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Predicting Early and Late Mortality After Transcatheter Aortic Valve Replacement

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ABSTRACT

BACKGROUND Few studies have examined the impact of novel indices of comorbidity, frailty, and disability on outcomes after transcatheter aortic valve replacement (TAVR).

OBJECTIVES This study analyzed patients from the Medtronic CoreValve U.S. Pivotal Trial program to develop a simple scoring system that incorporates standard and novel predictor variables.

METHODS A multidisciplinary heart team used objective criteria, such as The Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM), and subjective criteria to assess patients' eligibility for TAVR. The analysis included 3,687 patients randomly divided (2:1) into a derivation cohort (n = 2,482) and a validation cohort (n = 1,205). The study evaluated predictors of all-cause death, which were used to calculate a risk score for each patient.

RESULTS The overall mortality rate was 5.8% at 30 days and 22.8% at 1 year. Home oxygen use, assisted living, albumin levels <3.3 g/dl, and age >85 years predicted death at 30 days. Home oxygen use, albumin levels <3.3 g/dl, falls in the past 6 months, STS PROM score >7%, and severe (≥5) Charlson comorbidity score predicted death at 1 year. A simple scoring system created on the basis of these multivariable predictors effectively stratified risk at 30 days and 1 year into low-risk, moderate-risk, and high-risk subsets. This score showed a 3-fold difference in mortality rates for the low-risk and high-risk subsets at 30 days (3.6% and 10.9%, respectively) and 1 year (12.3% and 36.6%, respectively). The 1-year mortality model was more stable than the 30-day model (C-statistics: 0.79 vs. 0.75).

CONCLUSIONS A simple score dominated by novel predictors of outcome effectively stratified early and late mortality rates in extreme-risk and high-risk patients and may assist in selecting appropriate candidates for TAVR. (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Symptomatic Severe Aortic Stenosis in High Risk and Very High Risk Subjects Who Need Aortic Valve Replacement; NCT01240902) (J Am Coll Cardiol 2016;68:343–52)

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ABBREVIATIONS AND ACRONYMS

STS PROM = The Society of Transthoracic Surgeons Predictors of Mortality

TAVR = transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is superior to medical therapy in patients deemed unsuitable for surgery (1,2), and it is an alternative to surgical aortic valve replacement in selected patients deemed at high risk for surgery (3,4). Risk assessment is typically performed by a multidisciplinary heart team that considers conventional risk assessment algorithms (5,6), such as The Society for Thoracic Surgery Predictive Risk of Mortality (STS PROM) (7) or logistic European System for Cardiac Operative Risk Evaluation (logistic EuroSCORE) (8). There is increased awareness of the limitations of these conventional risk scores because they exclude factors often used by the heart team at the patient's bedside, such as the presence of liver disease, use of home oxygen, assessments of frailty, and consideration of functional disabilities that may render patients at higher risk for surgery (9). These evaluations are often challenging because the quantitative impact of disability, frailty, and nonconventional comorbidities has not been integrated into a simple assessment algorithm. No earlier studies integrated both conventional and novel risk factors to determine outcomes after self-expanding TAVR.

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The Medtronic CoreValve U.S. Pivotal Trial included patients deemed by 2 clinical site cardiac surgeons to be at either extreme risk or high risk for surgical aortic valve replacement, and risk assessments were confirmed by 2 national screening committee cardiac surgeons. This dataset comprehensively collected quantitative assessments of frailty and disability. The purpose of this study was to characterize the factors predicting 30-day and 1-year mortality rates after placement of a self-expanding transcatheter heart valve.

METHODS

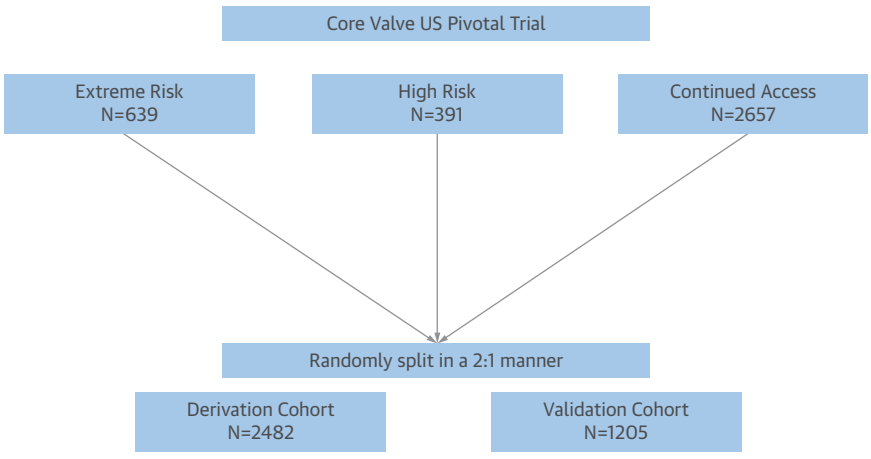
PATIENT SELECTION. Patients with New York Heart Association functional class II or greater symptoms related to aortic valve disease were eligible for the trial. Severe aortic stenosis was defined as an aortic valve area ≤0.8 cm^2 or an aortic valve index ≤0.5 cm^2/m^2 and either a mean aortic valve gradient >40 mm Hg or a peak aortic valve velocity >4.0 m/s, at rest or with dobutamine stress if the left ventricular ejection fraction was <50%. Patients were considered at extreme risk if 2 cardiac surgeons and 1 interventional cardiologist at the clinical site estimated a 50% or greater risk for surgical death or irreversible morbidity at 30 days (2) and at high risk if 2 cardiac surgeons and 1 interventional cardiologist at the clinical site estimated a 15% or greater risk of death at 30 days in the absence of extreme risk (4).

A case summary was created for each patient that included STS PROM and documentation of other comorbidities that increased surgical risk, and it was presented by the clinical site heart team to a national screening committee. At least 2 senior cardiac surgeons and 1 interventional cardiologist had to agree that the patient met study eligibility, risk, and imaging criteria for the trial. After completion of enrollment in both the Extreme Risk and High Risk Pivotal Trials, patients could still be treated with the CoreValve System (Medtronic, Minneapolis, Minnesota) by participating in a Continued Access Registry until approval by the U.S. Food and Drug Administration. The CoreValve Continued Access Study followed the same protocol and study procedures as that of the Extreme Risk and High Risk Pivotal Trials, including the same screening process as in the pivotal trials.

STUDY DEVICE. The self-expanding TAVR system contains a nitinol frame that supports a trileaflet porcine pericardial valve. This report includes 23-, 26-, 29-, and 31-mm diameter valves for treating patients with an aortic annulus ranging from 18 to 29 mm. The valve characteristics and implantation procedure have been previously described (2,4).

RISK FACTOR ASSESSMENTS. Detailed baseline patient-related information included quantification of comorbidities using STS PROM (7), EuroSCORE (8), and the Charlson comorbidity index (10). The Charlson comorbidity index was calculated using the following point system: 1 point each for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes mellitus; 2 points for hemiplegia, moderate-to-severe kidney disease, diabetes mellitus with end-organ damage, leukemia, and lymphoma; 3 points for moderate or severe liver disease; and 6 points for metastatic solid tumor and acquired immunodeficiency syndrome. A score of 5 or more is associated with a 1-year mortality rate of 85%. Data used to derive the score were obtained from the screening and baseline data collected on the Case Report Form. In addition, frailty was evaluated using the following: 5-m gait speed (11) and grip strength testing (12); body mass index; anemia requiring transfusion; hypoalbuminemia; unplanned weight loss; and mobility, determined on the basis of any recent falls or the condition of being wheelchair bound. Disabilities were assessed using the Katz

FIGURE 1 **Analysis Cohort**



Patients who underwent an attempted implantation procedure with the self-expanding transcatheter aortic valve replacement in the CoreValve U.S. Pivotal Extreme-Risk Cohort, High-Risk Cohort, and Continued Access Studies were randomized 2:1 to a derivation cohort or a validation cohort.

Index of Independence in Activities of Daily Living (13) and the mini-mental state examination for dementia (14). The primary endpoint for this report was the all-cause mortality rate 30 days and 1 year after the procedure in patients who underwent an attempted implantation procedure.

STATISTICAL ANALYSIS. Our primary analysis cohort included patients who underwent an attempted implantation of a self-expanding transcatheter valve through either an iliofemoral approach or an alternative access approach.

Categorical variables were compared with the use of the Fisher exact test. Continuous variables were presented as mean ± SD and compared with the use of the Student *t* test. All testing used a 2-sided alpha level of 0.05. The pooled TAVR dataset (**Figure 1**) was randomly split into a derivation cohort (n = 2,482) and a validation (n = 1,205) cohort in a 2:1 manner. The derivation cohort was used to identify the predictive variables and to develop risk scoring systems, which were tested in the validation cohort. Variables for the predictors in the mortality model were selected on the basis of clinical utility. Cox proportional hazards survival models were used for 30-day and 1-year mortality rates separately. The following variables were selected on the basis of clinical relevance and were included in the Cox model for 30-day mortality rates: age >85 years; New York Heart Association functional class IV; STS PROM >7%, logistic EuroSCORE >15%, STS severe lung disease; home oxygen use, forced expiratory volume of 1 breath ≤1,000 cc; albumin level <3.3 g/dl; unplanned weights loss; ≥2 Katz activities of daily living deficits; and residence in an assisted living facility. For the 1-year mortality model, the same variables listed here were included, with the following additions: male sex; peripheral vascular disease; left ventricular diastolic dysfunction III/IV; balloon valvuloplasty; presence of an implantable defibrillator; atrial fibrillation or flutter; Charlson comorbidity score ≥5, falls in the last 6 months; 5-m gait speed >6 s; grip strength below threshold; and wheelchair-bound status.

In the derivation cohort, univariable predictors with a $p < 0.05$ were included in a multivariable model. Stepwise multivariable analyses were performed. The significance level thresholds for entry and exit of independent variables were set at 0.10. Significant multivariable predictors ($p < 0.10$) were used to calculate a risk score for each patient on the basis of the sum of the estimated hazard ratios (HRs; rounded to the nearest integer) for each of the predictor variables from the Cox regression analysis. Risk levels were defined as low (Q1), moderate (Q2, Q3), and high (Q4). In both cohorts the predictive performance was assessed with the C-statistic. Kaplan-Meier estimates were used to construct the survival curves on the basis of all available follow-up for the time-to-event analysis and were plotted by risk levels. All statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

TABLE 1 Baseline Characteristics for All Patients and for the Derivation and Validation Cohorts

	All (N = 3,687)	Derivation (n = 2,482)	Validation (n = 1,205)	p Value*
Age, yrs,	83.3 ± 7.8	83.3 ± 7.8	83.3 ± 7.9	0.89
Male	1,979 (53.7)	1,305 (52.6)	674 (55.9)	0.56
NYHA functional class III/IV	3,218 (87.3)	2,148 (86.5)	1,205 (88.8)	0.22
STS PROM, %	8.9 ± 4.8	8.9 ± 4.8	8.9 ± 4.8	0.92
>7%	2,177 (59.0)	1,473 (59.3)	704 (58.4)	0.59
≤7%	1,510 (41.0)	1,009 (40.7)	501 (41.6)	0.59
Logistic EuroSCORE, %	22.2 ± 15.9	22.1 ± 15.6	22.3 ± 16.5	0.66
Diabetes mellitus	1,385 (37.6)	931 (37.5)	454 (37.7)	0.92
Creatinine level >2 mg/dl	165 (4.5)	109 (4.4)	56 (4.6)	0.72
Chronic kidney disease class 4/5	444/3,658 (12.1)	295/2,463 (12.0)	149/1,195 (12.5)	0.67
History of hypertension	3,418 (92.7)	2,298 (92.6)	1,120 (92.9)	0.69
Peripheral vascular disease	1,675/3,675 (45.6)	1,133/2,474 (45.8)	542/1,201 (45.1)	0.70
Previous stroke	486/3,681 (13.2)	325/2,478 (13.1)	161/1,203 (13.4)	0.82
Cardiac risk factors				
Coronary artery disease	2,911 (79.0)	1,960 (79.0)	951 (78.9)	0.97
Previous coronary artery bypass surgery	1,298 (35.2)	865 (34.9)	433 (35.9)	0.52
Previous percutaneous coronary intervention	1,406 (38.1)	961 (38.7)	445 (36.9)	0.29
Previous balloon valvuloplasty	475 (12.9)	315 (12.7)	160 (13.3)	0.62
Pre-existing ICD or pacemaker	833 (22.6)	551 (22.2)	282 (23.4)	0.41
Previous myocardial infarction	1,016/3,685 (27.6)	694/2,481 (28.0)	322/1,204 (26.7)	0.43
Congestive heart failure	3,596 (97.5)	2,416 (97.3)	1,180 (97.9)	0.28
Previous atrial fibrillation or atrial flutter	1,626/3,676 (44.2)	1,082/2,476 (43.7)	544/1,200 (45.3)	0.35
Comorbidities				
STS chronic lung disease				0.51
None	1,681/3,686 (45.6)	1,125 (45.3)	556/1,204 (46.2)	
Mild	759/3,686 (20.6)	506 (20.4)	253/1,204 (21.0)	
Moderate	542/3,686 (14.7)	373 (15.0)	169/1,204 (14.0)	
Severe	704/3,686 (19.1)	478 (19.3)	226/1,204 (18.8)	
Home oxygen	810/3,686 (22.0)	542/2,481 (21.8)	268 (22.2)	0.79
Nocturnal bipap	327 (8.9)	228 (9.2)	99 (8.2)	0.33
FEV_1 ≤1,000 cc	677/2,984 (22.7)	473/2,006 (23.6)	204/978 (20.9)	0.10
Liver cirrhosis	89/3,681 (2.4)	65/2,481 (2.6)	24/1,200 (2.0)	0.25
Connective tissue disease	98/3,682 (2.7)	68/2,477 (2.7)	30 (2.5)	0.65
Immunosuppressive therapy	539/3,686 (14.6)	366/2,481 (14.8)	173 (14.4)	0.75
Charlson comorbidity index ≥5	2,108/3,679 (57.3)	1,427/2,479 (57.6)	681/1,200 (56.8)	0.64
Frailty				
Anemia with transfusion	674/3,516 (19.2)	446/2,381 (18.7)	228/1,135 (20.1)	0.34
Body mass index <21 kg/m^2	311/3,686 (8.4)	203/2,481 (8.2)	108 (9.0)	0.42
Albumin <3.3 g/dl	615/3,631 (16.9)	427/2,442 (17.5)	188/1,189 (15.8)	0.21
Unplanned weight loss	411 (11.1)	273 (11.0)	138 (11.5)	0.68
Fall in past 6 months	722/3,686 (19.6)	482/2,481 (19.4)	240 (19.9)	0.73
5-m gait speed, s	10.6 ± 12.9 (3102)	10.5 ± 13.0 (2074)	10.7 ± 12.6 (1028)	0.76
Average 5-m gait speed >6 s†	2,555/3,102 (82.4)	1,,685/2,074 (81.2)	870/1,028 (84.6)	0.02
Grip strength below threshold‡	2,489/3,643 (68.3)	1679/2,451 (68.5)	810/1,192 (68.0)	0.74

Continued on the next page

STUDY OVERSIGHT. The Investigational Review Board at each site approved the protocol, and each patient provided signed, informed consent.

RESULTS

Baseline characteristics, cardiac risk factors, comorbidities, frailties, and disabilities for 3,687 high-risk and extreme-risk patients are shown in Table 1. The mean age was 83.3 ± 7.8 years, and 1,708 of the 3,687 patients (46.3%) were women. The baseline mean standard predictors of risk were 8.9 ± 4.8% for STS PROM and 22.2 ± 15.9% for the logistic EuroSCORE. Home oxygen was used in 22.0% of patients, and 57.3% had a Charlson comorbidity index of ≥5. Frailty measured as a reduced 5-m gait speed was present in 82.4% of patients, and 68.3% of patients had a reduced grip strength. A total of 448 (12.2%) of

TABLE 1 Continued

	All (N = 3,687)	Derivation (n = 2,482)	Validation (n = 1,205)	p Value*
Disabilities				
Mini-mental state examination score	26.5 ± 2.8 (3671)	26.5 ± 2.8	26.6 ± 2.7	0.10
Does not live independently	448 (12.2)	306 (12.3)	142 (11.8)	0.64
Does not bath independently	457 (12.4)	317 (12.8)	140 (11.6)	0.32
Does not dress independently	319 (8.7)	227 (9.1)	92 (7.6)	0.13
Does not toilet independently	176 (4.8)	122 (4.9)	54 (4.5)	0.56
Does not transfer independently	324 (8.8)	237 (9.5)	87 (7.2)	0.02
Incontinent	141 (3.8)	97 (3.9)	44 (3.7)	0.70
Does not feed independently	39 (1.1)	26 (1.0)	13 (1.1)	0.93
Deficit ≥2 Katz activities of daily living	381 (10.3)	268 (10.8)	113 (9.4)	0.18
Deficit ≥3 Katz activities of daily living	231 (6.3)	163 (6.6)	68 (5.6)	0.28

Values are mean ± SD, n (%), or n/N (%). *p values are reported for comparing between the patients in the derivation cohort and the validation cohort. †Each patient performed 3 trials that were averaged for the 5-m gait speed test. ‡Grip strength threshold as defined by Bohannon et al (12). The logistic EuroSCORE measures patients' risk at the time of cardiovascular surgery and is calculated by a logistic regression equation. Scores range from 0% to 100%, with higher scores indicating greater risk.

bipap = bilevel positive airway pressure; EuroSCORE = European System for Cardiac Operative Risk Evaluation; FEV_1 = forced expiratory volume in 1 s; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; STS = The Society for Thoracic Surgery.

patients required assisted living, and 10.3% had ≥2 Katz activities of daily living deficits. The derivation and validation cohorts were well matched (Table 1). Kaplan-Meier estimates of all-cause death were 5.8% at 30 days and 22.8% at 1 year.

SCORING SYSTEM FOR PREDICTING MORTALITY RATES.

Predictors of 30-day mortality rates. Univariable and multivariable predictors of 30-day mortality rates from the derivation cohort are found in Table 2. The following were significant independent predictors of early death: home oxygen use (HR: 1.74; 95% confidence interval [CI]: 1.16 to 2.61; p = 0.007); residence in an assisted living facility (HR: 1.68; 95% CI: 1.05 to 2.69; p = 0.03); an albumin level <3.3 g/dl (HR: 1.60 95% CI: 1.04 to 2.47; p = 0.03); and age >85 years (HR: 1.46; 95% CI: 0.99 to 2.15; p = 0.05)

Risk scores at 30 days. On the basis of the hazard ratios from the significant predictors of mortality from the derivation cohort, we created a scoring system that included home oxygen use (2 points), albumin level <3.3 mg/dl (2 points), assisted living (2 points), and age >85 years (1 point). This system effectively stratified patients who were at low risk (risk score = 0), moderate risk (risk score = 1 or 2), and high risk (risk score = 3 to 7) of death at 30 days. The validation cohort showed a 3-fold difference in mortality rates for the low-risk (3.6%) and high-risk subsets (10.9%). The mean weighted risk score was 1.52 ± 1.43 for the derivation cohort and 1.48 ± 1.41 for the validation cohort. Both cohorts showed similar results (Figures 2A and 2B), with a slightly higher C-statistic for the derivation cohort (C-statistic: 0.76; 95% CI: 0.56 to 0.92 vs. C-statistic: 0.75; 95% CI: 0.35 to 1.04).

Predictors of 1-year mortality rates. Univariable and multivariable predictors of 1-year mortality rates from the derivation cohort are found in Table 2. The following were significant independent predictors of late death: home oxygen use (HR: 1.90; 95% CI: 1.47 to 2.44; p < 0.001); albumin level <3.3 g/dl, (HR: 1.40; 95% CI: 1.04 to 1.91; p = 0.03); falls in the past 6 months (HR: 1.36; 95% CI: 1.03 to 1.81; p = 0.03); high Charlson comorbidity score (HR: 1.27; 95% CI: 0.98 to 1.65; p = 0.07); and STS PROM >7% (HR: 1.36; 95% CI: 1.05 to 1.77; p = 0.02).

Risk scores at 1 year. Furthermore, home oxygen use (2 points), albumin <3.3 mg/dl (1 point), falls in the past 6 months (1 point), STS PROM >7% (1 point), and a high (≥5) Charlson comorbidity score (1 point) effectively stratified patients who were at low risk (risk score = 0 or 1), moderate risk (risk score = 2 or 3), and high risk (risk score = 4 to 6) of death at 1 year (Central Illustration). The mean risk scores for the derivation and validation cohorts were 1.97 ± 1.33 and 1.95 ± 1.31. Both cohorts effectively demonstrated significant differences in 1-year mortality rates across the 3 risk score groups, with a higher C-statistic for the derivation cohort (C-statistic: 0.83; 95% CI: 0.73 to 0.90) than for the validation cohort (C-statistic: 0.79; 95% CI: 0.59 to 0.95). The validation cohort showed a 3-fold difference in mortality rates for the low-risk (12.3%) and high-risk subsets (36.6%). Our model overall was more stable at 1 year than at 30 days, with a higher C-statistic (0.79 vs. 0.75).

DISCUSSION

We identified several predictors of 30-day and 1-year mortality rates after self-expanding TAVR. Many of

TABLE 2 Univariable and Multivariable Predictors of Mortality Rates From the Derivation Cohort

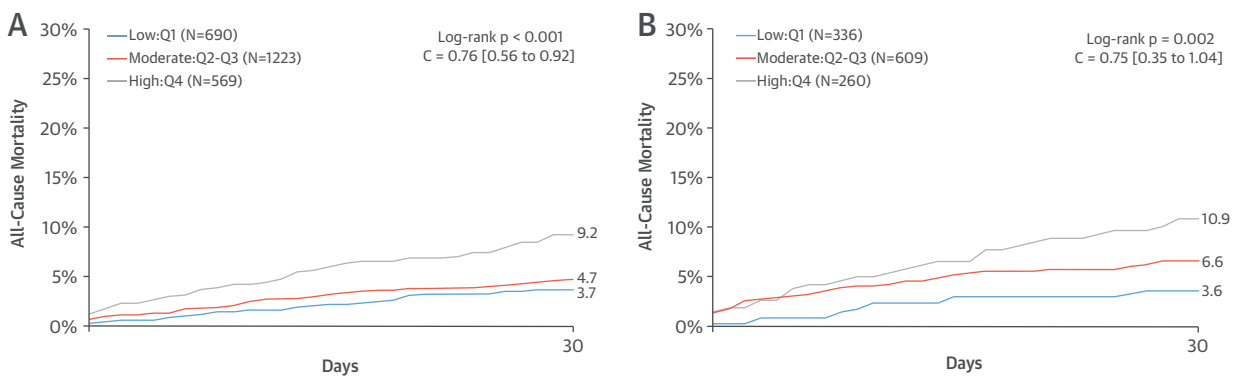
	Kaplan-Meier Rate (95% CI) N	Univariable Analysis			Multivariable			Risk Score Assigned Weight
		HR	95% CI	p Value	HR	95% CI	p Value	
Predictors of 30-day mortality								
Albumin <3.3 g/dl	8.7 (6.4–11.8) 427	1.89	1.29–2.76	0.001	1.60	1.04–2.47	0.03	2
Katz ADL ≥2 deficits	9.0 (6.1–13.2) 268	1.82	1.17–2.82	0.008	–	–	–	–
Assisted living	8.8 (6.2–12.6) 306	1.79	1.18–2.74	0.007	1.68	1.05–2.69	0.03	2
Home oxygen	8.0 (6.0–10.6) 542	1.71	1.19–2.45	0.004	1.74	1.16–2.61	0.007	2
Age >85 yrs	6.4 (5.2–8.0) 1,218	1.47	1.04–2.08	0.03	1.46	0.99–2.15	0.05	1
FEV >1,000 cc	4.9 (3.9–6.1) 1,533	0.63	0.42–0.94	0.02	–	–	–	–
Predictors of 1-yr mortality								
Katz ADL ≥2 deficits	35.3 (29.6–41.8) 268	1.94	1.54–2.45	<0.001	–	–	–	–
Assisted living	34.2 (28.9–40.2) 306	1.90	1.52–2.38	<0.001	–	–	–	–
Home oxygen	31.4 (27.4–35.8) 542	1.76	1.45–2.14	<0.001	1.90	1.47–2.44	<0.001	2
Albumin <3.3 g/dl	30.9 (26.4–36.0) 427	1.65	1.34–2.04	<0.001	1.40	1.04–1.91	0.03	1
Wheelchair bound	31.0 (24.8–38.4) 203	1.58	1.19–2.08	0.001	–	–	–	–
Severe Charlson score	25.1 (22.7–27.7) 1,427	1.51	1.24–1.83	<0.001	1.27	0.98–1.65	0.07	1
STS score >7%	24.9 (22.6–27.4) 1,473	1.48	1.22–1.80	<0.001	1.36	1.05–1.77	0.02	1
Grade III/IV LV diastolic dysfunction	30.5 (25.4–36.4) 320	1.56	1.23–1.98	<0.001	–	–	–	–
STS severe lung disease	28.2 (24.1–32.8) 478	1.44	1.17–1.78	<0.001	–	–	–	–
Unplanned weight loss	28.7 (23.2–35.1) 273	1.43	1.10–1.85	0.007	–	–	–	–
Prior BAV	28.7 (23.7–34.4) 315	1.42	1.12–1.81	0.004	–	–	–	–
Falls in past 6 months	27.9 (23.8–32.5) 482	1.42	1.15–1.74	0.001	1.36	1.03–1.81	0.03	1
5-m gait speed >6 s	21.9 (19.8–24.2) 1,685	1.42	1.06–1.91	0.02	–	–	–	–
Atrial fibrillation or flutter	24.4 (21.8–27.4) 1,082	1.30	1.08–1.56	0.005	–	–	–	–
Grip strength < threshold	23.1 (21.0–25.4) 1,679	1.26	1.03–1.55	0.03	–	–	–	–
FEV >1,000 cc	19.8 (17.7–22.1) 1,533	0.65	0.52–0.81	<0.001	–	–	–	–

ADL = activities of daily living; BAV = balloon aortic valvuloplasty; CI = confidence interval; FEV = forced expiratory volume; HR = hazard ratio; STS = The Society of Thoracic Surgeons.

these predictors are not found in conventional surgical risk assessments, such as STS PROM. These descriptors of comorbidity, frailty, and disability may be used to predict outcomes after TAVR. Furthermore, we constructed a simple scoring system on the basis of the multivariable predictors of death that effectively stratified 30-day and 1-year mortality rates.

One aspect of the current investigation is the rigor with which novel measures of surgical risk were collected in the CoreValve U.S. Pivotal Trial and

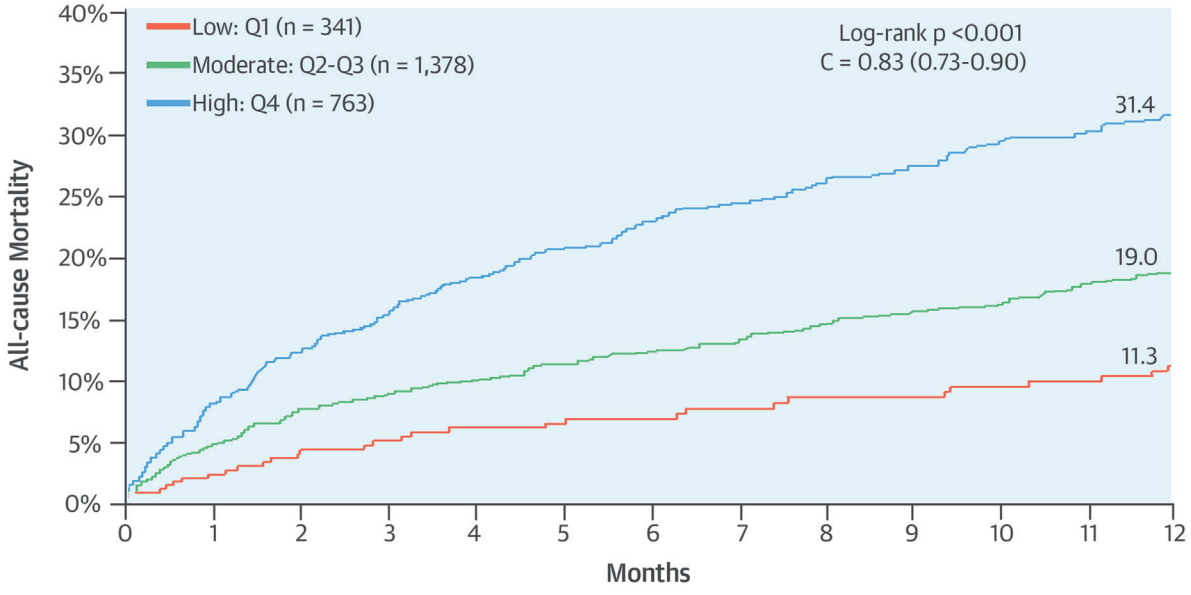
FIGURE 2 Kaplan-Meier Estimates of 30-Day Mortality



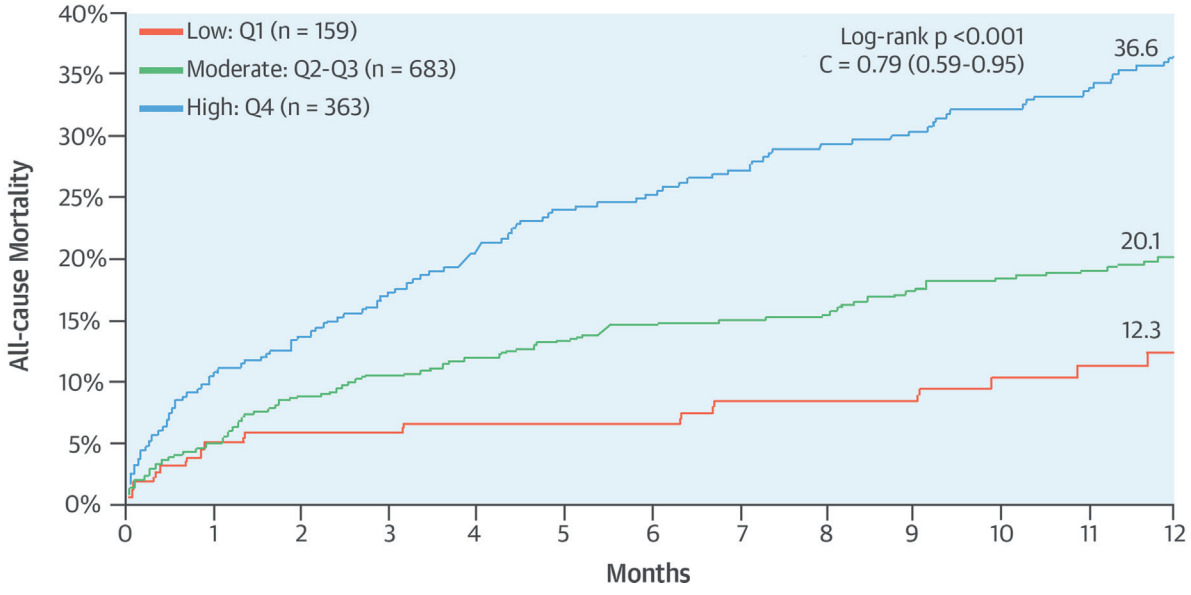
Kaplan-Meier estimates of 30-day mortality rates for the **(A)** derivation and **(B)** validation cohorts by risk score. The risk score showed a 3-fold difference in mortality rates for the low-risk and high-risk subsets at 30 days.

CENTRAL ILLUSTRATION **Mortality Risk Score for TAVR: Impact of Frailty and Disability on Outcome**

A. 1-year Mortality for the Derivation Cohort by Risk Score



B. 1-year Mortality for the Validation Cohort by Risk Score



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(A) Kaplan-Meier estimates of 1-year mortality rates for the derivation cohort by risk score. **(B)** Kaplan-Meier estimates of 1-year mortality rates for the validation cohort by risk score. The risk score showed a 3-fold difference in mortality rates for the low-risk and high-risk subsets also at 1 year with a more stable C-statistic than seen at 30 days. TAVR = transcatheter aortic valve replacement.

TABLE 3 Comparison of Significant Predictors of Mortality From Contemporary Risk Models

	CoreValve U.S. Program	FRANCE 2 (19)	$TAVI_2$-SCORe (18)	OBSERVANT (20)
Valve	CoreValve	CoreValve (67%) SAPIEN (33%)	CoreValve (2%) SAPIEN (98%)	CoreValve (52%) SAPIEN XT (48%)
Patient cohort	3,687	3,833	511	1,878
Derivation cohort	2,482	2,552	511	1,256
Validation cohort	1,205	1,281	100 (bootstrap)	622
30-day mortality predictors	Albumin ≤3.3 g/dl Assisted living Home oxygen Age >85 yrs	Age ≥90 yrs BMI <30 kg/m^2 NYHA functional class IV Pulmonary artery hypertension Critical hemodynamic state ≥2 acute pulmonary edemas Respiratory insufficiency* Dialysis* Non-IF approach		GFR <45 ml/min* Critical pre-operative state NYHA functional class IV Pulmonary artery hypertension Diabetes Prior BAV LVEF <40%
1-yr mortality predictors	Albumin ≤3.3 g/dl Severe Charlson score Home oxygen STS >7%*		Age >85 yrs Male Porcelain aorta Recent MI (<90 days)* CrCl <30 ml/kg/min Hemoglobin <10 g/dl LVEF <35% Baseline AVMG ≥70 mm Hg	

*STS variables. CoreValve, Medtronic, Minneapolis, Minnesota; SAPIEN XT, Edwards Lifesciences, Irvine, California.

AVMG = aortic valve mean gradient; BMI = body mass index; CrCl = creatinine clearance; FRANCE 2 = French Transcatheter Aortic Valve Intervention Registry; GFR = glomerular filtration rate; IF = iliofemoral; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OBSERVANT = Observational Study Of Appropriateness, Efficacy And Effectiveness of AVR-TAVR Procedures For the Treatment Of Severe Symptomatic Aortic Stenosis; $TAVI_2$-SCORe = porcelain Thoracic aorta, Anemia, left Ventricular dysfunction, recent myocardial Infarction, male Sex category, Critical aortic valve stenosis, Old age, and Renal dysfunction; other abbreviations as in Tables 1 and 2.

Continued Access Study including a comprehensive assessment of frailty, disability, and comorbidities. The results of our analyses confirm the importance of these assessments on early and late mortality rates. At 30 days, all 4 positive predictors of death are characteristics excluded from STS PROM, and 3 of the 4 are observational factors precluding the need for any type of invasive testing. The predictors of death at 1 year comprised 2 previously described scoring systems, which may reflect the complexity of competing baseline conditions and the number of comorbidities present in candidates for TAVR.

Frailty measures and geriatric domains were included as positive predictors of death; serum albumin <3.3 g/dl was a positive predictor of both early and late death, and falls within the past 6 months was a predictor at 1 year.

Characterization of lung disease is an important determinant of outcome (15,16). The use of home oxygen was a potent predictor of both early and late death. A forced expiratory volume in the first second ≤1,000 cc was shown to be a univariate predictor of 30-day and 1-year mortality rates; however, it was not a significant multivariable predictor.

Our simple scoring system effectively stratified risk for early and late death. The mortality rates for patients in the low-risk group were one-third of those in the high-risk group at both 30 days and 1 year (Central Illustration). The C-statistic for both the derivation subset and the validation subset showed good discrimination for the model, a finding suggesting a moderately high predictive ability.

PREVIOUS STUDIES. A conventional risk score, such as STS PROM, has been used as the reference standard for surgical risk assessment, but it includes only a limited number of variables and was not constructed to be able to predict long-term outcomes, although some investigators have found it to do so (17). STS PROM may be more predictive of 30-day mortality rates at lower STS scores, but it actually underestimates surgical risk at higher scores. In our study, STS PROM score was not a significant multivariable predictor of 30-day mortality but was at 1 year. Because patients with higher risk scores have not traditionally been offered aortic valve surgery, limited information exists on what truly defines a typical extreme-risk or high-risk group of patients undergoing TAVR.

A simple TAVR-dedicated prognostic risk score is an unmet clinical need, and other scoring systems have been presented (Table 3). Debonnaire et al. (18) created the $TAVI_2$-SCORe (porcelain Thoracic aorta,

Anemia, left Ventricular dysfunction, recent myocardial Infarction, male Sex category, Critical aortic valve stenosis, Old age, and Renal dysfunction) on the basis of a retrospective analysis of 511 consecutive patients who underwent TAVR. Patients stratified into 5 risk groups by a weighted point system with the $TAVI_2$-SCORe showed better discrimination ability compared with logistic EuroSCOREs (LES-I and LES-II) and STS scores (18). However, the lack of applicability to TAVR of these 3 predictors of surgical mortality rates is already known and served as the catalyst of our work.

Other researchers have reported alternatives to STS PROM to predict outcomes following TAVR. The FRANCE 2 (French Transcatheter Aortic Valve Intervention) Registry (19) developed a 21-point score on the basis of a patient cohort of similar size. Their results also included non-STS variables; however, application may be complicated by the different TAVR systems used and the use of the transapical approach (approximately 18%).

Capodanno et al. (20) created a simple 7-factor risk tool (OBSERVANT [Observational Study Of Appropriateness, Efficacy And Effectiveness of AVR-TAVR Procedures For the Treatment Of Severe Symptomatic Aortic Stenosis] score) for predicting 30-day mortality rates after TAVR. This score also includes variables easily noted during patient screening, although a geriatric status score was not found to be a positive independent predictor. It was not clear whether these other scores did not find frailty measures to be predictive because these measures were not predictive or because these frailty data were not collected.

RISK SCORES IN CLINICAL PRACTICE. Even though STS PROM continues to be touted as a poor tool for patient risk assessment in TAVR (21), it continues to define the low end of the risk threshold used for determining patients' eligibility in addition to heart team decisions. In practice, clinicians use multiple sources in decision making, including published trial results, national and international guidelines, and personal experiences. Now that TAVR is the preferred treatment in patients deemed to have too high a surgical risk, the quest for a similar risk tool has been extensive.

Patients screened for TAVR are by definition those with complex cardiac histories, multiple comorbidities, and often anatomical restrictions. The CoreValve U.S. Pivotal Trial Program included an intensive detailed screening and assessment process to create comprehensive patient profiles for patient screening. We found that simple, easily acquired patient characteristics predicted early outcomes after TAVR. Longer-term outcomes were predicted by a combination of unique complimentary variables in addition to the standard STS score. This simple scoring system may facilitate identifying particularly high-risk patients who may require more intensive screening by the heart team.

STUDY LIMITATIONS. Limitations of the study include its retrospective post hoc nature and inclusion in the study of both extreme-risk and high-risk patients for standard aortic valve surgery. This predictive model may not apply to modest-risk or lower-risk patients. We also acknowledge that our scoring system would be limited in practical terms by whether or not such detailed information on baseline frailties and disabilities is collected in other studies or in routine clinical practice.

CONCLUSIONS

Conventional risk score algorithms, such as that of STS-PROM used to predict mortality after aortic valve replacement, were supplemented by objective measures of comorbidity, frailty, and disability. Our simple score dominated by novel predictors of outcome effectively stratified early and late mortality in extreme-risk and high-risk patients and may assist in selecting those patients appropriate for TAVR.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Frailty and disability have a dominant impact on 30-day and 1-year mortality rates after TAVR, and simple metrics determined on the basis of these considerations had better predictive value than did standard indexes of comorbidity. Patients >85 years of age, who are receiving oxygen at home, and are unable to care for themselves are at high risk of early death following TAVR.

TRANSLATIONAL OUTLOOK: Prospective studies should incorporate additional measures of frailty and disability as predictors of outcomes including both survival and quality of life following TAVR.

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