Invited Commentary

Risk Stratification Science Goes to a New Level

Robert A. Harrington, MD; E. Magnus Ohman, MBBS

In this issue of *JAMA Cardiology*, Chew and colleagues[1] present the primary results of a cluster randomized trial (the Australian GRACE Risk Score Intervention Study [AGRIS]), which compared routine clinical care with a strategy of risk stratification and implementation of evidence-based therapies using the Global Registry of Acute Coronary Events (GRACE) risk score (GRS) among patients presenting to Australian hospitals with an acute coronary syndrome (ACS), either with ST elevation (STE) or without. The primary outcome was a clinical performance score based on guideline-based therapies (early invasive strategy, discharge medications, and cardiac rehabilitation referral). The authors[1] report no difference in the receipt of all 3 measures between the 2 study arms, although use of the GRS was associated with an increased use of an early invasive strategy compared with the control group. There was no difference between the groups in the occurrence of the composite of death or myocardial infarction at 12 months.

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Using various clinical, electrocardiographic, and laboratory variables to establish clinical risk and prognosis are critical steps, but not new notions, in the assessment of patients presenting for chest pain evaluation.[2] More specifically, the incorporation of various risk scores (Global Utilization of Streptokinase and TPA for Occluded Arteries [GUSTO], Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin [PURSUIT], the Thrombolysis In Myocardial Infarction [TIMI], GRACE, Fast Revascularization in Instability in Coronary Disease [FRISC], Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines [CRUSADE], and others) into clinical practice has been a foundational element in the ACS guidelines for more than 2 decades.[3] Twenty years ago, in *JAMA*, we provided an editorial comment[4] on the first report of the TIMI risk score as a way to assess risk and refer patients for certain advanced therapies. We noted that its use allowed rapid risk stratification and prognostication for all patients; multiple subsequent analyses have suggested that use of more aggressive therapies, particularly during the initial phase of hospitalization, preferentially benefit patients with ACS at higher risk, compared with patients at lower risk. For example, in the Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial, patients with non-STE ACS who were in the highest tertile of risk (as determined by the GRS) had a lower risk of the composite of death, myocardial infarction, or stroke at 6 months than those in the lower 2 tertiles of the GRS when comparing an early invasive strategy with a delayed intervention strategy.[5]

In the most recent non-STE ACS clinical practice guidelines,[6] the 2020 European Society of Cardiology Guidelines give a class IIa recommendation (weight of evidence: B) to the following statement: "GRACE risk score models should be considered for estimating prognosis."[6] But, as Chew and colleagues[1] note, guiding clinical practice through the use of risk scoring and stratification has apparently never been subjected to a randomized evaluation that would clearly delineate the benefits and risks of such a strategy. For attempting such a trial, the authors and investigators[1] deserve much credit.

Strategy trials generally are often more difficult to perform than trials with therapeutic interventions. And so, perhaps not surprisingly, this trial suffers from challenges and limitations.

The European Society of Cardiology recommendations for applying the GRS in the setting of non-STE ACS partially stem from the observation that better adherence to guideline-recommended therapy is associated with lower in-hospital mortality among hospitals that had better performance on these measures.[7] Applying a risk score allows the patients at highest risk to be better defined and therapies to be applied to those patients. How can we then square those findings with the current trial's neutral findings?

Closer examination of the data in this apparently first-of-its kind trial[1] suggests that risk stratification may still have a role. All-cause mortality, an important secondary end point, was numerically lower in the overall cohort at 12 months (intervention, 5.2% vs control, 8.0%; $P = .12$). In the high-risk risk cohort, mortality was significantly lower (intervention, 4.5% vs control, 8.8%; $P = .03$). The limited sample size and early termination prevent us from making a conclusive statement on mortality, but the findings are intriguing.

The investigators'[1] choice of including patients both with and without STE on the presenting electrocardiogram is a limitation of the study. This decision may have lessened their chance to observe a difference between the strategies, given the common use of primary percutaneous coronary intervention in most patients presenting with STE myocardial infarction, regardless of a risk score. There are also typically marked differences in patient characteristics between those with vs without STE, in that patients with non-STE ACS are typically older and have more comorbidities than those presenting with STE. Based on risk characteristics, one might expect to find greater benefit with risk stratification, with treatments based on those results, in the cohort with a non-STE ACS rather than an STE myocardial infarction.

The trial[1] ended prematurely after an interim analysis, requested by the study leadership to the independent data safety monitoring board because of slow recruitment, demonstrated futility in the likelihood of detecting a difference in the primary outcome of the trial. Thus, all the observed results, including the mortality findings, need to be viewed through that lens of a diminished sample-size attainment and the likelihood of a large type II error.

This remains a clinically important topic because risk scores and guiding practice on the concept of risk stratification are foundational to the ACS guidelines. That the investigators[1] actually tried to test this warrants our thanks and congratulations. Yet, by falling short of their enrollment goals, the answer remains uncertain. So, where does this leave us in the use of risk scores to guide decision-making in the setting of acute coronary syndromes?

Given the recent European Society of Cardiology non-STE ACS guidelines class IIa recommendation for the use of the GRS, this is a recommendation that should be consideredy, per the guidelines' methodology. The AGRIS trial[1] does not provide a definitive answer on this recommendation but suggests that pragmatic randomized clinical trials are a challenge to perform and other data sources from substantially larger populations may still have value.

In the contemporary era with much emerging technology, including digital tools and advanced computational methods, such as machine learning, available throughout the care continuum from presentation through hospitalization to the home and ambulatory settings, it is imperative that we overcome the inertia and resistance to implementing proven new therapies and strategies of care that remain in clinical practice. Electronic health record systems should be configured to continuously assess individual patient risk using the vast amounts of clinical, laboratory, and imaging data available at the population level throughout large health care systems. As risk is assessed, methods should be developed that do not just notify clinicians that they might consider treatment options but that actually implement these (with appropriate safeguards) when the evidence is clear. When the evidence is less certain (typically class II recommendations), the optimally deployed electronic health record systems will insist on studying the question using every patient's encounter as part of evidence generation. It is all technically possible. Chew and colleagues[1] have made the first attempt to clarify the science of risk stratification and implementation. We look forward to future investigations in which technology can assist us in performing much larger trials in risk stratification.

ARTICLE INFORMATION

Author Affiliations: Department of Medicine, Stanford University, Stanford, California (Harrington); Department of Medicine, Duke University, Durham, North Carolina (Ohman).

Corresponding Author: Robert A. Harrington, MD, Department of Medicine, Stanford University, 300 Pasteur Dr, S-102, MC 5110, Stanford, CA 94305 (robert.harrington@stanford.edu).

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