Risk scores for risk stratification in acute coronary syndromes: useful but simpler is not necessarily better

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KEYWORDS
Acute coronary syndromes; Risk scores; Risk stratification; Prognosis

Aims Our objectives were (i) to compare the discriminatory performance of the Thrombolysis in Myocardial Infarction risk score (TIMI RS), Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy risk score (PURSUIT RS), and Global Registry of Acute Cardiac Events risk score (GRACE RS) for in-hospital and 1 year mortality across the broad spectrum of non-ST-elevation acute coronary syndromes (ACS) and (ii) to determine their incremental prognostic utility beyond overall risk assessment by physicians.

Methods and results We calculated the TIMI RS, PURSUIT RS, and GRACE RS for 1728 patients with non-ST-elevation ACS in the prospective, multicentre, Canadian ACS II Registry. Discriminatory performance was measured by the c-statistic (area under receiver-operating characteristic curve) and compared by the method described by DeLong. TIMI RS, PURSUIT RS, and GRACE RS all demonstrated good discrimination for in-hospital death (c-statistics = 0.68, 0.80, 0.81, respectively, all P < 0.001) and 1 year mortality (c-statistics = 0.69, 0.77, 0.79, respectively, all P < 0.0001). However, PURSUIT RS and GRACE RS performed significantly better than the TIMI RS in predicting in-hospital (P = 0.036 and 0.02, respectively) and 1 year (P = 0.006 and 0.001, respectively) outcomes. In multivariable analysis adjusting for the use of in-hospital revascularization, stratification by tertiles of risk scores (into low, intermediate, and high-risk groups) furnished independent and greater prognostic information compared with risk assessment by treating physicians for 1 year outcome.

Conclusion Compared with TIMI RS, both PURSUIT RS and GRACE RS allow better discrimination for in-hospital and 1 year mortality in patients presenting with a wide range of ACS. All three risk scores confer additional important prognostic value beyond global risk assessment by physicians. These validated risk scores may refine risk stratification, thereby improving patient care in routine clinical practice.

Introduction

Early risk stratification plays a pivotal role in the optimal management of non-ST-elevation acute coronary syndromes (ACS), which represent a heterogeneous condition with variable short-term and long-term prognosis.¹² Over the past decade, a multitude of risk scores have been proposed to facilitate risk assessment.⁴–⁸ For example, the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT RS) and Thrombolysis in Myocardial Infarction (TIMI RS) risk scores were derived from clinical trial populations,⁶,⁷ and the Global Registry of Acute Cardiac Events risk score (GRACE RS) was developed from an international registry.⁸ Although these risk scores have been externally validated,⁶–¹³ their comparative performance in representative patient populations has not been well studied.¹²,¹³ Furthermore, it is not known whether application of these risk scores can refine risk assessment by physicians in routine clinical practice.

Using data from the prospective Canadian ACS II Registry, we sought to (i) compare the in-hospital and 1 year prognostic accuracy of the PURSUIT RS, TIMI RS, and GRACE RS and (ii) determine their incremental prognostic value beyond patient risk assessment by treating physicians.

Methods

Study design and population

The study design of the Canadian ACS Registry has been described.¹⁴ The Canadian ACS II Registry, which included only patients with non-ST-elevation ACS, was an extension of the ACS Registry. In brief, patients were eligible if they were (i) ≥18 years old on presentation; (ii) admitted to hospital with a suspected ACS (defined by symptoms consistent with acute cardiac ischaemia within 24 h of onset); and (iii) there was no serious concurrent illness such as
trauma or gastrointestinal bleeding. To reduce patient selection bias, there were no other specific exclusion criteria, and we encouraged all participating hospitals to enrol consecutive patients. At each site, the designated physician or study coordinator recorded demographic and clinical data, in-hospital treatment, and outcome on standardized case report forms, which were then forwarded to the Canadian Heart Research Centre and scanned into an electronic database (Teleform®, Version 7.0, Cardiff, San Diego, CA, USA). A brief summary of the contemporary Canadian practice guidelines on management of ACS was appended in the case report form (Appendix).15 Treating physicians were asked to categorize their patients into low, intermediate, and high-risk groups on the basis of overall risk assessment of medical history (e.g. age), physical examination (e.g. heart failure or haemodynamic instability), and laboratory investigations (e.g. ST-segment deviation on ECG). This approach was similar to the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) consensus guidelines.1,2

Risk scores for risk stratification in ACS

Risk score calculation

All three risk scores were calculated on the basis of clinical features at presentation. The TIMI RS (range 0–7) was the sum of seven dichotomous variables (1 point for each variable if present): age ≥65 years, ≥3 risk factors for coronary artery disease, use of aspirin within the past 7 days, known coronary artery stenosis ≥50%, ≥2 episodes of angina within the past 24 h, ST-segment deviation, and elevated cardiac biomarker.7 For patients without prior coronary angiography, we assigned 1 point if there was a history of myocardial infarction or coronary revascularization, in accordance with the suggestion by the authors of TIMI RS.9,10 In contrast, the PURSUIT RS and GRACE RS included both dichotomous and continuous variables, and published nomograms were available to convert the latter into points, which were then summed.6,8 The PURSUIT RS (range 0–25) comprised age, gender, worst Canadian Cardiovascular Society angina class in previous 6 weeks, heart rate, systolic blood pressure, signs of heart failure, and ST-depression (different points for age and heart rate variables were computed in patients with unstable angina vs. myocardial infarction).8 The components of the GRACE RS (range 1–372) were age, heart rate, systolic blood pressure, Killip class, cardiac arrest, serum creatinine, ST-segment deviation, and cardiac biomarker status.8

Between October 2002 and December 2003, the ACS II Registry recruited 2359 patients with suspected ACS from 36 participating hospitals in Canada; of these patients, 1956 (82.9%) had a final diagnosis of ACS. Compared with those given a final non-ACS diagnosis, patients with confirmed ACS had significantly higher TIMI RS, PURSUIT RS, and GRACE RS on presentation (all P < 0.001). Owing to missing data (which constituted <2% of cases for all variables, except 8.7% for Killip class), we could not calculate one or more risk scores for 228 patients (11.7%). These patients were excluded from the analysis; they did not differ significantly in most baseline characteristics and in-hospital mortality (1.8% vs. 1.8%, P = 0.97) from the remaining cohort. Thus, 1728 patients constituted the study cohort.

Outcome

Death included all-cause mortality. We focused on all-cause mortality because it was the most robust endpoint and had not been evaluated in a prior comparative study.13 Both PURSUIT RS and GRACE RS predict all-cause mortality.6,8 Although the TIMI RS was designed to predict the composite endpoint of death, myocardial (re-)infarction, or urgent revascularization [c-statistic (area under the receiver-operating characteristic curve) = 0.63], it demonstrated better discrimination for death alone in the original derivation and validation cohorts (c-statistic = 0.74).7

In-hospital outcome data were complete for all patients. At 1 year after discharge, follow-up data were collected via standardized telephone. Vital status could not be ascertained for 165 patients (9.5%); their TIMI RS, PURSUIT RS, and GRACE RS were similar (all P > 0.50) compared with patients with follow-up data.

Statistical analysis

Continuous data are summarized as medians and interquartile ranges (IQR), and categorical data as percentages. Group differences in continuous and categorical variables were compared by the Kruskal–Wallis test and chi-square test, respectively. We used Kendall’s τ-b test to examine correlations. The discriminatory abilities of the risk scores for in-hospital and 1 year mortality were measured by c-statistics, with standard errors estimated by a non-parametric method.16 We generated receiver-operating characteristic curves for each of the three risk scores and compared their areas according to the non-parametric method described by DeLong.17

To directly compare the utility of risk scores with global risk assessment by physicians (low, intermediate, and high risk, as recorded on the case report form) in predicting 1 year outcome, we categorized the study population into low, intermediate, and high-risk groups by ascending tertiles of risk scores. We then assessed the independent prognostic value of each risk score by entering it as categorical variable (tertiles) into separate multivariable logistic regression models, which adjusted for the global risk category according to treating physicians. Because patients deemed to be at high risk might have received more intensive treatment, which might impact on 1 year outcome and thereby negate the prognostic significance of physicians’ risk assessment, we also controlled for the use of in-hospital revascularization in multivariable analysis. Interaction terms were not significant and were not retained in the final model. The relative prognostic importance of each covariate was evaluated by the change in −2 log likelihood when the covariate was removed from the multivariable model.18 We analysed data using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) and considered two-sided P-values <0.05 to be statistically significant.

Results

Table 1 presents the baseline characteristics of the study population. The median TIMI RS was 3 (IQR 2–4); median PURSUIT RS was 7 (IQR 4–10); and median GRACE RS was 117 (IQR 95–143). There were moderate-to-strong positive correlations among the three risk scores, with the following correlation coefficients: 0.32 for TIMI RS and GRACE RS (P < 0.0001), 0.40 for TIMI RS and PURSUIT RS (P < 0.0001), and 0.66 for PURSUIT RS and GRACE RS (P < 0.0001). For classifying patients into low, intermediate, and high-risk groups, the kappa values were 0.27 for TIMI RS and PURSUIT RS (P = 0.0001), 0.19 for GRACE RS and TIMI RS (P < 0.0001), and 0.54 for PURSUIT RS and GRACE RS (P < 0.0001). According to the treating physicians, 16.4, 40.8, and 42.8% of patients were categorized as low, intermediate, and high risk, respectively. There were significant but only weak correlations between physicians’ assessment and TIMI RS (correlation coefficient = 0.09), PURSUIT RS (0.14), and GRACE RS (0.14) (all P < 0.0001).

Table 2 summarizes the in-hospital management of patients by risk groups. Patients considered to be at high risk by their physicians were more likely to undergo cardiac catheterization and coronary revascularization...
Prognostic accuracy of the risk scores

Figures 5 and 6 display the receiver-operating characteristic curves for the three risk scores in predicting in-hospital and 1 year death, respectively. For in-hospital mortality, the C-statistics (areas under the curves) were 0.68 (95% confidence interval [CI] 0.59–0.77, \( P < 0.001 \)) for TIMI RS, 0.80 (95% CI 0.71–0.88, \( P < 0.0001 \)) for PURSUIT RS, and 0.81 (95% CI 0.73–0.89, \( P < 0.0001 \)) for GRACE RS. Both PURSUIT RS and GRACE RS demonstrated better discrimination than TIMI RS in predicting in-hospital death \( (P = 0.036 \) and 0.02, respectively), but there was no significant difference between PURSUIT RS and GRACE RS \( (P = 0.69) \).

For 1 year mortality, the C-statistics were 0.69 (95% CI 0.64–0.74, \( P < 0.0001 \)) for TIMI RS, 0.77 (95% CI 0.72–0.81, \( P < 0.0001 \)) for PURSUIT RS, and 0.79 (95% CI 0.74–0.83, \( P < 0.0001 \)) for GRACE RS. The PURSUIT RS and GRACE RS showed similar predictive accuracy \( (P = 0.34) \), but were more accurate than the TIMI RS \( (P = 0.006 \) and 0.001, respectively) in predicting death at 1 year.

Comparison of risk scores and risk assessment by physicians

As shown in Figures 1–4, higher risk categories as per treating physicians or any of the risk score tertiles were associated with adverse outcome both during index hospitalization and at 1 year. However, for 1 year outcome, the risk gradient was steeper when patients were stratified by risk scores. Patients considered to be high risk by their physicians were three times more likely to die compared with those at low risk. The C-statistic for physicians’ risk assessment in predicting 1 year mortality was 0.59 (95% CI 0.54–0.64, \( P = 0.002 \)). In comparison, patients at the highest tertile of TIMI RS had a five-fold increased risk of death compared with those at the lowest tertile. Similarly, patients at high risk by virtue of their PURSUIT or GRACE risk scores had a 10 to 15-fold higher mortality rate than the low-risk group.

In multivariable analysis (Table 3), all three risk scores (by tertiles) were independently associated with 1 year mortality even after adjusting for risk assessment by physicians and the use of revascularization during index admission. Moreover, the greater changes in \( -2 \log \text{likelihood} \) indicate that all three risk scores consistently provided more prognostic information compared with risk assessment by physicians. Similar results were obtained after further adjustment for discharge use of evidence-based medical therapies among hospital survivors, and for the composite endpoint of death or myocardial infarction at 1 year. Finally, when PURSUIT RS and GRACE RS were analysed as continuous variables (instead of tertiles), risk assessment by physicians failed to confer any incremental prognostic value and was no longer an independent predictor of outcome.

Discussion

Across the broad spectrum of non-ST-elevation ACS, the TIMI RS, PURSUIT RS, and GRACE RS all demonstrated significant discriminatory ability for in-hospital and 1 year mortality. However, PURSUIT RS and GRACE RS were more accurate than TIMI RS in predicting these outcomes. Furthermore, to the best of our knowledge, the present study is the first to show that these risk scores confer additional prognostic value beyond risk assessment by physicians.

In an attempt to simplify and improve risk stratification, researchers have focused their attention on the development and validation of various risk scores over the past decade.\(^1\)\(^3\)\(^-\)\(^9\)\(^-\)\(^20\) To date, there are only limited data on the comparative accuracy of these risk scores,\(^1\)\(^1\)\(^-\)\(^3\)\(^-\)\(^13\) despite substantial differences in their complexity, derivation cohorts, and predicted endpoints. Singh et al.\(^1\)\(^1\) showed that the TIMI RS was inferior to the PREDICT score in forecasting death alone and the combined endpoint of death or re-infarction among 717 patients with non-ST-elevation myocardial infarction in Olmsted County. In the Canadian ACS I Registry, the GRACE RS and modified PURSUIT RS demonstrated similar discriminatory performance for in-hospital death, although model calibration was better for the former.\(^1\)\(^2\) Recently, de Araújo Gonçalves et al.\(^1\)\(^3\) compared the predictive accuracy of TIMI RS, PURSUIT RS, and GRACE RS among 460 ACS patients admitted to their coronary care unit. Both PURSUIT RS and GRACE RS demonstrated stronger discrimination than TIMI RS for death or myocardial
infarction at 1 year. The c-statistic for 1 month outcome was also lower for TIMI RS, although this difference did not reach statistical significance, plausibly due to inadequate power. Moreover, the generalizability of this single-centre study requires confirmation in other patient populations. The present study extends previous work by showing that PURSUIT RS and GRACE RS performed better than TIMI RS in identifying patients with poor outcome both in the short term and long term across the wide range of ACS.

A number of reasons may account for the differences in discriminatory capacities of TIMI RS, PURSUIT RS, and GRACE RS. Although advanced age, ST-segment deviation, and biomarker status are common components of all three risk scores, PURSUIT RS and GRACE RS incorporate haemodynamic variables also, whereas renal dysfunction is included in GRACE RS only. These clinical characteristics, which have been shown to be powerful independent prognosticators, were not evaluated as candidate variables when TIMI RS was initially developed. Exclusion of patients with these high-risk features from clinical trials might also have diminished the prognostic significance of these variables, which were therefore eliminated during model development. Furthermore, the TIMI RS, composed of dichotomous variables only and with a limited range of 0–7, likely incurred a trade-off between its ease of use and predictive accuracy.

Despite the proven utility of risk scores in prognostication and guidance of treatment strategies, it is not known how often they are actually used in routine practice. Physicians may be reluctant to use risk scores at the bedside because they find it inconvenient and time-consuming. Others believe that they can readily discern and integrate high-risk features into overall risk estimation without the aid of risk scores. Lack of definitive data demonstrating the incremental prognostic utility of risk scores beyond global risk assessment by physicians may have also contributed to their underuse. Although there are numerous

Table 2  In-hospital management by risk groups

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Risk Group</th>
<th>Cardiac Catheterization (%)</th>
<th>P for Trend</th>
<th>Coronary Revascularization (%)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians' assessment</td>
<td>Low risk (n = 283)</td>
<td>41.3</td>
<td>&lt;0.0001</td>
<td>15.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Intermediate risk (n = 705)</td>
<td>66.2</td>
<td>40.2</td>
<td>0.001</td>
<td>39.9</td>
</tr>
<tr>
<td></td>
<td>High risk (n = 740)</td>
<td>72.2</td>
<td>50.8</td>
<td>0.001</td>
<td>37.6</td>
</tr>
<tr>
<td>TIMI RS</td>
<td>Low risk (n = 548)</td>
<td>70.4</td>
<td>0.001</td>
<td>43.6</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Intermediate risk (n = 841)</td>
<td>62.6</td>
<td>39.9</td>
<td>0.001</td>
<td>37.6</td>
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<td></td>
<td>High risk (n = 339)</td>
<td>60.8</td>
<td>37.6</td>
<td>&lt;0.0001</td>
<td>32.3</td>
</tr>
<tr>
<td>PURSUIT RS</td>
<td>Low risk (n = 629)</td>
<td>75.3</td>
<td>&lt;0.0001</td>
<td>47.9</td>
<td>&lt;0.0001</td>
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<td></td>
<td>Intermediate risk (n = 609)</td>
<td>64.0</td>
<td>39.8</td>
<td>0.001</td>
<td>41.5</td>
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<tr>
<td></td>
<td>High risk (n = 490)</td>
<td>51.9</td>
<td>32.3</td>
<td>0.001</td>
<td>49.5</td>
</tr>
<tr>
<td>GRACE RS</td>
<td>Low risk (n = 579)</td>
<td>74.1</td>
<td>&lt;0.0001</td>
<td>49.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Intermediate risk (n = 578)</td>
<td>67.6</td>
<td>41.5</td>
<td>&lt;0.0001</td>
<td>49.5</td>
</tr>
<tr>
<td></td>
<td>High risk (n = 571)</td>
<td>52.3</td>
<td>30.7</td>
<td>&lt;0.0001</td>
<td>30.7</td>
</tr>
</tbody>
</table>

*aIncludes percutaneous coronary intervention or coronary bypass surgery.

Figure 1  In-hospital and 1 year outcomes by physicians' assessment.

Figure 2  In-hospital and 1 year outcomes by TIMI RS (tertiles).
established prognostic markers, they usually co-exist and their importance hinges on the inter-relationship of many factors. Because patients often present with complex risk profiles, assimilation of all the relevant information from history, physical examination, and laboratory investigations is a highly complicated process and a daunting task for a busy clinician. Consistent with this notion, our data show that there was poor correlation between risk assessment by treating physicians and all three risk scores. Using tertiles rather than the full range of risk scores in our main analysis, their prognostic utility was likely underestimated. Nevertheless, these risk scores still confer independent and greater prognostic information compared with physicians’ risk assessment after adjusting for treatment differences. Importantly, we observed the selective targeting of more aggressive therapies towards patients considered as high risk by their physicians, but a treatment-risk paradox became evident when patients were objectively stratified by risk scores. Although we realize that many other factors might have appropriately influenced management decisions, our findings offer a possible explanation for the documented treatment-risk paradox and the apparent lack of measurable benefit despite the proliferative use of invasive cardiac procedures in recent years. Therefore, dedicated efforts to improve risk stratification may enhance the overall care process and resource utilization. Yet, it should be emphasized that risk scores are clinical tools that can supplement but not replace sound clinical judgment—the astute clinician is well aware that none of the risk scores will necessarily encompass all the high-risk features. For instance, a high-risk patient with known three-vessel coronary artery disease and left ventricular systolic dysfunction presenting with crescendo angina may be haemodynamically stable without ECG changes or abnormal biomarker, and yet would be deemed to be at low risk on the basis of the calculated risk score.

Clinical implications

The ACC/AHA and the ESC consensus guidelines of 2002 recognize the importance of early risk stratification in the

![Figure 3](https://example.com/figure3.png) In-hospital and 1 year outcomes by PURSUIT RS (tertiles).

![Figure 4](https://example.com/figure4.png) In-hospital and 1 year outcomes by GRACE RS (tertiles).

![Figure 5](https://example.com/figure5.png) Receiver-operating characteristic curves for predicting in-hospital mortality.

![Figure 6](https://example.com/figure6.png) Receiver-operating characteristic curves for predicting 1 year mortality.

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A.T. Yan et al. 1076

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management of non-ST-elevation ACS and recommend an integrated approach to risk assessment.\textsuperscript{1,2} In addition, ACC/AHA guidelines state that 'estimation of the level of risk is a multivariable problem that cannot be accurately quantified with a simple table'.\textsuperscript{1} Accordingly, both ACC/AHA and ESC guidelines contain a list of high-risk clinical features to facilitate categorization of patients into low, intermediate, and high-risk groups.\textsuperscript{1,2} Since these risk scores had not been well validated in large external data sets when these guidelines were published, there were no explicit recommendations about their use.

With the subsequent external validation of several risk scores in representative patient populations,\textsuperscript{6–13} and their demonstrated superiority to subjective global risk assessment in the present study, risk scores should prove to be useful for risk stratification in clinical practice. Although the more sophisticated PURSUIT RS and GRACE RS may be more difficult to calculate than the TIMI RS, with wide availability of handheld computer devices and access to websites, these clinical tools can be easily employed at the point of care.\textsuperscript{19}

### Study limitations

Several study limitations should be discussed in the interpretation of our results. We encouraged but could not verify consecutive patient enrolment at all sites. The relatively low in-hospital mortality rate suggests that early deaths after presentation were likely excluded, although risk stratification is least applicable for these patients. Because of missing data, 11.7% of patients were excluded from the analysis, although their baseline characteristics and in-hospital outcome did not differ from the remaining cohort. At 1 year after index admission, 9.5% of patients were lost to follow-up. Despite their similar risk scores on presentation compared with patients with follow-up data, we could not rule out any potential bias. Since the three risk scores were originally developed to predict outcome at different time points, we could not assess calibration by comparing observed with predicted event rates. Physicians’ ability to risk-stratify patients may depend on their knowledge and experience, and this individual variability could not be determined in the present study. Nevertheless, more widespread and systematic application of a validated risk score will likely improve the process of risk stratification overall in the ‘real world’.

### Conclusion

Compared with the simpler TIMI RS, both PURSUIT RS and GRACE RS provide better discrimination for in-hospital and 1 year mortality among patients presenting with a wide spectrum of non-ST-elevation ACS. These validated risk scores are easy to use at the bedside and afford incremental prognostic value beyond global risk assessment by physicians. Because

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<th>Table 3 Multivariable analysis</th>
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<td>Model</td>
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<td>Physicians’ assessment and TIMI RS</td>
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<td>Intermediate risk</td>
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<td>High risk</td>
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<td>TIMI RS:</td>
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<td>Low risk</td>
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<td>Intermediate risk</td>
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<td>In-hospital revascularization</td>
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<td>Physicians’ assessment and PURSUIT RS</td>
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<td>Intermediate risk</td>
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<td>PURSUIT RS:</td>
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<td>In-hospital revascularization</td>
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<td>Physicians’ assessment and GRACE RS</td>
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<td>In-hospital revascularization</td>
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$x^2$ indicates the change in $–2 \log$ likelihood when the variable at hand was removed from the full model.
risk scores can refine risk stratification and inform therapeu-
tic decision-making, they have the potential to improve
patient care. We therefore advocate more wide-scale adop-
tion of validated risk scores in routine clinical practice.

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Canadian ACS II Registry.

Conflict of interest: none declared.

Appendix
The case report form is available as supplementary material at
European Heart Journal online.

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