Predicting mortality after transcatheter aortic valve replacement external validation of the Transcatheter Valve Therapy registry model

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Abstract: BACKGROUND: The Transcatheter Valve Therapy (TVT) registry model was recently developed to predict the risk of in-hospital mortality in patients undergoing transcatheter aortic valve replacement. We sought to externally validate the model in an independent data set of consecutively enrolled patients in the Swiss Transcatheter Aortic Valve Implantation registry. METHODS AND RESULTS: The original prediction model was retrospectively applied to 3491 consecutive patients undergoing transcatheter aortic valve replacement in Switzerland between February 2011 and February 2016. We examined model performance in terms of discrimination (Harrel C index) and calibration (Hosmer-Lemeshow goodness-of-fit test) for prediction of in-hospital and 30-day mortality and compared its predictive accuracy with the Society of Thoracic Surgeons Predicted Risk of Mortality score. Rates of in-hospital and 30-day mortality in the external validation cohort were 2.9% and 3.8%, respectively. The TVT registry model was found to have moderate discrimination (C index, 0.66; 95% confidence interval, 0.60-0.72 and C index, 0.67; 95% confidence interval, 0.62-0.72 for in-hospital and 30-day mortality, respectively) and good calibration. Compared with the Society of Thoracic Surgeons Predicted Risk of Mortality score, the TVT registry model demonstrated improved calibration for in-hospital (slope, 0.83; P=0.23 versus slope, 0.24; P<0.001, respectively) and 30-day (slope, 1.11; P=0.40 versus slope, 0.41; P<0.001, respectively) mortality. CONCLUSIONS: In a large, multicenter, non-US cohort of patients with transcatheter aortic valve replacement, the validation of the TVT registry model demonstrated moderate discrimination and good calibration for the prediction of in-hospital and 30-day mortality. As a result, the TVT registry model should be considered an alternative to the Society of Thoracic Surgeons Predicted Risk of Mortality score for decision making and assessment of early outcome in patients eligible for transcatheter aortic valve replacement.

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Predicting Mortality After Transcatheter Aortic Valve Replacement

External Validation of the Transcatheter Valve Therapy Registry Model

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Background—The Transcatheter Valve Therapy (TVT) registry model was recently developed to predict the risk of in-hospital mortality in patients undergoing transcatheter aortic valve replacement. We sought to externally validate the model in an independent data set of consecutively enrolled patients in the Swiss Transcatheter Aortic Valve Implantation registry.

Methods and Results—The original prediction model was retrospectively applied to 3491 consecutive patients undergoing transcatheter aortic valve replacement in Switzerland between February 2011 and February 2016. We examined model performance in terms of discrimination (Harrel C index) and calibration (Hosmer–Lemeshow goodness-of-fit test) for prediction of in-hospital and 30-day mortality and compared its predictive accuracy with the Society of Thoracic Surgeons Predicted Risk of Mortality score. Rates of in-hospital and 30-day mortality in the external validation cohort were 2.9% and 3.8%, respectively. The TVT registry model was found to have moderate discrimination (C index, 0.66; 95% confidence interval, 0.60–0.72 and C index, 0.67; 95% confidence interval, 0.62–0.72 for in-hospital and 30-day mortality, respectively) and good calibration. Compared with the Society of Thoracic Surgeons Predicted Risk of Mortality score, the TVT registry model demonstrated improved calibration for in-hospital (slope, 0.83; P=0.23 versus slope, 0.24; P<0.001, respectively) and 30-day (slope, 1.11; P=0.40 versus slope, 0.41; P<0.001, respectively) mortality.

Conclusions—In a large, multicenter, non-US cohort of patients with transcatheter aortic valve replacement, the validation of the TVT registry model demonstrated moderate discrimination and good calibration for the prediction of in-hospital and 30-day mortality. As a result, the TVT registry model should be considered an alternative to the Society of Thoracic Surgeons Predicted Risk of Mortality score for decision making and assessment of early outcome in patients eligible for transcatheter aortic valve replacement. **(*Circ Cardiovasc Interv*. 2017;10:e005481. DOI: 10.1161/CIRCINTERVENTIONS.117.005481.)**

Key Words: decision making ■ humans ■ mortality ■ risk ■ transcatheter aortic valve replacement

Fostered by refinements in device technology, improved imaging, and streamlining of the procedure, transcatheter aortic valve replacement (TAVR) plays an increasingly important role in the treatment of severe, symptomatic aortic stenosis.[1,2] A decline in periprocedural complications propelled expansion of TAVR to intermediate- and low-risk patients and has shifted the focus of ongoing investigations to determinants of long-term outcome. Risk scoring systems are instrumental to balance the expected benefits against the probability of adverse events and represent a useful tool to properly inform physicians, counsel patients, and optimize the allocation of healthcare resources. In the absence of a dedicated risk score

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WHAT IS KNOWN

- Prediction models may improve the management of patients with severe aortic valve stenosis undergoing transcatheter aortic valve replacement.
- Risk scoring systems derived from surgical cohorts proved suboptimal performance when applied to transcatheter aortic valve replacement populations.
- The Transcatheter Valve Therapy registry model has been derived to predict in-hospital mortality after transcatheter aortic valve replacement with modest discrimination and good calibration in the development cohort.

WHAT THE STUDY ADDS

- The predictive performance of the Transcatheter Valve Therapy registry model is preserved in an independent, non-US cohort of patients with transcatheter aortic valve replacement.
- The predictive accuracy is maintained ≤30 days after the procedure.
- In a comparative analysis with the Society of Thoracic Surgeons Predicted Risk of Mortality score, the Transcatheter Valve Therapy registry model showed better calibration for prediction of in-hospital and 30-day mortality.

for TAVR, the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) and the System for Cardiac Operative Risk Evaluation are routinely integrated in the heart team evaluation of patients with symptomatic severe aortic stenosis. However, both scores have been derived from cohorts of surgical patients; the extrapolation to patients with TAVR remains, therefore, challenging and their suitability arguable.[3,4] In recent years, several attempts to develop TAVR-specific risk models have been performed.[5–10] However, the majority of these novel scores have not been validated in external cohorts, limiting their adoption in clinical practice. Because prediction models are conceived to be applied to future patients, their value depends on the performance shown outside the development sample. To date, the Transcatheter Valve Therapy (TVT) registry model represents the score that has been derived from the largest cohort of patients with TAVR including 13 718 participants of the STS/American College of Cardiology TVT registry.[11]

The aim of this study was to evaluate the extent of generalizability of the TVT registry model by quantifying its performance in an independent data set. For this purpose, we investigated its prediction accuracy in patients included in the prospective Swiss Transcatheter Aortic Valve Implantation (TAVI) registry.

Methods

Participants

The external validation cohort included all patients with severe native aortic valve stenosis who were consecutively treated and entered into the Swiss TAVI registry (NCT01368250) between February 2011 and February 2016. The details of the rationale and design of the Swiss TAVI registry have been described previously.[12] In brief, the Swiss TAVI registry is a nationwide registry that prospectively collects clinical and procedural data of patients undergoing TAVR with CE-marked devices in Switzerland with regular follow-up at 30 days, 1 year, and yearly thereafter. A dedicated clinical committee is responsible for the adjudication of the clinical events occurring during the index hospitalization or at follow-up according to the definitions of the Valve Academic Research Consortium-2 criteria.[13] The registry has been approved by the local ethics committee of all recruiting centers, and all patients provided written informed consent to participate.

Measurements

The TVT registry model was applied through the automatic calculator accessible online at http://tools.acc.org/TAVRRisk/. The model includes the following variables: (1) age at admission; (2) estimated glomerular filtration rate, calculated on the basis of age, sex, race, preprocedure creatinine, and requirement of preprocedure dialysis; (3) hemodialysis or peritoneal dialysis on an ongoing basis as a result of renal failure; (4) New York Heart Association functional class IV, defined as cardiac disease with dyspnea at rest that increases with any physical activity, resulting in inability to perform any physical activity without discomfort; (5) history of severe chronic lung disease, defined as forced expired volume in 1 second <50% predicted and room air $p0_2$ <60 or room air Pco_2 >50; (6) nonfemoral access site; (7) acuity status 2 defined as urgent procedure status plus no preprocedure shock, inotropes, mechanical assist device, or cardiac arrest; (8) acuity status 3 defined as elective or urgent procedure status plus preprocedure shock, inotropes, or mechanical assist device plus no prior cardiac arrest within 24 hours of procedure; (9) acuity status 4 defined as emergency or salvage procedure or prior cardiac arrest within 24 hours of operation. Definitions used in the Swiss TAVI and the TVT registry were similar with respect to the variables used in the model. Specifically, our registry records age at admission, dialysis status, New York Heart Association functional class, severe chronic lung disease, and femoral access. Glomerular filtration rate was calculated according to the modification of diet in renal disease equation and presence of dialysis. Because acuity categories are not included in the Swiss TAVI registry variables, we derived acuity status (2, 3, or 4) by matching the setting of the procedure (elective or urgent) and hemodynamic status (cardiogenic shock).

The present study complies with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines for the reporting of studies that validate prediction scores (Table I in the Data Supplement).[14]

Statistical Analysis

Patient baseline characteristics were expressed as means and SD or frequencies (percentage). Validation of the TVT registry model was performed by examining measures of discrimination and calibration. Discrimination describes the power of models to distinguish patients who have events (death) from those who have no events. It was assessed using the C index that represents the area under the receiver operating characteristic curve and for which larger values are associates with better discrimination. Calibration is a measure of how closely the predicted probabilities (of death) reflect the actual risk; it was assessed by performing the Hosmer–Lemeshow goodness-of-fit test and was graphically depicted in the plot of observed versus predicted mortality with a value <0.05 indicating significant difference in expected versus observed mortality. Calibration was also assessed by testing for an intercept of zero and a slope of 1 when regressing observed proportion of deaths on predicted proportion of deaths based on the TVT. Deciles of the TVT score were used to calculate proportions. Although acknowledging that the TVT registry model was designed to predict in-hospital mortality, we additionally tested whether it could be predictive of mortality at 30 days after TAVR. Model performance in terms of calibration was also examined in prespecified subgroups defined by age of <85 years or older, estimated

glomerular filtration rate <60 mL/min, between 60 and 90 mL/min, or >90 mL/min, need for dialysis, New York Heart Association class IV or class I to III, nonfemoral access, acuity categories, and sex. The main analyses were repeated after multiple imputation of missing variables. In addition, we examined the predictive accuracy of the STS-PROM score and compared it with that of the TVT registry model using the DeLong method. The STS-PROM score was calculated at the time of intervention according to the models developed from the STS database, available at http://riskcalc.sts.org/stswebriskcalc/.

Analyses were conducted using Stata Statistical Software, Release 14.1 (StataCorp LP, College Station, TX), and statistical significance was defined as $P<0.05$.

Results

The validation cohort comprised 3491 consecutive patients included into the Swiss TAVI registry between February 2011 and February 2016. In-hospital and thirty-day survival data were available for the entire cohort. Rates of in-hospital and 30-day mortality amounted to 2.9% and 3.8%, respectively. Table 1 summarizes the baseline clinical characteristics of patients who died in hospital versus those who survived. Male and female patients were similarly represented in either group. Mean STS-PROM score was 5.8±4.5, and it was significantly higher in patients who died in hospital (7.6±5.9 versus 5.8±4.4; $P<0.001$). Nonsurvivors were older compared with survivors (84.2±5.7 versus 82.1±6.5 years; $P=0.001$) and more often presented with renal dysfunction. In addition, nonsurvivors more commonly presented with cardiogenic shock (5% versus 1%; $P<0.001$) and more often underwent urgent instead of elective TAVI (acuity category 2 or 4). Type of transcatheter heart valves used are reported in Table II in the Data Supplement. Overall, 43.6% of patients received early generation devices (Medtronic CoreValve or Edwards Sapien XT). The comparison between validation and development cohorts in terms of demographics is reported in Table III in the Data Supplement.

Performance of the TVT Registry Model

The performance of the TVT registry model in the Swiss TAVI cohort was assessed using the original coefficients that were obtained in the development sample. Refitted model coefficients and odds ratios with 95% confidence interval (CI) for each covariate in the validation cohort are reported for descriptive purposes in Table IV in the Data Supplement. In the Swiss TAVI registry cohort, the TVT registry model showed moderate discrimination, with a C index for in-hospital mortality of 0.66 and 95% CI, 0.60 to 0.72 (Figure 1A). Moreover, the C index for prediction of 30-day mortality was 0.67 and 95% CI, 0.65 to 0.69 (Figure 1C). The results were consistent when analyzing the performance of the model among patients included in the Swiss TAVI registry during the same period of patients included in the derivation cohort (Table V in the Data Supplement).

Calibration plots are shown in Figure 2A and 2C. A close agreement between predicted versus observed mortality was documented for both in-hospital and 30-day outcome. Model calibration was preserved across several prespecified subgroups; we recorded, however, an overestimation of in-hospital and 30-day mortality for patients on hemodialysis (Figure 3).

Table 1. Baseline Characteristics of the Entire Validation Cohort and Stratified According to In-Hospital Mortality

	All Patients	Survivors	Died in Hospital	
	n=3491	n=3390	n=101	*P* Value
Model covariates				
Age, y	82.1±6.5	82.1±6.5	84.2±5.7	0.001
STS-PROM score	5.8±4.5	5.8±4.4	7.6±5.9	0.001
Sex				0.10
Men	1760 (50%)	1701 (50%)	59 (58%)	
Women	1731 (50%)	1689 (50%)	42 (42%)	
Dialysis				0.27
No	3406 (98%)	3309 (98%)	97 (96%)	
Yes	81 (2%)	77 (2%)	4 (4%)	
Severe chronic lung disease				0.52
No	3045 (87%)	2959 (87%)	86 (85%)	
Yes	445 (13%)	430 (13%)	15 (15%)	
NYHA functional class				0.088
I	313 (9%)	307 (9%)	6 (6%)	
II	852 (25%)	835 (25%)	17 (17%)	
III	1848 (54%)	1790 (54%)	58 (59%)	
IV	401 (12%)	384 (12%)	17 (17%)	
Cardiogenic shock (class Killip 4)				<0.001
No	3457 (99%)	3361 (99%)	96 (95%)	
Yes	34 (1%)	29 (1%)	5 (5%)	
eGFR, mL/min	63.7±26.0	63.9±26.0	55.4±24.8	0.001
Access				<0.001
Femoral	3045 (87%)	2971 (88%)	74 (73%)	
Transapical	357 (10%)	337 (10%)	20 (20%)	
Subclavian	34 (1%)	32 (1%)	2 (2%)	
Direct aortic	34 (1%)	30 (1%)	4 (4%)	
Other	21 (1%)	20 (1%)	1 (1%)	
Acuity category				<0.001
1	3370 (97%)	3,281 (97%)	89 (88%)	
2	87 (2%)	80 (2%)	7 (7%)	
4	34 (1%)	29 (1%)	5 (5%)	
TVT score	3.9±3.1	3.9±2.9	6.1±5.7	<0.001
STS-PROM score	4.4 (3.0–7.0)	4.4 (2.9–7.0)	5.4 (3.6–10.0)	<0.001

Values are mean±SD or medians (25%–75% interquartile ranges). Definition of acuity categories is provided in the text. eGFR indicates estimated glomerular filtration rate; NYHA, New York Heart Association; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; and TVT, transcatheter valve therapy.

Performance of the STS-PROM Score

As shown in Figure 1B and 1D, the STS-PROM score achieved moderate discriminative ability for prediction of in-hospital

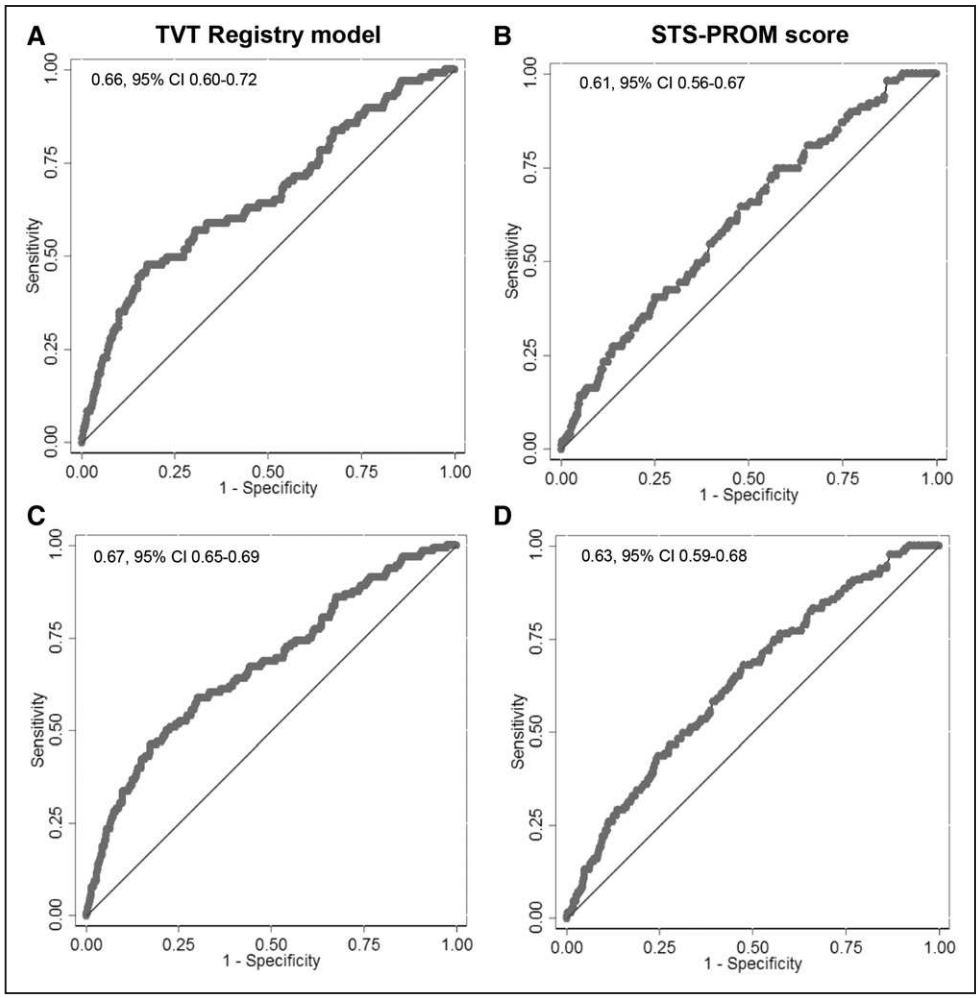

Figure 1. Receiving operating characteristic curve for prediction of in-hospital and 30-day mortality of the Transcatheter Valve Therapy (TVT) registry model (**A** and **C**) and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score (**B** and **D**). CI indicates confidence interval.

(C index, 0.61; 95% CI, 0.56–0.67) and 30-day (C index, 0.63; 95% CI, 0.59–0.68) mortality. Figure 2B and 2D displays a separation between observed and predicted mortality rates, especially for the higher values of estimated risk.

Comparative Performance of the TVT Registry Model and the STS-PROM Score in the Swiss TAVI Registry

Tables 2 and 3 report the comparison between the predictive accuracy of the TVT registry model and the STS-PROM score in our population. C index for the prediction of in-hospital and 30-day mortality were 0.66 versus 0.61 (P=0.14) and 0.67 versus 0.63 (P=0.12) for the TVT registry model and STS-PROM score, respectively. The Hosmer–Lemeshow statistics showed a better calibration ability of the TVT registry model compared with the STS-PROM score for in-hospital (slope, 0.83; P=0.23 versus slope, 0.24; P<0.001, respectively) and 30-day (slope, 1.11; P=0.40 versus slope, 0.41; P<0.001, respectively) mortality. Discrimination of the TVT registry model and STS-PROM score after multiple imputation of missing variables yielded comparable results (Table VI in the Data Supplement).

Discussion

The main findings of our study validating the performance of the TVT registry model in a large cohort of patients undergoing TAVR at multiple centers in Switzerland can be summarized as follows: (1) the TVT registry model showed moderate discrimination and adequate calibration for the prediction of in-hospital mortality after TAVR, (2) its predictive accuracy was maintained for mortality at 30 days, and (3) the TVT registry model showed significantly better predictive accuracy in terms of calibration as compared with the STS-PROM score, whereas discrimination was comparable.

The TVT registry model has been recently developed to predict in-hospital mortality in a cohort of >13 000 patients undergoing TAVR in the United States between 2011 and 2014. The internal validation cohort comprised >6000 patients treated between March and October 2014. The model showed moderate discrimination with a C index of 0.67 (95% CI, 0.65–0.69) in the development group and 0.66 (95% CI, 0.62–0.69) in the validation group, respectively, and good calibration. Although alternative scores have been both derived and validated in relatively small cohorts, the TVT registry model has been derived and validated in a cohort surpassing the

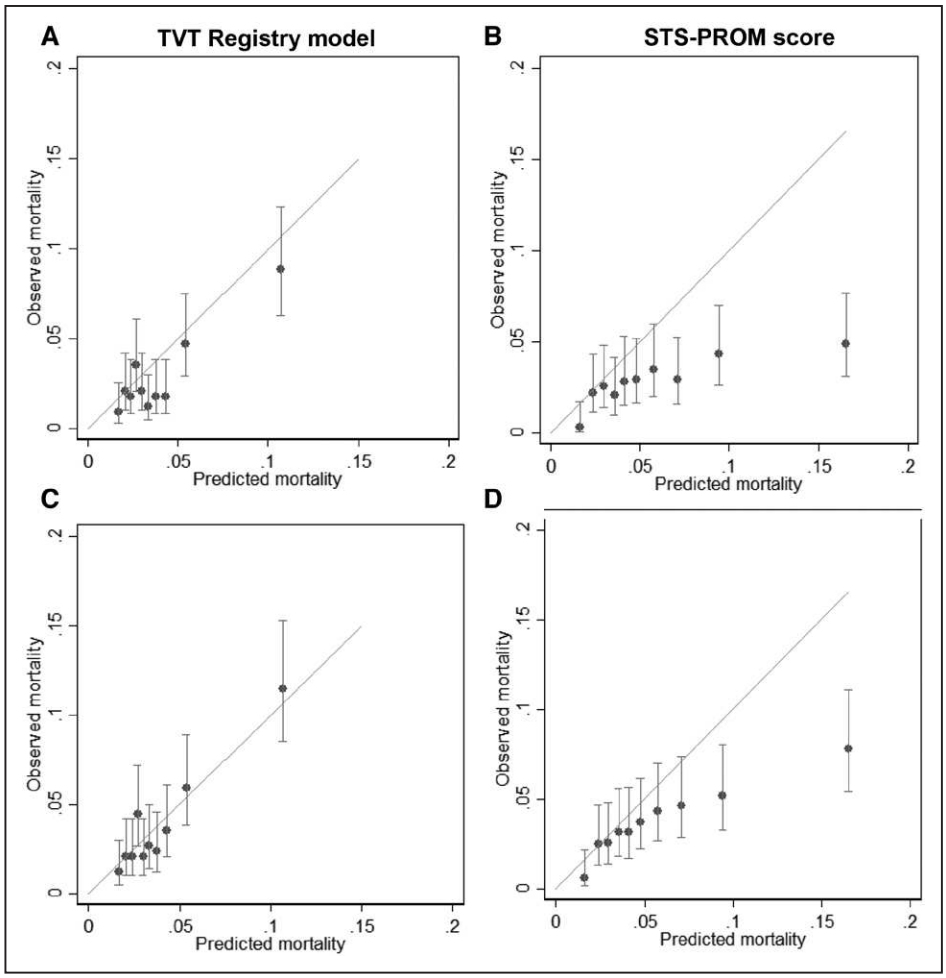

Figure 2. Calibration plots showing the predicted (*x* axis) probability vs observed (*y* axis) in-hospital and 30-day mortality after transcatheter aortic valve replacement for the Transcatheter Valve Therapy (TVT) registry model (**A** and **C**, respectively) and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score (**B** and **D**). The diagonal line represents the perfect calibration (observed=calibration). Observed mortality is represented with 95% confidence intervals (error bars).

next largest cohort used to build a risk score by a factor of 5. The time interval of patients included in the present analysis largely corresponded with the time interval of the STS/American College of Cardiology TVT registry. In our study, we found a discrimination of the TVT registry model for the prediction of in-hospital mortality comparable with the original report; moreover, discrimination was maintained at 30 days after the procedure. This clearly defined time window allows for a better assessment of early outcomes after TAVR because in-hospital length of stay may be highly variable across different centers.

A risk–benefit analysis is an integral part of the Heart Team assessment for the selection of the optimal treatment strategy for patients with severe aortic valve stenosis. Clinical and anatomic characteristics complement the multidisciplinary evaluation of the patient and are consolidated in specific scores quantifying periprocedural risk. Risk scores allow for the possibility of comparing health across different populations. Several risk scores have proven instrumental for surgical procedures and are regularly harmonized with updated information on contemporary event rates. In the absence of a tailored risk score for TAVR, risk models originally derived from surgical cohorts have been used for the definition of risk categories and patient selection in randomized trials of TAVR versus surgical aortic valve replacement.[15–17] However, there is a large body of evidence demonstrating a suboptimal performance of such scores in TAVR cohorts. Indeed, in the PARTNER I trial (Placement of Aortic Transcatheter Valves) and continued access registry, both the STS-PROM score and the Logistic System for Cardiac Operative Risk Evaluation overestimated the mortality occurring in-hospital or at 30 days after TAVR.[3] Along the same line, in a retrospective analysis of patients treated with the Medtronic CoreValve prosthesis at 2 European centers, both the Logistic System for Cardiac Operative Risk Evaluation and the STS-PROM algorithm were found to have suboptimal discriminatory power and calibration.[4] Consistently, in our cohort, the STS-PROM score showed poorer calibration among patients with higher estimated mortality risk. This finding does not only pertain to the field of TAVR but has already been reported in surgical series.[18]Arguably, such suboptimal calibration in high-risk categories may stem from high mortality rates in the original derivation cohort of the STS-PROM score.

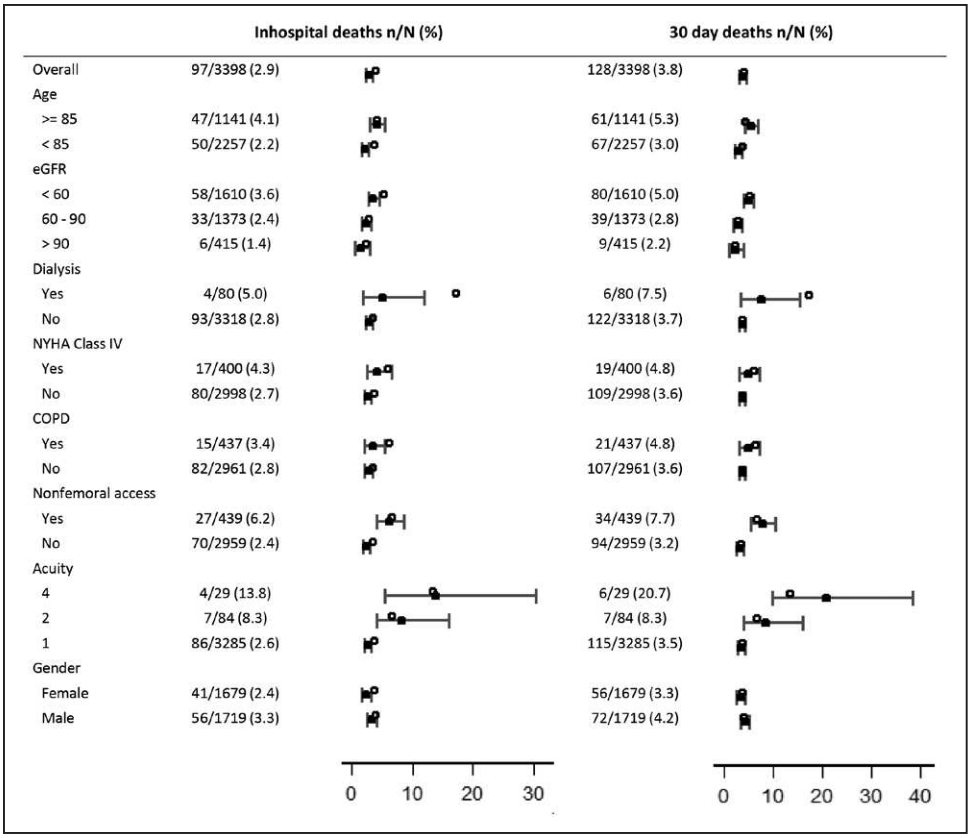

Figure 3. Observed (closed circle) vs predicted (open circle) in-hospital and 30-day mortality across prespecified subgroups. COPD indicates chronic obstructive pulmonary disease; eGFR, glomerular filtration rate; and NYHA, New York Heart Association.

More recently, several TAVR-specific risk scores have been suggested, as summarized in Table 4. Most scores have been validated for 30-day mortality and were found to have a C index ranging from 0.57 to 0.75. Although applicability of both the STS-PROM score and the System for Cardiac Operative Risk Evaluation has been repeatedly questioned in view of their derivation and validation in patients with surgical access, the TVT risk model is the first among the specific TAVR risk scores to differentiate between transfemoral and alternative (surgical) approach for TAVR.

Currently available risk scores for TAVR are limited by several factors. Time is an important covariable rarely accounted for in conventional risk scores. A discount in risk over time has been observed for the STS-PROM score resulting in a reclassification of more than half of patients originally deemed to be high risk to intermediate risk in an analysis repeated 6 to 7 years after the first analysis.[19] Sensitive scores work bidirectionally: they inform about anticipated risk, while regularly being updated by the most recent outcome data. This may be particularly important in a rapidly evolving field, such as TAVR, where device iterations have been shown to substantially reduce periprocedural complications as reflected by a large heterogeneity of reported outcomes across major studies. Moreover, deficiencies of standard modelling methods, relatively small and homogenous derivation cohorts, and absence of validation in external datasets further hamper the robustness of existing TAVR risk scores. To date, there were no studies assessing the reproducibility and transportability of the TVT registry model. Geographical variability in performance is mainly related to variation in case mix, that is dissimilarity between patients in different countries.[20] In our study, the predictive accuracy of the TVT registry model was confirmed in an unselected cohort of consecutive patients treated in Switzerland. The reproducibility of the results observed in the development cohort is an important finding in view of the expected differences between the 2 sides of the Atlantic in terms of patient features, devices, procedural characteristics, and postprocedural care. Some concerns may arise about model performance because its discrimination was

Table 2. Discrimination of the TVT Registry Model and the STS-PROM Score

	AUC (95% CI)	TVT Registry Model vs STS-PROM Score
		P Value
In-hospital mortality		0.14
TVT registry model	0.66 (0.60–0.72)	
STS-PROM score	0.61 (0.56–0.67)	
30-d mortality		0.12
TVT registry model	0.67 (0.62–0.72)	
STS-PROM score	0.63 (0.59–0.68)	

AUC indicates area under the receiver operating characteristic curve; CI, confidence interval; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; and TVT, transcatheter valve therapy.

Table 3. Calibration of the TVT Registry Model and the STS-PROM Score

	Hosmer–Lemeshow Test (*P* Value)	Intercept	*P* Value*	Slope	*P* Value†
TVT registry model					
In-hospital mortality	0.15	–0.00 (–0.02 to 0.01)	0.517	0.83 (0.58–1.08)	0.23
30-d mortality	0.36	–0.01 (–0.02 to 0.01)	0.323	1.11 (0.87–1.34)	0.40
STS-PROM score					
In-hospital mortality	0.58	0.01 (0.01–0.02)	0.006	0.24 (0.14–0.35)	<0.001
30-d mortality	0.58	0.01 (0.01–0.02)	0.003	0.41 (0.32–0.50)	<0.001

STS-PROM indicates Society of Thoracic Surgeons Predicted Risk of Mortality; and TVT, transcatheter valve therapy.
*Null hypothesis, calibration plot intercept=0.
†Null hypothesis, calibration plot slope=1.

only moderate in the original and current cohorts. However, this limitation is counterbalanced at least, in part, by the good calibration that was confirmed in this external cohort and preserved across several subgroups of patients. This property ensures high reliability in counseling patients and their relatives about the risk of death early after the procedure. At this regard, the considerable gain in terms of calibration of the TVT registry model compared with the STS-PROM score could have important clinical implications, especially when dealing with patients at the extremes of risk categories where the reliability of the STS-PROM score is poorer.

Limitations

We acknowledge the following limitations of our study: (1) although we were able to include a large contemporary TAVR population with excellent documentation of baseline and

Table 4. Main Features of the Currently Available TAVI Risk Scores

Score (Author, Year)	FRANCE-2 (Iung, 2014)[6]	TARIS (Seiffert, 2014)[5]	OBSERVANT (Capodanno, 2014)[8]	Predictor of Poor Outcomes (Arnold et al, 2014)[9]	$TAVI_2$ (Debonnaire, 2015)[7]	CoreValve US Program (Hermiller, 2016)[10]	TVT Registry Model (Edwards, 2016)[11]
Population	FRANCE-2 registry; derivation cohort, n=2552; validation cohort, n=1281	GARY registry; derivation cohort, n=845; validation cohort, n=333	OBSERVANT study derivation cohort, n= 1256; validation cohort, n=622	PARTNER program; derivation cohort, n=1420; validation cohort, n=717	Patients treated at 2 centers (the Netherlands and Italy); derivation cohort, n=511	Medtronic CoreValve US Pivotal trial; derivation cohort, n=2482; validation cohort, n=1205	STS/ACC TVT registry; derivation cohort, n=13718; validation cohort, n=6868
Variables	BMI <30; NYHA class IV; respiratory insufficiency; pulmonary hypertension; ≥2 episodes of pulmonary edema during past year; critical hemodynamic state; dialysis	BMI; eGFR; hemoglobin; pulmonary hypertension; mean transvalvular gradient; LVEF	GFR <45 mL/min; critical preoperative state; NYHA class IV; pulmonary artery hypertension; diabetes mellitus; prior BAV; LVEF <40%	Male sex; diabetes mellitus; major arrhythmia; serum creatinine; mean arterial pressure; body mass index; oxygen-dependent lung disease; mean aortic valve gradient; mini–mental status examination; 6-min walk test distance	Age >85 y; men; porcelain aorta; recent MI (<90 d); CrCl <30 $mL \cdot kg^{-1} \cdot min^{-1}$; hemoglobin <10 g/dL; LVEF <35%; baseline AVMG ≥70 mm Hg	Albumin ≤3.3 g/dL; assisted living; home oxygen; age >85 y. Albumin ≤3.3 g/dL; Seve Charlson score; home oxygen; STS >7%	Age; NYHA class IV; chronic lung disease (severe); acuity (3 levels); dialysis or glomerular filtration rate; nonfemoral approach
Predicted Outcomes	30-d mortality	30-d mortality	30-d mortality	Death, KCCQ-OS score <45, or ≥10-point decrease in KCCQ-OS score compared with baseline at 6 mo and 1 y	1-y mortality	30-d mortality; 1-y mortality	In-hospital mortality
C index	0.67	0.57	0.71	0.66	0.71	0.75 (30 d); 0.79 (1 y)	0.66

ACC indicates American College of Cardiology; AVMG, aortic valve mean gradient; BAV, balloon aortic valvuloplasty; BMI, body mass index; eGFR, estimated glomerular filtration rate; FRANCE-2, French Aortic National CoreValve and Edwards Registry; GARY, German Aortic Valve Registry; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire–Overall Summary Scale; LVEF, left ventricular ejection fraction; MI, myocardial infraction; NYHA, New York Heart Association; OBSERVANT, Observational Study of Approriateness, Efficacy and Effectiveness of AVR-TAVR Procedures for the Treatment of Severe Symptomatic Aortic Stenosis; PARTNER, placement of aortic transcatheter valves; STS, Society of Thoracic Surgeons; TARIS, TAVI Risk Score; TAVI, transcatheter aortic valve implantation; and TVT, transcatheter valve therapy.

follow-up status, the TVT registry model was validated in a retrospective manner; (2) we were unable to assess the added value of indices of frailty and measures of quality of life that were not included in the original model because they are not systematically collected in our database; (3) the results of our validation analysis may be affected by the impossibility to quantify the case-mix differences between development and validation samples because, with the exception of age and sex, no other baseline clinical characteristics of the original cohort were available; (4) although predicted versus observed mortality was consistent for both in-hospital and 30-day outcomes across several subgroups, an overestimation of in-hospital and 30-day mortality for patients on hemodialysis was observed. This should be carefully interpreted in view of multiple testing and the small number of patients included in this subgroup; (5) we were unable to assess the comparative performance of the TVT registry model and other risk scores because measures such as frailty, mini–mental status examination, 6-minute walk test distance, assisted living, home oxygen use, and Charlson Comorbidity Index are not systematically collected in our database; (6) in view of the ongoing expansion of TAVR adoption in lower-risk patients, further studies are needed to validate the accuracy of this model in low-risk populations.

Conclusions

In a large, multicenter, non-US cohort of patients with TAVR, the validation of the TVT registry model demonstrated moderate discrimination and good calibration for the prediction of in-hospital and 30-day mortality. As a result, the TVT registry model should be considered an alternative to the STS-PROM score for decision making and assessment of early outcome in patients eligible for TAVR.

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Disclosures

Dr Pilgrim serves as a consultant to Symetis, received speaker fees from Boston Scientific and Biotronik, and received research contracts to the institution from Edwards Lifesciences, Symetis, and Biotronik. Dr Nietlispach serves as consultant to Edwards Lifesciences and St. Jude Medical. Dr Tueller received speaker fees from Edwards Lifesciences and travel expenses from Medtronic. Dr Toggweiler serves as a consultant for Symetis and New Valve Technology and received speaker fees from Symetis, Edwards Lifesciences, and Medtronic. Dr Jeger serves as a consultant to St. Jude Medical and has received reimbursement for travel expenses from Medtronic, Boston Scientific, and Edwards Lifesciences. Dr Ferrari is a proctor and consultant for Edwards Lifesciences. Dr Noble serves as consultant for Medtronic. Dr Roffi received institutional research grants from Abbott Vascular, Boston Scientific, Biotronik, Terumo, and Medtronic. Dr Huber is a proctor for Edwards Lifesciences and Symetis and has received speaker fees from Edwards Lifesciences, Symetis, and Medtronic. Dr Windecker has received research contracts to the institution from Abbott, Boston Scientific, Biosensors, Cordis, Medtronic, and St. Jude. Dr Wenaweser serves as proctor for Medtronic, Edwards Lifesciences, and Boston Scientific and has received an unrestricted grant from Medtronic to the institution (University of Bern). The other authors report no conflicts.

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Predicting Mortality After Transcatheter Aortic Valve Replacement: External Validation of the Transcatheter Valve Therapy Registry Model

Thomas Pilgrim, Anna Franzone, Stefan Stortecky, Fabian Nietlispach, Alan G. Haynes, David Tueller, Stefan Toggweiler, Oliver Muller, Enrico Ferrari, Stéphane Noble, Francesco Maisano, Raban Jeger, Marco Roffi, Jürg Grünenfelder, Christoph Huber, Peter Wenaweser and Stephan Windecker

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Predicting Mortality after Transcatheter Aortic Valve Replacement: External Validation of the TVT Registry Model

SUPPLEMENTAL MATERIAL

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Supplemental Table 1. TRIPOD Checklist

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	3
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
	5b	D;V	Describe eligibility criteria for participants.	4
	5c	D;V	Give details of treatments received, if relevant.	4
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	4-5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	N.A.
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	4-5
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	N.A.
Sample size	8	D;V	Explain how the study size was arrived at.	N.A.
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5.
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	N.A.
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	5
	10c	V	For validation, describe how the predictions were calculated.	5
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	5-6
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N.A.
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	5
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	N.A.
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	6.
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	6
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	N.A.
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	6
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Supplemental Table 2
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	6
	15b	D	Explain how to the use the prediction model.	10
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	6 and Figure 1 and 2
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	N.A.
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	10
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	9
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	8-10
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	8-10
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	N.A
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	N.A.

Supplemental Table 2. Type and frequency of transcatheter heart valves in the Swiss TAVI cohort

	All patients	**Survivors**	**Died in hospital**
	n= 3,491	n= 3,390	n= 101
Medtronic CoreValve	917 (26%)	892 (26%)	25 (25%)
Edwards Sapien XT	606 (17%)	582 (17%)	24 (24%)
Symetis Acurate	98 (3%)	96 (3%)	2 (2%)
JenaValve	57 (2%)	53 (2%)	4 (4%)
SJM Portico	87 (3%)	85 (3%)	2 (2%)
Medtronic Engager	2 (0%)	1 (0%)	1 (1%)
Direct Flow Medical	34 (1%)	33 (1%)	1 (1%)
Edwards Sapien 3	1163 (33%)	1131 (33%)	32 (32%)
BSC Lotus	186 (5%)	186 (6%)	0 (0%)
Medtronic Evolut R	330 (9%)	321 (9%)	9 (9%)

Supplemental Table 3. Baseline clinical characteristics of patients in the validation and development cohorts

	SWISS TAVI Registry n= 3491	STS/ACC TVT Registry n= 13718
Age (years)	82.1 ± 6.5	82.1 ± 8.3
Male gender (%)	1760 (50%)	6680 (48.7%)

Values are mean ± SD or percentages.

Supplemental Table 4. Univariable and multivariable predictors of mortality rates from the external validation cohort

	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
In-hospital mortality				
Age (5 year intervals)	1.36 (1.13 - 1.63)	0.001	1.41 (1.16 - 1.71)	0.001
GFR (5-U increments)	0.91 (0.87 - 0.95)	<0.001	0.92 (0.87 - 0.98)	0.005
Dialysis	1.77 (0.64 - 4.94)	0.27	1.20 (0.38 - 3.79)	0.76
NYHA class IV	1.60 (0.94 - 2.73)	0.083	1.04 (0.58 - 1.89)	0.89
Severe chronic lung disease	1.20 (0.69 - 2.10)	0.52	1.30 (0.73 - 2.33)	0.37
Non femoral access	2.59 (1.65 - 4.07)	<0.001	2.97 (1.86 - 4.73)	<0.001
Acuity category 2	3.08 (1.39 - 6.85)	0.006	3.25 (1.41 - 7.52)	0.006
Acuity category 4	6.04 (2.29 - 15.93)	<0.001	6.20 (1.90 - 20.24)	0.003
30 day mortality				
Age (5 year intervals)	1.34 (1.14 - 1.58)	<0.001	1.39 (1.17 - 1.64)	<0.001
GFR (5-U increments)	0.89 (0.85 - 0.93)	<0.001	0.90 (0.86 - 0.95)	<0.001
Dialysis	2.08 (0.89 - 4.87)	0.091	1.15 (0.44 - 3.03)	0.78
NYHA class IV	1.39 (0.85 - 2.26)	0.191	0.79 (0.45 - 1.38)	0.40
Severe chronic lung disease	1.31 (0.81 - 2.11)	0.27	1.47 (0.89 - 2.41)	0.13
Non femoral access	2.48 (1.66 - 3.72)	<0.001	2.80 (1.85 - 4.25)	<0.001
Acuity category 2	2.30 (1.04 - 5.07)	0.04	2.45 (1.07 - 5.63)	0.034
Acuity category 4	8.27 (3.67 - 18.64)	<0.001	8.56 (3.06 - 23.89)	<0.001

Refitted coefficients are shown for descriptive purpose only. Original coefficients were used to assess the predictive performance of the TVT Registry model in the external validation cohort. Missing data was imputed using chained equations to generate 20 imputations sets. Estimates were combined using Rubin's rule. No acuity category 3 patients defined. eGFR, Estimated glomerular filtration rate; NYHA, New York Heart Association.

Supplemental Table 5. Performance of the TVT Registry Model across different time periods

	AUC (95% CI)	χ^2*	p value*
November 2011- February 2014 (N = 1317)			
In-hospital death	0.68 (0.59 - 0.76)	11.51	0.174
30 day death	0.68 (0.61 - 0.75)	7.59	0.475
March 2014-February 2016 (N = 2174)			
In-hospital death	0.63 (0.54 -0.71)	4.2	0.839
30 day death	0.66 (0.59 - 0.73)	2.97	0.936

November 2011- February 2014 corresponds to the same time period of the derivation cohort. *Hosmer-Lemeshow test. **Combination of Chi² statistics in MI result in values from an F distribution.

Supplemental Table 6. Model fit statistics after multiple imputation of missing variables

	AUC (95% CI)	p value*
TVT Registry Model		
In-hospital mortality	0.66 (0.60 - 0.71)	0.25
30-day mortality	0.68 (0.63 - 0.73)	0.46
STS-PROM score		
In-hospital mortality	0.61 (0.56 - 0.67)	0.63
30-day mortality	0.64 (0.59 - 0.68)	0.56

Combination of Chi^2 statistics in MI result in values from an F distribution. *Hosmer-Lemeshow test. The following variables were imputed: age(0.26% of cases), estimated glomerular filtration rate (0.43%), dialysis (0.11%), NYHA class 4 (2.21%).