Cox-adjusted (B) survival among patients with no Class I trigger (blue line), symptoms (green line), and left ventricular ejection fraction <50% (red line). The doted black line represents the age- and sex- matched general population. The adjustments included age, diabetes, coronary artery disease, renal function, and aortic valve area. LVEF = left ventricle ejection fraction.

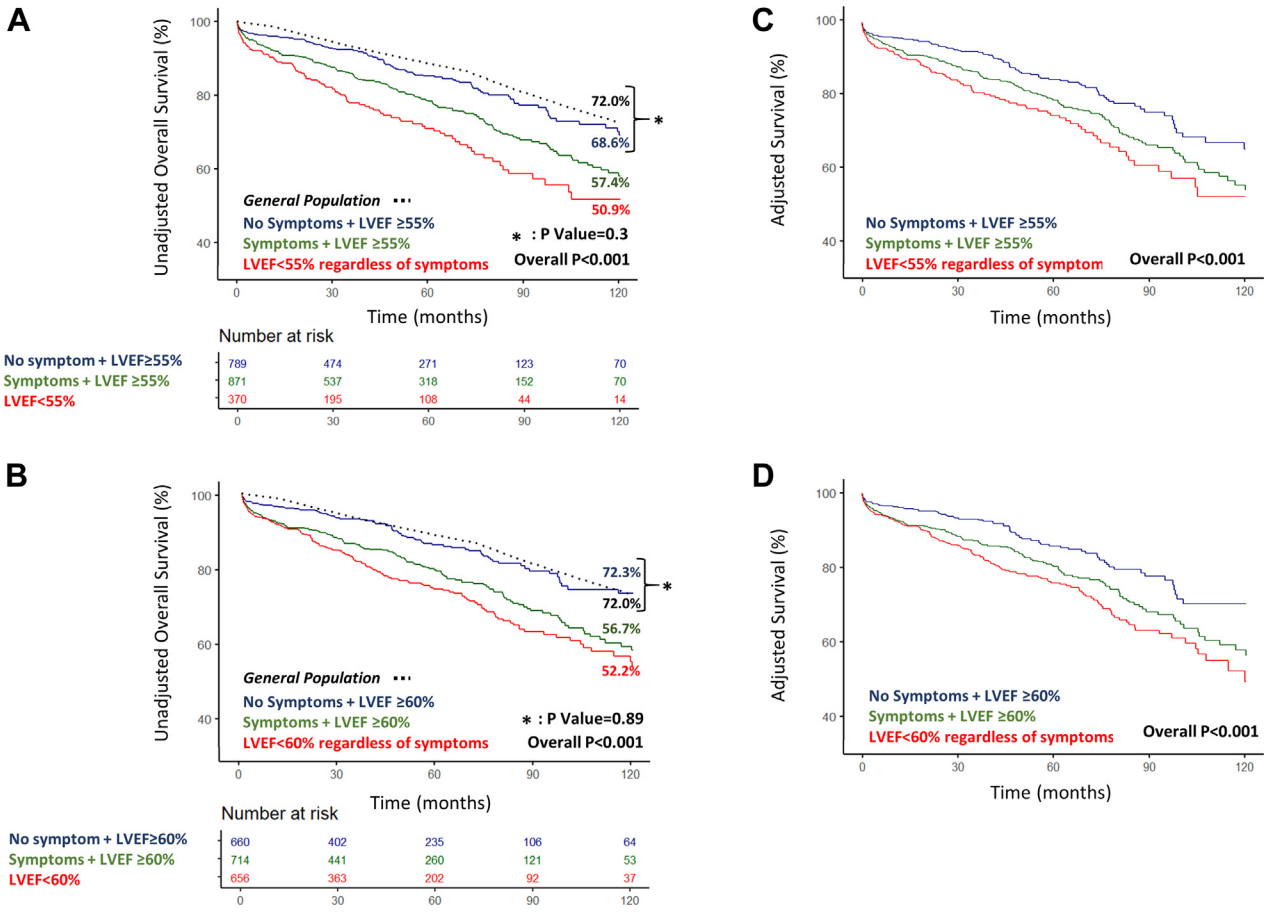
TABLE 2 Multivariate Cox Models

	HR (95% CI)	*P* Value
Basal model		
Age (per 5 y)	1.24 (1.14-1.35)	<0.001
Diabetes	1.43 (1.14-1.79)	0.002
CAD	1.37 (1.11-1.70)	0.003
GFR (per 5 mL)	0.95 (0.93-0.98)	0.002
AVA	0.40 (0.21-0.77)	0.006
Additional prognostic variables to basal model		
Model 1		
Symptoms	1.46 (1.17-1.81)	<0.001
LVEF by 5%	0.95 (0.91-0.99)	0.019
Model 2		
No Class I trigger	Ref	-
Symptoms + LVEF >50%	1.45 (1.15-1.82)	0.002
LVEF <50%	1.47 (1.05-2.06)	0.024
Model 3		
No Symptoms + LVEF >55%	Ref	-
Symptoms + LVEF >55%	1.50 (1.17-1.92)	0.001
LVEF <55%	1.92 (1.44-2.55)	<0.001
Model 4		
No Symptoms + LVEF >60%	Ref	-
Symptoms + LVEF >60%	1.60 (1.21-2.11)	<0.001
LVEF <60%	2.00 (1.52-2.65)	<0.001

AVA = aortic valve area; CAD = coronary artery disease; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction.

patients with a LVEF <50%, asymptomatic patients without LV dysfunction had a better survival rate compared to symptomatic patients or those presenting with LV dysfunction, regardless of whether the LVEF threshold was set at LVEF <55% (68.6% ± 3% vs 57.4% ± 3% vs 50.9% ± 5%, respectively, $P < 0.001$), or LVEF <60% (72.3% ± 3% vs 56.7% ± 3% vs 52.2% ± 4%, respectively, $P < 0.001$) (Figure 4). Interestingly, performing AVR in asymptomatic patients with LVEF >55% yielded similar outcomes to those observed in the general population (Figure 4A). This was even more striking for asymptomatic patients operated on with an LVEF >60% (Figure 4B). After adjustment, 10-year survival curves showed a better survival in asymptomatic patients without LV dysfunction compared to those with symptoms or with depressed LVEF regardless of EF (Figures 4C and 4D). We also observed a survival penalty among asymptomatic patients who underwent surgery with a LVEF ranging from 55% to 60% (Figure 5), suggesting that it is primarily asymptomatic patients operated on with an LVEF >60% who achieved a prognosis comparable to the general population. The relationship between LVEF and the postoperative death risk was represented as a penalized smoothing spline function. After adjustment for confounding variables, there was an increased mortality risk with a decreasing LVEF significant below 60% (Figure 6). The risk increased with a higher slope in the LVEF

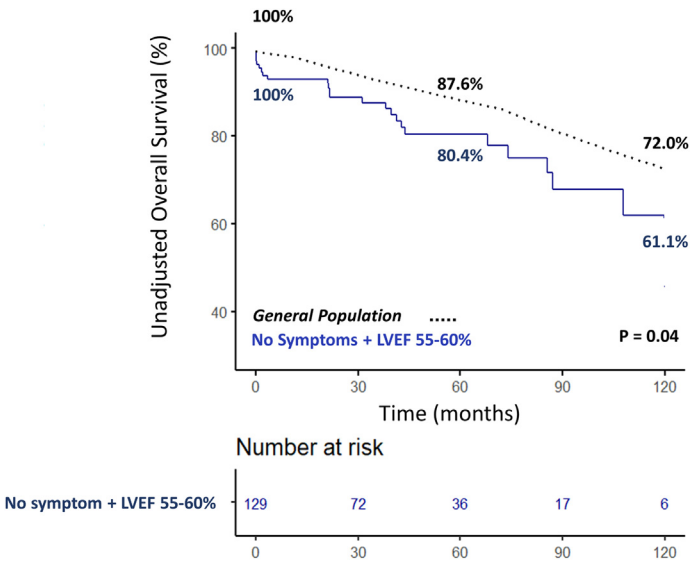
FIGURE 4 10-Year Postoperative Survival Curves of High-Gradient Severe Aortic Stenosis Patients According to LVEF Thresholds and Symptoms



(A) Graph comparing unadjusted survival among asymptomatic patients with LVEF ≥55% (blue line), symptoms (green line), and LVEF <55% (red line). (B) Graph comparing unadjusted survival among asymptomatic patients with LVEF ≥60% (blue line), symptoms (green line), and LVEF <60% (red line). The doted black line represents the age- and sex-matched general population. (C) Graph comparing Cox-adjusted survival among asymptomatic patients with LVEF ≥55% (blue line), symptoms (green line), and LVEF <55% (red line). (D) Graph comparing Cox-adjusted survival among asymptomatic patients with LVEF ≥60% (blue line), symptoms (green line), and LVEF <60% (red line). The adjustments included age, diabetes, coronary artery disease, renal function, and aortic valve area. LVEF = left ventricular ejection fraction.

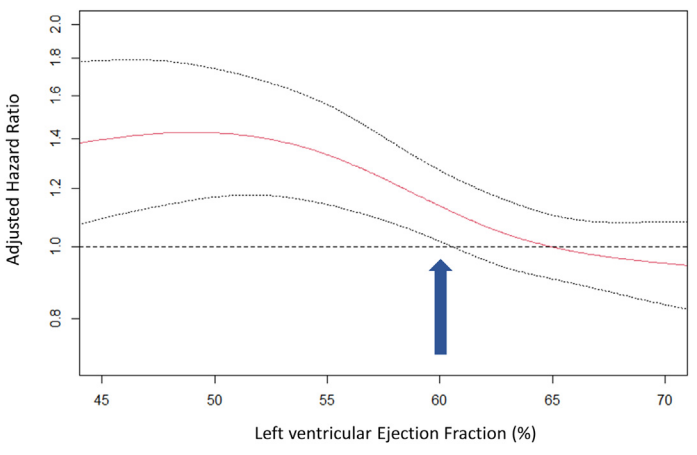
range between 60 and 55% and then flattened out between 55 and 50%. When considering the lowest HR point in the spline shape as reference, all patients with LVEF <60%, LVEF <55%, or LVEF <50% had significantly worse prognosis (HR: 1.14, 95% CI: 1.02-1.27; HR: 1.33, 95% CI: 1.14-1.56 and HR: 1.43, 95% CI: 1.17-1.74, respectively), pointing out that patients with LVEF <60% were already at risk. Then, survival differences were analyzed using the maximum log-rank statistics (**Figure 7**). Compared with LVEF <50% threshold (maximum log rank statistic: 2.8; $P = 0.002$) (**Figure 7A**), the maximum statistic was observed for a LVEF <55% threshold (log rank statistic: 4.2; $P < 0.001$) (**Figure 7B**) and for a LVEF <60% threshold (log rank statistic: 4.2; $P < 0.001$) (**Figure 7C**) resulting in a greater separation of the survival curves. Finally, IPW was used to comprehensively balance the baseline characteristics between groups and to compare survival. After IPW, no significant difference in baseline characteristics persisted (Supplemental Tables 4A and 4B). IPW showed that in comparison with patient without Class I trigger, symptoms at the time of AVR was associated with excess postoperative mortality (HR: 1.43; 95% CI: 1.13-1.82) and a LVEF <55% or a LVEF <60% at the time of AVR had an even higher excess risk (HR: 1.63; 95% CI: 1.19-2.23, and HR: 1.79; 95% CI: 1.36-2.36, respectively), similar to standard Cox-proportional hazard analysis.

FIGURE 5 Unadjusted 10-Year Postoperative Survival Curves of Asymptomatic Patients With a LVEF Ranging From 55% to 60%



The doted black line represents the age- and sex-matched general population. LVEF = left ventricular ejection fraction.

FIGURE 6 Postoperative Mortality Risk Estimated Using Spline Function for Left Ventricular Ejection Fraction



HR (solid red line) and 95% CI (dashed lines) were estimated using a Cox multivariate model, with left ventricular ejection fraction represented as a penalized spline function. There was an increased mortality risk with decreasing LVEF which becomes significant below 60% (arrow). The model was adjusted for age, diabetes, aortic valve area, coronary artery disease, renal function, and symptoms.

RMST ANALYSIS. The RMST analysis was performed on the IPW-adjusted population. A mean survival penalty was estimated at 10 years following AVR by comparing groups based on their guideline triggers. After 10 years, when compared with patients operated on without any triggers (no symptoms or LV dysfunction defined by a LVEF <60%), operating on patients with symptoms at the time of surgery was associated with an estimated mean survival penalty of 8.3 months (95% CI: 2.5-11.9, $P = 0.003$). Even more impressively, when compared with patients operated on without any triggers, operating on patients with a LVEF <60% at the time of AVR was associated with an estimated mean survival penalty of 11.4 months (95% CI: 3.1-17.9, $P = 0.005$) after 10 years.

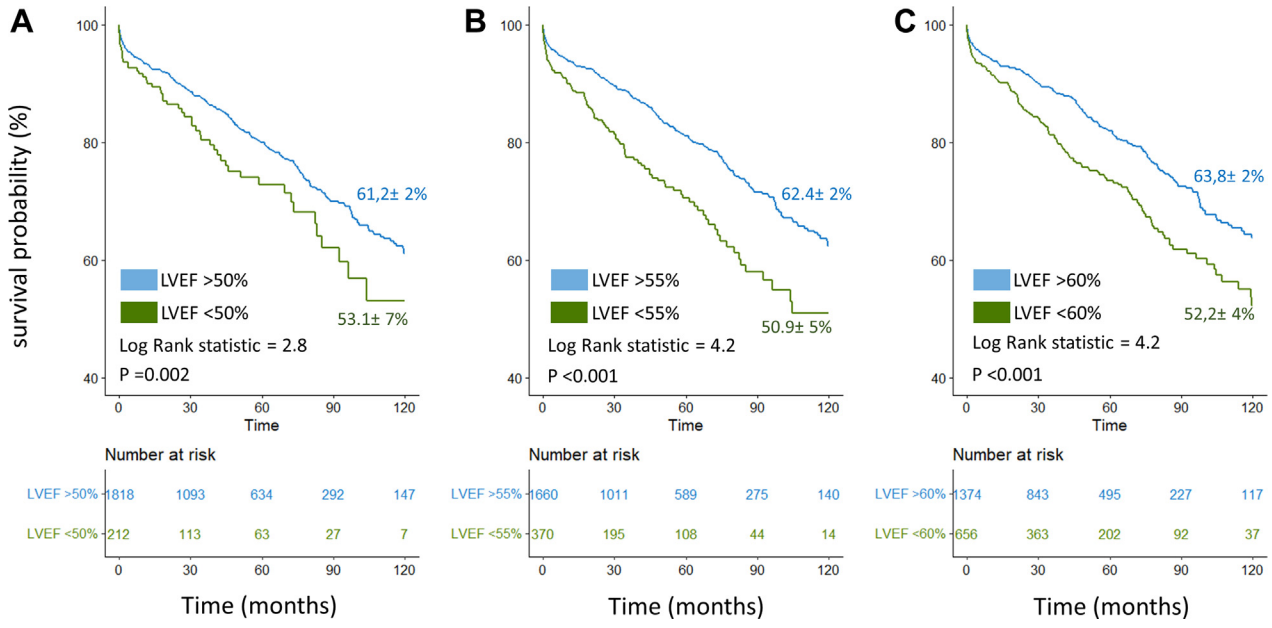
DISCUSSION

The current work investigated long-term postoperative survival of HGSAS patients from a large multicenter cohort according to American Heart Association/American College of Cardiology Class I triggered interventions. The relevant findings were (Central Illustration):

1. Class I trigger presence (ie, symptoms or LVEF <50%) at the time of intervention in HGSAS patients was deleterious, followed by an increased long-term postoperative mortality risk compared with those without triggers (about 45% more postoperative death risk vs no trigger at 10 years).
2. An LVEF <60% at the time of AVR was already associated with a 10-year postoperative survival penalty while performing AVR in asymptomatic HGSAS patients with an LVEF >60% produced similar outcomes to the general population.
3. Symptomatic patients or those with LVEF <60% who underwent AVR had a 8.3- and 11.4-month survival loss, respectively, after 10 years and compared with those operated on without symptoms and a LVEF >60%.

Controversy regarding the surgical correction timing for severe asymptomatic AS still exists[14] despite compelling data establishing a better outcome in operated patients at an earlier time compared with those who experienced a watchful waiting strategy.[15,16] While data on the natural disease history already represent a strong argument for proposing early intervention, our work exclusively focused on postoperative survival reinforces the message that waiting for symptoms or LV dysfunction should be restricted. Indeed, the existing practice of

FIGURE 7 Ten-Year Survival Curves Based on LVEF Thresholds



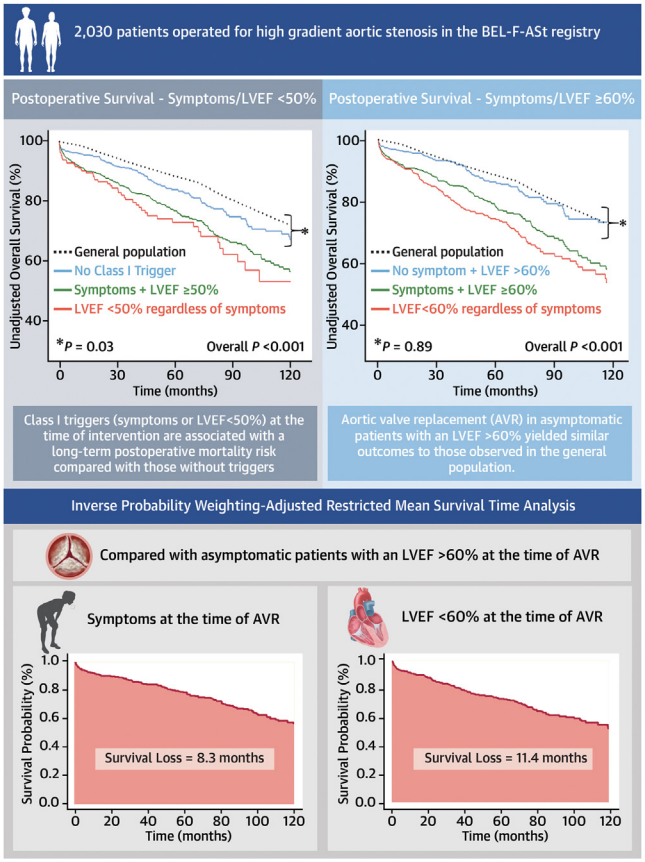
Compared to the threshold of left ventricular ejection fraction (LVEF) <50% (A), the maximum Log Rank-statistic was observed for an LVEF <55% and LVEF <60% threshold resulting in a greater separation of the survival curves (B and C). Numbers indicate patients at risk.

deferring AVR until symptoms or LV dysfunction occur lead to rescue surgery as it is accompanied by a postoperative survival penalty for the patient. Therefore, the optimal surgical timing must be prior to trigger onset.

PREOPERATIVE SYMPTOMS AND POSTOPERATIVE SURVIVAL. When SAS is accompanied by symptoms, AVR is recommended because of its well-established dismal outcome (≈50% mortality within 3 years) in unoperated patients. Thus, despite the absence of data from a randomized clinical trial, symptomatic SAS is considered as a Class I trigger for AVR by professional organizations.[4,5] Nevertheless, a substantial number of patients with severe AS deny symptoms for many years, by subconsciously reducing their activity level, thereby masking their true symptoms or exercise intolerance.[14] In addition, some patients may disavow or downplay their symptoms out of fear or anxiety regarding therapeutic interventions. Thus, physicians frequently face difficulties in treating AS patients, especially the older ones claiming to be asymptomatic. A supervised stress-test may unmask symptoms. Indeed, international guidelines recommend exercise testing in asymptomatic SAS patients,[4,5] but it is only performed in a small portion of eligible HGSAS patients. Besides the fact that stress testing is underused in routine practice, it is more alarming to note that 48% of the patients referred for AVR already had severe symptoms and that 12% were hospitalized for acute heart failure.[7] Moreover, the ability of exercise testing to predict symptom onset and outcomes at 1 year is poor (positive predictive value of 55%-65%) and based on small patient's series.[17,18] Furthermore, exercise tests can only be performed by relatively young patients, which do not reflect the usual AS population age.[18] Our data suggest that waiting for symptoms in HGSAS cases is accompanied by survival loss. Thus, based on the principle that preemptive AVR can only be justified when there is clear evidence that it actually improves long-term survival (with an acceptable perioperative risk) compared with periodic clinical reassessment until symptoms onset, our data and those from other studies[15,19] support earlier intervention strategies.

LEFT VENTRICULAR DYSFUNCTION AS A PREDICTOR OF OUTCOMES. LVEF is generally used as a surrogate of LV systolic function and is recognized as a Class I trigger for AVR when <50% in SAS.[4,5] However, the

CENTRAL ILLUSTRATION **Survival Loss Associated With Late Therapeutic Indication in High-Gradient Severe Aortic Stenosis**



De Azevedo D, et al. JACC Adv. 2024;3(3):100830.

Delaying AVR for HGSAS patients until symptoms or left ventricular dysfunction onset has a negative impact on long-term postoperative survival. Patients without Class I triggers (blue line) had better survival rates than symptomatic patients with preserved LVEF (green line) and patients with reduced LVEF (red line), regardless of LVEF-threshold. AVR did not restore normal life expectancy in asymptomatic patients with LVEF <60%. However, asymptomatic patients with LVEF >60% had similar survival rates to the general population (dotted black line). AVR in patients with symptoms or LVEF <60% resulted in 8.3- and 11.4-month survival losses, respectively, after 10 years compared to those operated on without symptoms and with LVEF >60% ($P < 0.001$). AVR = aortic valve replacement; HGSAS = high-gradient severe aortic stenosis; IPW = inverse probability weighting; LVEF = left ventricle ejection fraction; RMST = restricted mean survival time.

best EF threshold remains largely debated. Recently, data have shown that treatment benefits can be expected in asymptomatic HGSAS patients regardless of their EF, thus questioning the need for an EF threshold recommending AVR.[13,15,20,21] In AS, the calcified aortic valve creates an obstacle hampering the LV outflow, prompting a compensatory response for hypertrophic LV remodeling caused by the addition of sarcomeres in parallel. This adaptive mechanism aims to mitigate wall stress and sustain adequate cardiac output. Consequently, LVEF may appear preserved despite underlying reduced contractility and therefore fails to accurately reflect the underlying ongoing cardiac damage. Decreased contractility can be identified in 68% of patients at the time of diagnosis of SAS.[22,23] When compensatory mechanisms are exhausted, LVEF decreases and normal LV function recovery after AVR may not be complete. Furthermore, due to these mechanisms, LV dysfunction defined by an LVEF <50% occurs very late in the AS natural history, and at this stage, patients are rarely asymptomatic.[24] Structural myocardial changes can be identified before LVEF declines, may persist after AVR, and are

independently associated with poor outcomes.[25,26] Although new risk indices such as global longitudinal strain, replacement fibrosis, and specific biomarkers are highly desirable and could radically transform the existing clinical decision paradigm,[6] it must be acknowledged that they are not widely used in routine clinical practice and highly depend on local expertise.[22] Moreover, the limited accessibility and high cost of certain examinations limit their broader utilization. Thus, LVEF remains the only imaging parameter used by clinicians to propose or delay AVR in SAS patients. In line with previous research,[13] our study confirms that there is already a postoperative survival penalty when the LVEF is below 60%. Our findings provide a crucial prognostic factor, indicating that operated asymptomatic patients with an LVEF >60% experienced a survival prognosis close to that of the general population. These findings prompt the inquiry regarding the necessity of establishing a LVEF threshold for advocating an intervention. This could be evaluated in controlled randomized trial.

OPERATING HGSAS EARLIER. As aforementioned, performing surgery on HGSAS patients earlier in the disease stage (ie, asymptomatic and with an LVEF >60%) is only justified if the operative mortality is low (1.8% in our series, mean age: 74 years), and if the intervention improves the outcomes. To date, 2 randomized controlled trials have compared the "early AVR strategy" with the "watchful waiting strategy" for asymptomatic SAS patient management[27,28] and these studies support an early interventional approach. However, the patients included were not necessarily those encountered in clinical routine, as they were on average 7 years younger than the patients in our study. It should be emphasized that these studies showed the superiority of the 'early intervention' approach after a relatively short follow-up period. Our study highlighted the late persistent survival penalty associated with waiting for symptoms onset before AVR. We can assert that when considering the collective evidence, earlier interventions will likely become more common in the future. This trend has already been observed in our study including data from the last 2 decades (**Figure 2**). Ultimately, adopting an earlier interventional approach relies on the durability of valve substitutes and therapeutic option availability for patients in the event of reintervention. Indeed, AVR in asymptomatic patients will undoubtedly be accompanied by a repeat valve procedure increase. In this regard, the transcatheter valve-in-valve technique has a promising potential.

STUDY LIMITATIONS. The study has several limitations that should be acknowledged. Because follow-up data were obtained retrospectively, this study presents the limitations inherent to this type of analysis. First, the indications for AVR could not be identified in all patients with no Class I indication. Secondly, biomarkers were only available in a limited number of patients (n = 690) (Supplemental Table 5), natriuretic peptides being unavailable in the early 2000s. As observed in many European countries, we could not provide information regarding exercise testing in asymptomatic patients[7] or data regarding global longitudinal strain. Despite completeness of our follow-up data and using sophisticated statistical methods like IPW to reduce biases, our patients were not randomized between early surgery and active surveillance. Accordingly, we cannot exclude unaccounted confounding factors contributing to our results. Prospective, randomized trials with long follow-up would undoubtedly provide a more definite demonstration of the superiority of early AVR vs "waiting Class I triggers."

CONCLUSIONS

This large international cohort of patients who underwent AVR for HGSAS provides new crucial insights for the SAS patient management. IPW matching revealed the intrinsic implications of surgical indications, as waiting for Class I triggers onset before performing surgery on HGSAS patients was associated with a definite postoperative survival penalty compared with operated patients without any triggers. These data should encourage clinicians to adopt an early surgical strategy in HGSAS patients for whom AVR can be safely offered. Performing AVR in asymptomatic HGSAS patients with LVEF>60% produced similar outcomes to those observed in the general population whereas operating asymptomatic patients with LVEF <60% did not. This questions the need for an EF threshold recommending AVR in HGSAS patients.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Grant support from the Fondation Nationale de la Recherche Scientifique of the Belgian Government (FRSM PDR T.0237.21). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Waiting for symptoms or LV dysfunction to occur before operating on HGSAS patients is deleterious, since such delay is accompanied by a long-term postoperative survival loss when compared with patients without any Class I trigger. As a result, clinicians should adopt an early surgical strategy in HGSAS patients for whom AVR can be safely offered. The absence of symptom and/or LV dysfunction should not be interpreted as a "license to wait"

TRANSLATIONAL OUTLOOK: Undertaking early AVR (when LVEF >60%) is expected to reduce the late postoperative mortality risk and restore a prognosis similar to that of the general population. Randomized trials are needed to confirm these data. Surgical and percutaneous techniques advances for AS treatment have changed AVR's risk-benefit ratio, especially in patients at low surgical risk. Combined with strong prognostic data linking late treatment with postoperative survival penalty, asymptomatic SAS patient management is expected to involve earlier intervention in the foreseeable future.

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KEY WORDS aortic stenosis, guidelines, international registry, left ventricular ejection fraction, survival, symptoms

APPENDIX For supplemental tables, please see the online version of this paper.