Evidence-Based Risk Stratification to Target Therapies in Acute Coronary Syndromes

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With the ever-increasing number of new treatments for the wide spectrum of patients with acute coronary syndromes (ACS), risk stratification has become the centerpiece of initial evaluation for these patients. The overriding principle is to target more aggressive antithrombotic and interventional therapies in patients at higher risk.1,2

The approach to risk stratification has evolved during the past 2 decades from a practice that once involved an evaluation for residual ischemia and for left ventricular dysfunction after myocardial infarction (MI). However, risk stratification has now evolved more to include assessment of the risk of future cardiac events, which can be predicted on the basis of clinical features at the time of the initial assessment in the emergency department. This change in timing parallels the change in nomenclature of ACS from Q-wave/non-Q wave MI to ST-elevation MI (STEMI) versus non-STEMI, a change that was made necessary by the need to make immediate treatment decisions about reperfusion therapy for those with ST elevation (and not for those without ST elevation).2 Similarly, risk stratification is now performed immediately (not days later) to assist in decisions on appropriate initial therapy and triage.

This notion of immediate risk assessment was first proposed in the 1994 unstable angina guidelines,3 and is now strongly evidence based, with numerous studies supporting the need to target the newer antithrombotic and interventional therapies to higher-risk ACS patients.4–18 Thus, risk stratification is key to the initial evaluation of patients with ACS because physicians will treat patients differently on the basis of their risk.

One of the first studies that reported a differential effect of a new intervention based on patient risk with unstable angina or non-ST elevation MI (UA/NSTEMI) was a study by Lindahl and colleagues4 that showed that the benefit of low-molecular-weight heparin versus placebo was seen only in patients who had an elevated troponin. This was followed by numerous studies that found benefits in patients with an elevated troponin %, new interventions such as enoxaparin versus unfractionated heparin,6 IIb/IIIa inhibitors versus placebo,9–12 and an early invasive versus conservative strategy,14,15,18 whereas there were no differences seen with these interventions in patients with a negative troponin. The same has also been seen for ST-segment changes, with benefit of the newer therapies in those with ST-segment changes.5,15,18

Other factors found to be associated with increased risk include diabetes, with one recent study showing a mortality benefit of IIb/IIIa inhibition for diabetic patients with ACS versus no mortality difference in nondiabetics.20 Increasing age has also been universally shown to be a risk factor for higher rates of adverse outcomes, although a similar benefit has been seen in older versus younger patients for therapies in ACS,5,15,19 Prior aspirin use has also been noted to be associated with increased risk.7,21 Other factors noted in the American College of Cardiology/American Heart Association (ACC/AHA) UA/NSTEMI guideline as high-risk features are prior revascularization and evidence of congestive heart failure.2 New markers have also been identified, including C-reactive protein and B-type natriuretic peptide, which are associated with increased mortality after ACS,22–24 but to date, no therapies have yet been identified that are of a particular benefit in ACS patients with an elevated versus normal C-reactive protein level or B-type natriuretic peptide.

The TIMI risk score is a means of integrating all of the clinical factors and markers to be a comprehensive risk stratification tool. Antman et al2 developed this score with the use of multivariate analysis in the TIMI 11B trial of patients with UA/NSTEMI. He used the end point of death and recurrent ischemic events, including MI and severe recurrent ischemia requiring urgent revascularization. He identified 7 independent risk factors that had approximately equal weight in this model and, thus, were given equal weight in the TIMI risk score. As the TIMI risk score increased, the risk of all events increased.7

The most intriguing observation was that the relative benefit of enoxaparin versus unfractionated heparin was also significantly greater in higher-risk patients, which was true in TIMI 11B and validated in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial. Notably, this is an increase in both the relative benefit and the absolute benefit in terms of number of events prevented. The TIMI risk score has also been applied to evaluate the benefit of enoxaparin on long-term outcomes,8 of glycoprotein IIb/IIIa inhibition,13 and of an early invasive

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strategy\textsuperscript{15,17} in which there was, in each case, an increasing benefit in higher-risk patients. The TIMI risk score has also been validated in 2 different, unselected patient populations, including the TIMI-III Registry\textsuperscript{25,26} and thus is valid in standard clinical practice, not just in the clinical trials from which it was derived. A program for Palm personal digital assistants of the TIMI risk score has been developed and is available (http://www.timi.org).\textsuperscript{27}

The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) investigators have now applied the TIMI risk score to evaluate the newest of the beneficial treatments in UA/NSTEMI, clopidogrel.\textsuperscript{28} They validated the TIMI risk score and found that there was an increasing risk for their primary composite end point at 1 year, cardiovascular death, MI, and stroke, as well as each of the components individually.\textsuperscript{28}

Two novel findings have emerged from this analysis. First, in contrast to the studies cited above, clopidogrel had the same relative benefit across all of the risk strata. The relative benefit was \( \approx 20\% \) in the low-risk, intermediate-risk, and high-risk patients.\textsuperscript{17} It is worth noting that because the baseline risk is higher, the absolute benefit (ie, the number of events prevented) is greatest in the highest-risk patients. The second novel finding of this analysis is that there was a statistically significant benefit of clopidogrel plus aspirin over aspirin alone in the low-risk patients. To date, this is the only intervention that has been demonstrated to be of significant incremental benefit over aspirin in patients with low-risk ACS. The take-home message from this analysis is that clopidogrel is beneficial across the full spectrum of UA/NSTEMI patients.

The striking difference of the benefit of clopidogrel (across the full risk spectrum) versus that of enoxaparin, IIb/IIIa inhibition, and early invasive strategy (with benefit present only in high-risk patients) speaks to a potential difference in the pharmacological effect of this agent. Clopidogrel inhibits platelet aggregation and decreases platelet activation by blocking the adenosine diphosphate (P\textsubscript{2}Y\textsubscript{12}) receptor.\textsuperscript{29} This decreases the number of “angry platelets” circulating in the patient’s bloodstream, as well as the overall propensity toward development of thrombosis and MI, which appears to occur in both low-risk and high-risk patients. In contrast, the acute treatment with glycoprotein IIb/IIIa inhibitors and/or low-molecular-weight heparin is focused on treatment of the acute thrombus rather than long-term prevention of the prothrombotic milieu.

This finding in the CURE study parallels a recent analysis from the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events trial (CAPRIE), in which a risk score was developed to predict MI during long-term secondary prevention.\textsuperscript{30} With the use of this risk score, the same relative benefit in reducing myocardial infarction (19% overall) was seen in both the low-risk and high-risk patients.\textsuperscript{30} These data also parallel the univariate subgroup analyses seen with aspirin versus placebo, in which there is benefit again in both low-risk and high-risk patients,\textsuperscript{31} lending support to the notion that decreasing platelet activation is beneficial to both low-risk and high-risk patients.

The above findings have now been adopted in the new 2002 update of the ACC/AHA UA/NSTEMI guidelines, in which baseline therapy includes aspirin, clopidogrel, one of the heparins (with a class IIa recommendation for enoxaparin, especially in higher-risk patients) \( \beta \)-blockers, and nitrates. Then, the use of glycoprotein IIb/IIIa inhibitors and an early invasive strategy are recommended only for high-risk patients (Figure). Thus, although first proposed in the guidelines in 1994,\textsuperscript{1} the notion of risk stratification to target therapy is now strongly evidence based.\textsuperscript{4–18}

How does the TIMI risk score compare to other risk stratification scores? First, it was developed on the basis of the end points of death, MI, or severe recurrent ischemia. Other risk stratification scores that have focused on mortality, such as the TIMI STEMI risk score and the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) score,\textsuperscript{32–34} have different risk factors. The factors that predict mortality are frequently related to left ventricular dysfunction (eg, higher Killip class, lower blood pressure). It is of great interest to note that the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy trial (PURSUIT) risk score for mortality derived in patients with UA/NSTEMI\textsuperscript{15} is very similar to that of the TIMI STEMI (mortality) risk score.

Because the TIMI UA/NSTEMI risk score was developed to predict both death and nonfatal ischemia events, it has been found to be very useful in identifying the relative benefit of new interventions, most of which reduce nonfatal ischemic events. Thus, in terms of clinical utility, the TIMI risk score appears to be very useful as a simple bedside tool that will predict both the risk of death and recurrent ischemic events, but also the benefit of newer therapies, thereby allowing targeting of different therapies to appropriate patients.

Risk scores are also very useful in other areas of cardiology. For STEMI, before the TIMI STEMI risk scores,\textsuperscript{32,33} 2 scores were developed that predicted the benefit of thrombolysis versus placebo\textsuperscript{36} and of tissue plasminogen activator versus streptokinase.\textsuperscript{34} For stable coronary disease, the Framingham risk score, recently adapted by the National Cholesterol Education Program Guidelines,\textsuperscript{37} has been found
to be very useful in stratifying risk. In this setting, high-sensitivity C-reactive protein has also been a potent tool for risk stratification and has identified the differential benefit of both aspirin and statin therapy in patients with elevated C-reactive protein.38,39 Given the utility of using risk stratification to target therapy, it is hoped that this approach would be applied to other areas, such as percutaneous coronary intervention, and for predicting nonfatal events after STEMI, or for predicting major bleeding or the need for bypass surgery. One risk score has been developed for intracranial hemorrhage that may be helpful in choosing reperfusion strategies.40

Finally, the new frontier is in the development of new markers of cardiac risk, such as markers of inflammation or neurohormonal activation, and soon, genetic factors.31 These may be added to the TIMI (or other) risk scores to expand the overall risk assessment.24 This multimarker approach will help identify not only the differential pathophysiology of various types of patients, but also help determine more disease-specific therapies. We have thus entered the era of truly evidence-based risk stratification, which will allow us to target our newer therapies to the appropriate patients.

References


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