Clinical Prediction Models for Valvular Heart Disease

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***Background*—**While many clinical prediction models (CPMs) exist to guide valvular heart disease treatment decisions, the relative performance of these CPMs is largely unknown. We systematically describe the CPMs available for patients with valvular heart disease with specific attention to performance in external validations.

***Methods and Results*—**A systematic review identified 49 CPMs for patients with valvular heart disease treated with surgery (n=34), percutaneous interventions (n=12), or no intervention (n=3). There were 204 external validations of these CPMs. Only 35 (71%) CPMs have been externally validated. Sixty-five percent (n=133) of the external validations were performed on distantly related populations. There was substantial heterogeneity in model performance and a median percentage change in discrimination of −27.1% (interquartile range, −49.4%–−5.7%). Nearly two-thirds of validations (n=129) demonstrate at least a 10% relative decline in discrimination. Discriminatory performance of EuroSCORE II and Society of Thoracic Surgeons (2009) models (accounting for 73% of external validations) varied widely: EuroSCORE II validation c-statistic range 0.50 to 0.95; Society of Thoracic Surgeons (2009) Models validation c-statistic range 0.50 to 0.86. These models performed well when tested on related populations (median related validation c-statistics: EuroSCORE II, 0.82 [0.76, 0.85]; Society of Thoracic Surgeons [2009], 0.72 [0.67, 0.79]). There remain few (n=9) external validations of transcatheter aortic valve replacement CPMs.

***Conclusions*—**Many CPMs for patients with valvular heart disease have never been externally validated and isolated external validations appear insufficient to assess the trustworthiness of predictions. For surgical valve interventions, there are existing predictive models that perform reasonably well on related populations. For transcatheter aortic valve replacement (CPMs additional external validations are needed to broadly understand the trustworthiness of predictions. **(*J Am Heart Assoc*. 2019;8:e011972. DOI: 10.1161/JAHA.119.011972.)**

Key Words: clinical prediction models • risk • valvular heart disease

Treatments for patients with advanced valvular heart disease (VHD) are increasingly offered to patients with advanced age and elevated pre-procedural risk.[1–3] Clinical predictive models (CPMs) have assumed a central role in clinical decision making and current guidelines link VHD treatment decisions to predicted risk.[4–6] CPMs can potentially enhance shared decision making,[7,8] when they perform well and are appropriately matched to the correct decisional context, though there remain major questions about how well CPMs for patients with VHD perform in external validations.

It is well recognized that many of the best known (and most widely used) CPMs for VHD were derived on patients receiving surgical interventions[9,10] and do not accurately predict outcomes for patients treated with percutaneous interventions,[11] though they continue to be used for this purpose. While there are newer efforts to create CPMs specific to percutaneous valve interventions, the relative performance of these models and their performances in external validations remains largely unknown. Generally, the performance of CPMs has often been underreported and incompletely assessed[12] and since CPMs that perform poorly can yield misleading predictions that motivate harmful decision making,[13] it is essential that clinicians understand CPM performance before leveraging outputs to inform decisions. This is especially important for VHD treatment decisions, given the importance of these tools.

Here, using the Tufts PACE (Predictive Analytics and Comparative Effectiveness) CPM Registry, we describe the

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Accompanying Tables S1 through S3 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.011972

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Clinical Perspective

What Is New?

- Risk prediction is central to decision making for patients with advanced valvular heart disease; however, the performance of clinical predictive models in external validations is often substantially worse than expected based on derivation data set performance.

What Are the Clinical Implications?

- Isolated external validations appear insufficient to broadly understand the performance of valvular heart disease clinical predictive models.
- There are clinical predictive models for surgical valvular heart disease interventions that perform well across multiple external validations.
- The trustworthiness of transcatheter aortic valve replacement predictions is largely unknown as these models have not been widely tested in external validations.

available CPMs for patients with VHD treated with percutaneous or surgical interventions. This analysis focuses on comparative model performance during external validations.

Methods

General Approach

The data that support the findings of this study are available from the corresponding author upon reasonable request. This study analyzed data from the Tufts PACE (Predictive Analytics and Comparative Effectiveness) CPM Registry, a database created to describe the CPM literature for patients at risk for and with known cardiovascular disease. The registry, which is free and available to the public at http://pace.tuftsmedicalcenter.org/cpm, encompasses a field synopsis of CPMs for patients with VHD. The methods have been previously reported.[12] Briefly, we had previously searched PubMed for English-language articles containing CPMs for cardiovascular disease published from January 1990 through 2015. We extended the search for VHD CPMs to January 2017 to include more recent CPM development (Table S1, Figure S1). Citations were reviewed to confirm completeness of our review. All citations and data fields were extracted in duplicate to ensure accuracy. Discrepancies were discussed until consensus was achieved.

For inclusion in the registry, articles had to meet the following criteria: (1) develop a CPM as a primary aim, (2) contain a model predicting the development of a specified clinical diagnosis (diagnostic models) or the probability of developing a clinical outcome (prognostic models), (3) contain at least 2 outcome predictors, and (4) present enough information to estimate the probability for an individual patient. Articles were excluded if they did not provide enough information to predict a patient's risk or if the described models predicted surrogate outcomes. We also excluded non-English reports, pharmacology reports, cost-effectiveness models, decision-analysis models, systematic reviews, and editorials.

Model Selection

This report focuses on CPMs predicting outcomes for patients with VHD. CPMs predicting natural history outcomes and outcomes after surgical and percutaneous procedures were included. CPMs were grouped based on underlying valve pathology and procedure. CPMs were also included if they were derived on cardiac surgery cohorts where at least 50% of patients received treatment for VHD. CPMs derived exclusively on coronary artery bypass populations were excluded.

CPM Reporting

Information was extracted on CPM derivation and reporting. Collected fields included: index clinical condition, predicted outcome, timeframe of prediction, sample size, cohort size, and number of events. We calculated the events per variable (EPV) based on the number of variables included in the model. We also extracted information on modeling method and performance with specific attention to reporting of discrimination and calibration (Table S2).

Validation Search

Citations for each CPM article through September 2017 were identified using Scopus and reviewed for inclusion as external validations. An external validation was defined as any evaluation of CPM performance (assessment of either discrimination or calibration) on a data set distinct from the derivation data set.[14] External validations included validations that were done on the same cohort but temporally or geographically distinct from the derivation cohort or on an entirely separate cohort. Each validation citation was reviewed by 2 investigators for inclusion and discrepancies were reviewed with an additional investigator to arrive at consensus.

Validation Reporting

Information on validation reporting was extracted, including sample size, continent of study, number of events, and reporting of measures of discrimination and calibration (Table S3). The validation performance analysis focused on whether CPM discrimination changed when compared with

that seen in the derivation population. Because the c-statistic ranges from 0.5 (no discriminatory ability) to 1.0 (perfect discrimination), it has been rescaled as Somer's D statistic[15] ($2\times(c-0.5)$) so that discrimination ranges from 0 (no discrimination) to 1.0 (perfect discrimination). We describe changes on this scale because it more intuitively reflects the true changes in discriminatory power. The percentage change in discrimination [(Validation AUC−0.5)−(Derivation AUC−0.5)/(Derivation AUC−0.5)×100] is presented. We also document whether validations include any assessment of CPM calibration. There is currently no literature standard for assessing calibration. Given this lack of consistency and interpretability, we have only reported on whether this dimension of performance was assessed. Calibration assessment included any comparison of observed versus expected outcomes. Examples include a Hosmer-Lemeshow statistic or calibration plot. For this study we also included measures of global fit, where overall observed event rates are compared with predicted rates (ie, calibration-in-the-large).

Relatedness

To assess the similarity between the derivation population and the validation population for each validation, we created a relatedness rubric to divide validations into 2 categories —"related" and "distantly related." The rubric contained 3 domains: (1) type of intervention (ie, percutaneous or surgical), (2) percentage of the population undergoing isolated valve procedures (as opposed to valve procedures in combination with revascularization), and (3) calendar years of enrollment. We considered a validation population to be "related" if all of the following criteria were met: (1) same type of intervention (eg, both surgical populations), (2) ± 10% absolute difference in the proportion of isolated valve procedure (eg, derivation population was 100% isolated valve and validation population was 95% isolated valve), and (3) overlapping years of enrollment. Matches that did not meet all 3 criteria were deemed "distantly related."

Results

VHD CPMs

We identified 49 CPMs predicting clinical outcomes for patients with VHD, which were cited a total of 1296 times (Table 1, Table S2).[7,9,16–43] Thirty-four (69%) predict outcomes following surgical interventions, 12 (24%) predict outcomes following percutaneous interventions, and 3 (6%) predict outcomes in the absence of intervention (Table 2). Overall, the most commonly predicted outcomes were 30-day mortality (n=14, 29%) and in-hospital mortality (n=14, 29%). Twenty-four models (46%) were derived from patients in North America, followed by 12 (23%) from Europe and 8 (15%) from Asia (Figure 1). The median derivation sample size was 4510 (interquartile range [IQR], 1087–18 686), median event rate was 8.3% (IQR, 4.5%–14.8%), and median EPV was 40 (IQR, 20–92) (Table 2). The median number of covariates was 10 (IQR, 7–19).

Among models that reported a c-statistic (n=37, 76%), the overall median ROC was 0.76 (IQR, 0.72–0.78) (Table 2). When stratified by intervention type, the median c-statistic was 0.77 (IQR, 0.75–0.79) for CPMs predicting outcomes following surgical interventions, 0.68 (IQR, 0.67–0.74) for CPMs for percutaneous interventions, and 0.81 (IQR, 0.77–0.86) for CPMs predicting outcomes in the absence of intervention (Table 2).

CPMs for Isolated Valve Disease

There are 31 CPMs for isolated valve disease. Sixteen (52%) predict outcomes following surgical intervention and 12 (39%) predict outcomes following percutaneous interventions (transcatheter aortic valve replacement [TAVR], balloon aortic valvuloplasty, and percutaneous mitral balloon valvuloplasty). Three CPMs (10%) predict outcomes for patients with aortic stenosis in the absence of intervention. The median derivation sample size was 2552 (IQR, 1064–108 410) and the median age was 70 (IQR, 64–82). The median number of events was 360 (IQR, 104–2021) and the median EPV was 55 (IQR, 18–112). The median event rate was 10% (IQR, 4.6%–18.3%). For the 27 (87%) models reporting discrimination, the median c-statistic was 0.74 (IQR, 0.69–0.78).

CPMs for Isolated or Multiple Valve Disease

There are 11 CPMs that predict outcomes for patients undergoing either single or multiple valve surgical procedures. The median derivation sample size was 3544 (IQR, 2297–12 079) and the median age was 60 (IQR, 54–65). The median number of events was 303 (IQR, 139–507) and the median EPV was 26 (IQR, 20–40). The median event rate was 5.1% (IQR, 4.1%–9.5%). For the 10 (91%) models reporting discrimination, the median c-statistic was 0.78 (IQR, 0.76–0.79).

CPMs for Multiple Valve Disease

There are 7 CPMs that predict outcomes specifically for multiple valve surgical interventions. These CPMs include the Society of Thoracic Surgeons (STS) Multi-Valve Risk Models[43] and the median derivation sample size was 18 686 (IQR, 4510–22 861). The median number of events was 1420 (IQR, 591–1981) and the median EPV was 71 (IQR, 48–92). Median age was 70 (IQR, 70–71). The median event rate was 9.4% (IQR, 7.6%–11.3%). Median number of covariates was 20 (IQR, 14–23).

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Table 1. De Novo VHD CPMs Overview

Author, Model Name	Publication, y	Valve	Standardized Type of Intervention	Outcome	Model Method	C-Statistic	Calibration Measure	Externally Validated?
Isolated valve								
Edwards,[16] STS (original) Isolated Valve	2001	Aortic/Mitral	Surgery	30 d operative mortality	Logistic regression	0.766	HL statistic, Calibration plot	Yes
Nowicki,[17] NNE Aortic and Mitral Models	2004	Aortic	Surgery	In-hospital mortality	Logistic regression, score	0.75	HL statistic	Yes
		Mitral	Surgery	In-hospital mortality	Logistic regression, score	0.79	HL statistic	Yes
Kuduvalli,[18] NWQIP	2007	Aortic	Surgery	In-hospital mortality	Logistic regression, score	0.78	HL statistic	Yes
Cruz-Gonzalez,[19] PMV Score	2009	Mitral	Percutaneous	Procedural success	Logistic regression, score	NR	HL statistic	Yes
Monin[20]	2009	Aortic stenosis	Natural History	Composite (Non-MACE)	Logistic regression, score	0.90	HL statistic	Yes
O'Brien,[9] STS (2009)—Composite AEs	2009	Aortic/Mitral	Surgery	Composite (Non-MACE)	Logistic regression	0.721	None	Yes
O'Brien,[9] STS (2009)—DSWI	2009	Aortic/Mitral	Surgery	DSWI	Logistic regression	0.704	None	Yes
O'Brien,[9] STS (2009)—Mortality	2009	Aortic/Mitral	Surgery	30 d mortality	Logistic regression	0.805	None	Yes
O'Brien,[9] STS (2009)—Prolonged LOS	2009	Aortic/Mitral	Surgery	Prolonged LOS	Logistic regression	0.77	None	Yes
O'Brien,[9] STS (2009)—Prolonged Ventilation	2009	Aortic/Mitral	Surgery	Prolonged ventilation	Logistic regression	0.77	None	Yes
O'Brien,[9] STS (2009)—Renal Failure	2009	Aortic/Mitral	Surgery	Renal failure	Logistic regression	0.782	None	Yes
O'Brien,[9] STS (2009)—Reoperation	2009	Aortic/Mitral	Surgery	Reoperation	Logistic regression	0.643	None	Yes
O'Brien,[9] STS (2009)—Short LOS	2009	Aortic/Mitral	Surgery	Prolonged LOS	Logistic regression	0.738	None	No
O'Brien,[9] STS (2009)—Stroke	2009	Aortic/Mitral	Surgery	Stroke	Logistic regression	0.694	None	Yes
Guaragna,[21] GuaragnaSCORE	2010	Aortic/Mitral	Surgery	In-hospital mortality	Logistic regression, score	0.82	HL statistic, Calibration plot	Yes
Guo[22]	2010	Aortic	Surgery	In-hospital mortality	Logistic regression	NR	HL statistic	No
		Mitral	Surgery	In-hospital mortality	Logistic regression	NR	HL statistic	No
Elmariah,[23] CRRAC the AV Score	2011	Aortic	Percutaneous	30 d mortality	Cox regression, score	0.754	HL statistic	No
Bouleti[24]	2012	Mitral	Percutaneous	Composite (MACE)	Cox regression, score	0.74	Calibration plot	No
Cioffi[25]	2012	Aortic stenosis	Natural History	Composite (MACE)	Cox regression, score	NR	None	No

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Table 1. Continued

Author, Model Name	Publication, y	Valve	Standardized Type of Intervention	Outcome	Model Method	C-Statistic	Calibration Measure	Externally Validated?
Holme,[26] SEAS Score	2012	Aortic stenosis	Natural History	5 y mortality	Cox regression	0.722	HL statistic, Calibration plot, Brier score	No
Kötting,[27] German Aortic Valve Score	2013	Aortic	Percutaneous	In-Hospital Mortality	Logistic regression, score	0.808	HL statistic	Yes
Arnold,[28] 6 mo and 1 y Models	2014	Aortic stenosis	Percutaneous	Composite (Non-MACE)	Logistic regression	0.66	HL statistics, Calibration plot	Yes
		Aortic stenosis	Percutaneous	Composite (Non-MACE)	Logistic regression	0.66	HL statistics, Calibration plot	Yes
Capodanno,[29] OBSERVANT Score	2014	Aortic stenosis	Percutaneous	30 d mortality	Logistic regression, score	0.73	HL statistic, Calibration plot, Brier score	Yes
D'Ascenzo,[30] Survival Post-TAVI (STT)—30 d and 1 y Models	2014	Aortic	Percutaneous	30 d mortality	Logistic regression, score	0.66	HL statistic	Yes
		Aortic	Percutaneous	1 y mortality	Logistic regression, score	0.68	HL statistic	Yes
Iung[31]	2014	Aortic	Percutaneous	30 d mortality	Logistic regression, score	0.67	HL statistic, Calibration in the large, Calibration plot	No
Debonnaire,[32] TAVI2-SCORe	2015	Aortic	Percutaneous	1 y mortality	Cox regression, score	0.715	HL statistic, Calibration in the large	Yes
Edwards[7]	2016	Aortic	Percutaneous	In-hospital mortality	Logistic regression	0.67	HL statistics, Calibration in the large, Calibration plot	Yes
Isolated or multiple valve								
Koplan[33]	2003	All	Surgery	Pacemaker placement	Logistic regression, score	NR	None	No
Ambler[34]	2005	Aortic, mitral	Surgery	In-hospital mortality	Logistic regression, Score	0.77	HL statistic, Calibration plot	Yes
Xu[35]	2006	All	Surgery	Prolonged LOS	Logistic regression	0.81	Calibration in table form	No
Hannan[36]	2007	Aortic, mitral	Surgery	In-hospital mortality	Logistic regression, Score	0.794	HL statistic, Calibration plot	Yes

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Table 1. Continued

Author, Model Name	Publication, y	Valve	Standardized Type of Intervention	Outcome	Model Method	C-Statistic	Calibration Measure	Externally Validated?
Xu,[37] Fuwai Score	2007	All	Surgery	Prolonged LOS	Logistic regression, Score	0.76	HL statistic, Calibration plot	Yes
Shi[38]	2010	Aortic, mitral	Surgery	In-hospital mortality	Logistic regression	0.7358	None	No
Ariyaratne,[39] Aus-AVR Score	2011	Aortic, mitral	Surgery	30 d mortality	Logistic regression, Score	0.78	HL statistic, Calibration in the large	Yes
Nashef,[10] EuroSCORE II	2012	All	Surgery	In-hospital mortality	Logistic regression	0.8095	None	Yes
Hannan,[40] NY Operative Mortality Risk Score	2013	Aortic, mitral	Surgery	30 d mortality	Logistic regression, Score	0.781	HL statistic	Yes
Wang[41]	2013	All	Surgery	Prolonged ventilation	Logistic regression	0.789	HL statistic	No
Zheng[42]	2013	Aortic, mitral	Surgery	In-hospital mortality	Logistic regression, Score	0.76	HL statistic, Chi-square statistic, Calibration plot	No
Multiple valve								
Guo[22]	2010	Aortic, mitral	Surgery	In-hospital mortality	Logistic regression	NR	HL statistic	No
Rankin,[43] AM Preop	2013	Aortic, mitral	Surgery	30 d mortality	Logistic regression	NR	Calibration plot	Yes
Rankin,[43] MT Preop	2013	mitral, tricuspid	Surgery	30 d mortality	Logistic regression	NR	Calibration plot	Yes
Rankin,[43] AMT Preop	2013	Aortic, mitral, tricuspid	Surgery	30 d mortality	Logistic regression	NR	Calibration plot	Yes
Rankin,[43] AM Preop + Intraop	2013	Aortic, mitral	Surgery	30 d mortality	Logistic regression	NR	Calibration plot	Yes
Rankin,[43] MT Preop + Intraop	2013	Mitral, tricuspid	Surgery	30 d mortality	Logistic regression	NR	Calibration plot	Yes
Rankin,[43] AMT Preop + Intraop	2013	Aortic, mitral, tricuspid	Surgery	30 d mortality	Logistic regression	NR	Calibration plot	Yes

AEs indicates adverse events; AM, aortic, mitral ; AMT, aortic, mitral, tricuspid; AV, aortic valvuloplasty; Aus-AVR, Australian aortic valve replacement; CRRAC, critical status, renal dysfunction, right atrial pressure, and cardiac output; DSWI, deep sternal wound infections; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HL, Hosmer-Lemeshow; LOS, length of stay; MACE, major adverse cardiovascular events; MT, mitral, tricuspid; NNE, Northern New England; NR, not reported; NWQIP, North West Quality Improvement Programme in Cardiac Interventions; NY, New York; OBSERVANT, Observational Study of Appropriateness, Efficacy and Effectiveness of AVR-TAVR Procedures for the Treatment of Severe Symptomatic Aortic Stenosis; PMV, percutaneous mitral valvuloplasty; SEAS, Simvastatin and Ezetimibe in Aortic Stenosis; STS, Society of Thoracic Surgeons; STT, Survival posT-TAVI; TAVI, transcatheter aortic valve implantation; TAVR, Transcatheter Aortic Valve Replacement.

Table 2. Reported Characteristics of De Novo Valvular Heart Disease CPMs

Characteristic*	Overall (n=49)	Surgical (n=34)	Percutaneous (n=12)	Natural History (n=3)
Publication range†	2001 to 2016	2001 to 2013	2009 to 2016	2009 to 2012
Age, y	69 (61–79)	65 (58–70)	82 (82–83)	68 (67–70)
Sample size	4510 (1087–18 686)	12 079 (3125–92 563)	1160 (752–2241)	772 (440–1169)
Event rate	0.08 (0.05–0.15)	0.07 (0.04–0.11)	0.14 (0.06–0.37)	0.35 (0.23–0.47)
Events per variable	40 (20–92)	46 (25–110)	42 (18–81)	11 (10–45)
C-statistic	0.76 (0.72–0.78)	0.77 (0.75–0.79)	0.68 (0.67–0.74)	0.81 (0.77–0.86)
% Externally validated	71.4	73.5	83.3	33.3

CPM indicates clinical predictive models.
*Values are reported as median (interquartile range), unless otherwise specified.
†De novo CPM search spans January 1, 1990 to January 1, 2017.

CPMs for Percutaneous VHD Interventions

Since 2009, there have been 12 CPMs presented that predict outcomes following percutaneous VHD interventions. Two models predict outcomes following mitral percutaneous mitral balloon valvuloplasty.[24,44] There were 9 CPMs that predict outcomes following TAVR with a median derivation sample size of 2130 (IQR, 10 642 552). The median age of patients in the TAVR CPMs was 82 (IQR, 82–83). TAVR CPMs had a median number of events of 253 (IQR, 80–704) and the median EPV was 28 (IQR, 20–70). The median event rate was 9.9% (IQR, 5.6%–15.7%). All of the CPMs predicting outcomes following TAVR reported discrimination with a median c-statistic of 0.67 (IQR, 0.66–0.72).

External Validations

Two hundred and four external validations of these CPMs were identified, of which 190 (93%) report a c-statistic. Overall, 35 (71%) of the VHD CPMs have been externally validated and 20 (37%) have been externally validated more than once. External validations were most commonly done in cohorts of patients from Europe (n=93, 46%), Asia (n=38, 19%), and North America (n=37, 18%) (Figure 1). Fifty-three (26%) validations were performed on populations from the same continent as the derivation population, with a median c-statistic of 0.71 (IQR, 0.66–0.77). Seventy-one (35%) were done on populations from a different continent, with a median c-statistic of 0.68 (IQR, 0.64–0.73). External validations overall had a median c-statistic of 0.71 (IQR, 0.65– 0.77) (Table 3). For the models that were externally validated, we noted an overall median percentage change in discrimination of −27.1% (IQR, −49.4–−5.7). Just under two-thirds of validations (n=129) demonstrate at least a 10% relative decline in discriminatory power, and 18 (9%) showed a decline of >80%. Thirty-three (16%) validations showed CPM discrimination at or above that seen in the derivation cohort.

The distribution of number of validations was skewed towards a small number of CPMs. Two CPMs (EuroSCORE II and STS [2009] Models[9]) accounted for 73% of the external validations. EuroSCORE II has been validated 78 times across 5 continents (Table 4). Validation c-statistics ranged from 0.50 to 0.95 with a median percentage change of −23.4% (range −100%–+46.7%). For the STS (2009) Models, validation c-statistics ranged from 0.50 to 0.86 (Table 5). The median percentage change was −31.8% and ranged from −100% to +18%. The STS (2009) Models have been validated 70 times across 5 continents.

Of CPMs that have been validated at least 2 times (n=17) in related populations, the highest median validation c-statistic was seen for EuroSCORE II (0.82 [IQR, 0.76–0.85]), followed by the North West Quality Improvement Programme in Cardiac Interventions model (0.78 [IQR, 0.77–0.78]), and the Northern New England Aortic model (0.76 [IQR, 0.75–0.77]) (Table 6).

Forty-five (22%) external validations did not report any measure of calibration. Of the 159 validations that did report calibration, 103 (65%) reported the Hosmer-Lemeshow statistic, 87 (55%) reported calibration-in-the-large, and 46 (29%) included a calibration plot. Median c-statistic was 0.71 (IQR, 0.65–0.77) for validations that reported some measure of calibration and 0.68 (IQR, 0.63–0.74) for validations that did not report any calibration.

Clinical relatedness between the development and validation populations was assessed using a novel rubric. Seventy-one validations (35%) were performed on related populations, while the remaining 133 (65%) were performed on distantly-related populations. The median validation c-statistic was 0.73 (IQR, 0.67–0.79) for related validations and 0.70 (IQR, 0.62–0.76) for distantly-related validations (P=0.009). There was a significant difference in percentage change in discrimination: the median change in c-statistic was −12.2% (IQR,

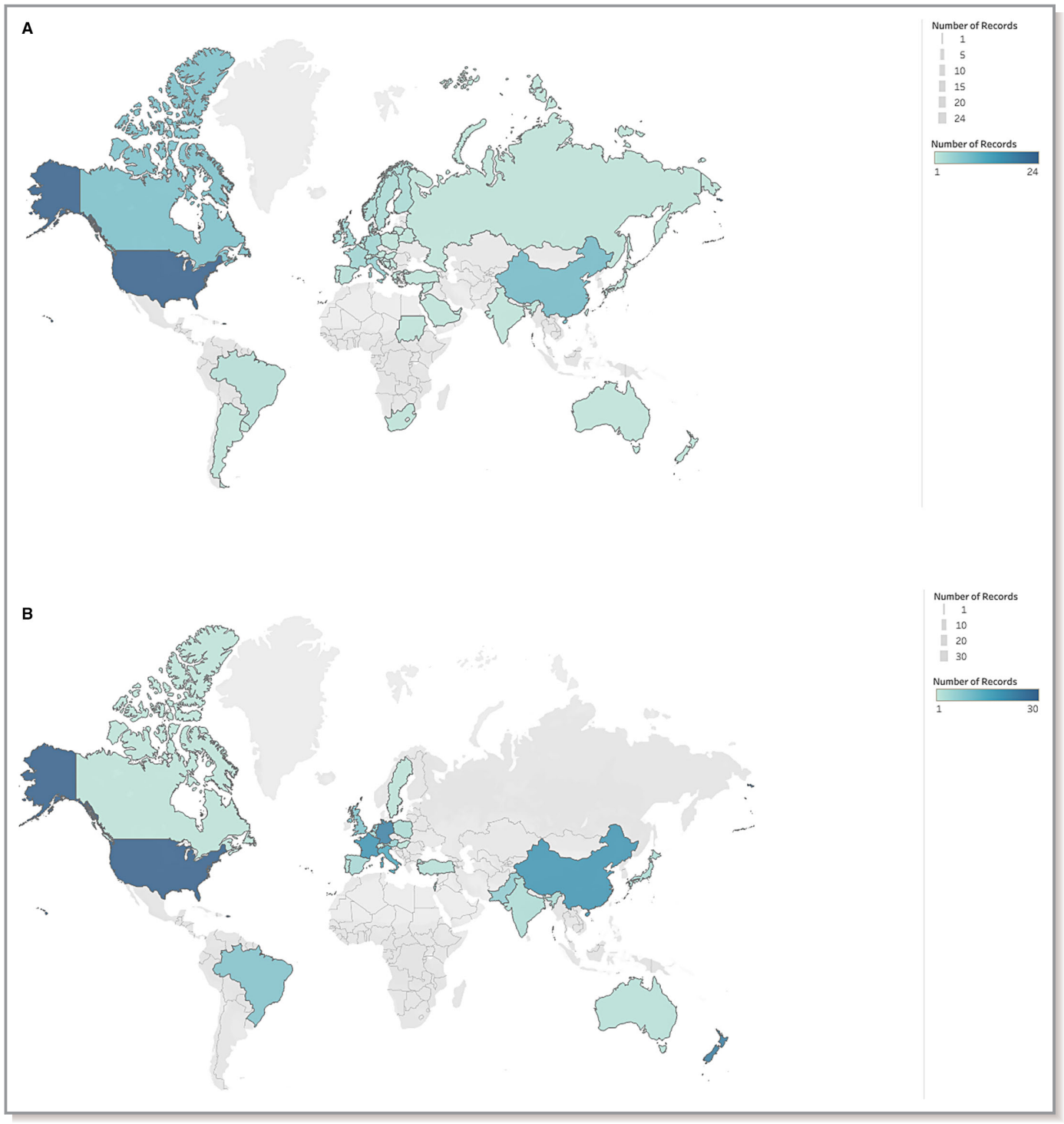

Figure 1. Geography of derivation and validation cohorts. Country of origin for derivation (**A**) and validation (**B**) populations. Maps created in Tableau Public.

−28.3%–+2.5%) for related validations and −32.1% (IQR, −54.9%–−12.8%) for distantly-related validations (Figure 2, $P<0.0001$).

CPMs that were derived on percutaneously-treated VHD populations and externally validated (n=9) underwent a total of 19 validations, almost all of which were on percutaneous populations. CPMs that were derived on surgical VHD populations and externally validated (n=25) underwent a total of 184 validations, of which 130 (71%) were on surgical populations, 52 (28%) were on percutaneous populations, and

Table 3. Reported Characteristics of Valvular Heart Disease External Validations[‡]

Characteristic*	Overall (n=204)[†]	Surgical (n=131)	Percutaneous (n=70)
Sample size	450 (249–1495)	809 (407–3306)	304 (180–453)
Number of events	38 (15–95)	48 (14–119)	38 (15–56)
Event rate	0.06 (0.03–0.12)	0.04 (0.03–0.07)	0.11 (0.08–0.17)
% Men	53 (47–62)	57 (53–66)	47 (43–52)
C-statistic	0.71 (0.65–0.77)	0.74 (0.70–0.79)	0.63 (0.57–0.68)

*Values are reported as median (interquartile range).
[†]Validations done on populations treated with surgical and percutaneous interventions that did not disaggregate results (n=2) are only included in the overall count.
[‡]Validation search includes citations through September 8, 2017.

2 (1%) were on populations including both surgical and percutaneous interventions. For validations of surgical VHD models discrimination was better when CPMs were tested on cohorts treated with surgical versus percutaneous interventions (median c-statistic 0.74 versus 0.63, $P<0.001$).

Of the surgical VHD CPMs validated on percutaneous populations (n=52 validations), the CPM most often validated was the STS (2009) model predicting mortality (n=27, median c-statistic 0.64 [IQR, 0.58–0.67]). EuroSCORE II (n=20) had the highest discrimination in this setting, with a median c-statistic of 0.67 (IQR, 0.55–0.71).

Discussion

Here we show that there are many CPMs available for patients with VHD and that many of these CPMs have not been externally validated. For the CPMs that have been externally

Table 4. EuroSCORE II Population Compared With External Validation Populations, Stratified by Relatedness

Statistic*	EuroSCORE II	Validation Populations[†,‡]	
		Related	Distantly Related
Total patients (n)	16 828	14 382	98 744
Total validations (n)	NA	5	73
Age, y	Mean (SD): 64.6 (12.5)	63.4 (62.7–67.0)	67.1 (61.1–80.5)
Number of events (n)	656	123 (53–215)	27 (12–57)
Event rate, %	3.9	5.7 (5.7–6.1)	6.3 (3.0–10.5)
Sex reported, n (%)	NA	5 (100%)	50 (68%)
Men, %	69.1	65.2 (62.5–66.5)	52.5 (46.8–64.1)
Type of intervention, n (%)			
Surgery	1 (100%)	5 (100%)	52 (71.2%)
Percutaneous	0 (0%)	0 (0%)	20 (27.4%)
Both	0 (0%)	0 (0%)	1 (1.4%)
Valve-related, %	53.3	56 (54.6–56.1)	100 (100–100)
Enrollment, y (range)	2010	2005 to 2013	1999 to 2015
C-statistic	0.8095	0.82 (0.76–0.85)	0.72 (0.67–0.78)
C-statistic (range)	NA	0.737 to 0.861	0.50 to 0.95
Any calibration reported, n (%)	0 (0%)	4 (80%)	65 (89%)
Change in discrimination,[§] %	NA	2.6 (−16.0–13.1)	−28.9 (−45.3–−9.5)

EuroSCORE indicates European System for Cardiac Operative Risk Evaluation.
*All values are reported as median (interquartile range) unless otherwise specified.
[†]Validation data is reported at the population level only; patient-level data was not available.
[‡]Validation population are "related" if it meets all of the following criteria: (1) same type of intervention (eg, both surgical populations), (2) ±10% absolute difference in the proportion of isolated valve procedure (eg, derivation population was 100% isolated valve and validation population was 95% isolated valve), and (3) overlapping years of enrollment. A validation population that does not meet all 3 criteria is "distantly related."
[§]Change in discrimination is calculated as [(Validation AUC−0.5)−(Derivation AUC−0.5)]/(Derivation AUC−0.5)×100.

Table 5. STS (2009) Population Compared With External Validation Populations, Stratified by Relatedness

Statistic*	STS Models (n=9)	Validation Populations†,‡	
		Related	Distantly Related
Total patients, n	109 759	37 395	49 530
Total validations, n	NA	33	37
Age, y	Not Reported	64.7 (56.6–73)	81.6 (74.5–83)
Number of events, n	9164 (3706–12 892)	29 (12–82)	38 (18–57)
Event rate, %	8.3 (3.4–11.7)	4.9 (2.7–12.6)	9.1 (3.7–11.7)
Men, %	55.4	56 (56.0–74.9)	47.8 (43.6–55.3)
Type of intervention, n (%)			
Surgery	9 (100%)	33 (100%)	8 (21.6%)
Percutaneous	0 (0%)	0 (0%)	28 (75.7%)
Both	0 (0%)	0 (0%)	1 (2.7%)
Valve-related, %	100	100 (100–100)	100 (100–100)
Enrollment, y (range)	2002–2006	1997–2014	1999–2015
C-statistic, median, IQR	0.74 (0.70–0.77)	0.72 (0.67–0.79)	0.65 (0.6–0.71)
C-statistic (range)	0.643 to 0.805	0.612 to 0.86	0.5 to 0.81
Calibration reported, n (%)	9 (100%)	18 (54.5%)	28 (75.7%)
Change in discrimination,§ %	NA	−21.3 (−34.4–2.3)	−50.8 (−67.2–−25.1)

IQR indicates interquartile range; STS, Society of Thoracic Surgeons.
*All values are reported as median (interquartile range) unless otherwise specified.
†Validation data is reported at the population level only; patient-level data was not available.
‡Validation population is "related" if it meets all of the following criteria: (1) same type of intervention (eg, both surgical populations), (2) ±10% absolute difference in the proportion of isolated valve procedure (eg, derivation population was 100% isolated valve and validation population was 95% isolated valve), and (3) overlapping years of enrollment. A validation population that does not meet all 3 criteria is "distantly related."
§Change in discrimination is calculated as [(Validation AUC−0.5)−(Derivation AUC−0.5)]/(Derivation AUC−0.5)×100.

validated, models often perform substantially worse than expected based on performance in derivation data sets. Notably, isolated external validations of VHD CPMs appear insufficient for broadly understanding CPM performance in the context of specific clinical decisions as predictive models may have highly variable performance across various databases. For patients under consideration for surgical VHD interventions, there are CPMs that have been extensively validated. The fidelity of TAVR CPM predictions is largely unknown, as these models have not been widely tested in external validations.

Predicted risk is central to procedural decision making for patients with VHD, however. individual risk estimates using published CPMs for VHD appear more uncertain than originally thought, especially when prediction models are derived on patients who are not closely related to the patients being treated. CPM performance (specifically discrimination) substantially degrades from the derivation population to the validation population, particularly when populations are "distantly related" with respect to procedure type (percutaneous versus open surgical), therapeutic era, and the need for concurrent revascularization. Without attention to these patient-level specifics, it is likely that there is widespread inappropriate use of CPMs that are informing treatment decisions for patients with VHD. While it is encouraging that newer models have been developed for TAVR patients, these CPMs have not been widely validated or integrated into contemporary guidelines, and have risk estimates that may become inaccurate as devices continue to improve and procedural techniques mature. The attenuated performance of these TAVR CPMs may also be related to the magnitude and significance of comorbid illnesses that are common for older treated adults and are rarely included as part of parsimonious modeling efforts.[45] More work is needed to understand these risk factors.

The decrease in discrimination that is observed in this study may be attributable to model overfitting, differences in case mix (ie, narrower populations in the validation data set), and phenotypic heterogeneity. Ultimately, the relevant performance metrics for clinicians relate to the patients they are treating (with a specific intervention), not to performance measured at the time of CPM development. Rarely, discrimination appears to improve during validations. This is likely the result of differences between the derivation population and the validation population where some models are developed on more highly selected (narrow case-mix) cohorts than they are testing on. The data presented here demonstrates that CPMs externally validated multiple times show substantial variation in performance. This strongly suggests that adequate

Table 6. CPMs that Have Been Validated ≥2 Times in Related Populations

De Novo CPM		External Validations in Related Populations (n)	Validation C-statistic, median (IQR)	% Change in Discrimination,* Median (IQR)	Any Calibration Reported (%)
Pub., Y	Model Name				
2001	STS (original): Isolated Valve	2	0.77 (0.77, 0.77)	2.6 (2.6–2.6)	100
2004	NNE Aortic	2	0.76 (0.76, 0.77)	4.0 (2.0–6.0)	100
2007	NWQIP	2	0.78 (0.77, 0.78)	−1.8 (−2.7–−0.9)	100
2005	Ambler	4	0.73 (0.72, 0.76)	−15.2 (−18.9–−2.2)	100
2009	STS: Mortality	19	0.74 (0.71, 0.79)	−21.3 (−31.5–−4.8)	95
2009	STS: Stroke	2	0.65 (0.65, 0.66)	−20.9 (−23.8–−17.9)	0
2009	STS: Prolonged Ventilation	2	0.72 (0.68, 0.75)	−20.2 (−33.8–−6.6)	0
2009	STS: Prolonged LOS	2	0.67 (0.65, 0.68)	−38.1 (−43.5–−32.8)	0
2009	STS: Renal Failure	2	0.76 (0.72, 0.79)	−9.6 (−22.5–3.4)	0
2009	STS: DSWI	2	0.68 (0.65, 0.70)	−13.7 (−24.8–−2.7)	0
2009	STS: Composite AEs	2	0.68 (0.65, 0.71)	−18.8 (−30.7–−6.9)	0
2009	STS: Reoperation	2	0.64 (0.63, 0.65)	−2.1 (−11.9–7.7)	0
2011	Aus-AVR Score	3	0.72 (0.67, 0.72)	−22.9 (−40.4–−20.4)	100
2012	EuroSCORE II	5	0.82 (0.76, 0.85)	2.6 (−16.0–13.1)	80
2013	NY Operative Mortality Risk Score	3	0.73 (0.71, 0.75)	−18.1 (−26.5–−9.8)	66.7
2014	OBSERVANT Score	4	0.60 (0.58, 0.61)	−57.8 (−63.7–50.7)	50
2014	STT: 30 d	2	0.66	0	50

AEs indicates adverse events; Aus-AVR, Australian aortic valve replacement; CPM indicates clinical predictive models; DSWI, deep sternal wound infections; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; LOS, length of stay; NNE, Northern New England; NWQIP, North West Quality Improvement Programme in Cardiac Interventions; NY, New York; OBSERVANT, Observational Study of Appropriateness, Efficacy and Effectiveness of AVR-TAVR Procedures for the Treatment of Severe Symptomatic Aortic Stenosis; STS, Society of Thoracic Surgeons; STT, Survival posT-TAVI; TAVI, transcatheter aortic valve implantation.
*Change in discrimination is calculated as [(Validation AUC−0.5)−(Derivation AUC−0.5)]/(Derivation AUC−0.5)×100.

performance demonstrated in a single external validation may be insufficient to assess the quality (and utility) of VHD CPMs and that a more tailored approach is needed to understand the trustworthiness of CPM predictions in specific settings.

There is increasing recognition of the central importance of CPM calibration. Surprisingly, calibration was reported in only 78% of the external validations of VHD CPMs. There is no agreed-upon standard for reporting model calibration and no consensus on interpreting this metric. Moreover, there are well-recognized limitations to the most commonly reported measure, the Hosmer-Lemeshow statistic (eg, sample-size dependence).[46] Reporting of model calibration represents a major shortcoming in the assessment and overall trustworthiness of VHD CPMs, as adequate calibration can protect against harm.[13] Ongoing efforts, including the Transparent Reporting of a Multivariable Model for Individual Prognosis or Diagnosis statement[47] and the Prognosis Research Strategy,[48] should lead to more consistent evaluation and better reporting of this important performance metric. For currently available CPMs, it is important for clinicians to know whether predictions over- or underestimate risk when compared with observed event rates in similar patients, especially when the decision for or against a particular intervention is informed by this output (as is the case for percutaneous VHD treatments). Poor calibration can often be overcome with a variety of updating techniques that can substantially improve accuracy of predictions.[49]

There is much that remains unknown about these predictive models. CPM performance has not been studied for patients treated in many areas of Eastern Europe, Asia, Central America, South America, and Africa. This is especially important considering the many regional differences in VHD etiology, access to technologies, care systems, and guidelines.[50–52] The optimal number of validations required to adequately assess CPM performance remains unknown. Ideally, CPMs are serially validated and recalibrated (if necessary) to optimize performance for specific, local clinical decision making. Without addressing these limitations, clinical decisions that leverage CPM outputs may be inaccurate and lead to harmful decisions.

This analysis offers a structure to consider which CPMs are most accurate (discrimination and calibration) and trustworthy (consistent performance in multiple external validations). For patients being considered for surgical valve interventions, EuroSCORE II (median validation c-statistic 0.82 [0.76, 0.85]), North West Quality Improvement Programme in Cardiac

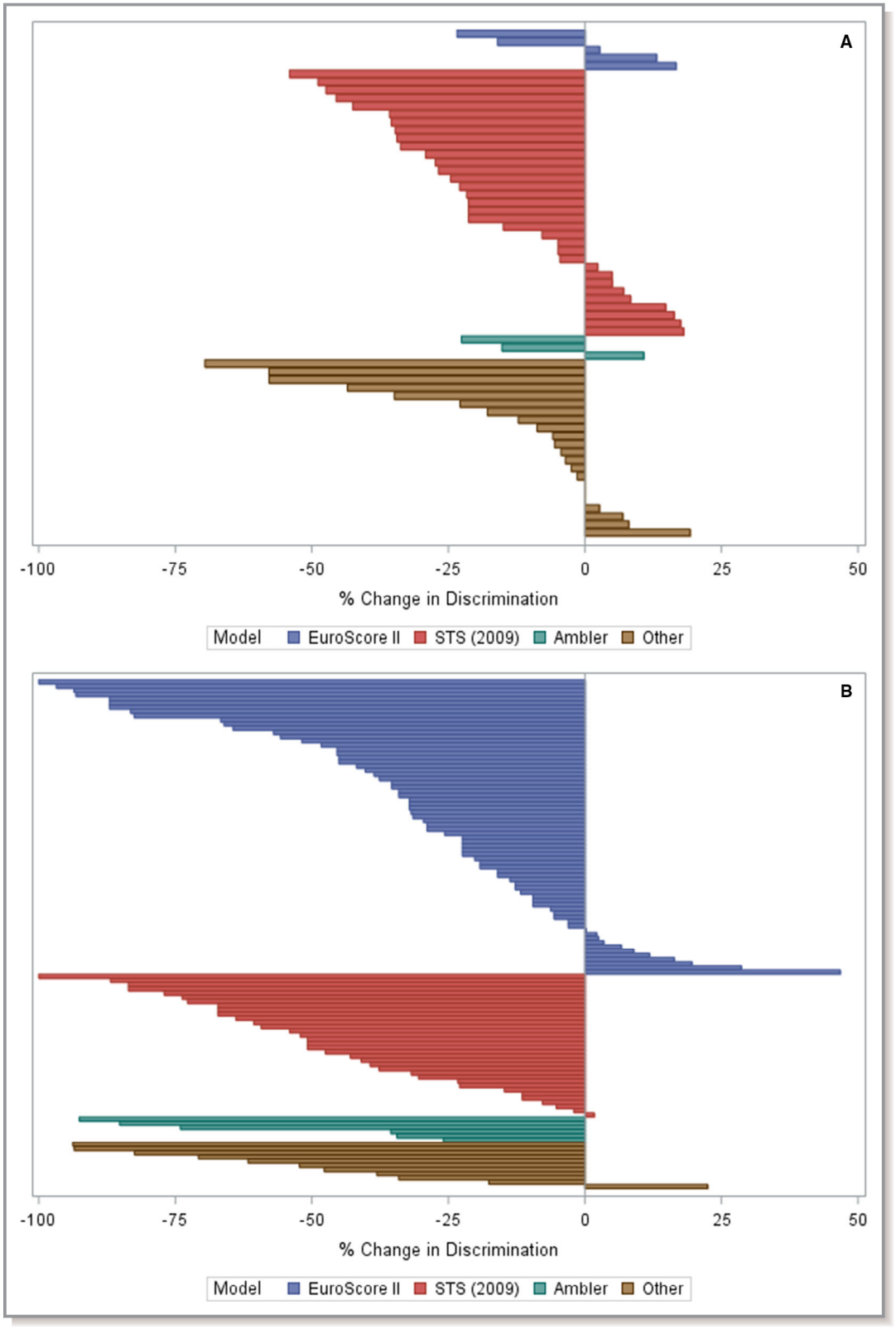

Figure 2. Percentage change in discrimination in external validations of valvular heart disease clinical prediction models, stratified by relatedness. Each bar represents a unique external validation that reports a c-statistic (n=205). Society of Thoracic Surgeons (2009) Models. Percentage change in discrimination is calculated as ([validation c-statistic–0.5]–[derivation c-statistic–0.5])/[derivation c-statistic–0.5]×100. STS indicates Society of Thoracic Surgeons

Interventions Model (median validation c-statistic 0.78 [0.77, 0.78]), Northern New England Aortic Model (median validation c-statistic 0.76 [0.76, 0.77]), Ambler (median validation c-statistic 0.73 [0.72, 0.76]), and STS (2009) Mortality (median validation c-statistic 0.74 [0.71, 0.79]) have reasonable discrimination and multiple assessments of discrimination and calibration in external data sets. There are no CPMs for patients treated with TAVR that demonstrate good performance across multiple related validation databases. The trustworthiness of these newer risk estimates for TAVR remains under-studied.

There are several limitations to this work. Our review was limited to CPMs that provide enough information in the published report to calculate a risk prediction for a patient. Logistic regression models that did not report a full equation or intercept were not included. Cox regression models that did not report a point score or baseline hazard were excluded. The search for de novo VHD CPMs was last run in January 2017. While newer CPMs have been developed, there is often substantial delay before the publication of subsequent external validations. Notably, we present relative changes in discrimination to more accurately document changes on a clinically relevant scale, where small decreases in the C-statistic can result in large changes in clinically relevant performance. Lastly, this study was limited in its examination of CPM calibration, which is an important measure of model performance, but often poorly reported and without a widely-accepted summary measure.

While there are numerous available CPMs for patients with VHD, many have never been externally validated, and for those that have, discriminatory performance is often much worse than originally reported. We note that CPM performance is highly dependent on the cohort selected for study, suggesting that one-off external validations may inadequately assess performance. Instead of new CPM development, robust external validations of established TAVR CPMs and an understanding of the updating techniques that best optimize model performance are needed.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Search strategy used to identify all CVD/Cerebrovascular and VHD-specific CPMs.

All CPM Search Terms
((predict$ adj1 model$) or (predict$ adj1 instrument$) or (predict$ adj1 score$) or (predict$ adj1 index)).mp.
((prognos$ adj1 model$) or (prognos$ adj1 instrument$) or (prognos$ adj1 score$) or (prognos$ adj1 index)).mp.
((risk adj1 model$) or (risk adj1 instrument$) or (risk adj1 score$) or (risk adj1 index) or (risk assessment model or risk assessment instrument or risk assessment score)).mp.
atrial fib$.mp. or exp Atrial Fibrillation/ or exp coronary artery disease/ or exp coronary disease/ or exp myocardial infarction/ or Myocardial infarct$.mp. or exp Heart Failure, Congestive/ or exp myocardial ischemia/ or exp cardiovascular diseases/ or exp Cerebrovascular Accident/ or *heart failure/ or *stroke/ or *acute coronary syndrome/
limit 6 to yr="1990 -Current" **Where current = May 15, 2012 publications
(201205$ or 201206$ or 201207$ or 201208$ or 201209$ or 201210$ or 201211$ or 201212$ or 2013$ or 2014$ or 201501$ or 201502$ or 201503$).ed.
VHD CPM Search Terms
((predict$ adj1 model$) or (predict$ adj1 instrument$) or (predict$ adj1 score$) or (predict$ adj1 index)).mp.
((prognos$ adj1 model$) or (prognos$ adj1 instrument$) or (prognos$ adj1 score$) or (prognos$ adj1 index)).mp.
((risk adj1 model$) or (risk adj1 instrument$) or (risk adj1 score$) or (risk adj1 index) or (risk assessment model or risk assessment instrument or risk assessment score)).mp.
heart valve prosthe$.mp. or exp cardiovascular surg$.mp. or exp valve replacement/ or exp valve intervention/ or exp aortic valve/ or exp mitral valve/ or exp tricuspid valve/ or exp pulmonic valve/
(201504$ or 201505$ or 201506$ or 201507$ or 201508$ or 201509$ or 201510$ or 201511$ or 201512$ or 2016$ or 2017$).ed.

Table S2. De Novo Model Unabridged Overview.

Author, Model Name	Year	Valve	Standardized Type of Intervention	Specific Intervention	Outcome	Centers	Sample Size	Number of Events	EPV	Age	Continent	Model Method	C-statistic	Calibration Measure	Externally Validated?
Isolated Valve Intervention (+/- CABG)															
Edwards[1], STS (original) -- Isolated Valve	2001	Aortic/ Mitral	Surgery	AVR or MVR	30 Day Operative Mortality	Multi-center	49073	2291	121	63.7	North America	Logistic regression	0.766	HL statistic, Calibration plot	Yes
Nowicki[2], NNE Aortic and Mitral Models	2004	Aortic	Surgery	AVR +/- CABG	In-Hospital Mortality	Multi-center	5793	360	40	69.5	North America	Logistic regression, Score	0.75	HL statistic	Yes
		Mitral	Surgery	MVR or MVRepair	In-Hospital Mortality	Multi-center	3150	296	30	66.7	North America	Logistic regression, Score	0.79	HL statistic	Yes
Kuduvalli[3], NWQIP	2007	Aortic	Surgery	AVR +/- CABG	In-Hospital Mortality	Multi-center	4550	207	21	69	Europe	Logistic regression, Score	0.78	HL statistic	Yes
Cruz-Gonzalez[4], PMV Score	2009	Mitral	Percutaneous	Percutaneous Mitral Valvuloplasty	Procedural Success	Single center	800	544	91	54.9	North America	Logistic regression, Score	NR	HL statistic	Yes
Monin[5]	2009	Aortic Stenosis	Natural History	None	Composite (Non-MACE)	Single center	107	62	9	72	Europe	Logistic regression, Score	0.90	HL statistic	Yes
O'Brien[6], STS (new) – Composite AEs	2009	Aortic/ Mitral	Surgery	AVR or MVR or MVRepair	Composite (Non-MACE)	Multi-center	109759	20074	574	NR	North America	Logistic regression	0.721	None	Yes
O'Brien[6], STS (new) -- DSWI	2009	Aortic/ Mitral	Surgery	AVR or MVR or MVRepair	DSWI	Multi-center	109759	307	26	NR	North America	Logistic regression	0.704	None	Yes

Author, Model Name	Year	Valve	Standardized Type of Intervention	Specific Intervention	Outcome	Centers	Sample Size	Number of Events	EPV	Age	Continent	Model Method	C-statistic	Calibration Measure	Externally Validated?
O'Brien[6], STS (new) -- Mortality	2009	Aortic/ Mitral	Surgery	AVR or MVR or MVRepair	30 Day Mortality	Multi-center	109759	3706	100	NR	North America	Logistic regression	0.805	None	Yes
O'Brien[6], STS (new) – Prolonged LOS	2009	Aortic/ Mitral	Surgery	AVR or MVR or MVRepair	Prolonged LOS	Multi-center	109759	9718	270	NR	North America	Logistic regression	0.77	None	Yes
O'Brien[6], STS (new) – Prolonged Ventilation	2009	Aortic/ Mitral	Surgery	AVR or MVR or MVRepair	Prolonged Ventilation	Multi-center	109759	12892	331	NR	North America	Logistic regression	0.77	None	Yes
O'Brien[6], STS (new) – Renal Failure	2009	Aortic/ Mitral	Surgery	AVR or MVR or MVRepair	Renal Failure	Multi-center	107060	4673	173	NR	North America	Logistic regression	0.782	None	Yes
O'Brien[6], STS (new) -- Reoperation	2009	Aortic/ Mitral	Surgery	AVR or MVR or MVRepair	Reoperation	Multi-center	109759	9164	305	NR	North America	Logistic regression	0.643	None	Yes
O'Brien[6], STS (new) – Short LOS	2009	Aortic/ Mitral	Surgery	AVR or MVR or MVRepair	Prolonged LOS	Multi-center	109759	41214	1178	NR	North America	Logistic regression	0.738	None	No
O'Brien[6], STS (new) -- Stroke	2009	Aortic/ Mitral	Surgery	AVR or MVR or MVRepair	Stroke	Multi-center	109759	1751	92	NR	North America	Logistic regression	0.694	None	Yes
Guaragna[7], GuaragnaSCORE	2010	Aortic/ Mitral	Surgery	Isolated Cardiac Valve Surgery +/- CABG	In-Hospital Mortality	Single center	699	128	16	55.5	South America	Logistic regression, Score	0.82	HL statistic, Calibration plot	Yes
Guo[8]	2010	Aortic	Surgery	AVR	In-Hospital Mortality	Single center	1087	45	6	60.24	Asia	Logistic regression	NR	HL statistic	No
		Mitral	Surgery	MVR	In-Hospital Mortality	Single center	1752	79	16	50.89	Asia	Logistic regression	NR	HL statistic	No
Elmariah[9], CRRAC the AV Score	2011	Aortic	Percutaneous	Balloon Aortic Valvuloplasty	30 Day Mortality	Single center	281	36	9	83	North America	Cox regression, Score	0.754	HL statistic	No

Author, Model Name	Year	Valve	Standardized Type of Intervention	Specific Intervention	Outcome	Centers	Sample Size	Number of Events	EPV	Age	Continent	Model Method	C-statistic	Calibration Measure	Externally Validated?
Bouleti[10]	2012	Mitral	Percutaneous	Percutaneous Mitral Commissurotomy	Composite (MACE)	Single center	609	309	77	49	Europe	Cox regression, Score	0.74	Calibration plot	No
Cioffi[11]	2012	Aortic Stenosis	Natural History	None	Composite (MACE)	Multi-center	1566	550	79	67	Europe	Cox regression, Score	NR	None	No
Holme[12], SEAS Score	2012	Aortic Stenosis	Natural History	None	5 Year Mortality	Multi-center	772	78	11	67.7	Europe	Cox regression	0.722	HL statistic, Calibration plot, Brier score	No
Kötting[13], German Aortic Valve Score	2013	Aortic	Percutaneous	AVR or TAVR	In-Hospital Mortality	Multi-center	11147	416	28	NR	Europe	Logistic regression, Score	0.808	HL statistic	Yes
Arnold[14], 6 Month and 1 Year Models	2014	Aortic Stenosis	Percutaneous	TAVR	Composite (Non-MACE)	Multi-center	2137	704	70	84	North America, Europe	Logistic regression	0.66	HL statistics, Calibration plot	Yes
		Aortic Stenosis	Percutaneous	TAVR	Composite (Non-MACE)	Multi-center	2130	1073	134	84	North America, Europe	Logistic regression	0.66	HL statistics, Calibration plot	Yes
Capodanno[15], OBSERVANT Score	2014	Aortic Stenosis	Percutaneous	AVR or TAVR	30 Day Mortality	Multi-center	1256	77	11	81.9	Europe	Logistic regression, Score	0.73	HL statistic, Calibration plot, Brier score	Yes
D'Ascenzo[16], Survival Post-TAVI (STT) - 30 Days and 1 Year Models	2014	Aortic	Percutaneous	TAVR	30 Day Mortality	Multi-center	1064	60	20	81.6	Europe	Logistic regression, Score	0.66	HL statistic	Yes
		Aortic	Percutaneous	TAVR	1 Year Mortality	Multi-center	1064	165	55	81.6	Europe	Logistic regressi	0.68	HL statistic	Yes

Author, Model Name	Year	Valve	Standardized Type of Intervention	Specific Intervention	Outcome	Centers	Sample Size	Number of Events	EPV	Age	Continent	Model Method	C-statistic	Calibration Measure	Externally Validated?
												on, Score			
Iung[17]	2014	Aortic	Percutaneous	TAVR	30 Day Mortality	Multi-center	2552	253	28	82.9	Europe	Logistic regression, Score	0.67	HL statistic, Calibration in the large, Calibration plot	No
Debonnaire[18], TAVI2-SCORe	2015	Aortic	Percutaneous	TAVR	1 Year Mortality	Multi-center	509	80	10	82	Europe	Cox regression, Score	0.715	HL statistic, Calibration in the large	Yes
Edwards[19]	2016	Aortic	Percutaneous	TAVR	In-Hospital Mortality	Multi-center	13672	730	104	82.1	North America	Logistic regression	0.67	HL statistics, Calibration in the large, Calibration plot	Yes
Isolated or Multiple Valve (+/- CABG)															
Koplan[20]	2003	All	Surgery	Cardiac Valve Surgery	Pacemaker Placement	Single center	3116	168	24	65	North America	Logistic regression, Score	NR	None	No
Ambler[21], Ambler	2005	Aortic, Mitral	Surgery	AVR and/or MVR	In-Hospital Mortality	Multi-center	16679	1067	76	64.8	Europe	Logistic regression, Score	0.77	HL statistic, Calibration plot	Yes
Xu[22]	2006	All	Surgery	Valve Surgery	Prolonged LOS	Single center	507	75	11	55.5	Asia	Logistic regression	0.81	Calibration in table form	No
Hannan[23]	2007	Aortic, Mitral	Surgery	Isolated Valve Surgery	In-Hospital Mortality	Multi-center	10702	472	43	NR	North America	Logistic regression, Score	0.794	HL statistic, Calibration plot	Yes

Author, Model Name	Year	Valve	Standardized Type of Intervention	Specific Intervention	Outcome	Centers	Sample Size	Number of Events	EPV	Age	Continent	Model Method	C-statistic	Calibration Measure	Externally Validated?
Xu[24], FUWAI Score	2007	All	Surgery	Valve Surgery +/- CABG	Prolonged LOS	Single center	2193	345	27	53.29	Asia	Logistic regression, Score	0.76	HL statistic, Calibration plot	Yes
Shi[25]	2010	Aortic, Mitral	Surgery	AVR and/or MVR	In-Hospital Mortality	Single center	158	8	1	NR	Asia	Logistic regression	0.7358	None	No
Ariyaratne[26], Aus-AVR Score	2011	Aortic, Mitral	Surgery	AVR +/- CABG +/- MVR	30 Day Mortality	Multi-center	3544	147	16	NR	Australia	Logistic regression, Score	0.78	HL statistic, Calibration in the large	Yes
Nashef[27], EuroSCORE II	2012	All	Surgery	Major Cardiac Surgery	In-Hospital Mortality	Multi-center	16828	656	36	64.6	International	Logistic regression	0.8095	None	Yes
Hannan[28], NY Operative Mortality Risk Score	2013	Aortic, Mitral	Surgery	Isolated Valve Surgery	30 Day Mortality	Multi-center	13455	542	49	NR	North America	Logistic regression, Score	0.781	HL statistic	Yes
Wang[29]	2013	All	Surgery	Valve Surgery	Prolonged Ventilation	Single center	2400	303	25	NR	Asia	Logistic regression	0.789	HL statistic	No
Zheng[30]	2013	Aortic, Mitral	Surgery	AV and/or MV Surgery	In-Hospital Mortality	Multi-center	6677	130	26	48	Asia	Logistic regression, Score	0.76	HL statistic, Chi-square statistic, Calibration plot	No
Multiple Valve															
Guo[8]	2010	Aortic, Mitral	Surgery	AVR + MVR	In-Hospital Mortality	Single center	818	55	14	58.4	Asia	Logistic regression	NR	HL statistic	No
Rankin[31], AM Preop	2013	Aortic, Mitral	Surgery	AVR + MVR	30 Day Mortality	Multi-center	27035	2541	116	70	North America	Logistic regression	NR	Calibration plot	Yes

Author, Model Name	Year	Valve	Standardized Type of Intervention	Specific Intervention	Outcome	Centers	Sample Size	Number of Events	EPV	Age	Continent	Model Method	C-statistic	Calibration Measure	Externally Validated?
Rankin[31], MT Preop	2013	Mitral, Tricuspid	Surgery	MVR + TVR	30 Day Mortality	Multi-center	18686	1420	71	70	North America	Logistic regression	NR	Calibration plot	Yes
Rankin[31], AMT Preop	2013	Aortic, Mitral, Tricuspid	Surgery	AVR + MVR + TVR	30 Day Mortality	Multi-center	4510	591	74	71	North America	Logistic regression	NR	Calibration plot	Yes
Rankin[31], AM Preop + Intraop	2013	Aortic, Mitral	Surgery	AVR + MVR	30 Day Mortality	Multi-center	27035	2541	110	70	North America	Logistic regression	NR	Calibration plot	Yes
Rankin[31], MT Preop + Intraop	2013	Mitral, Tricuspid	Surgery	MVR + TVR	30 Day Mortality	Multi-center	18686	1420	71	70	North America	Logistic regression	NR	Calibration plot	Yes
Rankin[31], AMT Preop + Intraop	2013	Aortic, Mitral, Tricuspid	Surgery	AVR + MVR + TVR	30 Day Mortality	Multi-center	4510	591	26	71	North America	Logistic regression	NR	Calibration plot	Yes

* ‘Isolated Valve’ indicates a single valve procedure; ‘Multiple Valve’ indicates intervention to > 1 valve; AVR indicates aortic valve replacement; MVR, mitral valve replacement; HL, Hosmer-Lemeshow; CABG, coronary artery bypass grafting; NR, not reported; MACE, major adverse cardiovascular events; AEs, adverse events; DSWI, deep sternal wound infections; LOS, length of stay; TAVR, transcatheter aortic valve replacement; TVR, tricuspid valve replacement.

Table S3. External Validations Overview.

De novo	*Validation*									
Model	**Author, Year**	**Index Condition**	**Outcome**	**Timeframe**	**Continent**	**Sample Size**	**Number of Events**	**C-statistic**	**Calibration Reported?**	**Change in Discrimination (%)**
Isolated Valve										
STS (original) – Isolated Valve[1]	Edwards, 2001[1]	AVR or MVR	operative mortality	30 days	North America	25640	1231	0.773	Yes	2.631578947
	Brown, 2009[32]	AVR	mortality	hospitalization period	North America	108,687	3197	NA	Yes	NA
NNE Aortic[2]	Jin, 2005[33]	AVR	operative mortality	until discharge	North America	3324	142	0.75	Yes	0
	Ariyaratne, 2011[26]	AVR	early postop mortality	30 days	Australia	3544	147	0.77	Yes	8
	Wang, 2013[34]	valve surgery	in-hospital mortality	until discharge	Asia	12412	260	0.706	Yes	-17.6
NNE Mitral[2]	Jin, 2005[33]	MVR	operative mortality	until discharge	North America	1596	95	0.81	Yes	6.896551724
NWQIP[3]	Kuduvalli, 2007[3]	AVR +/- CABG	in-hospital mortality	hospitalization period	Europe	816	33	0.78	Yes	0
	Ariyaratne, 2011[26]	AVR +/- CABG	in-hospital mortality or mortality within 30 days of surgery	30 days	Australia	3306	120	0.77	Yes	-3.571428571
PMV Score[4]	Cruz-Gonzalez, 2009[4]	percutaneous mitral valvuloplasty	PMV success	1 year	North America	285	213	NR	No	NA
Monin, 2009[5]	Monin, 2009[5]	valve surgery +/- CABG	morbidity/mortality	mean 21 months	Europe	107	56	0.89	Yes	-2.5
STS (new)– Composite AEs[6]	Watanabe, 2013[35]	TAVR	composite safety endpoint	30 days	Europe	453	94	0.59	No	-59.2760181
	Wang, 2016[36]	AVR +/- CABG	composite morbidity	30 days	Australia	450	152	0.627	No	-42.53393665
	Wang, 2017[37]	MVR or MVRepair	composite morbidity	30 days	Australia	407	77	0.732	No	4.977375566
STS (new)– DSWI[6]	Wang, 2016[36]	AVR +/- CABG	DSWI	30 days	Australia	450	6	0.631	No	-35.78431373
	Wang, 2017[37]	MVR or MVRepair	mediastinitis	30 days	Australia	407	4	0.721	No	8.333333333

De novo	*Validation*									
Model	**Author, Year**	**Index Condition**	**Outcome**	**Timeframe**	**Continent**	**Sample Size**	**Number of Events**	**C-statistic**	**Calibration Reported?**	**Change in Discrimination (%)**
STS (new) – Mortality[6]	Piazza, 2010[38]	TAVR	periprocedural mortality	30 days	Europe	168	19	0.69	Yes	-37.70491803
	Basraon, 2011[39]	AVR	perioperative mortality	30 days	North America	537	32	0.73	Yes	-24.59016393
	Zhang, 2011[40]	valve surgery	prolonged postop ICU stay	mean LOS 79.44 +/- 59.76 hrs	Asia	1333	187	0.70	Yes	-34.42622951
	Durand, 2013[41]	TAVR	mortality	30 days	Europe	250	19	0.58	Yes	-73.7704918
	Durand, 2013[41]	TAVR (transapical access)	mortality	30 days	Europe	60	7	0.55	Yes	-83.60655738
	Durand, 2013[41]	TAVR (transfemoral access)	mortality	30 days	Europe	190	12	0.66	Yes	-47.54098361
	Haensig, 2013[42]	TA-AVI	mortality	30 days	Europe	360	38	0.64	Yes	-54.09836066
	Haensig, 2013[42]	TA-AVI	in-hospital mortality	until discharge	Europe	360	41	0.65	Yes	-50.81967213
	Laurent, 2013[43]	AVR	operative mortality	30 days	Europe	314	18	0.77	Yes	-11.47540984
	Wang, 2013[34]	valve surgery	in-hospital mortality	until discharge	Asia	12412	260	0.735	Yes	-22.95081967
	Watanabe, 2013[35]	TAVR	mortality	30 days	Europe	453	57	0.6	Yes	-67.21311475
	Watanabe, 2013[35]	TAVR (transfemoral)	mortality	30 days	Europe	249	28	0.6	Yes	-67.21311475
	Watanabe, 2013[35]	TAVR (transfemoral approach, without early experience)	mortality	30 days	Europe	NR	NR	0.65	Yes	-50.81967213
	Watanabe, 2013[35]	TAVR (transapical/transaortic)	mortality	30 days	Europe	330	27	0.61	Yes	-63.93442623
	Barili, 2014[44]	MV surgery	in-hospital mortality	until discharge	Europe	1239	NR	0.82	Yes	4.918032787
	Barili, 2014[44]	MV surgery +/- CABG	in-hospital mortality	until discharge	Europe	2202	NR	0.76	Yes	-14.75409836

De novo	*Validation*									
Model	**Author, Year**	**Index Condition**	**Outcome**	**Timeframe**	**Continent**	**Sample Size**	**Number of Events**	**C-statistic**	**Calibration Reported?**	**Change in Discrimination (%)**
	Beohar, 2014[45]	TAVR	mortality	30 days	North America	2552	165	0.6	Yes	-67.21311475
	Chan, 2014[46]	MVR or MVRepair	perioperative mortality	30 days	North America	1154	11	0.74	Yes	-21.31147541
	Osnabrugge, 2014[47]	AVR	in-hospital mortality	until discharge	North America	4107	119	0.74	Yes	-21.31147541
	Osnabrugge, 2014[47]	AVR +/- CABG	in-hospital mortality	until discharge	North America	3480	143	0.74	Yes	-21.31147541
	Osnabrugge, 2014[47]	MVRepair	in-hospital mortality	until discharge	North America	1059	13	0.86	Yes	18.03278689
	Osnabrugge, 2014[47]	MVR	in-hospital mortality	until discharge	North America	1071	59	0.79	Yes	-4.918032787
	Rabbani, 2014[48]	valve replacement surgery	mortality	30 days	Asia	576	28	0.812	Yes	2.295081967
	Wendt, 2014[49]	AVR or TAVR	mortality	30 days	Europe	1512	95	0.708	Yes	-31.80327869
	Wang, 2014[50]	isolated or multiple valve surgery	in-hospital mortality	until discharge	Asia	9846	176	0.712	Yes	-30.49180328
	Adamo, 2015[51]	percutaneous MVRepair	mortality	30 days	Europe	304	10	0.62	Yes	-60.6557377
	Debonnaire, 2015[18]	TAVR	all-cause mortality	1 year	Europe	471	80	0.5	Yes	-100
	Holinski, 2015[52]	repeat AVR	mortality	30 days	Europe	78	8	0.64	Yes	-54.09836066
	Silaschi, 2015[53]	TAVR (transfemoral or transapical)	mortality	30 days	Europe	457	44	0.57	Yes	-77.04918033
	Silva, 2015[54]	TAVR	mortality	30 days	South America	418	38	0.54	Yes	-86.8852459
	Sinning, 2015[55]	TAVR	all-cause mortality	1 year	Europe	310	80	0.685	No	-39.3442623
	Tralhao, 2015[56]	AVR	operative mortality	30 days	Europe	106	6	0.702	Yes	-33.7704918
	Vassileva, 2015[57]	repeat AVR after prior CABG	operative mortality	median LOS 6 days (IQR 5-9)	North America	6534	236	NR	Yes	NA

De novo	*Validation*									
Model	**Author, Year**	**Index Condition**	**Outcome**	**Timeframe**	**Continent**	**Sample Size**	**Number of Events**	**C-statistic**	**Calibration Reported?**	**Change in Discrimination (%)**
	Wang, 2015[58]	AVR	operative mortality	30 days	Australia	620	18	0.716	Yes	-29.18032787
	Wang, 2015[59]	AVR	post-operative complications	14 days	Australia	620	115	0.666	Yes	-45.57377049
	Barili, 2016[60]	AVR	mortality	30 days	Europe	1444	NR	0.79	Yes	-4.918032787
	Collas, 2016[61]	TAVR	mortality	1 year	Europe	225	38	NR	No	NA
	Halkin, 2016[62]	TAVR	all-cause mortality	30 days	Asia	1327	45	0.68	No	-40.98360656
	Kortlandt, 2016[63]	percutaneous MVRepair	periprocedural mortality	30 days	Europe	136	5	0.65	Yes	-50.81967213
	Peguero, 2016[64]	cardiac surgery	operative mortality	30 days	North America	2263	48	0.77	Yes	-11.47540984
	Rosa, 2016[65]	TAVR	in-hospital mortality	until discharge	South America	59	6	NR	Yes	NA
	Rosa, 2016[65]	TAVR	30-day mortality	30 days	South America	59	8	0.81	Yes	1.639344262
	Wang, 2016[36]	AVR +/- CABG	operative mortality	30 days	Australia	450	29	0.699	Yes	-34.75409836
	Wang, 2016[66]	valve surgery	in-hospital mortality	until discharge	Asia	12412	260	0.735	Yes	-22.95081967
	Yamaoka, 2016[67]	AVR +/- CABG	operative mortality	30 days	Asia	406	14	0.781	Yes	-7.868852459
	Zbroński, 2016[68]	TAVR	mortality	30 days	Europe	156	15	0.55	Yes	-83.60655738
	Balan, 2017[69]	TAVR	mortality	30 days	North America	426	18	0.674	No	-42.95081967
	Balan, 2017[69]	SAVR	mortality	30 days	North America	297	14	0.791	No	-4.590163934
	Balan, 2017[69]	TAVR (transfemoral)	mortality	30 days	North America	NR	NR	0.789	No	-5.245901639
	Balan, 2017[69]	TAVR (transapical)	mortality	30 days	North America	NR	NR	0.583	No	-72.78688525
	Schmid, 2017[70]	TAVR	all-cause mortality	1 year	Europe	74	10	0.734	No	-23.27868852
	Schmid, 2017[70]	TAVR	all-cause mortality	2 years	Europe	74	18	0.646	No	-52.13114754
	Wang, 2017[37]	MVR or MVRepair	operative mortality	30 days	Australia	407	10	0.850	Yes	14.75409836

De novo	*Validation*									
Model	**Author, Year**	**Index Condition**	**Outcome**	**Timeframe**	**Continent**	**Sample Size**	**Number of Events**	**C-statistic**	**Calibration Reported?**	**Change in Discrimination (%)**
STS (new)– Prolonged LOS[6]	Wang, 2016[36]	AVR +/- CABG	LOS > 14 days	14 days	Australia	450	86	0.638	No	-48.88888889
	Wang, 2017[37]	MVR or MVRepair	prolonged LOS	14 days	Australia	407	56	0.696	No	-27.40740741
STS (new)– Prolonged Ventilation[6]	Wang, 2016[36]	AVR/CABG	ventilation > 24 hours	30 days	Australia	450	124	0.642	No	-47.40740741
	Wang, 2017[37]	MVR or MVRepair	ventilation > 24 hours	30 days	Australia	407	54	0.789	No	7.037037037
STS (new)– Renal Failure[6]	Peguero, 2016[64]	valve surgery +/- CABG	operative mortality	30 days	North America	2263	48	0.76	Yes	-7.80141844
	Wang, 2016[36]	AVR +/- CABG	renal failure	30 days	Australia	450	6	0.682	No	-35.46099291
	Wang, 2017[37]	MVR or MVRepair	renal failure	30 days	Australia	407	12	0.828	No	16.31205674
STS (new)– Reoperation[6]	Wang, 2016[36]	AVR/CABG	reoperation	30 days	Australia	450	54	0.612	No	-21.67832168
	Wang, 2017[37]	MVR or MVRepair	return to theater	30 days	Australia	407	33	0.668	No	17.48251748
STS (new)– Stroke[6]	Peguero, 2016[64]	valve surgery +/- CABG	operative mortality	30 days	North America	2263	48	0.69	Yes	-2.06185567
	Wang, 2016[36]	AVR/CABG	stroke	30 days	Australia	450	15	0.642	No	-26.80412371
	Wang, 2017[37]	MVR or MVRepair	stroke	30 days	Australia	407	7	0.665	No	-14.94845361
GuaragnaSCORE[7]	Sa, 2012[71]	valve surgery +/- CABG	perioperative mortality	until discharge	South America	491	74	0.781	Yes	-12.1875
	Silva, 2015[54]	TAVR	mortality	30 days	South America	418	38	0.52	Yes	-93.75
German Aortic Valve Score[13]	Sinning, 2015[55]	TAVR	all-cause mortality	1 year	Europe	310	80	0.661	No	-47.72727273
	Sinning, 2015[55]	TAVR	all-cause mortality or rehospitalization	1 year	Europe	310	132	0.618	No	-61.68831169
	Halkin, 2016[62]	TAVR	all-cause mortality	30 days	Asia	1327	45	0.52	No	-93.50649351
	Kalendar, 2017[72]	AVR	mortality	until discharge	Asia	35	6	0.647	Yes	-52.27272727
	Martin, 2017[73]	TAVR	mortality	30 days	Europe	6676	360	0.59	Yes	-70.77922078

De novo	*Validation*									
Model	**Author, Year**	**Index Condition**	**Outcome**	**Timeframe**	**Continent**	**Sample Size**	**Number of Events**	**C-statistic**	**Calibration Reported?**	**Change in Discrimination (%)**
	Schmid, 2017[70]	TAVR	all-cause mortality	1 year	Europe	74	10	0.703	No	-34.09090909
	Schmid, 2017[70]	TAVR	all-cause mortality	2 years	Europe	74	18	0.554	No	-82.46753247
Arnold – 6 Month Model[14]	Arnold, 2016[74]	TAVR	poor outcome	6 months	North America	2830	882	0.646	Yes	-8.75
Arnold – 1 Year Model[14]	Arnold, 2016[74]	TAVR	poor outcome	1 year	North America	2325	1181	0.653	Yes	-4.375
OBSERVANT Score[15]	Collas, 2016[61]	TAVR	mortality	1 year	Europe	225	38	NR	No	NA
	Halkin, 2016[62]	TAVR	all-cause mortality	30 days	Asia	1327	45	0.63	No	-43.47826087
	Zbroński, 2016[68]	TAVR	mortality	30 days	Europe	156	15	0.597	Yes	-57.82608696
	Martin, 2017[73]	TAVR	mortality	30 days	Europe	6676	360	0.57	Yes	-69.56521739
Survival Post-TAVI (STT) – 30 days[16]	D'Ascenzo, 2014[16]	TAVR	mortality	30 days	Europe	180	13	0.66	Yes	0
	Collas, 2016[61]	TAVR	mortality	1 year	Europe	225	38	NR	No	NA
Survival Post-TAVI (STT) – 1 year[16]	D'Ascenzo, 2014[16]	TAVR	mortality	1 year	Europe	180	63	0.67	Yes	-5.555555556
TAVI2-SCORe[18]	Collas, 2016[61]	TAVR	mortality	1 year	Europe	225	38	NR	No	NA
Edwards, 2016[19]	Edwards, 2016[19]	TAVR	in-hospital mortality	until discharge	North America	6868	300	0.66	Yes	-5.882352941
Isolated or Multiple Valve										
Ambler[21]	De Bacco, 2008[75]	implantation of bovine pericardial bioprosthesis	in-hospital mortality	until discharge	South America	703	101	0.729	Yes	-15.18518519
	Dewey, 2008[76]	AVR	mortality	mean 4.2 +/- 2.7 years	North America	97	39	NR	Yes	NA
	Tran, 2010[77]	AVR	mortality	1 year	North America	394	23	0.799	Yes	10.74074074
	Laurent, 2013[43]	AVR	operative mortality	30 days	Europe	314	18	0.70	Yes	-25.92592593
	Wang, 2013[34]	valve surgery	in-hospital mortality	until discharge	Asia	3479	112	0.677	Yes	-34.44444444

De novo	*Validation*									
Model	**Author, Year**	**Index Condition**	**Outcome**	**Timeframe**	**Continent**	**Sample Size**	**Number of Events**	**C-statistic**	**Calibration Reported?**	**Change in Discrimination (%)**
	Silaschi, 2015[53]	TAVR (transfemoral or transapical)	mortality	30 days	Europe	457	44	0.52	Yes	-92.59259259
	Silva, 2015[54]	TAVR	mortality	30 days	South America	418	38	0.57	Yes	-74.07407407
	Wang, 2016[66]	valve surgery	in-hospital mortality	until discharge	Asia	12412	260	0.674	Yes	-35.55555556
	Yamaoka, 2016[67]	AVR +/- CABG	operative mortality	30 days	Asia	406	14	0.709	Yes	-22.59259259
	Zbroński, 2016[68]	TAVR	mortality	30 days	Europe	156	15	0.54	Yes	-85.18518519
Hannan, 2007[23]	Hannan, 2007[23]	isolated valve surgery	in-hospital mortality		North America	9662	504	NR	No	NA
	van Gameren, 2008[78]	isolated valve surgery	hospital mortality	hospitalization period	Europe	904	25	0.86	Yes	22.44897959
	Wang, 2013[34]	valve surgery +/- CABG	in-hospital mortality	hospitalization period	Asia	3479	112	0.682	Yes	-38.0952381
FUWAI Score[24]	Zhang, 2011[40]	valve surgery	prolonged postop ICU stay	mean LOS 79.44 +/- 59.76 hrs	Asia	1333	187	0.81	Yes	19.23076923
Aus-AVR Score[26]	Ariyaratne, 2011[26]	AVR	early postoperative mortality	30 days	Australia	3544	147	0.73	Yes	-17.85714286
	Wang, 2015[58]	AVR	operative mortality	30 days	Australia	620	18	0.716	Yes	-22.85714286
	Wang, 2015[59]	AVR	post-operative complications	14 days	Australia	620	115	0.618	Yes	-57.85714286
EuroSCORE II[27]	Barili, 2013[79]	MV surgery	in-hospital mortality	until discharge	Europe	NR	NR	0.79	No	-6.300484653
	Barili, 2013[79]	AV, MV, or TV surgery	in-hospital mortality	until discharge	Europe	NR	NR	0.8	No	-3.069466882
	Carnero-Alcazar, 2013[80]	cardiac surgery	post-operative mortality	30 days	Europe	3798	215	0.85	Yes	13.08562197
	Chalmers, 2013[81]	AVR	in-hospital mortality	until discharge	Europe	814	19	0.69	Yes	-38.61066236
	Chalmers, 2013[81]	AVR +/- CABG	in-hospital mortality	until discharge	Europe	517	23	0.74	Yes	-22.45557351
	Chalmers, 2013[81]	MV surgery	in-hospital mortality	until discharge	Europe	340	5	0.87	Yes	19.54765751

De novo	*Validation*									
Model	**Author, Year**	**Index Condition**	**Outcome**	**Timeframe**	**Continent**	**Sample Size**	**Number of Events**	**C-statistic**	**Calibration Reported?**	**Change in Discrimination (%)**
	Durand, 2013[41]	TAVR (all)	mortality	30 days	Europe	250	19	0.66	Yes	-48.30371567
	Durand, 2013[41]	TAVR (transapical)	mortality	30 days	Europe	60	7	0.52	Yes	-93.53796446
	Durand, 2013[41]	TAVR (transfemoral)	mortality	30 days	Europe	190	12	0.71	Yes	-32.14862682
	Haensig, 2013[42]	TA-AVI	in-hospital mortality	until discharge	Europe	360	38	0.51	Yes	-96.76898223
	Haensig, 2013[42]	TA-AVI	mortality	30 days	Europe	360	41	0.50	Yes	-100
	Howell, 2013[82]	valve surgery +/- CABG	in-hospital mortality	until discharge	Europe	933	90	0.67	Yes	-45.0726979
	Sedaghat, 2013[83]	TAVR (transfemoral)	mortality	30 days	Europe	206	14	0.71	Yes	-32.14862682
	Sedaghat, 2013[83]	TAVR (transfemoral)	mortality	1 year	Europe	206	56	0.70	Yes	-35.37964459
	Wang, 2013[34]	valve surgery	in-hospital mortality	until discharge	Asia	12412	260	0.693	Yes	-37.64135703
	Watanabe, 2013[35]	TAVR	mortality	30 days	Europe	453	57	0.68	Yes	-41.84168013
	Watanabe, 2013[35]	TAVR (transfemoral)	mortality	30 days	Europe	249	28	0.74	Yes	-22.45557351
	Watanabe, 2013[35]	TAVR (transfemoral approach, without early experience)	mortality	30 days	Europe	NR	NR	0.75	Yes	-19.22455574
	Watanabe, 2013[35]	TAVR (transapical/transaortic)	mortality	30 days	Europe	330	27	0.61	Yes	-64.45880452
	Zhang, 2013[84]	isolated or multiple valve surgery	in-hospital mortality	until discharge	Asia	3479	112	0.69	Yes	-40.22617124
	Zhang, 2013[84]	isolated valve surgery	in-hospital mortality	until discharge	Asia	1106	26	0.792	Yes	-5.654281099
	Zhang, 2013[84]	multiple valve surgery	in-hospital mortality	until discharge	Asia	2373	86	0.605	Yes	-66.07431341
	Barili, 2014[44]	isolated MV surgery	in-hospital mortality	until discharge	Europe	1239	NR	0.81	Yes	0.161550889

De novo	*Validation*									
Model	**Author, Year**	**Index Condition**	**Outcome**	**Timeframe**	**Continent**	**Sample Size**	**Number of Events**	**C-statistic**	**Calibration Reported?**	**Change in Discrimination (%)**
	Barili, 2014[44]	associated MV surgery	in-hospital mortality	until discharge	Europe	NR	NR	0.75	Yes	-19.22455574
	Barili, 2014[44]	MV surgery +/- CABG	in-hospital mortality	until discharge	Europe	NR	NR	0.74	Yes	-22.45557351
	Barili, 2014[85]	elective major cardiac surgery	in-hospital mortality	until discharge	Europe	12201	210	0.80	Yes	-3.069466882
	Koszta, 2014[86]	major cardiac surgery	mortality	30 days	Europe	2287	123	0.8177	Yes	2.649434572
	Osnabrugge, 2014[47]	AVR	in-hospital mortality	until discharge	North America	4107	119	0.71	Yes	-32.14862682
	Osnabrugge, 2014[47]	AVR +/- CABG	in-hospital mortality	until discharge	North America	3480	143	0.72	Yes	-28.91760905
	Osnabrugge, 2014[47]	MVRepair	in-hospital mortality	until discharge	North America	1059	13	0.82	Yes	3.392568659
	Osnabrugge, 2014[47]	MVR	in-hospital mortality	until discharge	North America	1071	59	0.78	Yes	-9.531502423
	Rabbani, 2014[48]	valve replacement surgery	mortality	30 days	Asia	576	28	0.816	Yes	2.100161551
	Rabbani, 2014[48]	MVR	mortality	30 days	Asia	247	7	0.898	Yes	28.59450727
	Rabbani, 2014[48]	AVR	mortality	30 days	Asia	137	4	0.747	Yes	-20.19386107
	Rabbani, 2014[48]	DVR	mortality	30 days	Asia	86	2	0.637	Yes	-55.73505654
	Rabbani, 2014[48]	MVR +/- CABG	mortality	30 days	Asia	57	11	0.773	Yes	-11.79321486
	Rabbani, 2014[48]	AVR +/- CABG	mortality	30 days	Asia	49	4	0.521	Yes	-93.21486268
	Spiliopoulos, 2014[87]	AVR +/- CABG	perioperative mortality	30 days	Europe	222	14	0.77	Yes	-12.76252019
	Spiliopoulos, 2014[87]	AVR +/- CABG	late mortality	beyond 30 days	Europe	202	21	0.718	Yes	-29.5638126
	Wang, 2014[88]	valve surgery	in-hospital mortality	until discharge	Asia	11170	226	0.72	Yes	-28.91760905
	Wang, 2014[88]	isolated non-CABG surgery	in-hospital mortality	until discharge	Asia	3696	NR	0.76	Yes	-15.99353796
	Wang, 2014[88]	2 procedures	in-hospital mortality	until discharge	Asia	5006	NR	0.67	Yes	-45.0726979

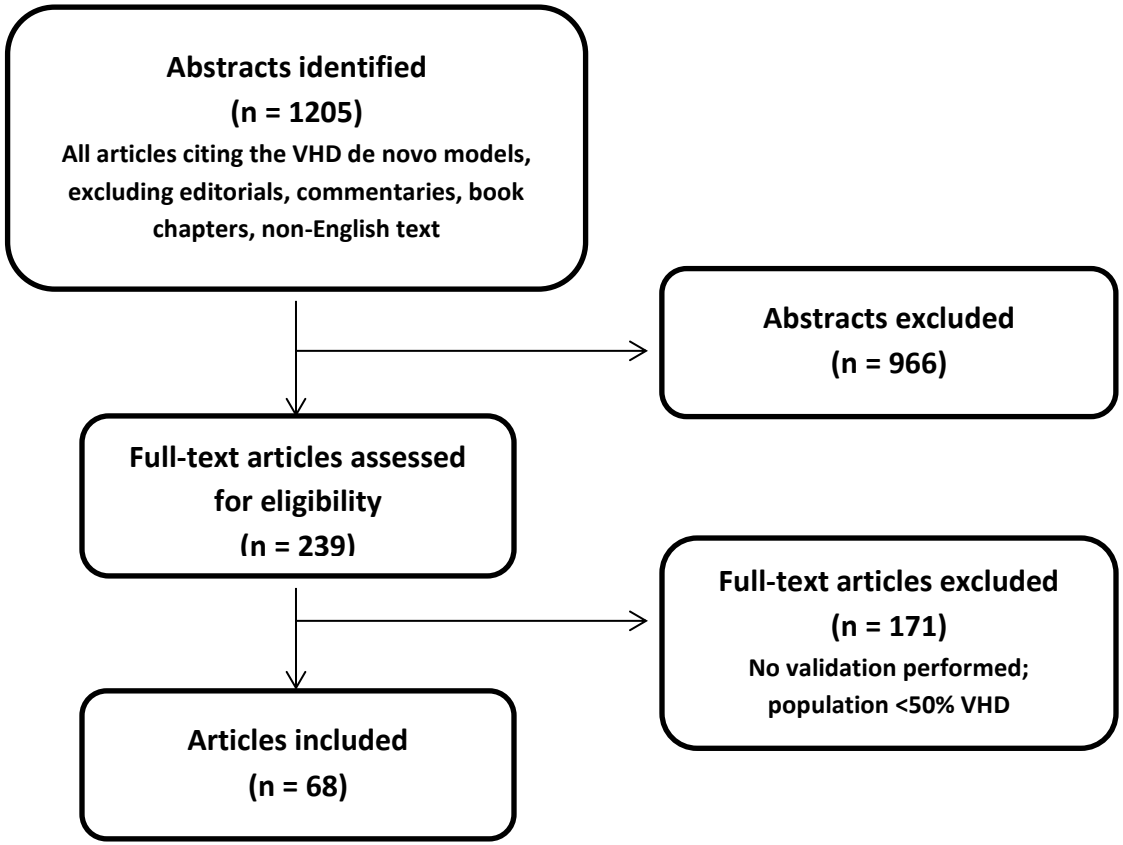
De novo	*Validation*									
Model	**Author, Year**	**Index Condition**	**Outcome**	**Timeframe**	**Continent**	**Sample Size**	**Number of Events**	**C-statistic**	**Calibration Reported?**	**Change in Discrimination (%)**
	Wang, 2014[88]	3+ procedures	in-hospital mortality	until discharge	Asia	2468	NR	0.73	Yes	-25.68659128
	Wendt, 2014[49]	AVR or TAVR	mortality	30 days	Europe	1512	95	0.712	Yes	-31.50242326
	Wendt, 2014[49]	TAVR (transfemoral)	mortality	30 days	Europe	291	34	0.554	Yes	-82.55250404
	Wendt, 2014[49]	TAVR (transapical)	mortality	30 days	Europe	155	12	0.837	Yes	8.885298869
	Debonnaire, 2015[18]	TAVR	all-cause mortality	1 year	Europe	471	80	0.633	Yes	-57.02746365
	Holinski, 2015[52]	repeat AVR	mortality	30 days	Europe	78	8	0.86	Yes	16.31663974
	Moscarelli, 2015[89]	minimally invasive MV surgery +/- TVR	in-hospital mortality	until discharge	Europe	1609	28	0.846	Yes	11.79321486
	Poullis, 2015[90]	AVR	in-hospital mortality	until discharge	Europe	814	NR	NR	Yes	NA
	Poullis, 2015[90]	MVR	in-hospital mortality	until discharge	Europe	340	NR	NR	Yes	NA
	Poullis, 2015[90]	AVR +/- CABG	in-hospital mortality	until discharge	Europe	517	NR	NR	Yes	NA
	Silaschi, 2015[53]	TAVR (transfemoral or transapical)	mortality	30 days	Europe	457	44	0.54	Yes	-87.07592892
	Silva, 2015[54]	TAVR	mortality	30 days	South America	418	38	0.54	Yes	-87.07592892
	Tralhao, 2015[56]	AVR	operative mortality	30 days	Europe	106	6	0.792	Yes	-5.654281099
	Wang, 2015[58]	AVR	operative mortality	30 days	Australia	620	18	0.711	Yes	-31.82552504
	Wang, 2015[59]	AVR	morbidity/mortality	30 days	Australia	620	115	0.649	Yes	-51.85783522
	Halkin, 2016[62]	TAVR	all-cause mortality	30 days	Asia	1327	45	0.70	No	-35.37964459
	Kortlandt, 2016[63]	MVR	periprocedural mortality	30 days	Europe	136	5	0.54	Yes	-87.07592892
	Patrat-Delon, 2016[91]	cardiac surgery for acute	in-hospital mortality	until discharge	Europe	149	32	0.78	Yes	-9.531502423

De novo	*Validation*									
Model	**Author, Year**	**Index Condition**	**Outcome**	**Timeframe**	**Continent**	**Sample Size**	**Number of Events**	**C-statistic**	**Calibration Reported?**	**Change in Discrimination (%)**
		infective endocarditis								
	Rosa, 2016[65]	TAVR	mortality	30 days	South America	59	8	0.77	Yes	-12.76252019
	Wang, 2016[36]	AVR/CABG	operative mortality	30 days	Australia	450	29	0.669	Yes	-45.39579968
	Wang, 2016[66]	valve surgery	in-hospital mortality	until discharge	Asia	12412	260	0.704	Yes	-34.08723748
	Yamaoka, 2016[67]	AVR +/- CABG	operative mortality	30 days	Asia	406	14	0.704	Yes	-34.08723748
	Allyn, 2017[92]	elective cardiac surgery with CPB	post-operative mortality	until discharge	Europe	6520	411	0.737	No	-23.42487884
	Bomberg, 2017[93]	cardiac surgery	mortality	30 days	Europe	856	27	0.74	No	-22.45557351
	Bomberg, 2017[93]	cardiac surgery	mortality	6 months	Europe	809	49	0.76	No	-15.99353796
	Bomberg, 2017[93]	cardiac surgery	mortality	2 years	Europe	809	84	0.74	No	-22.45557351
	Kalender, 2017[72]	AVR	mortality	until discharge	Asia	35	6	0.603	Yes	-66.72051696
	Kar, 2017[94]	valve surgery +/- CABG	mortality	until discharge	Asia	911	52	0.76	Yes	-15.99353796
	Kar, 2017[94]	valve surgery	mortality	until discharge	Asia	427	18	0.83	Yes	6.62358643
	Kar, 2017[94]	valve surgery +/- CABG	mortality	until discharge	Asia	49	5	0.78	Yes	-9.531502423
	Mateos-Pañero, 2017[95]	valve surgery +/- CABG	mortality	until discharge	Europe	866	53	0.861	Yes	16.63974152
	Mateos-Pañero, 2017[95]	valve surgery	mortality	until discharge	Europe	427	NR	0.767	Yes	-13.73182553
	Mateos-Pañero, 2017[95]	valve surgery +/- CABG	mortality	until discharge	Europe	119	NR	0.954	Yes	46.68820679
	Schmid, 2017[70]	TAVR	all-cause mortality	1 year	Europe	74	10	0.669	No	-45.39579968
	Schmid, 2017[70]	TAVR	all-cause mortality	2 years	Europe	74	18	0.552	No	-83.19870759
	Wang, 2017[37]	MVR or MVRepair	operative mortality	30 days	Australia	407	10	0.817	Yes	2.423263328

De novo	*Validation*									
Model	**Author, Year**	**Index Condition**	**Outcome**	**Timeframe**	**Continent**	**Sample Size**	**Number of Events**	**C-statistic**	**Calibration Reported?**	**Change in Discrimination (%)**
NY Operative Mortality Risk Score[28]	Hannan, 2013[28]	isolated valve surgery	in-hospital/30-day mortality	30 days	North America	12354	NR	NR	No	NA
	Jin, 2013[96]	isolated valve surgery	in-hospital/30-day mortality	30 days	Europe	4021	105	0.777	Yes	-1.423487544
	Wang, 2016[66]	isolated valve surgery	in-hospital mortality	hospitalization period	Asia	5152	84	0.683	Yes	-34.87544484
Multiple Valve										
AM Preop[31]	Rankin, 2013[31]	AV + MV surgery	operative mortality	30 days	North America	NR	NR	0.71	Yes	NA
MT Preop[31]	Rankin, 2013[31]	AV + MV surgery	operative mortality	30 days	North America	NR	NR	0.722	Yes	NA
AMT Preop[31]	Rankin, 2013[31]	AV + MV surgery	operative mortality	30 days	North America	NR	NR	0.702	Yes	NA
AM Preop + Intraop[31]	Rankin, 2013[31]	AV + MV surgery	operative mortality	30 days	North America	NR	NR	0.714	Yes	NA
MT Preop + Intraop[31]	Rankin, 2013[31]	AV + MV surgery	operative mortality	30 days	North America	NR	NR	0.727	Yes	NA
AMT Preop + Intraop[31]	Rankin, 2013[31]	AV + MV surgery	operative mortality	30 days	North America	NR	NR	0.706	Yes	NA

* 'Isolated Valve' indicates a single valve procedure; 'Multiple Valve' indicates intervention to > 1 valve; AVR indicates aortic valve surgery (repair or replacement); HL, Hosmer-Lemeshow; MVR, mitral valve surgery (repair or replacement); NR, not reported; NA, not applicable; CABG, coronary artery bypass grafting; TAVR, transcatheter aortic valve replacement; TA-AVI, transapical aortic valve implantation; AEs, adverse events; TVR, tricuspid valve surgery (repair or replacement); DVR, double valve surgery (repair or replacement); MACE, major adverse cardiovascular events.

Figure S1. Literature Search Overview.



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