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ORIGINAL RESEARCH

Estimating the Risk of Cardiovascular Events in U.S. Veterans Using the SMART Risk Score

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ABSTRACT

BACKGROUND Estimation of long-term risk for cardiovascular events using the SMART (Secondary Manifestations of Arterial Disease) risk score can be potentially valuable in devising risk mitigation strategies.

OBJECTIVES The objective of this study was to apply the SMART risk score to compute the risk for major adverse cardiovascular events (MACE) in the U.S. Veteran patient population.

METHODS We used the Veterans Affairs (VA) informatics and computing infrastructure to identify patients referred for an initial outpatient cardiology evaluation between the years 2003 and 2010 to estimate 10-year risk for composite MACE (all-cause death, ischemic stroke, and nonfatal myocardial infarction). Cox regression and survival curves were used to develop and validate the VA SMART score.

RESULTS The study population included 472,702 patients (mean age 60 $\pm$ 8.9 years, 96% male) who were allocated into development (n = 94,091) and test cohorts (n = 378,611). The median follow-up time was 7.9 years (IQR: 6.0-9.9). The VA-SMART score allowed accurate estimation of MACE. Patients were stratified in low (<10%), moderate (10% to 20%), high (20% to 30%), and very high (≥30%) risk groups with observed events rates of 6.8%, 17.9%, 28.5%, and 49.5%, respectively, in the test cohort ($P < 0.0001$ for all intergroup comparisons). Most MACE events were all-cause death, with nonfatal myocardial infarction and stroke also being high, especially in the very high-risk group. The VA SMART score performed similar to other established risk prediction models (C-statistic = 0.67).

CONCLUSIONS The VA SMART risk score can estimate the long-term risk of recurrent cardiovascular events in U.S. Veterans and could help implement individualized risk mitigation strategies. (JACC Adv. 2025;4:101459) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CVD = cardiovascular disease

DM = diabetes mellitus

eGFR = estimated glomerular filtration rate

hsCRP = high-sensitivity C-reactive protein

K-M = Kaplan-Meier

MACE = major adverse cardiovascular events

MI = myocardial infarction

VA = Veterans Affairs

Patients with established cardiovascular disease (CVD) are at higher risk for recurrent cardiovascular events with the 10-year risk exceeding 20%.[1] The observed risk for such patients varies greatly and depends on a variety of factors including medical comorbidities, cardiometabolic disease control, extent of disease, and employment of risk reduction strategies.[2,3] Identifying patients at high risk for recurrent events is critical given the high morbidity and mortality with each recurrent event. With increasing availability of often novel, but costly risk mitigating strategies, identifying appropriate risk patients, with the greatest potential to benefit from these strategies is important.[4-6]

Several clinical risk assessment tools are available for estimating atherothrombotic risk in clinical practice; however, there are concerns about the performance of these scores in stable outpatients with CVD.[7] In addition, most existing CVD risk scores are focused on in-hospital stratification of acute coronary syndrome patients. The SMART (Secondary Manifestations of Arterial Disease) risk score was developed and validated by researchers in the Netherlands to effectively identify patients with pre-existing CVD who are at the highest risk for recurrent cardiovascular events and may benefit from more aggressive therapy and medical management.[8] The validated TIMI risk score for atherothrombosis in diabetes includes 16 routinely accessed clinical variables and serves as a good discriminator of 3-year risk of myocardial infarction (MI) and ischemic stroke in patients with diabetes mellitus (DM).[9] In a landmark study, the SMART investigators prospectively followed 5,788 vascular patients over 7 years to build a model. Inputs to the SMART risk score include 14 readily ascertained measures used to derive analytical variables.[8] The exception was high-sensitivity C-reactive protein (hsCRP) that was not routinely measured in all patients. The model was revised several times and applied to different patient groups. The model was externally validated in 18,436 vascular patients with multinational backgrounds by Kaasenbrood et al.[10] However, the external test cohort comprised clinical trial population with strict inclusion and exclusion criteria and limited availability of many SMART risk score variables.

It is well known that U.S. Veterans have higher associated cardiovascular morbidity and mortality, with a nearly 1.5 relative risk for CVD compared to similar nonveteran counterparts.[11] Predictive models of cardiovascular events have been evaluated in U.S. women Veteran patients and more recently in U.S. Veterans after a coronary artery bypass graft.[12,13] The aim of this study is to apply the techniques used to derive a SMART risk score for an all-comer outpatient U.S. Veteran patient population and to optimize their computed risk for predicting 10-year major adverse cardiovascular events (MACE), a composite of all-cause death, nonfatal MI, and ischemic stroke.

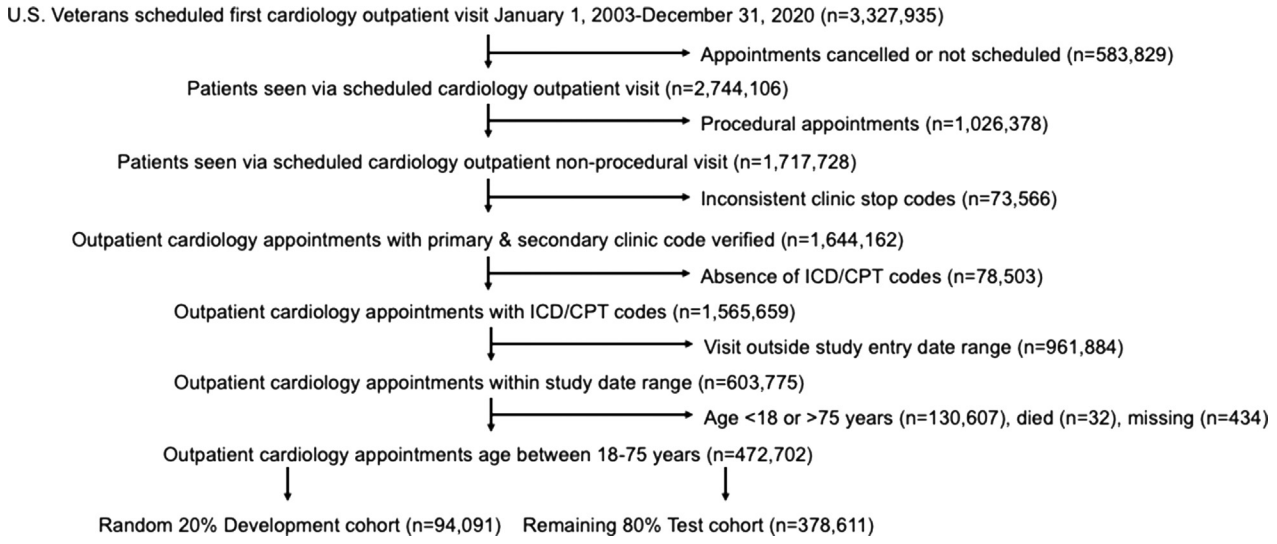
METHODS

PATIENTS. We used the U.S. Veteran Affairs (VA) Informatics and Computing infrastructure (VINCI) to identify patients from a database with longitudinal health records (Computerized Patient Record System) with established CVD, referred for an initial outpatient cardiovascular evaluation within the VA Healthcare System. Approximately 91% of 472,702 patients were referred for either angina pectoris, chest pain, abnormal electrocardiogram, or coronary artery disease (CAD) International Classification of Diseases diagnosis codes. Patients were included in the study if they fulfilled criteria for calculating the SMART risk score between January 1, 2003, and December 31, 2010. VINCI provides secure access with high-quality computing capabilities to integrated Veterans Health Administration patient data from patient health records recorded in the VA Corporate Data Warehouse. **Figure 1** shows patient sample size, selection criteria for the study. The primary outcome was MACE, a composite of all-cause death, ischemic stroke, and nonfatal MI rates. These data were collected until December 30, 2020, using the VA Corporate Data Warehouse, and using applicable International Classification of Diseases-9 and -10 and Current Procedural Terminology codes. Patients were followed until an outcome event or for up to 10 years (**Central Illustration**). The study was approved by the Institutional Review Board of the VA North Texas Health Care System.

MISSING VALUE IMPUTATION. Missing values were imputed using multiple imputation (n = 100) with the multiple linear regression using variables from the Cox model. The proportion of missing variables in our study is 11.4%. For categorical variables, logistic regression was used. Missing values were imputed separately for the development and test cohorts.

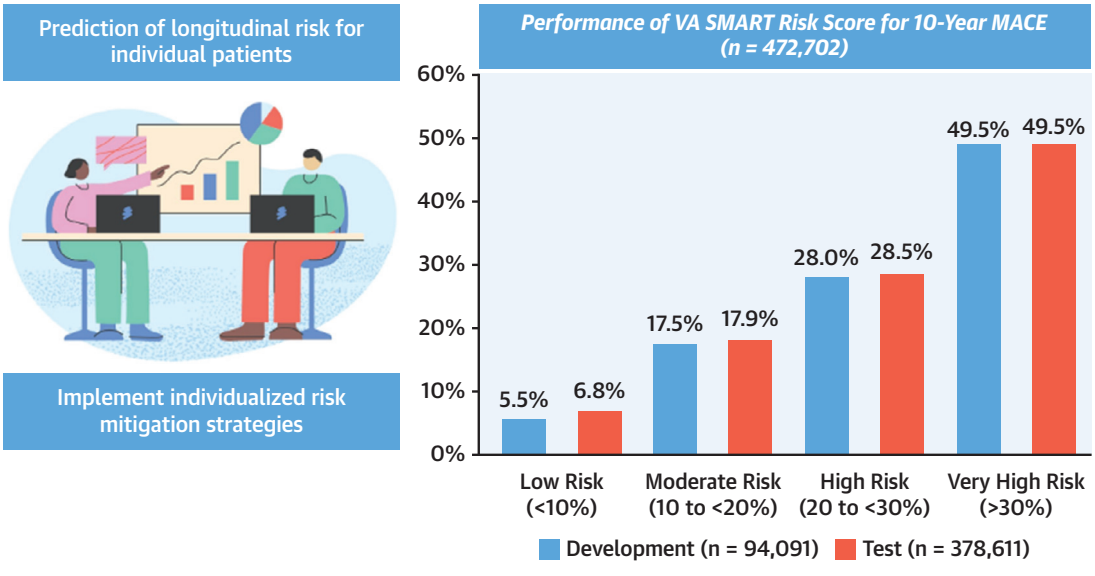
Inclusion of all 2-way categorical variable interactions was included in the missing model. An iterative Markov chain Monte Carlo method was used.

FIGURE 1 Study Cohort



Describes development of the study cohort. CPT = current procedural terminology; ICD = International Classification of Diseases (includes ICD-9 and -10).

CENTRAL ILLUSTRATION Estimating the Risk of Cardiovascular Events in U.S. Veterans Using the SMART Risk Score



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MACE = major adverse cardiovascular event.

To each predicted value, a residual was obtained from a randomly selected complete case. Error terms were chosen randomly from the observed residuals of complete cases to be added to the regression estimates. Singularity tolerance was set at 1×10^{-8}.

We tested the ability of the missing value approach we used to predict missing values, with 2.6% valid data. From a data set that had complete hsCRP data (n = 12,683), we randomly selected 97.4% of the cases to have a missing hsCRP. We then used the imputation of missing values (details above), to create an imputed data set. The difference between observed and predicted hsCRPs was −0.10 (SD = 1.40, skew = 0.60, kurtosis = −0.08). This indicates that even with a high rate of missing values, and 15 predictors, hsCRP was imputed with a moderate degree of accuracy (Supplemental Table 1, Supplemental Figure 1).

The pattern of missing values was analyzed using Little's missing completely at random test statistic to assess the data bias(es) in patterns of missing values. A nonsignificant Little's statistic ($P \geq 0.05$) indicates no departure from randomness in the missing values analyzed. Homogeneity of error variances was assessed using the Levene's test. Continuous predictors were trimmed at the 1st and 99th percentile to limit the effect of outliers, thus excluding medically implausible missing value estimates from analyses (n = 434). The sample was split into development (20% random sample without replacement) and test (80% random sample without replacement) cohorts. Following the split, missing values were imputed (n = 100 imputations before convergence). The Cox regression model was developed using a random 20% sample of the study data (n = 94,091) following imputation. A Cox regression proportional hazards model predicted MACE in the development cohort (n = 378,611) using independent variables of age, sex, smoking, time (in years) with CVD diagnoses from the first VA cardiology visit and clinical parameters (average systolic blood pressure, history of DM, CAD, cerebrovascular disease, abdominal aortic aneurysm, peripheral vascular disease, high-density lipoprotein cholesterol, total cholesterol, estimated glomerular filtration rate [eGFR], and hsCRP). Clinical variables included in our VA SMART risk score model were based on the SMART risk score originally proposed by Dorresteijn et al in 2013. Model fit was improved by adding the quadratic of age and eGFR since they had a nonlinear component. In addition, hsCRP was not linear, and the natural log transformation was used in the analysis. Model coefficients were estimated using the maximum likelihood method. The MACE prediction model was fitted for predicting 10-year risk. Patients who did not have MACE during the follow-up period in the study, and who survived event free to 10 years were censored from the survival analysis. The −2 log likelihood and Gronnesby and Borgan tests were used to assess Cox regression model fit. The proportional hazard assumption was assessed by testing the correlations between scaled Schoenfeld residuals for the various predictors and time. This VA SMART risk score test performance was tested in the remaining 80% of the study population (n = 378,611). The model's ability to discriminate between groups (ie, the ability to correctly classify patients with MACE events from those who did not) was evaluated with the concordance statistic, indicating the correctness of individuals classified. It was computed for the development, test, and overall cohorts for MACE. Model calibration, reflecting the precision of how closely predicted probabilities were to the observed risk, was demonstrated by calibration plots. The event indicator variables and time to event were regressed on the Cox regression-derived probabilities. Within each category, predicted risk was compared to observed Kaplan-Meier (K-M) survival. Log-rank, Breslow, and Tarone-Ware tests were conducted for the K-M model. All quantitative variables were used for Cox regression and K-M estimation. The hsCRP variable was estimated in 98% of cases as in the original SMART risk score analysis.

For the test cohort, the calibrated curve was projected using a slope of 0.84 SE = 0.06. The 4 SMART risk groups: <10% (low), 10 to <20% (moderate), 20 to <30% (high) were very close to the line of identity. The ≥30% (very high) group is an aggregate that runs from 30% to 90% and was not able to calibrate to the reference line.

Goodness-of-fit tests were used to assess the development and test cohorts with −2 log likelihood test and the Gronnesby and Borgan test. The net benefit of prediction-based decision-making was determined using decision curve analysis. Analyses were conducted with SAS v9.4 (SAS Institute Inc), IBM SPSS v29 (IBM), and R statistical software V.4.2.1 (R Foundation for Statistical Computing) using add-on packages.

RESULTS

STUDY POPULATION. Baseline characteristics of 472,702 patients were identified and stratified into VA SMART risk score low, moderate, high, and very

TABLE 1 Baseline Characteristics: SMART Risk Score Variables

	Low Risk (n = 18,839)	Moderate Risk (n = 69,033)	High Risk (n = 113,315)	Very High (n = 271,515)	*P* Value		
					Low Vs Moderate	Moderate Vs High	High Vs Very High
Age at first cardiology visit (y)	38.5 ± 8.40	51.4 ± 6.38	57.7 ± 5.19	64.7 ± 6.04	<0.001	<0.001	<0.001
Time from diagnosis to first cardiology visit (y)	2.67 ± 1.47	2.45 ± 1.58	2.53 ± 1.77	3.32 ± 2.38	<0.001	<0.001	<0.001
Average of closest 5 systolic blood pressures (mm Hg)	127.4 ± 13.7	130.5 ± 15.0	131.4 ± 15.4	132.3 ± 15.8	<0.001	<0.001	<0.001
hsCRP (mg/L)	0.928 ± 2.64	1.24 ± 3.44	1.45 ± 4.08	1.78 ± 5.31	0.008	0.011	<0.001
eGFR (mL/min/m^2)	92.2 ± 22.1	86.1 ± 22.3	81.4 ± 22.4	72.2 ± 24.1	<0.001	<0.001	<0.001
HDL (mg/dL)	43.7 ± 13.3	41.4 ± 12.9	41.0 ± 12.8	40.7 ± 13.2	<0.001	<0.001	<0.001
Total cholesterol (mg/dL)	198.2 ± 52.7	192.7 ± 46.5	180.4 ± 42.6	165.2 ± 39.5	<0.001	<0.001	<0.001
Body mass index (kg/m^2)	30.9 ± 6.72	31.3 ± 6.57	30.8 ± 6.48	30.3 ± 6.30	<0.001	<0.001	<0.001
Hemoglobin A1c	5.76 ± 1.05	6.27 ± 1.68	6.58 ± 1.58	6.90 ± 2.86	<0.001	<0.001	<0.001
LDL (mg/dL)	122 ± 38.6	117 ± 38.0	107 ± 35.4	95 ± 32.6	<0.001	<0.001	<0.001
Triglycerides (mg/dL)	176 ± 254	188 ± 187	173 ± 145	161 ± 120	<0.001	<0.001	<0.001
Erythrocyte sedimentation rate	16.7 ± 18.9	19.0 ± 21.8	21.9 ± 23.8	28.7 ± 27.9	<0.001	<0.001	<0.001

eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.

high-risk groups (Tables 1 and 2). Majority of patients included were men and nearly 65% assigned to the very high-risk group. The mean age ranged between 38.5 ± 8.4 years in the low-risk group to 64.7 ± 6.0 years in the very high ($P = 0.0001$). The prevalence of DM, CAD, CVD, peripheral artery disease, abdominal aortic aneurysm, and the duration of CVD were expectedly higher in the very high-risk group compared with other groups. All comparisons were statistically significant ($P < 0.001$). Mean values for total cholesterol, low-density lipoprotein, high-density lipoprotein, and eGFR were lower in the very high-risk group compared with low, moderate, and high risk. Mean systolic blood pressure was highest in the very high-risk group. These comparisons were statistically significant with $P < 0.001$.

The entire study cohort (n = 472,702) was randomly divided into development (n = 94,091) and test cohorts (n = 378,611) using random sampling without replacement. The median follow-up time was 7.9 years (IQR: 6.0-9.9 years).

TABLE 2 Baseline Characteristics: Risk Factors and Medications

	Low Risk (n = 18,839)	Moderate Risk (n = 69,033)	High Risk (n = 113,315)	Very High Risk (n = 271,515)	*P* Value		
					Low Risk Vs Moderate	Moderate Vs High Risk	High Vs Very High
Male	12,584 (66.7%)	62,618 (90.7%)	110,536 (97.5%)	269,414 (99.2%)	<0.001	<0.001	<0.001
Coronary artery disease	3,286 (17.4%)	29,159 (42.2%)	62,866 (55.5%)	189,022 (69.6%)	<0.001	<0.001	<0.001
Abdominal aortic aneurysm	32 (0.2%)	243 (0.35%)	995 (0.9%)	13,873 (5.1%)	<0.001	<0.001	<0.001
Cerebrovascular disease	186 (1.0%)	1,277 (1.8%)	3,777 (3.3%)	29,691 (10.9%)	<0.001	<0.001	<0.001
Diabetes mellitus	496 (2.6%)	7,265 (10.5%)	25,874 (22.8%)	142,225 (52.4%)	<0.001	<0.001	<0.001
Peripheral vascular disease	11 (0.1%)	117 (0.2%)	760 (0.7%)	23,362 (8.6%)	0.001	<0.001	<0.001
Smoking (active)	3,044 (16.2%)	19,677 (28.5%)	41,990 (37.1%)	132,156 (48.7%)	<0.001	<0.001	<0.001
White	11,396 (60.5%)	48,214 (69.8%)	85,150 (75.1%)	207,888 (76.6%)	<0.001	<0.001	<0.001
African American	5,445 (28.9%)	14,544 (21.1%)	17,838 (15.7%)	35,426 (13.0%)	<0.001	<0.001	<0.001
Chronic kidney disease	11,187 (59.4%)	46,260 (67.0%)	80,475 (71.0%)	213,365 (78.6%)	<0.001	<0.001	<0.001
Statin	5,958 (31.6%)	41,286 (59.8%)	79,212 (70.0%)	216,888 (79.9%)	<0.001	<0.001	<0.001
Beta-blockers	4,830 (25.6%)	30,091 (43.6%)	57,141 (50.4%)	152,888 (56.3%)	<0.001	<0.001	<0.001
Aspirin	4,789 (25.4%)	32,531 (47.1%)	64,030 (56.5%)	181,745 (66.9%)	<0.001	<0.001	<0.001
Angiotensin converting enzyme inhibitor/ angiotensin receptor blocker	5,570 (29.6%)	36,846 (53.4%)	72,464 (63.9%)	209,227 (77.1%)	<0.001	<0.001	<0.001

TABLE 3 Model Coefficients and Hazard Ratios

	B	Standard Error	*P* Value	HR	95% CI
Age	0.033	0.007	0.001	1.033	1.019-1.048
Age^2	0.00015	0.000003	0.014	1.000	1.000-1.000
Male	0.445	0.042	0.001	1.560	1.437-1.694
Smoker	0.450	0.011	0.001	1.569	1.535-1.603
Systolic blood pressure	0.00043	0.00035	0.217	1.000	0.000-1.000
Diabetes mellitus	0.373	0.011	0.001	1.452	1.421-1.484
Coronary artery disease	0.198	0.012	0.001	1.219	1.191-1.247
Cerebrovascular disease	0.260	0.017	0.001	1.297	1.253-1.342
Abdominal aortic aneurysm	0.246	0.015	0.001	1.279	1.219-1.342
Peripheral vascular disease	0.432	0.019	0.001	1.540	1.482-1.599
Time from diagnosis to first cardiology visit (y)	0.019	0.002	0.001	1.019	1.015-1.024
HDL	0.106	0.017	0.001	1.112	1.075-1.150
Total cholesterol	−0.055	0.005	0.001	0.947	0.937-0.957
eGFR	−0.027	0.001	0.001	0.973	0.972-0.975
eGFR^2	0.00016	0.000005	0.001	1.000	1.000-1.000
Ln hsCRP	0.008	0.003	0.022	1.008	1.001-1.015

Abbreviations as in Table 1.

MODEL DEVELOPMENT. Penalized maximum likelihood estimation was used. The coefficients of 14 predictors and HRs for MACE are presented but required no penalty factor (Table 3). Minor nonproportionality was found for eGFR^2 and age^2, but it was insufficient to violate Cox proportional hazards assumptions. However, coefficients for eGFR^2 and age^2 were consistently positive over time. Nonproportionality was not noted for other coefficients. Cox proportional hazards assumptions were satisfied. The most notable and statistically significant modifiable risk factors that increased the probability of MACE were smoking, DM, and peripheral artery disease.

MODEL TEST. Table 4 includes the summary statistics of performance and shows that our model had a good fit for the development and test data sets. The lack of significance in the summary statistic of performance indicates a good fit. Goodness of fit for the Cox regression for the development and test cohorts are shown in Tables 5 and 6, respectively, using the Mantel-Cox, Breslow, and Taron-Ware tests for survival analyses. Here, a significant *P* value indicates a good fit. The calibration plots of 10-year versus observed event-free survival (ie,1-risk) for the model improved the line fit with respect to the line of identity (Supplemental Figures 2A and 2B). The uncalibrated model underestimated the observed probability of MACE. The calibrated model overestimated the observed probability of MACE, in the highest risk group.

SURVIVAL ANALYSIS. Figure 2 depicts VA SMART risk score prediction in development and test cohorts. Figure 3 depict the survival analyses of the development and test cohorts, respectively. The figures include K-M survival curves for the 4 SMART risk groups along with the HRs from a Cox regression analyses for each of the groups. They demonstrate that the predicted risk closely parallels

TABLE 4 Summary Statistics of Model Performance

Development cohort (n = 94,901)	
Goodness of fit test	*P* = 0.59
Concordance	67.7
Test cohort (n = 378,611)	
Goodness of fit test	*P* = 0.60
Concordance	66.7
Overall cohort (n = 472,702)	
Goodness of fit test	*P* = 0.67
Concordance	66.6

TABLE 5 Goodness of Fit Tests for the Derivation Cohort

Overall Comparisons			
	Chi-Square	df	*P* Value
Log rank (Mantel-Cox)	6,409.773	1	<0.001
Breslow (generalized Wilcoxon)	6,256.187	1	<0.001
Tarone-Ware	6,361.698	1	<0.001

The vector of trend weights are −3, −1, 1, 3. This is the default.

TABLE 6 Goodness of Fit Tests for the Test Cohort

Overall Comparisons			
	Chi-Square	df	*P* Value
Log rank (Mantel-Cox)	28,287.740	1	<0.001
Breslow (generalized Wilcoxon)	27,583.545	1	<0.001
Tarone-Ware	28,060.733	1	<0.001

The vector of trend weights are −3, −1, 1, 3. This is the default.

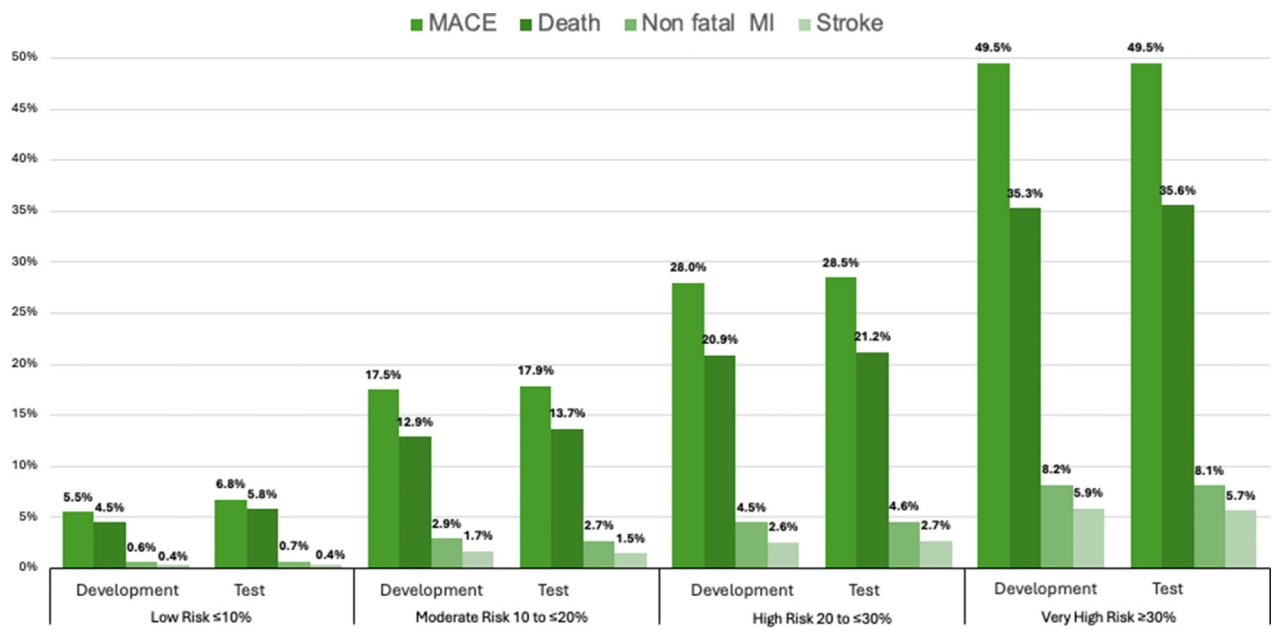
the observed risk. K-M event rates for MACE and its components for all SMART risk score groups in the development and test cohorts are shown in Tables 7 and 8. Time to event analyses for the development and test cohorts are shown in Tables 9 and 10. The very high SMART risk group includes the largest number of patients with the highest MACE rates, primarily driven by all-cause death and shortest time to event.

The decision curve analysis for MACE indicates that at the threshold probability between approximately 25% (lower) and 75% (upper), interventions based on the VA SMART risk score may prove beneficial in favorably impacting the probability of MACE (Figure 4). The net benefit, however, is small, does not exceed 25% and is likely to reduce the risk for MACE by <10% under most circumstances. The threshold probability represents treatment decision preference. A threshold probability of 50% or preference 1:1, interprets as missing to prevent a single MACE is equally worse as treating an unnecessary patient with a high-risk and expensive medication. Hence, at this threshold probability using VA SMART risk score model would be most beneficial. The unit of net benefit is individuals saved from MACE. A net benefit of 0.4, for instance, means 40 patients prevented from MACE for every 100 patients treated in the target population by applying the VA SMART risk score model for risk stratification.

DISCUSSION

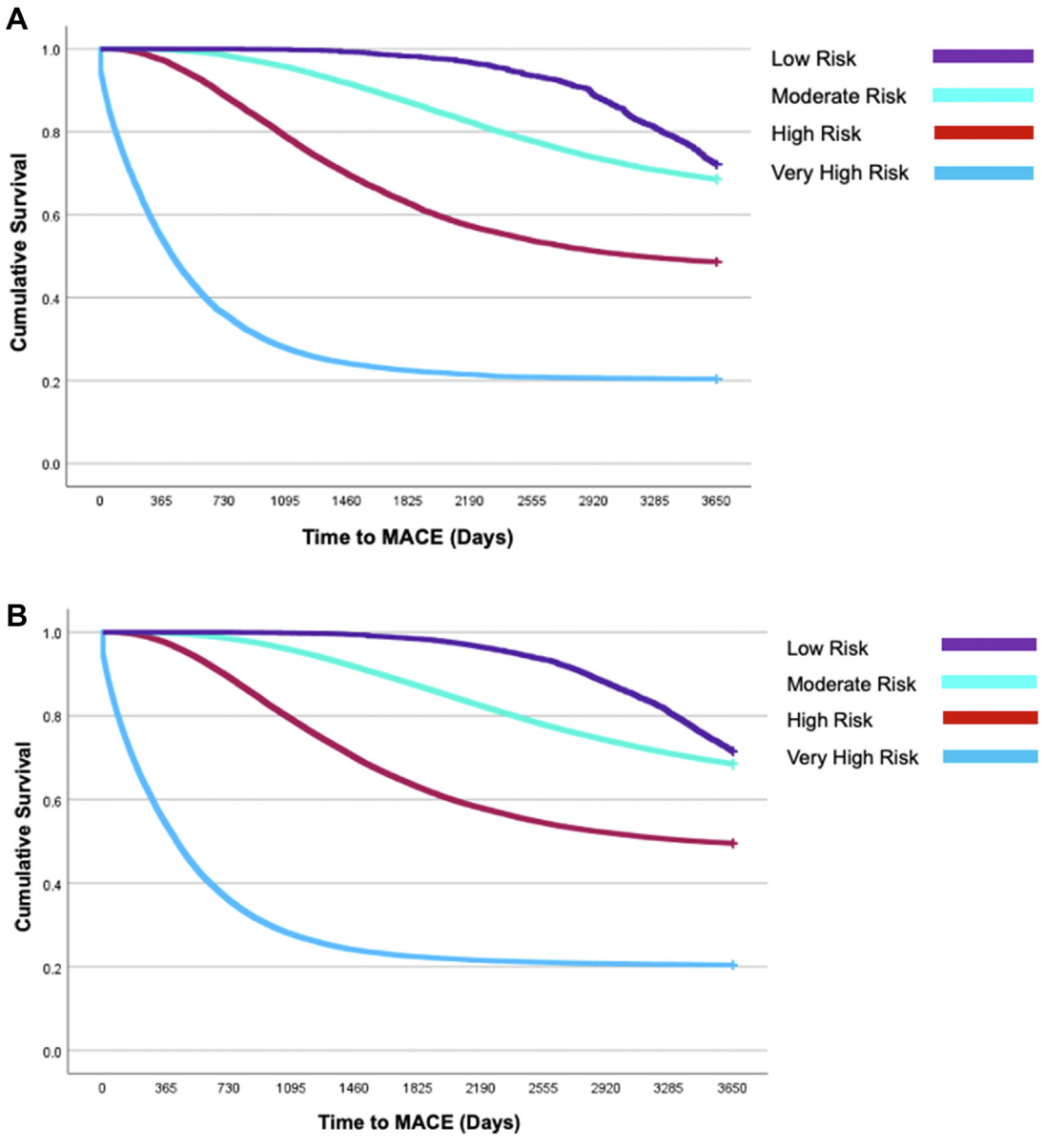
In our study of 472,702 U.S. Veterans, one of the largest to date application of the SMART risk score method, the calibrated and validated VA SMART risk score model predicted 10-year MACE rates in patients with established CVD referred for cardiovascular evaluation in the VA Healthcare System. The VA SMART risk score model was developed from a 94,091-patient cohort and validated in a 378,611-patient cohort with predicted MACE risk that was closely aligned to the observed risk. The 4 SMART risk score groups demonstrated substantial variation in 10-year risk of MACE. As with the original SMART risk

FIGURE 2 Performance of VA SMART Risk Score Prediction in Development and Test Cohorts



MACE = major adverse cardiovascular event; MI = myocardial infarction; Stroke = ischemic stroke.

FIGURE 3 Survival Analysis for Major Adverse Cardiovascular Events in Development Cohort and in the Test Cohort



(A) survival analysis for major adverse cardiovascular events in development cohort. (B) survival analysis for major adverse cardiovascular events in test cohort. Abbreviation as in Figure 2.

score, the risk score comprises 14 easy to derive clinical risk predictors that can be readily utilized in clinical practice to risk stratify patients with CVD, direct cost-effective secondary prevention measures, and inform patients of their personalized longitudinal cardiovascular event risk.

Our results are based on seminal work conducted by Dorresteijn and colleagues who originally conceptualized and validated the SMART risk score in a Dutch population.[8] The SMART risk score has also been applied to clinical trial populations and to those enrolled in international registries such as The

TABLE 7 Kaplan-Meier Major Adverse Cardiovascular Event Rates for the Development Cohort

Smart Score Risk Prediction[a]	Sample Size	MACE	Death	MI	Ischemic Stroke
Low risk	3,741	205 (5.5)	169 (4.5)	21 (0.6)	15 (0.4)
Moderate risk	13,644	2,382 (17.5)	1,755 (12.9)	398 (2.9)	229 (1.7)
High risk	22,569	6,333 (28.0)	4,728 (20.9)	1,014 (4.5)	591 (2.6)
Very high risk	54,137	26,782 (49.5)	19,122 (35.3)	4,460 (8.2)	3,200 (5.9)

Values are n or n (%). [a]Every comparison between groups is significant ($P < 0.001$).
MACE = major adverse cardiovascular event.

UCC-SMART (Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease) and the REACH (REduction of Atherothrombosis for Continued Health).[14,15] The attributes of the VA Healthcare System as one of the world's largest integrated health benefit plans was crucial in compiling longitudinal data in our study with low historic rates of out of network care episodes over the study period.[16] We believe that our effort will help pave the way for applying the SMART risk score to diverse health care system electronic medical records.[17]

Health care providers have traditionally used their clinical experience and judgment to assess risk and prognosis of patients by ascribing relative weights to variables such as baseline characteristics, clinical signs, and laboratory or imaging tests.[18] Subgroup analyses and meta-analyses of clinical trials often demonstrate similar relative risk reduction for most patients. Therefore, risk assessment scores derived from multivariable predictors can provide a more objective and unbiased estimation of risk and prognosis. This is depicted by the test of the SMART risk score in a broad U.S. Veteran population with a C-statistic of 0.67. This C-statistic value may be considered in the moderate range; however, it is comparable to other concordance statistics reported in secondary prevention risk estimation studies.[15] Calibration in our study was good, except for an overestimation in the group with >30% 10-year risk, which could arguably be further stratified. We therefore believe that the SMART risk score could assist clinicians improve their risk estimation of CVD patients.

Our analysis could be interpreted to improve clinical outcomes through optimal targeting of high-risk individuals. Such individuals may have a potentially larger absolute risk reduction with personalized interventions. It can also help avoid prescribing certain costly and often unnecessary treatments to those at a lower risk of MACE. Such an interpretation is in line with previous studies of SMART risk score-based stratification of patients with cardiovascular diagnoses.[19] However, the uniqueness of the current analysis from the VA Healthcare System is that the very high-risk cohort is most populous, with the highest MACE rates (≥30%), shortest time to MACE, and a steep downward trajectory of MACE-free survival within the first year of follow-up. A prudent interpretation of these findings could be that highly efficacious secondary prevention interventions with a large absolute risk reduction would be needed to alter the impending risk of MACE over a relatively short period of time for individuals predicted to be at the highest risk based on their VA SMART risk score. Such medical interventions are unknown at this time.[20] Further analyses assessing the benefit of early screening and potentially of early intervention in these individuals are necessary to estimate the net

TABLE 8 Kaplan-Meier Major Adverse Cardiovascular Event Rates for the Test Cohort

Smart Score Risk Prediction[a]	Sample Size	MACE	Death	MI	Ischemic Stroke
Low risk	15,098	1,022 (6.8)	869 (5.8)	100 (0.7)	53 (0.4)
Moderate risk	55,389	9,924 (17.9)	7,591 (13.7)	1,508 (2.7)	825 (1.5)
High risk	90,746	25,845 (28.5)	19,220 (21.2)	4,168 (4.6)	2,457 (2.7)
Very high risk	217,378	107,564 (49.5)	77,433 (35.6)	17,716 (8.1)	12,415 (5.7)

Values are n or n (%). [a]Every comparison between groups is significant ($P < 0.001$).
Abbreviation as in Table 7.

TABLE 9 Time to Major Adverse Cardiovascular Event Analysis Rates for the Development Cohort

Smart Score Risk Prediction[a]	Sample Size	MACE	Time to MACE (Days)	
			Mean	95% CI
Low risk	3,741	205 (5.5)	3,545	3,529-3,562
Moderate risk	13,644	2,382 (17.5)	3,323	3,309-3,337
High risk	22,569	6,333 (28.0)	3,111	3,097-3,124
Very high risk	54,137	26,782 (49.5)	2,636	2,626-2,647

Values are n or n (%) unless otherwise indicated. [a]Every comparison between groups is significant ($P < 0.001$). Abbreviation as in Table 7.

benefit of specific treatments. These data have the granularity to provide individual estimates of benefits of specific intervention. Through an analysis of longitudinal prescription data of patients, it may be possible to suggest medication(s) with the greatest efficacy. Additional studies assessing marginal risk reduction using novel therapies in each patient group are needed to evaluate the optimal benefit and the most efficient resource allocation for risk reduction strategies.[21-23] Perhaps, only operative or device interventions such as transcatheter aortic valve implantation or aortic aneurysm repair are examples of therapies with a large absolute benefit that could be more applicable to the appropriately selected very high-risk patients with precipitously low rates of event-free survival.[24,25]

The decision curve analysis shows the highest estimated clinical usefulness of the VA SMART risk score is when the decision-threshold is between 25% and 75%.[26] Adopting a lower threshold would favor sensitivity (clinicians concerned about not missing true positives). While choosing a higher threshold would favor specificity by minimizing false positives. The application of the VA SMART risk score could provide an incremental net benefit for more aggressive treatment to prevent MACE, across increasing risk, but greatest likelihood occurring where the area under the curve in the decision curve is the greatest. Therefore, the decision curve analysis in our study provides a measure of clinical utility of the VA SMART risk score, the net benefit. By accounting for both discrimination and calibration properties of the model, it provides an estimate of the net balance of benefits and harms of an intervention.

TABLE 10 Time to Major Adverse Cardiovascular Event Analysis Rates for the Test Cohort

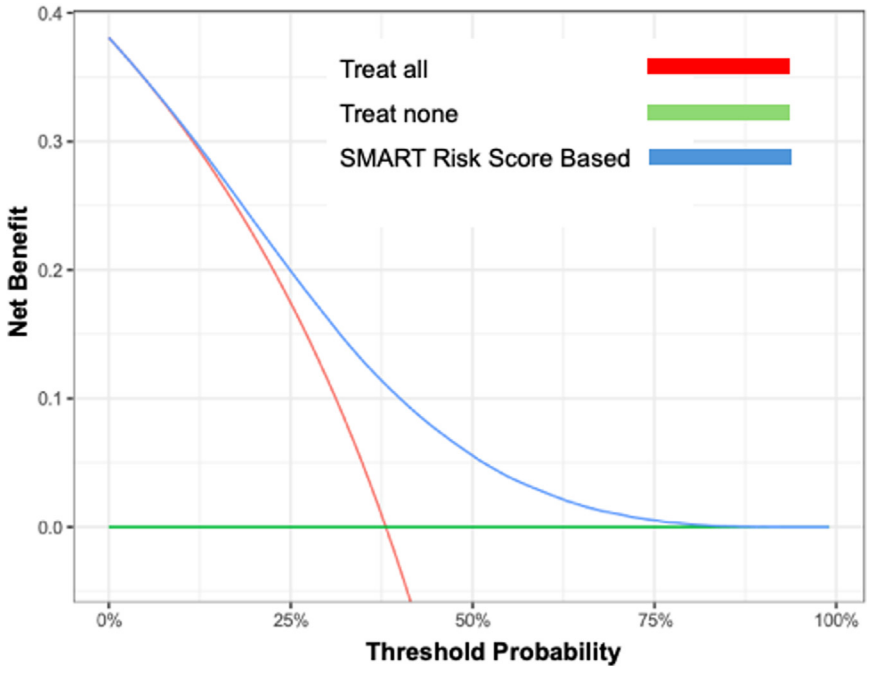
Smart Score Risk Prediction[a]	Sample Size	MACE	Time to MACE (Days)	
			Mean	95% CI
Low risk	15,098	1,022 (6.8)	3,523	3,514-3,532
Moderate risk	55,389	9,924 (17.9)	3,308	3,301-3,315
High risk	90,746	25,845 (28.5)	3,101	3,094-3,108
Very high risk	217,378	107,564 (49.5)	2,640	2,634-2,645

Values are n or n (%) unless otherwise indicated. [a]Every comparison between groups is significant ($P < 0.001$). Abbreviation as in Table 7.

Other risk scores discriminate between patients with pre-existing CVD who are at low to very high risk of MACE. Among these secondary prevention scores, the TIMI Risk Score for Atherothrombosis in Diabetes is the only 1 that has been applied to clinical settings, the TIMI Risk Score, however, does not account for atherosclerotic disease across coronary and non-coronary arterial beds or multivascular disease in non-DM patients.[9] The REACH Registry highlighted the relevance of polyvascular disease by reporting 1-year cardiovascular event rates of approximately 13%, 21%, and 26% for individuals with atherosclerotic disease involving 1, 2, and 3 arterial beds, respectively.[27] Similar attempts at developing risk assessment tools have been previously based on available clinical trial data. These include the Framingham Risk Score in post-PCI patients, EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease), ACTION (Effect of Long-acting Nifedipine on Mortality and Cardiovascular Morbidity in Patients with Stable Angina Requiring Treatment), GISSI-Prevenzione (Gruppo Italiano per lo Studio della Sopravvivenza Nell'Infarto Miocardico Acuto-1 Prevenzione), and LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) trials.[28-31] The key limitations of these studies in addition to being restricted to specific patient groups, such as post-PCI or post-MI, are that they were invariably restricted by the enrollment criteria of the parent studies, included narrowly defined atherosclerotic cardiovascular disease diagnoses, and limited follow-up duration.

Based on the VA SMART risk score's potential for personalized clinical decision-making, the present model can aid clinicians and health policymakers in identifying and directing secondary prevention medical therapies. These may include proprotein convertase subtilisin/kexin type 9 inhibitors, anti-interleukin1ß monoclonal antibodies, low-dose colchicine, interference silencing low-density lipoproteins or lipoprotein A mRNA, low-dose rivaroxaban, or extended durations of P2Y12 inhibitors.[32] Inclusion of measures such as functional status, frailty, coronary calcification burden, and coronary angiographic variables could further enhance the performance of the SMART risk score. A relevant and under-explored dimension of the VA SMART risk score is its utility for analysis and prediction of

FIGURE 4 SMART Risk Score Decision Analysis Curve for Major Adverse Cardiovascular Events



longitudinal risk for individual patients, inclusive of a paradigm to visualize alterations of their risk profile by changing parameters of the risk with treatment and/or life-style modification. This could be captured via a patient engagement portal and potentially incentivize adoption and compliance with secondary prevention recommendations.

STUDY LIMITATIONS. First, our study lacks external validation outside the high-risk VA patient population, although one such validation is planned to utilize a non-VA Healthcare System electronic medical record. Also, the VA SMART risk score prediction for MACE omits medication use data, and in turn, includes values such as blood pressure, lipoprotein levels, and eGFR. Finally, the C-statistic of the VA SMART risk score is modest, however in-line with other secondary prevention score models. The Decision Support System stop codes within the VA Healthcare system was used for identification of patient referrals. Our patient segmentation is based on such stop codes and limited by the accuracy of such documentation available within the VINCI database used for this study. Finally, there is nearly no gender diversity in our study of U.S. Veterans. Given the homogeneity of age and traditional risk factor profiles of patients with established CVD, future risk of MACE can often be hard to predict using clinical variables such as age or risk factors alone, and application of the VA SMART risk score can certainly improve discrimination.

CONCLUSIONS

The VA SMART score can effectively predict risk for cardiovascular events in U.S. Veteran patients with established atherosclerotic cardiovascular disease. Further test studies are required to confirm the applicability of the VA-SMART score to the larger and more diverse civilian U.S. population.

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GE Healthcare, IMDS, Medtronic, and Teleflex; has received research support from Boston Scientific, GE Healthcare; is an owner of Hippocrates LLC; is a shareholder in MHI Ventures, Cleerly Health, Stallion Medical. Dr Stoler is a consultant and advisory board member for Medtronic, Boston Scientific Corporation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Wong ND, Budoff MJ, Ferdinand K, et al. Atherosclerotic cardiovascular disease risk assessment: an American society for preventive cardiology clinical practice statement. *Am J Prev Cardiol*. 2022;10:100335.

2. Zelko A, Salerno PRVO, Al-Kindi S, et al. Geographically weighted modeling to explore social and environmental factors affecting county-level cardiovascular mortality in people with diabetes in the United States: a cross-sectional analysis. *Am J Cardiol*. 2023;209:193–198.

3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American college of cardiology/American Heart association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73(24):e285–e350. https://doi.org/10.1016/j.jacc.2018.11.003

4. Virani SS, Smith SC Jr, Stone NJ, Grundy SM. Secondary prevention for atherosclerotic cardiovascular disease: comparing recent US and European guidelines on dyslipidemia. *Circulation*. 2020;141(14):1121–1123.

5. Sedhom R, Hamed M, Tan W, et al. Meta-analysis on the clinical outcomes with polypills for cardiovascular disease prevention. *Am J Cardiol*. 2023;201:211–218.

6. Mhaimeed O, Burney ZA, Schott SL, Kohli P, Marvel FA, Martin SS. The importance of LDL-C lowering in atherosclerotic cardiovascular disease prevention: lower for longer is better. *Am J Prev Cardiol*. 2024;18:100649.

7. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American college of cardiology/American heart association task force on practice guidelines. *Circulation*. 2014;129(25 Suppl 2):S49–S73. https://doi.org/10.1161/01.cir.0000437741.48606.98

8. Dorresteijn JA, Visseren FL, Wassink AM, et al. Development and test of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. *Heart*. 2013;99(12):866–872.

9. Berg DD, Moura FA, Bellavia A, et al. Assessment of atherothrombotic risk in patients with type 2 diabetes mellitus. *J Am Coll Cardiol*. 2023;81(25):2391–2402.

10. Kaasenbrood L, Boekholdt SM, van der Graaf Y, et al. Distribution of estimated 10-year risk of recurrent vascular events and residual risk in a secondary prevention population. *Circulation*. 2016;134(19):1419–1429.

11. Vance MC, Wiitala WL, Sussman JB, Pfeiffer P, Hayward RA. Increased cardiovascular disease risk in veterans with mental illness. *Circ Cardiovasc Qual Outcomes*. 2019;12(10):e005563.

12. Jeon-Slaughter H, Chen X, Tsai S, Ramanan B, Ebrahimi R. Developing an internally validated veterans Affairs women cardiovascular disease risk score using veterans Affairs National electronic health records. *J Am Heart Assoc*. 2021;10(5):e019217.

13. Deo SV, Althouse A, Al-Kindi S, et al. Validating the SMART2 score in a racially diverse high-risk nationwide cohort of patients receiving coronary artery bypass grafting. *J Am Heart Assoc*. 2023;12(21):e030757.

14. Castelijns MC, Helmink MAG, Hageman SHJ, et al. Cohort profile: the utrecht cardiovascular cohort-second manifestations of arterial disease (UCC-SMART) study-an ongoing prospective cohort study of patients at high cardiovascular risk in The Netherlands. *BMJ Open*. 2023;13(2):e066952.

15. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, et al. Estimated life expectancy without recurrent cardiovascular events in patients with vascular disease: the SMART-REACH model. *J Am Heart Assoc*. 2018;7(16):e009217.

16. Rose L, Tran D, Wu S, Dalton A, Kirsh S, Vashi A. Payer shifting after expansions in access to private care among veterans. *Health Serv Res*. 2023;58(6):1189–1197.

17. Heider AK, Mang H. Integration of risk scores and integration capability in electronic patient records. *Appl Clin Inform*. 2022;13(4):828–835.

18. Khambhati J, Allard-Ratick M, Dhindsa D, et al. The art of cardiovascular risk assessment. *Clin Cardiol*. 2018;41(5):677–684. https://doi.org/10.1002/clc.22930

19. Siniawski D, Masson G, Masson W, et al. Residual cardiovascular risk, use of standard care treatments, and achievement of treatment goals in patients with cardiovascular disease. *Int J Cardiol Cardiovasc Risk Prev*. 2023;18:200198.

20. Morgan DJ, Pineles L, Owczarzak J, et al. Clinician conceptualization of the benefits of treatments for individual patients. *JAMA Netw Open*. 2021;4(7):e2119747.

21. Waters DD, Hsue PY. PCSK9 inhibition to reduce cardiovascular risk: tempering expectations. *Circ Res*. 2017;120(10):1537–1539.

22. Lamy A, Eikelboom J, Tong W, et al. The cost-effectiveness of rivaroxaban plus aspirin compared with aspirin alone in the compass trial: a US perspective. *Am J Cardiovasc Drugs*. 2024;24(1):117–127.

23. Agnello F, Ingala S, Laterra G, Scalia L, Barbanti M. Novel and emerging LDL-C lowering strategies: a new era of dyslipidemia management. *J Clin Med*. 2024;13(5):1251.

24. Kumar V, Sandhu GS, Harper CM, Ting HH, Rihal CS. Transcatheter aortic valve replacement programs: clinical outcomes and developments. *J Am Heart Assoc*. 2020;9(8):e015921.

25. Reimerink JJ, Hoornweg LL, Vahl AC, et al. Endovascular repair versus open repair of ruptured abdominal aortic aneurysms: a multicenter randomized controlled trial. *Ann Surg*. 2013;258(2):248–256. https://doi.org/10.1097/SLA.0b013e31828d4b76

26. Piovani D, Sokou R, Tsantes AG, Vitello AS, Bonovas S. Optimizing clinical decision making with decision curve analysis: insights for clinical investigators. *Healthcare (Basel)*. 2023;11(16):2244.

27. Suárez C, Zeymer U, Limbourg T, et al. Influence of polyvascular disease on cardiovascular event rates. Insights from the REACH Registry. *Vasc Med*. 2010;15(4):259–265.

28. Sara JD, Lennon RJ, Gulati R, et al. Utility of the Framingham Risk Score in predicting secondary events in patients following percutaneous coronary intervention: a time-trend analysis. *Am Heart J*. 2016;172:115–128.

29. Battes L, Barendse R, Steyerberg EW, et al. Development and test of a cardiovascular risk assessment model in patients with established coronary artery disease. *Am J Cardiol*. 2013;112(1):27–33.

30. Clayton TC, Lubsen J, Pocock SJ, et al. Risk score for predicting death, myocardial infarction, and stroke in patients with stable angina, based on

a large randomised trial cohort of patients. *BMJ*. 2005;331(7521):869.

31. Marschner IC, Colquhoun D, Simes RJ, et al. Long-term intervention with Pravastatin in ischemic disease (LIPID) study. Long-term risk stratification for survivors of acute coronary syndromes. Results from the long-term intervention with Pravastatin in ischemic disease (LIPID) study. LIPID study investigators. *J Am Coll Cardiol*. 2001;38(1):56–63.

32. Kalbacher D, Waldeyer C, Blankenberg S, Westermann D. Beyond conventional secondary prevention in coronary artery disease-what to choose in the era of CANTOS, COMPASS, FOURIER, ODYSSEY and PEGASUS-TIMI 54? A review on contemporary literature. *Ann Transl Med*. 2018;6(16):323.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.