ORIGINAL RESEARCH

International Validation of the Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention in Post-MI Patients: A Collaborative Analysis of the Chronic Kidney Disease Prognosis Consortium and the Risk Validation Scientific Committee

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***Background*—**The Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRS2°P), a 0-to-9-point system based on the presence/absence of 9 clinical factors, was developed to classify the risk of major adverse cardiovascular events (MACE) (a composite of cardiovascular death, recurrent myocardial infarction, or ischemic stroke) among patients with a recent myocardial infarction. Its performance has not been examined internationally outside of a clinical trial setting.

***Methods and Results*—**We evaluated the performance of TRS2°P for predicting MACE in 53 599 patients with recent myocardial infarction in 5 international cohorts from New Zealand, South Korea, Sweden, and the United States participating in the Chronic Kidney Disease Prognosis Consortium. Overall, there were 19 444 cases of MACE across 5 cohorts over a mean follow-up of 5 years, and the overall MACE rate ranged from 5.0 to 18.4 (per 100 person-years). The TRS2°P showed modest calibration (Brier score ranged from 0.144 to 0.173) and discrimination (C-statistics >0.61 in all studies except 1 from Korea with 0.55) across cohorts relative to its original Brier score of 0.098 and C-statistic of 0.67 in the derived data set. Although there was some heterogeneity across cohorts, the 9 predictors in the TRS2°P were generally associated with higher MACE risk, with strongest associations observed (meta-analyzed adjusted hazard ratio 1.6–1.7) for history of heart failure, age ≥75 years, and prior stroke, followed by peripheral artery disease, kidney dysfunction, diabetes mellitus, and hypertension (hazard ratio 1.3–1.4). Prior coronary bypass graft surgery and smoking did not reach statistical significance (hazard ratio ≈1.1).

***Conclusions*—**TRS2°P, a simple scoring system with 9 routine clinical factors, was modestly predictive of secondary events when applied in patients with recent myocardial infarction from diverse clinical and geographic settings. **(*J Am Heart Assoc*. 2018;7: e008426. DOI: 10.1161/JAHA.117.008426.)**

Key Words: myocardial infarction • secondary prevention • validation

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Accompanying Data S1 through S3, Table S1, and Figures S1 through S6 are available at http://jaha.ahajournals.org/content/7/14/e008426/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- The Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention, a simple scoring system with 9 routine clinical factors predicting adverse outcome after recent myocardial infarction, is modestly predictive in international settings with different demographic and clinical characteristics.

What Are the Clinical Implications?

- The Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention is useful to estimate the risk of secondary events among patients with a recent myocardial infarction in a broad range of clinical settings.
- Given its simple scoring system with routinely collected variables, the Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention will help healthcare providers easily acknowledge the risk of patients based on patients' clinical conditions and guide risk-centered management in patients with recent myocardial infarction.

Patients with recent myocardial infarction (MI) are generally at high risk of subsequent adverse events.[1–5] Of importance, a large risk variation is recognized among patients with MI depending on demographics, comorbidities, and severity of MI.[6,7] Risk stratification is important because it may influence the selection of secondary preventive therapy, such as intensive antiplatelet therapy where benefit may only outweigh harm in higher risk patients but not among lower risk ones.[8–10] In this context, the Thrombolysis in Myocardial Infarction (TIMI) Study Group recently developed a simple scoring system, the TIMI Risk Score for Secondary Prevention (TRS2°P).[10] This risk stratification tool is for classifying the risk of secondary outcomes among patients with recent MI, using 9 clinical and behavioral factors readily available in clinical practice. TRS2°P has been recently validated outside of a clinical trial setting in 2 US regional healthcare systems[11] but not in other countries or regions. External validation and replication in diverse real-world settings should be requisite for implementation of the algorithm in clinical practice. Therefore, we examined the performance of TRS2°P for predicting major adverse cardiovascular events (MACEs) after recent MI in 5 cohorts (from New Zealand, South Korea, Sweden, and the United States) participating in an international consortium, the Chronic Kidney Disease Prognosis Consortium (CKD-PC). To identify potential explanations for varying performance of TRS2°P across those 5 cohorts, we quantified the associations of each predictor with MACEs as well.

Methods

Because of the data use agreement with participating cohorts of the CKD-PC, the study data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. However, it is possible to obtain ARIC (Atherosclerosis Risk in Communities Study) data from the National Heart, Lung, and Blood Institute BioLINCC repository.[12]

Study Design and Participants

This study was performed as an ancillary study of CKD-PC. CKD-PC currently consists of >11 million participants from >70 cohorts with detailed clinical and outcome data (eg, mortality and end-stage renal disease) from >40 countries.[13,14] For this specific study, based on data collected as part of the CKD-PC, we identified 5 studies with ≥1000 MI cases during follow-up that could be linked to data on the 9 predictors of TRS2°P. These 5 studies included the ARIC and the RCAV (Racial and Cardiovascular Risk Anomalies in CKD Cohort) from the United States, the SCREAM (Stockholm Creatinine Measurements Cohort) from Sweden, the KHS (Korean Heart Study) from South Korea, and the NZDCS (New Zealand Diabetes Cohort Study) from New Zealand. A total of 53 599 patients with recent acute MI who survived at least 2 weeks from index date of MI were included in this study, to be in line with inclusion criteria of the derived study population of TRA2°P (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Event)-TIMI50.[10] Details of the study design and the approach for identifying recent MI cases in each cohort are summarized in Data S1 and S2. This study was approved as not human subject research by the institutional Review Board at the Johns Hopkins Bloomberg School of Public Health because of its nature of pre-existing deidentified secondary data analysis.

Nine Predictors Used in TRS2°P

The following 9 predictors in TRS2°P were identified in each of the 5 studies (Data S1): heart failure (yes versus no), hypertension (yes versus no), age (≥ versus <75 years), diabetes mellitus (yes versus no), prior stroke (yes versus no), prior coronary artery bypass grafting (CABG) (yes versus no), peripheral artery disease (yes versus no), reduced kidney function (estimated glomerular filtration rate < versus ≥60 mL/min per 1.73 m^2), and current smoking (yes versus no).[10] We calculated estimated glomerular filtration rate using the creatinine equation from the Chronic Kidney Disease Epidemiology Collaboration.[15] Based on the presence and absence of these 9 predictors, TRS2°P ranged from 0 to 9.

Outcomes

The primary outcome of interest was MACE, defined by a composite of cardiovascular death, recurrent MI, or ischemic

stroke.[10] Cardiovascular death was defined as death caused by MI, heart failure, stroke, or sudden cardiac death as the primary cause. All-cause death was investigated in RCAV since cause of death was not available. Patients were followed until date of MACE, death, or the end of follow-up, whichever came first.

Statistical Analysis

Baseline characteristics of individuals with recent MI in each study were summarized as mean and SD or median and interquartile range for continuous variables and percentage for categorical variables. Subsequently, we determined prediction statistics in a 3-year time frame with fine categories of TRS2°P 0, 1, 2, 3, 4, 5, 6, and ≥7 as carried out in its derived data set.[10] As a measure of discrimination, we estimated Harrell's C-statistic.[16] For calibration, we plotted predicted risk based on TRS2°P against observed risk in each study and calculated a modified Hosmer-Lemeshow χ^2 statistic.[17] We also calculated the Brier score,[18] the average squared deviation between predicted by TRS2°P and observed event rates (a lower score represents better calibration). Observed risk was estimated using the Kaplan–Meier method in each study.

Since we observed suboptimal calibration in several cohorts as presented subsequently, we tried to recalibrate using 2 methods: applying the risk difference between observed versus predicted in the most prevalent score category in each cohort to the predicted risk of every patient (Recalibration 1) and applying the weighted mean risk difference between observed versus predicted risk across score categories in each cohort to the predicted risk of every patient (Recalibration 2).

In RCAV without data on cause of mortality, the Harrell's C-statistic and Brier score, which require individual-level outcome information, were based on the combination of all-cause mortality, recurrent MI, or ischemic stroke. However, where individual data were not required, the Hosmer–Lemeshow χ^2 statistic was based on 2 scenarios of cardiovascular death accounting for 50% and 41% of all-cause death based on the distributions observed in the other 4 cohorts. In 2 cohorts without data on smoking (RCAV and SCREAM), we simulated the 3-year risk in smokers and nonsmokers based on reported prevalence and relative risk of smoking. Details of this hypothetical estimation are summarized in Figure S1.

To examine variation in discrimination of TRS2°P across the 5 cohorts, we first quantified the independent association of the 9 predictors with the risk of MACE. We used Cox proportional hazards models as done in the original study that developed TRS2°P.[10] Pooled hazard ratios and 95% confidence intervals (CIs) were estimated using a random-effects meta-analysis. Heterogeneity was evaluated by the χ^2 test and the I^2 statistic.

For sensitivity analyses, we repeated analyses by stratifying the study sample by sex and race. For race, according to availability and diversity of racial groups, we only analyzed whites and blacks in 2 US cohorts (ARIC and RCAV).

All analyses were conducted with the use of Stata software, version 14.2, and a P value of <0.05 was deemed statistically significant.

Results

Baseline Characteristics

Baseline characteristics of a total of 53 599 patients with recent MI in each study are shown in Table 1. The median age of patients with MI ranged from 61 to 72 years across the 5 studies. About 40% were women in ARIC, SCREAM, and NZDCS, whereas RCAV and KHS had lower proportions of women (2% and 19%, respectively). Whites made up the majority among racial groups in all studies except KHS, which included 100% Asians. There were 26% of patients with black race in ARIC and 15% in RCAV. The prevalence of heart failure was lowest in KHS (2%). The prevalence of history of CABG was ≈10% in ARIC, RCAV, and NZDCS, but 2% to 3% in SCREAM and KHS. The prevalence of peripheral artery disease was strikingly high in RCAV (51% versus ≤13% in the other cohorts). The prevalence of smoking was highest in KHS (50%).

The distribution of TRS2°P risk scores among patients with MI in each cohort is shown in Figure 1. In the 3 studies with all 9 predictors available, the most prevalent score was 2 in ARIC and KHS but 3 in NZDCS, which by design only enrolled individuals with diabetes mellitus. In SCREAM without data on smoking status, the score 0 to 1 was most prevalent. Despite the same level of missing data on smoking status, the most prevalent score was 3 to 4 in RCAV. The prevalence of high-risk category with TRS2°P ≥3[10] was the highest in NZDCS (67%), followed by RCAV (52%), ARIC (40%), and KHS (28%), and SCREAM (19%).

Descriptive Statistics of MACE

There were 19 444 cases of MACE across 5 studies over a median follow-up of 1 to 5 years (Table 2). The proportion of censoring varied from 0% in NZDCS to ≈24% in KHS. In terms of the pattern of individual cardiovascular outcomes, recurrent MI was consistently more common than ischemic stroke in all studies, although the degree of difference varied substantially across the studies. The crude incidence rates of cardiovascular death and recurrent MI were similar in ARIC and SCREAM. The crude incidence rate of recurrent MI was

Table 1. Basic Characteristics of Included Studies

	ARIC	RCAV	SCREAM	KHS	NZDCS	TRA2°P-TIMI50*
Cohort characteristics						
Region	US	US	Sweden	South Korea	New Zealand	32 countries in Europe, America, Africa, Asia, and Oceania
Database	Community-based	EMR-based	EMR-based	Health check-up data	EMR-base for diabetes mellitus	Clinical trial
MI cases	1711	9090	38 171	2912	1715	8598
Median follow-up, y†	5.2	0.8	3.9	3.4	4.8	2.5
Calendar year	1987–2013	2006–2013	1996–2012	2004–2013	2000–2007	2007–2009
Demographics						
Age, y	68 (62, 74)	64 (60, 72)	61 (51, 71)	61 (53, 68)	72 (62, 79)	59 (51, 66)
Female	41%	2%	38%	19%	40%	20%
Race						
White	74%	81%	100%	0%	65%	88%
Black	26%	15%	0%	0%	0%	NA
Asian	0.2%	0.2%	0%	100%	6%	NA
Others	0%	4%	0%	0%	29%	NA
TRS2°P predictors						
Heart failure	17%	43%	26%	2%	5%	9%
Hypertension	75%	94%	44%	75%	93%	63%
Age (75 y+)	23%	19%	15%	22%	40%	8%
Diabetes mellitus	39%	61%	19%	31%	100%	22%
Stroke	8%	11%	9%	8%	2%	3%
CABG	10%	9%	2%	3%	7%	14%
Peripheral artery disease	11%	51%	6%	3%	13%	13%
Kidney dysfunction‡	33%	39%	15%	6%	28%	12%
Current smoking	11%	NA	NA	50%	16%	20%

Continuous variable presented as median (interquartile range). ARIC indicates Atherosclerosis Risk in Communities; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; EMR, electronic medical record; *ICD*, *International Classification of Diseases*; KHS, Korean Heart Study; MI, myocardial infarction; NA, not available; NZDCS, New Zealand Diabetes Cohort Study; RCAV, Racial and Cardiovascular Risk Anomalies in CKD Cohort; SCREAM, Stockholm Creatinine Measurements Cohort; TRA2°P-TIMI50, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Event-TIMI 50.

*Basic characteristics were derived from TRA2°P-TIMI 50 study that has been reported.[10] Races other than White are not available.

†Follow-up after incident MI.

‡Kidney dysfunction: eGFR <60 mL/min per 1.73 m^2 or chronic kidney disease based on *ICD* codes.

much higher in RCAV compared with other cohorts (10.5 versus ≤4.0 incidence rate per 100 person-years). As noted, cardiovascular deaths accounted for 41% to 50% of all deaths in the 4 studies with available data.

Prediction Statistics

Figure 2 contrasts predicted risk based on fine categories of TRS2°P and observed risk in each study. Overall, patients with higher predicted risk of MACE tended to have higher observed risk in all studies, indicating reasonable risk discrimination. The C-statistic was highest in SCREAM (0.685 [95% CI 0.679–0.691]), followed by RCAV (0.631 [0.622–0.639]), NZDCS (0.614 [0.586–0.643]), and ARIC (0.612 [0.584–0.640]). The C-statistic was lowest in KHS (0.545 [0.519–571]). The C-statistics in SCREAM and RCAV were comparable with the original C-statistic in the TRS2°P derived data set of 0.67.[10]

In terms of calibration, predicted risk by TRS2°P tended to be lower than the observed risk of MACE (ie, underestimation) consistently in all 5 cohorts, with particularly evident difference in SCREAM (Figure 2). Hosmer-Lemeshow χ^2 indicated a significant difference between the predicted and observed risks in every study (P<0.001). For RCAV, the alternative assumption of 41% of all-cause death from cardiovascular causes demonstrated similar patterns (Figure S1). For KHS,

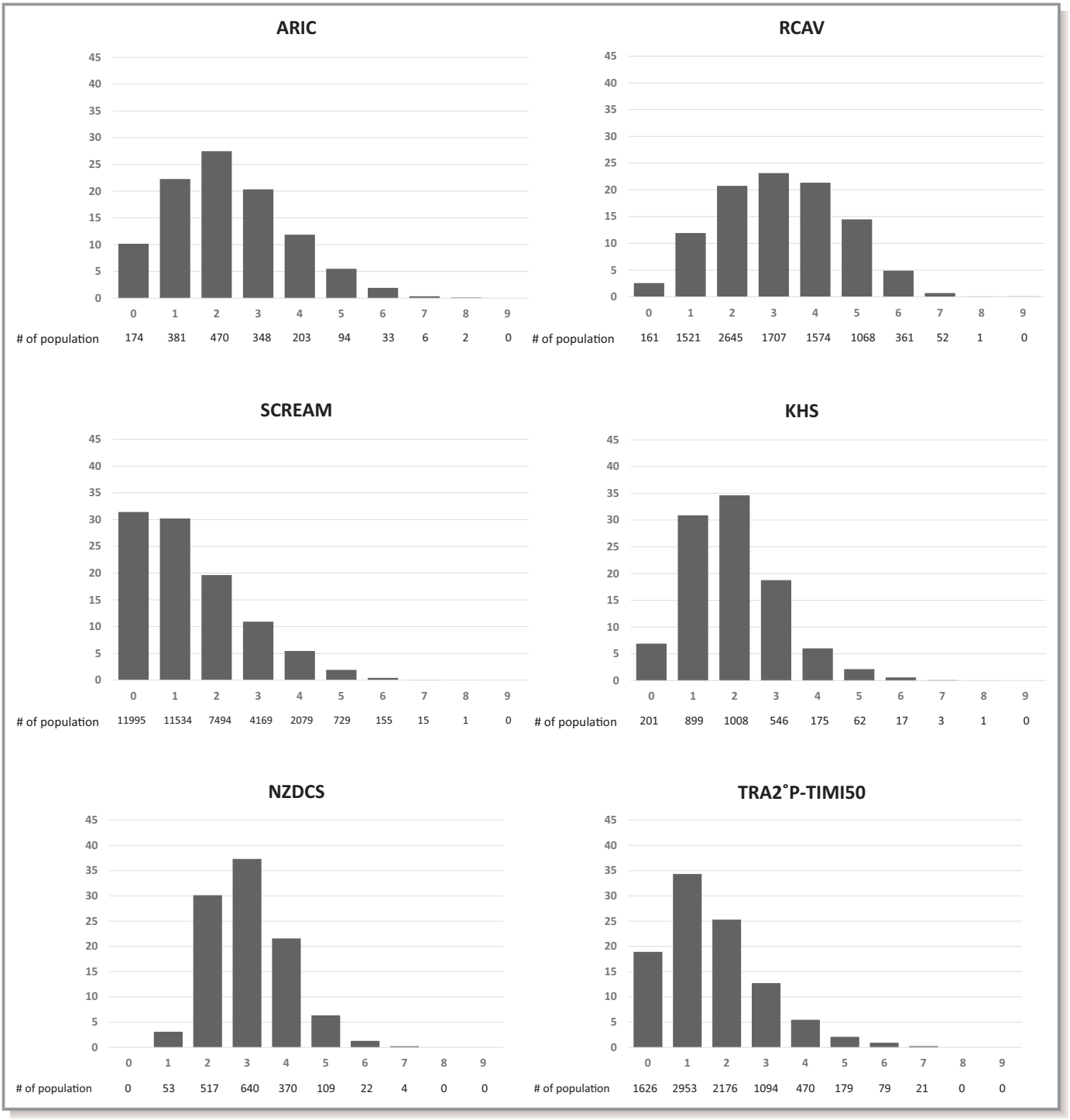

Figure 1. Distribution (%) of the TRS2°P risk score in the 5 cohorts. RCAV and SCREAM do not have smoking data. ARIC indicates Atherosclerosis Risk in Communities Study; KHS, Korean Heart Study; NZDCS, New Zealand Diabetes Cohort Study; RCAV, Racial and Cardiovascular Risk Anomalies in CKD Cohort; SCREAM, Stockholm Creatinine Measurements Cohort; TRA2°P-TIMI50, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Event-TIMI50.

the difference between the predicted and observed risks were evident at the score <3 and ≥6. The Brier score, which is an overall performance measure, was 0.144 to 0.173 across 5 studies, while the original Brier score for TRS2°P in its derived data set was 0.098.[10] Both recalibration approaches substantially improved the calibration of TRS2°P in most cohorts (Figure S2), with calibration χ^2 statistics <50 in ARIC, RCAV, KHS, and NZDCS.

When we analyzed men and women separately, we observed largely similar results for both sexes within each

Table 2. Number of Cardiovascular Outcomes and Follow-Up Time

	ARIC (N=1711)	RCAV (N=9090)	SCREAM (N=38 171)	KHS (N=2912)	NZDCS (N=1715)
MACE*					
Cases	762	4853	12 702	586	541
Follow-up, y	5.2 (1.4, 11.0)	0.8 (0.3, 3.4)	3.9 (1.3, 7.5)	3.4 (0.9, 6.6)	4.8 (1.5, 7.9)
Crude IR (per 100 PYs)	6.5	18.4	6.9	5.0	6.5
Cumulative incidence at 3 y	23.1%	43.1%	22.2%	18.9%	21.0%
Censoring other than deaths within 3 y	7.1%	15.5%	15.1%	24.4%	0%
Cardiovascular death					
Cases	433	NA	6142	134	198
Follow-up, y	7.6 (2.7, 13.6)	NA	5.1 (2.2, 8.8)	4.5 (1.7, 7.3)	6.3 (2.2, 8.4)
Crude IR (per 100 PYs)	2.9	NA	2.8	1.0	2.1
Cumulative incidence at 3 y	10.1%	NA	8.3%	3.4%	8.0%
Recurrent MI					
Cases	442	2794	6991	468	292
Follow-up, y	5.7 (1.6, 11.4)	0.9 (0.0, 3.5)	4.2 (1.5, 7.9)	3.4 (0.9, 6.6)	5.2 (1.7, 8.0)
Crude IR (per 100 PYs)	3.6	10.5	3.6	4.0	3.4
Cumulative incidence at 3 y	14.3%	28.5%	13.4%	16.3%	10.7%
Ischemic stroke					
Cases	149	282	3482	33	154
Follow-up, y	6.8 (2.2, 12.7)	2.7 (0.8, 5.0)	4.8 (1.9, 8.4)	4.5 (1.7, 7.3)	5.8 (2.0, 8.3)
Crude IR (per 100 PYs)	1.1	0.9	1.7	0.2	1.7
Cumulative incidence at 3 y	4.3%	2.4%	5.5%	0.6%	5.7%
All-cause death					
Cases	974	3128	15 123	320	1029
Follow-up, y	7.6 (2.7, 13.6)	2.8 (0.9, 5.2)	5.1 (2.2, 8.8)	4.5 (1.7, 7.3)	6.3 (2.2, 8.4)
Crude IR (per 100 PYs)	6.6	9.3	6.9	2.3	11.0
Cumulative incidence at 3 y	20.2%	23.8%	17.4%	8.0%	31.1%

Follow-up presented as median (interquartile range). ARIC indicates Atherosclerosis Risk in Communities; IR, incidence rate; KHS, Korean Heart Study; MACE, major adverse cardiovascular event; MI, myocardial infarction; NA, not available; NZDCS, New Zealand Diabetes Cohort Study; PYs, person-years; RCAV, Racial and Cardiovascular Risk Anomalies in CKD Cohort; SCREAM, Stockholm Creatinine Measurements Cohort; TRA2°P-TIMI50, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Event-TIMI50.
*MACE was defined as cardiovascular death, recurrent MI, and ischemic stroke. RCAV does not have cardiovascular death data, so all-cause death is reflected.

cohort (Figure S3). For racial groups in 2 US cohorts, risk discrimination was similar in whites and blacks in both cohorts (Figure S4). For calibration, the difference between observed versus predicted risk appeared greater in blacks than whites in ARIC (Brier score 0.231 versus 0.147). However, such a racial difference was not observed in RCAV.

When we simulated current smoking status in SCREAM and RCAV under the assumption of current smoking prevalence rates of 29% for SCREAM[19] and 45% for RCAV[20] and a hazard ratio of 1.47,[10] the calibration plots were similar to the primary analysis (which did not account for smoking status) except for the score ≥7 in SCREAM (Figure S5). The variation of these assumptions influenced estimated risk by not >10% in general (Table S1).

Figure 3 shows 3-year risk estimates of MACE by the broader categories of TRS2°P corresponding to low, intermediate, and high risk (0, 1–2, and ≥3, respectively) proposed in the original TRS2°P article.[10] In every cohort, overall, higher TRS2°P (particularly ≥3) was consistently associated with higher risk of MACE, with risk gradient of 3- to 5-fold between low- and high-risk categories in ARIC, RCAV, and SCREAM. NZDCS demonstrated a 2-fold risk gradient between high versus intermediate risk, which is similar to the aforementioned 3 studies. KHS demonstrated the least separation of risk among the 3 risk categories based on TRS2°P.

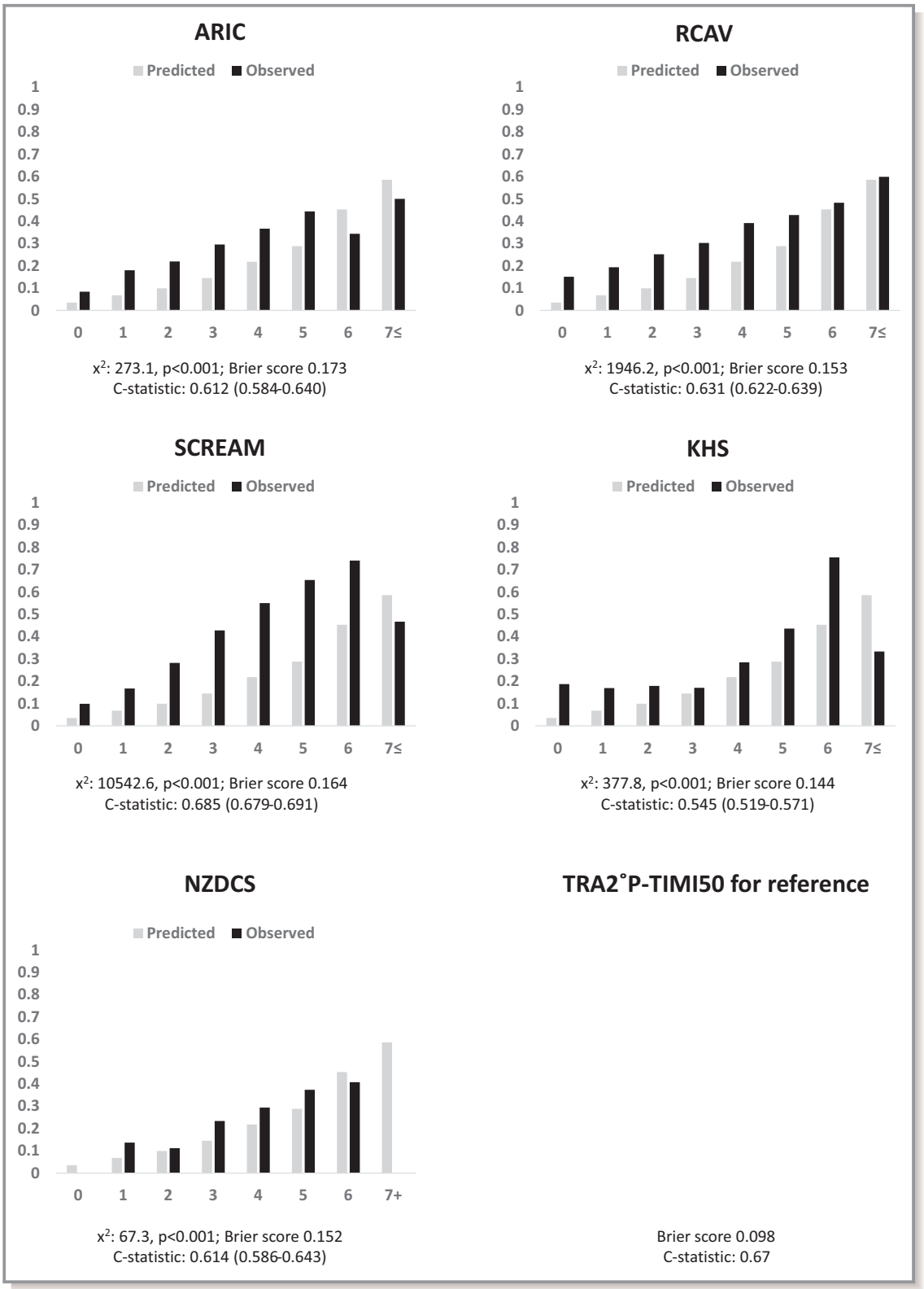

Figure 2. Three-year probability of major adverse cardiovascular event (MACE) by the TRS2°P. For RCAV, cardiovascular death was assumed to be 50% of all-cause death because of lack of information on cardiovascular death, but the C-statistic is not reflected. All NZDCS participants had a diagnosis of diabetes mellitus according to their primary care provider. The 9 risk predictors are heart failure, hypertension, age (≥75 y), diabetes mellitus, stroke, coronary bypass graft surgery, peripheral artery disease, kidney dysfunction, and smoking. ARIC indicates Atherosclerosis Risk in Communities Study; KHS, Korean Heart Study; NZDCS, New Zealand Diabetes Cohort Study; RCAV, Racial and Cardiovascular Risk Anomalies in CKD Cohort; SCREAM, Stockholm Creatinine Measurements Cohort; TRA2°P-TIMI50, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Event-TIMI50.

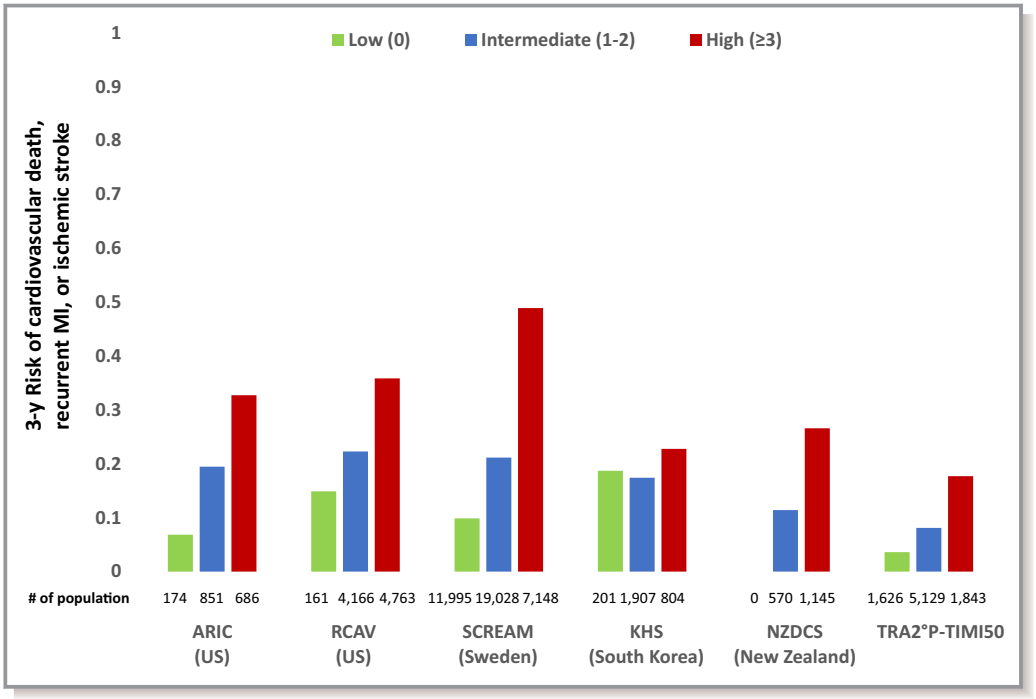

Figure 3. Three-year risk for major adverse cardiovascular event (MACE) by categories based on TRS2°P (0 point=low 1–2=intermediate ≥3=high). For RCAV, cardiovascular death was assumed to be 50% of all-cause death because of lack of information on cardiovascular death. The NZDCS cohort participants all have diabetes mellitus and thus none are considered low risk. The 9 risk predictors are heart failure, hypertension, age (≥75 y), diabetes mellitus, stroke, coronary bypass graft surgery, peripheral artery disease, kidney dysfunction, and smoking. ARIC indicates Atherosclerosis Risk in Communities Study; MI, myocardial infarction; KHS, Korean Heart Study; NZDCS, New Zealand Diabetes Cohort Study; RCAV, Racial and Cardiovascular Risk Anomalies in CKD Cohort; SCREAM, Stockholm Creatinine Measurements Cohort; TRA2°P-TIMI50, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Event-TIMI50.

Relative Risk of MACE for Individual Predictors Across 5 Studies

When we looked at the hazard ratio of MACE for each of the 9 predictors, age ≥75 years was the only risk factor significantly associated with MACE in every cohort, with the highest meta-analyzed hazard ratio of 1.68 (95% CI, 1.25–2.26) (Table 3). History of heart failure and stroke showed similar meta-analyzed hazard ratios (1.67 [1.50–1.85] and 1.62 [1.36–1.92], respectively), although they did not reach statistical significance in NZDCS. Peripheral artery disease, hypertension, diabetes mellitus, and kidney dysfunction had significant associations, with slightly smaller meta-analyzed hazard ratios of 1.3 to 1.4 compared with the aforementioned 3 potent risk factors. Prior CABG demonstrated significantly positive associations with MACE in ARIC, SCREAM, and NZDCS, but its meta-analyzed hazard ratios were ≈1.1 and did not reach statistical significance. Current smoking was not significantly associated with MACE in any of the 3 studies with available data. I^2 statistic indicated high heterogeneity for age, stroke, CABG, kidney dysfunction, and current smoking, but a majority of cohorts demonstrated qualitatively consistent associations even for these risk factors (Figure S6).

Discussion

We evaluated the predictive performance of TRS2°P, a simple scoring system with 9 routine clinical factors predicting 3-year prognosis after recent MI, in 5 cohorts outside of a clinical trial setting from 4 countries with different demographic and clinical characteristics, and subsequently different adverse outcome event rates. Our cohorts tended to have higher scores than the original TRA2°P–TIMI50 population.[10] Despite these demographic and clinical variations, we confirmed that higher TRS2°P was consistently associated with higher risk of MACE, indicating reasonable risk discrimination, with C-statistics ranging from 0.60 to 0.69 in most studies, which are comparable with those originally reported in the derivation data set of TRS2°P. Although we recognized a few caveats of underestimation of absolute risk of MACE by TRS2°P in all 5 cohorts and suboptimal discrimination in a South Korean study, TRS2°P demonstrated decent risk prediction among

Table 3. Multivariable Risk Stratification Model for MACE

9 Predictors	ARIC (N=1711) HR (95% CI)	RCAV* (N=9090) HR (95% CI)	SCREAM (N=38 171) HR (95% CI)	KHS (N=2912) HR (95% CI)	NZDCS† (N=1715) HR (95% CI)	Pooled‡ (N=53 599) HR (95% CI)
Heart failure	1.94 (1.62–2.33)§	1.51 (1.38–1.66)§	1.73 (1.67–1.80)§	1.71 (1.09–2.70)§	1.29 (0.86–1.95)	1.67 (1.50–1.85)§
Hypertension	1.30 (1.09–1.54)§	1.23 (1.06–1.43)§	1.25 (1.21–1.30)§	1.13 (0.92–1.38)	1.18 (0.81–1.70)	1.25 (1.21–1.29)§
Age (≥75 y)	1.32 (1.08–1.62)§	1.41 (1.28–1.56)§	2.40 (2.29–2.51)§	1.44 (1.18–1.76)§	1.99 (1.67–2.38)§	1.68 (1.25–2.26)§
Diabetes mellitus	1.54 (1.33–1.79)§	1.26 (1.17–1.37)§	1.28 (1.23–1.34)§	1.09 (0.91–1.30)	…	1.29 (1.19–1.40)§
Stroke	1.69 (1.32–2.16)§	1.42 (1.25–1.62)§	1.86 (1.76–1.96)§	1.72 (1.34–2.21)§	0.69 (0.29–1.67)	1.62 (1.36–1.92)§
CABG	1.42 (1.14–1.78)§	0.87 (0.80–0.95)	1.14 (1.02–1.27)§	0.86 (0.51–1.44)	1.56 (1.17–2.10)§	1.15 (0.92–1.43)
Peripheral artery disease	1.34 (1.08–1.67)§	1.34 (1.24–1.46)§	1.55 (1.46–1.65)§	1.34 (0.88–2.05)	1.34 (1.04–1.71)§	1.42 (1.29–1.56)§
Kidney dysfunction	0.90 (0.77–1.06)	1.34 (1.24–1.46)§	1.71 (1.63–1.80)§	1.26 (0.92–1.74)	1.47 (1.22–1.77)§	1.32 (1.06–1.64)§
Current smoking‖	0.91 (0.73–1.14)	NA	NA	1.14 (0.96–1.35)	1.03 (0.81–1.32)	1.04 (0.91–1.19)

All predictors listed in table were included in a Cox proportional hazards model estimating the association between TRS2°P components and composite cardiovascular death, myocardial infarction, or ischemic stroke. ARIC indicates Atherosclerosis Risk in Communities; CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; KHS, Korean Heart Study; MACE, major adverse cardiovascular event; NA, not available; NZDCS, New Zealand Diabetes Cohort Study; RCAV, Racial and Cardiovascular Risk Anomalies in CKD Cohort; SCREAM, Stockholm Creatinine Measurements Cohort; TRA2°P-TIMI50, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Event-TIMI50.

*RCAV does not have cardiovascular death data, so all cause is reflected.

†All NZDCS participants had a diagnosis of diabetes mellitus according to their primary care provider.

‡Estimated using a random effects meta-analysis.

§*P*-value <0.05.

‖RCAV and SCREAM do not have smoking data.

patients with MI in diverse clinical and regional settings. Of the 9 predictors, our meta-analysis confirmed 7 (heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, peripheral artery disease, and kidney dysfunction) as significant risk factors; we did not find significant risk associated with current smoking and CABG overall.

The most common scores in our cohorts were either 2 or 3, whereas a score of 1 was most prevalent in the original TRA2°P–TIMI50.[10] We observed higher TRS2°P scores in our cohorts, despite the lack of smoking information in 2 cohorts. Our observation may not be surprising since clinical trials often enroll selected healthier populations because of stringent inclusion and exclusion criteria.[21] Indeed, compared with patients in TRA2°P–TIMI50, participants in our 5 cohorts were older and more likely to have comorbidities (eg, much higher prevalence of peripheral artery disease in RCAV and current smoking in KHS).

The difference in characteristics between our cohorts and TRA2°P–TIMI50 may be important in explaining why TRS2°P tended to underestimate the risk of an adverse outcome in our cohorts. For example, RCAV in our study had a higher prevalence of comorbidities, as noted above, as well as higher incidence of cardiovascular outcomes than TRA2°P–TIMI50.[10] Indeed, when clinical trials were investigated, TRS2°P demonstrated good calibration for secondary adverse outcome.[22] Also, we should keep in mind that TRA2°P–TIMI50 used adjudicated outcomes, whereas some of our cohorts relied on discharge diagnosis to identify MACE. Nonetheless, the Brier score, a measure of overall model performance, ranged from 0.144 to 0.173 across 5 studies, while the Brier score in the TRA2°P–TIMI50 was 0.098.[10] Although we should keep in mind the tendency of underestimation in real-world cohorts, overall, TRS2°P demonstrated decent risk prediction among patients with recent MI in international non–clinical trial settings, despite its simple scoring system.

Since the issue of calibration may be fixable by recalibration,[23] as seen in some of our cohorts, discrimination ability is essential for risk prediction.[24] In our study, the ability of TRS2°P to discriminate the risk of subsequent cardiovascular outcomes among patients with MI was reasonably good. Four cohorts from the United States, Sweden, and New Zealand showed C-statistics around 0.61 to 0.69, which are largely comparable to the original C-statistic in TRA2°P–TIMI50 of 0.67.[10] This may reflect the fact that the relative risk for a key risk factor is often generally consistent across different clinical and geographic settings,[25,26] since discrimination reflects the strength of relative risk relationship. Therefore, TRS2°P seems particularly useful in stratifying patients into risk categories (as shown in Figure 3) rather than predicting the absolute risk of having an adverse outcome. Nonetheless, unlike primary prevention therapy (eg, statin therapy in 10-year risk of incident atherosclerotic cardiovascular disease ≥7.5%),[27] to our knowledge, there are no established long-term risk thresholds influencing secondary prevention therapy among patients with MI. Thus, once such a threshold is established for some specific treatments in the future among MI patients, TRS2°P should be tested in the context of that specific threshold.

The suboptimal discrimination of TRS2°P in a Korean cohort in our study may deserve some discussion. The low prevalence of heart failure, one of the strongest predictor in TRS2°P, might be related to this observation. Regarding the lack of association between diabetes mellitus and MACE in our Korean cohort, a previous study from the Korean MI registry showed similar results from our Korean cohort and indicates a potentially unique risk factor profile in Korean patients with MI.[28] In addition, a relatively high proportion of censoring within 3 years in this cohort might play a role as well. Also, it seems worth recognizing that TRA2°P–TIMI50 did not include patients from Korea, although it included some patients from other East Asian countries such as Japan and China. Nonetheless, future investigations are warranted because it is critical to develop or validate prediction models for post-MI patients in Asia.

In terms of each of the 9 predictors in TRS2°P, the meta-analyzed hazard ratio in our study was similar to the hazard ratio in TRA2°P-TIMI50 for the following 7 risk factors: heart failure, hypertension, age, diabetes mellitus, stroke, peripheral artery disease, and kidney dysfunction. These clinical and demographic factors have been recognized as important risk factors among patients with MI in clinical guidelines.[29] Moreover, these risk factors are incorporated in a number of risk prediction models for patients with MI.[6,7,28,30–34]

In contrast, current smoking and CABG were not evidently associated with adverse outcomes after MI in our meta-analysis. For current smoking, interestingly, a few studies reported that their presence (together with other traditional atherosclerotic risk factors such as dyslipidemia) was counterintuitively associated with better prognosis among patients with MI.[35–37] Although the exact reasons are not clear, investigators from those studies made several speculations. For example, there may be misclassification of those factors after MI. Specifically, patients with cardiovascular disease may incorrectly self-report smoking status since they are under the pressure to quit smoking.[38] For CABG, several trials have shown its survival benefits compared with percutaneous revascularization or medical treatments in patients with severe coronary heart disease.[39–41] Thus, the prognostic value of CABG may depend on patient characteristics. Also, it is noteworthy that prior CABG was significantly associated with increased risk of MACE in 3 out of 5 cohorts.

Our study has several clinical implications. First, TRS2°P seems generally useful to classify 3-year risk among patients with recent MI in a broad range of clinical settings. Although there are a few validated risk stratification tools (eg, GRACE score and TIMI risk score) for patients with acute coronary syndrome,[30,31] most of these mainly aim to predict short-term risk (eg, in-hospital or 14-day) to make the decision of urgent revascularization.[42,43] Therefore, if the goal is to estimate longer-term risk over a few years, TRS2°P would be a reasonable option. While more complex models (eg, equation-based models including alternative parameterization of TRS2°P predictors[44] or dynamic models using time-varying electronic health records[45]) would outperform TRS2°P for accurately predicting the risk, its simple scoring system will help healthcare providers easily acknowledge the risk of patients based on patients' clinical conditions without using a computer-based risk calculator. This simple scoring system may be used even in low resource settings, although this concept should be tested in low resource settings since our 5 cohorts are from high-income countries.

Second, since TRS2°P tended to underestimate the risk of adverse outcomes in our setting, in case a more precise absolute risk estimate is needed for clinical decisions, some kind of recalibration, as we demonstrated, may be needed for personalized clinical decisions. Finally, TRS2°P demonstrated decent risk prediction even among studies without data on smoking. Although it is definitely important for healthcare providers to assess smoking status in daily clinical practice, data availability of smoking status in clinical database studies has been challenging.[46,47] In this context, our results suggest that TRS2°P without smoking data may still be useful to identify high-risk patients with recent MI to be targeted for research or health promotion.

Our study has several limitations. First, although we did our best to standardize variable definitions across cohorts, heterogeneity still remained, as noted above. Specifically, some cohorts lacked information on smoking status and cardiovascular death. From another point of view, decent prediction performance of TRS2°P in most studies despite this limitation seems to indicate its potential generalizability in broad settings. Second, measurement of the 9 predictors and ascertainment of outcomes were not necessarily standardized in all cohorts. Third, black patients in this analysis were only from the 2 US cohorts, so generalizing to diverse populations should be done with caution. Fourth, information on ST-elevation versus non-ST–elevation MI was not available in every cohort, and thus whether the performance of TRS2°P differs in these 2 types of MI is yet to be investigated. Nonetheless, TRS2°P was developed from data without differentiating MI types. Finally, since we were limited with only 1 or 2 cohorts from a country or region, we cannot differentiate study-specific versus country/region-specific results related to local practice.

In conclusion, TRS2°P reasonably predicted secondary events among patients with recent MI in international non–clinical trial settings, with some caveats to be explored in future studies (eg, general underestimation of the risk of adverse outcomes and suboptimal discrimination in a Korean cohort). Particularly given its simple feature of a 0 to 9 scoring system with routinely collected variables, TRS2°P may be considered for classifying the prognosis and to guide risk-centered management among patients with recent MI.

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Supplemental Material

Data S1.

Data analysis overview and analytic notes for some of individual studies

Overview

As previously described,[1] the collaborating cohorts were asked to prepare a dataset with approximately 20 variables (follow-up time, event variable, nine predictors, and medication uses). To minimize heterogeneity, the CKD-PC Data Coordinating Center sent definitions of variables and dataset preparation. We instructed studies not to impute any variables.

For 3 of the 5 cohorts in this study,[2, 3] the Data Coordinating Center at Johns Hopkins University conducted analysis; the remainder ran the standard code written in STATA by the Data Coordinating Center and shared the output with the Data Coordinating Center. Standard code was designed to automatically save all output including categorical/continuous analyses and survival analyses.

As detailed in our previous report,[2, 3] each cohort was instructed to standardize their serum creatinine and report its method when available. The reported creatinine standardization allows grouping studies into studies that reported using a standard IDMS traceable method or conducted some serum creatinine standardization to IDMS traceable methods (ARIC, RCAV, SCREAM) and studies where the creatinine standardization was not done (KHS, NZDCS). For those cohorts without standardization, the creatinine levels were reduced by 5%, the calibration factor used to adjust non-standardized MDRD Study samples to IDMS.[2, 4]

We calculated eGFR using the CKD-EPI equation[5]: eGFR = 141 × (minimum of standardized serum creatinine [mg/dL]/κ or 1)$^{\alpha}$ × (maximum of standardized serum creatinine [mg/dL]/κ or 1)$^{-1.209}$ × 0.993^{age} × (1.018 if female) × (1.159 if black), where κ is 0.7 if female and 0.9 if male and α is -0.329 if female and -0.411 if male. Smoking status and eGFR were identified within 1 year prior to incident MI and if not, they were missing. To update information on kidney dysfunction, we defined chronic kidney disease based on ICD codes.

Notes for individual parent studies (Note: only incident MI cases during follow-up from these studies were analyzed for this study)

ARIC: This cohort is a community-based cohort of participants middle-aged men and women (45-64 years old) at baseline 1987-1989. Study participants were predominantly whites and blacks and were recruited from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland.

RCAV: US veterans with serum creatinine measurements performed from October 1, 2004, to September 30, 2006, were identified from the national Veterans Affairs (VA) Corporate Data Warehouse LabChem data files. Veterans had at least 1 available serum creatinine measurement, representing ~94% of all veterans who received VA health care during this time period. This cohort has very low rates of female (<6%) and race other than black or white (<4%). This cohort does not have data on smoking and cause of death.

SCREAM: This cohort is a health care use cohort from the sole health care provider of the region of Stockholm, Sweden. All Stockholm residents aged 18 years or older with data on serum creatinine in either inpatient or outpatient care from 2006 to 2011 were included. Given serum creatinine as a common test in healthcare, ~66% of the adult population in Stockholm were covered. This cohort does not have data on smoking.

KHS: This cohort included individuals who had voluntarily undergone a health checkup in 18 centers located in the capital, Seoul, and 6 provinces in South Korea in 1996 to 2004. Educational attainment and socioeconomic status were higher in this cohort relative to overall Korean population.

NZDCS: This study included participants with a diagnosis of diabetes and no known previous cardiovascular event at baseline according to primary care provider in New Zealand. Almost all data were collected by 26 organizations around country, all of whom were invited to provide data for this study.

Cohort specific definition of recent myocardial infarction (MI)

Cohort	Definition of recent MI
ARIC	Definite and probable MI cases adjudicated by ARIC physician panel
RCAV	Defined as if MI related hospitalization ICD-9 code 410
SCREAM	Defined as if MI related hospitalization ICD-10 code I21
KHS	Defined as if MI related hospitalization ICD-10 code I21
NZDCS	Defined as if MI related hospitalization ICD-9 code 410

Cohort specific definition of nine predictors

Cohort	HF	HTN	Age	DM	Stroke	CABG	PAD	Kidney dysfunction	Current smoking
ARIC	ICD-9 428 or ICD-10 I50	BP (≥140/90 mmHg) or self-reported doctor diagnosed HTN	At MI	Fasting glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, self-reported doctor diagnosed diabetes, or medication	Definite or probable strokes were identified by computer algorithm and review by a physician	ICD-9 36.1	ICD-9 440.2 440.3 440.4 443.9 707.1 785.4 38.18 39.25 39.29 39.50 84.1	eGFR<60 ml/min/1.73m^2 within 1 year prior to MI or CKD based on ICD codes	Within 1 year prior to MI
RCAV	ICD-9 428	ICD-9 401-405	At MI	ICD-9 250*	ICD-9 430 431 432 433.*1 434.*1	CPT 33510 - 33519 33521-33523 33533-33536	ICD-9 codes 440.X, leg revascularization, leg amputation	eGFR<60 ml/min/1.73m^2 within 1 year prior to MI or CKD based on ICD codes	NA
SCREAM	ICD-10 I50	ICD-10 I10-I15	At MI	ICD-10 E10 E11 E13	ICD-10 I61-I63	NOMESCO classification FN FNA FNB FNC FND FNE	ICD-10 I70.2x or I70.92, leg revascularization, leg amputation	eGFR<60 ml/min/1.73m^2 within 1 year prior to MI or CKD based on ICD codes	NA
KHS	ICD-10 I50	BP (≥140/90 mmHg), self-reported doctor diagnosed HTN or medication history or ICD-10 I10-I15	At MI	Fasting glucose ≥126 mg/dL, self-reported doctor diagnosed diabetes or medication history or ICD-10 E10 E11 E13	ICD-10 I61-I69	ICD-10 I20-I25 Z95.1 Z98.61, leg revascularization	ICD-10 I70.0I70.1 I70.2 I70.8 I72.4 I73.1 I73.8 I73.9 I74.2 I74.3 I74.4 I74.5 I96 E11.5 E12.5 E13.5 E14.5	eGFR<60 ml/min/1.73m^2 within 1 year prior to MI or CKD based on ICD codes	Within 1 year prior to MI
NZDCS	ICD-9 40201, 40211, 40291, 40401, 40403, 40411, 40413, 40491, 40493, 4280, 4281, 4289, 4282, 4284 ICD-10 I110, I130, I132, I50, J81	BP (≥140/90 mmHg), on antihypertensives/ ACEI	At MI	Doctor diagnosed diabetes or medication history or Glycated hemoglobin A1c ≥6.5%	ICD-9 431, 4329, 43401, 43411, 43491, 438 or ICD-10 I61, I630, I631, I632, I633, I634, I635, I637, I638, I639, I64, I693, I690, I691, I692, I694, I698	ICD-9 V4581 or ICD-10 Z951	ICD-9 25073, 380, 381, 3840, 3841, 3842, 3843, 3844, 3845, 3846, 3848, 3849, 3922, 3924, 3925, 3926, 3928, 3929, 44021, 44022, 44023, 44024 or ICD-10 E1051, E1052, E1151, E1152, E1451, E1452, I7021, I7022, I7023, I7024, 273300, 327000, 327630, 327631, 3270010, 3270011, 3270300, 3270800, 3270801, 3270802, 3270803, 3271200, 3271201, 3271500, 3271501','3271502, 3271503, 3271800, 3271801, 3273000, 3273001, 3273301, 3273600, 3273900, 3274200, 3274500, 3274800, 32751, 3275200, 3275201, 3275202, 3275203, 3275400, 3275401, 3275402, 3275700,	eGFR<60 ml/min/1.73m^2 within 1 year prior to MI or CKD based on ICD-9 codes 2504, 582, 583, 5853, 5854, 5855, 5856, 586, 587, 588, 5939, 403, 404, V420 or ICD-10 codes E1021, E1029, E1065, E1121, E1129, E1165, I120, I129, I130, I131, I132, N032, N033, N035, N038, N039, N052, N055, N058, N059, N08, N171, N172, N183, N184, N185, N186, N19, N250, N251, N258, N259, N269, N289, Z940	Within 1 year prior to MI

							3275701, 3530306, 3530307, 3530906, 3530907, 3530908, 3530909, 3350000, 3350600, 3350601, 3350900, 3351200, 3351500, 3351501, 3351800, 3352100, 3352400, 3352700, 3353000, 3353001, 3353300, 3353600		

Abbreviations: BP, blood pressure; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CPT, Current Procedure Terminology; DM, diabetes; eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension; ICD, International Classification of Diseases; MI, myocardial infarction; NOMESCO, Nordic Medico-Statistical Committee; PAD, peripheral artery disease

Exclusion criteria

ARIC: 1,795 participants developed incident MI during follow-up. We excluded 45 participants who did not have complete information on nine predictors in TRS2°P and 39 participants who died within 14 days after incident MI, leaving a sample of 1,711 participants.

RCAV: 10,720 participants developed incident MI during follow-up. We excluded 511 participants who died within 14 days after incident MI. Of these participants, we included those who had any outpatient visits after incident MI, leaving a sample of 9,090 participants.

SCREAM: 41,247 participants developed incident MI during follow-up. We excluded 603 participants who did not have complete information on nine predictors in TRS2°P and 2,473 participants who died within 14 days after incident MI, leaving a sample of 38,171 participants.

KHS: 3,043 participants developed incident MI during follow-up. We excluded 13 participants who did not have complete information on nine predictors in TRS2°P and 118 participants who died within 14 days after incident MI, leaving a sample of 2,912 participants.

NZDCS: 4,914 participants developed incident MI during follow-up (2000 to 2007). Then we excluded 2,738 participants who did not have complete information on nine predictors in TRS2°P and 461 participants who died within 14 days after incident MI, leaving a sample of 1,715 participants.

Data S2.

Acronyms or abbreviations for studies included in the current report and their key references linked to the Web references

ARIC:	Atherosclerosis Risk in Communities Study[6]
RCAV:	Racial and Cardiovascular Risk Anomalies in CKD Cohort[7]
SCREAM:	Stockholm CREAtinine Measurements Cohort[8]
KHS:	Korean Heart Study[9]
NZDCS:	New Zealand Diabetes Cohort Study[10]

Data S3.

Acknowledgements and funding for collaborating cohorts

Study	List of sponsors
ARIC	The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (HHSN268201700001I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I, HHSN2682017000021). The authors thank the staff and participants of the ARIC study for their important contributions.
RCAV	This study was supported by grant R01DK096920 from NIH-NIDDK and is the result of work supported with resources and the use of facilities at the Memphis VA Medical Center and the Long Beach VA Medical Center. Support for VA/CMS data is provided by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development, VA Information Resource Center (project numbers SDR 02-237 and 98-004).
SCREAM	This study was supported by Stockholm County Council and the Swedish Heart and Lung Foundation.
KHS	This study was funded by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea HI14C2686 and HI13C0715.
NZDCS	New Zealand Health Research Council, Auckland Medical Research Foundation and New Zealand Society for the Study of Diabetes

Table S1. Three-year cumulative incidence of hypothetically incorporated smoking status by the TRS2˚P risk score in SCREAM and RCAV.

		TRS2˚P risk score							
HR	**PR_{smk}**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7+**
SCREAM	**Not accounting**	0.0987	0.1674	0.2822	0.4277	0.5505	0.6539	0.7410	0.4668
1.07	25%	0.0971	0.1490	0.2432	0.3743	0.5042	0.6092	0.6969	0.6733
	29%	0.0969	0.1462	0.2379	0.3673	0.4982	0.6042	0.6929	0.6813
	35%	0.0965	0.1419	0.2301	0.3574	0.4899	0.5974	0.6878	0.6904
1.17	25%	0.0949	0.1481	0.2432	0.3759	0.5081	0.6169	0.7088	0.6895
	29%	0.0944	0.1452	0.2378	0.3690	0.5024	0.6122	0.7051	0.6974
	35%	0.0935	0.1408	0.2301	0.3592	0.4943	0.6056	0.6999	0.7058
1.27	25%	0.0929	0.1472	0.2432	0.3775	0.5118	0.6240	0.7197	0.7041
	29%	0.0920	0.1442	0.2378	0.3707	0.5063	0.6196	0.7163	0.7118
	35%	0.0907	0.1398	0.2301	0.3609	0.4983	0.6132	0.7111	0.7198
1.37	25%	0.0909	0.1464	0.2432	0.3790	0.5153	0.6306	0.7297	0.7171
	29%	0.0897	0.1433	0.2378	0.3723	0.5099	0.6265	0.7265	0.7248
	35%	0.0880	0.1388	0.2301	0.3625	0.5021	0.6202	0.7213	0.7325
1.47	25%	0.0890	0.1456	0.2433	0.3805	0.5186	0.6368	0.7389	0.7289
	29%	0.0876	0.1424	0.2378	0.3738	0.5134	0.6329	0.7359	0.7366
	35%	0.0856	0.1379	0.2301	0.3640	0.5056	0.6267	0.7307	0.7440
1.57	25%	0.0872	0.1448	0.2433	0.3819	0.5218	0.6426	0.7474	0.7395
	29%	0.0856	0.1416	0.2379	0.3752	0.5167	0.6389	0.7446	0.7473
	35%	0.0832	0.1370	0.2301	0.3655	0.5090	0.6329	0.7395	0.7545
RCAV	**Not accounting**	0.1489	0.1930	0.2529	0.3088	0.4084	0.4512	0.5339	0.6011
1.07	40%	0.1452	0.1860	0.2339	0.2815	0.3661	0.4317	0.4847	0.5626
	45%	0.1447	0.1850	0.2312	0.2786	0.3610	0.4296	0.4809	0.5605
	50%	0.1443	0.1839	0.2285	0.2759	0.3560	0.4275	0.4774	0.5585
1.17	40%	0.1402	0.1807	0.2309	0.2830	0.3654	0.4341	0.4922	0.5766
	45%	0.1392	0.1791	0.2280	0.2801	0.3603	0.4319	0.4882	0.5737
	50%	0.1381	0.1775	0.2251	0.2773	0.3553	0.4298	0.4844	0.5708
1.27	40%	0.1356	0.1757	0.2280	0.2843	0.3648	0.4363	0.4991	0.5894
	45%	0.1340	0.1737	0.2250	0.2815	0.3597	0.4341	0.4949	0.5858
	50%	0.1326	0.1717	0.2220	0.2786	0.3546	0.4319	0.4907	0.5820
1.37	40%	0.1313	0.1711	0.2253	0.2856	0.3642	0.4383	0.5056	0.6013
	45%	0.1293	0.1687	0.2222	0.2827	0.3591	0.4361	0.5011	0.5969
	50%	0.1274	0.1663	0.2192	0.2798	0.3540	0.4338	0.4966	0.5923
1.47	40%	0.1273	0.1668	0.2229	0.2868	0.3637	0.4402	0.5115	0.6123
	45%	0.1250	0.1640	0.2197	0.2839	0.3585	0.4380	0.5069	0.6073
	50%	0.1227	0.1614	0.2166	0.2810	0.3535	0.4356	0.5020	0.6019
1.57	40%	0.1235	0.1627	0.2205	0.2879	0.3632	0.4419	0.5171	0.6226
	45%	0.1209	0.1597	0.2173	0.2849	0.3580	0.4397	0.5122	0.6169
	50%	0.1184	0.1568	0.2142	0.2820	0.3529	0.4373	0.5071	0.6108

For RCAV, cardiovascular death was assumed to be 50% of all-cause death due to lack of information on cardiovascular death.

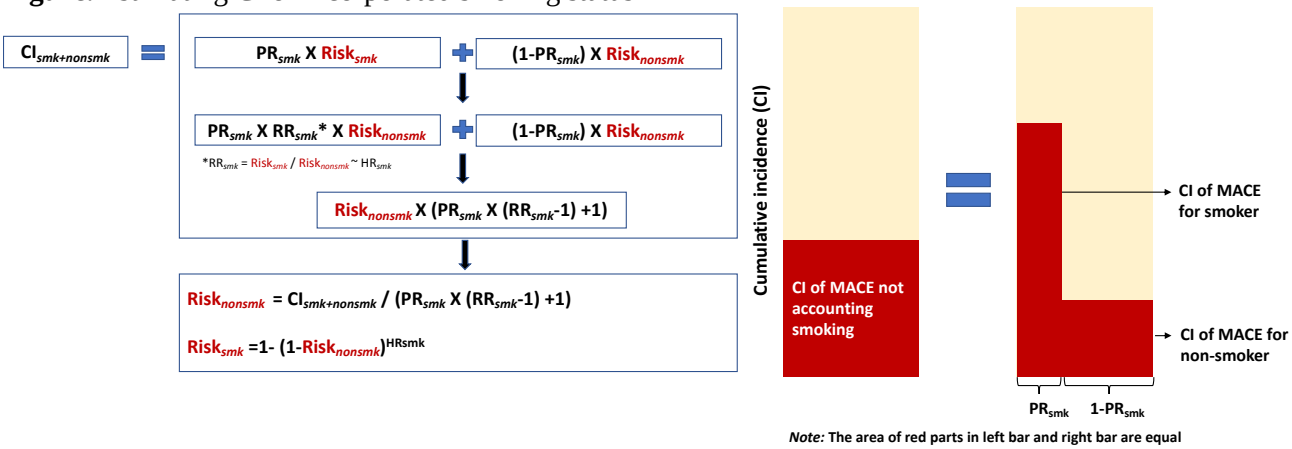
Two key elements determining the MACE cumulative incidence within smokers and non-smokers are the prevalence of smokers and the relative risk of smokers compared with non-smokers.

$Risk_{nonsmk} = CI_{nonsmk+smk} / ((PR_{smk} * (RR_{smk} -1))+1)$ and $Risk_{smk} = (1-(1- Risk_{nonsmk})^{HR_{smk}}$

Here $CI_{nonsmk+smk}$ is observed cumulative incidence of cardiovascular events at a given TRS2°P category not accounting for smoking status (in other words, cumulative incidence lumping non-smokers and smokers). PR_{smk} is the prevalence of smokers, and we primarily used the prevalence of smokers (29%) in SWEDEHEART,[11] a Swedish registry of MI cases, for SCREAM and the prevalence of smokers (45%) among US veterans with coronary heart disease [12] for RCAV. RR_{smk} is relative risk of smokers compared with non-smokers, and we primarily used the hazard ratio of 1.47 in the derived dataset of TRS2°P (TRA 2°P–TIMI50) but also explored other hazard ratios including the

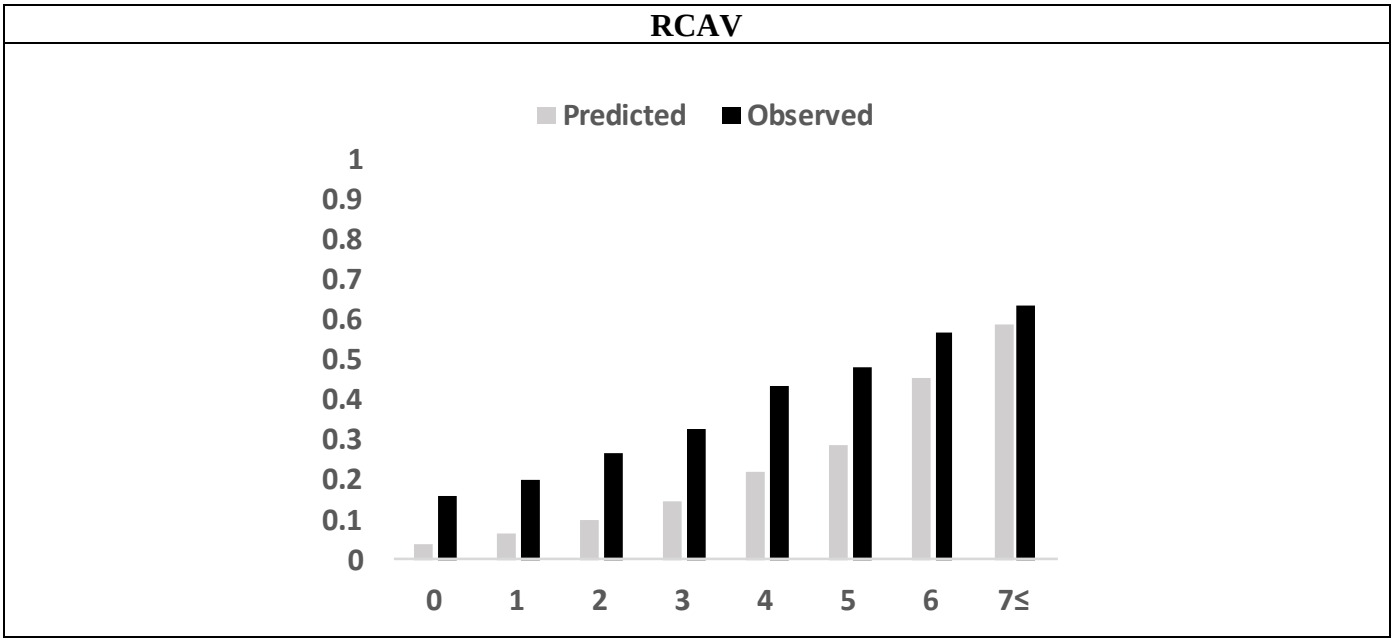
one from our meta-analysis shown subsequently.[13] We used hazard ratios from TRS2°P and our meta-analysis as approximation of relative risk. Cumulative incidence accounting for smoking is a weighted average of MACE cumulative incidence in smokers and that in non-smokers.

Figure. Estimating CI of incorporated smoking status



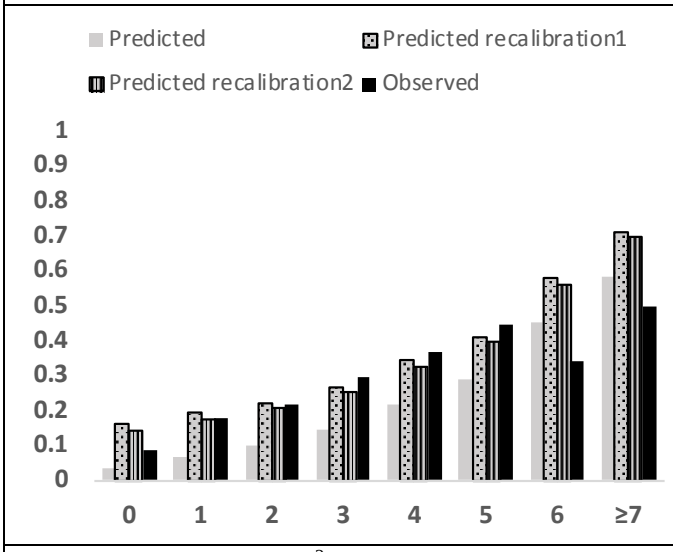
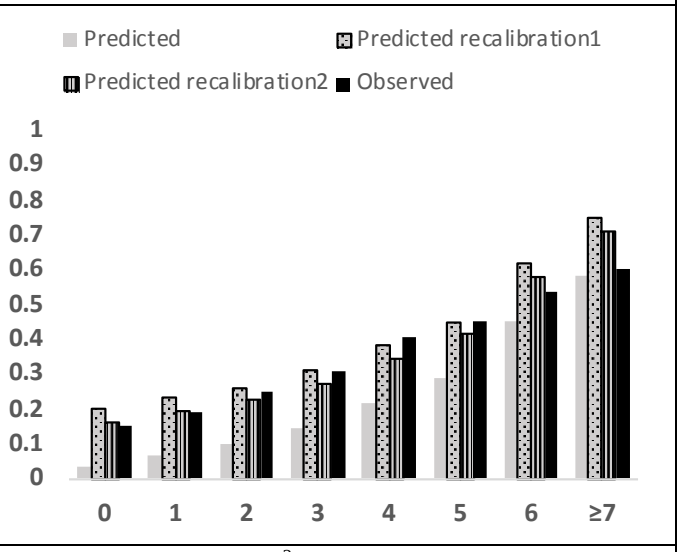
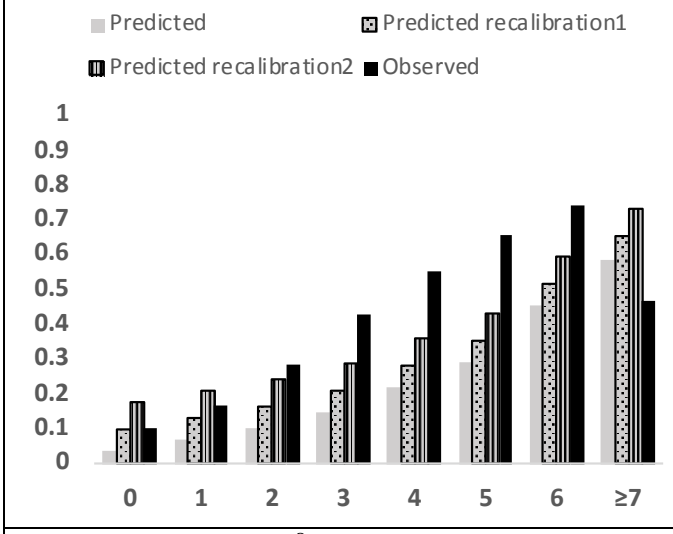
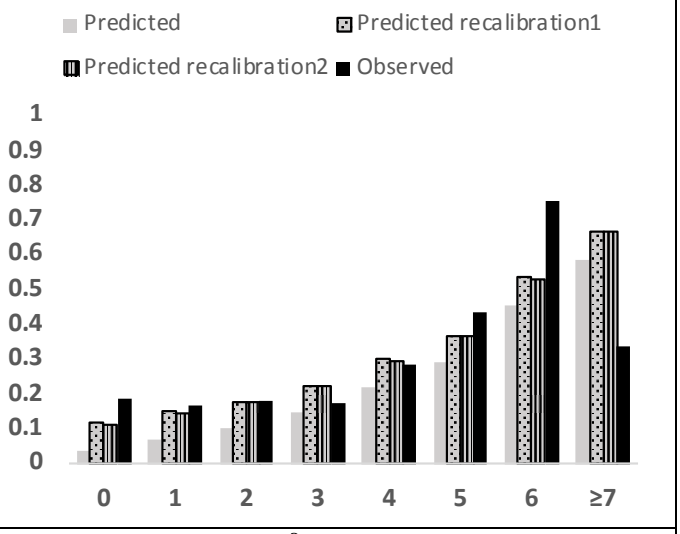
CI, cumulative incidence; HR, hazard ratio; PRsmk, prevalence of current smoking

Figure S1. Calibration plot for major adverse cardiovascular event (MACE) by categories of TRS2˚P risk score in RCAV.

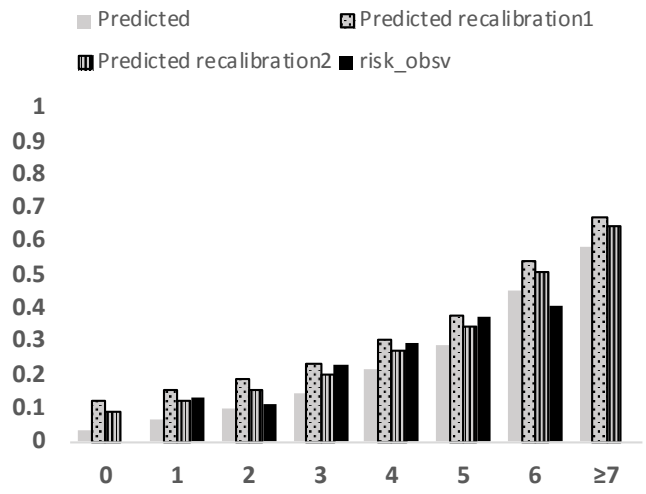


Cardiovascular death was assumed to be 41% of all-cause death due to lack of information on cardiovascular death.

Figure S2. Three-year probability of major adverse cardiovascular event (MACE) of recalibrated predicted risk and observed risk by the TRS2°P.

ARIC	RCAV
	
Original x^2: 273.1, p<0.001	**Original** x^2: 1946.2, p<0.001
Calibration1 x^2: 14.8, p=0.098	**Calibration1** x^2: 41.0, p<0.001
Calibration2 x^2: 12.1, p=0.205	**Calibration2** x^2: 37.4, p<0.001
SCREAM	**KHS**
	
Original x^2: 10,542.6, p<0.001	**Original** x^2: 377.8, p<0.001
Calibration1 x^2: 3,189.8, p<0.001	**Calibration1** x^2: 29.3, p=0.001
Calibration2 x^2: 1,599.4, p<0.001	**Calibration2** x^2: 28.2, p=0.001

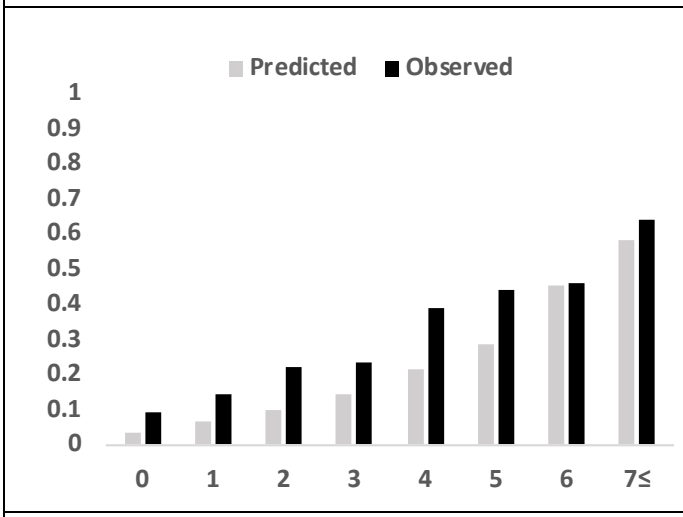
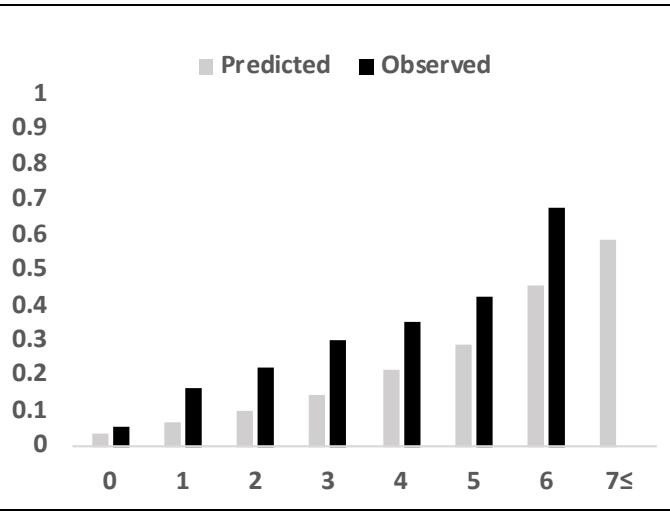
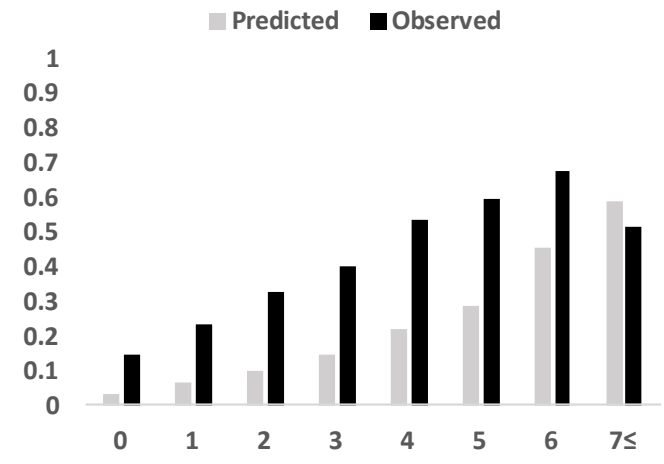
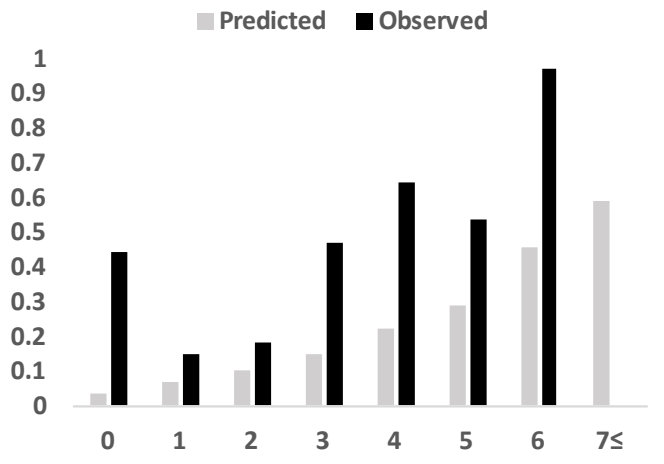
NZDCS	

	
Original x^2: 67.3, p<0.001	
Calibration1 x^2: 29.7, p<0.001	
Calibration2 x^2:20.8, p=0.013	

For RCAV, cardiovascular death was assumed 50% of all-cause death due to lack of information on cardiovascular death; All NZDCS participants had a diagnosis of diabetes according to primary care provider. Calibration 1: $P_{recalibrated} = P_{original} + (O_i - P_i)$, Calibration 2: $P_{recalibrated} = P_{original} + \frac{\Sigma_{j=0}^{7} f_j \times (O_j - P_j)}{N}$ Where, $P_{recalibrated}$ is recalibrated predicted risk at a given TRS2°P category and $P_{original}$ is original predicted risk at a given TRS2°P category. O_i is observed risk at the most prevalent score in each cohort, P_i is original predicted risk at the most prevalent score in each cohort. $f_j = f_0, f_1, f_2, ..., f_7$ is frequency corresponding to each TRS2°P category and $O_j = O_0, O_1, O_2, ..., O_7$ is observed risk corresponding to each category.

Figure S3. Three-year probability of major adverse cardiovascular event (MACE) by categories of TRS2˚P and sex.

For RCAV, cardiovascular death was assumed 50% of all-cause death due to lack of information on cardiovascular death, but, in number of cases, all-cause reflected; All NZDCS participants had a diagnosis of diabetes according to primary care provider.

Men	Women
ARIC	
	
Cases/N: 442/1,013	Cases/N: 320/698
x^2: 117.4, p<0.001; Brier score: 0.162	x^2: 102.2, p<0.001; Brier score: 0.180
C statistic: 0.631 (0.593-0.669)	C statistic: 0.628 (0.587-0.669)
RCAV	
	
Cases/N: 4,779/8,951	Cases/N: 74/139
x^2: 5,219.6, p<0.001; Brier score: 0.186	x^2: 115.1, p<0.001; Brier score: 0.208
C statistic: 0.617 (0.608-0.626)	C statistic: 0.645 (0.571-0.720)
SCREAM	

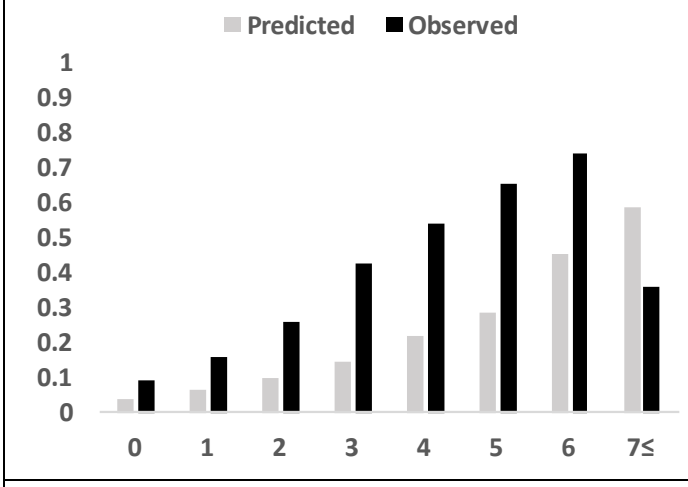
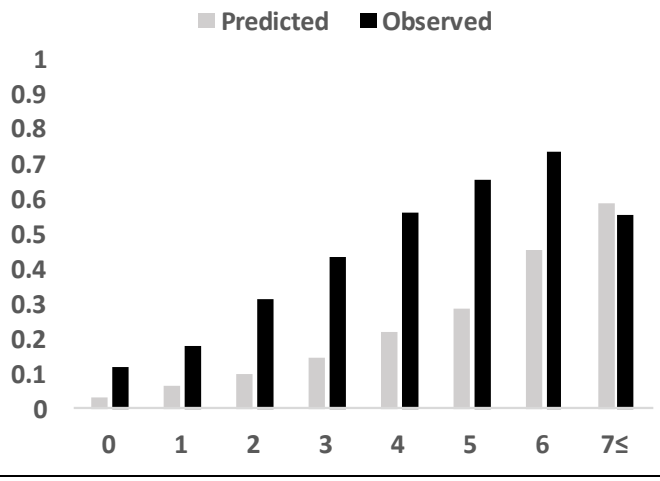
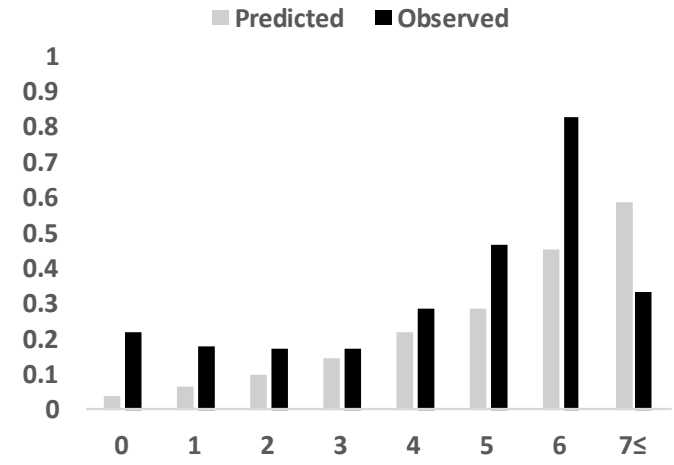
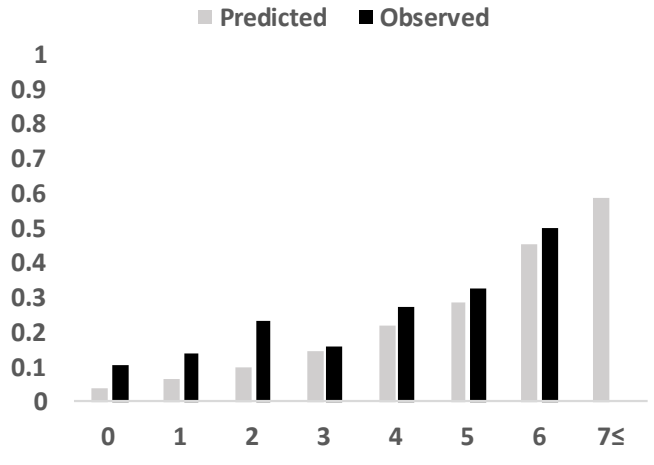
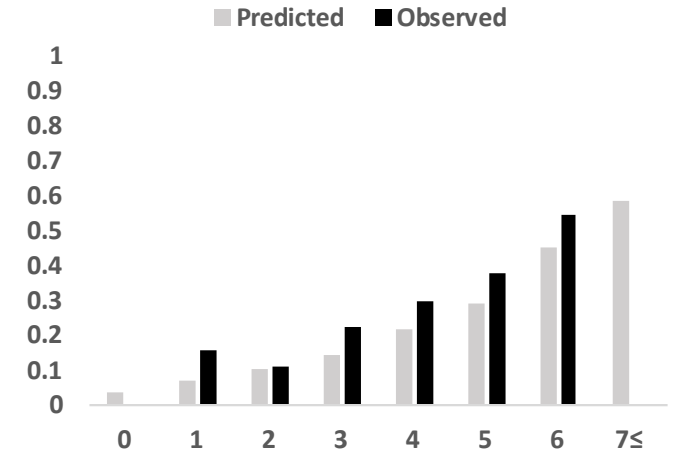
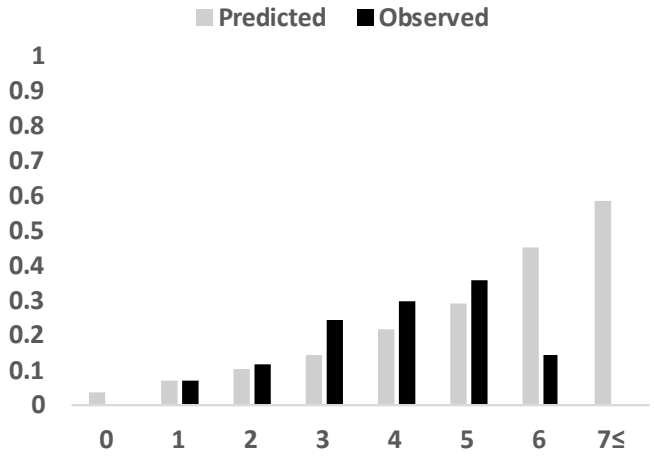
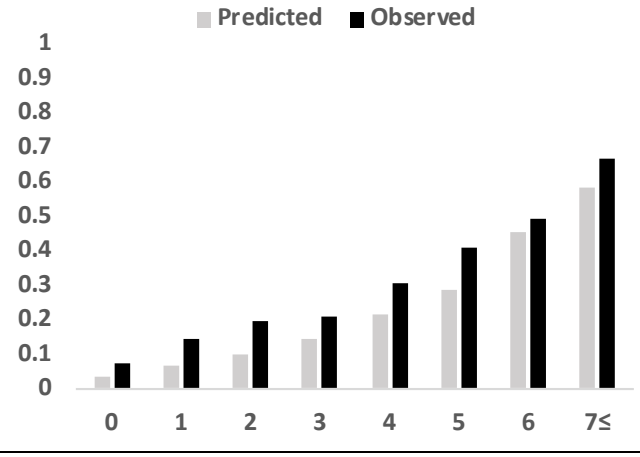
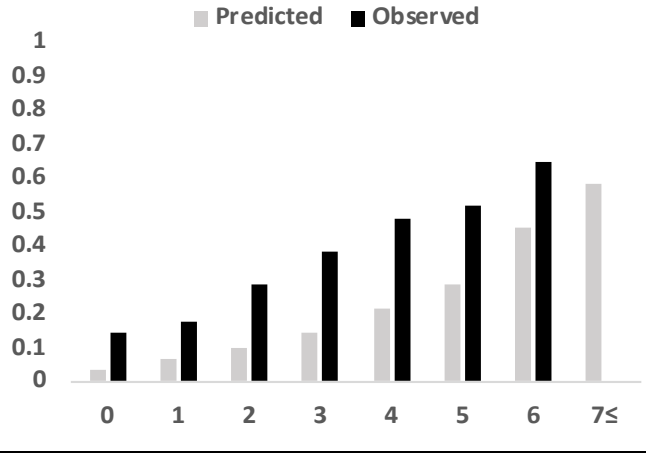
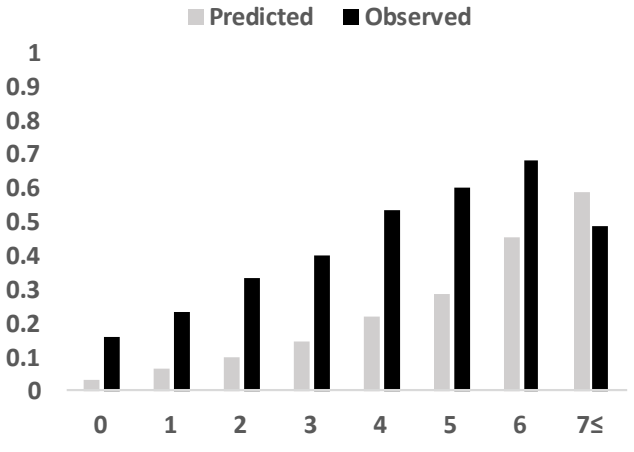
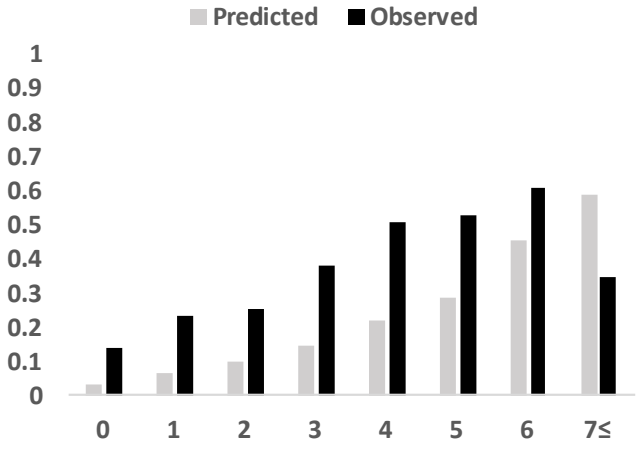
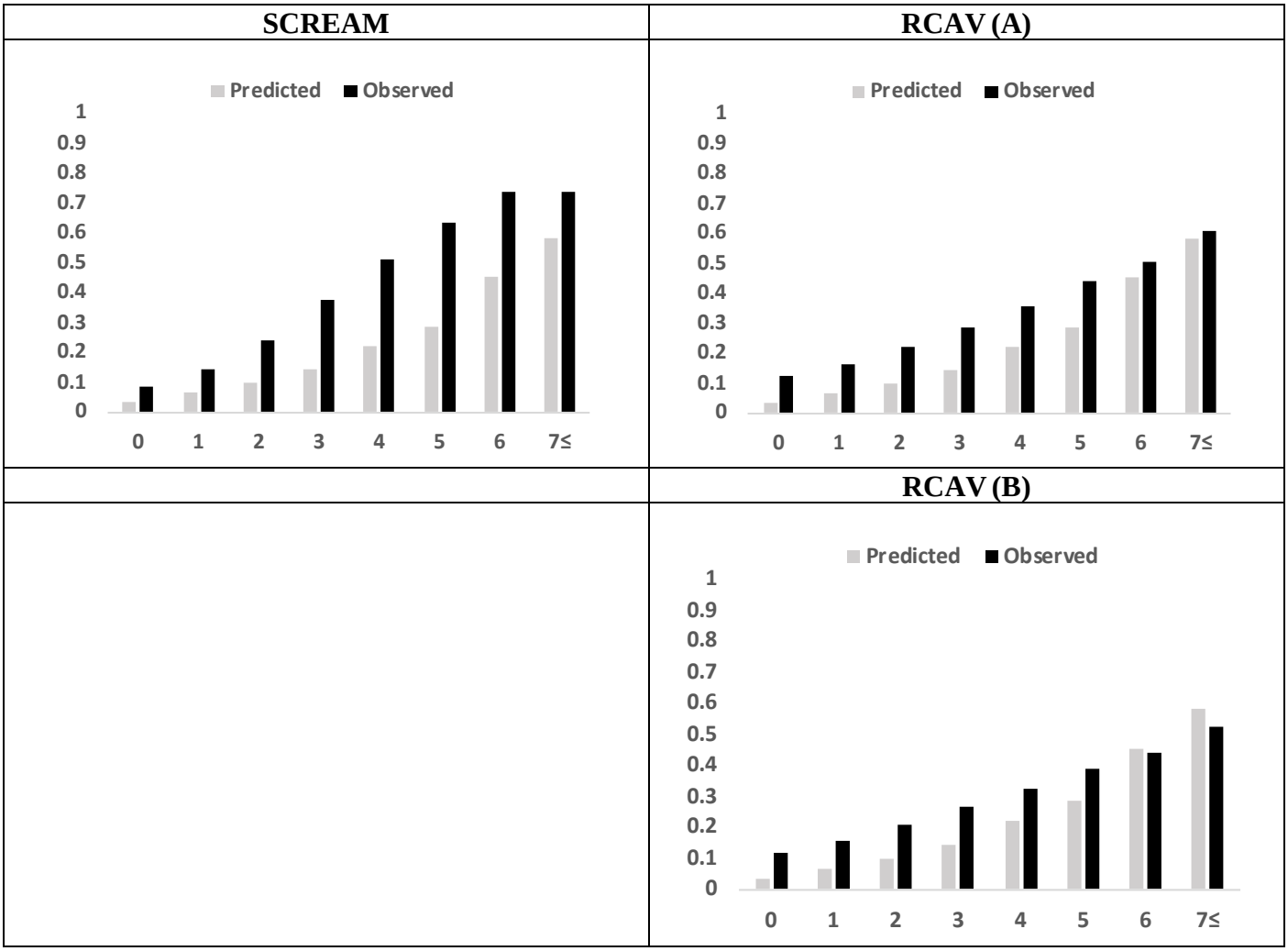
	
Cases/N: 7,099/23,479	Cases/N: 5,603/14,692
x^2: 5097.4, p<0.001; Brier score: 0.148	x^2: 5668.2, p<0.001; Brier score: 0.196
C statistic: 0.683 (0.675-0.691)	C statistic: 0.674 (0.666-0.683)
KHS	
	
Cases/N: 478/2,371	Cases/N: 108/541
x^2: 351.5, p<0.001; Brier score: 0.145	x^2: 54.8, p<0.001; Brier score: 0.140
C statistic: 0.553 (0.524-0.582)	C statistic: 0.579 (0.521-0.637)
NZDCS	
	
Cases/N: 311/1,026	Cases/N: 230/689
x^2: 39.1, p<0.001; Brier score: 0.148	x^2: 32.9, p<0.001; Brier score: 0.157
C statistic: 0.626 (0.588-0.664)	C statistic: 0.598 (0.554-0.643)

Figure S4. Three-year probability of major adverse cardiovascular event (MACE) by categories of TRS2˚P risk score and race in ARIC and RCAV.

White	Black
ARIC	
	
Cases/N: 520/1,260	Cases/N: 241/447
x^2: 90.5, p<0.001; Brier score: 0.147	x^2: 166.5, p<0.001; Brier score: 0.231
C statistic: 0.625 (0.590-0.660)	C statistic: 0.622 (0.576-0.668)
RCAV	
	
Cases/N: 3,898/7,226	Cases/N: 378/1,317
x^2: 4,408.7, p<0.001; Brier score: 0.189	x^2: 581.2, p<0.001; Brier score: 0.168
C statistic: 0.616 (0.606-0.626)	C statistic: 0.625 (0.602-0.649)

For RCAV, cardiovascular death was assumed 50% of all-cause death due to lack of information on cardiovascular death, but, in number of cases, all-cause reflected.

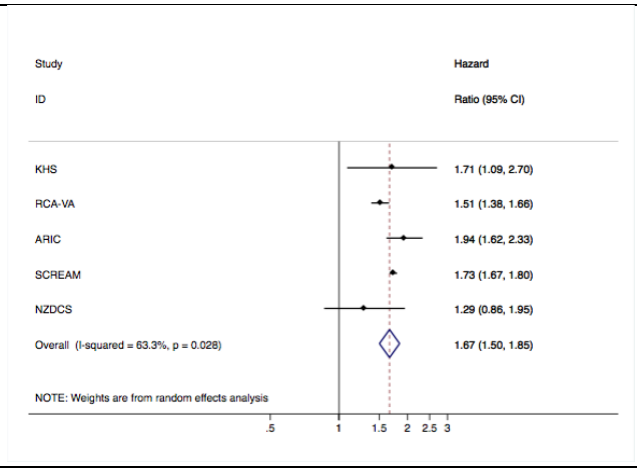
Figure S5. Calibration plot for major adverse cardiovascular event (MACE) according to TRS2˚P in SCREAM and RCAV after hypothetically implementing smoking status.



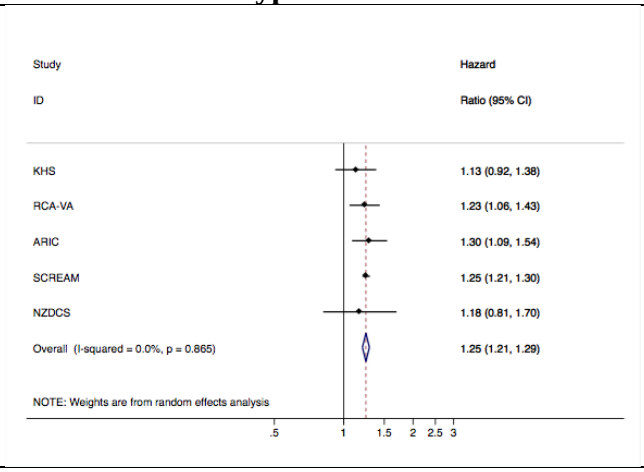
For SCREAM, the assumed prevalence of current smoking was 29% and the assumed hazard ratio was 1.47. For RCAV, the assumed prevalence of current smoking was 45% and the assumed hazard ratio was 1.47. Cardiovascular death was assumed to be 50% (A) and 41% (B) of all-cause death due to lack of information on cardiovascular death.

Figure S6. Forest plots for major adverse cardiovascular event (MACE) by each of the nine predictors.

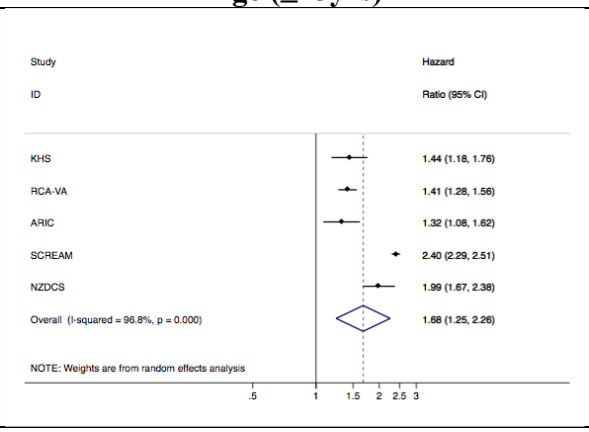
Heart failure



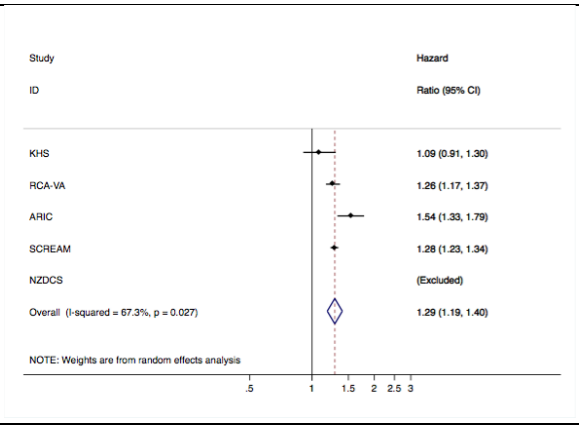
Hypertension



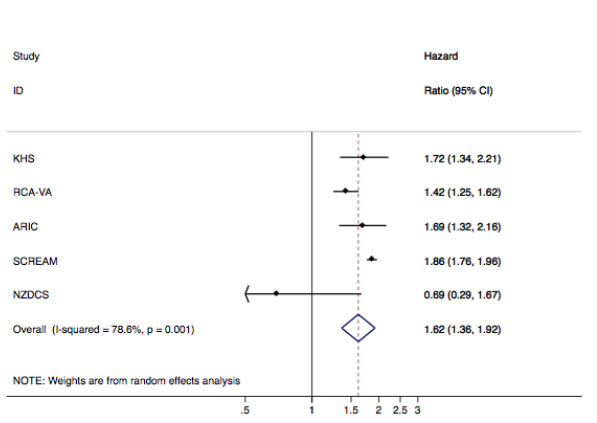
Age (≥75yrs)



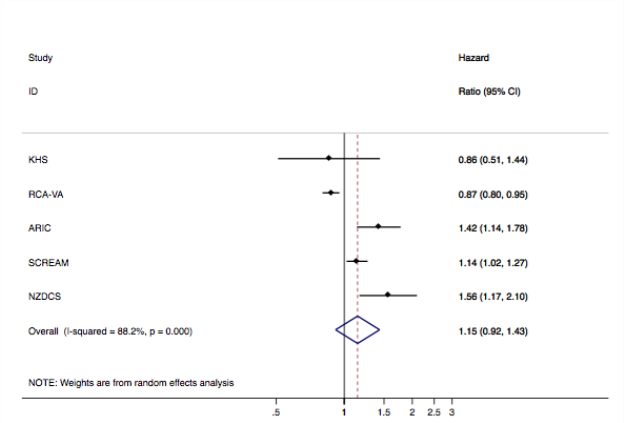
Diabetes



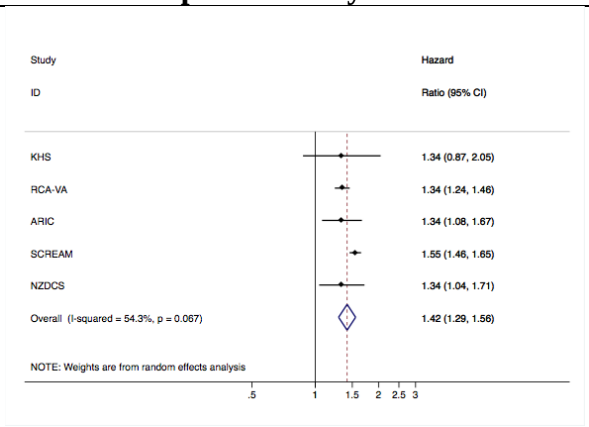
Stroke



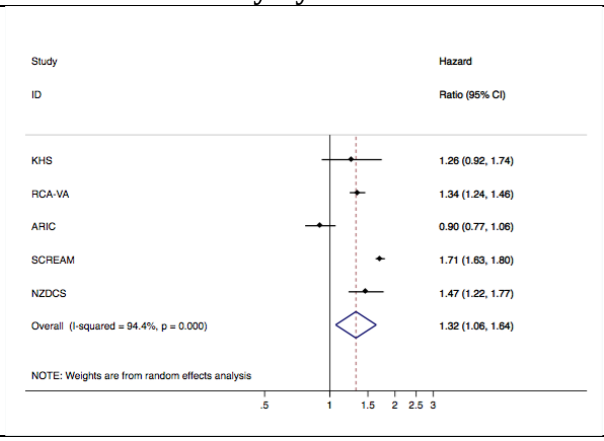
CABG



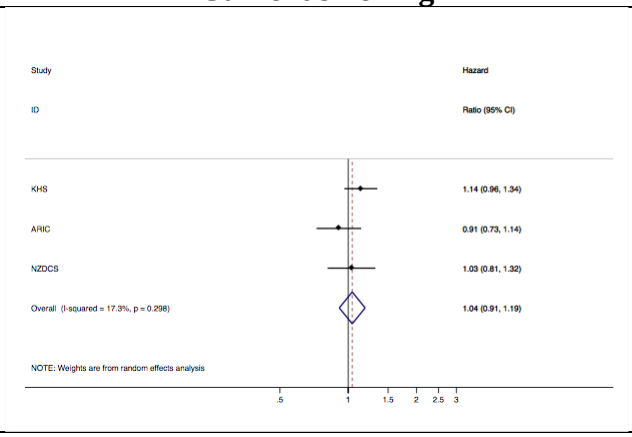
Peripheral artery disease



Kidney dysfunction



Current smoking



RCAV do not have cardiovascular death data, so all-cause death is reflected
CABG, coronary artery bypass graft

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