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Editorial

Predicting Prognosis in Acute Coronary Syndromes: Makeover Time for TIMI and GRACE?

David D. Waters, MD,[a] and Benoit J. Arsenault, PhD[b]

[a] Division of Cardiology, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco, California, USA

[b] Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec, Québec, Québec, Canada

See article by Mehta et al., pages 1332–1339 of this issue.

In this issue, Mehta et al.[1] introduce a new risk score for patients with non–ST-elevation acute coronary syndrome. The score is derived from 6447 of the patients in the Clopidogrel to prevent Recurrent Events trial who had baseline measurements of C-reactive protein (CRP), NT-pro-brain-natriuretic peptide (NT-proBNP), and haemoglobin A1C (HbA1C). The score is a composite of clinical variables (age, gender, prior myocardial infarction [MI] or stroke, ST deviation, elevated troponin T), and categories of NT-proBNP and HbA1C, and can range from 0 to 20. Although each of the 3 biomarkers predicted cardiovascular (CV) events, only NT-proBNP and HbA1C improved model discrimination, and thus were retained in the score.

CV death, MI, or stroke within 1 year occurred in 3.7%, 9.1%, and 17.8% of low-, intermediate-, and high-score groups, respectively. The absolute benefit of dual antiplatelet therapy compared with aspirin alone was 1.0%, 4.7%, and 3.0% in low-, intermediate-, and high-risk groups, indicating the risk stratification aids in selection of patients with non–ST-elevation acute coronary syndrome for this therapy.

History of Risk Classification in ACS

Risk stratification in patients with acute coronary syndrome (ACS) goes back almost 50 years. At the dawn of coronary care in 1967, Killip and Kimball[2] described a simple bedside classification to stratify patients with acute MI. Class I patients had no clinical signs of heart failure; class II patients had pulmonary rales, an S3, and elevated jugular venous pressure; class III patients had acute pulmonary oedema; and class IV patients had cardiogenic shock. In a series of 250 patients with MI, 32% were in class I, 30% in class II, 19% in class III, and 10% in class IV. In-hospital mortality was 6%, 17%, 38%, and 81% from class I to IV, respectively.

Although the Killip classification finds some use today, mainly as a component of other risk scores, it has lost much of its value because heart failure is no longer such an overwhelming threat to most patients with MI. As the disease has changed over time, different variables have gained or lost importance as prognostic indicators. As short-term mortality has decreased dramatically, we now prefer predictors over a longer term, variables that also predict recurrent MI and stroke, and perhaps the need for revascularization, not just mortality.

For more than 3 decades after Killip, no ACS risk scoring system became popular, although many adverse prognostic factors were documented. For example, persistent angina with ST segment shifts was shown to adversely affect prognosis,[3] and importantly, serum troponin became widely used to detect myocardial necrosis and an adverse prognosis among patients previously classified as having unstable angina.[4] During this period, the pathophysiology of MI and the importance of reperfusion for ST elevated myocardial infarction (STEMI) became understood. New treatments that improved prognosis were widely adopted.

The thrombolysis in myocardial infarction (TIMI) risk score for unstable angina and/or non-STEMI was introduced in 2000.[5] The TIMI score counted 7 clinical characteristics: age $\geq$ 65 years, at least 3 coronary risk factors, prior coronary stenosis $\geq$ 50%, ST deviation, $\geq$ 2 angina events in preceding 24 hours, use of aspirin within 7 days, and elevated serum cardiac markers. The endpoint used to validate the TIMI score was all-cause mortality, MI, or urgent revascularization within 14 days. The risk of one of these events increased from 4.7% among patients with a score of 0-1 to 40.9% among those with a score of 6-7 in the derivation cohort. The score performed almost as well in a validation cohort.

A TIMI risk score has also been developed for STEMI.[6] It includes 8 variables counting for from 1 to 3 points, for a total of 0-14. Mortality at 30 days was 0.8% for a score of 0, ranging up to 35.9% for a score $>$ 8.

Among several other ACS risk scores that have been described, GRACE (Global Registry of Acute Coronary Events) is the most notable. The original GRACE score predicted in-hospital mortality after ACS and included 8 risk

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Corresponding author: Dr David D. Waters, Room 5G1, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, California 94114, USA. Tel.: +1-415-420-6646.

E-mail: David.Waters@ucsf.edu

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factors: age, Killip class, systolic blood pressure, ST-segment deviation, cardiac arrest during presentation, serum creatinine level, positive initial cardiac enzymes, and heart rate.[7]

The most recent version, GRACE score (2.0), is available online and can be downloaded to portable electronic devices.[8] It was derived from 32,037 patients in the GRACE registry, covering 14 countries and 94 hospitals, and validated in a French registry of 3059 patients with STEMI and non-STEMI.[9] GRACE score 2.0 provides in-hospital, 6-month, 1-year, and 3-year mortality, as well as the 1-year rate of death plus MI.

This risk calculator has the advantage of being based on a registry and not a clinical trial, so that the results might be more broadly applicable. Patients were enrolled from many hospitals in several countries. The score is simple to calculate and can deal with missing values for Killip class and creatinine. GRACE exhibited better discrimination than TIMI for in-hospital and 1-year mortality in a Canadian registry with a wide range of patients with ACS.[10]

Should Biomarkers Be Added to ACS Risk Prediction Tools?

In recent years many biomarkers have been reported to predict outcomes in patients with ACS, often adding additional prognostic information to traditional risk predictors. A biomarker used for this purpose would ideally be involved in the pathophysiological process that caused the bad outcome, analogous to how serum cholesterol is a risk factor for coronary disease but is also involved in the pathophysiology of atherosclerosis. Like cholesterol, the ideal biomarker post-ACS would also be actionable; that is, treatment of it could improve prognosis.

BNP or NT-proBNP as a Predictor in ACS

BNP is synthesized and released from the cardiac ventricles in response to increased wall tension.[11] BNP is produced as a prohormone, proBNP, which is cleaved enzymatically into BNP and the amino-terminal part of the prohormone, NT-proBNP. Elevated levels of BNP or NT-proBNP in patients with ACS reflect the degree of left ventricular dysfunction because of MI, but also reflect transient ischemia in patients without necrosis.[11]

Several studies indicate that BNP or NT-proBNP is a strong predictor of adverse events among patients with ACS. For example, in 6809 patients with ACS in a clinical trial, increasing quartiles of NT-proBNP measured soon after admission were associated with 1-year mortality rates of 1.8%, 3.9%, 7.7%, and 19.2%.[12] Levels of troponin T, CRP, heart rate, and creatinine clearance, in addition to ST-segment depression, were also correlated independently with 1-year mortality, but NT-proBNP was the marker with the strongest relationship. In contrast, NT-proBNP did not predict future MI.

HbA1C as a Predictor in ACS

Diabetes has long been recognized as an ominous prognostic factor among patients suffering an MI. In a Finnish Registry of patients enrolled from 1988 to 1992, diabetes increased the 1-year mortality post-MI from 32.6% to 44.2% in men and from 20.2% to 36.9% in women.[13] Less well documented is the notion that fasting blood glucose or HbA1C levels in post-ACS patients without diabetes might also be predictive of future events. However, in a series of 4176 patients with STEMI without diabetes undergoing PCI, where mean HbA1C was 5.54% (interquartile range 5.36%-5.8%), HbA1C levels predicted 1-year and long-term mortality, as well as mortality after 30 days.[14]

As obesity, glucose intolerance, and prediabetes have become more prevalent in patients with ACS, and as other adverse prognostic factors have receded or come under control, HbA1C has become a stronger long-term prognostic indicator.

Other Potentially Useful Biomarkers in ACS

Many other biomarkers have been shown to predict CV events in patients with ACS; a few of particular interest (at least to us) will be mentioned in this section. Lipoprotein(a) [Lp(a)] was shown in a recent meta-analysis of 11 studies with 18,978 patients with coronary disease to predict CV events.[15] In a small study of patients with ACS followed for a median of 3 years, high Lp(a) levels predicted cardiac death.[16] The utility of Lp(a) in predicting events after ACS needs to be assessed in larger studies and needs to be shown to be superior to other variables before it is adopted for clinical use. Lp(a) is attractive because it is actionable; specifically, PCSK9 inhibitors reduce Lp(a) levels by up to 30%.[17]

Resistin, an adipokine secreted by macrophages and inflammatory cells linked to insulin resistance and inflammation, was shown to be an independent marker of residual risk in a case-controlled study of post-ACS patients.[18] Copeptin, a compound secreted by the pituitary early in the course of MI, appears to be useful in the early diagnosis of MI, and may have long-term predictive value,[19] as may heart-type fatty acid-binding protein, a small-sized molecule released from damaged myocardium.[20] Soluble urokinase plasminogen activator receptor is a novel inflammatory biomarker that correlates with NT-proBNP, predicts CV events, and outperforms CRP in several important ways.[21]

DNA-based biomarkers are beginning to be tested for their ability to improve risk prediction in patients with ACS. Two circulating microRNAs, microRNA-197, and microRNA-223, were recently shown to predict CV death in a cohort of patients with symptomatic coronary disease.[22] High-density lipoproteins have been shown to carry microRNA-223 and to deliver it to endothelial cells, where it exerts anti-inflammatory properties by repressing intercellular adhesion molecule 1.[23] On the other hand, a panel of 30 single nucleotide polymorphisms associated with an increased risk of MI, aggregated into a genetic risk score, failed to predict recurrent CV events within 1 year in 3 cohorts.[24]

Limitations and Caveats

The study of Mehta et al. has important limitations, as acknowledged by the authors. They did not test their score in a validation cohort, where it might have been somewhat less accurate at predicting events. Ideally, they would have measured a large array of potentially useful biomarkers, and included only the best ones in their model. Instead they measured only 3 and selected 2 of them. Nevertheless, this

study is an important step forward. We look forward to future well-validated risk scores incorporating the power of biomarkers.

Clinical Implications

As noted by Mehta et al.[1], the American, European, and Canadian guidelines each recommend that all patients with ACS undergo risk stratification. Risk stratification is important because clinicians do not assess risk accurately[25] and because level of risk determines optimal treatment. Unfortunately, risk stratification is underused in patients with ACS. In a recent study of 13 hospitals and 1788 patients in the Netherlands, physicians documented the use of a risk score in only 57% of patient charts, with wide variation across hospitals (16.7%-87%).[26]

Although the risk score proposed by Mehta et al. requires validation in other datasets before it is ready for clinical use, we should all be using an ACS risk calculator. A meta-analysis of 40 derivation studies on 216,552 patients and 42 validation studies on 31,625 patients indicates that GRACE performs better than TIMI.[27] If you treat patients with ACS, consider downloading the GRACE 2.0 ACS Risk Calculator to your cellphone right now.

Disclosures

The authors have no conflicts of interest to disclose.

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