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ORIGINAL RESEARCH

CORONARY, PERIPHERAL, AND STRUCTURAL INTERVENTIONS

Multimarker Approach to Improve Risk Stratification of Patients Undergoing Transcatheter Aortic Valve Implantation

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ABSTRACT

BACKGROUND A blood multimarker approach may be useful to enhance risk stratification in patients undergoing TAVI.

OBJECTIVES The objective of this study was to determine the prognostic value of multiple blood biomarkers in transcatheter aortic valve implantation (TAVI) patients.

METHODS In this prospective study, several blood biomarkers of cardiovascular function, inflammation, and renal function were measured in 362 patients who underwent TAVI. The cohort was divided into 3 groups according to the number of elevated blood biomarkers (ie, ≥ median value for the whole cohort) for each patient before the procedure. Survival analyses were conducted to evaluate the association between blood biomarkers and risk of adverse event following TAVI.

RESULTS During a median follow-up of 2.5 (IQR: 1.9-3.2) years, 34 (9.4%) patients were rehospitalized for heart failure, 99 (27%) patients died, and 113 (31.2%) met the composite endpoint of all-cause mortality or heart failure rehospitalization. Compared to patients with 0 to 3 elevated biomarkers (referent group), those with 4 to 7 and 8 to 9 elevated biomarkers had a higher risk of all-cause mortality (HR: 1.54 [95% CI: 0.84-2.80], $P = 0.16$, and HR: 2.81 [95% CI: 1.53-5.15], $P < 0.001$, respectively) and of the composite endpoint (HR: 1.65 [95% CI: 0.95-2.84], $P = 0.07$, and HR: 2.67 [95% CI: 1.52-4.70] $P < 0.001$, respectively). Moreover, adding the number of elevated blood biomarkers into the clinical multivariable model provided significant incremental predictive value for all-cause mortality (Net Reclassification Index = 0.71, $P < 0.001$).

CONCLUSIONS An increasing number of elevated blood biomarkers is associated with higher risks of adverse clinical outcomes following TAVI. The blood multimarker approach may be helpful to enhance risk stratification in TAVI patients. (JACC Adv 2024;3:100761) © 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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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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ABBREVIATIONS AND ACRONYMS

ALP = alkaline phosphatase

AS = aortic stenosis

GDF = growth differentiation factor

HE4 = human epididymis protein 4

HF = heart failure

hs-CRP = high-sensitivity C-reactive protein

hs-cTnT = high-sensitivity cardiac troponin test

IL = interleukin

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

SAVR = surgical aortic valve replacement

TAVI = transcatheter aortic valve implantation

Transcatheter aortic valve implantation (TAVI) is a valuable alternative to surgical aortic valve replacement (SAVR) for the treatment of patients with symptomatic severe aortic stenosis (AS) at high, intermediate, and low surgical risk.[1-4] However, a substantial proportion of patients die shortly after TAVI or do not experience any improvement in quality of life.[5-7] Although several factors have been associated with the risk of TAVI futility, including severe frailty, severe noncardiac comorbidities, or mental health disorders, this adverse outcome remains difficult to predict. In the current guidelines for the management of valvular heart disease, there is minimal role and emphasis on the utilization of blood biomarkers, except that of markedly elevated brain natriuretic peptide for the consideration of SAVR in asymptomatic patients with severe AS.[3,4] In patients undergoing SAVR, we previously reported that an approach using several blood biomarkers of cardiovascular stress and heart failure (HF) provides incremental value over baseline clinical variables and risk score to predict postoperative mortality.[8]

The objective of this prospective observational cohort study was to assess the prognostic value of multiple blood biomarkers of cardiovascular function, HF, inflammation, and renal function in patients with symptomatic severe AS undergoing TAVI.

METHODS

POPULATION. We prospectively enrolled 362 consecutive patients in the unicentric TAVI-B (Transcatheter Aortic Valve Implantation Biomarkers) study from January 2017 to August 2020. Briefly, patients were included if they had symptomatic severe AS and were candidate for TAVI. Exclusion criteria included surgical reinterventions on the aortic valve. The Institutional Review Board committee of the participating center approved the study and the subjects provided written informed consent. All standard echocardiographic, demographic, and clinical variables were collected at hospitalization prior to TAVI procedure, at discharge, and at annual follow-up.

BLOOD BIOMARKERS. Plasma and serum samples were collected before the TAVI procedure and stored at −80 C. The analyses of the biomarkers were performed in a core laboratory using enzyme-linked immunosorbent assay kits approved for clinical use and commercialized by Roche Diagnostics. The blood biomarkers included markers of: 1) myocardial damage: creatine kinase myocardial band, growth differentiation factor (GDF)-15, high-sensitivity cardiac troponin test (hs-cTnT), N-terminal B-type natriuretic peptide (NT-proBNP), human epididymis protein 4 (HE4), and cancer antigen 125; 2) inflammation: interleukin (IL)-6, high-sensitivity C-reactive protein (hs-CRP), ferritin, lactate dehydrogenase, soluble fms-like tyrosine kinase-1, procalcitonin, alkaline phosphatase (ALP), alanine aminotransferase; and 3) renal function: creatinine (Supplemental Tables 1 and 2).

A blood biomarker was considered elevated in a given patient if its value was ≥ median value for this biomarker in the whole cohort (**Table 1**). To evaluate the prognostic value of the blood biomarkers, the cohort was divided into 3 groups according to the number of elevated biomarkers for each patient before the procedure: 0 to 3, 4 to 7, and 8 to 9.

DOPPLER-ECHOCARDIOGRAPHIC DATA. Analyses of echocardiogram were performed using the TomTec Imaging Platform (V.4.6, Image Arena) software. Mean transvalvular pressure gradient (MG) was measured with the simplified Bernoulli formula.[9] The stroke volume was calculated by multiplying the cross-sectional area of the left ventricular outflow tract with the velocity-time integral measured below the valve.[9] Aortic valve area was calculated using the continuity equation. Aortic, mitral, and tricuspid valve regurgitations were assessed using a multiparameter integrative approach as previously described.[10] Left ventricular (LV) systolic function was assessed by the measurement of left ventricular ejection fraction using the biplane Simpson method.[11] All other measurements were performed according to the European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines.[11]

STUDY ENDPOINTS. The primary endpoints were: 1) all-cause mortality; and 2) the composite of all-cause mortality and rehospitalization for HF. Mortality and hospitalization data, as well as their causes, were obtained from the central Québec Institute of Statistics database.

The secondary endpoints were: 1) treatment futility defined as NYHA functional class ≥III, rehospitalization for HF, or all-cause mortality at 1 year; 2) HF symptoms as assessed by NYHA functional class; 3) Duke Activity Status Index (DASI) score; 4) Kansas City Cardiomyopathy Questionnaire (KCCQ); and 5) 6-minute walk test (6MWT).

STATISTICAL ANALYSES. Continuous variables were first tested for normality by the Shapiro and Wilk test or the Kolmogorov-Smirnov test and expressed as

median (IQR) or mean ± SD, as appropriate. Univariable Cox proportional hazards regression analysis and logistic regression analysis were used to evaluate the association between each blood biomarker with treatment futility (**Table 1**, Supplemental Table 3). The cohort was then divided into 3 groups (0-3, 4-7, and 8-9) according to the number of elevated biomarkers for each patient. Kruskal-Wallis tests were performed to evaluate differences between groups. Categorical variables were compared using the chi-square or Fisher exact test and expressed in number of patients with percentages. Cumulative incidence of 4-year all-cause mortality was calculated for each group using Kaplan-Meier analysis and compared using the log-rank test. To account for factors influencing blood biomarker levels and confounding variables, multivariable Cox proportional hazards regression analyses were performed adjusting for age, sex, Society of Thoracic Surgeons (STS) score, diabetes mellitus, congestive HF, chronic obstructive pulmonary disease, history of atrial fibrillation, pacemaker, coronary artery disease for the primary endpoints. HR (95% CI) were reported for each group and compared. The proportional hazards assumption was confirmed through the evaluation of scaled Schoenfeld residuals. A subgroup analysis was conducted in order to examine the robustness of the result with and without valve-in-valve procedure. In addition, 3 models were built to assess and compare the predictive value of the blood biomarkers. The first model included baseline variables associated with all-cause mortality (age, sex, diabetes mellitus, congestive HF, chronic obstructive pulmonary disease, history of atrial fibrillation, pacemaker, and coronary artery disease) without the addition of blood biomarkers (ie, clinical model). The second model included only blood biomarkers: hs-cTnT, NT-proBNP, IL-6, GDF-15, hs-CRP, HE4, creatinine, procalcitonin, and ALP (ie, multimarker model). The third model included baseline clinical variables associated with all-cause mortality with the addition of blood biomarkers. The predictive value of each model and the STS score was assessed using receiver operating characteristics analysis. The incremental predictive value of the model including both clinical variable and blood biomarkers vs the clinical model was assessed using the net reclassification index. Multivariable linear mixed regressions adjusted for age, sex, body mass index, renal failure, and STS score were used to assess the association between the number of elevated blood biomarkers and the KCCQ, DASI score, and 6MWT over the following time points: baseline, 1 to 3 months, and 1 year. All tests were 2-sided and P values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corporation) and STATA (StataCorp 2017).

TABLE 1 Univariate Analysis of the Association Between Elevated Blood Biomarkers and 4-Year All-Cause Mortality

		Univariable Analysis	
Biomarkers	**Median Value**	**HR (95% CI)**	***P* Value**
CK-MB, ng/mL	2.3 (1.7-3.2)	0.87 (0.58-1.29)	0.485
CA-125, U/mL	15.2 (9.6-28.8)	0.78 (0.52-1.16)	0.226
Ferritin, μg/L	127.4 (65.4-242.2)	1.12 (0.76-1.67)	0.564
LDH, U/L	194.5 (170-238)	1.22 (0.82-1.82)	0.303
sFlt-1, pg/mL	189.3 (86.8-582.5)	1.01 (0.67-1.55)	0.960
hs-cTnT, ng/L	28.5 (16.7-50.1)	2.82 (1.81-4.39)	**<0.001**
NT-proBNP, pg/mL	1,371 (493.8-3,646)	1.98 (1.31-2.98)	**<0.001**
IL-6, pg/mL	5.8 (3.1-11.2)	2.20 (1.43-3.39)	**<0.001**
GDF-15, pg/mL	2286.5 (1,518-3,598)	1.78 (1.19-2.68)	**0.005**
hs-CRP, mg/L	3.5 (1.6-9.6)	1.61 (1.07-2.41)	**0.021**
HE4, pmol/L	115 (80.7-162)	3.23 (2.03-5.12)	**<0.001**
Creatinine, μmol/L	89 (70-117.7)	1.61 (1.07-2.42)	**0.021**
Procalcitonin, ng/mL	0.056 (0.037-0.083)	2.50 (1.62-3.86)	**<0.001**
ALP, U/L	73 (60-92)	1.49 (0.99-2.24)	0.051
ALT, U/L	13.9 (10.2-20.0)	1.03 (0.69-1.53)	0.867

Values are median (IQR) unless otherwise indicated. **Bold** values denote statistical significance at the $P < 0.05$ level.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; CA-125 = cancer antigen 125; CK-MB = creatine kinase-myocardial band; GDF = growth differentiation factor; HE4 = human epididymis protein 4; hs-CRP = high-sensitivity C-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; IL = interleukin; LDH = lactate dehydrogenase; NT-proBNP = N-terminal B-type natriuretic peptide; sFlt-1 = soluble fms-like tyrosine kinase 1.

RESULTS

STUDY POPULATION. **Table 2** presents the baseline characteristics according to the number of elevated biomarkers. Among the 362 patients included in this study, 141 (39.0%) had 0 to 3 elevated biomarkers, 116 (32.0%) 4 to 6, and 105 (29.0%) 8 to 9 before TAVI. Overall, the mean age of the study population was 79.6 ± 8.2 years and most of the patients were male (57.3%). Patients with 8 to 9 elevated biomarkers were older, more often males and had a higher prevalence of comorbidities, worse NYHA functional class and a higher European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) and STS score compared to the 2 other groups of elevated biomarkers (**Table 2**). The prevalence of symptoms according to the groups of elevated biomarkers is presented in Supplemental Figures 1 and 2. Medications of the cohort at baseline are presented in Supplemental Table 4. Left ventricular ejection fraction and MG decreased significantly as the number of elevated biomarkers per patient increased ($P < 0.001$) (**Table 3**). The proportion of patients with low-gradient severe AS (ie, MG <40 mm Hg and aortic valve area <1.0 cm^2) was 33.6%; 29.4% and 37.1% in

TABLE 2 Baseline Characteristics According to the Number of Elevated Blood Biomarkers

	All Patients (N = 362)	0-3 Biomarkers Elevated (n = 141, 39.0%)	4-7 Biomarkers Elevated (n = 116, 32.0%)	8-9 Biomarkers Elevated (n = 105, 29.0%)	*P* Value
Age, y	79.6 ± 8.2	76.4 ± 8.7	80.2 ± 7.7	81.1 ± 8[a,b]	0.683
Male	208 (57.3)	66.8 (46.8)	63 (54.3)	79 (74.5)[a,b]	**<0.001**
Body mass index, kg/m^2	28.1 ± 6.6	28.3 ± 7.3	27.9 ± 5.7	28.2 ± 6.7	**0.006**
Hypertension	322 (88.7)	124 (87.9)	105 (94.5)	93 (87.7)	0.745
Dyslipidemia	304 (83.7)	114 (80.9)	100 (86.2)	90 (84.9)	0.475
Diabetes mellitus	132 (36.4)	41 (29.1)	44 (37.9)	47 (44.3)[b]	**0.043**
Smoking history	92 (25.5)	29 (20.5)	31 (24.2)[a]	32 (30.5)[a,b]	**0.033**
Cancer	72 (19.6)	24 (17.1)	25 (21.5)[a]	23 (21.7)[a]	0.162
CHF	118 (32.7)	30 (21.4)	39 (33.3)[a]	49 (46.7)[a,b]	**<0.001**
Previous MI	37 (10.2)	9 (6.4)	9 (7.8)	19 (17.9)[a,b]	**0.008**
COPD	81 (22.3)	24 (17.0)	25 (21.6)	32 (30.2)[b]	**0.047**
History of AF	125 (34.7)	36 (25.9)	40 (34.8)	49 (46.2)[b]	**0.004**
Pacemaker	60 (16.3)	12 (8.5)	28 (24.1)	20 (18.9)[b]	**0.003**
Prior LBBB	28 (7.7)	7 (5.0)	12 (10.3)	9 (8.5)	0.441
CAD	218 (60.2)	74 (52.9)	64 (55.2)	80 (75.5)[a,b]	**0.001**
History of CABG	93 (25.6)	31 (22.0)	29 (25.0)	33 (31.1)	0.260
History of PCI	153 (42.1)	49 (34.8)	47 (40.5)	57 (53.8)[a,b]	**0.010**
Cerebrovascular disease	31 (8.5)	8 (5.7)	15 (12.9)	8 (7.5)	0.106
History of TIA	36 (9.9)	9 (6.4)	14 (12.9)	13 (12.3)	0.199
Peripheral vascular disease	81 (22.3)	21 (14.9)	28 (24.1)[a]	32 (30.2)[b]	**0.014**
Renal failure	174 (48.5)	35 (25.2)	58 (50.9)	81 (76.6)[a,b]	**<0.001**
EuroSCORE II, %	4.0 (2.3-7.7)	2.6 (1.7-4.4)	4 (2.7-8.4)[a]	7.1 (3.4-12.6)[a,b]	**<0.001**
STS score	3.9 (2.79-6.0)	3 (2.1-4.1)	4 (3-5.3)[a]	6 (4.3-9.5)[a,b]	**<0.001**
NYHA functional class ≥ III	235 (64.7)	80 (56.7)	74 (63.8)	81 (76.4)[a,b]	**0.006**

Values are mean ± SD, n (%), or median (25th-75th interquartile range). **Bold** values denote statistical significance at the $P < 0.05$ level. *P* values refer to comparison between group of number biomarkers elevated. [a]$P < 0.05$ vs 4 to 7 biomarkers elevated group. [b]$P < 0.05$ vs 8 to 9 biomarkers elevated group.

AF = atrial fibrillation; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; EuroSCORE II = European System for Cardiac Operative Risk Evaluation II; LBBB = left bundle branch block; MI = myocardial infarction; PCI = percutaneous coronary intervention; STS score = Society of Thoracic Surgeons score; TIA = transient ischemic attack.

the 0 to 3; 4 to 7 and 8 to 9 elevated biomarkers groups, respectively ($P = 0.009$). The prevalence of significant (ie, ≥moderate) mitral and tricuspid regurgitation increased as the number of elevated biomarkers increased ($P < 0.001$). The other echocardiographic characteristics were similar between groups (Table 3).

PROCEDURAL AND SHORT-TERM OUTCOMES. Procedural data are shown in Supplemental Table 5. Briefly, 225 (62.2%) and 85 (23.5%) patients received balloon expandable and self-expanding transcatheter valves, respectively. Transfemoral access was used in 66.9% of patients. The rate of pre- and post-dilatation was low (10.3% and 13.6%, respectively) and procedural success was achieved in 98.6% of cases. The short- and long-term outcomes following the procedure are presented in Supplemental Table 6. In comparison with patients with low circulating levels of hs-cTnT, NT-proBNP, IL-6, GDF-15, hs-CRP, HE4, creatinine, procalcitonin and ALP, patients with at least 4 elevated biomarkers had significantly higher length of hospital stay, as well as higher rates of 1- and 4-year all-cause mortality, cardiovascular mortality and rehospitalization for HF ($P < 0.001$).

PROGNOSTIC VALUE OF BLOOD BIOMARKERS. During a median follow-up of 2.5 (IQR: 1.9-3.2) years, 34 (9.4%) patients were rehospitalized for HF, 99 (27.3%) died, and 113 (31.2%) met the composite endpoint of all-cause mortality or rehospitalization for HF. The association between each blood biomarker and all-cause mortality is shown in Table 1 and the association between clinical and echocardiographic variables and all-cause mortality in Supplemental Table 7. Kaplan-Meier survival estimates at 4 years were 67%, 62%, and 33% in the 0 to 3, 4 to 7, and 8 to 9 elevated biomarkers groups, respectively (log-rank, $P < 0.001$) (Figure 1).

In multivariable Cox regression analysis adjusted for age, sex, STS score, diabetes mellitus, congestive HF, chronic obstructive pulmonary disease, history of atrial fibrillation, pacemaker, coronary artery disease and compared to patients with 0 to 3 elevated biomarkers, a larger number of elevated biomarkers was associated with an increased risk of all-cause

TABLE 3 Baseline Echocardiographic Characteristics

	All Patients (N = 362)	0-3 Biomarkers Elevated (n = 141, 39.0%)	4-7 Biomarkers Elevated (n = 116, 32.0%)	8-9 Biomarkers Elevated (n = 105, 29.0%)	*P* Value
LVEF, %	53.6 ± 11.8	58.4 ± 7.9	52.9 ± 10.9[a]	48.1 ± 14[a,b]	**<0.001**
AV PG, mm Hg	71.7 ± 26.8	77.1 ± 26.2	70.9 ± 27.2	65.6 ± 25.6[a,b]	**0.002**
MG, mm Hg	43.2 ± 17.5	46.2 ± 17.5	43.2 ± 18	39.3 ± 16.2[a,b]	**0.009**
EOA, cm^2	0.71 ± 0.25	0.70 ± 0.19	0.71 ± 0.25	0.72 ± 0.70	0.940
EOAi, cm^2/m^2	0.38 ± 0.11	0.36 ± 0.9	0.35 ± 0.10	0.36 ± 0.07	0.236
SVi, mL/m^2	36.49 ± 8.7	38.44 ± 9.9	35.45 ± 7.6	35.25 ± 8.4	0.588
SVi ≤35 mL/m^2	80 (22.0)	34 (24.1)	31 (26.7)	15 (14.2)	0.059
AR ≥ moderate	60 (16.5)	20 (14.2)	24 (20.7)	15 (15.1)	0.337
MR ≥ moderate	84 (23.1)	17 (12.1)	30 (35.7)[a]	37 (44.0)[b]	**<0.001**
TR ≥ moderate	42 (18.8)	11 (12.1)	6 (9.1)	25 (37.3)[a,b]	**<0.001**
PAPs ≥50 mm Hg	141 (38.4)	53 (37.6)	41 (35.3)	47 (44.3)	0.361

Values are mean ± SD or n (%). **Bold** values denote statistical significance at the $P < 0.05$ level. [a]$P < 0.05$ vs 4 to 7 biomarkers elevated group. [b]$P < 0.05$ vs 8 to 9 biomarkers elevated group.

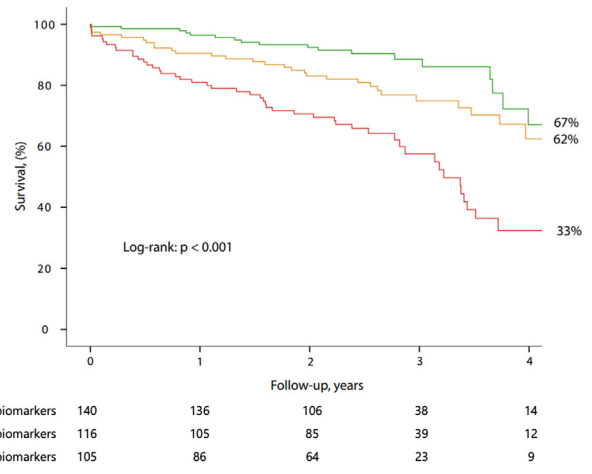
AR = aortic regurgitation; AV PG = aortic valve peak gradient; EOA = effective orifice area; LVEF = left ventricular ejection fraction; MG = mean transvalvular pressure gradient; MR = mitral regurgitation; PAPs = systolic pulmonary artery pressure; SVi = stroke volume indexed; TR = tricuspid regurgitation.

mortality over a 4-year period after TAVI (4-7 elevated biomarkers: HR: 1.54 [95% CI: 0.84-2.80], $P = 0.16$, and 8 to 9 elevated biomarkers: HR: 2.81 [95% CI: 1.53-5.15], $P < 0.001$) (**Central Illustration**). A larger number of elevated biomarkers was associated with a significantly higher risk of the composite endpoint of rehospitalization for HF and all-cause mortality: 19.3% in the 0 to 3 elevated biomarkers group; 33.6% in the 4 to 7 group and 44.3% in the 8 to 9 group ($P < 0.001$). In multivariable analysis, a larger number of elevated blood biomarkers was associated with higher risk of the composite of rehospitalization for HF and all-cause mortality (4-7 elevated biomarkers: HR: 1.65 [95% CI: 0.95-2.84], $P = 0.07$; 8 to 9 elevated biomarkers: HR: 2.67 [95% CI: 1.52-4.70] $P < 0.001$) (**Central Illustration**). Similar results were obtained regarding rehospitalization for HF (Supplemental Figure 3).

These results were confirmed in a subgroup analysis excluding 42 patients who underwent valve-in-valve procedure (Supplemental Table 8). In this subgroup, 90 (28.3%) patients died, 102 (32.1%) met the composite endpoint of all-cause mortality or rehospitalization for HF, and 63 (19.9%) met the composite endpoint of treatment futility.

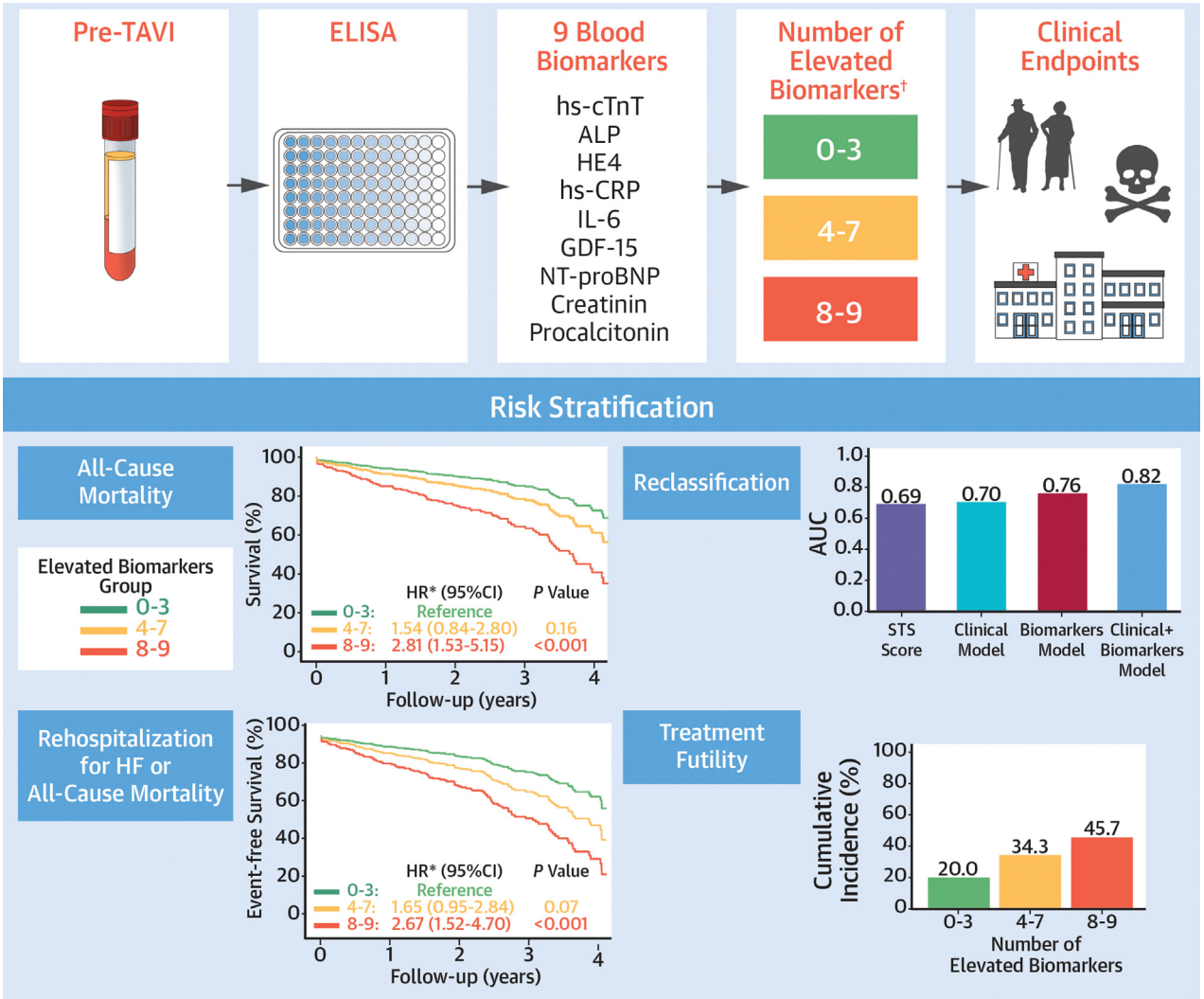
The C-statistics for 4-year all-cause mortality was: area under the curve (AUC); 0.69 (95% CI: 0.62-0.75), $P < 0.001$ for STS score; area under the curve (AUC); 0.70 (95% CI: 0.65-0.76), $P < 0.001$ for the clinical model (age, sex, diabetes mellitus, congestive HF, chronic obstructive pulmonary disease, history of atrial fibrillation, pacemaker, and coronary artery diseases); AUC: 0.76 (95% CI: 0.71-0.81), $P < 0.001$ for the model including only the blood biomarkers; and AUC: 0.82 [95% CI: 0.77-0.87], $P < 0.001$ for the model including both the clinical variables and the blood biomarkers (**Figure 2**). The addition of the number of elevated blood biomarkers to the clinical model provided significant and important incremental predictive value for all-cause mortality at 4 years (Net Reclassification Index = 0.71, $P < 0.001$).

FIGURE 1 Kaplan-Meier Survival Curves According to the Number of Elevated Blood Biomarkers



Kaplan-Meier estimates of all-cause mortality according to the number of elevated biomarkers per patients treated with transcatheter aortic valve implantation. Kaplan-Meier curves represents mortality according to the number of elevated biomarkers: 0 to 3 (green), 4 to 7 (orange), and 7 to 9 (red).

CENTRAL ILLUSTRATION **Multimarker Approach to Improve Risk Stratification of Patients Undergoing Transcatheter Aortic Valve Implantation**



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*Adjusted for age, sex, STS score, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, history of atrial fibrillation, pacemaker, coronary artery disease. †A blood biomarker was considered elevated in a given patient if its value was greater than the median value for this biomarker in the whole cohort. 6MWT = 6-minute walk test; ALP = alkaline phosphatase; DASI = Duke Activity Status Index; ELISA = enzyme-linked immunoassay; GDF= growth differentiation factor; HE4 = human epididymis protein 4; HF = heart failure; hsCRP = high-sensitivity C-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; IL = interleukin; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal B-type natriuretic peptide; STS = Society of Thoracic Surgeons Score; TAVI = transcatheter aortic valve implantation.

In subgroup analyses (Supplemental Figure 4), a larger number of elevated biomarkers (>4) was associated with a markedly increased risk of mortality in patients with STS score was ≥4 (HR: 2.72 [95% CI: 1.35-4.51]) but not in those with STS score <4 (HR: 1.39 [95% CI: 0.65-3.15]; *P* value for interaction <0.001).

BLOOD BIOMARKERS AND TREATMENT FUTILITY. In a subgroup analysis of 326 patients, 70 (21%) met the composite endpoint of treatment futility, and the rate of this endpoint increased as the number of elevated biomarkers increased (Supplemental Table 8, **Central Illustration**). In multivariable analysis adjusted for age, sex, body mass index, renal failure, STS score and using patients with 0 to 3 elevated biomarkers as the referent group, a larger number of elevated biomarkers was independently associated

with an increased risk of treatment futility defined as the composite of all-cause mortality, NYHA functional class ≥III or rehospitalization for HF at 1 year (4-7 elevated biomarkers: OR: 2.15 [95% CI: 1.00-4.66], $P = 0.050$, and 8 to 9 elevated biomarkers: OR: 2.93 [95% CI: 1.23-7.01], $P = 0.015$) (Supplemental Table 9).

BLOOD BIOMARKERS AND QUALITY OF LIFE. The association between the number of elevated blood biomarkers with KCCQ, DASI, and 6MWT during the first year of follow-up is presented in Supplemental Figures 5-7, respectively. There was no significant association between the number of elevated biomarkers and KCCQ at 1 to 3 months and 1 year after TAVI, but a trend toward worse KCCQ as the number of elevated biomarkers increased (Supplemental Figure 5). In comparison with the referent group (0-3 elevated biomarkers), patients with 4 to 7 and 8 to 9 elevated biomarkers had a significantly lower DASI score at 1 to 3 months and 1 year after TAVI (Supplemental Figure 6). Patients with 8 to 9 elevated biomarkers had a significantly shorter 6MWT distance at baseline, 1 to 3 months, and 1 year after TAVI when compared to patients with the referent group (Supplemental Figure 7).

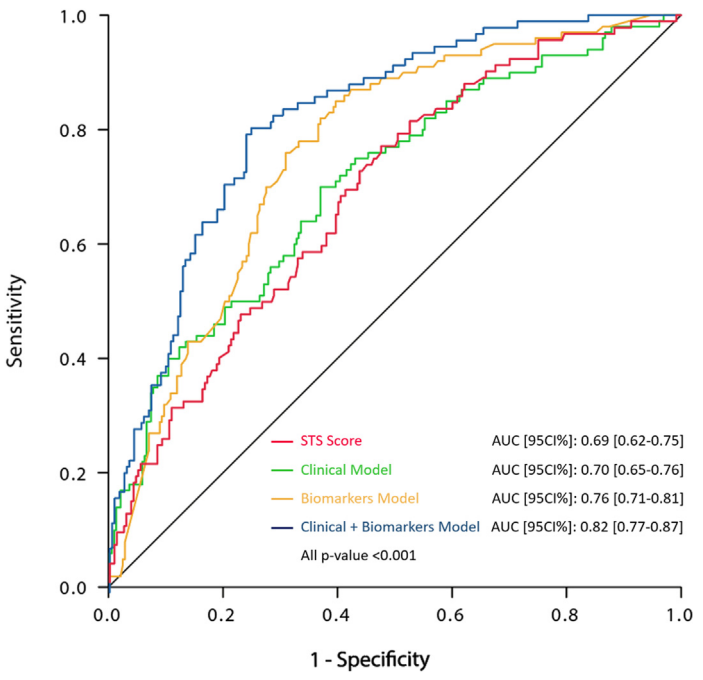
DISCUSSION

The main findings of the study are: 1) a larger number of elevated biomarkers of cardiac damage, HF, inflammation, and renal function before TAVI procedure is associated with increased risk of all-cause mortality, rehospitalization for HF, treatment futility, and worse quality of life following TAVI; and 2) the multivariable model including only blood biomarkers performed as well as the model including baseline clinical variables to predict all-cause mortality. Furthermore, the addition of blood biomarkers panels provided clinically significant incremental predictive value over the clinical model, thereby suggesting a potential role of a multiple biomarker approach in risk stratification in patients undergoing TAVI.

MULTIMARKER APPROACH. There are few studies that reported the prognostic ability of multiple blood biomarkers approach to predict all-cause mortality in patients with severe AS undergoing AVR.[8,12] Consistent with previous studies,[8,12-22] we found that blood biomarkers of myocardial damage such as Nt-proBNP, GDF-15, and hs-cTnT as well as biomarkers of inflammation (IL-6 and CRP, procalcitonin, ALP) are associated with a worse prognosis and cardiovascular events after TAVI. HE4 was originally used to diagnose ovarian cancer; this secretory protein has been shown to be associated with higher rates of rehospitalization and mortality in HF population and might be a marker of myocardial fibrosis.[23-26] In the present study, HE4 was strongly associated with increased rates of adverse events (ie, death or HF rehospitalization) following TAVI. Several previous studies reported that SAVR or TAVI is associated with reduced renal function following the procedure.[27-29] In the present study, a higher circulating level of creatinine was also associated with an increased risk of mortality following TAVI. In contrast to previous studies that reported an association between higher circulating levels of cancer antigen 125 and adverse outcomes following TAVI,[30-32] we did not find such an association in the present study.

RISK STRATIFICATION IN TAVI PATIENTS. The existing risk scores (STS score, EuroSCORE, Charlson index) are not necessarily adapted to the TAVI population and have a modest accuracy to predict

FIGURE 2 Incremental Prognostic Value of Blood Biomarkers to Predict All-Cause Mortality



ROC curve analysis assessing the prognostic value of the multimarker model (ie, hs-cTnT, NT-proBNP, IL-6, GDF-15, hs-CRP, HE4, creatinine, procalcitonin and ALP [orange line]) and the clinical model (ie, age, sex, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, history of atrial fibrillation, pacemaker, coronary artery diseases and STS score [green line]), the STS score (red line) and the mixed model (blue line) to predict all-cause mortality. ALP = alkaline phosphatase; GDF = growth differentiation factor; HE4 = human epididymis protein 4; hsCRP = high-sensitivity C-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; IL = interleukin; NT-proBNP = N-terminal B-type natriuretic peptide; ROC = receiver operating curve; STS = Society of Thoracic Surgeons Score.

mortality and rehospitalization following this procedure.[33,34] The blood multimarker approach proposed and validated in the present study provides a simple tool to enhance the risk stratification process to identify patients in whom TAVI may be futile. In particular, we found that a larger number of elevated biomarkers before the procedure is associated with an increased rate of treatment futility: that is, 20.0%, 34.3%, and 45.7% regarding the composite of all-cause mortality, NYHA functional class ≥III or rehospitalization for HF at 1 year in the 0 to 3, 4 to 7, and 8 to 9 elevated biomarkers groups, respectively. Moreover, we found that when the number of elevated blood biomarkers is ≥4, the risk of mortality and/or HF rehospitalization increases markedly and, to a much larger extent, when the number of elevated biomarkers is ≥8. Furthermore, the association between the number of elevated blood biomarkers and mortality was observed only in the patients with intermediate or high surgical risk (STS score >4) but not in those with low surgical risk.

Given that the patients undergoing TAVI often have concomitant noncardiac comorbidities and diseases, we used a panel including not only biomarkers of cardiac damage and dysfunction but also biomarkers of inflammatory, fibrosis, renal dysfunction, and cancer. Our findings corroborate and expand those that we reported in a previous study, in which a larger number of elevated blood biomarkers cardiac damage, inflammation, and fibrosis was associated with a higher rate of all-cause mortality and cardiovascular hospitalization following SAVR.[8] Furthermore, there was no association between the number of elevated biomarkers and the distribution of NYHA functional class at baseline.[8] In the present study, a larger number of elevated biomarkers tended to be associated with a worse NYHA functional class at baseline but not at follow-up post-TAVI (Supplemental Figures 1 and 2).

We previously proposed a classification scheme, based on multiple echocardiographic parameters and criteria to stage the extent of extra-valvular cardiac damage, which provided important incremental value to predict mortality before and after SAVR or TAVI.[35-37] Further studies are needed to determine: 1) how a model including the number of elevated blood biomarkers and/or the baseline clinical variables compare to the cardiac damage stage classification with respect to the prediction mortality and rehospitalization following TAVI; and 2) whether the addition of the number of elevated blood biomarkers in the staging classification scheme (eg, 1-3 in stage 1, 4 to-7 in stage 2, and 8-7 in stage 4) improve or not the prognostic ability of the staging.

Further studies are also needed to determine whether the number of elevated blood biomarkers should be used as an argument to consider early AVR in patients with asymptomatic severe AS and to select TAVI rather than SAVR in symptomatic patients with severe AS.

STUDY LIMITATIONS. This is a single-center prospective and observational study, the blood multimarker approach will need to be validated in other independent TAVI series. Transfemoral access was used in 66.9% of patients and 26.5% had a transcarotid access. Due to its high device success rate at our institution, transcarotid access has become the preferred alternative to transfemoral access, accounting for approximately one-third of TAVI procedures. Of note, the access route (alternative vs transfemoral access) was not associated with worse prognosis.[38] For the vast majority of the biomarkers analyzed in the present study, there is no cutoff value previously reported and validated to determine if a blood biomarker is abnormally high. Therefore, we elected to use the median value for the whole cohort to confirm that the biomarker level is elevated for a given patient. These cutoff values, defined a priori, may not be optimal for all biomarkers and further studies are needed to determine the most sensitive and specific cutoff values of the biomarkers to predict adverse outcomes following TAVI.

CONCLUSIONS

The blood multimarker approach proposed and validated in the present study outperforms and enhances standard clinical risk scores or multivariable models to predict mortality and HF rehospitalization following TAVI. This approach that includes 9 blood biomarkers of cardiac damage and dysfunction, fibrosis, inflammation, and renal function may help to enhance risk stratification and potentially identify the patients in whom TAVI may be beneficial vs futile. In the future, such an approach may also be helpful to optimize the timing of intervention and the selection of the type of AVR in patients with AS.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The number of elevated blood biomarkers of cardiac damage, heart failure, inflammation, and renal function outperforms standard risk scores and clinical models to predict adverse outcomes following TAVI. This simple tool may enhance risk stratification and be helpful to identify TAVI patients who are at risk for treatment futility.

TRANSLATIONAL OUTLOOK: Further studies are needed to independently validate the blood multimarker approach and to determine whether this approach outperforms or provides incremental predictive value vs the echocardiographic multiparameter integrative approach previously proposed to stage the extent of extra-valvular cardiac damage.

REFERENCES

1. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380:1706-1715.

2. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695-1705.

3. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol*. 2021;77:450-500.

4. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561-632.

5. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597-1607.

6. Lindman BR, Alexander KP, O'Gara PT, Afilalo J. Futility, benefit, and transcatheter aortic valve replacement. *J Am Coll Cardiol Intv*. 2014;7:707-716.

7. Svensson LG, Blackstone EH, Rajeswaran J, et al. Comprehensive analysis of mortality among patients undergoing TAVR: results of the PARTNER trial. *J Am Coll Cardiol*. 2014;64:158-168.

8. Lindman BR, Clavel MA, Abu-Alhayja`a R, et al. Multimarker approach to identify patients with higher mortality and rehospitalization rate after surgical aortic valve replacement for aortic stenosis. *J Am Coll Cardiol Intv*. 2018;11:2172-2181.

9. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30:372-392.

10. Lancellotti P, Pibarot P, Chambers J, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular imaging endorsed by the Chinese Society of Echocardiography, the Interamerican Society of Echocardiography and the Brazilian Department of cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:589-590.

11. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1-39.

12. Sinning JM, Wollert KC, Sedaghat A, et al. Risk scores and biomarkers for the prediction of 1-year outcome after transcatheter aortic valve replacement. *Am Heart J*. 2015;170:821-829.

13. Bergler-Klein J, Gyöngyosi M, Maurer G. The role of biomarkers in valvular heart disease: focus on natriuretic peptides. *Can J Cardiol*. 2014;30:1027-1034.

14. Stahli BE, Gebhard C, Saleh L, et al. N-terminal pro-B-type natriuretic peptide-ratio predicts mortality after transcatheter aortic valve replacement. *Catheter Cardiovasc Interv*. 2015;85:1240-1247.

15. Chorianopoulos E, Krumsdorf U, Geis N, et al. Preserved prognostic value of preinterventional troponin T levels despite successful TAVI in patients with severe aortic stenosis. *Clin Res Cardiol*. 2014;103:65-72.

16. Frank D, Stark S, Lutz M, et al. Preprocedural high-sensitive troponin predicts survival after transcatheter aortic valve implantation (TAVI). *Int J Cardiol*. 2013;169:e38-e39.

17. Zhang B, Xu H, Zhang H, et al. Prognostic value of N-Terminal pro-B-type natriuretic peptide in elderly patients with valvular heart disease. *J Am Coll Cardiol*. 2020;75:1659-1672.

18. Kim JB, Kobayashi Y, Moneghetti KJ, et al. GDF-15 (growth differentiation factor 15) is associated with Lack of ventricular Recovery and mortality after transcatheter aortic valve replacement. *Circ Cardiovasc Interv*. 2017;10:e005594.

19. Hoffmann J, Mas-Peiro S, Berkowitsch A, et al. Inflammatory signatures are associated with increased mortality after transfemoral transcatheter aortic valve implantation. *ESC Heart Fail*. 2020;7:2597-2610.

20. Keranov S, Kim WK, Arsalan M, et al. Predictive value of preprocedural procalcitonin for short- and long-term mortality after transfemoral transcatheter aortic valve implantation. *Heart Ves*. 2019;34:1993-2001.

21. Ben-Dor I, Minha S, Barbash IM, et al. Correlation of brain natriuretic peptide levels in patients with severe aortic stenosis undergoing operative valve replacement or percutaneous transcatheter intervention with clinical, echocardiographic, and hemodynamic factors and prognosis. *Am J Cardiol*. 2013;112:574-579.

22. Krau NC, Lunstedt NS, Freitag-Wolf S, et al. Elevated growth differentiation factor 15 levels predict outcome in patients undergoing transcatheter aortic valve implantation. *Eur J Heart Fail*. 2015;17:945-955.

23. Hellstrom I, Raycraft J, Hayden-Ledbetter M, et al. The HE4 (WFDC2) protein is a biomarker for

ovarian carcinoma. *Cancer Res*. 2003;63:3695–3700.

24. Bingle CD, Vyakarnam A. Novel innate immune functions of the whey acidic protein family. *Trends Immunol*. 2008;29:444–453.

25. Piek A, Meijers WC, Schroten NF, Gansevoort RT, de Boer RA, Silljé HH. HE4 serum levels are associated with heart failure severity in patients with chronic heart failure. *J Card Fail*. 2017;23:12–19.

26. de Boer RA, Cao Q, Postmus D, et al. The WAP four-disulfide core domain protein HE4: a novel biomarker for heart failure. *J Am Coll Cardiol HF*. 2013;1:164–169.

27. Elhmidi Y, Bleiziffer S, Deutsch MA, et al. Acute kidney injury after transcatheter aortic valve implantation: incidence, predictors and impact on mortality. *Arch Cardiovasc Dis*. 2014;107:133–139.

28. Allende R, Webb JG, Munoz-Garcia AJ, et al. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. *Eur Heart J*. 2014;35:2685–2696.

29. Sinning JM, Ghanem A, Steinhauser H, et al. Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. *J Am Coll Cardiol Intv*. 2010;3:1141–1149.

30. Husser O, Nunez J, Nunez E, et al. Tumor marker carbohydrate antigen 125 predicts adverse outcome after transcatheter aortic valve implantation. *J Am Coll Cardiol Intv*. 2013;6:487–496.

31. Husser O, Nunez J, Burgdorf C, et al. Improvement in risk stratification in transcatheter aortic valve implantation using a combination of the tumor marker CA125 and the logistic EuroSCORE. *Rev Esp Cardiol (Engl Ed)*. 2017;70:186–193.

32. Rheude T, Pellegrini C, Reinhard W, et al. Determinants of elevated carbohydrate antigen 125 in patients with severe symptomatic aortic valve stenosis referred for transcatheter aortic valve implantation. *Biomarkers*. 2018;23:299–304.

33. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. *Eur J Cardio Thorac Surg*. 2012;41:734–744.

34. Beohar N, Whisenant B, Kirtane AJ, et al. The relative performance characteristics of the logistic European System for cardiac operative risk evaluation score and the Society of Thoracic Surgeons score in the placement of aortic transcatheter valves trial. *J Thorac Cardiovasc Surg*. 2014;148:2830–2837.e1.

35. Tastet L, Tribouilloy C, Maréchaux S, et al. Staging cardiac damage in patients with asymptomatic aortic valve stenosis. *J Am Coll Cardiol*. 2019;74:550–563.

36. Vollema EM, Amanullah MR, Ng ACT, et al. Staging cardiac damage in patients with symptomatic aortic valve stenosis. *J Am Coll Cardiol*. 2019;74:538–549.

37. Généreux P, Pibarot P, Redfors B, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J*. 2017;38:3351–3358.

38. Junquera L, Kalavrouziotis D, Côté M, et al. Results of transcarotid compared with transfemoral transcatheter aortic valve replacement. *J Thorac Cardiovasc Surg*. 2020;163(1):69–77.

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