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FOCUS: TAVR

ORIGINAL RESEARCH: STRUCTURAL

Prevalence and Consequences of Guideline-Directed Indications for Aortic Valve Replacement in the EARLY TAVR Trial

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ABSTRACT

BACKGROUND The current American College of Cardiology/American Heart Association valvular heart disease guidelines were published before several recent trials that provide greater support for early intervention in patients with asymptomatic severe aortic stenosis (AS).

OBJECTIVES This study sought to investigate the prevalence and clinical impact of American College of Cardiology/American Heart Association Class II recommendations for AVR in the EARLY TAVR trial.

METHODS The EARLY TAVR trial randomized patients with asymptomatic severe AS to transfemoral transcatheter aortic valve replacement (TAVR) with a balloon-expandable valve or clinical surveillance (CS) with conversion to TAVR based on development of ACC/AHA Class I indications. Patients in the intention-to-treat cohort were stratified by presence of a Class II indication for AVR at randomization. The primary endpoint of the present analysis was the composite of all-cause death, stroke, or heart failure hospitalization. Interaction tests were performed to assess whether the treatment effect differed by level of guideline recommendation. Timing of conversion to AVR in the CS group according to the presence/absence of Class II indications was also assessed.

RESULTS Of the 901 patients randomized to TAVR (N = 445) and CS (N = 446), 636 (70.6%) patients had no guideline recommendation, and 265 (29.4%) had at least1 1 Class II recommendation for AVR at the time of randomization. At a median follow-up of 3.8 years, patients with a Class II indication for AVR experienced higher rates of the primary endpoint (Class II: 24.5% vs no recommendation: 14.5%; HR = 1.78; 95% CI: 1.30-2.44; $P < 0.001$) and were more likely to have acute valve syndrome at the time of conversion. Compared with CS, the relative benefit of early TAVR on the primary endpoint was similar regardless of the presence or absence of a Class II guideline recommendation (HR = 0.62; 95% CI: 0.37-1.02 vs 0.61; 95% CI: 0.40-0.92; $P_{interaction} = 0.96$).

CONCLUSIONS Among patients in the EARLY TAVR trial, Class II indications for AVR were present in almost one-third of patients at baseline. The benefit of early TAVR was consistent regardless of the presence or absence of Class II indications. These findings support the strategy of early TAVR over CS in asymptomatic patients with severe AS, independent of guideline indications. Clinical Trial Registration: https://clinicaltrials.gov/study/NCT03042104; Unique Identifier: NCT03042104 (JACC Cardiovasc Interv. 2026;19:2876-2888) © 2026 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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There is increasing interest in understanding whether upstream management may improve outcomes in patients with asymptomatic severe aortic stenosis (AS). A developing body of evidence supports the clinical benefits of aortic valve replacement (AVR) over clinical surveillance (CS) in patients with asymptomatic severe AS, including the most recent studies which have assessed the use of transcatheter AVR (TAVR) in this setting.[1-7] The largest such study was the EARLY TAVR trial (evaluation of TAVR compared with surveillance for patients with asymptomatic severe AS), which demonstrated the superiority of the early TAVR strategy vs CS with respect to death, stroke, or unplanned cardiovascular hospitalization.

The current American College of Cardiology/American Heart Association (ACC/AHA) guideline for the management of patients with valvular heart disease was developed before completion of the most recent studies focused on asymptomatic patients with severe AS.[1,2,8] These guidelines reserve Class I indications for AVR to individuals with severe AS with symptoms, asymptomatic individuals with LVEF <50%, and asymptomatic individuals with severe AS undergoing cardiac surgery for other indications.[8] Class II recommendations in asymptomatic patients were derived mainly from observational studies and refer only to surgical AVR.[8] It is unknown whether these recommendations are applicable to patients being considered for TAVR. We thus sought to evaluate the prevalence and clinical impact of the current ACC/AHA Class II indications on outcomes in patients randomized to clinical surveillance and TAVR in the EARLY TAVR trial.

METHODS

DATA SHARING STATEMENT. Requests to access the raw data and proposals for other sub-analyses from researchers trained in human subject confidentiality protocols may be sent to the corresponding investigator.

Study design and patient population: The study design, rationale, and principal findings of the EARLY TAVR trial have been previously described.[3,9] The trial is registered on ClinicalTrials.gov (NCT03042104). The protocol was designed by physician leadership and the steering committee and the trial sponsor (Edwards Lifesciences) in conjunction with U.S. Food & Drug Administration guidance and was approved by institutional review boards at each site. Eligibility criteria included age ≥65, presence of severe AS, asymptomatic status defined by negative treadmill stress test or physician assessment of patient history if unable to perform stress testing, left ventricular ejection fraction (LVEF) ≥50%, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) ≤10%, and absence of any ACC/AHA Class I recommendations for AVR. The complete eligibility criteria have been published previously.[3,9] Eligible patients who provided

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

AS = aortic stenosis

AVR = aortic valve replacement

AVS = acute valve syndrome

BNP = B-type natriuretic peptide

CS = clinical surveillance

GR = (ACC/AHA) guideline recommendation

HFH = heart failure hospitalization

ITT = intention-to-treat

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal-pro-B-type natriuretic peptide

STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality

TAVR = transcatheter aortic valve replacement

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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.

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informed consent were enrolled and randomized in a 1:1 fashion to early TAVR with transfemoral access using a balloon-expandable transcatheter heart valve (SAPIEN 3 or SAPIEN 3 Ultra, Edwards Lifesciences) or CS. Patients who underwent randomization were part of the intention-to-treat (ITT) population. Follow-up was for a minimum of 2 years.

Baseline asymptomatic status was assessed with a treadmill stress test or by physician assessment of patient history if the patient was unable to perform a stress test. Details regarding the stress test protocol have previously been presented.[3,9] For this analysis, patients were stratified according to presence or absence of ACC/AHA Class II (IIa or IIb) recommendations for AVR in asymptomatic patients with severe AS (Supplemental Table 1).[8] Individuals without guideline recommendations (GR) for AVR were included in the no GR group. Patients were included in the Class IIa group if they met ≥1 Class IIa guideline. Timing and clinical indications for conversion to AVR were assessed in patients randomized to CS. Echocardiograms were assessed by an independent core laboratory. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were analyzed by a biomarker core laboratory.[10]

Clinical outcomes: Selected for clinical generalizability, the primary endpoint of this analysis was the nonhierarchical composite of all-cause death, stroke, or heart failure hospitalization (HFH). HFH was defined as hospitalization for symptoms of congestive heart failure with objective signs and administration of intravenous diuresis or inotropic therapy, institution of mechanical support (intra-aortic balloon pump or ventilation for pulmonary edema), or hemodialysis for volume overload; this definition did not include unplanned cardiovascular hospitalization. The prespecified primary endpoint of the EARLY TAVR trial, the composite of all-cause death, stroke, or unplanned cardiovascular hospitalization (including aortic valve intervention/reintervention within 6 months of randomization), as well as the exploratory composite endpoint of all-cause death, all-cause stroke, unplanned CV hospitalization, or intervention/reintervention with advanced signs or symptoms were also assessed. Individual components of these composites were also examined. The incidence of progressive valve syndrome and acute valve syndrome (AVS) was also assessed.[11-13] All endpoints were adjudicated by the clinical events committee according to prespecified definitions. Members of the clinical events committee were not blinded to treatment arm.

Statistical analysis: Continuous variables are presented as mean ± SD or median (25th percentile, 75th percentile), and categorical and binary variables are presented as count (%). Continuous and ordinal variables were compared using the Wilcoxon rank-sum test for 2 groups (Class II vs no GR) or the Jonckheere-Terpstra test for 3 ordinal groups (Class IIa, Class IIb and no GR). Binary variables were compared using Fisher's exact test for 2 groups or the Cochran-Armitage test among 3 ordinal groups. Clinical outcomes were examined from the time of randomization using all available data and are presented as Kaplan-Meier curves and compared using the log-rank test; the proportional hazards assumption was examined by an interaction term of log-time and the grouping variable in Cox proportional hazards models. Subgroup analyses of treatment effects by different levels of GR were assessed with interaction P values and are presented as HR with 95% confidence intervals. Additionally, comparisons of the 2 Class II guideline levels vs no GR were performed as sensitivity analyses. A 2-sided P value <0.05 ($P < 0.1$ for interaction test) was considered statistically significant, and no adjustments for multiple comparisons were applied. All statistical analyses were performed with the use of SAS software, Version 9.4 (SAS Institute Inc).

RESULTS

Among the 901 patients (N = 455 for TAVR; N = 446 for CS) with asymptomatic severe AS enrolled in the EARLY TAVR trial, 636 (70.6%) patients had no GR, and 265 (29.4%) had Class II recommendations for AVR at the time of randomization (Table 1, Figure 1). Of the patients with only Class II recommendations, 202 patients (76.2%) had Class IIa recommendations for AVR, and 63 patients (23.8%) had Class IIb recommendations. Of patients with Class II indications, 27.9% had a peak transaortic velocity of ≥5 m/s, 57.4% had a B-type natriuretic peptide (BNP) >3 times normal, and 23.8% had an LVEF <60%. By design, no patients had a Class I recommendation for AVR at the time of randomization.

BASELINE CLINICAL CHARACTERISTICS. Baseline clinical characteristics of the ITT cohort stratified by guideline levels of recommendation are presented in Table 2. Summary statistics for the overall trial population include mean age: 75.8 ± 6.0 years, mean STS-PROM score: 1.8% ± 1.0%, mean peak velocity: 4.3 ± 0.4 m/s, and the percentage of patients with bicuspid aortic valve disease was 8.4%. In addition, because of differences in the definitional elements of Class II indications, there were other differences

TABLE 1 ACC/AHA Indications for Aortic Valve Replacement at Time of Randomization

Guideline Recommendation	Intention-to-Treat Cohort (N = 901)
Class I (symptoms or LVEF <50%)[a]	0 (0)
Any Class II (IIa or IIb)	265 (29.4)
Class IIa	202 (22.4)
Peak velocity ≥5 m/s	74 (8.2)
BNP >3 times normal	152 (16.9)
Peak velocity progression rate ≥0.3 m/s[b]	N/A
Decreased exercise tolerance or drop >10 mm Hg in systolic BP with stress test[c]	N/A
Class IIb, LVEF <60%	63 (7.0)
Class IIa and IIb	38 (4.2)
No GR	636 (70.6)

Values are N (%). Patients were hierarchically included in the Class IIa group if concurrently meeting indications for both IIa and IIb guidelines. [a]Patients with Class I indications were excluded at the time of randomization. [b]Serial echocardiograms before randomization were not available; however, baseline echocardiograms were core-lab adjudicated. [c]Stress tests were performed per standard protocols, and patients meeting exercise-triggered Class I indications were excluded from randomization. Serial stress tests were not recommended in the trial.

BNP = B-type natriuretic peptide; GR = guideline recommendation; LVEF = left ventricular ejection fraction.

between groups. Patients in the Class II group had higher STS-PROM scores and more frequently had prior atrial fibrillation and established peripheral vascular disease compared with individuals without GR for AVR. Cardiac troponin levels were higher in patients in the Class II group. Class II patients were less frequently able to perform a treadmill stress test and had lower mean 6-minute walk test distance. No significant differences were noted between groups for other baseline characteristics presented in Table 2.

BASELINE ECHOCARDIOGRAPHIC DATA. In addition to differences because of Class II definitions, several significant differences in baseline echocardiographic data were observed in patients with and without Class II guideline indications (Table 2). Patients with Class II indications had smaller aortic valve areas (with and without indexing for body size), lower LVEF and global longitudinal strain, greater mean left ventricular mass, and larger mean left atrial volume index values. Patients with Class II recommendations also more frequently had evidence of at least moderate mitral regurgitation or at least 1 valve with at least moderate regurgitation compared with individuals without guideline-directed indications for AVR. No significant differences in stroke volume index or moderate or greater aortic regurgitation were observed between groups (Table 2).

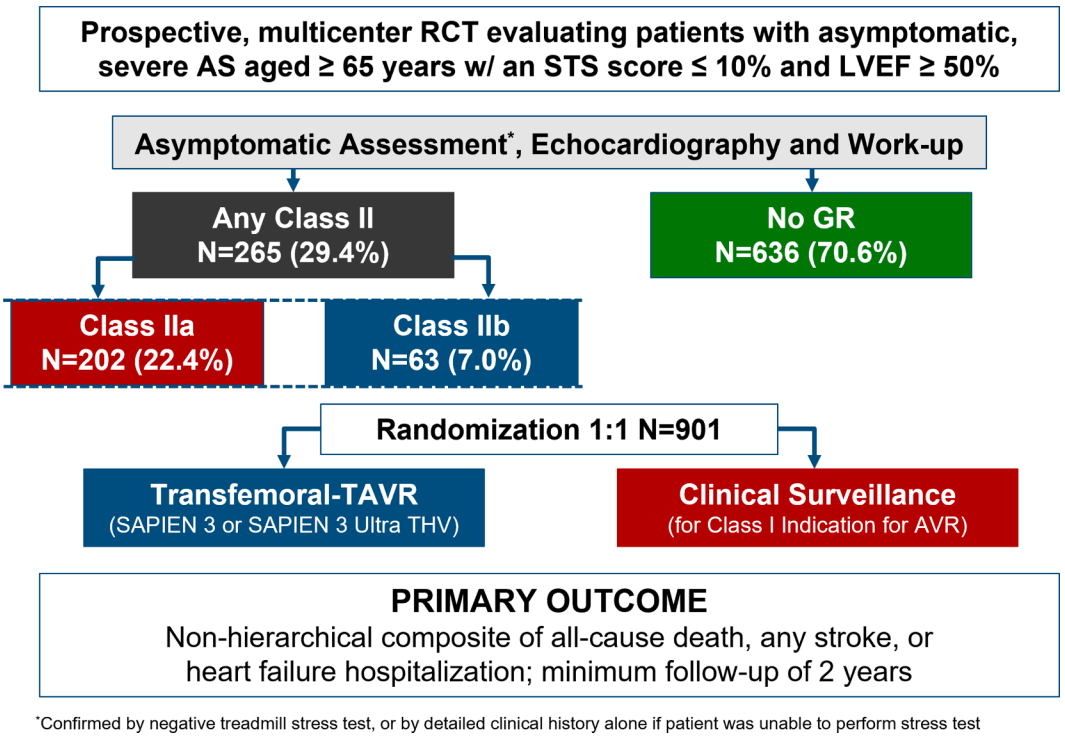
CLINICAL OUTCOMES BY GR. Clinical outcomes for the ITT population stratified by ACC/AHA GR are presented in Table 3, Figure 2, and Supplemental Figure 1. Patients with Class II recommendations experienced significantly higher rates of the primary endpoint of this analysis compared with individuals without a recommendation at baseline (Class II: 24.5% vs no GR: 14.5% during median follow-up of 3.8 years; HR = 1.78; 95% CI: 1.30-2.44; log-rank $P < 0.001$). This was driven by directionally consistent trends in all endpoint components. There was no significant difference in the composite of death, stroke, or unplanned cardiovascular hospitalization (Class II: 40.4% vs no GR: 34.1%; HR = 1.19; 95% CI: 0.94-1.50; log-rank $P = 0.14$). Rates of the exploratory composite endpoint of death, stroke, unplanned cardiovascular hospitalization, or aortic valve intervention with AVS were significantly higher in patients with Class II indications for AVR.

IMPACT OF GRs ON OUTCOMES BY TREATMENT STRATEGY. The impact of treatment strategy on the composite of death, stroke, or HFH was consistent, regardless of the presence or absence of a Class II recommendation, with similar findings across each of the endpoint components (Figure 3A). Similarly, there were no significant interactions between treatment effect and the presence/absence of GR for the other composite endpoints, cardiovascular death, or disabling stroke (Figure 3B).

CONVERSION TO AVR IN THE CS ARM. A total of 388 (87%) patients randomized to the CS arm converted to delayed AVR during follow-up. Of the 388 patients who had converted to AVR, 381 (98.2%) underwent TAVR, and 7 (1.8%) underwent surgical AVR. Patients with Class II indications converted to AVR earlier compared with individuals without GR (HR = 1.26; 95% CI: 1.02-1.56; log-rank $P = 0.03$) (Figure 4A).

Indications for conversion to delayed AVR stratified by presence of Class II indications are presented in Supplemental Table 2. The most common symptoms at the time of conversion were dyspnea (83.3%), angina (25.5%), and dizziness (24.7%). Syncope was observed in 7.2% of patients before conversion. Patients with Class II indications for AVR were more likely to develop NYHA functional class III/IV symptoms at the time of conversion to delayed AVR compared with individuals without GR at baseline. Similarly, individuals with Class II indications were more likely to convert to delayed AVR with LVEF <50% and symptoms compared with individuals without GR at baseline.

FIGURE 1 Study Flow Diagram



Flow diagram presenting stratification of the EARLY transcatheter aortic valve replacement (TAVR) trial intention-to-treat population into no guideline recommendation (GR) and any class II GR groups, clinical randomization arms, and primary outcome. AS = aortic stenosis; AVR = aortic valve replacement; LVEF = left ventricular ejection fraction; RCT = randomized clinical trial; STS = Society of Thoracic Surgeons; THV = transcatheter heart valve.

Figure 4B shows the incidence of AVS and progressive valve syndrome stratified by presence of Class II guideline indications at the time of delayed AVR conversion in the CS group. Patients in the CS cohort with Class II recommendations for AVR were more likely to present with AVS at the time of conversion compared with individuals without GR for AVR (47.6% vs 35.2%; $P = 0.04$).

IMPACT OF INDIVIDUAL CLASS II RECOMMENDATIONS. Baseline clinical and echocardiographic data presented by Class IIa, IIb, and no GR level of recommendations are presented in Supplemental Table 3. Rates of the primary endpoint were highest among patients with Class IIa recommendations, intermediate for patients with Class IIb recommendations, and lowest for patients without GR for early AVR (Supplemental Table 4, Supplemental Figure 2). Findings were generally similar for the other composite endpoints. Across each of the 3 composite endpoints and their components, there was no evidence of treatment effect heterogeneity between Class IIa, Class IIb, and no GR (Supplemental Figures 3A and 3B). Supplemental Figure 4 presents rates of the primary composite endpoint in patients with Class IIa, Class IIb, and no GR stratified by the early TAVR and CS treatment arms. Although rates of the primary endpoint were significantly higher with CS compared with early TAVR in patients with both Class IIb (log-rank $P = 0.048$) and no GR (log-rank $P = 0.017$) present at the time of randomization, this did not meet statistical significance in patients with Class IIa recommendations.

Kaplan-Meier curves presenting delayed conversion to AVR in CS patients stratified by Class IIa, Class IIb, and no GR are presented in Supplemental Figure 5. Patients in the CS arm with Class IIb indication (41.7%) had a numerically higher rate of conversion to AVR in the first 6 months after randomization compared with patients in the no GR

(26.0%) and Class IIa (21.0%) groups, but this did not meet statistical significance ($P = 0.06$).

DISCUSSION

This is the first study to explore the relationship between the current ACC/AHA guidelines and the benefit of an early TAVR strategy in patients with asymptomatic severe AS. The principal findings of this analysis are: 1) approximately one-third of asymptomatic patients carried Class II indications for AVR based on the 2020 ACC/AHA guidelines and these patients were at risk for higher rates of the primary endpoint of death, stroke, or HFH over a median 3.8 years of follow-up; 2) the benefit of early TAVR in asymptomatic patients was consistent regardless of the presence or absence of Class II indications; 3) CS patients with Class II indications for AVR were more likely to present with AVS compared with individuals without indications for AVR at baseline (**Central Illustration**).

Approximately 40% to 50% of patients with severe AS are asymptomatic at the time of diagnosis,[14-16] and prior studies have demonstrated that these patients frequently develop indications for AVR.[17] However, it remains unclear whether continued surveillance until development of Class I indications is the optimal management strategy for patients with asymptomatic severe AS. This analysis from EARLY TAVR provides much-needed high-quality data regarding outcomes in asymptomatic severe AS patients undergoing both TAVR and CS stratified by current guideline indications for AVR.

In addition to presenting the prevalence of Class II indications for AVR in an asymptomatic AS patient cohort, the results of this analysis confirmed the results of previous studies demonstrating that very high peak velocity (≥5 m/s), elevated BNP, or reduced ejection fraction (<60%) are associated with increased risk of adverse outcomes in patients with asymptomatic severe AS.[17-19] Specifically, the primary composite endpoint of death, stroke, or HFH was more common in patients with1 1 or more Class II indications for AVR compared with patients without any of these criteria. Similar findings were observed for the individual components of stroke or HFH. Stroke occurred at a significantly higher rate in patients with Class IIa indications for AVR. Potential mechanisms that may explain this increased risk of stroke include higher prevalence of critical AS, heavily calcified and bicuspid aortic valves, atrial fibrillation, and extravalvular sequelae of severe AS given more advanced cardiac damage before, and a higher rate of progression to AVS.[11,20,21] Although comparisons for all-cause death did not meet statistical significance, rates of cardiovascular death were significantly higher in patients with Class II compared with those without Class II recommendations at baseline.

Patients with Class II guideline indications differed with regard to several baseline characteristics and echocardiographic variables compared

TABLE 2 Baseline Clinical Characteristics and Screening Echocardiographic Data by ACC/AHA Indication at Time of Randomization in the Intention-to-Treat Cohort

	No GR (n = 636)	Any Class II GR (n = 265)	*P* Value[a]
Clinical characteristics			
Age, y	76.0 ± 5.87 (636)	75.2 ± 6.28 (265)	0.03
Male	70.3 (447/636)	66.4 (176/265)	0.27
White race	95.0 (604/636)	95.8 (254/265)	0.73
BMI, kg/m^2	28.4 ± 4.44 (636)	28.7 ± 5.25 (265)	0.80
STS score, %	1.7 ± 0.95 (636)	1.9 ± 1.05 (265)	0.03
Bicuspid aortic valve disease	7.9 (50/635)	9.8 (26/264)	0.36
Diabetes mellitus	25.9 (165/636)	25.7 (68/265)	>0.99
Prior atrial fibrillation	11.3 (72/636)	21.9 (58/265)	<0.001
Prior stroke	3.6 (23/636)	6.0 (16/265)	0.11
Coronary artery disease	26.7 (170/636)	28.7 (76/265)	0.57
Myocardial infarction	3.9 (25/636)	6.0 (16/265)	0.17
Peripheral vascular disease	4.7 (30/636)	9.1 (24/265)	0.02
COPD	2.8 (18/636)	3.8 (10/265)	0.53
hs-cTnT, ng/L	14.1 (9.9, 19.6)	16.0 (11.3, 24.1)	<0.001
NT-proBNP, pg/mL	204.5 (108.6, 362.1)	689.8 (396.6, 1,482.0)	<0.001
eGFR, mL/min/1.73 m^2	72.0 (60.5, 85.7)	71.4 (61.2, 82.9)	0.47
Performed treadmill stress test[b]	92.0 (585/636)	87.2 (231/265)	0.03
6-minute walk test, meters	378.2 ± 99.24 (622)	358.7 ± 116.60 (261)	0.02
KCCQ score	92.8 ± 8.81 (626)	92.4 ± 9.63 (265)	0.62
Echocardiographic variables			
Aortic valve peak velocity, m/s	4.2 ± 0.32 (629)	4.6 ± 0.59 (263)	<0.001
Mean gradient, mm Hg	44.6 ± 7.26 (630)	52.5 ± 13.91 (263)	<0.001
Aortic valve area, cm^2	0.9 ± 0.22 (606)	0.8 ± 0.25 (255)	<0.001
Aortic valve area index, cm^2/m^2	0.45 ± 0.10 (606)	0.41 ± 0.11 (255)	<0.001
Left ventricular ejection fraction, %	69.2 ± 4.95 (630)	63.2 ± 8.05 (265)	<0.001
Stroke volume index, mL/m^2	45.2 ± 7.66 (606)	44.7 ± 8.71 (255)	0.20
LV global longitudinal strain, %	17.8 ± 2.07 (595)	16.6 ± 2.28 (252)	<0.001
LV mass index, g/m^2	99.1 ± 21.58 (618)	110.2 ± 26.52 (264)	<0.001
LA volume index, mL/m^2	35.8 ± 9.68 (627)	40.7 ± 13.73 (262)	<0.001
Moderate or greater AR	2.2 (14/627)	3.8 (10/263)	0.26
Moderate or greater MR	0.8 (5/620)	3.4 (9/263)	0.007
1 + valve with ≥moderate regurgitation	4.2 (26/614)	9.3 (24/258)	0.01

Values are mean ± SD (N), median (Q1, Q3), or % (n/N). [a]*P* values are based on the Wilcoxon Rank-Sum, test for continuous variables and Fisher's exact test for categorical and binary variables for a difference between No GR and Class IIb/IIa. [b]Some patients are unable to perform stress testing because of orthopedic and/or neurologic reasons.

AR = aortic regurgitation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; hs-cTnT = high sensitivity cardiac troponin T; KCCQ = Kansas City Cardiomyopathy Questionnaire; LA = left atrial; LV = left ventricular; MR = mitral regurgitation; NT-proBNP = N-terminal pro-B-type natriuretic peptide; STS = Society of Thoracic Surgeons; other abbreviations as in **Table 1**.

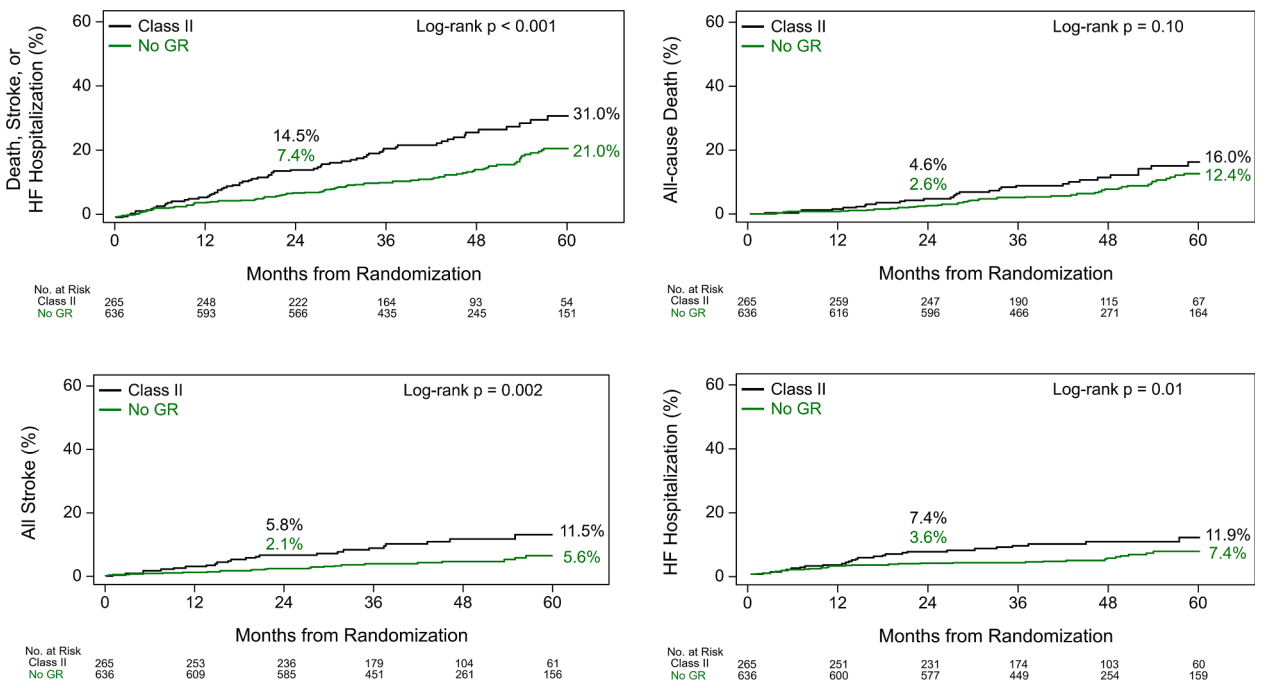
TABLE 3 Clinical Outcomes by ACC/AHA Indication in the Intention-to-Treat Cohort (Any Class II Compared With No GR)

	No GR (n = 636)	Any Class II GR (n = 265)	Log-Rank *P* Value
Death, stroke, or heart failure hospitalization	14.5 (92)	24.5 (65)	<0.001
Death, stroke, or unplanned CV hospitalization	34.1 (217)	40.4 (107)	0.14
Death, stroke, unplanned CV hospitalization, or AV intervention with acute valve syndrome	34.4 (219)	45.3 (120)	0.004
Death	7.7 (49)	11.3 (30)	0.10
Cardiovascular	3.6 (23)	6.8 (18)	0.04
Noncardiovascular	4.1 (26)	4.5 (12)	0.78
Stroke	3.9 (25)	9.1 (24)	0.002
Disabling	1.7 (11)	3.8(10)	0.06
Nondisabling	2.5 (16)	5.3 (14)	0.04
Heart failure hospitalization	5.2 (33)	9.8 (26)	0.01
Death or heart failure hospitalization	11.2 (71)	18.1 (48)	0.006

Values are % (N).
AV = aortic valve; CV = cardiovascular; other abbreviations as in Table 2.

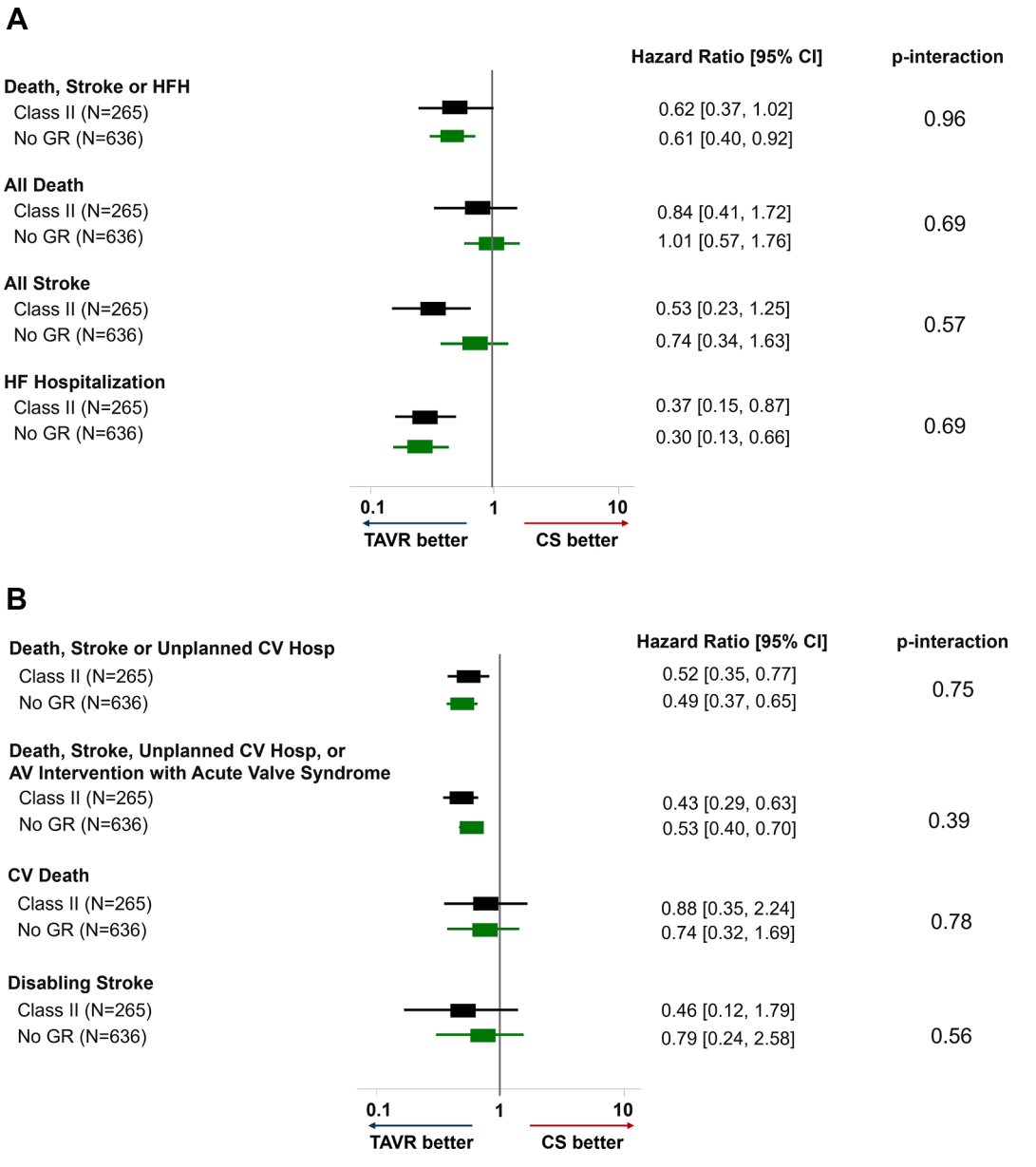
with individuals without guideline indications for AVR at baseline. Although some of these differences were the result of guideline definitions (aortic valve peak velocity, BNP level, and LVEF), differences were also observed in STS-PROM, history of atrial fibrillation or peripheral vascular disease, baseline cardiac troponin level, exercise capacity as assessed by exercise treadmill stress test and 6-minute walk test, left ventricular global longitudinal strain, left ventricular mass index, left

FIGURE 2 Kaplan-Meier Curves for Clinical Outcomes Stratified by Presence of Any Class II Guideline Recommendation for Aortic Valve Replacement at the Time of Randomization in the Intention-to-Treat Cohort



Kaplan-Meier rates of the primary composite endpoint stratified by presence of any Class II (IIa or IIb) guideline recommendation (GR) for aortic valve replacement. The proportional hazards assumption was met. HF = heart failure.

FIGURE 3 Forest Plot for Clinical Outcomes Stratified by Presence of Any Class II Guideline Recommendation for AVR at the Time of Randomization in the Intention-to-Treat Cohort

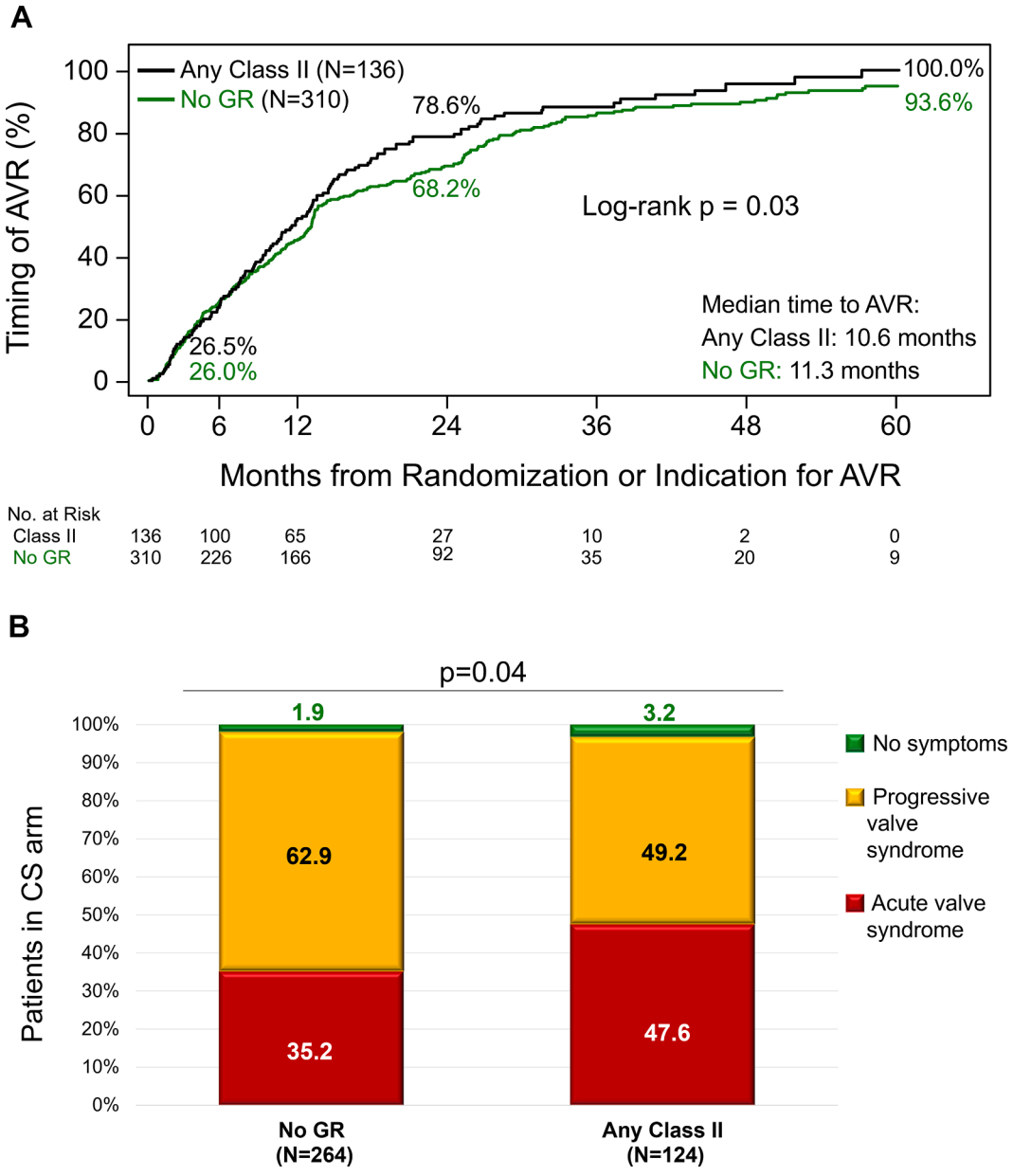


Interaction analysis between guideline recommendations (GR) level, treatment group, and the primary composite endpoint and its components is presented (A). Interaction analysis between GR level, treatment group, and additional clinical endpoints is presented (B). Treatment effects are analyzed using Cox proportional hazards models with $P_{interaction}$ values and are presented as HR with 95% confidence intervals. AV = aortic valve; CS = clinical surveillance; CV = cardiovascular; HFH = heart failure hospitalization.

atrial volume index, and presence of regurgitant valve lesions. These baseline differences between groups likely contributed to observed higher adverse event rates in Class II patients. Thus, given evidence of more cardiac damage, it is not surprising that Class II patients were more likely to have a higher burden of comorbidities at baseline and ultimately worse prognosis.[22]

Importantly, despite the higher rates of adverse clinical events in patients with Class II indications compared with those without GR for AVR at baseline, the benefit of early TAVR over CS was consistent,

FIGURE 4 Conversion to Delayed Aortic Valve Replacement (AVR) in the Clinical Surveillance (CS) Arm



Kaplan-Meier curves for rates of conversion to delayed aortic valve replacement in the clinical surveillance group stratified by presence or absence of Class II recommendations out to 5 years are presented (A). Comparison of the proportion of patients in the clinical surveillance valve implant population with no symptoms, progressive valve syndrome, and acute valve syndrome by presence of baseline Class II guideline recommendation (GR) at the time of delayed aortic valve replacement is presented (B). *P* value is based on a Wilcoxon rank-sum test.

regardless of the presence or absence of a Class II indication. Thus, based on these findings, factors included in the current Class II recommendations for AVR in patients with asymptomatic severe AS are indicators of increased risk, but their absence should not be used to justify a conservative management strategy. The current guidelines favor surgery over TAVR in patients with asymptomatic,

CENTRAL ILLUSTRATION **Outcomes in the EARLY TAVR Trial Based on Guideline-Directed Indications**

Outcomes in the EARLY TAVR Trial Based on 2020 Guideline-Directed Indications for Aortic Valve Replacement[1]

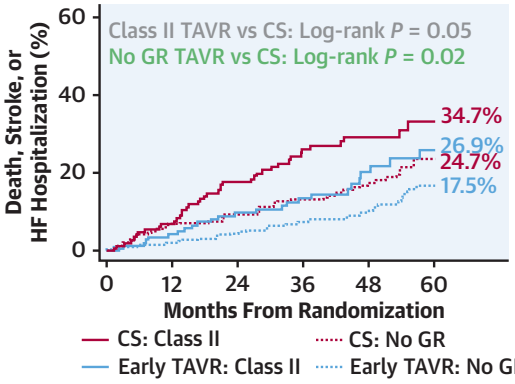
901 patients enrolled in the EARLY TAVR trial: a prospective, multicenter RCT evaluating patients with asymptomatic, severe AS

- Any Class II GR 29.4% (n = 265)
  - Class IIa GR 22.4% (n = 202)
  - Class IIb GR 7.0% (n = 63)
- No GR 70.6% (n = 636)

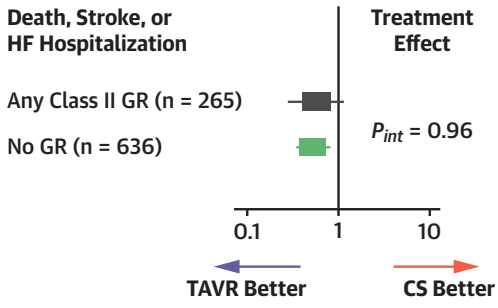
Death, Stroke, or HF Hospitalization (Median 3.8 Years Follow-Up)

Guideline Indication at Randomization	Event Rate %, (no. of events)	Log rank *P* value
2-group comparison		
No GR (n = 636)	14.5% (92)	0.0003
Any Class II (n = 265)	24.5% (65)	
3-group comparisons vs no GR		
Class IIb (n = 63)	22.2% (14)	0.001
Class IIa (n = 202)	25.2% (51)	

Kaplan-Meier Estimates for Death, Stroke, or HFH: By Treatment Arm



Impact of Guideline Recommendations on the Effect of Early TAVR



- In patients with asymptomatic, severe AS, ~30% had Class II recommendations for AVR at the time of randomization.
- Patients with Class II recommendations for AVR are at elevated risk for adverse clinical events.
- The relative benefit of prompt TAVR over CS was consistent regardless of the presence or absence of Class II recommendations for AVR at randomization.
- These data support the strategy of early TAVR over CS for individuals with asymptomatic severe AS, independent of ACC/AHA Class II recommendations.

Madhavan MV, et al. JACC Cardiovasc Interv. 2026;19(21):2876-2888.

Results from this analysis from the EARLY TAVR (transcatheter aortic valve replacement) trial demonstrate a consistent benefit of early TAVR over clinical surveillance for patients with asymptomatic severe aortic stenosis (AS) independent of the presence or absence of 2020 American College of Cardiology/American Heart Association (ACC/AHA) guideline indications at baseline. Otto et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease. *JACC*. 2020.[1] AVR = aortic valve replacement; CS = clinical surveillance; GR = guideline recommendation; HFH = heart failure hospitalization; RCT = randomized clinical trial.

severe AS who meet Class II indications.[8] However, our study supports broader consideration of TAVR in patients with asymptomatic severe AS who meet Class II indications.[3] This approach is consistent with the updated 2025 European Society of Cardiology/European Association of Cardiothoracic Surgery guidelines that provide a new Class IIa recommendation for consideration of intervention for asymptomatic severe high-gradient AS with LVEF ≥50% as an alternative to close active surveillance in low-procedural risk patients.[23] Importantly, this guidance is agnostic to type of AVR in light of contemporary studies demonstrating similar outcomes between TAVR and surgery across surgical risk strata.[24-31]

PRACTICAL IMPLICATIONS. The findings of this analysis have implications for clinical practice. These data support the superiority of the strategy of early TAVR over CS for individuals with asymptomatic severe AS, independent of ACC/AHA Class II recommendations. Given that patients with Class II recommendations for AVR were at heightened risk for adverse clinical outcomes, the present analysis also supports consideration for relative prioritization of these patients in circumstances where there are limited resources or waitlists for AVR.

STUDY LIMITATIONS. This study has limitations that should be acknowledged. As a retrospective analysis of a prospective randomized clinical trial, the present results should be considered hypothesis-generating and may be impacted by unmeasured confounders. With respect to analyzing the trial population according to the 2020 ACC/AHA valvular heart disease guidelines, trial randomization was not stratified by guideline indication and subgroup analysis is limited with regard to the number of patients in each group (particularly the Class IIb subgroup). Though the ACC/AHA Class IIa guidelines are specifically relevant to low surgical risk patients, patients were not required to be low surgical risk to enroll in the EARLY TAVR trial. However, the mean STS-PROM of patients in this trial was 1.8% ± 1.0%, and thus a significant proportion of patients enrolled in this study were considered low risk. As serial echocardiograms were not performed before randomization, information regarding progression of disease as manifested by an increase in peak velocity ≥0.3 m/s per year was not available at the time of screening, and thus, this guideline indication could not able to be evaluated in this analysis (Class IIa). With regard to Class IIb guidelines, LVEF <60% was determined by an independent core laboratory as opposed to at least 3 separate echocardiograms.

CONCLUSIONS

Among patients with asymptomatic severe AS enrolled in the EARLY TAVR trial, approximately 30% of patients had Class II recommendations at the time of randomization. Although patients with Class II recommendations were at increased risk of adverse events, the benefits of early TAVR compared with CS were present independent of the presence or absence of current Class II GR.

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PERSPECTIVES

WHAT IS KNOWN? The current U.S. clinical guidelines on timing of aortic valve replacement recommend prompt treatment for patients with severe aortic stenosis with symptoms, LVEF <50%, or asymptomatic individuals with severe AS undergoing cardiac surgery for other indications. The EARLY TAVR trial demonstrated the superiority of the early TAVR strategy compared with guideline-recommended CS for patients with asymptomatic, severe AS. This study examines the prevalence of Class II guideline indications at the time of randomization for patients enrolled in the EARLY TAVR trial and the associated impact on clinical outcomes.

WHAT IS NEW? Among patients with asymptomatic, severe AS enrolled in the EARLY TAVR trial, approximately 30% of patients had a Class II indication at the time of randomization. Patients with a Class IIa/IIb indication were at increased risk of death, stroke, or HFH. There was a consistent benefit of Early TAVR for clinical outcomes including death, stroke, or HFH, compared with CS across all guideline indications.

WHAT IS NEXT? These data support a strategy of early TAVR over CS for individuals with asymptomatic, severe AS, independent of guideline indication, and could be taken into consideration in subsequent updates to the clinical guidelines on timing of treatment for patients with severe AS.

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KEY WORDS **aortic stenosis, aortic valve replacement, asymptomatic, clinical guidelines, surveillance, symptoms, transcatheter aortic valve replacement**

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