Risk Score for Long-Term Survival and Major Adverse Cardiovascular and Cerebrovascular Events After Coronary Artery Bypass Grafting Surgery



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To develop risk scoring models predicting long-term survival and major adverse cardiovascular and cerebrovascular events (MACCEs), including myocardial infarction and stroke after coronary artery bypass grafting (CABG). All 4,821 consecutive patients who underwent isolated CABG at Lankenau between January 2005 and July 2021 were included. MACCE was defined as all-cause mortality + myocardial infarction + stroke. Variable selection for both outcomes was obtained using a double-selection logit least absolute shrinkage and selection operator with adaptive selection. Model performance was internally evaluated by calibration and accuracy using bootstrap cross-validation. Mortality and MACCEs were compared in patients split into 3 groups based on the predicted risk scores for all-cause mortality and MACCEs. An external validation of our database was performed with 665 patients from the University of Brescia, Italy. Preoperative risk predictors were found to be predictors for all-cause mortality and MACCEs. In addition, being of African-American ethnicity is a significant predictor for MACCEs after isolated CABG. The areas under the curve (AUCs), which measures the discrimination of the models, were 80.4%, 79.1%, 81.3%, and 79.2% for mortality at 1, 2, 3, and 5 years follow-up. The AUCs for MACCEs were 75%, 72.5%, 73.8%, and 72.7% at 1, 2, 3, and 5 years follow-up. For external validation, the AUCs for all-cause mortality and MACCEs at 1, 2, 3, and 5 years were 73.7%, 70.8%, 68.7%, and 72.2% and 72.3%, 68.2%, 65.6%, and 69.6%, respectively. The Advanced (AD) Coronary Risk Score for All-Cause Mortality and MACCE provide good discrimination of long-term mortality and MACCEs after isolated CABG. External validation observed a more AUCs greater than 70%. Elsevier Inc. All rights reserved. (Am J Cardiol 2024;225:10-21)

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Coronary artery bypass grafting (CABG) is the most performed cardiac surgery operation in the world, with over 800,000 patients who underwent CABG only in North America. Correct risk stratification is essential in the shared clinical decision-making process. The Society of Thoracic Surgeons (STS) predicted risk of mortality (PROM) risk score and EuroSCORE II are used to predict short-term prognosis in patients who underwent CABG.^{2,3}

However, both scores have major drawbacks, including the tendency to overestimate the mortality risk, being unreliable in high-risk patients, and lacking the ability to predict long-term outcomes.^{4,5} Therefore, an educated guess often replaces a precise estimation of the risk when a patient is interested in knowing of the risk of debilitating stroke or need repeat interventions beyond 30 days after CABG. In this context, patients deserve to know what their chance is

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to survive more than 30 days after the operation not only based on clinical trials outcomes but also mostly based on their unique individual risk profile. In addition, patients deserve to know if they are going to have a stroke event after 30 days from the operation because life after a devastating stroke event can be miserable. Being aware of this information will allow to create a major bond between surgeons and patients. In addition, this information is important, especially in low-resource countries where patients can afford only a single lifetime operation because of either medical costs or physical anatomy. Moreover, the existing risk score exclude important patient demographics, such as ethnicity, and is not externally validated. In this context, African-American patients have a higher rate of long-term complications than white patients. 7-10 Therefore, it is important for race to be included in a risk score. The goal of this manuscript is to develop a risk score for long-term all-cause mortality and another for major adverse cardiovascular and cerebrovascular events (MACCEs) after CABG that factors in race among the included predicting variables.

Methods

We identified all consecutive patients who underwent isolated CABG between May 2005 and June 2021 at the Lankenau Heart Institute (Lankenau Medical Center, Pennsylvania). The study protocol was approved by the Main Line Health Hospitals Institutional Review Board (45CFR164.512). Individual patient written informed consent was waived because of the retrospective nature of the study. The inclusion criteria were all patients aged >18 years who underwent isolated CABG. Patients with concomitant surgical procedures were excluded from the analysis. Patients were identified from a centralized cardiac surgery database for all isolated CABG operations. Clinical data were collected retrospectively from medical records. The underlying in-hospital outcomes were recorded from the charts and death certificate. Follow-up was done at our outpatient's clinic and from the hospital registry. The database used for external validation from the University of Brescia, included patients aged between 18 and 90 years who underwent isolated CABG. The local ethical committee approved the use of the database for the external validation of this

The primary objective was to develop a risk score for overall all-cause death and a risk score for MACCE in patients who underwent isolated CABG. MACCEs included all-cause mortality, nonfatal stroke, or myocardial infarction (MI).

Categorical variables were summarized as frequency and percentages, whereas continuous variables were summarized as mean and SD or median and interquartile range according to the variable distribution. Age and creatinine levels were represented as categorical variables in the models instead of continuous variables. All preoperative variables and the entire data set were included in the model-building process. Creatinine clearance was calculated according to the Cockcroft—Gault equation. Follow-up was based on the last clinical follow-up date or date of death, MI, or stroke. Patients lost to follow-up were

censored at the date of last known clinical follow-up. The risk factors to include in the models were based on literature review and then selected based on logit LASSO (least absolute shrinkage and selection operator) with adaptive selection. We tested risk score models by way of logit LASSO, double-selection LASSO, and Cox regression with stepwise selection. The final variable selection and estimates for both outcomes were obtained using a double-selection logit LASSO with adaptive selection, which was deemed superior to the Cox regression models because of the lower risk of overfitting. The results include odds ratios and confidence intervals. After the models were built, we internally validated the models by assessing calibration and accuracy (area under the receiver operating characteristic curve [AUC]) using bootstrap cross-validation. Calibration was assessed for 1-, 2-, 3-, and 5-year risk of all-cause mortality and MACCEs. Predicted probabilities were estimated using logistic regression with the outcome and the risk score. Ejection Fraction was categorized into 5 categories: 50+%, 40% to 49%, 30% to 39%, 20% to 29%, and <20%. The data were split into 10 groups based on the predicted probability and graphed against the observed risk for each group. We obtained the following calibration statistics: ratio of observed to expected risk and slope, with an optimal value when closer to 1, and the calibration in the large (CITL), with an optimal value close to 0. Statistics for cross-validation are the root mean square error and the AUC with bootstrap 95% confidence intervals. Lastly, we divided the patients into 3 groups based on the median and interquartile range of the predicted risk for all-cause mortality and MACCEs. These groups represent the low-, medium-, and high-risk groups. We graphed these risk groups using Kaplan—Meier and tested the differences by log-rank test. All analyses were performed in Stata 17.0 (StataCorp, LLC, College Station, Texas). The 95% confidence intervals and p values are reported, with a p <0.05 considered significant.

A data set of 988 patients who underwent CABG from Spedali Civili di Brescia, University of Brescia was used for external validation. We excluded any patients who were missing follow-up survival data, leaving 655 patients for the analysis. To create variables needed for the risk score, we categorized age into 5 age groups: <50, 50 to 59, 60 to 69, 70 to 79, and ≥80 years. We also created a binary variable for body mass index (BMI) >40 kg/m² and ejection fraction <50%. A total of 2 differences occurred in the external data set; there was no race variable, creatinine clearance, or an indicator for dialysis. To account for these differences, we left race out of the risk score and used the variable for chronic kidney disease for creatinine clearance and dialysis. The score for creatinine clearance <60 but no dialysis and dialysis were summed and divided, rounding to the nearest whole number. Therefore, chronic kidney disease was given a weight of 4 and 3 for all-cause mortality and MACCEs, respectively. An MACCE was defined as all-cause mortality, MI, or stroke.

Baseline characteristics were defined with standard statistics for this data set and the original data set. The proportion of all-cause mortality and MACCEs were displayed for 1, 2, 3, and 5 years by data set. The risk scores were calculated in the external data set, then tested with an AUC.

Predicted probabilities were estimated using logistic regression with the outcome and the risk score. For each period, the data were split into 10 groups based on the predicted probability and graphed against the observed risk for each group. We obtained calibration statistics for the ratio of expected to observed risk and slope (both of which we want to be close to 1) and the CITL, which should be close to 0.

Finally, the risk scores for all-cause mortality and MAC-CEs were categorized into 8 categories and a graph was created for the quadratic of the 5-year predicted and observed proportions.

Results

There was a total of 4,872 consecutive patients. Table 1 lists all preoperative characteristics included as covariates in the primary analysis. Table 2 lists that higher risk of mortality was associated with age 60 to 69, 70 to 79, \geq 80 years; BMI \geq 40 kg/m²; creatinine clearance <60; chronic dialysis; chronic obstructive pulmonary disease; diabetes; peripheral vascular disease; history of atrial fibrillation; history of MI; and ejection fraction (EF) <50+%, 40% to 49%, 30% to 39%, 20% to 29%, and <20%. Table 3 lists that a higher risk of MACCEs was associated with age 50 to 59, 60 to 69, 70 to 79, >80 years; creatinine clearance <60; chronic dialysis; dyslipidemia; peripheral vascular disease; history of MI; diabetes; EF 50+%, 40% to 49%, 30% to 39%, 20% to 29%, and <20%; BMI >40 kg/m²; chronic obstructive pulmonary disease; African-American ethnicity; and history of atrial fibrillation. Table 2 lists that chronic dialysis, age \geq 70 years, and EF <50% had the highest hazard ratios for long-term mortality after CABG. Table 3 lists that chronic dialysis, age ≥70 years, dyslipidemia, and BMI >kg/m² had the highest hazard ratios for MACCEs after CABG. In addition, African-American ethnicity is a significant predictor for MACCEs. The AUCs, which measures the discrimination of the models, were 80.4%, 79.1%, 81.3%, and 79.2% for mortality at 1-, 2-, 3-, and 5-year follow-up (Table 4). The AUCs for MACCEs were 75%, 72.5%, 73.8%, and 72.7% at 1-, 2-, 3-, and 5-year followup (Table 4). Figure 1 shows good agreement between the observed mortality rates and predicted mortality rates at 1-, 2-, 3-, and 5-year follow-up. Figure 2 shows good agreement between the observed MACCE rates and predicted MACCE rates at 1-, 2-, 3-, and 5-year follow-up. Figures 3 to 4 shows the Kaplan-Meier rates of observed mortality and MACCEs in low-, medium-, and high-risk patients. The expected to observed risk (E:O), slopem and CITL were 1.0, 1.0, and 0.000 for all time points and outcomes indicating excellent calibration (Figures 3 to 4, Tables 5 to 7). The Kaplan-Meier graphs showed significant risk differences between the low-, medium-, and high-risk groups (Figures 3 to 4). Finally, the out-of-sample validation by k-fold cross-validation showed good mean AUCs with 95% bootstrap confidence intervals. At 1, 2, 3, and 5 years, all-cause mortality and MACCEs had AUCs of 80.4% (72.6% to 83.8%), 79.1% (74.7% to 82.6%), 81.3% (77.1% to 83.7%), 79.2% (75.7% to 81.2%) and 75% (66.9% to 78.7%), 72.5% (66.8% to 76.4%), 73.8% (68.3%) to 75.6%), 72.7% (68.4% to 74.2%), respectively (Figures 6 and 7).

Table 1
Preoperative patients demographics and characteristics

| Preoperative patients demographics and characteristic | cs |
|---|---------------------------------------|
| Pre-operative Variables | Patients $n = 4,821$ |
| Age years (Mean/SD) | 66.1 (10.7) |
| Age years n (%) | |
| < 50 | 351 (7.3%) |
| 50-59 | 910 (18.9%) |
| 60-69 | 1656 (34.4%) |
| 70-79 | 1404 (29.1%) |
| 80+ | 500 (10.4%) |
| Gender n (%) | |
| Female | 1162 (24.1%) |
| Male | 3659 (75.9%) |
| Race n (%) | |
| White | 4264 (88.5%) |
| Afro-American | 453 (9.4%) |
| Other | 104 (2.2%) |
| STS-PROM % (Median/IQR) | 0.98 (0.5-2.1) |
| BMI kg/m ² (Mean/SD) | 29.3 (8.5) |
| BMI kg/m ² n (%) | |
| < 19 | 40 (0.8%) |
| 19 to < 25 | 997 (20.7%) |
| 25 to < 40 | 3571 (74.1%) |
| ≥ 40 | 213 (4.4%) |
| Creatine Clearance (CrCl) (Median/IQR) | 76.6 (56.2-101) |
| Renal Function n (%) | · · · · · · · · · · · · · · · · · · · |
| CrCl ≥ 60 | 3396 (70.4%) |
| CrCl < 60 & | 1314 (27.3%) |
| Chronic Dialysis n (%) | 111 (2.3%) |
| Smoking n (%) | 2248 (46.6%) |
| COPD n (%) | 757 (15.7%) |
| Hypertension n (%) | 4161 (86.3%) |
| Dyslipidemia n (%) | 4183 (86.8%) |
| Diabetes n (%) | 1991 (41.3%) |
| CBVD n (%) | 886 (18.4%) |
| PVD n (%) | 708 (14.7%) |
| Liver Disease n (%) | 61 (1.3%) |
| Prior Mediastinal Radiation n (%) | 45 (0.9%) |
| History of Atrial Fibrillation n (%) | 587 (12.2%) |
| Previous PCI n (%) | 1794 (37.2%) |
| Prior CABG n (%) | 109 (2.3%) |
| Prior MI n (%) | 2686 (55.7%) |
| Prior Valve Surgery n (%) | 30 (0.6%) |
| EF% (Mean/SD) | 52.6 (13.2) |
| EF < 50% n% | 1380 (28.6%) |
| Diseased Vessels n% | (_0,0,0) |
| 1 | 458 (9.5%) |
| 2 | 1214 (25.2%) |
| 3 | 2970 (61.6%) |
| 4 | 179 (3.7%) |
| Left Main Coronary Artery Stenosis > 50% n% | 1213 (25.2%) |
| Severe Prox. LAD Stenosis > 70% n% | 4050 (84.0%) |
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BMI = body mass index; CABG = coronary artery bypass grafting; CBVD = cerebrovascular disease; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; LAD = left anterior descending; MI = myocardial infarction; PVD = peripheral vascular disease.

The patients in the external data set were older (age 68.3 vs 66.1 years) (Table 7). There were also less patients with a BMI \geq 40 (0.6% vs 4.4%). A higher percentage of patients in the external sample had diabetes (62.4% vs 41.3%) but a lower proportion had dyslipidemia (68.8% vs 86.8%). The rate of all-cause mortality was higher in the external data set for the 1-, 2-, 3-, and 5-year periods

Table 2
Risk model for all-cause mortality

| Variables | Coef | OR | 95% CI | |
|---------------------------------------|----------|-----|-----------|--|
| Age Years | | | | |
| < 50 | Ref | | | |
| 50-59 | 0.197941 | 1.2 | 0.6, 2.4 | |
| 60-69 | 0.843903 | 2.3 | 1.3, 4.3 | |
| 70-79 | 1.522391 | 4.6 | 2.5, 8.5 | |
| >80 | 1.759656 | 5.8 | 3.0, 11.2 | |
| $BMI > 40 \text{ kg/m}^2$ | 0.601111 | 1.8 | 1.2, 2.8 | |
| Creatinine Clearance ≥ 60 | Ref | | | |
| Creatinine Clearance < 60 No Dialysis | 0.269076 | 1.3 | 1.03, 1.7 | |
| Chronic Dialysis | 1.557577 | 4.7 | 3.0, 7.6 | |
| COPD | 0.438338 | 1.6 | 1.2, 2.0 | |
| Diabetes | 0.36716 | 1.4 | 1.2, 1.8 | |
| PVD | 0.447975 | 1.6 | 1.3, 2.0 | |
| History of Atrial Fibrillation | 0.344562 | 1.4 | 1.1, 1.8 | |
| Prior MI | 0.307096 | 1.4 | 1.1, 1.7 | |
| $EF \ge 50\%$ | Ref | | | |
| 40-49% | 0.363 | 1.4 | 1.1, 1.9 | |
| 30-39% | 0.389 | 1.5 | 1.1, 2.1 | |
| 20-29% | 0.746 | 2.1 | 1.4, 3.1 | |
| <20% | 1.25 | 3.5 | 2.0, 6.1 | |

BMI = body mass index; CABG = coronary artery bypass grafting; CBVD = cerebrovascular disease; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; LAD = left anterior descending; MI = myocardial infarction; PVD = peripheral vascular disease.

Table 3 Risk model for MACCE

| | Coef | OR | 95% CI |
|--------------------------------|----------|-----|-----------|
| Age Years | | | |
| < 50 | Ref | | |
| 50-59 | 0.37878 | 1.5 | 0.9, 2.4 |
| 60-69 | 0.532395 | 1.7 | 1.1, 2.7 |
| 70-79 | 1.045955 | 3 | 1.9, 4.8 |
| 80+ | 1.193922 | 3.5 | 2.1, 5.9 |
| $CrCl \ge 60$ | Ref | | |
| CrCl < 60 No Dialysis | 0.267148 | 1.3 | 1.1, 1.6 |
| Chronic Dialysis | 1.335001 | 3.9 | 2.4, 6.0 |
| PVD | 0.405465 | 1.5 | 1.2, 1.8 |
| Prior MI | 0.326169 | 1.4 | 1.1, 1.7 |
| Diabetes | 0.249087 | 1.3 | 1.1, 1.5 |
| $EF \ge 50\%$ | Ref | | |
| 40-49% | 0.19 | 1.2 | 0.9, 1.5 |
| 30-39% | 0.211 | 1.2 | 0.9, 1.7 |
| 20-29% | 0.396 | 1.5 | 1.02, 2.2 |
| <20% | 0.882 | 2.4 | 1.4, 4.1 |
| $BMI > 40 \text{ kg/m}^2$ | 0.621461 | 1.9 | 1.3, 2.7 |
| COPD | 0.290391 | 1.4 | 1.1, 1.7 |
| Afro-American Race | 0.358375 | 1.5 | 1.1, 1.9 |
| History of Atrial Fibrillation | 0.259128 | 1.3 | 1.01, 1.6 |

BMI = body mass index; CABG = coronary artery bypass grafting; CBVD = cerebrovascular disease; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; LAD = left anterior descending; MI = myocardial infarction; PVD = peripheral vascular disease.

(Table 8). For instance, the 5-year mortality was 13.4% in the external data set versus 5.2% in the original data set. The same trend occurs for MACCEs, where the 5-year rate of MACCEs in the external data set was 15.9% vs 6.9% in

Table 4 Internal K-fold cross validation

| | AUC | 95% CI |
|---------------------|-------|------------|
| MACCE | | |
| 1 year | 75.0% | 66.9, 78.7 |
| 2 years | 72.5% | 66.8, 76.4 |
| 3 years | 73.8% | 68.3, 75.6 |
| 5 years | 72.7% | 68.4, 74.2 |
| All-Cause Mortality | | |
| 1 year | 80.4% | 72.6, 83.8 |
| 2 years | 79.1% | 74.7, 82.6 |
| 3 years | 81.3% | 77.1, 83.7 |
| 5 years | 79.2% | 75.7, 81.2 |

the original. The AUCs for all-cause mortality and MACCEs at 1, 2, 3, and 5 years were 73.7%, 70.8%, 68.7%, and 72.2% and 72.3%, 68.2%, 65.6%, 69.6%, respectively (Figures 5 to 8, Tables 8 to 9). For all outcomes and times, the E:O and slope were 1.0, and the CITL was 0.

Discussion

We provided a risk score to assess long-term mortality and MACCEs after isolated CABG. In addition, we performed and external validation of our data set, which is not present in other long-term CABG scores. The risk score includes race among the predictive factors and provides good matching between the observed and predicted outcomes. The results from this score may help to increase the bond between surgeons and patients. In addition, knowing the chance of having a stroke or an MI event after 30 days from CABG is important in low-resource countries where patients can afford only 1 lifetime operation.

In this study, we fit a LASSO proportional hazards model that identified the risk factors for long-term mortality of patients who underwent isolated CABG surgery. Based on the model, we developed and evaluated a risk score that can be used to estimate the risk of long-term complications, including mortality and MACCEs, after isolated CABG surgery. We decided to name it the Advanced (AD) Coronary Risk Score for All-Cause Mortality and MACCE.

Although many factors have been associated with complications after CABG surgery, there is no consensus as to which factors are most important and which factors are associated with a higher incidence of death, MACCEs, and rehospitalization. To date, the STS-PROM risk score and EuroSCORE II are the only 2 risk scores used to predict long-term outcomes in patients who underwent CABG.^{2,3} The main limitations that those risk scores have include overestimation of 30-day mortality and inaccuracy in predicting long-term prognosis. In addition, no risk score can predict MACCEs; therefore, no risk score can predict stroke, MI, or repeat intervention.⁶

Predicting MACCEs is crucial because it allows doctors to notify patients on the probability of having a complication after CABG, other than all-cause death. In this context, this risk score can predict all-cause mortality and MACCEs. In addition, it includes race among the risk predictors.

These 2 crucial additions will allow to count race as an indiscriminate risk factor for MACCEs, therefore allowing

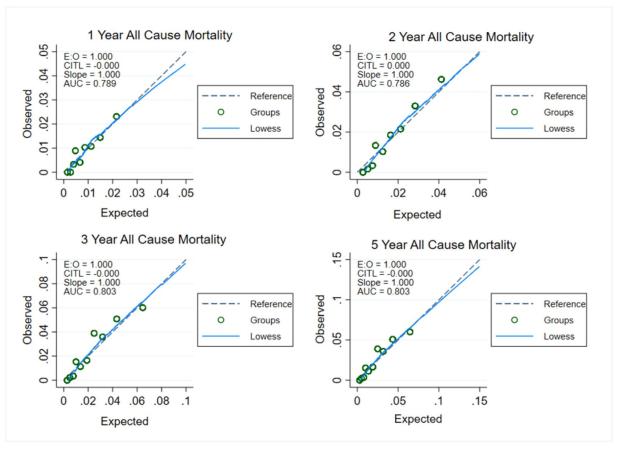


Figure 1. Calibration graphs of observed mortality versus expected mortality with statistics. (A) 1-year all-cause mortality, (B) 2-year all-cause mortality, (C) 3-year all-cause mortality, and (D) 5-year all-cause mortality.

an increase in accuracy in predicting long-term complications. In addition, the prediction of MACCEs will provide a new tool to physicians and patients, increasing patient-physician collaboration, allowing the correct treatment interventional choice.

Simplified risk scores have been developed to predict short- and long-term mortality after isolated CABG scores have a low C-statistics (AUC 0.67). The C-statistic gives the probability that a randomly selected patient who experienced an event has a higher risk score than a patient who has not experienced the event. A value of 0.5 means that the model is no better than predicting an outcome than random chance, whereas a value between 0.5 and 0.69 is considered to have a low predictability, and >0.7 indicates a good model. Compared with other risk score models, this risk score has a strong model for all-cause mortality and MACCEs, which is critical for accurately predicting an event in high-risk patients.

Clinical studies found that the inclusive nature of EuroSCORE II for numerous procedures provides more flexibility than the STS score for complex procedures. ¹⁴ In addition, the outcomes of octogenarians who underwent CABG appears to have a stronger correlation with the EuroSCORE II than STS-PROM and EuroSCORE I. ¹⁵ In summary, the poor external validity of these studies is the limiting factor because of the inclusion of only

a small number of patients (between 1,000 and 1,500 patients). Therefore, the provided outcomes appear difficult to put in practice in real—life scenarios. With respect to long—term outcomes, only a couple of studies pushed the boundaries evidencing the capability of EuroSCORE II to predict mortality in the long—term. However, the small number of patients included in these studies hinders the ability of the results to be generalized. This risk score includes almost 5,000 patients who underwent isolated CABG, has a strong C-statistics, and had a double internal and external validation. All these combined features provide a high accuracy in predicting long-term survival an MACCE.

Polygenic risk scores (PRSs) are central to the development of precision medicine; however, the current PRSs may provide weaker predictions for populations with significant non-European ancestry. A significant concern about personalized PRSs is that they have been developed, optimized, and validated in white participants with European ancestry. As a result, personalized genetic risk scores have not been as validated in nonwhite demographics. In fact, these risk scores have a poorer performance in nonwhite groups and may misrepresent their genetic risk for poorer clinical outcomes after CABG. African-descent populations, which have the most health disparities worldwide, are expected to benefit the least from risk score

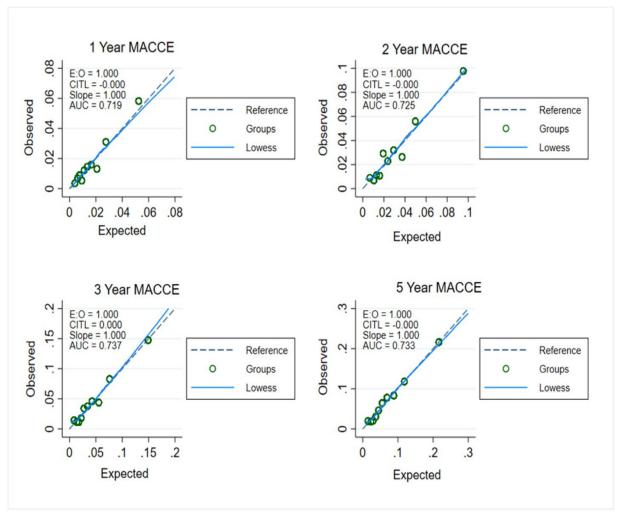


Figure 2. Calibration graphs of observed mortality versus expected MACCE with statistics. (A) 1-year MACCE, (B) 2-year MACCE, (C) 3-year MACCE, and (D) 5-year MACCE.

assessments, which do not include race among the predictors for long-term prognosis.

In this context, this risk score provides an accurate impact of race on long-term prognosis because a fair portion of our population has African descendants.

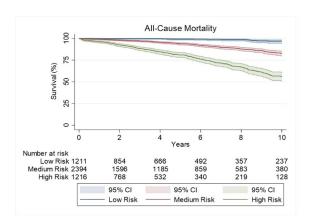


Figure 3. All-cause death Kaplan-Meier Graphs of low-, medium-, and high-risk groups.

A limitation of this risk score is the single-center data. Multiple external validations may consolidate the outcomes from this score.

In conclusion, the AD Coronary Risk Score for All-Cause Mortality and MACCE provides good discrimination of

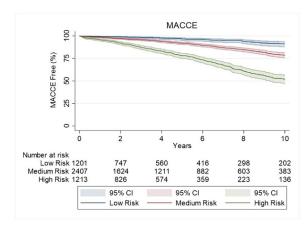


Figure 4. MACCE Kaplan-Meier graphs of low-, medium-, and high-risk groups.

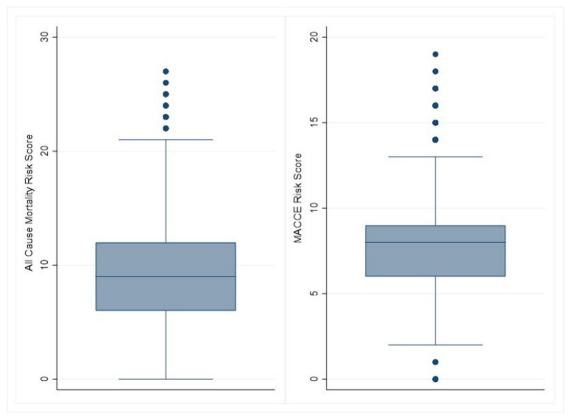


Figure 5. Box plot for all-cause mortality and MACCE.

Table 5
Predicted risk score at 5-year for all-cause mortality

| Risk Score | Predicted 5-Year Mortality |
|------------|----------------------------|
| 0-1 | 0.5% |
| 2-3 | 0.8% |
| 4-5 | 1.2% |
| 6-7 | 2.0% |
| 8-9 | 3.0% |
| 10-11 | 4.0% |
| 12-13 | 7.0% |
| 14-15 | 10.0% |
| 16+ | 20.0% |

Table 6
Predicted risk score at 5-year for MACCE

| Risk Score | Predicted 5-Year MACCE |
|------------|------------------------|
| 0-3 | 1.1% |
| 4-5 | 2.1% |
| 6 | 3.1% |
| 7 | 4.2% |
| 8 | 5.6% |
| 9 | 7.5% |
| 10 | 10.0% |
| 11 | 13.1% |
| 12+ | 22.8% |

Table 7
Risk score prediction for observed vs predicted

| Risk Score | Survived | Not Survived | Predicted | Total | Observed | MACCE Predicted | MACCE Observed |
|------------|----------|--------------|-----------|-------|----------|-----------------|----------------|
| 0-1 | 231 | 5 | 0.005 | 236 | 0.000 | 1.1 | 1.3 |
| 2-3 | 374 | 4 | 0.008 | 378 | 0.003 | 2.1 | 1.9 |
| 4-5 | 549 | 11 | 0.012 | 560 | 0.005 | 3.1 | 2.4 |
| 6-7 | 647 | 28 | 0.020 | 675 | 0.015 | 4.2 | 4.6 |
| 8-9 | 684 | 61 | 0.030 | 745 | 0.028 | 5.6 | 5.5 |
| 10-11 | 683 | 100 | 0.040 | 783 | 0.052 | 7.5 | 8.2 |
| 12-13 | 480 | 88 | 0.070 | 568 | 0.083 | 9.9 | 9.3 |
| 14-15 | 337 | 83 | 0.100 | 420 | 0.095 | 13.1 | 15.3 |
| 16+ | 320 | 136 | 0.200 | 456 | 0.190 | 22.8 | 21.9 |

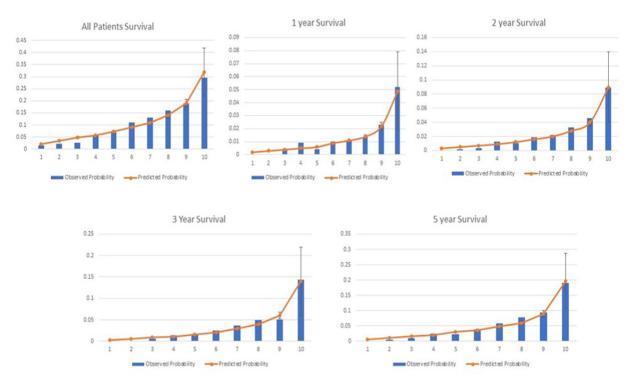


Figure 6. Validation calibration for all-cause mortality.

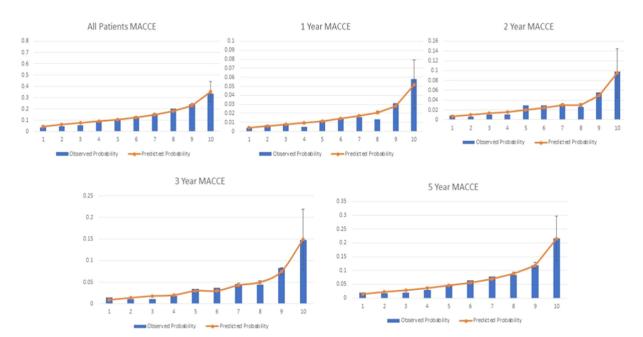


Figure 7. Validation calibration for MACCEs.

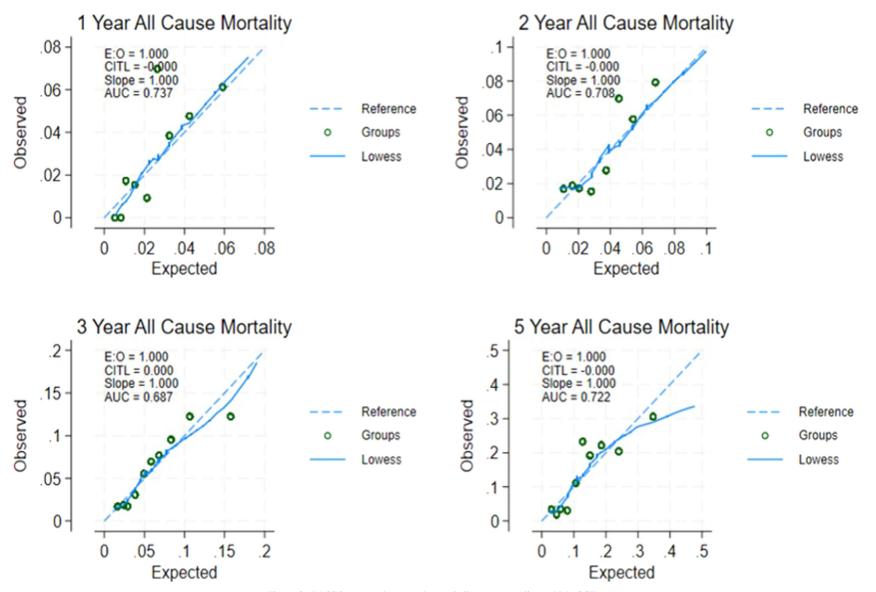


Figure 8. LASSO expected versus observed all-cause mortality and MACCEs.

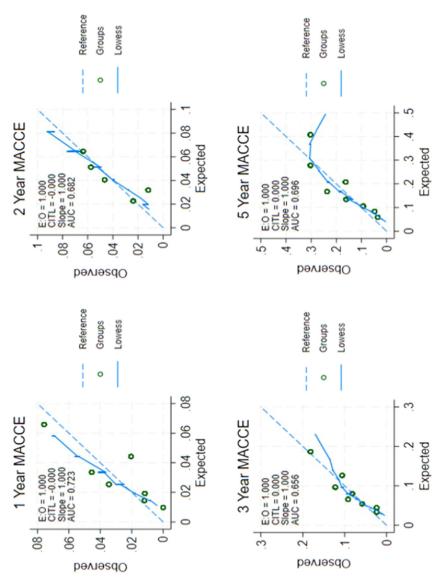


Figure 8. Continued

Table 8
External dataset comparison/validation

| Baseline Characteristics | External Sample n = 655 | Original Sample n = 4.821 |
|---------------------------------------|-------------------------------|---------------------------|
| Age | 68.3 (10.0) | 66.1 (10.7) |
| Age n (%) | | |
| < 50 years | 29 (4.5%) | 351 (7.3%) |
| 50-59 years | 98 (15.3%) | 910 (18.9%) |
| 60-69 years | 191 (29.8%) | 1656 (34.4%) |
| 70-79 years | 249 (38.9%) | 1404 (29.1%) |
| 80+ Years | 74 (11.5%) | 500 (10.4%) |
| Gender (Female) | 144 (22.0%) | 1162 (24.1%) |
| Body Mass Index $>= 40 \text{ kg/m}$ | 4 (7.1%) | 213 (4.4%) |
| Body Mass Index (mean/sd) | 25.2 (8.5) | 29.3 (8.5) |
| Chronic Kidney Disease | 76 (11.6%) | 1425* (29.6%) |
| Chronic Obstructive Pulmonary Disease | 92 (14.1%) | 757 (15.7%) |
| Peripheral Vascular Disease | 101 (15.4%) | 708 (14.7%) |
| Diabetes | 409 (62.7%) | 1991 (41.3%) |
| Hypertension | 536 (82.4%) | 4161 (86.3%) |
| Dyslipidemia | 448 (68.8%) | 4183 (86.8%) |
| Cerebrovascular Events | 105 (16.0%) | 886 (18.4%) |
| Previous Percutaneous | 103 (15.8%) | 1794 (37.2%) |
| Coronary Intervention | | |
| Atrial Fibrillation | 35 (15.8%) | 587 (12.2%) |
| Myocardial Infarction | 265 (41.7%) | 2686 (55.7%) |
| Ejection Fraction (Mean/SD) | 50.6 (10.5) | 52.6 (13.2) |
| Ejection Fraction < 50% n (%) | 194 (31.1%) | 1380 (28.6%) |

Table 9
Percentage of All-Cause Mortality and MACCE for 1, 2, 3, and 5 years for External and Original Sample, and AUC for each time period

| All-Cause Mortality | External n = 655 | Original n = 4821 | Validation AUC |
|---------------------|------------------|----------------------|-------------------|
| 1 year | 20 (3.1%) | 60 (1.2%) | 73.7% |
| 2 year | 32 (4.9%) | 113 (2.3%) | 70.8% |
| 3 year | 40 (6.1%) | 162 (3.4%) | 68.7% |
| 5 year | 88 (13.4%) | 249 (5.2%) | 72.2% |
| MACCE | | | |
| 1 year | 22 (3.4%) | 81 (1.7%) | 72.3% |
| 2 year | 41 (6.3%) | 144 (3.0%) | 68.2% |
| 3 year | 50 (7.6%) | 214 (4.4%) | 65.6% |
| 5 year | 104 (15.9%) | 333 (6.9%) | 69.6% |

long-term mortality and MACCEs after isolated CABG in low- and high-risk patients. We anticipate that this new risk score can become a handy risk stratification tool that can be used from clinicians and patients in the choice of treatment for severe coronary disease after isolated CABG. It will help to create mutual trust between surgeons and patients and will be an important tool in low-resource countries.

Declaration of competing interest

The authors have no competing interest to declare.

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- review & editing. **Fabrizio Rosati:** Conceptualization, Data curation, Investigation, Project administration, Software, Supervision, Validation, Visualization, Writing original draft. Claudio Muneretto: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. Andrea Amabile: Writing - original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization, Data curation, Formal analysis, Investigation. Marjela Pernoci: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Marco **Gemelli:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. Ali Fatehi Hassanabad: Writing - review & editing, Writing - original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. Serge **Sicouri:** Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing - review & editing. Noah Sicouri: Conceptualization, Data curation, Funding acquisition, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. Yoshiyuki Yamashita: Conceptualization, Data curation, Investigation, Project administration, Software, Supervision, Visualization, Writing - original draft, Writing review & editing. Massimo Baudo: Writing - review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Massimo Bonacchi: Writing - review & editing, Writing - original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. Francesco Cabrucci: Writing - original draft, Visualization, Validation, Methodology, Investigation, Data curation, Conceptualization. Beatrice Bacchi: Writing - original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. Nitin Ghorpade: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Supervision, Validation, Visualization, Writing - original draft. Ashish Shah: Conceptualization, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. Lindita Coku: Conceptualization, Data curation, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing - original draft. Matteo Cameli: Visualization, Conceptualization, Data curation, Formal analysis, Methodology, Resources, Supervision, Validation. Giulia Elena Mandoli: Writing - review & editing, Writing - original draft, Visualization, Validation, Supervision, Software, Methodology, Formal analysis, Data curation, Conceptualization. Stephanie Kjelstrom: Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. Georgia Montone: Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Validation, Visualization, Writing - original draft, Writing - review & editing. Maryann Wertan: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. Basel Ramlawi: Writing - review & editing, Writing - original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Arnaldo DiMagli:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. Francis P. **Sutter:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Investigation, Formal analysis, Data curation, Conceptualization.

Data Availability

The data that support the findings of this study are available upon reasonable request to Dr. Sicouri, pending institutional approval.

Ethical Approval

The study protocol was approved by Lankenau Institute for Medical Research Institutional Review Board 45CFR164.512. Patients' individual written informed consent was waived because of the retrospective nature of the study.

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