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Performance of Current Risk Models in Predicting Short-Term Mortality After Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis

Short Title: Performance of TAVR Risk Models

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Abstract:

Aim: To evaluate the performance of risk stratification models (RSMs) in predicting short-term mortality after transcatheter aortic valve replacement (TAVR).

Methods and Results: MEDLINE and Scopus were queried to identify studies which validated RSMs designed to assess 30-day or in-hospital mortality after TAVR. Discrimination and calibration were assessed using C-statistics and observed/expected ratios (OERs), respectively. C-statistics were pooled using a random-effects inverse-variance method, while OERs were pooled using the Peto odds ratio. A good RSM is defined as one with c-statistic >0.7 and OER close to 1.0. Twenty-four studies (n=68,215 patients) testing 11 different RSMs were identified. Discrimination of all RSMs was poor (C-statistic<0.7); however, certain TAVR-specific RSMs such as the in-hospital STS/ACC TVT (C-statistic=0.65) and STT (C-statistic=0.66) predicted individual mortality more reliably than surgical models (C-statistic range=0.59-0.61). A good calibration was demonstrated by the in-hospital STS/ACC TVT (OER=0.99), 30-day STS/ACC TVT (OER=1.08) and STS (OER=1.01) models. Baseline dialysis (OER: 2.64 [1.88, 3.70]; p<0.001) was the strongest predictor of mortality.

Conclusion: This study demonstrates that the STS/ACC TVT model (in-hospital and 30-day) and the STS model have accurate calibration, making them useful for comparison of center-level risk-adjusted mortality. In contrast, the discriminative ability of currently available models is limited.

Classifications:

1) Aortic Stenosis
2) TAVI
3) Death

Condensed Abstract:

This meta-analysis aimed to evaluate the performance of current risk stratification models (RSMs) in predicting short-term mortality TAVR. C-statistics and observed/expected ratios (OERs) from all studies validating a RSM were pooled to accurately assess the model's discrimination and calibration, respectively. A good RSM is defined as one with c-statistic >0.7 and OER close to 1.0. The results show that the STS/ACC TVT model (in-hospital and 30-day) and the STS model have accurate calibration, making them useful for comparison of center-level risk-adjusted mortality. Discrimination of all RSMs was poor; however, certain TAVR-specific predicted individual mortality more reliably than surgical models.

Abbreviations:

AHA: American Heart Association.

AUC: area under the curve

CIs: confidence intervals

ESC/EACTS: European Society of Cardiology/European Association for Cardiothoracic Surgery

EuroSCORE: European System for Cardiac Operative Risk Evaluation.

France 2 : FRench Aortic National CoreValve and Edwards;GS:Guaragna score; German AV Score: German Aortic Valve Score.

German AV Score: German Aortic Valve Score.

MeSH: Medical subject heading

NYHA: New York Heart Association.

OBSERVANT: Observational Study Of Appropriateness, Efficacy And Effectiveness of AVR-TAVR Procedures For the Treatment Of Severe Symptomatic Aortic Stenosis.

OERs: observed/expected ratios

PRISMA: Preferred Reporting Items for Systematic review and Meta-Analyses

PROBAST: The Prediction Model Risk of Bias Assessment Tool.

RSMs: risk stratification models

SAVR: surgical aortic valve replacement

STS/ACC TVT: Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy

STS: Society of Thoracic Surgeon

STT: survival post TAVI

TAVR: transcatheter aortic valve replacement

UK TAVI CPM: UK Transcatheter Aortic Valve Implantation Clinical Prediction Models

Introduction:

The European Society of Cardiology/European Association for Cardiothoracic Surgery (ESC/EACTS) guidelines recommend transcatheter aortic-valve replacement (TAVR) instead of surgical aortic valve replacement (SAVR) to improve survival and/or symptoms in patients with aortic stenosis who are at intermediate-to high surgical risk (1). Recent evidence suggests that the recommendation for TAVR might be extended to low surgical risk patients as well (2). Although the use of TAVR is increasing, candidate selection for TAVR in whom the expected benefits of the intervention outweigh risks remains a challenge. Accurate risk stratification models (RSMs) can aid this process by determining the probability of a futile procedure, and thereby helping avoid hopeless procedures and simplifying treatment decisions. Initially, surgical RSMs such as the Society of Thoracic Surgeon (STS) score and the European System for Cardiac Operative Risk Evaluation (EuroSCORE), were used for this purpose (3). However, their prognostic value has been questioned, and concerns have been raised that they tend to overestimate mortality risk.

Consequently, multiple RSMs have been developed from TAVR populations; however, their reliability is not well-established, and it remains unclear which of these RSMs is optimal for clinical use (4-10). Furthermore, the external generalizability of these models is limited given the heterogenous patient populations, procedural and operator specific factors. Therefore, pooling data from different validation studies can provide a more accurate assessment of the performance of the RSM compared to individual studies. The purpose of this study was to systematically analyze clinical practicability, productiveness and discriminative performance of each RSM by meta-analyzing data from all studies validating the particular RSM. Furthermore, we aimed to assess whether TAVR-dedicated risk scores are superior to surgical risk scores in predicting

survival. In addition, we sought to review the predictors used by each RSM, and evaluate which patient-specific parameters were the best predictors of post-TAVR mortality.

Methods:

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines (11).

Details on search strategy **(supplementary table 1)**, study selection, data extraction and quality assessment is provided in the supplementary appendix. (5, 10)

Effect size estimation

Discrimination and calibration are relative and absolute measures, respectively, that are essential to have in a useful and reliable RSMs. Discrimination is defined as the ability of RSMs to yield a higher 'risk' for individuals who experience an event in the future, when compared with patients who do not experience the event. To evaluate discrimination, we used the C-statistic (also known as 'area under the curve' or AUC). The C-statistic ranges from 1.0 (perfect concordance between model-based risk estimates and observed events) to 0.5 (random concordance). C-statistic values have been categorized as follows: (a) 0.81-0.90 = good; (b) 0.71-0.80 = fair; (c) 0.61-0.70 = poor; and (d) 0.50-0.60 = very poor/almost no association (12). For this meta-analysis, C-statistics and their corresponding 95% CIs were extracted from each validation study. The 95% CIs were used to compute standard errors (SEs).

Calibration is the measure of how accurately the model's predictions match overall observed events in a cohort of patients (observed/expected ratio or OER). OERs of ~1 suggest good calibration. OERs >1 suggest underprediction, while ratios <1 suggest over-prediction.

From each study, we extracted the expected mortality (as predicted by the risk model) and the observed (actual) mortality. These values were then used to compute the observed – expected (O-E) value and the variance, using an online calculator (http://www.hutchon.net/peto%20vers%202.html).

Statistical Analysis

The C-statistics and corresponding SEs were meta-analyzed using an inverse variance random-effects model to determine the pooled discrimination. Before pooling, logit transformation of the C-statistic values was carried out. The OER and variance were measured using Peto-odds-ratio. The OERs from each study validating a particular model were pooled together to accurately estimate the calibration of that scale. Log transformation of the OER values was done prior to pooling. We also sought to assess the association of specific predictors with short-term mortality. A covariate was selected for meta-analysis if data (odds ratios (OR) and 95% CIs) on it were provided by at least two studies. Q statistics and Higgins I^2 were used to evaluate heterogeneity across studies and a value of I^2=25%-50% was considered mild, 50%-75% as moderate, and >75% as severe. A p value of <0.05 was considered significant for all analyses. Review Manager (Version 5.5; Cochrane Collaboration, Oxford, UK) was used to perform the statistical analyses.

Results:

Search results

The initial search produced 6,099 articles, 2,930 were reviewed at title and abstract level and additional 2,906 articles were removed based on pre-determined selection criteria. Ultimately, 24 articles including 68,215 patients were finalized for this analysis (**Figure 1**) (4-10, 13-30). These 24 studies tested 11 different RSMs (seven TAVR-specific; 3 surgical; and one designed for use in both TAVR and SAVR patients). **Supplementary table 2** provides a list of all included studies along with relevant study characteristics. **Supplementary table 3** displays the predictors that make up each included RSM. Assessment of risk of bias using the PROBAST scale revealed that all the new TAVR-specific models were developed using robust methodological methods (**Supplementary Table 4**). Similarly, all of these models were found to have good applicability except for the UK TAVI CPM, which was adjudicated to have low applicability as it was derived from a small, selected population.

The summarized forest plots display the pooled discrimination (**Figure 2**) and calibration (**figure 3**) of each RSM. The detailed forest plots are provided in the supplementary appendix (**Supplementary figures 1-4**).

TAVR Specific Models

STS/ACC TVT – Meta-analysis of 2016 and 2018 in-hospital risk models demonstrated a C-statistic of 0.65 (95% CI: 0.62-0.68; I^2=0%) and an OER of 0.99 (95% CI: 0.92-1.07; I^2=82%), indicating poor discrimination and good calibration, respectively. We could not estimate the discrimination of the 30-day model due to lack of data. The OER for this model was

1.08 (95% CI: 0.93-1.27). The 30-day mortality model has not yet been externally validated as of March 2019.

OBSERVANT: The model was found to have a poor discrimination (C-statistic: 0.57; 95% CI: 0.54-0.60; I^2=0%) and a significantly over-predictive calibration (OER: 0.75; 95% CI: 0.56-0.65).

France 2: The Pooled results demonstrated poor discrimination (C-statistic: 0.61; 95% CI: 0.59-0.64; I^2=13%). The calibration of the scale was found to be significantly over-predictive for 30-day mortality (OER: 0.57; 95% CI: 0.50-0.65; I^2=0%).

CoreValve: This model demonstrated a fair discriminative ability, (C-statistic: 0.75; 95% CI: 0.35-1.15); however, a wide confidence interval makes this result unreliable. OER was not reported by the single study validating this model. To the best of our knowledge, this RSM has not been externally validated.

STT (Survival posT TAVI): The STT model demonstrated poor discriminative ability (C-statistic: 0.66; 95% CI: 0.56-0.76). OER was not reported; and our search revealed no studies which externally validated this model and met the inclusion criteria.

UK TAVI CPM: This model demonstrated a poor discriminative ability (C-statistic: 0.66; 95% CI: 0.61-0.71). OER was not reported in the publication in which this model was derived and validated. This model has not yet been validated in an external sample.

German AV Score: This model showed a very poor discrimination (C-statistic: 0.59; 95% CI: 0.56-0.62) and a significantly over-predictive calibration (OER: 0.72; 95% CI: 0.62-0.82).

SAVR Specific Models

STS – This surgical risk model showed a poor discrimination (C-statistic: 0.60; 95% CI: 0.58-0.64; I^2=34%); however, the calibration was good (OER: 1.01; 95% CI: 0.90-1.13; I^2=70%).

Logistic EUROSCORE: It showed very poor discrimination (C-statistic: 0.59; 95% CI: 0.56-0.62; I^2=54%). Similarly, this model showed a significantly over-predictive calibration (OER: 0.30; 95% CI: 0.27-0.33; I^2=88%).

EUROSCORE II: This model showed poor discrimination (C-statistic: 0.61; 95% CI: 0.58-0.64; I^2=30%). The calibration of this model was over-predictive (OER: 0.79; 95% CI: 0.71-0.88; I^2=80%).

P-interaction between subgroups

The overall p-interactions for both discrimination (p=0.03) and calibration (p<0.001) signify significant differences between subgroups. **Supplementary table 5 and 6** give p-interaction values between individual subgroup pairs in the discrimination and calibration analysis, respectively.

Predictors of short-term mortality (Figure 4)

Baseline dialysis was the strongest predictor of short-term mortality (OR: 2.64 [1.88, 3.71]; p<0.001; I^2=0%). **Figure 4** displays all the predictors studied.

Discussion:

This meta-analysis of 68,215 patients shows that RSMs designed specifically for TAVR patients show poor discrimination (C-statistic range: 0.57-0.66); however, some of these models,

such as the in-hospital STS/ACC TVT (C-statistic=0.65), STT (C-statistic=0.66), and UK TAVI CPM (C-statistic = 0.66) predicted individual mortality more reliably than surgical models (C-statistic range: 0.59-0.61). Amongst the new TAVR-specific models that reported data on calibration, the STS/ACC TVT (both the in-hospital as well as 30-day mortality versions) had the best performance. When both discrimination and calibration were considered together, the in-hospital STS/ACC TVT was the best performing RSM. Amongst the individual parameters analyzed, baseline dialysis and non-femoral access site were the strongest predictors of 30-day mortality.

Globally, in the last few years TAVR has been performed in more than 400,000 patients and indications keep growing at a rate of 40% annually (28). This has presented the need for RSMs that can predict 30-day mortality; thereby allowing patient selection and provider comparisons (28). Due to the lack of TAVR-specific models initially, several investigators tested the usefulness of surgical RSMs in assessing the risk of mortality in patients undergoing TAVR. However, valid concerns were raised about the limitations of surgical models. For example, these models do not include crucial factors that are strongly believed to affect candidacy for TAVR; such as home oxygen use, access site, assessments of frailty, and consideration of functional disabilities. Since 2014, several TAVR-specific models have emerged. However, reports concerning the applicability of these TAVR-specific RSMs have varied markedly in their findings.

A model with a discriminative capacity of C>0.80 provides strong support to guide medical decision-making and can reliably dictate whether a patient will experience an event. Strongly discriminative models can also be relevant for research purposes, such as covariate adjustment in RCTs. Unfortunately, our study finds that neither surgical nor TAVR-specific risk

models currently meet the threshold of C>0.80. The highest C-statistic was of the CoreValve model (C-statistic = 0.75), but it was unreliable due to a wide 95% CI (0.35-1.15). This unreliability may be because only a single, relatively small-sized study developed and validated this RSM, and due the lack of external validation studies. The discriminative ability of the CoreValve model will become clearer as additional studies validate it. When both the C-statistic and 95% CI are considered, the in-hospital STS/ACC TVT model appears to currently have the best discrimination (C-statistic: 0.65; 95% CI: 0.62-0.68). We were only able to meta-analyze the C-statistics from an older version of this model - an updated version demonstrated an even better C-statistic reaching up to 0.70 for in-hospital mortality and 0.71 for 30-day mortality (10). However, there still remains room for improvement. For example, other cardiovascular risk models, such as the ones for the management of heart failure and percutaneous coronary intervention demonstrate C-statistics >0.80 for 30-day mortality (31). There could be a couple of explanations as to why the TAVR-specific risk models do not currently achieve this level of discrimination. First, this could be due to limitations in the model, such as an insufficient number of predictors or due to predictors being dichotomized for simplicity. Additionally, relatively small and homogenous derivation cohorts, and absence of validation in external datasets could also be responsible. If this is the case, additional data (for example, from the continuously growing TVT registry), along with periodic model refinements will likely improve the discrimination. Regular model updates using the most recent outcome data is particularly important in a rapidly evolving field, such as TAVR, where device and procedural advancements have been shown to significantly reduce periprocedural complications, as reflected by a large heterogeneity of reported outcomes across major studies (23). A second reason for the weak discrimination could be the inherent inability to discriminate between patients who will or will

not die post TAVR. However, a poorly discriminating model (e.g. C~0.6), may be useful (when used in conjunction with clinical judgment) in a situation that does not have one outcome or choice that is clearly better or more likely than another.

RSMs with a good calibration (OER ~1) are useful for benchmarking and comparison of center-level risk-adjusted outcome. This can be used by providers and sites to spur quality improvement, resulting in improved outcomes in patients with different risk profiles. According to our study, both the STS/ACC TVT (in-hospital and 30-day versions) and STS models demonstrate good calibration and may be used for this purpose. Our study demonstrates that there is considerable heterogeneity in the covariates incorporated by the TAVR specific risk prediction models. This underscores the need for combining these covariates to form an RSM that outperforms the currently available RSMs.

Limitations

This meta-analysis has limitations that need to be considered while interpreting the results. First, this meta-analysis is based only on retrospective observational studies and some bias may be present as not all parameters may have been available for calculation in the risk models. In the future, large prospective validation cohorts are needed to assess the accuracy of such RSMs and validate our results. Second, some validation studies had to be excluded from our analysis as relevant data were not provided, which could have contributed to bias. Third, these estimates are derived from individual studies as we did not have access to the individual patient data. Fourth, most of these models were derived from patient populations with high to intermediate risk. Amongst the low risk patient population, comorbidities are a less relevant part of risk scores to predict outcomes; other factors such as anatomical and procedural variables maybe more important but are traditionally not included in PSMs. The publication of studies in

lower risk populations (such as PARTNER 3 and Evolut trials) is likely to shift the TAVR use to lower risk patients, and the applicability of these scales in a lower risk population is currently not known. While the focus if this manuscript is short term mortality it must be noted that it is not the only outcome driving clinical decisions. Long term efficacy, functional outcomes and quality of life are also important and must be considered.

Conclusions:

In conclusion, our study demonstrates that the in-hospital STS/ACC TVT model, the 30-day STS/ACC TVT model, and the STS model have accurate calibration in predicting short-term mortality. This makes these models useful for comparison of center-level risk-adjusted mortality. In contrast, the discriminative ability of currently available models is limited, and room for improvement exists before wide clinical implementation.

Impact on daily practice:

This study demonstrates that the STS/ACC TVT models (in-hospital and 30-day) and the STS model have accurate calibration and can therefore help physicians and administrators compare center-level risk-adjusted mortality. Discrimination of all RSMs was poor, and room for improvement exists before these can be used to reliably predict the risk of individual patient mortality. This study also reviews the predictors that make up each RSM and highlights the strongest predictors of mortality, which can assist in the development of new, better-performing models.

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Figures Legends:

Figure 1: PRISMA flow chart outlining literature search.

Figure 2: Summarized forest plot displaying results of meta-analysis of discrimination of each risk stratification model.

AUC: Area under the curve

FRANCE-2: FRench Aortic National CoreValve and Edwards .

German AV Score: German Aortic Valve Score.

OBSERVANT Observational Study Of Appropriateness, Efficacy And Effectiveness of AVR-TAVR Procedures For the Treatment Of Severe Symptomatic Aortic Stenosis.

STS ACC/TVT: Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy.

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STT:survival post TAVI.

UK TAVI-CPM:UK Transcatheter Aortic Valve Implantation Clinical Prediction Models

Figure 3: Summarized forest plot displaying results of meta-analysis of calibration of each risk stratification model.

AUC: Area under the curve

STS-PROM: The Society of Thoracic Surgeons Predicted Risk of Mortality

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Figure 4: Forest plots displaying the association of each predictor with short-term mortality. Baseline dialysis (A) was the strongest predictor of short-term mortality, followed by critical preoperative state (B); non-femoral access site (C); NYHA class IV (D); pulmonary hypertension (E); home oxygen use (F); age greater than 85 (G); and GFR (per 5 units decrease) (H).

GFR: Glomerular Filtration Rate

NYHA: NewYork Heart Association

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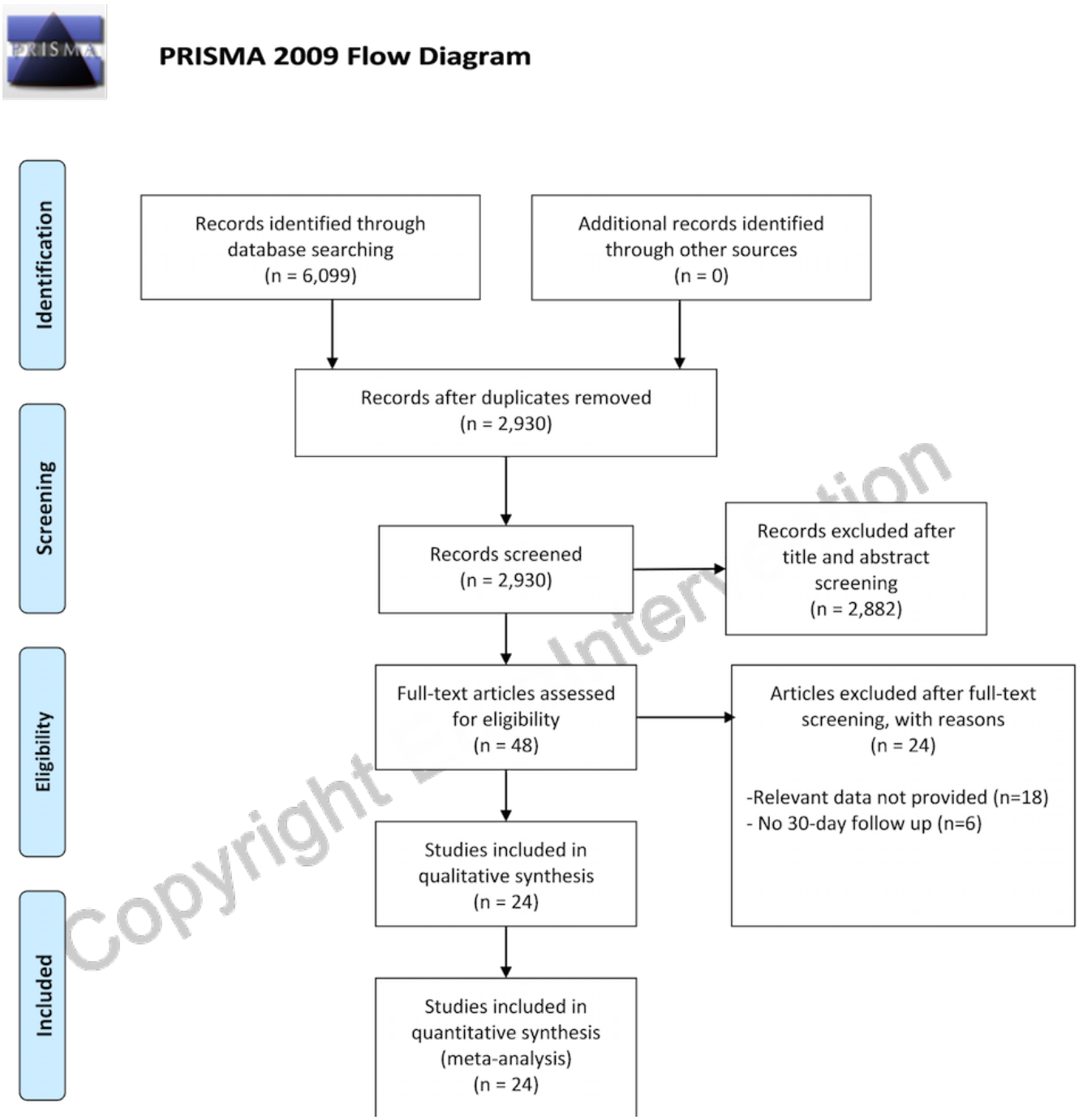
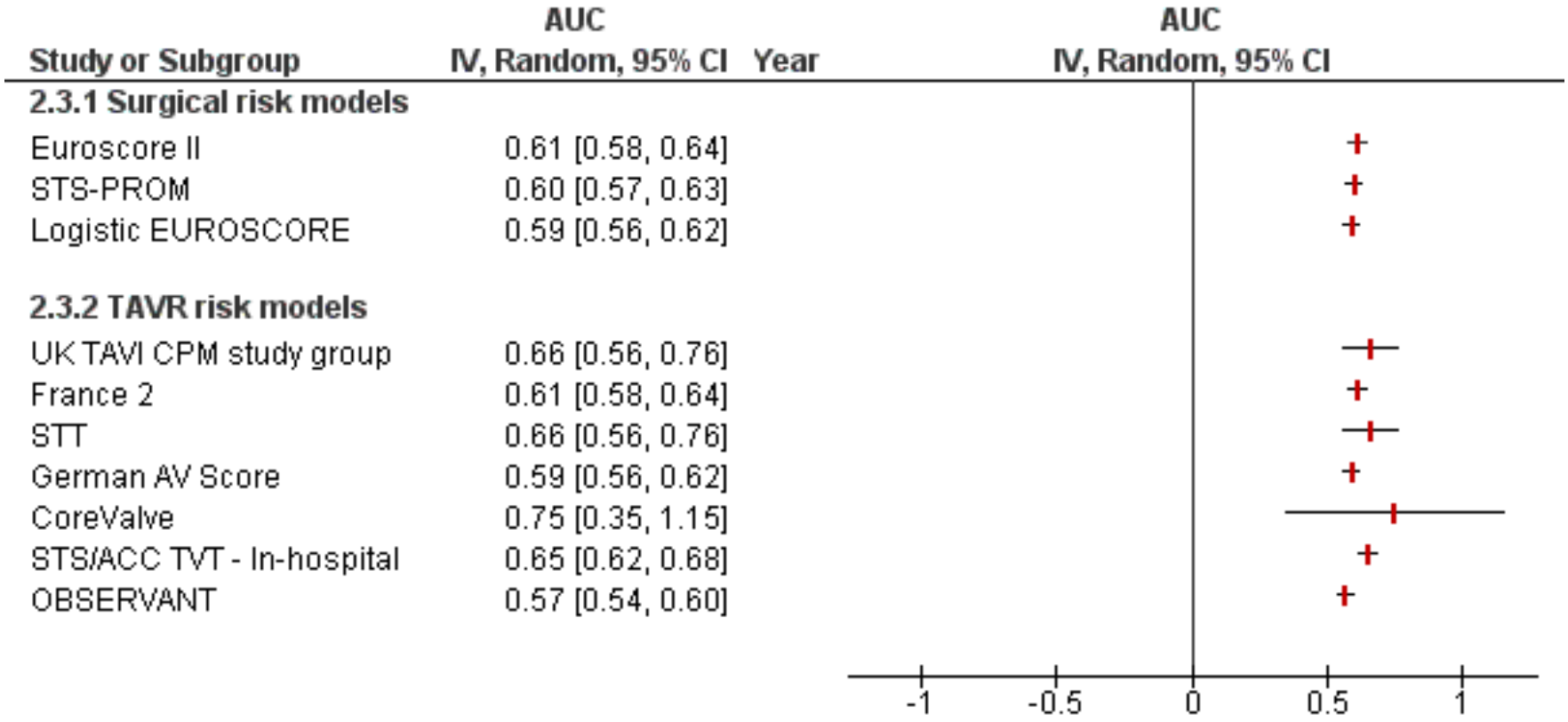
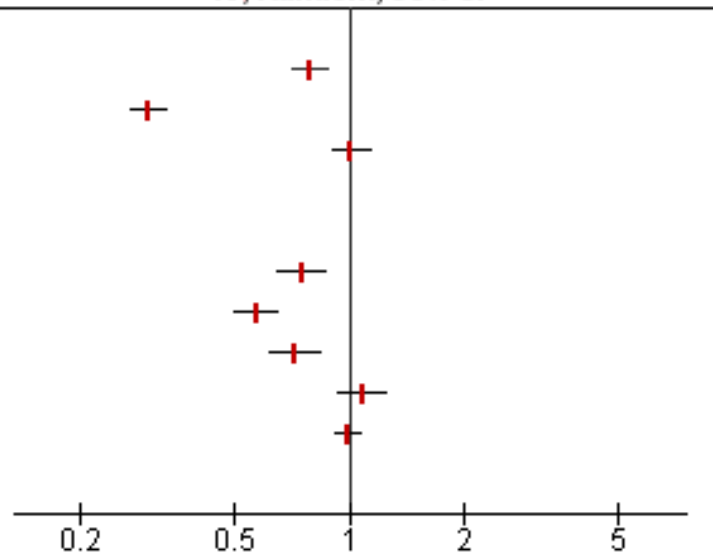




Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Random, 95% CI
1.2.1 Surgical risk models			
Euroscore II	-0.2357	0.0545	0.79 [0.71, 0.88]
Logistic EUROSCORE	-1.204	0.0538	0.30 [0.27, 0.33]
STS-PROM	0.01	0.0588	1.01 [0.90, 1.13]
1.2.2 TAVR risk models			
OBSERVANT	-0.2877	0.073	0.75 [0.65, 0.87]
France 2	-0.5621	0.0669	0.57 [0.50, 0.65]
German AV Score	-0.3285	0.0763	0.72 [0.62, 0.84]
STS/ACC TVT - 30-day	0.077	0.0763	1.08 [0.93, 1.25]
STS/ACC TVT - In-hospital	-0.0101	0.0374	0.99 [0.92, 1.07]



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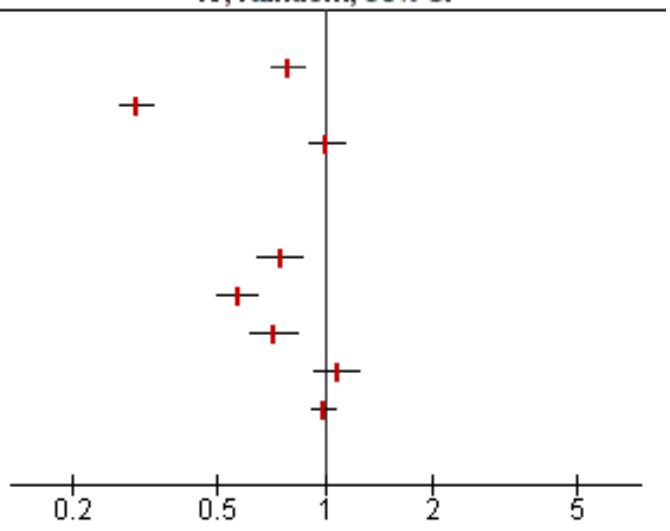

Online Data Supplement

Appendix Text:

Data sources and search strategy

Two reviewers (MAAK and MSU) independently queried MEDLINE and Scopus databases up till June 2019. No time or language restrictions were placed. The search strategy involved using MeSH to determine the different keywords for the RSMs and TAVR coupled with Boolean operators AND and OR. Detailed search strategy for each database is provided in the supplementary files **(Appendix Table 1).** In order to cast a broad net, our search was conducted using the 'keywords, abstract and title' filter. Other data sources included bibliographies of editorials and relevant reviews from major medical journals, conference proceedings for indexed abstracts, and databases of grey/unpublished literature.

Study selection

The predefined eligibility criteria were: (1) studies that sought to validate RSMs to be used in TAVR patients; (2) the RSMs were designed to predict short-term (30-day or in-hospital) mortality (3) reported C-statistic (also known as area under the curve or AUC) with respective 95% confidence intervals (CIs) and/or expected and observed mortality rates.

All articles retrieved from the systematic search were exported to Endnote Reference Library (Version X8.1; Clarivate Analytics, Philadelphia, Pennsylvania) software, where duplicates were removed. Remaining articles were initially short-listed at title and abstract level, after which the full text articles were reviewed based on pre-defined criteria. Two reviewers (MAAK and MSU) independently carried out this process under supervision of a third reviewer (TJS).

Data extraction and quality assessment

Data were abstracted on a standardized data collection from the short-listed articles and verified by two reviewers (MAAK and MSU). In case of any discrepancy, the original reference article was reviewed again. Discrimination and calibration data were extracted from each study. Following information was abstracted: study characteristics, sample size, models derived and/or validated, follow-up duration, data registry and type of RSM (i.e. surgical or TAVR-specific). Additionally, the predictors used in each RSM were recorded.

It is important to note that different studies compared different subsets of risk models. We extracted data relevant to following TAVR specific models: (a) STS/ACC TVT (Society for Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy; this model was developed in 2016 by Edwards et al. to predict in-hospital mortality (10). It was then updated in 2018 and a new 30-day mortality risk model was also designed (15). For the purposes of this study, information on the 2016 and 2018 in-hospital risk models were considered as the same model); (b) OBSERVANT (Observational Study Of Appropriateness, Efficacy And Effectiveness of AVR-TAVR Procedures For the Treatment Of Severe Symptomatic Aortic Stenosis); (c) France 2; (d) CoreValve; (e) STT and (f) UK TAVI models. Data were extracted on following SAVR specific models: (a) STS, (b) Logistic EUROSCORE, and (c) EUROSCORE II models. CPM German AV Score is used for both TAVR and SAVR.

The Prediction model Risk of Bias Assessment Tool (PROBAST) was used to assess the risk of bias of the new TAVR-specific risk models (18). This scale enables critical appraisal of a particular RSM by assessment of four domains: participants, predictors, outcome, and analysis. A total of 20 signaling questions within these domains help to assess the structured judgment of risk of bias.

Appendix Table 1: Detailed search strategy used in each database.

Database	Search Strategy	Articles retrieved
MEDLINE	(("transcatheter aortic valve replacement"[MeSH Terms] OR ("transcatheter"[All Fields] AND "aortic"[All Fields] AND "valve"[All Fields] AND "replacement"[All Fields]) OR "transcatheter aortic valve replacement"[All Fields]) OR TAVR[All Fields] OR ("transcatheter aortic valve replacement"[MeSH Terms] OR ("transcatheter"[All Fields] AND "aortic"[All Fields] AND "valve"[All Fields] AND "replacement"[All Fields]) OR "transcatheter aortic valve replacement"[All Fields] OR ("transcatheter"[All Fields] AND "aortic"[All Fields] AND "valve"[All Fields] AND "implantation"[All Fields]) OR "transcatheter aortic valve implantation"[All Fields]) OR TAVI[All Fields] OR (Percutaneous[All Fields] AND ("aortic valve"[MeSH Terms] OR ("aortic"[All Fields] AND "valve"[All Fields]) OR "aortic valve"[All Fields]) AND ("replantation"[MeSH Terms] OR "replantation"[All Fields] OR "replacement"[All Fields])) OR (Percutaneous[All Fields] AND ("aortic valve"[MeSH Terms] OR ("aortic"[All Fields] AND "valve"[All Fields]) OR "aortic valve"[All Fields]) AND ("embryo implantation"[MeSH Terms] OR ("embryo"[All Fields] AND "implantation"[All Fields]) OR "embryo implantation"[All Fields] OR "implantation"[All Fields]))) AND ((("risk"[MeSH Terms] OR "risk"[All Fields]) AND Model[All Fields]) OR (("risk"[MeSH Terms] OR "risk"[All Fields]) AND Prediction[All Fields]) OR (("risk"[MeSH Terms] OR "risk"[All Fields]) AND Stratification[All Fields]) OR (("risk"[MeSH Terms] OR "risk"[All Fields]) AND Score[All Fields]) OR ("risk assessment"[MeSH Terms] OR ("risk"[All Fields] AND "assessment"[All Fields]) OR "risk assessment"[All Fields])) AND	1,545

	(("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]) OR ("mortality"[Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms]) OR ("death"[MeSH Terms] OR "death"[All Fields]))	
Scopus	((TITLE-ABS-KEY (transcatheter AND aortic AND valve AND replacement) OR TITLE-ABS-KEY (tavr) OR TITLE-ABS-KEY (transcatheter AND aortic AND valve AND implantation) OR TITLE-ABS-KEY (tavi) OR TITLE-ABS-KEY (percutaneous AND aortic AND valve AND replacement) OR TITLE-ABS-KEY (percutaneous AND aortuc AND valve AND implantation))) AND ((TITLE-ABS-KEY (risk AND model) OR TITLE-ABS-KEY (risk AND prediction) OR TITLE-ABS-KEY (risk AND stratificatiom) OR TITLE-ABS-KEY (risk AND score) OR TITLE-ABS-KEY (risk AND assessment))) AND ((TITLE-ABS-KEY (mortality) OR TITLE-ABS-KEY (survival) OR TITLE-ABS-KEY (death)))	2,662
EMBASE	(Transcatheter aortic valve replacement OR TAVR OR Transcatheter Aortic Valve Implantation OR TAVI OR Percutaneous Aortic Valve Replacement OR Percutaneous Aortic Valve Implantation) AND (Risk Model OR Risk Prediction OR Risk Stratification OR Risk Score OR Risk Assessment) AND (Mortality OR Survival OR Death)	1,892

Appendix Table 2: Characteristics of Included Studies.

Author	Year	Study population	Models compared	Follow up used for analysis	Sample size	Type of Study	Inclusion Criteria	Data Sample (Validation)	Country
D'Ascenzo	2014	Single center	STT, LES, STS	30 day	180	Derivation (STT) + Validation	All consecutive patients with severe symptomatic aortic stenosis referred for transcatheter aortic valve implantation	Bologna	Italy
Hermiller	2016	Single center	CoreValve	30 day	1205	Derivation (CoreValve) +Validation	Patients with New York Heart Association functional class II or greater symptoms related to aortic valve disease were eligible for the trial from which data was used to derive and validate the model.	Core Valve US Pivotal trial (USA)	USA
Iung	2014	Single center	France 2, LES	30 day	1281	Derivation (France 2) +Validation	Patients were selected for transcatheter aortic valve implantation if they had severe,	data from the French Aortic National CoreValve	Monaco and France

							symptomatic aortic stenosis and if surgery was contraindicated or judged to be high risk by a multidisciplinary team.	and Edwards (FRANCE 2)	
Arnold	2018	Single center	STS/ACC TVT (30-day)	30 day	26687	Derivation (STS/ACC TVT - 30 day) +Validation	-	ACC/TVT	USA
UK TAVI CPM study group	2017	Single center	UK TAVI CPM	30 day	6339	Derivation (UK TAVI CPM) +Validation	-	UK-TAVI	UK
Edwards	2016	Multicenter	STS/ACC TVT	in-hospital mortality	13718	Derivation (STS/ACC TVT - in-hospital) +Validation	The appropriate clinical indication for transcatheter aortic valve implantation was determined by at least 2 cardiothoracic surgeons. In general, the patients undergoing TAVR were considered to be unsuitable for or at extreme risk with Surgical aortic valve replacement.	ACC/TVT	USA

Arai	2015	Multicenter	STS, LES, LES-II, ACEF	12 month	703	Validation	From October 2006, all consecutive high-risk patients with severe symptomatic aortic stenosis treated with transcatheter aortic valve implantation were prospectively	-	France, Japan
Durand	2013	Multicenter	STS, LES, LES-II	30 day	250	Validation	The patients were considered candidates for transcatheter aortic valve replacement when the logistic EuroSCORE was >20%, in case of frailty (by agreement between cardiologists and cardiac surgeons), or in case of co-morbidities contraindicating surgical aortic valve replacement (porcelain aorta, chest irradiation, or deformation)	University Hospital of Rouen, Hospital Charles Nicolle, INSERM UMR 1096, Rouen, France.	France

Haesnig	2013	Single center	STS, LES, LES-II	30 day	360	Validation	Clinical inclusion criteria were age ≥75 years, NewYork Heart Association functional class II or higher, written informed consent and comorbidities leading to a logistic EuroSCORE ≥15%.	-	Germany
Piazza	2009	Multicenter	STS, LES	30 day	168	Validation	Patients were referred for transcatheter aortic valve implantation implantation after a team of physicians (typically including interventional cardiologists and cardiac surgeons) agreed that surgical replacement would be associated with either high or prohibitive risk.	Bern University Hospital, Erasmus Medical Center	Switzerland, Netherlands
Sedaghat	2013	Multicenter	STS, LES, LES-II	1 year	206	Validation	-	Universitatsklinikum Bonn, Med. Klinik und Poliklinik II	Germany

Silva	2015	Multicenter	STS, LES, LES-II, AG, GS	30 day	418	Validation	-	Brazilian Society of Interventional Cardiology	Brazil
Watanabe	2013	Single center	STS, LES, LES-II	30 day	453	Validation	Patients with severe symptomatic aortic stenosis (valve area <1.0 cm2) were considered candidates for transcatheter aortic valve implantation if they had an LES >20%	Institut Cardiovasculaire Paris Sud	France
Sirotina	2013	Multicenter	STS, LES, LES-II	30 day	450	Validation	-	-	Germany
Ben-Dor	2011	Single center	STS, LES	30 day	718	Validation	-	Washington Hospital Center	USA
Yatsynovich	2016	Single center	STS, LES, LES-II, TAVR-RS	30 day	182	Validation	-	Kettering Medical Center	USA

Wendt	2014	Single center	STS, ACEF, LES-II	30 day	1512	Validation	Patients undergoing reoperation, emergency procedures, myectomy, aortic-root enlargement to prevent patient prosthesis mismatch, or simple wrapping/plication of the ascending aorta were included.	West-German Heart Center Essen	Germany
Martin	2016	Multicenter	German AV, FRANCE-2, OBSERVANT, STS/ACC TVT, LES, ES-II, STS	30 day	6676	Validation	-	UK-TAVI	UK
Pilgrim	2017	Multicenter	STS, STS/ACC TVT	30 day	3491	Validation	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.	Swiss TAVI registry (NCT01368250)	Switzerland

Halkin	2016	Multicenter	STS, LES, LES-II, OBSERVANT, FRANCE-2, GERMAN AV SCORE	30 day	1327	Validation	the Institutional Review Board of each of the participating centers. Eligibility for transcatheter aortic valve replacement was established by a multidisciplinary heart team based on the calculated STS or EuroSCORE, or, for cases with an STS score b8, surgical risk was considered high based on other factors and comorbidities absent from the surgical risk scores (e.g., frailty measures)	Israeli TAVR Registry Risk Model Accuracy Assessment (IRRMA) stud	Israel
Silaschi	2014	Single center	STS, LES, LES-II	30 day	457	Validation	Patients were allocated to transcatheter aortic valve implantation when deemed unsuitable for conventional surgery due to contraindications or high risk by the local interdisciplinary heart team consisting of cardiologists and cardiac surgeons.	University Heart Center Hamburg,	Germany

Codner	2018	Single center	STS,STS/ACC TVT,LES II	30 day and in-hospital mortality	1038	Validation	Severe AS was defined as a valvular orifice area <1.0 cm2 or <0.6 cm2/m2 and/or mean pressure gradient >40 mmHg and/or jet velocity >4.0 m/s. Selected patients with discordant echocardiographic findings underwent dobutamine echocardiography.	NewYork-Presbyterian Hospital/Columbia University Medical Center	USA
Carmo	2018	Single center	FRANCE-2,EuroSCORE II and STS scores	30 day mortality	240	Validation	-	Departament of Cardiology, Hospital of Santa Cruz,	Portugal
Zbroński	2016	Single center	OBSERVANT, ACEF, SURTAVI, LESII,STS	30 day mortality	156	Validation	-	Department of Cardiology, Medical University of Warsaw	Poland

ACEF :Age, Creatinine, and Ejection Fraction SCORE ;AS: Ambler score; FRANCE-2: FRench Aortic National CoreValve and Edwards; GS:Guaragna score; German AV Score:German Aortic Valve Score; LES: Logistic EuroSCORE; LES II:Logistic EuroSCORE 2; OBSERVANT Observational Study Of Appropriateness, Efficacy And Effectiveness of AVR-TAVR Procedures For the Treatment Of Severe Symptomatic Aortic Stenosis; STS ACC/TVT: Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy; STT:survival post TAVI; UK TAVI-CPM:UK Transcatheter Aortic Valve Implantation Clinical Prediction Models

Appendix table 3: Covariates included in each RSM.

Variables	German AV score	STT	STS/ACC TVT (in-hospital - updated)	STS/ACC TVT (30-day)	CoreValve	France 2	OBSERVANT	UK TAVI CPM	STS	LES	ESII
ACE inhibitors use									*		
Active Endocarditis									*	*	*
ADP inhibitors use									*		
Age	*		*	*	*	*		*	*	*	*
Albumin Level <3.3 G/Dl					*						
Alcohol									*		
Anemia											
Aortic Insufficency									*		
Aortic Stenosis									*		
Approach (Transfemoral,Transapical Etc)						*					
Aortic valve Disease etiology									*		
Body Mass Index (Kg/M²)	*					*			*		
Cardiac Surgery	*									*	*

Cardiogenic Shock									*		
Clinical Preoperative State	*							*		*	*
Concomitant Surgery									*		
Coronary Artery Disease			*								
Critical Preoperative State	*					*	*	*			
Diabetes on insulin									*		*
Dialysis						*					
Ejection Fraction									*		
Emergency	*									*	*
Extracardiac Arteriopathy	*							*	*		*
Female Sex Category	*							*	*	*	*
Forced Expiratory Volume Of 1 Breath					*						
Glomerular Filtration Rate			*				*	*			
Gp2/3ba inhibitor use									*		
Heart Block									*		
Hematocrit									*		
Hemodialysis			*	*					*		
Hemoglobin											

Home Oxygen Use				*	*				*		
Illicit Drug Use									*		
Immunocompromise									*		
Inability to complete 5m walk test			*	*							
Inverse renal function		*									
KATZ Index of activities of daily living					*			*			
Last Creatinine Level									*		
Left Ventricular Ejection Fraction	*						*	*			
Liver dysfunction									*		
Logistic Euroscore					*						
Lower body surface area			*	*							
Lower KCCQ Scores			*	*							
Left Ventricle dysfunction										*	*
Male Sex Category											
Mean Transvalvular Gradient											
Mitral Insuffciency									*		

Mitral Stenosis									*		
Neurological dysfunction										*	
New York Heart Association (NYHA) Functional Class IV	*		*		*	*	*		*		*
Non-Elective Procedure								*			
Nonfemoral Access Site			*	*							
Pulmonary Artery Systolic Pressure >50 Mm Hg		*									
Pulmonary Artery Systolic Pressure >60 Mm Hg								*			
Percent stenosis									*		
Peripheral artery disease		*	*								
Platelet Count			*						*		
Pneumonia									*		
Poor Mobility								*			
Porcelain Thoracic Aorta											
Postinfarct septal rupture										*	
Previous Myocardial Infarction	*		*						*	*	*
Previous stroke		*									

Prior Balloon Aortic Valvuloplasty							*				
Procedural Acuity			*	*							
Pulmonary Hypertension	*					*	*			*	*
Pulmonary Oedema						*		*			
Race									*		
Renal Dysfunction	*			*					*		*
Residence In An Assisted Living Facility					*						
Serum creatinine										*	
Severe Chronic Lung Disease	*		*						*	*	*
Steroid use									*		
STS PROM					*						
STS Severe Lung Disease					*						
Surgery on thoracic aorta										*	*
Syncope									*		
Trciupsid Insufficency			*	*					*		
Unplanned Weights Loss					*						
Unstable angina										*	*

Ventricular Dysfunction											
WBC count									*		
Weight of the intervention											*

KCCQ**:** The Kansas City Cardiomyopathy Questionnaire Score; STS-PROM: Society of Thoracic Surgeons Predictor of Mortality; WBC: White blood cell count. FRANCE-2: FRench Aortic National CoreValve and Edwards; German AV Score:German Aortic Valve Score; LES: Logistic EuroSCORE; LES II:Logistic EuroSCORE 2; OBSERVANT Observational Study Of Appropriateness, Efficacy And Effectiveness of AVR-TAVR Procedures For the Treatment Of Severe Symptomatic Aortic Stenosis; STS ACC/TVT: Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy; STT:survival post TAVI; UK TAVI-CPM:UK Transcatheter Aortic Valve Implantation Clinical Prediction Models

Appendix table 4: Risk of Bias assessment of TAVR-specific risk models using the PROBAST scale.

Study	Risk of Bias				Applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
German AV score	-	-	-	-	-	-	-	-	-
STT	-	-	+	+	-	-	-	+	-
STS/ACC TVT (in-hospital)	+	-	-	-	-	-	-	-	-
STS/ACC TVT (30-day)	?	-	-	+	-	-	-	-	-
CoreValve	-	-	-	+	+	+	-	-	-
France 2	+	-	+	-	-	-	-	+	-
OBSERVANT	?	-	?	-	-	-	-	?	-
UK TAVI CPM	+	-	-	-	+	+	+	-	+

(+) High risk of bias; (-) Low risk of bias; (?) Unclear risk of bias

TAVR: Transcatheter aortic valve replacement; FRANCE-2: FRench Aortic National CoreValve and Edwards; German AV Score: German Aortic Valve Score; OBSERVANT: Observational Study Of Appropriateness, Efficacy And Effectiveness of AVR-TAVR Procedures For the Treatment Of Severe Symptomatic Aortic Stenosis; ROB: Risk of Bias, STS ACC/TVT: Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy; STT:survival post TAVI; UK TAVI-CPM: UK Transcatheter Aortic Valve Implantation Clinical Prediction Models

Appendix Table 5: P-interaction values for differences in discrimination between individual pairs of risk stratification models

Comparison	P-interaction	Comment
STS/ACC TVT vs OBSERVANT	P<0.001	Favors STS/ACC TVT
STS/ACC TVT vs France 2	p=0.03	Favors STS/ACC TVT
STS/ACC TVT vs Corevalve	p=0.64	No difference
STS/ACC TVT vs STT	p=0.90	No difference
STS/ACC TVT vs UK TAVI CPM	p=0.82	No difference
STS/ACC TVT vs German AV Score	p=0.002	Favors STS/ACC TVT
STS/ACC TVT vs STS	p=0.009	Favors STS/ACC TVT
STS/ACC TVT vs Logistic Euroscore	p=0.002	Favors STS/ACC TVT
STS/ACC TVT	p=0.049	Favors STS/ACC TVT
Observant vs France 2	p=0.11	No difference
Observant vs Corevalve	p=0.39	No difference
Observant vs STT	p=0.10	No difference
Observant vs UK TAVI CPM	p=0.003	Favors UK TAVI CPM
Obsevrant vs German AV score	p=0.44	No difference
Obsevrant vs STS	p=0.15	No difference
Observant vs Logistic Euroscore	p=0.53	No difference
Observant vs Euroscore II	P=0.10	No difference
France 2 vs Corevalve	p=0.48	No difference

France 2 vs STT	p=0.32	No difference
France 2 vs UK TAVI CPM	p=0.07	No difference
France 2 vs German AV Score	p=0.43	No difference
France 2 vs STS	p=0.81	No difference
France 2 vs Logistic Euroscore	p=0.36	No difference
France 2 vs Logistic Euroscore 2	p=0.89	No difference
Corevalve vs STT	p=0.67	No difference
Corevalve vs UK TAVI CPM	p=0.66	No difference
Corevalve vs German AV Score	p=0.43	No difference
Corevalve vs STS	p=0.47	No difference
Corevalve vs Logistic Euroscore	p=0.43	No difference
Corevalve vs Euroscore 2	p=0.49	No difference
STT vs UK TAVI CPM	p=1.00	No difference
STT vs German AV Score	p=0.19	No difference
STT vs STS	p=0.27	No difference
STT vs Logistic Euroscore	p=0.17	No difference
STT vs Logistic Euroscore 2	p=0.35	No difference
UK TAVI CPM vs German AV Score	p=0.02	Favors UK TAVI CPM
UK TAVI CPM vs STS	p=0.049	Favors UK TAVI CPM
UK TAVI CPM vs Logistic Euroscore	p=0.02	Favors UK TAVI CPM
UK TAVI CPM vs Euroscore 2	p=0.10	No difference

German AV Score vs STS	p=0.56	No difference
German AV Score vs Logistic Euroscore	p=0.89	No difference
German AV Score vs Logistic Euroscore 2	p=0.38	No difference
STS vs Logistic Euroscore	P=0.47	No difference
STS vs Logistic Euroscore 2	p=0.71	No difference

Appendix table 6: P-interaction values for differences in calibration between individual pairs of risk stratification models

Comparison	P-interaction	Comment
STS/ACC TVT in-hospital vs STS/ACC 30-day	p=0.33	No Difference
STS/ACC TVT in-hospital vs Observant	p<0.001	Favors STS/ACC TVT in-hospital
STS/ACC TVT in-hospital vs France 2	P<0.001	Favors STS/ACC TVT in-hospital
STS/ACC TVT in-hospital vs German AV Score	p<0.001	Favors STS/ACC TVT in-hospital
STS/ACC TVT in-hospital vs STS	P=0.82	No Difference
STS/ACC TVT in-hospital vs Logistic Euroscore	p<0.001	Favors STS/ACC TVT in-hospital
STS/Acc in-hospital vs Euroscore 2	p<0.001	Favors STS/ACC TVT in-hospital
STS/ACC 30-day vs Observant	p<0.001	Favors STS/ACC TVT in-hospital
STS/ACC 30-day vs France 2	p<0.001	Favors STS/ACC TVT in-hospital
STS/ACC 30-day vs German AV Score	p<0.001	Favors STS/ACC TVT in-hospital
STS/ACC 30-day vs STS	p=0.47	No difference
STS/ACC 30-day vs Logistic Euroscore	p<0.001	Favors STS/ACC TVT in-hospital
STS/ACC 30-day vs Euroscore 2	p<0.001	Favors STS/ACC TVT in-hospital

Observant vs France 2	p<0.001	Favors Observant
Observant vs German AV Score	p=0.66	No Difference
Observant vs STS	p<0.001	Favors Observant
Observant vs Logistic Euroscore	p<0.001	Favors Observant
Observant vs Euroscore 2	p=0.53	No difference
France 2 vs German AV Score	p=0.02	Favors German AV Score
France 2 vs STS	p<0.001	Favors STS
France 2 vs Logistic Euroscore	p<0.001	Favors France 2
France 2 vs Euroscore 2	p<0.001	Favors Euroscore 2
German AV Score vs STS	p<0.001	Favors STS
German AV Score vs Logistic Euroscore	p<0.001	Favors German AV Score
German AV Score vs Euroscore 2	p=0.26	No Difference
STS vs Logistic Euroscore	p<0.001	Favors STS
STS vs Euroscore 2	p<0.002	Favors STS
Logistic Euroscore vs Euroscore 2	p<0.001	Favors Euroscore 2

Appendix Figure 1: Discrimination of each TAVR-specific risk stratification model

Appendix Figure 2: Discrimination of each surgical risk stratification model

Appendix Figure 3: Calibration of each TAVR-specific risk stratification model

Appendix Figure 4: Calibration of each surgical risk stratification model