Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention of Recurrent Cardiovascular Events in a Real-World Cohort of Post-Acute Myocardial Infarction Patients

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Background: Patients who survive myocardial infarction (MI) are at risk of recurrent cardiovascular (CV) events. This study stratified post-MI patients for risk of recurrent CV events using the Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRS 2°P).

Methods and Results: This was an observational study that applied TRS 2°P to a consecutive cohort of post-MI patients. The primary outcome was a composite endpoint of CV death, non-fatal MI, and non-fatal ischemic stroke. A total of 1,688 post-MI patients (70.3±13.6 years; male, 63.1%) were enrolled. After a mean follow-up of 41.5±44.4 months, 405 patients (24.0%) had developed a primary outcome (9.3%/year) consisting of 278 CV deaths, 134 non-fatal MI, and 33 non-fatal strokes. TRS 2°P was strongly associated with the primary outcome. The annual incidence of primary composite endpoint for patients with TRS 2°P 0 was 1.0%, and increased progressively to 39.9% for those with TRS 2°P ≥6 (HR, 27.6; 95% CI: 9.87–77.39, P<0.001). The diagnostic sensitivity of TRS 2°P for the primary composite endpoint was 76.3% (95% CI: 72.1–80.5%). Similar associations were also observed between TRS 2°P and CV death and non-fatal MI, but not non-fatal ischemic stroke.

Conclusions: TRS 2°P reliably stratified post-MI patients for risk of future CV events.

Key Words: Myocardial infarction; Secondary prevention; TRS 2°P

Atherosclerotic cardiovascular (CV) disease is currently one of the most common causes of morbidity and mortality worldwide. Patients who survive a major CV event such as myocardial infarction (MI) are considered at highest risk of a future major CV event and should therefore be managed very aggressively. This includes prolonged dual antiplatelet therapy, potent statin therapy, and non-statin therapy, ezetimibe, as well as certain novel therapeutic agents such as proprotein convertase subtilisin/kexin type 9 inhibitors, and the glucagon-like peptide 1 analogue, liraglutide, in patients with type 2 diabetes mellitus. Although these therapies have been shown to effectively reduce recurrent CV events, they may...
be accompanied by adverse effects such as bleeding and may also be prohibitively expensive.\textsuperscript{9,11} As such, accurate assessment of the absolute risk of future major CV events to identify very high-risk patients will allow efficient and appropriate use of these agents. The risk of future CV events such as recurrent MI, stroke and CV death in patients who survive MI nonetheless varies widely. In primary prevention, several CV risk-stratification schemes are available to guide long-term clinical decisions, such as Framingham risk score,\textsuperscript{12} SCORE,\textsuperscript{13} and QRISK.\textsuperscript{14} In contrast, existing risk stratification models for secondary prevention, for example in patients with recent acute coronary syndrome (ACS), focus largely on short-term prognostication and do not assist long-term therapeutic decision-making.

Recently, the Thrombolysis in Myocardial Infarction (TIMI) group has developed a simple 9-point risk stratification tool to predict recurrent CV events using data from the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events, TIMI 50 trial that involved stable patients with previous MI.\textsuperscript{15,16} This TIMI Risk Score for Secondary Prevention (TRS 2°P) incorporates 9 readily available clinical characteristics: congestive heart failure (CHF), hypertension, diabetes mellitus, age ≥75 years, prior stroke, prior coronary artery bypass graft (CABG), peripheral artery disease (PAD), estimated glomerular filtration rate (eGFR) <60, and smoking and is able to identify an approximately 5-fold gradient in the risk of recurrent major CV events across low-, intermediate-, and high-risk categories.\textsuperscript{17} Using data from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT),\textsuperscript{17} the score has been further validated for prediction of recurrent CV events following ACS in patients with established coronary artery disease (CAD). To date, TRS 2°P has been primarily validated in patient cohorts from randomized controlled trials (RCT), and its relevance to real-world clinical practice, particularly in different ethnicities, is uncertain. The aim of this study was therefore to describe the risk of major CV events in a large contemporary real world cohort of post-MI patients with detailed long-term follow-up, and to assess the prognostic performance of TRS 2°P in this population.

### Methods

#### Study Design and Patients

This was an observational study using a hospital-based acute MI registry.\textsuperscript{18} The study protocol was approved by the local institutional review board. Informed consent was not obtained from patients given the registry nature of the study; nonetheless all patient records/information were anonymized prior to analysis. Patients diagnosed with acute MI based on the standard 9th International Classification of Disease (ICD-9) codes of 410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91 and/or 411.1 at Queen Mary Hospital, Hong Kong, from February 2004 to January 2011, were identified via the computerized database of the clinical management system. Patients who died during hospitalization for the index MI were excluded from the final analysis. In Hong Kong, all hospital admissions, outpatient clinic visits, laboratory results and radiology have been recorded in a computer-based clinical management system since 1996. The hospital records of the index acute MI were reviewed to confirm the authenticity of the diagnosis. Demographic data, CV risk factors, and medications were recorded at baseline. The index date was defined as the date of the first occurrence of acute MI. For registration of outcome during follow-up, a blanking period of 14 days after the index date was applied.

### Table 1. Baseline Characteristics, In-Patient Revascularization and Discharge Medication

| Demographics (n=1,688) |
|-----------------------|
| Age (years)           | 70.3±13.6 |
| Male                  | 1,065 (63.1) |
| Hypertension          | 976 (57.8) |
| Diabetes mellitus     | 600 (35.5) |
| Smoker                | 767 (45.4) |
| STEMI                 | 797 (47.2) |
| NSTEMI                | 891 (52.8) |
| Heart failure         | 135 (8.0) |
| PAD                   | 65 (3.9) |
| Prior coronary rervascularization | 172 (10.2) |
| Prior stroke          | 243 (14.4) |
| Prior CABG            | 86 (5.1) |
| eGFR <60 mL/min/1.73 m² | 765 (45.3) |
| Mean TRS 2°P          | 2.6±1.6 |
| TRS 2°P               |            |
| 0                     | 126 (7.5) |
| 1                     | 328 (19.4) |
| 2                     | 394 (23.3) |
| 3                     | 366 (21.7) |
| 4                     | 262 (15.5) |
| 5                     | 140 (8.3) |
| 6–9                   | 72 (4.3) |

| Discharge medication and inpatient revascularization |
|-----------------------------------------------------|
| Aspirin                                             | 1,510 (89.5) |
| P2Y12 inhibitor                                     | 918 (54.4) |
| Warfarin                                            | 49 (2.9) |
| ACEI                                                | 1,118 (66.2) |
| β-blocker                                           | 1,180 (69.9) |
| CCB                                                 | 274 (16.2) |
| Statin                                              | 1,204 (71.3) |
| Inpatient PCI                                       | 699 (41.4) |
| Inpatient CABG                                      | 39 (2.3) |

Data given as mean ± SD or n (%). ACEI, angiotensin-converting enzyme inhibitor; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; NSTEMI, non-ST-elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TRS 2°P, TIMI (Thrombolysis in Myocardial Infarction) Risk Score for Secondary Prevention score.
Outcomes, Variables and Data Source
The primary outcome was a composite of (1) non-fatal MI; (2) non-fatal ischemic stroke; and (3) CV death. Secondary outcomes included CV death, non-fatal MI, fatal MI, non-fatal ischemic stroke and fatal ischemic stroke. MI was defined as a clinical scenario consistent with MI requiring hospitalization, confirmed by the presence of either electrocardiograph evidence or cardiac marker evidence. Ischemic stroke was defined as a neurological deficit of sudden onset, persisting >24 h, corresponding to a vascular territory with neuroimaging evidence, either computed tomography or magnetic resonance imaging confirming the diagnosis. CV death was defined as death that occurred during hospitalization for a documented MI, stroke, other non-cerebral, non-coronary vascular disease, HF, and/or ventricular tachyarrhythmia, in which there was no conclusive evidence of another cause of death; as well as sudden cardiac death classified according to the Modified Hinkle-Thaler scheme. All patients were monitored until the follow-up date in the cardiac outpatient clinic or until they died. Data were retrieved from the medical records and discharge summaries from the territory-wide information network of all public hospitals in Hong Kong. Patients who were lost to follow-up were contacted by phone. In addition, survival data were obtained from the Births and Deaths General Register Office.

Statistical Analysis
Continuous and discrete variables are expressed as mean±SD and percentages, respectively. Statistical comparison of the baseline clinical characteristics was performed using Student’s t-test or 1-way ANOVA as appropriate. Kaplan-Meier survival analyses with the log-rank test were carried out, and Cox proportional hazards regression modeling was used to calculate hazard ratios (HR) of some predictive factors and their 95% CI for the incidence of different outcomes. The diagnostic performance of the TRS 2°P for the primary composite endpoint and secondary endpoints was further assessed using the c-statistic (area under the curve). The c-statistic for the receiver operating characteristic curve was calculated using Analyze-It for Excel with previously described. Subsequent occurrence of risk factors that could contribute to TRS 2°P were not taken into account. Patients were stratified according to TRS 2°P.

Table 2. Baseline Indicators of Composite Endpoint (Cardiovascular Death, Non-Fatal MI, and Non-Fatal Stroke)

| No. composite endpoints | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
|-------------------------|-------------|---------|-------------|---------|-------------|---------|
| Age ≥75 years           | 3.65 (2.94–4.53) | <0.001 | 2.00 (1.57–2.55) | <0.001 | 1.45 (1.06–1.99) | 0.02 |
| Male                    | 0.53 (0.43–0.64) | <0.001 | 1.05 (0.86–1.30) | 0.634 | 0.95 (0.76–1.19) | 0.647 |
| Hypertension            | 1.96 (1.59–2.45) | <0.001 | 1.38 (1.10–1.73) | 0.006 | 1.01 (0.76–1.35) | 0.912 |
| Diabetes mellitus       | 1.62 (1.33–1.97) | <0.001 | 1.26 (1.02–1.55) | 0.031 | 0.99 (0.75–1.30) | 0.94 |
| Smoker                  | 0.90 (0.74–1.10) | 0.304 | -             | -       | -            | -       |
| NSTE MI                 | 2.25 (1.82–2.78) | <0.001 | 1.16 (0.92–1.46) | 0.222 | 1.16 (0.92–1.47) | 0.205 |
| Heart failure           | 3.21 (2.47–4.16) | <0.001 | 1.34 (1.02–1.76) | 0.036 | 1.14 (0.82–1.59) | 0.435 |
| PAD                     | 2.72 (1.90–3.91) | <0.001 | 1.29 (0.89–1.88) | 0.181 | 1.11 (0.73–1.71) | 0.621 |
| Prior coronary revascularization | 1.28 (0.95–1.71) | 0.103 | -             | -       | -            | -       |
| Prior stroke            | 2.52 (2.02–3.15) | <0.001 | 1.33 (1.05–1.68) | 0.181 | 1.08 (0.79–1.41) | 0.649 |
| Prior CABG              | 0.91 (0.58–1.43) | 0.683 | -             | -       | -            | -       |
| eGFR <60 mL/min/1.73 m² | 3.22 (2.61–3.98) | <0.001 | 1.71 (1.35–2.16) | <0.001 | 1.23 (0.91–1.67) | 0.186 |

Medications
| HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
|-------------|---------|-------------|---------|-------------|---------|
| Aspirin     | 0.25 (0.20–0.32) | <0.001 | 0.47 (0.36–0.61) | <0.001 | 0.48 (0.37–0.62) | <0.001 |
| P2Y12 inhibitor | 0.31 (0.25–0.38) | <0.001 | 0.71 (0.53–0.94) | 0.018 | 0.69 (0.52–0.92) | 0.011 |
| Warfarin    | 0.83 (0.45–1.50) | 0.53 | -             | -       | -            | -       |
| ACEI        | 0.48 (0.38–0.58) | <0.001 | 0.86 (0.70–1.07) | 0.178 | 0.83 (0.67–1.03) | 0.084 |
| β-blocker   | 0.50 (0.41–0.61) | <0.001 | 0.84 (0.68–1.04) | 0.11 | 0.86 (0.69–1.06) | 0.159 |
| Statin      | 0.46 (0.38–0.56) | <0.001 | 0.94 (0.75–1.18) | 0.600 | 0.95 (0.75–1.19) | 0.629 |
| CCB         | 1.34 (1.05–1.71) | 0.018 | 0.76 (0.59–0.98) | 0.034 | 0.75 (0.58–0.96) | 0.024 |
| Inpatient PCI | 0.28 (0.22–0.35) | <0.001 | 0.61 (0.44–0.85) | 0.004 | 0.62 (0.44–0.87) | 0.005 |
| Inpatient CABG | 0.09 (0.01–0.62) | 0.015 | 0.10 (0.01–0.69) | 0.02 | 0.07 (0.01–0.49) | 0.008 |

TRS 2°P

| 0   | 1   | 2   | 3   | 4   | 5   | 6–9 |
|-----|-----|-----|-----|-----|-----|-----|
| 4   |     |     |     |     |     |     |
| Ref. |     |     |     |     |     |     |
| Ref. |     |     |     |     |     |     |
| Ref. |     |     |     |     |     |     |
| Ref. |     |     |     |     |     |     |

*P<0.05; †parameters with P<0.05 on univariate analysis except TRS 2°P; ‡parameters with P<0.05 on univariate analysis together with TRS 2°P. MI, myocardial infarction. Other abbreviations as in Table 1.
Results

From February 2004 to January 2011, 1,931 patients were hospitalized with a documented MI, of whom 243 died during the index hospitalization. As a result, the final analysis involved 1,688 patients hospitalized for acute MI. Table 1 summarizes their clinical characteristics, inpatient

Figure 1. Kaplan-Meier estimates of (A) primary composite endpoint-free survival; (C) cardiovascular death-free survival; (E) non-fatal myocardial infarction (MI)-free survival; (G) MI-free survival; (I) non-fatal ischemic stroke-free survival; and annual incidence of (B) primary composite endpoint; (D) cardiovascular death; (F) non-fatal MI; (H) MI; and (J) non-fatal ischemic stroke in post-MI patients stratified according to Thrombolysis In Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRP 2°P).
A total of 797 patients (47.2%) presented with previous stroke. In addition, 45.3% had eGFR <60 mL/min/1.73 m², requiring revascularization, and 14.4% had had a note. 57.8% of patients had hypertension, 10.2% had prior ischemic stroke, renal impairment with eGFR <60 mL/min/1.73 m², NSTEMI at the index MI and the prescription of calcium channel blocker (CCB) upon discharge were associated with lower risk of discharge medications. Mean age was 70.3±7.6 years with a male predominance (63.1%). Of note, 57.8% of patients had hypertension, 10.2% had prior CAD requiring revascularization, and 14.4% had had a previous stroke. In addition, 45.3% had eGFR <60 mL/min/1.73 m². A total of 797 patients (47.2%) presented with acute ST-elevation MI (STEMI) and the remaining 891 patients (52.8%) with non-ST-elevation MI (NSTEMI). Mean TRS 2°P was 2.6±1.6. Inpatient coronary revascularization including both percutaneous coronary intervention and CABG was performed in 738 patients (43.7%). Upon discharge, most patients were prescribed aspirin (89.5%), 54.4% were prescribed a P2Y12 inhibitor, and 2.9%, warfarin. In addition, 71.3% of patients were prescribed a statin; 69.9%, a β-adrenergic blocker, and 66.2% an angiotensin-converting enzyme inhibitor (ACEI; Table 1, Supplementary Table 1).

### Table 3. Baseline Indicators of Cardiovascular Death

| No. cardiovascular deaths | Univariate analysis | HR (95% CI) | P-value | Multivariate analysis† | HR (95% CI) | P-value | Multivariate analysis‡ | HR (95% CI) | P-value |
|---------------------------|---------------------|-------------|---------|------------------------|-------------|---------|------------------------|-------------|---------|
| Age ≥75 years             | 218                 | 5.10 (3.84–6.77) | <0.001* | 2.70 (1.98–3.68)       | <0.001*     | 1.81 (1.22–2.68)       | <0.001*     | 0.003* |
| Male                      | 137                 | 0.54 (0.43–0.68) | <0.001* | 1.20 (0.94–1.53)       | 0.154       | 1.07 (0.82–1.40)       | 0.695 |
| Hypertension              | 204                 | 2.16 (1.66–2.82) | <0.001* | 1.50 (1.13–1.98)       | 0.005*      | 1.03 (0.73–1.46)       | 0.706 |
| Diabetes mellitus         | 121                 | 1.45 (1.14–1.83) | 0.002*  | 1.11 (0.87–1.43)       | 0.405       | 0.83 (0.61–1.17)       | 0.288 |
| Smoker                    | 122                 | 0.95 (0.75–1.20) | 0.641   | 0.99 (0.75–1.30)       | 0.917       | 1.00 (0.76–1.32)       | 0.161 |
| NSTEMI                    | 196                 | 2.28 (1.76–2.94) | <0.001* | 1.42 (1.04–1.94)       | 0.027*      | 1.14 (0.78–1.67)       | 0.047* |
| Heart failure             | 54                  | 3.67 (2.73–4.95) | <0.001* | 1.20 (0.77–1.86)       | 0.423       | 0.95 (0.58–1.57)       | 0.512 |
| PAD                       | 23                  | 2.73 (1.78–4.18) | <0.001* | 1.41 (1.07–1.85)       | 0.014*      | 1.06 (0.73–1.54)       | 0.054 |
| Prior coronary revascularization | 35             | 1.26 (0.89–1.80) | 0.196   | 1.76 (1.32–2.34)       | <0.001*     | 1.19 (0.82–1.71)       | 0.019* |
| Prior stroke              | 79                  | 2.81 (2.17–3.65) | <0.001* | 1.41 (1.07–1.85)       | 0.014*      | 1.06 (0.73–1.54)       | 0.054 |
| Prior CABG                | 16                  | 1.09 (0.66–1.81) | 0.726   | 1.76 (1.32–2.34)       | <0.001*     | 1.19 (0.82–1.71)       | 0.019* |
| eGFR <60mL/min/1.73m²      | 202                 | 3.65 (2.81–4.75) | <0.001* | 1.76 (1.32–2.34)       | <0.001*     | 1.19 (0.82–1.71)       | 0.019* |
| Medications               |                     |             |         |                        |             |         |                        |             |         |
| Aspirin                   | 200                 | 0.18 (0.14–0.23) | <0.001* | 0.36 (0.27–0.48)       | <0.001*     | 0.37 (0.27–0.49)       | <0.001* |
| P2Y12 inhibitor           | 69                  | 0.24 (0.18–0.31) | <0.001* | 0.62 (0.43–0.88)       | <0.001*     | 0.58 (0.41–0.84)       | 0.003* |
| Warfarin                  | 9                   | 1.01 (0.52–1.97) | 0.97    | 0.61 (0.47–1.04)       | 0.097       | 0.76 (0.59–0.99)       | 0.038* |
| ACEI                      | 138                 | 0.40 (0.32–0.51) | <0.001* | 0.61 (0.47–0.79)       | <0.001*     | 0.62 (0.48–0.80)       | <0.001* |
| β-blocker                 | 138                 | 0.34 (0.27–0.44) | <0.001* | 0.88 (0.67–1.16)       | 0.371       | 0.89 (0.68–1.17)       | 0.395 |
| Statin                    | 142                 | 0.35 (0.28–0.45) | <0.001* | 0.88 (0.67–1.16)       | 0.371       | 0.89 (0.68–1.17)       | 0.395 |
| CCB                       | 51                  | 0.34 (0.86–1.57) | 0.34    | 0.65 (0.42–1.00)       | 0.048*      | 0.67 (0.43–1.03)       | 0.065 |
| Inpatient PCI             | 43                  | 0.22 (0.16–0.31) | <0.001* | 0.20 (0.03–1.47)       | 0.114       | 0.13 (0.02–0.97)       | 0.046* |
| Inpatient CABG            | 1                   | 0.13 (0.09–0.94) | 0.043*  | 0.13 (0.02–0.97)       | 0.046* |
| TRS 2°P                   |                     | 0.046*       |         |                        |             |         |                        |             |         |

*P<0.05; †parameters with P<0.05 on univariate analysis except TRS 2°P; ‡parameters with P<0.05 on univariate analysis together with TRS 2°P. Abbreviations as in Table 1.

Primary Composite Outcomes

After a mean follow-up of 41.5±34.4 months, 405 patients (24.0%) developed a primary composite endpoint with an annual incidence of 9.3% per year. Table 2 summarizes the factors that were predictive of a primary composite endpoint together with the corresponding HR based on Cox proportional hazard modeling and 95% CI. On univariate analysis, age ≥75 years, female gender, hypertension, diabetes mellitus, PAD, history of HF, prior ischemic stroke, renal impairment with eGFR <60 mL/min/1.73 m², NSTEMI at the index MI and the prescription of calcium channel blocker (CCB) upon discharge were associated with an increasing risk for a primary composite endpoint. In addition, the prescription of aspirin, P2Y12 inhibitor, ACEI, β-adrenergic blocker, statin, and in-hospital revascularization were associated with lower risk of primary composite endpoint. There was a progressive increase in the annual incidence of primary composite endpoint with increasing TRS 2°P. Figure 1A shows a Kaplan-Meier analysis of composite endpoint in patients stratified according to TRS 2°P (log-rank, 222; P<0.0001). For instance, the annual incidence of primary composite endpoint for patients with TRS 2°P 0 was 1.0% per year, increasing to 39.9% per year for those with TRS 2°P ≥6 (HR, 27.6; 95% CI: 9.87–77.39, P<0.001; Figure 1B; Table 2).

On the first multivariate analysis that did not incorporate TRS 2°P into the model, age ≥75 years, hypertension,
diabetes, history of HF, prior ischemic stroke, and renal impairment with eGFR <60 mL/min/1.73 m² at the index MI remained independently associated with increasing risk of primary composite endpoint. In contrast, prescription of aspirin, P2Y12 inhibitors, CCB, and in-hospital revascularization were associated with lower risk of primary composite endpoint. In the second multivariate analysis that included TRS 2°P in the model, age ≥75 years, and TRS 2°P remained independently associated with increasing risk of primary composite endpoint; and the prescription of aspirin, P2Y12 inhibitor, and/or CCB as well as in-hospital revascularization remained independently associated with lower risk of primary composite endpoint.

CV Death
There were 278 CV deaths during the study period. The annual CV mortality was 5.86% per year. Similar to the primary composite endpoint, TRS 2°P together with age ≥75 years, history of HF, and renal impairment with eGFR <60 mL/min/1.73 m², and NSTEMI at index MI were associated with increasing risk of CV death both on univariate analysis and on multivariate analysis (Table 3). Figure 1C shows a Kaplan-Meier analysis of CV death for patients stratified according to TRS 2°P (log-rank, 197, P<0.0001; Figure 1D; Table 3). In an additional analysis stratifying the risk of CV death separately for patients with and without in-hospitalization revascularization, while patients receiving in-hospital revascularization had an overall lower risk of primary composite endpoint compared with those without in-hospital revascularization (3.5%/year vs. 15.3%/year), such risk increased progressively with increasing TRS 2°P in both groups (Supplementary Figure A).

Table 4. Baseline Indicators of Non-Fatal MI

| No. non-fatal MI | Univariate analysis | Multivariate analysis† | Multivariate analysis‡ |
|------------------|---------------------|------------------------|------------------------|
|                  | HR (95% CI)         | P-value                | HR (95% CI)            | P-value                | HR (95% CI)            | P-value                |
| Age ≥75 years    | 2.34 (1.65–3.32)    | <0.001*                | 1.49 (1.01–2.20)       | 0.046*                | 1.44 (0.87–2.40)       | 0.159                 |
| Male             | 68                  | 0.56 (0.40–0.79)       | 0.001*                | 0.92 (0.64–1.32)       | 0.654                 | 0.92 (0.61–1.36)       | 0.662                 |
| Hypertension     | 96                  | 1.96 (1.34–2.85)       | <0.001*               | 1.28 (0.85–1.88)       | 0.258                 | 1.20 (0.72–1.99)       | 0.485                 |
| Diabetes mellitus| 73                  | 2.27 (1.62–3.19)       | <0.001*               | 1.74 (1.22–2.50)       | 0.002*                | 1.71 (1.06–2.77)       | 0.028*                |
| Smoker           | 57                  | 0.88 (0.62–1.24)       | 0.46                  | 1.55 (0.96–2.49)       | 0.072                 |
| NSTEMI           | 94                  | 2.28 (1.57–3.30)       | <0.001*               | 1.38 (0.91–2.09)       | 0.125                 | 1.39 (0.92–2.10)       | 0.122*                |
| Heart failure    | 17                  | 2.06 (1.24–3.42)       | 0.006*                | 1.05 (0.61–1.78)       | 0.868                 | 1.07 (0.58–1.98)       | 0.838                 |
| PAD              | 13                  | 3.18 (1.79–5.63)       | <0.001*               | 1.73 (0.95–3.15)       | 0.071                 | 1.82 (0.89–3.72)       | 0.103                 |
| Prior coronary revascularization | 20 | 1.55 (0.96–2.49) | 0.072 |
| Prior stroke     | 30                  | 1.97 (1.31–2.96)       | 0.001*                | 1.17 (0.76–1.79)       | 0.481                 | 1.19 (0.68–2.07)       | 0.546                 |
| Prior CABG       | 5                   | 0.70 (0.29–1.71)       | 0.43                  | 0.15 (0.01–3.73)       | 0.874                 |
| eGFR <60 mL/min/1.73 m² | 87 | 2.55 (1.79–3.63) | <0.001* |

Medications

|                      | No. non-fatal MI | Univariate analysis | Multivariate analysis† | Multivariate analysis‡ |
|----------------------|------------------|---------------------|------------------------|------------------------|
| Aspirin              | 121              | 0.68 (0.38–1.21)    | 0.187                 | 0.97 (0.62–1.52)       | 0.896                 | 0.96 (0.62–1.53)       | 0.919                 |
| P2Y12 inhibitor      | 55               | 0.50 (0.35–0.70)    | <0.001*               | 0.97 (0.62–1.52)       | 0.896                 | 0.96 (0.62–1.53)       | 0.919                 |
| Warfarin             | 0                | 0.00 (0.00–3.38)    | 0.161                 | 0.82 (0.56–1.18)       | 0.281                 |
| ACEI                 | 80               | 0.63 (0.45–0.89)    | 0.009*                | 0.97 (0.67–1.40)       | 0.868                 | 0.96 (0.66–1.38)       | 0.818                 |
| β-blocker            | 101              | 1.13 (0.76–1.67)    | 0.557                 | 1.17 (0.79–1.74)       | 0.455                 | 1.16 (0.78–1.74)       | 0.469                 |
| Statin               | 95               | 0.82 (0.56–1.18)    | 0.281                 | 0.82 (0.56–1.18)       | 0.281                 |
| CCB                  | 36               | 1.94 (1.33–2.84)    | <0.001*               | 0.63 (0.37–1.06)       | 0.083                 | 0.63 (0.37–1.07)       | 0.088                 |
| Inpatient PCI        | 32               | 0.38 (0.26–0.57)    | <0.001*               | 0.38 (0.26–0.57)       | 0.083                 | 0.38 (0.26–0.57)       | 0.083                 |
| Inpatient CABG       | 0                | 0.21 (0.00–5.35)    | 0.206                 |

TRS 2°P

| 0 | 3 | Ref. | Ref. |
|---|---|-----|-----|
| 1 | 14 | 1.81 (0.52–6.31) | 0.349 |
| 2 | 17 | 1.90 (0.56–6.47) | 0.307 |
| 3 | 34 | 4.34 (1.33–14.12) | 0.015* |
| 4 | 33 | 6.08 (1.86–19.82) | 0.003* |
| 5 | 20 | 7.76 (2.31–26.13) | 0.001* |
| 6–9 | 13 | 10.73 (3.06–37.69) | <0.001* |

*P<0.05; †parameters with P<0.05 on univariate analysis except TRS 2°P; ‡parameters with P<0.05 on univariate analysis together with TRS 2°P. Abbreviations as in Tables 1,2.
risk of CV death compared with those without in-hospital revascularization (1.9%/year vs. 9.7%/year), the risk of CV death increased progressively with increasing TRS 2°P in both groups (Supplementary Figure B). The association between TRS 2°P and CV death remained highly significant after multivariate analysis (Table 3). The sensitivity of TRS 2°P (81.0% with optimal cut-off at 3) was highest compared with other baseline demographic factors as a single criterion to predict CV death (sensitivity, 76.4–85.6%). The c-statistic of TRS 2°P as a predictor of CV death was 0.74 (95% CI: 0.711–0.769; Supplementary Table 3).

Ischemic Stroke

During the study period there were 49 ischemic strokes, of which 33 were non-fatal and 16 were fatal. Figure 1I shows Kaplan-Meier analyses of non-fatal ischemic stroke for patients stratified according to TRS 2°P (log-rank, 3.19, P=0.074). The annual incidence of non-fatal stroke was 0.71% per year. On univariate analysis, only female gender and renal impairment with eGFR <60 mL/min/1.73 m² were associated with increasing risk of non-fatal ischemic stroke (Supplementary Table 6). Although the annual incidence of non-fatal stroke appeared to increase with TRS 2°P, the association did not reach statistical significance (Figure 1J; Supplementary Table 6). Further, patients receiving in-hospital revascularization had an overall lower risk of ischemic stroke compared with those without in-hospital revascularization (0.3%/year vs. 1.1%/year; Supplementary Figure D). In addition, there were altogether 18 hemorrhagic strokes during the study period. Nonetheless, there was no statistically significant difference across TRS 2°P strata.

Discussion

To the best of our knowledge, this is the first study to validate TRS 2°P for stratifying patients who survive MI for risk of recurrent CV events in a real-world clinical setting. We first showed that patients who survive MI were at high risk of subsequent major CV events, with an annual incidence of a primary composite endpoint (CV death, non-fatal MI and non-fatal stroke) of 9.3%. This high annual incidence was primarily driven by the high annual incidence of CV death (5.86%) and non-fatal MI (3.03%), rather than non-fatal stroke (0.71%). Second, we demonstrated a strong gradient of primary composite endpoint
stratified using TRS 2°P in a real-world cohort of patients who survived MI and in concordance with previous analyses using data from 2 large RCT. The annual incidence of primary composite endpoints in patients with TRS 2°P > 0 was 1.0% per year, and progressively increased to 39.9% per year in those with TRS 2°P ≥ 26, nearly a 40-fold gradient increase. The diagnostic performance of TRS 2°P to predict a primary composite endpoint appears to be reasonable for clinical application (c-statistic, 0.724; 95% CI: 0.697–0.752). Third, TRS 2°P demonstrated similar gradients for the risk of CV death and non-fatal MI to that for the primary composite endpoint, but not for non-fatal stroke, presumably due to the low annual incidence.

Current international guidelines emphasize the need for total CV risk assessment in order to assign preventive measures of appropriate intensity according to an individual patient’s risk. The recommended risk assessment schemes typically define CV risk on the basis of risk score in an apparently healthy person (primary prevention), or on the basis of existing CV disease (secondary prevention). Unlike the primary prevention setting in which patients are stratified into different risk categories for preventive measures of different intensities, those who survive MI are homogeneously classified into a single “very high-risk” category, and warrant the most aggressive secondary preventive measures. In the past decade, treatment options and strategies for secondary prevention in patients who survive MI have expanded rapidly. Although effective, these novel therapeutic options and strategies are expensive and might sometimes cost, thereby facilitating treatment allocation. Further subclassification of these very high-risk patients according to individual absolute risk for major CV events is therefore necessary to enable efficient and appropriate use of these new agents.

Until recently, there has been no validated risk assessment scheme to guide secondary prevention. Using data from the TIMI 50 trial and the IMPROVE-IT trial, TRS 2°P has been developed and validated to predict recurrent CV events in patients with previous coronary events. Indeed, TRS 2°P identifies an approximately 5-fold gradient in the risk of subsequent major CV events in post-coronary event patients across low, intermediate-, and high-risk categories. Similar to the CHA2DS2-VASc score for stroke risk stratification in the setting of atrial fibrillation, TRS 2°P consists of readily available clinical characteristics. This allows easy clinical translation and rapid, widespread application in real-world clinical practice after further validation using real-world clinical data. In agreement with previous analyses using RCT data, the TRS 2°P score likewise identifies a strong gradient of risk for subsequent CV events in a real-world, unselected cohort of patients who survive MI. Nonetheless quantitative differences exist between the present real-world cohort and that of the 2 previous RCT. Compared with corresponding annualized rates of major CV events from previous analyses, patients with low TRS 2°P (0–1) in the present study were at similar risk of major CV events, but those with an intermediate score (TRS 2°P ≥ 2) or high score (TRS 2°P ≥ 3) had a much higher risk of major CV events (2–3-fold; Figure 2).

Obviously, patients from these RCT were highly selected based on stringent inclusion and exclusion criteria, and were often not comparable with the more heterogeneous patients in the real-world registries. In particular there were fewer patients at the extremely high-risk end of the spectrum. Of note, patients from the 2 studies: IMPROVE IT trial and TIMI 50 trial, were substantially younger, 63.6 years and 59 years, respectively, than those in the present study, 70.3 years. Equally important, much higher proportions of patients in the 2 studies were prescribed guideline-recommended medical therapy such as P2Y12 inhibitor, ACEI/angiotensin receptor blocker, β-adrenergic blocker or statin compared with the current study. Furthermore, the differences in type of index coronary event and the duration from the index acute coronary event to study recruitment may at least partly explain the much higher event rate in the present study. In the IMPROVE-IT study, although all patients had had recent ACS (within 10 days), only 29% had STEMI, and 47% had an NSTEMI, with the remaining 24% having only unstable angina. In the TIMI-50 trial, although all patients had a history of spontaneous MI, only 45% occurred in the 3 months prior to recruitment. In the present real-world registry, all patients who survived MI (both STEMI and NSTEMI) and who were discharged from hospital during the study period were included in the final analysis, thereby providing an inclusive cohort to estimate the natural risk of MI. Nonetheless, TRS 2°P in both a clinical trial setting and in the present real-world registry has consistently demonstrated a high discriminating power to identify extremely high-risk post-coronary event patients (TRS 2°P ≥ 3).

Expectedly, the ability to further stratify the CV risk of individual patients who survive an MI enables more quantitative decision-making, which involves a delicate balance between potential benefits and adverse effects, and sometimes cost, thereby facilitating treatment allocation. For instance, using the TIMI 50 trial data, a gradient of absolute risk reduction with vorapaxar across TRS 2°P was clearly demonstrated: patients at a higher absolute risk could derive greater absolute benefit than those at lower risk from the same effective treatment. The much greater absolute risk reduction in patients with high TRS 2°P outweighs the accompanying bleeding from vorapaxar, thereby justifying the use of such treatment. Likewise, in the analysis of the IMPROVE-IT trial data, patients with TRS 2°P ≥ 3 derived a 6.6% absolute reduction in risk of CV death, major coronary event, or stroke from the addition of ezetimibe to simvastatin therapy, whereas patients with the lowest risk (TRS 2°P 0–1) had no such reduction from ezetimibe over the study period of 7 years. Furthermore, in the present study, patients receiving in-hospital revascularization had an overall lower risk of primary composite endpoint, CV death, non-fatal MI and ischemic stroke compared with patients who did not undergo in-hospital revascularization. Patients with higher TRS 2°P had a higher absolute risk reduction in the primary composite endpoint compared with patients with lower TRS 2°P. It has been shown in the Timing of Intervention in ACS (TIMACS) trial involving patients with ACS that early intervention compared with late intervention reduced the rate of the composite outcome of death, MI, or refractory ischemia, particularly in high-risk patients. Nonetheless, it is important to stress that the timing of coronary intervention in the present study was not chosen in a randomized fashion, and it is possible that residual confounding may be evident such that patients with and without in-hospital revascularization were in some ways different from each other.
Study Limitations
This study was limited by its registry-based and single-center observational design in primarily hospital-based patients. Due to the observational nature, the use of guideline-recommended medical therapy was suboptimal compared with RCT; nonetheless it represents a typical pattern of real-world clinical practice. In addition, data pertaining to medication adherence, another important factor to determine outcome, were unfortunately not available in the present study. Although we carefully ascertained all MI and strokes by careful examination of hospital records, laboratory and imaging results, patients with a milder form of MI and/or stroke who were not hospitalized were not included.

Conclusions
Taken collectively, the present study provides additional supporting evidence using real-world clinical data for the use of TRS 2P to stratify patients with established CV disease for future risk of CV events.

Disclosures
The authors declare no conflicts of interest.

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Supplementary Files
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