ORIGINAL RESEARCH

Long-Term Risk Stratification of Patients Undergoing Coronary Angiography According to the Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention

Barak Zafrir, MD; Salim Adawi, MD; Marah Khalaily, BS; Ronen Jaffe, MD; Amnon Eitan, MD; Ofra Barnett-Griness, PhD; Walid Saliba, MD

***Background*—**A risk score for secondary prevention after myocardial infarction (Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention [TRS2P]), based on 9 established clinical factors, was recently developed from the TRA2°P-TIMI50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) trial. We aimed to evaluate the performance of TRS2P for predicting long-term outcomes in real-world patients presenting for coronary angiography.

***Methods and Results*—**A retrospective analysis of 13 593 patients referred to angiography for the assessment or treatment of coronary disease was performed. Risk stratification for 10-year major adverse cardiovascular events was performed using the TRS2P, divided into 6 categories (0 to ≥5 points), and in relation to the presenting coronary syndrome. All clinical variables, except prior coronary artery bypass grafting, were independent risk predictors. The annualized incidence rate of major adverse cardiovascular events increased in a graded manner with increasing TRS2P, ranging from 1.65 to 16.6 per 100 person-years (P_{trend}<0.001). Compared with the lowest-risk group (risk indicators=0), the hazard ratios (95% CIs) for 10-year major adverse cardiovascular events were 1.60 (95% CI, 1.36–1.89), 2.58 (95% CI, 2.21–3.02), 4.31 (95% CI, 3.69–5.05), 6.43 (95% CI, 5.47–7.56), and 10.03 (95% CI, 8.52–11.81), in those with 1, 2, 3, 4 and ≥5 risk indicators, respectively. Risk gradation was consistent among individual clinical end points. TRS2P showed reasonable discrimination with C-statistics of 0.693 for major adverse cardiovascular events and 0.758 for mortality. The graded relationship between the risk score and event rates was observed in both patients presenting with acute and nonacute coronary syndromes.

***Conclusions*—**The use of TRS2P, a simple risk score based on routinely collected variables, enables risk stratification in patients undergoing coronary angiography. Its predictive value was demonstrated in a real-world setting with long-term follow-up and regardless of the acuity of coronary presentation. **(*J Am Heart Assoc*. 2019;8:e012433. DOI: 10.1161/JAHA.119.012433.)**

Key Words: acute coronary syndrome • cardiovascular outcomes • coronary angiography • risk score • risk stratification

The development of cardiac care units and revascularization methods, as well as the advancement in pharmacotherapy and secondary prevention measures, have led to improved outcomes in patients after acute coronary syndromes (ACS) in recent decades.[1,2] However, residual cardiovascular risk is still significant, and patients with coronary artery disease (CAD) often have increased risk for future atherothrombotic events, including myocardial infarction (MI), ischemic stroke, and death.[3,4] Risk stratification during and after ACS enables identification of patients at higher relative risk who are likely to benefit from prompt medical and interventional therapy, with intensive secondary prevention measures in the long-term. It may also identify patients at lower predicted risk, in which close monitoring and intensive management is less warranted. This personalized, risk-centered approach may help guide therapeutic decisions and was the basis for the development of several risk prediction models that estimate short-term cardiovascular events or mortality after ACS.[5–7] Risk models for secondary cardiovascular events in stable patients or with longer-term outcomes are less common and rarely implemented in clinical practice.[8,9] Nevertheless, this may be changing with the recent rapid increase in the generation of digital data, as large health organizations with sufficient computer resources are focusing more on prevention. Furthermore, validated risk scoring systems may also be useful as clinical research tools

From the Department of Cardiology (B.Z., S.A., R.J., A.E.), Statistical Unit (O.B.-G.), and Department of Community Medicine and Epidemiology (O.B.-G., W.S.), Lady Davis Carmel Medical Center, Haifa, Israel; Faculty of Medicine, Technion, Israel Institute of Medicine, Haifa, Israel (B.Z., S.A., M.K., R.J., W.S.).

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Correspondence to: Barak Zafrir, MD, Cardiovascular Department, Lady Davis Carmel Medical Center, 7 Michal Street, Haifa, Israel. Email: barakzmd@gmail.com

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Clinical Perspective

What Is New?

- The Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention, a simple clinical scoring system based on 9 routinely collected risk indicators predicting adverse outcomes after recent myocardial infarction, was shown to enable risk stratification in patients undergoing coronary angiography with reasonable discriminatory capacity.
- Its predictive value was demonstrated in a real-world setting with long-term follow-up and irrespective of the acuity of coronary presentation.

What Are the Clinical Implications?

- The Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention may have the potential to be a useful tool in the risk assessment of a wide range of populations undergoing coronary angiography in different clinical settings.
- The results may increase the generalizability of the Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention to real-life populations and may contribute to a more personalized risk approach.

and can help identify patients at different levels of risk, thus maintaining balance in clinical studies or helping recruit the patients at high risk for intervention.

The TIMI (Thrombolysis in Myocardial Infarction) research group has recently developed a simple scoring system for predicting adverse outcomes after a recent MI.[10] The TIMI Risk Score for Secondary Prevention (TRS2P) is based on data of patients enrolled in the TRA2°P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) randomized clinical trial.[10] The study compared the efficacy and safety of vorapaxar antiplatelet medication with placebo in patients with recent MI, stroke, or symptomatic peripheral artery disease.[11] The TRS2P was derived from patients whose qualifying event was recent (2–52 weeks) MI and consisted of 9 variables routinely available in clinical practice including: heart failure, prior stroke, hypertension, diabetes mellitus, current smoking, prior coronary artery bypass graft surgery, age 75 years and older, peripheral artery disease, and renal dysfunction, which was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2. The TRS2P is the sum of the number of the clinical risk indicators available in each patient. Each positive risk variable equally receives 1 point, resulting in a total risk score ranging from 0 to 9.

This risk score displayed reasonable discrimination for predicting secondary cardiovascular events among patients with recent MI in few external validation cohorts.[12–15] In addition, risk stratification using the TRS2P has also identified high-risk patients who derived the greatest benefit from the addition of ezetimibe to statin therapy in a randomized trial for secondary prevention after ACS.[16] Whether the TRS2P is useful to estimate the risk of future adverse events in additional clinical settings of patients with cardiovascular disease is a subject for further research. We aimed to investigate the performance of the TRS2P system for predicting long-term outcomes in real-world clinical practice of patients presenting to coronary angiography for evaluation and treatment of CAD in both the acute and nonacute setting.

Methods

Anonymized data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Retrospective analysis of the cardiac catheterization laboratory database at Carmel Medical Center, Haifa, Israel, between the years 2000 and mid-2015 was performed. During that period 14 337 patients were referred to coronary angiography for the assessment and/or treatment of CAD. This analysis was restricted to 13 593 patients who are members of the Clalit Health Service (CHS), the largest nonfor-profit healthcare provider in Israel, for whom we had full access to outcomes data during follow-up. Only the first angiography of each patient during the study period was included. The study population was classified into 3 groups of angiographic indications: (1) unstable angina pectoris (UAP) or acute non–ST-segment–elevation MI (NSTEMI), (2) acute ST-segment–elevation MI (STEMI), and (3) evaluation or treatment of CAD with stable clinical presentation (non-ACS). Demographic data, risk factors, and comorbidities were most often prospectively collected from patients' medical files at the time of coronary angiography. Data that were not originally collected were retrieved from a computerized database of CHS. The primary study end point was major adverse cardiovascular events (MACEs), defined as a composite of MI, ischemic stroke, or death. The cause of death was not consistently available and therefore we included all-cause and not cardiovascular death. Data on MI and ischemic stroke during follow-up were retrieved from the CHS hospitalizations database and were defined as primary discharge with *International Classification of Diseases, Ninth Revision* (*ICD-9*) code (410.xx) for MI and *ICD-9* codes (433.x1, 434.x1, 436) for ischemic stroke. Data on vital status were retrieved from the Ministry of Interior. Cohort participants were

followed-up until reaching the first occurrence of study outcomes (MACEs), a maximum 10 years of follow-up, or end of follow-up at November 2018, whichever came first.

The study database was approved by Carmel Medical Center's ethics committee with waiving of the need for individual patient consent because of the retrospective nature of the study.

Statistical Analysis

To assess the association between TRS2P and MACEs, TRS2P was classified into 6 categories; 0, 1, 2, 3, 4, and ≥5 points. TRS2P values of 5 to 9 were pooled into 1 high-risk category (≥5) because of the relatively low frequency of high-risk scores. Continuous data are reported as means and SDs and categorical variables as numbers and percentages. One-way ANOVA or Kruskal–Wallis tests, as appropriate, were used to compare continuous variables and chi-square to compare categorical variables.

For each TRS2P risk category (0, 1, 2, 3, 4, and ≥5 risk indicators), the number of events and incidence rates per 100 person-years were calculated for the primary composite end point (MACEs) and its individual components. Cox proportional hazard regression models were used to assess the association between TRS2P and time to each end point, and to estimate the hazard ratios (HRs) and 95% CIs, with the group of 0 risk indicators serving as the reference category. Kaplan–Meier curves were used to estimate the 10-year cumulative incidence of MACEs and individual end points according to TRS2P risk categories, with comparison between curves performed using the log-rank test. In addition, all 9 predictors included in the TRS2P were modeled in a Cox proportional hazard regression model to estimate the association between TRS2P components and MACEs.

The discriminatory performance of the TRS2P in predicting MACEs was estimated using Harrell's C-statistic.[17] Calibration of 3-year predicted risk by the TRA2°P-TIMI 50 derivation trial to our data was evaluated by plotting MACE rates among TRS2P risk categories in the observed study population compared with those reported in the TRA2°P-TIMI 50 study. The calibration assessment was performed according to 3-year Kaplan–Meier estimates of MACEs and 0 to ≥7 risk categories, in order to match the data reported by the TRA2°P-TIMI 50 study group in placebo-treated patients with previous MI.[10] The observed versus predicted differences among 0 to ≥7 risk categories were summarized using the modified Hosmer-Lemshow goodness-of-fit test.[18] Calibration-in-the-large was assessed using the overall 3-year risk in our sample and associated CI. As we observed some overestimation of risk, we applied recalibration of predictions by adding to the predicted risk of every patient a fixed amount, calculated by the weighted mean risk difference between observed and predicted risk among score categories.[12]

Additional exploratory analysis was performed by examining the performance of TRS2P separately for each of the 3 subgroups of patients presenting to coronary angiography (STEMI, UAP/NSTEMI, non-ACS). The results were considered statistically significant when the 2-sided P value was <0.05. SPSS statistical software version 20.0 (SPSS Inc), SAS version 9.4 software (SAS Institute), and MedCalc version 16.8.4 (MedCalc Software) were used to perform all statistical analyses.

Results

A total of 13 593 patients underwent coronary angiography during the study period. Median follow-up was 95 months (interquartile range, 53–120 months). The mean age of patients was 64.5±11.5 years and 72% were men. Baseline patient characteristics are presented in Table 1 and classified according to risk groups (0 to ≥5 risk indicators).

Each of the 9 clinical variables in the TRS2P was an independent predictor of MACEs, except for prior coronary artery bypass graft surgery (Table 2). Age 75 years and older (HR, 2.26; 95% CI, 2.12–2.41 [P<0.0001]) and the presence of heart failure (HR, 2.14; 95% CI, 2.01–2.29 [P<0.0001]) were the strongest risk predictors.

The incidence rate per 100 person-years of MI, ischemic stroke, and all-cause death, as well as MACEs, increased progressively with the increase in the number of positive risk indicators from 0 to ≥5 (Table 3). A graded increment in the HRs for both MACEs and the individual end points was observed with the rise in the number of risk indicators. Compared with 0 risk indicators, the HRs for MACEs were 1.60 (95% CI, 1.36–1.89), 2.58 (95% CI, 2.21–3.02), 4.31 (95% CI, 3.69–5.05), 6.43 (95% CI, 5.47–7.56), and 10.03 (95% CI, 8.52–11.81) for TRS2P 1, 2, 3, 4, and ≥5 indicators, respectively. MI was consistently more common than ischemic stroke among the risk categories. Kaplan–Meier plots displaying the distribution of time to MACE stratified by the number of risk indicators are presented in Figure 1 (P for trend <0.001) and for the individual end points in Figures S1 through S3.

Of the overall study population, 6788 patients (49.9%) underwent coronary angiography for evaluation or treatment of CAD in the nonacute setting (non-ACS), and 6804 (50.1%) in the setting of an ACS (5335 [39%] caused by UAP or acute NSTEMI, and 1470 [11%] caused by acute STEMI). All of the risk indicators, except diabetes mellitus, were more prevalent in patients presenting with ACS than without ACS (Table S1). The graded association between the risk score (0 to ≥5 risk indicators) and the HR for MACEs was observed in each of the

Table 1. Baseline Patient Characteristics

No. of Risk Indicators		0	1	2	3	4	≥5
No. of Patients (%) Variables	Overall N=13 593 (100)	1354 (10)	3183 (23.4)	3934 (28.9)	2698 (19.8)	1384 (10.2)	1040 (7.7)
Age, y	64.5±11.5	57.4±9.5	60.2±10.0	63.4.±10.7	67.6.±11.3	70.9.±10.6	74.0.±9.5
≥75	2938 (22)	0	143 (5)	641 (16)	874 (32)	646 (47)	634 (61)
Men	9814 (72)	1031 (76)	2337 (73)	2844 (72)	1924 (71)	970 (70)	708 (68)
BMI, kg/m^2	28.27±4.59	27.7.±3.9	28.1.±4.4	28.7.±4.8	28.6.±4.8	28.0.±4.7	28.0.±4.5
Hypertension	9611 (71)	0	1672 (53)	3209 (82)	2427 (90)	1297 (94)	1006 (97)
Hyperlipidemia	9508 (70)	571 (42)	2035 (64)	2870 (73)	2068 (77)	1102 (80)	862 (83)
Smoking	3029 (22)	0	678 (21)	996 (25)	759 (28)	365 (26)	231 (22)
Diabetes mellitus	5089 (37)	0	238 (8)	1597 (40)	1547 (58)	901 (65)	806 (77)
eGFR <60 mL/min per 1.73 m^2	3012 (22)	0	190 (6)	534 (14)	884 (33)	670 (48)	734 (71)
Heart failure	2194 (16)	0	105 (3)	342 (9)	545 (20)	554 (40)	648 (62)
Peripheral artery disease	1888 (14)	0	39 (1)	207 (5)	406 (15)	503 (36)	733 (70)
Prior PCI	3749 (28)	216 (16)	835 (26)	1202 (31)	822 (31)	401 (29)	273 (26)
Prior CABG	1667 (12)	0	113 (4)	276 (7)	476 (18)	367 (26)	435 (42)
Prior stroke	931 (7)	0	5 (0.2)	66 (2)	176 (7)	233 (17)	451 (43)
Non-ACS	6788 (50)	821 (61)	1725 (54)	2078 (53)	1258 (47)	571 (41)	599 (58)
UAP/NSTEMI	5335 (39)	387 (29)	1076 (34)	1427 (36)	1165 (43)	681 (49)	106 (10)
STEMI	1470 (11)	146 (11)	382 (12)	429 (11)	275 (10)	132 (10)	832 (80)

Variables are presented as number (percentage) or mean±SD. P<0.05 for all variable comparisons between risk indicator groups. ACS indicates acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft surgery; eGFR, estimated glomerular filtration rate; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; UAP, unstable angina pectoris.

3 clinical presentations with acute (UAP/NSTEMI or STEMI) and non-ACS (P for trend <0.0001 for each presentation; Figure 2).

The Harrell's C-statistic of the TRS2P model in the overall study population was 0.692 (95% CI, 0.685–0.700) for MACE and 0.758 (95% CI, 0.750–0.766) for all-cause death. In the non-ACS cohort, the C-statistic was 0.682 (95% CI, 0.670–0.694) and 0.728 (95% CI, 0.714–0.741), and in the UAP/NSTEMI cohort: 0.695 (95% CI, 0.684–0.706) and 0.774 (95% CI, 0.762–0.785), and in the STEMI cohort 0.664 (95% CI, 0.642–0.686) and 0.776 (95% CI, 0.752–0.799), for MACE and all-cause death, respectively (P<0.0001 for all calculations).

Overall, observed 3-year MACE risk was 0.15, which is higher than the predicted risk of 0.13 according to the TRA2°P-TIMI 50 trial derivation cohort. The 95% CI for our observed risk ranged between 0.145 to 0.157, thus excluding the predicted 0.13 and demonstrating a lack of calibration-in-the-large. The observed 3-year event rates in our study tended to be higher by a small amount compared with those predicted by the TRA2°P-TIMI 50 trial among all risk categories except for the group of 6 risk indicators (Figure 3A). Summarizing the observed versus predicted differences using the Hosmer-Lemshow goodness-of-fit test confirmed the discrepancy, with a chi-square statistic of 88.986 (P<0.001). After recalibration, the Hosmer-Lemshow statistic was improved, with chi-square <50.

Three-year estimated MACE cumulative incidence rates increased consistently among the TRS2P categories in both

Table 2. Multivariable HRs for the Association Between the Individual Components of TRS2P and MACEs

9 Risk Indicators	HR (95% CI)	P Value
Age ≥75, y	2.259 (2.116–2.412)	<0.0001
Hypertension	1.185 (1.103–1.273)	<0.0001
Diabetes mellitus	1.430 (1.347–1.517)	<0.0001
Current smoking	1.327 (1.234–1.427)	<0.0001
Peripheral artery disease	1.389 (1.286–1.500)	<0.0001
Kidney dysfunction (eGFR <60)	1.553 (1.457–1.656)	<0.0001
Heart failure	2.143 (2.008–2.288)	<0.0001
Prior stroke	1.271 (1.150–1.404)	<0.0001
Prior CABG	1.071 (0.988–1.161)	0.097

CABG indicates coronary artery bypass graft surgery; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MACEs, major adverse cardiovascular events (first occurrence of myocardial infarction, ischemic stroke, or all-cause death); TRS2P, Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention.

Table 3. Descriptive Statistics, Incidence Density Rate, and HRs for the Association Between the Number of TRS2P Risk Indicators and MACEs

No. of Risk Indicators	0	1	2	3	4	≥5
No. of Patients (%)	1354 (10)	3183 (23.4)	3934 (28.9)	2698 (19.8)	1384 (10.2)	1040 (7.7)
MI						
No. of events	73	286	515	442	255	247
Incidence rate per 100 person-y	0.67	1.14	1.77	2.49	3.24	5.21
HR (95% CI)	1 (Reference)	1.70 (1.31–2.19)	2.61 (2.04–3.33)	3.62 (2.82–4.64)	4.61 (3.55–5.98)	7.09 (5.46–9.21)
Ischemic stroke						
No. of events	10	79	150	127	79	69
Incidence rate per 100 person-y	0.09	0.30	0.49	0.67	0.93	1.32
HR (95% CI)	1 (Reference)	3.39 (1.76–6.55)	5.48 (2.89–10.39)	7.60 (3.99–14.47)	10.86 (5.63–20.98)	15.78 (8.12–30.66)
All-cause death						
No. of events	103	350	741	877	672	690
Incidence rate per 100 person-y	0.92	1.33	2.37	4.50	7.75	12.79
HR (95% CI)	1 (Reference)	1.45 (1.16–1.80)	2.59 (2.11–3.19)	4.99 (4.07–6.12)	8.75 (7.11–10.77)	14.76 (12.00–18.17)
MACEs						
No. of events	179	655	1224	1232	811	767
Incidence rate per 1000 person-y	1.65	2.64	4.25	7.09	10.56	16.61
HR (95% CI)	1 (Reference)	1.60 (1.36–1.89)	2.58 (2.21–3.02)	4.31 (3.69–5.05)	6.43 (5.47–7.56)	10.03 (8.52–11.81)

HRs indicates hazard ratios; MACEs, major adverse cardiovascular events (first occurrence of myocardial infarction, ischemic stroke, or all-cause death); MI, myocardial infarction; TRS2P, Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention.

our cohort and the derivation cohort of the TRA2°P-TIMI 50 trial (Figure 3B). Three-year estimated MACE cumulative incidence rates among the TRS2P risk categories were generally higher in patients presenting with acute STEMI compared with those with UAP/NSTEMI, and both were significantly higher than patients presenting to coronary angiography without ACS (Figure 4).

Discussion

The TRS2P is a simple risk scoring system based on 9 routinely measured clinical variables that predicted 3-year cardiovascular outcomes after recent MI in a large randomized clinical trial.[10] In the current study, the performance of the TRS2P was demonstrated in an unselected real-world population of patients undergoing coronary angiography, with long-term follow-up. Despite the clinical variation from the derived study population, our results confirm a consistent graded association of the TRS2P with increased risk of MACEs and its individual components, with acceptable risk discrimination. This relationship was observed not only in the overall population undergoing coronary angiography but also in various coronary presentations, including patients referred for evaluation or treatment of CAD in the nonacute setting, as well as those with ACS presenting with UAP/NSTEMI or STEMI.

Risk Assessment and Clinical Risk Scores

Patients with CAD are at heightened risk for future atherothrombotic events.[19] The risk further increases after an ACS, with significant morbidity and mortality that often persists beyond the first year post-ACS.[4,20] This highlights the need for prolonged surveillance with meticulous control of cardiovascular risk factors, particularly in patients with multimorbidity. The aim of risk assessment is to guide therapeutic decision-making, evaluate the need for additional diagnostic testing, allocate clinical resources, and inform patients more objectively on the perception of risk.[7] These goals are shared in both acute and nonacute settings of patients with CAD. Accurate risk assessment may lead to more effective patient care with appropriate implementation of preventive interventions according to the individual level of risk. Several clinical risk scores have been developed and

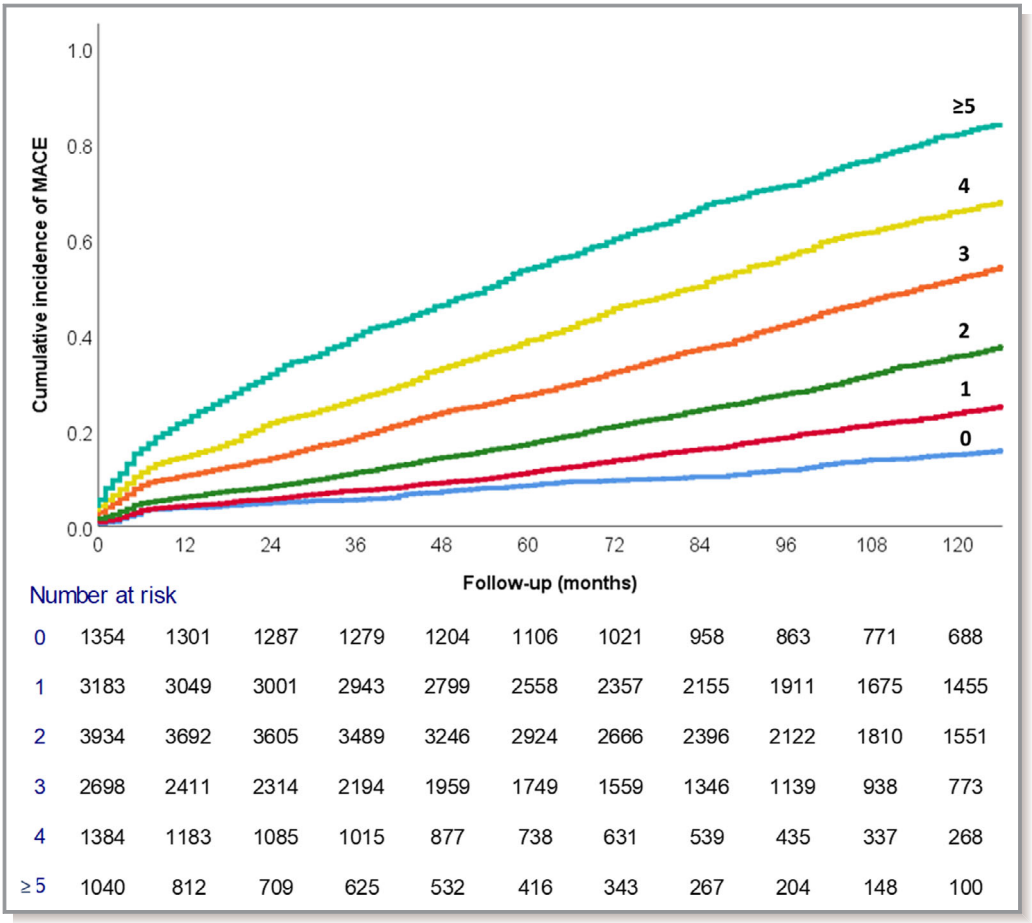

Figure 1. Cumulative 10-year incidence of major adverse cardiovascular events (MACEs; first occurrence of myocardial infarction, ischemic stroke, or all-cause death) according to the number of risk indicators.

validated in patients with ACS, integrating demographic, physiological, and laboratory parameters to improve risk prediction.[21] Clinical scoring systems should be simple to calculate and practical for bedside implementation in order to enhance risk stratification.[22] For patients with CAD evaluated in the non-ACS setting, fewer risk scores exist, which are uncommonly integrated in clinical practice.[8,9]

TRS2P System

The TRS2P is a novel risk score for better determination of an individual patient's risk for MACEs after MI.[10] The score is calculated based on the presence of 9 routinely available risk factors, each contributing equally 1 point. The TRS2P was developed with the use of data from a large randomized clinical trial and was recently validated in several external cohorts.[12–14] The TRS2P system displayed an ability to predict benefit from the antiplatelet agent varopaxar, as well as the lipid-modifying agent ezetimibe, both showing increasing efficacy with the increase in TRS2P.[10,16] In addition, Bonaca and colleagues[15] analyzed the performance of TRS2P in the DYSIS II (Dyslipidemia International Study II) CAD study population, concluding that maximal intensive treatment should be considered for all patients with high TRS2P in order to achieve a low-density lipoprotein cholesterol level as low as possible. Risk prediction models may help to apply therapeutic measures in a more cost-efficient way and to stratify patients according to objective clinical judgment. This risk-centered approach may be useful when prescribing novel medications that could not be supplied to a wide population because of cost restrains and limited resources. A recent example is the application of proprotein convertase subtilisin/kexin type 9 monoclonal antibodies in clinical practice, in which cost-benefit was shown particularly in patients defined as very high risk, with the lowest number needed to treat to achieve maximal clinical benefit.[23]

TRS2P in Patients Undergoing Coronary Angiography

The TRS2P is composed of risk indicators that have significant clinical relevance in patients undergoing coronary

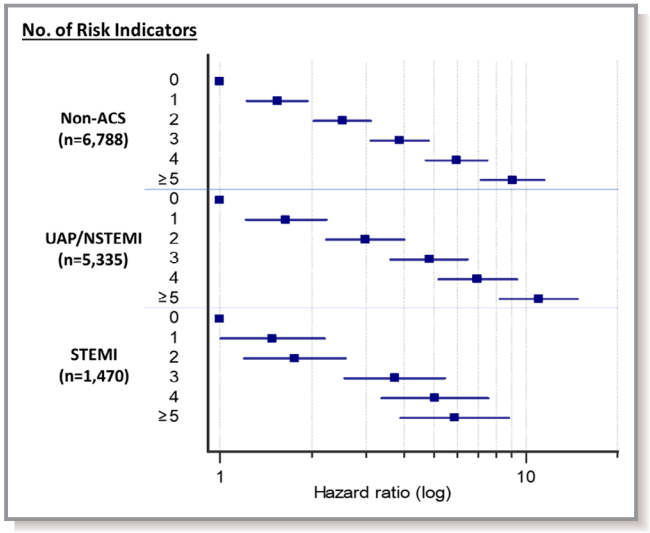

Figure 2. Hazard ratios for major adverse cardiovascular events (MACEs) according to presentation to coronary angiography. *P* for trend <0.0001 for each presentation. ACS indicates acute coronary syndrome; NSTEMI, non–ST-segment–elevation myocardial infarction; STEMI, ST-segment–elevation myocardial infarction; UAP, unstable angina pectoris.

angiography irrespective of the acuity of presentation. Hypertension, diabetes mellitus, and smoking are independent cardiovascular risk factors.[24] Advanced age, renal dysfunction, and heart failure are parameters that may impact the choice of revascularization strategy and are associated with postprocedural complications.[25] Prior history of stroke and peripheral artery disease are associated with lower use of medical and interventional therapies, leading to worse short-term prognosis.[26] Our results suggest that the application of the TRS2P in routine clinical practice may identify patients undergoing coronary angiography who are at the highest risk for cardiovascular events and death, and therefore may derive the greatest absolute risk reduction with intensive management and preventive care. The discrimination ability of the TRS2P for long-term MACEs (10 years) in patients undergoing coronary angiography was comparable and even better than that originally reported in the derivation data set of the TRS2P (3 years)[10] and in additional external validation cohorts.[12–14] The risk gradation was evident not only for MACEs but also for each of the individual end points of MI, ischemic stroke, and all-cause death, emphasizing the atherothrombotic risk associated with CAD when multiple risk indicators are present. Moreover, the performance of TRS2P was consistent among the different presentations to coronary angiography, with and without ACS, including patients admitted with acute STEMI that was associated with significantly higher risk for adverse events among risk categories. This adds important information to the current literature, as the TRS2P was developed from data without differentiating MI types. Moreover, the risk prediction of the TRS2P in the present study was evident with significantly longer-term follow-up than the derived study population and previous validation studies, which further extend the predictive performance of the TRS2P.[10,12–15]

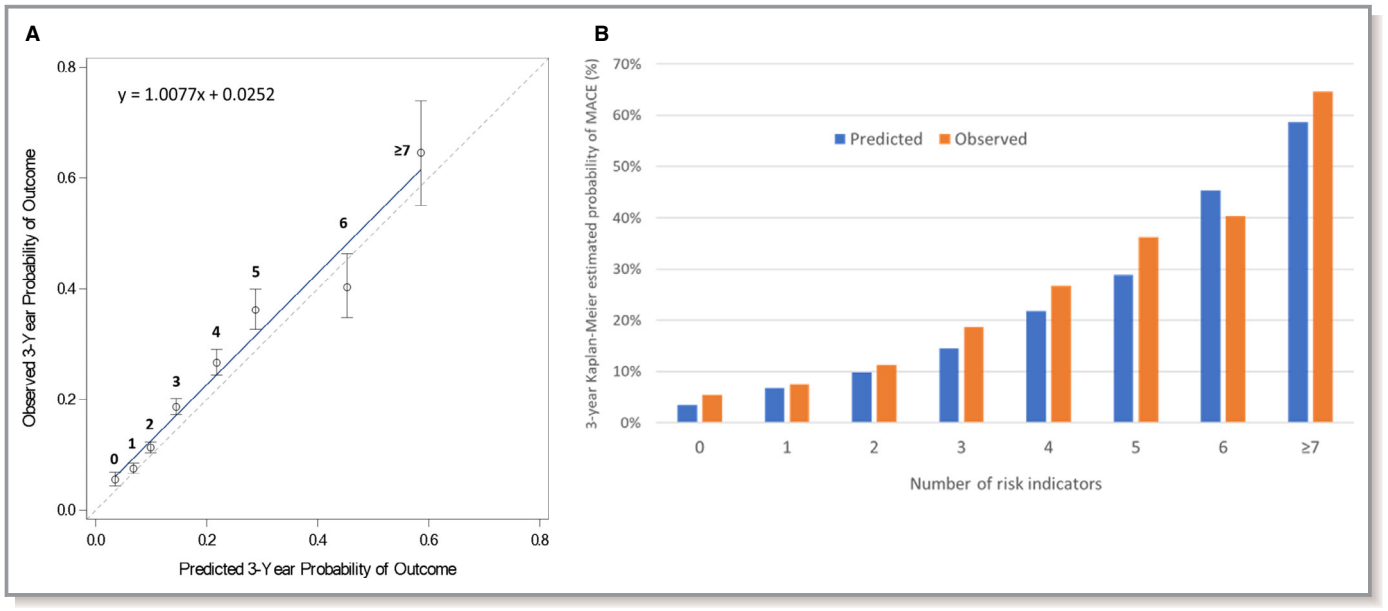

Figure 3. **A**, Observed vs predicted 3-year probability of major adverse cardiovascular events (MACEs) among risk categories. In A, the dashed line is the identity line. The solid line represents the regression line. For each dot, the bar represents 95% CI for the observed risk. **B**, Three-year estimated MACE (myocardial infarction, ischemic stroke, or death, which was defined as all-cause death in the current study [observed cohort] compared with cardiovascular death in the TRA2°P-TIMI 50 [Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events] trial [predicted cohort]) rates among TRS2P categories in the study cohort compared with the TRA2°P-TIMI 50 trial.

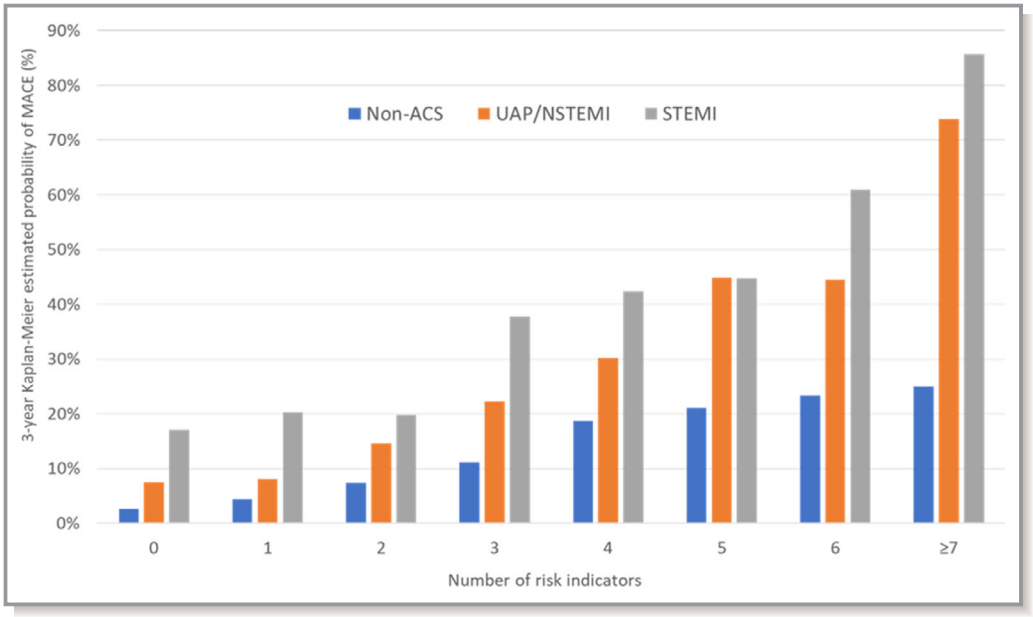

Figure 4. Three-year estimated major adverse cardiovascular events (MACEs; myocardial infarction, ischemic stroke, or all-cause death) cumulative incidence among Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention (TRS2P) categories according to the 3 coronary presentations. ACS indicates acute coronary syndrome; NSTEMI, non–ST-segment–elevation myocardial infarction; STEMI, ST-segment–elevation myocardial infarction; UAP, unstable angina pectoris.

Overall, our results highlight the potential use of TRS2P in risk stratifying patients referred to coronary angiography beyond the risk associated with the acuity of coronary presentation. The results may increase the generalizability of the TRS2P to real-life populations, who often tend to have more comorbidities than patients recruited in randomized clinical trials but receive less-intensive and guideline-directed medical therapies.[27] The use of TRS2P in clinical practice may contribute to the personalized risk approach, concentrating on the "overall" patient risk and not only on a specific risk factor level.

Study Limitations

Several limitations of this study should be noted. The data were acquired from a general population setting of patients presenting to coronary angiography, and therefore the results are limited to this study population. The cause of death was unknown and therefore we could not use cardiovascular death as part of the definition of MACE. Accordingly, the observed event rates tended to be higher than those predicted from the derivation cohort. Moreover, additional parameters may have further improved the performance of the TRS2P system. This may include additional risk factors and biomarkers or data regarding type and completeness of revascularization, which were not evaluated in the current study and may have impacted the results. This may also be the case with providing different relative weight to the 9 risk indicators of the risk model. Finally, the risk score was determined at 1 time point during performance of cardiac catheterization. Therefore, we did not take into account the impact of risk factor control over time on adverse outcomes.

Conclusions

The use of TRS2P, a simple, straightforward clinical risk score based on routinely collected risk indicators, enables risk stratification in patients undergoing coronary angiography with reasonable discriminatory capacity. Its predictive value was demonstrated in a real-world setting with long-term follow-up and irrespective of the acuity of coronary presentation. The TRS2P may have potential to be a useful clinical tool in the care of patients undergoing coronary angiography, as part of an integrated approach to risk assessment in the short-term and a more personalized administration of preventive medicine in the longer-term, aiming to reduce atherothrombotic risk.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Risk indicators according to presentation with or without ACS.

Variable	Overall n=13,593	Non-ACS n=6,788 (49.9%)	ACS n=6,805 (50.1%)	P value
Age ≥75 (years)	2938 (21.6%)	1172 (17.3%)	1766 (26%)	<0.001
Hypertension	9611 (70.7%)	4729 (69.7%)	4882 (71.7%)	0.008
Smoking	3029 (22.3%)	1187 (17.5%)	1842 (27.1%)	<0.001
Diabetes	5089 (37.4%)	2525 (37.2%)	2564 (37.7%)	0.563
eGFR<60	3012 (22.2%)	1376 (20.3%)	1636 (24%)	<0.001
Heart failure	2194 (16.1%)	783 (11.5%)	1411 (20.7%)	<0.001
Peripheral artery disease	1888 (13.9%)	846 (12.5%)	1042 (15.3%)	<0.001
Prior CABG	1667 (12.3%)	691 (10.2%)	976 (14.3%)	<0.001
Prior stroke	931 (6.8%)	420 (6.2%)	511 (7.5%)	0.002

ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; eGFR, estimated glomerular filtration rate

Figure S1. Cumulative 10-year incidence of stroke, according to the number of risk indicators.

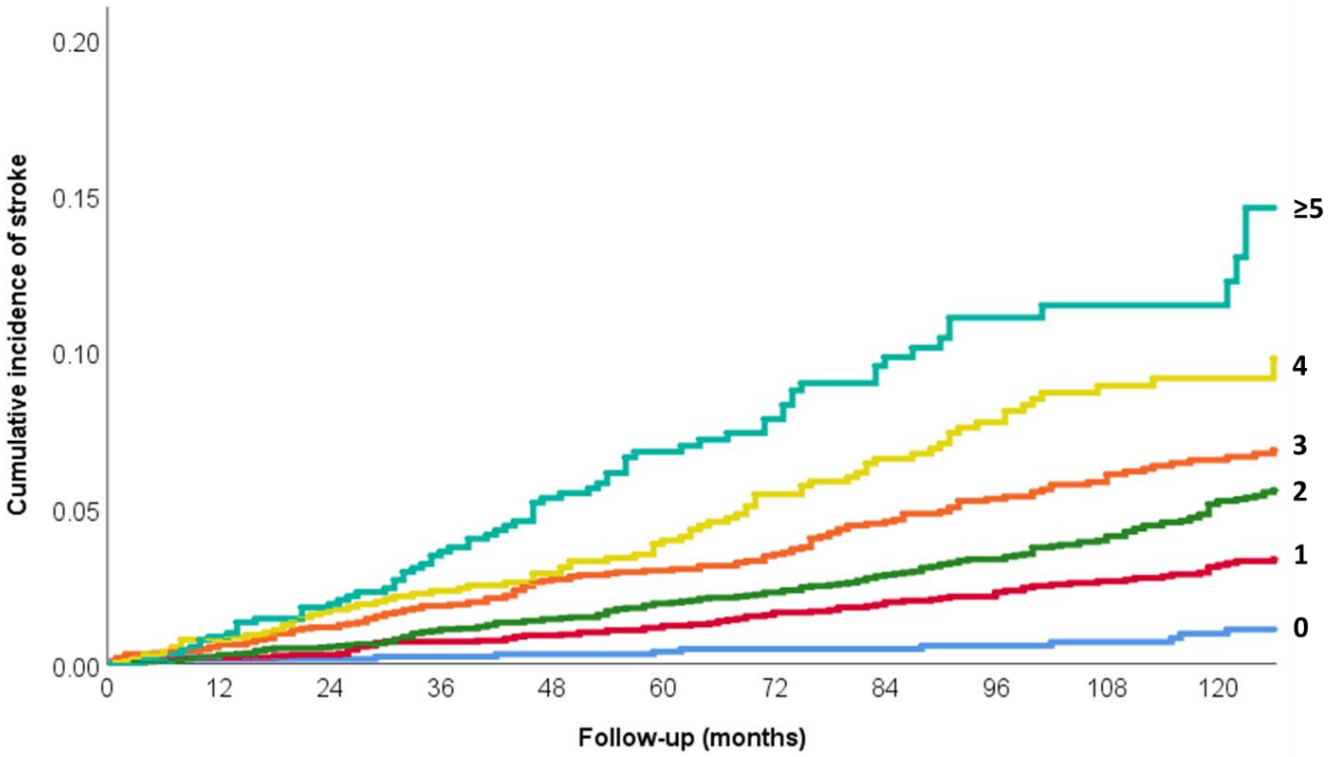

Figure S2. Cumulative 10-year incidence of myocardial infarction, according to the number of risk indicators.

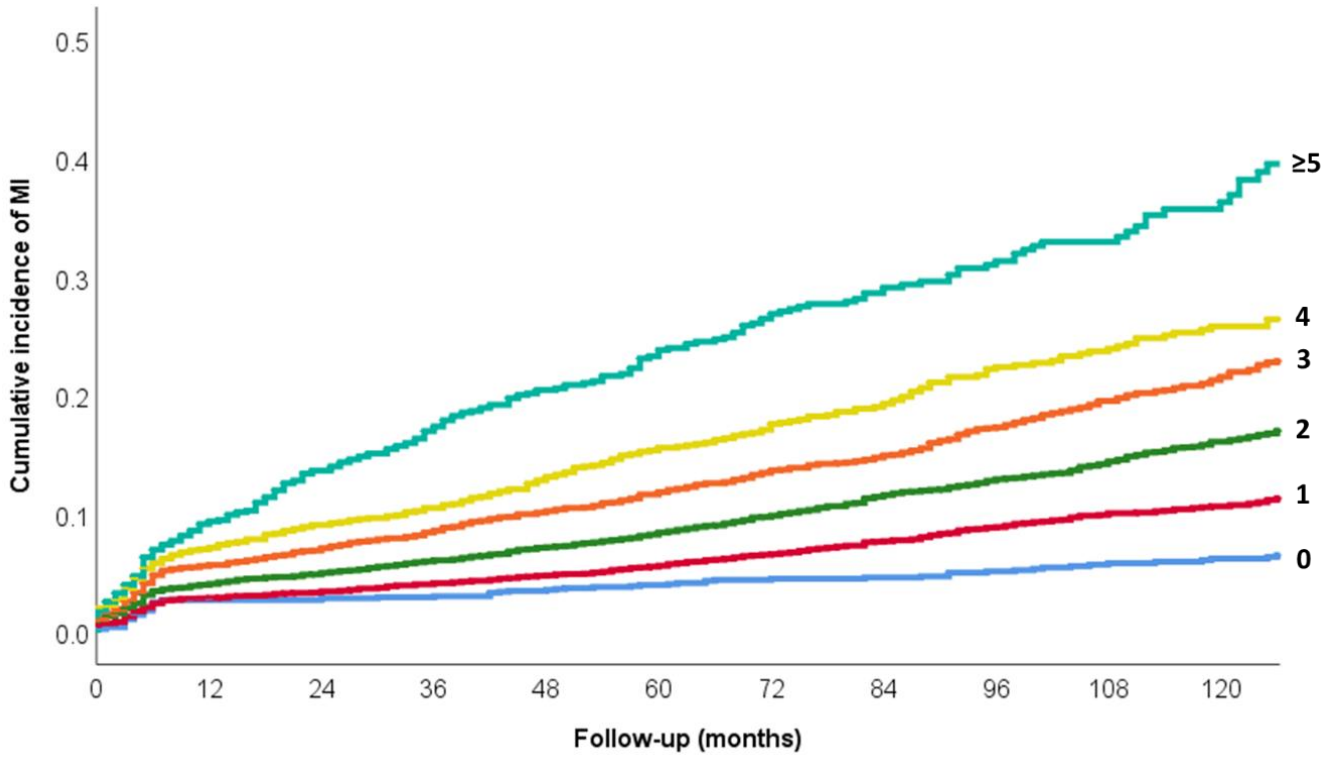

Figure S3. Cumulative 10-year incidence of all-cause death, according to the number of risk indicators.