Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndromes

Derek P. Chew, MBBS, MPH; Ge Junbo, MD; William Parsonage, MBBS; Prafulla Kerkar, DM, DNB; Vitaly A. Sulimov, MD, PhD; Matthew Horsfall, RN; Sue Mattchoss, RN; for the Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndrome Patients (PREDICT) Study Investigators

Background—Acute coronary syndrome registries report the use of incomplete guideline therapies, especially among the highest risk patients. Whether this treatment gap results from misperceptions of risk by physicians is uncertain.

Methods and Results—The Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndrome Patients (PREDICT) study was a prospective acute coronary syndrome registry in Australia, China, India, and Russia, involving 58 hospitals between May 2009 and February 2011. In-hospital care and events up to 6 months were assessed. At least 2 clinicians involved in patient care estimated the untreated risk and change in risk with each therapy. Physician risk assessment and objective risk measures (eg, Global Registry of Acute Coronary Events [GRACE] score) for death, death/myocardial infarction, and bleeding events were compared using the c statistic and integrated discrimination improvement. In total, 1542 patients and 4230 patient-specific physician estimates were obtained. Of responding clinicians, 81.9% were cardiovascular specialists (years of practice: mean [SD], 11.5 [7.7] years). The median physician-perceived risk of 6-month death was 25% (interquartile range, 14%–35%). The GRACE score was superior to physician estimation (c statistic: GRACE score, 0.812 [95% confidence interval, 0.772–0.851] versus physician, 0.652 [95% confidence interval, 0.596–0.708]; \(P<0.0001\)). The GRACE score added to clinician intuition improved discrimination (integrated discrimination improvement, 0.0632 [SE, 0.012]; \(P<0.0001\)). Invasive management correlated with physician-estimated risk but not with GRACE risk. Among patients not at high risk by physician estimation, increased risk by GRACE score was associated with higher mortality (3.7% versus 0.8%; \(P<0.001\)).

Conclusions—Objective risk assessment provides superior risk discrimination when compared with physician-estimated risk. Whether systematic use of objective risk stratification improves clinical outcomes should be studied in appropriately designed clinical trials. (Circ Cardiovasc Qual Outcomes. 2013;6:299-308.)

Key Words: acute coronary syndromes ■ quality of care ■ risk estimation ■ risk scores

In terms of recurrent ischemic and bleeding events, patients presenting with acute coronary syndromes (ACS) represent a diverse spectrum of clinical risk. The application of current therapies, including invasive management, based on risk is advocated by clinical guidelines.1–4 Hence, the translation of evidence-based clinical guidelines to optimal clinical outcomes is dependent on accurate risk assessment, the appropriate balancing of risk and benefit within the individual patient, and the availability of these proven technologies and therapies. Furthermore, this complex assessment often also needs to be performed in a time-critical manner.5,6 Several national and international registries continue to document the incomplete application of clinical guideline–recommended therapies in most parts of the developing and developed world, spurring several initiatives focused on improving the quality of ACS care.6–8 Interestingly, the largest evidence-practice gap seems to be among the patients at highest risk of recurrent ischemic events.9–11 However, these patients are also at the greatest risk of bleeding events and other adverse outcomes associated with several therapies.12,13 The factors contributing to this disconnect are not well documented but may include the following: the limited evidence in these high-risk (HR) groups often excluded from clinical trials, a perception that the risk of adverse events with therapy may exceed the benefits, a misperception of risk leading to an underappreciation of the benefit associated with therapies, and a possible sense of futility in which little benefit is expected among patients at the extremes of risk.

Consequently, we sought to explore how well clinicians estimated the risk of mortality and bleeding events among patients with ACS, weighed the benefits and risks of current ACS guideline-recommended therapies in a patient-specific context, and evaluated whether care provided correlated with perceived and calculated risk factors within several culturally diverse societies.
WHAT IS KNOWN

- Practice guidelines for acute coronary syndromes recommend calibrating the intensity of therapies to estimated patient risk.
- Some data suggest that physician estimates of risk are not well correlated with objective risk scores.

WHAT THE STUDY ADDS

- In this multicenter international study, objective risk stratification using the Global Registry of Acute Coronary Events risk score had superior discrimination compared with physician-perceived risk (c indices of 0.81 versus 0.65, respectively).
- Physicians overestimate risk among patients at low risk and underestimate risk among those at high risk.
- Although rates of use of invasive therapies correlated with physician-perceived risk of mortality, suggesting that physicians attempt to calibrate the intensity of their therapy to risk, there was not a correlation with risk using the Global Registry of Acute Coronary Events score.

Methods

Study Design

The Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndrome Patients (PREDICT) was a prospective, multicenter, international registry including 4 countries (Australia, China, India, and Russia) and involving 58 hospitals enrolling ACS patients between May 2009 and February 2011. Ethics committee approval was provided at each site, and informed consent was obtained from all patients before enrollment in the study.

Patient Population

A structured enrollment process (eg, first patient of the day, first 5 patients of the week, etc) was encouraged at each site, but consecutive recruitment was not required. Patients were considered eligible for enrollment if they presented with suspected ST-segment-elevation myocardial infarction (STEMI) HR and intermediate-risk non–ST-segment elevation ACS. Specifically, patients with symptoms suggestive of angina or angina-equivalent were included as suspected STEMI if they had persistent ST elevation >1 mm in 2 contiguous leads or new/presumed new left bundle-branch block. Patients were included as non–ST-segment–elevation ACS-HF if ECG findings demonstrated ST depression >0.5 mm, or T wave inversion ≥1.0 mm in >2 contiguous leads, biomarker elevation (troponin or creatine kinase-MB [CK-MB] fraction), hemodynamic compromise (cardiogenic shock, Killip class >1 or mitral regurgitation, or syncope), known left ventricular ejection fraction <40%, ventricular arrhythmias, previous coronary revascularization, a history of diabetes mellitus, or creatinine clearance <60 mL/min per 1.72 m². Patients were included as non–ST-segment–elevation ACS–intermediate risk in the absence of HR characteristics but with 1 of the following present: Q waves or ST/T changes in 2 leads, age >65 years, a history of previous coronary artery disease (previous event or coronary angiogram with a lesion >50%), known ejection fraction 40% to 50%, 2 or more coronary risk factors, and previous aspirin use. ACS admission deemed secondary to other causes such as major trauma or surgery was excluded. Allocation to each risk stratum was centrally adjudicated to ensure consistency of enrollment criteria. The primary discharge diagnosis was determined by the investigator but confirmed by a central query process.

Clinical Factors and Hospital Management

Within the baseline hospitalization, clinical characteristics required for calculating the Global Registry of Acute Coronary Events (GRACE), Thrombolysis in Myocardial Infarction (TIMI), and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) risk scores for recurrent ischemic events and the Acute Catheterization and Urgent Intervention Triage Strategy (ACUTY) and Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early implementation of the ACC/AHA Guidelines CRUSADE scores for bleeding were obtained through the completion of a standard case-record form.14-17 The provision of clinical guideline recommendations including reperfusion therapy (by either fibrinolysis or primary percutaneous coronary intervention [PCI]); early invasive management; prescription of aspirin, clopidogrel, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, β-blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists at discharge was also assessed at the time of discharge. Early invasive management was defined as angiography at any time within the acute hospital stay, regardless of transfer between immediate care hospitals. Patients discharged with planned outpatient angiography were not considered as having received an early invasive management strategy. All baseline clinical and outcome data were abstracted by trained clinical trial coordinators or clinicians, and at study completion, independent country-specific monitors audited data pertaining to clinical events and vital status.

Clinical Events

All-cause mortality, new or recurrent myocardial infarction (MI), stroke, and clinical bleeding events were sought during the initial hospital admission at 30 days, 3 months, and 6 months using standard definitions. Late events were obtained at the time of clinical review or by telephone. MI required a rise in biomarkers greater than the local threshold definition for troponin and more than twice the upper limit of normal for CK-MB (In the absence of CK-MB, CK was used). Recurrent MI required a further ≥25% rise and ≥50% rise in troponin and CK-MB, respectively, ≥24 hours after admission. After PCI and coronary artery bypass graft, a level of CK-MB >3 and >5 times the upper limit of normal within 48 hours or new Q-waves, respectively, was required, consistent with the universal definition.20 Stroke required a sudden onset of a new neurological deficit consistent with a single vascular territory supported by cerebral imaging reports when possible. Bleeding events were defined using the ACUTY criteria, specifically a decrease in hemoglobin of ≥3 g/dL, any blood transfusion, bleeding requiring a surgical/procedural intervention, or a vascular access site hematoma >5 cm in diameter.21 TIMI and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) bleeding criteria were also applied.22 All events were independently adjudicated by a clinical events committee.

Physician Assessment of Risk

Using a standardized case-record form, translated into the local language where required, physicians directly involved in the care of each specific patient were asked to assess the patient’s individual baseline untreated risk of death, new or recurrent MI, stroke, or bleeding at 30 days, 3 months, and 6 months in absolute terms; eg, among 100 patients like this patient, how many will have died by 6 months if they received no treatment? Or for the same patient, they were asked to estimate the risk of these ischemic and bleeding events associated with the provision of early invasive management and guideline-advocated pharmacotherapies. Other medical and nonmedical barriers to care such as cost or patient refusal were also recorded. At least 2 physician assessments were obtained per patient, and these assessments were completed as close to admission as possible before the provision of coronary angiography or other discharge medication. Self-reported physician characteristics, including the year of primary medical degree, specialist cardiologist qualification, and year this qualification was obtained, were also recorded.
### Table 1. Demographic and Clinical Characteristics

|                              | Australia (n=416) | China (n=495) | India (n=384) | Russia (n=247) | Total (n=1542) | P Value  
|------------------------------|------------------|---------------|---------------|----------------|----------------|----------
| Age, mean (SD), y            | 60.9 (12.6)      | 60.7 (11.6)   | 57.4 (11.2)   | 58.6 (12.0)    | 60.3 (12.0)    | <0.001   
| Female sex, n (%)            | 92 (22.1)        | 114 (23.0)    | 92 (24.0)     | 52 (21.1)      | 350 (22.7)     | 0.864    
| STEMI, n (%)                 | 122 (29.3)       | 359 (72.5)    | 208 (54.2)    | 147 (59.5)     | 836 (54.2)     | <0.001   
| NSTEMI, n (%)                | 292 (70.2)       | 136 (27.4)    | 175 (45.6)    | 99 (40.1)      | 702 (45.5)     | <0.001   
| Diabetes mellitus, n (%)     | 132 (31.7)       | 102 (20.6)    | 142 (37.0)    | 32 (13.0)      | 408 (26.5)     | <0.001   
| Hypertension, n (%)          | 248 (59.6)       | 278 (56.2)    | 171 (44.5)    | 185 (74.9)     | 882 (57.2)     | <0.001   
| Dyslipidemia, n (%)          | 262 (63.0)       | 131 (26.5)    | 45 (11.8)     | 165 (66.8)     | 603 (39.1)     | <0.001   
| Current smoking, n (%)       | 130 (31.3)       | 212 (42.8)    | 80 (20.9)     | 106 (42.9)     | 528 (34.2)     | <0.001   
| Family history of CAD, n (%) | 169 (40.6)       | 61 (12.3)     | 34 (8.9)      | 109 (44.1)     | 373 (24.2)     | <0.001   
| Previous CAD, n (%)          | 264 (36.5)       | 69 (13.9)     | 49 (12.8)     | 105 (42.5)     | 375 (24.3)     | <0.001   
| Previous MI, n (%)           | 99 (23.8)        | 29 (5.9)      | 49 (12.8)     | 60 (24.3)      | 237 (15.4)     | <0.001   
| Previous CABG, n (%)         | 63 (15.1)        | 0             | 1 (0.3)       | 5 (2.0)        | 69 (4.5)       | <0.001   
| Previous atrial fibrillation, n (%) | 14 (3.4) | 8 (1.6) | 1 (0.3) | 21 (8.5) | 44 (2.9) | <0.001   
| Known PAD, n (%)             | 7 (1.7)          | 13 (2.6)      | 1 (0.3)       | 13 (5.6)       | 34 (2.2)       | <0.001   
| Previous CVA, n (%)          | 15 (3.6)         | 30 (6.1)      | 3 (0.8)       | 15 (6.1)       | 63 (4.1)       | <0.001   
| Creatinine clearance, median (25–75th percentile), mL/min | 65.4 (52.2–82.1) | 69.3 (57.4–87.2) | 62.0 (53.3–79.7) | 61.2 (50.9–74.6) | 65.3 (53.7–81.4) | <0.001   
| Dialysis dependent           | 2 (0.5)          | 4 (0.8)       | 2 (0.5)       | 0              | 8 (0.5)        | 0.552    
| Killip class, median (25–75th percentile) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1–2) | <0.001   
| White cell count, median (25–75th percentile) | 8.7 (7.1–11.1) | 8.7 (7.0–11.4) | 10.6 (8.4–13.5) | 9.2 (7.3–11.9) | 9.2 (7.2–12.0) | <0.001   
| Presentation with cardiogenic shock, n (%) | 2 (0.5) | 15 (3.0) | 21 (5.5) | 10 (4.0) | 48 (4.1) | <0.001   
| Presentation with cardiac arrest, n (%) | 13 (3.1) | 6 (1.2) | 11 (2.9) | 3 (1.2) | 33 (2.1) | 0.138    
| Frailty score 1–7, median (25–75th percentile) | 2 (2–3) | 3 (2–4) | 2 (2–3) | 3 (2–4) | 3 (2–4) | <0.001   
| Physician-predicted 6-mo death, median (25–75th percentile) | 15 (8–25) | 30 (20–40) | 20 (13–30) | 30 (19–43) | 25 (14–35) | <0.001   
| GRACE risk score, median (25–75th percentile) | 98 (79–122) | 106 (88–129) | 109 (88–125) | 105 (86–127) | 105 (85–125) | <0.001   
| TIMI risk score STEMI, median (25–75th percentile) | 3 (1–4) | 2 (2–5) | 3 (1–5) | 3 (2–5) | 3 (2–5) | <0.001   
| TIMI risk score NSTEMACS, median (25–75th percentile) | 4 (3–5) | 3 (3–4) | 3 (3–4) | 3 (3–4) | 3 (3–4) | <0.001   
| PURSUIT risk score STEMI median (25–75th percentile) | 21 (16–22) | 21 (16–22) | 21 (20–22) | 21 (19–21) | 21 (19–22) | 0.0022   
| ACUITY risk score median (25–75th percentile) | 10 (7–14) | 12 (9–15) | 12 (8–15) | 12 (9–16) | 11 (8–15) | <0.001   
| CRUSADE risk score median (25–75th percentile) | 26 (19–35) | 25 (18–33) | 32 (24–39) | 30 (22–37) | 29 (19–36) | <0.001   

ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation; CVA, cerebrovascular accident; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; NSTEMACS, non–ST–segment acute coronary syndromes; NSTEMI, non–ST–segment elevation myocardial infarction; PAD, peripheral artery disease; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; STEMI, ST–segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.
undertaken. The physician-estimated bleeding risk, ACUITY, and CRUSADE risk scores for bleeding were correlated with all bleeding events, as well as those bleeding events adjudicated by the ACUITY, TIMI, and GUSTO definitions using the same methodology.

The perceived relative mortality risk (reduction or increase) associated with each therapy was calculated for each doctor-patient interaction in the following manner: perceived relative risk = perceived risk (treated)/perceived risk (untreated). A similar calculation was used to estimate the perceived relative increased risk of bleeding events. To explore the relationship between the care provided and perceived or predicted risk, respectively, the physician-perceived risk of mortality at 6 months was stratified into <10%, 10.1% to 20%, 20.1% to 30%, and >30.1%, whereas the GRACE score was stratified into low, intermediate, high, and very high at the cut points of <100, 100 to 150, 151 to 200, and 201+. Use of therapies and invasive management were examined by χ² test within each classification only. To examine the relationship between unrecognized risk and outcome, the GRACE risk score was dichotomized at 150 (HR >150), whereas recognized HR was arbitrarily determined to be those patients identified as being in the top 25% of risk estimated by physicians. Comparisons of the clinical outcomes of 6-month death were then examined in 4 groups: 2 concordant (considered high or low by both GRACE score and physician estimate) and 2 discordant (considered high by GRACE score but low by physician or high by physician but low by GRACE criteria). All analyses were undertaken using STATA 11.2. For all analyses, a value of $P<0.05$ was considered statistically significant.

Table 2. Clinical Outcomes Stratified by Enrolling Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Total (n=1542)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Australia (n=416)</td>
</tr>
<tr>
<td>30-d mortality, n (%)</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>3-mo mortality, n (%)</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>6-mo mortality, n (%)</td>
<td>11 (2.6)</td>
</tr>
<tr>
<td>30-d MI, n (%)</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>3-mo MI, n (%)</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>6-mo MI, n (%)</td>
<td>12 (2.9)</td>
</tr>
<tr>
<td>30-d CVA, n (%)</td>
<td>1 (0.24)</td>
</tr>
<tr>
<td>3-mo CVA, n (%)</td>
<td>1 (0.24)</td>
</tr>
<tr>
<td>6-mo CVA, n (%)</td>
<td>1 (0.24)</td>
</tr>
<tr>
<td>30-d protocol bleed, n (%)</td>
<td>33 (7.9)</td>
</tr>
<tr>
<td>3-mo protocol bleed, n (%)</td>
<td>40 (9.6)</td>
</tr>
<tr>
<td>6-mo protocol bleed, n (%)</td>
<td>45 (10.8)</td>
</tr>
<tr>
<td>6-mo death or MI, n (%)</td>
<td>21 (5.1)</td>
</tr>
<tr>
<td>6-mo MACE, n (%)</td>
<td>63 (15.1)</td>
</tr>
</tbody>
</table>

CVA indicates cardiovascular accident; MACE, major adverse cardiac events; and MI, myocardial infarction.

Results

Patient Population

In total, 1575 patients with MI or HR ACS provided informed consent and were enrolled in the study, of whom 1542 had all components required for analysis of the GRACE score. Of these, 495, 416, 384, and 247 patients were enrolled from China, Australia, India, and Russia, respectively. The majority of the participating hospitals were in metropolitan centers.
Rural hospitals comprised a small proportion of participating hospitals (Australia [3 of 12], China [1 of 16], India [5 of 10], and Russia [2 of 20]). The median age of these patients was 60.3 years (SD±12.0 years), and 350 (22.7%) patients were women. Hypertension, diabetes mellitus, hypercholesterolemia, and current smoking were reported in 882 of 1542 (57.2%), 408 of 1542 (26.5%), 603 of 1542 (39.1%), and 528 of 1542 (34.2%) patients, respectively. Patients presenting with STEMI constituted 836 of 1542 (54.2%) of the population. Demographic and clinical characteristics and outcomes of the patients stratified by country of enrollment are presented in Tables 1 and 2. The overall median GRACE score was 105 (85–125), leading to a predicted risk of 6-month mortality of ≈5%, and death by 6 months was observed in 48 of 1542 (3.1%) patients. Of the 4230 patient-specific physician estimates of risk and benefit provided, 47.4% were men and 81.9% identified themselves as having a country-specific cardiovascular specialist qualification, with a mean of 11.5 years (SD, 7.7 years) of clinical practice. The median physician-perceived risk of 6-month death was 25% (interquartile range, 14%–35%).

Correlation Between Perceived Risk and Estimated Risk
Physician-perceived risk and GRACE risk score–predicted risk of death by 6 months, along with the observed 6-month mortality rate, plotted by the GRACE risk score are presented in Figure 1. The variation in physician-estimated risk for all levels of the GRACE risk score was substantial. The rise in median physician-perceived risk was modest except in the patients with the highest risk by GRACE risk score. Hence, physicians commonly overestimated the risk of 6-month mortality among those with a low GRACE score and underestimated risk among those with a high GRACE score.

Figure 2 displays the discriminatory characteristics for physician-estimated risk, the GRACE risk score, the TIMI risk score, and the PURSUIT risk score. The GRACE risk score demonstrated significantly superior discrimination to physician risk estimation with a c statistic of 0.812 (95% confidence interval [CI], 0.772–0.851) compared with 0.652 (95% CI, 0.596–0.708; *P*<0.0001). Results were similar when stratified by enrolling country (physician, 0.695 [95% CI, 0.629–0.740] versus GRACE, 0.818 [95% CI, 0.779–0.857]; *P*<0.001). Using the average physician estimate for each patient showed a modest improvement (average of physicians, 0.679 [95% CI, 0.629–0.740] versus GRACE, 0.815 [95% CI, 0.754–0.874]; *P*=0.0016). Similarly, a moderate improvement in physician prediction was evident when 30-day mortality was assessed (physician estimate, 0.713 [95% CI, 0.653–0.773] versus GRACE, 0.793 [95% CI, 0.744–0.842]; *P*=0.0183).

Adding the GRACE score to physician estimation improved the discrimination with an integrated discrimination improvement of 0.0632 (SE, 0.012; *P*<0.001). Calibration
with actual outcomes was modest with both GRACE and physician-estimated risk with Hosmer-Lemeshow statistic $P$ values of 0.0149 and 0.220, respectively, with both approaches overestimating actual risk. Among STEMI patients, the TIMI risk score performed as well as the GRACE score, but this was not observed among non-STEMI patients.

Within this study, the PURSUIT risk score demonstrated very poor predictive performance. Both the GRACE risk score and physician-estimated risk performed less well for the end point of death or MI within 6 months (Table 3).

When assessing bleeding risk, physician estimated and the CRUSADE and ACUITY risk scores demonstrated poor discriminatory capacity for bleeding events using all definitions. Predictive capacity of the ACUITY risk score was modestly improved when applied to bleeding events adjudicated by the TIMI major and minor definitions but was less discriminatory when the TIMI minimal bleeding was included in the end point. A similar relationship was observed with the GUSTO definitions of bleeding (Table 3).

### Table 3. Risk Discrimination by Physician Estimation and Risks Scores for Ischemic and Bleeding Events

<table>
<thead>
<tr>
<th>End point</th>
<th>$c$ Statistic (95% CI)</th>
<th>$P$ Value</th>
<th>IDI (SE)</th>
<th>$P$ Value</th>
<th>$c$ Statistic</th>
<th>$P$ Value</th>
<th>IDI (SE)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician determined</td>
<td>0.652 (0.596–0.708)</td>
<td>&lt;0.001</td>
<td>0.0632 (0.0122)</td>
<td>&lt;0.001</td>
<td>0.629 (0.596–0.663)</td>
<td>0.102</td>
<td>0.0182 (0.0031)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GRACE risk score</td>
<td>0.812 (0.772–0.851)</td>
<td>&lt;0.001</td>
<td>0.0659 (0.0188)</td>
<td>&lt;0.001</td>
<td>0.576 (0.527–0.625)</td>
<td>&lt;0.001</td>
<td>0.0094 (0.0026)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI risk score (STEMI)</td>
<td>0.779 (0.713–0.845)</td>
<td>&lt;0.001</td>
<td>0.0737</td>
<td>0.0042</td>
<td>0.581 (0.522–0.640)</td>
<td>&lt;0.001</td>
<td>0.0010 (0.0021)</td>
<td>0.654</td>
</tr>
<tr>
<td>TIMI risk score (NSTEACS)</td>
<td>0.675 (0.601–0.748)</td>
<td>0.737</td>
<td>0.0059 (0.015)</td>
<td>&lt;0.001</td>
<td>0.484 (0.446–0.522)</td>
<td>&lt;0.001</td>
<td>0.0020 (0.0006)</td>
<td>0.00157</td>
</tr>
<tr>
<td>PURSUIT risk score</td>
<td>0.426 (0.362–0.489)</td>
<td>&lt;0.001</td>
<td>0.0059 (0.015)</td>
<td>&lt;0.001</td>
<td>0.484 (0.446–0.522)</td>
<td>&lt;0.001</td>
<td>0.0020 (0.0006)</td>
<td>0.00157</td>
</tr>
</tbody>
</table>

$P$ values represent comparisons of $c$ statistics between risk scores and physician estimation (analysis not stratified by country). ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; CI, confidence interval; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation; GRACE, Global Registry of Acute Coronary Events; IDI, integrated discrimination improvement; NSTEACS, non–ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

### Table 4. Perceived Relative Risk of Guideline-Recommended Therapies on Specific Outcomes by 6 Months

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>New/Recurrent MI</th>
<th>CVA</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin, mean (SD)</td>
<td>0.81 (0.40)</td>
<td>0.80 (0.54)</td>
<td>0.89 (0.68)</td>
<td>1.42 (1.25)</td>
</tr>
<tr>
<td>Clopidogrel, mean (SD)</td>
<td>0.76 (0.40)</td>
<td>0.76 (0.82)</td>
<td>0.85 (0.42)</td>
<td>1.47 (1.13)</td>
</tr>
<tr>
<td>Statin, mean (SD)</td>
<td>0.77 (0.44)</td>
<td>0.75 (0.53)</td>
<td>0.83 (0.57)</td>
<td>N/A</td>
</tr>
<tr>
<td>ACE-I/ARB, mean (SD)</td>
<td>0.76 (0.50)</td>
<td>0.75 (0.46)</td>
<td>0.83 (0.46)</td>
<td>N/A</td>
</tr>
<tr>
<td>β-Blocker, mean (SD)</td>
<td>0.75 (0.41)</td>
<td>0.74 (0.65)</td>
<td>0.85 (0.48)</td>
<td>N/A</td>
</tr>
<tr>
<td>Invasive management, mean (SD)</td>
<td>0.64 (0.43)</td>
<td>0.63 (0.70)</td>
<td>0.86 (0.58)</td>
<td>1.56 (1.48)</td>
</tr>
</tbody>
</table>

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CVA, cerebrovascular accident; MI, myocardial infarction; and N/A, not asked.

### Physician-Estimated Benefits With Evidence-Based Therapies

By contrasting the physician-estimated 6-month event rates associated with each of the guideline-recommended therapies, an estimate of the perceived relative risk reduction or increase of each therapy was derived and is presented in Table 4. Although individual estimates varied greatly, these estimated benefits for aspirin, clopidogrel, and statins were generally consistent with literature-based estimates of efficacy with these therapies with the exception of early invasive management, angiotensin-converting enzyme inhibition or angiotensin receptor blockers, and β-blockers, for which the perceived benefits were greater than those observed in clinical trials.

### Relationship Between Perceived Risk and the Use of Guideline Recommendations

Figure 3 describes the rate of guideline-recommended therapies stratified by physician-perceived risk. Although
Figure 3. Rates of (A) angiography and (B) percutaneous coronary intervention (PCI) and prescription at discharge of (C) aspirin, (D) clopidogrel, (E) β-blockers, (F) angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor antagonists (angiotensin receptor blocker [ARB]), and (G) statins stratified by Global Registry of Acute Coronary Event (GRACE) risk score (categorized as low, <100; intermediate, <100–150; high, 150–200; very high, >200) and physician-predicted risk of death by 6 months (categorized as <10%, 10%–20%, 20%–30%, >30%).
there was a high use of aspirin, clopidogrel, and statins among all the perceived risk groups, there seemed to be a greater use of PCI and to a lesser degree β-blockers among patients perceived to be at greater risk. However, when stratified by GRACE risk score, this relationship is no longer seen, with reductions in PCI, clopidogrel, β-blockers, and, to a moderate degree, angiotensin-converting enzyme-inhibitors/angiotensin receptor antagonists among the highest-risk patients.

Mortality by Concordant/Discordant Risk Estimation

Mortality rates among patients deemed to be at HR or not HR by both GRACE score and physician estimation (concordant estimation) were clearly at high and low, respectively. However, 6-month mortality among patients not at HR by physician estimation but at HR by GRACE risk score was significantly higher than those perceived to be at HR by clinicians with a low GRACE risk (P=0.008) and those concordantly deemed to be at low risk by both scores (P<0.001; Figure 4).

Discussion

By formally assessing physician-estimated risk of clinical events without treatment and with various therapies, this study has provided several clinical insights that may have implications for how we translate our established ACS evidence base into more complete care and outcome. First, when directly questioned about the estimated risk of clinical events, clinicians generally overestimated the risk of recurrent ischemic and bleeding events, but this estimation of risk was insensitive to risk as quantified by the GRACE risk score except in the patients with very high risk. Second, risk estimation using the GRACE and TIMI risk scores was superior to physician-estimated risk, whereas the PURSUIT risk score performed poorly. Third, bleeding estimation by clinicians and the ACUITY and CRUSADE risk scores remains poor, although these results may be influenced by event recognition. Fourth, physicians seemed to overvalue the relative impact of invasive management, β-blockers, and angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists compared with literature-based estimates. Fifth, clinical perception of risk and misclassification of risk seem to influence PCI rates and may be associated with differences in clinical outcomes.

Prediction of mortality risk based on objectively quantified clinical criteria provides superior risk estimation compared with clinical impression. Although similar performance was observed among STEMI patients, the GRACE risk score derived from a large-scale registry seemed to perform better than those derived from randomized clinical trials for non-STEMI patients.23 This may reflect the more selected populations included in trials compared with registries. Nevertheless, the discrimination of the GRACE risk score within populations drawn from emerging economies is reassuring of the relevance of this score in clinical practice. However, although discrimination remains robust, the calibration of risk estimation within this study was poor. This likely reflects the nonconsecutive nature of the enrollment design of this study and the consequent selection of lower-risk patients for inclusion that differed between countries. In contrast, the clinical and ACUITY and CRUSADE score capacity to discriminate the risk of bleeding events by any of the accepted definitions was poor. Differences between countries may reflect variations in the local practices that therefore influence the detection of late bleeding events. However, these observations suggest a need to better evaluate factors associated with bleeding within prospective large-scale registries, to enable development of more discriminatory bleeding risk scores, and to establish robust systems for evaluating bleeding events, given the emergence of more potent long-term antithrombotic therapies.26–28

The correlation between patient-specific physician estimates of treatment benefit combined and the greater provision of PCI is reassuring of an evidence-based approach to coronary revascularization, as observed by others.29 However, the lower rate of PCI among the GRACE-identified patients with HR, combined with the increased mortality risk among
physician-deemed non-HR but GRACE-estimated HR, raises the possibility that more widespread and systematic use of risk stratification may lead to improved outcomes among patients presenting across the spectrum of ACS.29,30 This observational study was not designed to address such a question, but with the emergence of electronic medical records, the capacity to formally integrate risk prediction into the patient admission process, while prompting the delivery of evidence-based recommendations, raises the potential that integrated electronic systems may be able to improve outcomes. Formal appropriately designed and cluster-randomized studies of electronic risk stratification combined with guideline recommendations represent an opportunity to validate a system-based approach to improve ACS outcomes in the developing and developed world.

Conclusion
Risk prediction with the GRACE risk score provides superior risk discrimination when compared with physician-estimated risk and other clinical trial–derived risk scores. Estimation of bleeding events clinically or with the ACUITY and CRUSADE risk scores is poor. Systematic uptake of objective risk stratification should be studied in appropriately designed clinical trials.

Sources of Funding
This study was sponsored by Sanofi-Aventis Asia-Pacific. However, the protocol was conceived and designed by Dr Chew, and the sponsor has not had direct access to the data. The sponsor has reviewed the article but has not influenced its content.

Disclosures
Dr Chew has advised the National Heart Foundation of Australia in the development of a clinical risk stratification tool aimed at improving clinical care in regional Australia. W. Parsons has received grant support from Abbott, Roche, and Siemens with respect to biomarker research that pertains to risk stratification. The other authors have no conflict to report.

References

Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndromes
Derek P. Chew, Ge Junbo, William Parsonage, Prafulla Kerkar, Vitaly A. Sulimov, Matthew Horsfall and Sue Mattchoss

Circ Cardiovasc Qual Outcomes. 2013;6:299-308; originally published online May 7, 2013;
doi: 10.1161/CIRCOUTCOMES.111.000072

Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/6/3/299

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Quality and Outcomes can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Quality and Outcomes is online at:
http://circoutcomes.ahajournals.org/subscriptions/