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Cardiac Risk Assessment: Matching Intensity of Therapy to Risk

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The concept of cardiac risk assessment is applicable to many settings, from primary prevention and preoperative evaluation to post–myocardial infarction (MI) management. In the context of emergency cardiac care, cardiac risk assessment is typically focused on the evaluation of acute coronary syndrome (ACS): ST-segment elevation MI (STEMI), non–ST-segment elevation MI (NSTEMI), and unstable angina (UA). The likelihood of cardiac death and significant morbidity guides management decisions, including the need for further diagnostic evaluation, specific treatment, and the degree of monitoring for complications. Risk scores of varying complexity are available to guide early management. This article briefly describes the clinical spectrum of NSTE ACS, which encompasses NSTEMI and UA, and focuses on the use of scoring systems in tandem with clinical guidelines to determine the intensity and timing of early therapy. Discussion then focuses on the process of developing these tools and potential future developments in risk assessment.

The rationale of a risk stratification system

The goal of risk assessment is to predict the likelihood of occurrence of a clinically significant outcome, given a complex initial presentation. Risk models can be used in stratification within clinical trials, in quality of care evaluation based on expected outcomes, and, as described here, in medical decision making [1]. Once a risk model is developed and validated, the frequency of clinical outcomes (beneficial and adverse) following a specific therapy can be determined within the risk levels. The high risk of morbidity and mortality from ACS must be balanced with the degree of benefit and risk of adverse events inherent in the various therapeutic options available for ACS. For instance, antiplatelet therapy with a platelet glycoprotein (Gp) IIb/IIIa receptor antagonist improves outcome in many patients who have ACS but is associated with increased rates of thrombocytopenia and bleeding. A risk stratification system (RSS), through a standardized assessment scheme, allows a concise and simplified method for characterizing this risk. Once derived and validated, risk models can be tested prospectively to assess their predictive capacity. If effective, they can help the clinician make the risk–benefit calculation. Optimal risk stratification and delivery of care remains a moving target, however. The understanding of the pathophysiology of ACS and available treatment options constantly evolve. As additional risk factors and therapies arise, an RSS can become outdated because these new features are not included in the model. Therefore, the optimal use of an RSS depends on an understanding of the strengths and weaknesses of the RSS, including the setting in which it was developed.

Mortality from acute ischemic heart disease has fallen considerably during the past 2 decades because of advances in prevention, diagnosis, and treatment. Despite well-established consensus guidelines, however, many patients do not receive recommended treatments or are given medications that may actually increase risk. Observational studies from the early 1990s (Thrombolysis In

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Myocardial Infarction [TIMI] 3 registry) [2] to 2002 (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines [CRUSADE]) [3] confirm the increased use of aspirin (from 82% to 90%) and beta-blockers (from 45% to 76%) but demonstrate low rates of use of heparin (53%) and, recently, Gp IIb/IIIa inhibitors (31%).

RSSs may improve compliance with the national guidelines, however, they have the potential for being very complicated. The measurement of the biomarkers including troponin, C-reactive peptide, and B-type natriuretic peptide (BNP), each give independent and additive prognostic information [4]. Table 1 provides a more complete list of variables that have been associated with increased mortality in NSTE ACS. A scoring system that incorporates all of them would be time-consuming; and time-to-treatment itself is an important risk factor. While some variables can be determined quickly, others require improvements in the speed of laboratory testing or in computer processing. Furthermore, certain predictors are strong and consistently associated with risk, such as the peak level of cardiac troponin I (or T) [2]. The peak level is not known for several days in NSTE ACS, however, so therapy cannot be guided in the first few hours of presentation.

The consensus guidelines for NSTE ACS introduce the concept of matching intensity of therapy to risk identified during a hospitalization, but no randomized controlled trials have focused on a strategy based entirely on risk scoring. According to the class I recommendations from the guidelines, high-risk and low-risk patients have clearly identified pathways with different treatment strategies. Patients at intermediate risk typically 30% to 40% of all patients, probably account for much of the variability in treatment prescription.

Interaction of consensus guidelines and quality improvement studies

An individual's risk during an episode of ACS is determined by factors unique to that patient and factors related to the pathophysiology of ACS. Patient factors include age, known prior ischemic heart disease, and evidence of heart failure on presentation. Angina pectoris can be classified as unstable in three scenarios: rest angina (angina occurring at rest and continuing for longer than 20 minutes), new-onset angina (new onset with slight limitation of ordinary activity), and increasing angina (previously present but now more frequent, longer in duration, and with decreased exertional threshold) [14]. The Canadian Cardiovascular Society [15] classification system differentiates symptoms into four grades based on exertional tolerance, but descriptive classification of angina pectoris based on severity of symptoms has been found to be unreliable in providing prognostic information [15,16].

There are five mechanisms underlying myocardial ischemia in NSTE ACS, resulting in disproportionate supply and demand of myocardial oxygen [17]. Decreased myocardial perfusion and oxygen delivery are common to four mechanisms; nonocclusive thrombus and microembolization are the most common. Dynamic obstruction from epicardial vasospasm, progressive severe narrowing without spasm, and localized inflammation also decrease oxygen delivery. Secondary UA is caused by either decreased supply (anemia and hypoxemia) or increased demand (fever and hypotension), typically in the setting of underlying CAD. These mechanisms are nonexclusive and do not offer reliable prognostic information within the initial evaluation period.

When facing an ACS presentation, the clinician's first critical decision point is excluding STEMI. An ECG should be obtained within the first 10 minutes of arrival (or sooner if possible). The first set of biomarkers should be available within 60 minutes [18]. This inherent delay results in reduced efficiency in identifying and treating high-risk patients; therefore risk assessment tools were developed. Aspirin, heparin (unfractionated or low molecular weight) and beta-blockers are given to all patients who do not have contraindications, and Gp IIb/IIIa inhibitors are used in high-risk patients for whom early cardiac catheterization is also recommended. Although patients who have ACS are, as a group, at increased risk of death and nonfatal ischemic complications, the spectrum of disease severity and subsequent outcomes remains wide. Initial evaluation should focus on immediate management of hemodynamic instability and identifying patients at significant risk for death, recurrent MI, stroke, heart failure, and recurrent ischemic symptoms. Because the intensity of therapy typically depends on this prognostic information, risk assessment facilitates further decisions on the type of antithrombin and antiplatelet therapy, the indications for and timing of invasive angiographic evaluation, and the appropriate level of further monitoring

Table 1
Variables associated with increased mortality in acute coronary syndrome

	TIMI [5]	PURSUIT [6]	GRACE [7]	Other
Demographics				
Age ≥65 y	+	.	.	.
Latin American race	.	+	.	.
Female gender	.	.	+	.
Medical history				
≥3 CAD risk factors*	+	.	.	.
Diabetes mellitus	*	+	+	.
Hypertension	*	.	+	.
Hyperlipidemia	*	+	+	.
Current smoking	*	+	-	.
Family history of CAD	*	+	.	.
Congestive Heart Failure	.	+	+	.
Stroke	.	+	+	.
Peripheral vascular disease	.	+	+	.
Renal dysfunction	.	.	+	+ [8]
Angina	.	.	-	.
Atrial fibrillation	.	.	+	.
Prior (+) exercise stress test	.	.	+	.
Bleeding	.	.	+	.
CAD history				
Coronary stenosis ≥50%	+	.	.	.
Prior angioplasty	+	+	-	.
Coronary artery bypass	.	+	+	.
Myocardial infarction	.	+	.	.
Presentation				
Cardiac arrest	.	.	+	.
Severe angina	+	+	.	.
Enrolled as MI, not UA	.	+	.	.
Rales (≥1/3 of lung fields)	.	+	.	.
ECG changes				
ST deviation	+	.	+	.
ST depression	.	+	+	.
Anterior ST depression	.	.	+	.
Inferior ST depression	.	.	+	.
T-wave inversion	.	+	-	.
Significant Q-wave	.	.	+	.
Left bundle branch block	.	.	+	.
Right bundle branch block	.	.	+	.
Prior medication use				
Aspirin	+	+	-	.
Statin	.	.	-	.
β-blocker	.	+	.	.
Calcium channel blocker	.	+	.	.
Nitrates	.	+	.	.
ACE inhibitor	.	+	.	.
Biomarkers				
Troponin I (or T)	+	.	+	+ [9]
CK-MB	+	.	+	.
Myoglobin	.	.	.	+ [10]
NT-proBNP	.	.	.	+ [9]
C-reactive protein	.	.	.	+ [11]
Hemoglobin	.	.	.	+ [12]
White blood cell count	.	.	.	+ [13]

Abbreviations: ACE, angiotensin-converting enzyme; CAD, coronary artery disease; CK-MD, MB isoenzyme of creatine kinase; GRACE, Global Registry of Acute Coronary Events; NT-proBNP, N-terminal probrain natriuretic peptide; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy Trail.

(ranging from evaluation in the chest pain unit and outpatient follow-up to critical care admission).

What makes a risk stratification system useful?

As a clinical tool, the usefulness of an RSS depends on its accuracy (ie, predictive capacity) and applicability (ie, ease of use). The number and type of variables used in the system, the endpoints for which the system is meant to predict, and the populations in which a system is tested and to which a system is applied are important for the success of an RSS. Ideally, an RSS can be used at the bedside to provide highly accurate and relevant prognostic information within a short time frame. The clinical variables should be informative and obtained easily and quickly. Intuitively, the more variables there are within a risk stratification model, the more informative it is likely to be. As knowledge of the pathophysiology of ACS continues to expand, so do the number and complexity of the potential variables available for use within an RSS. As additional factors are used to provide more predictive capacity, each additional variable can add potential time and difficulty for use, making the system more cumbersome and thus less applicable.

A typical RSS design is based on a point system, in which points are assigned for the presence (or absence) of specific clinical factors. The sum of these points correlates to a specific risk level. An RSS with absolute discriminatory capacity would account for all of the variables influencing a particular outcome. If such a system were composed of five independent risk factors (A, B, C, D, and E) of equal impact to the overall risk, each factor would account for 20% of the overall risk burden. If, however, factor A portrays twice the level of risk as the others A would represent 33.3% of the overall risk burden, and each of the remaining four factors would represent 16.6% of the overall risk. This variability in attributable risk must be accounted for in risk stratification to maximize accuracy. In point-system risk models, accuracy is maximized by weighing each factor by the percentage of its contribution to total risk of the outcome (eg, factor A, 2 points; factors B, C, D, and E, 1 point each) [1]. As additional, appropriately weighted factors are added to a system for improved accuracy, the system's complexity expands and can potentially become a hindrance to its quick and appropriate use.

ACS has many potential adverse outcomes, including need for urgent revascularization, recurrent MI, and death. To provide clinically useful prognostic information, an RSS may be developed with these relevant outcomes combined into a composite endpoint, with the perspective that the risk of any one of the outcomes is pertinent to optimizing management. A composite endpoint such as a major adverse cardiac event (MACE), is easier to use clinically, in that a therapeutic option can be provided if the risk of MACE (any one of the many outcomes included in MACE) is not too high. If a health care provider is attempting to avoid any and all of these outcomes, combining them in one RSS is simpler than having an RSS for each of the individual outcomes. Specific factors within an RSS, however, may be predictive only of certain events within a composite endpoint (ie, urgent revascularization but not death). If the practitioner is primarily concerned about mortality, a scale with an accurate predictor of risk of death should be chosen.

Finally, the practitioner using the RSS should be aware of the patient population in which the scale was derived. An RSS is best developed in a diverse patient population to allow applicability to a similarly wide population. If an RSS is developed in a selective population, significant factors may exist within that population that are not accounted for but that uniformly add risk to the general population. If those factors do not exist in a subsequent patient, the predicted risk may be less accurate. For example, if the derivation cohort of an RSS for ACS outcomes contains a high prevalence of smoking, then smoking may not add predictive capacity to the RSS and may not be included in the final model. If that RSS is then applied to a nonsmoking patient, the RSS may suggest higher risk than the patient really has. The application of an RSS to a patient not similar to the derivation cohort or subsequently verified population may thus provide inaccurate information. The responsibility for the appropriate use of an RSS thus falls on the user, who must maintain this perspective when relying on an RSS to assist in medical decision making.

Anatomy of a risk stratification system: the Thrombolysis In Myocardial Infarction risk score for unstable angina/non–ST-segment elevation myocardial infarction

Among the types of RSS available for clinical use, models developed through multivariable

regression are frequently employed [19]. Multiple clinical characteristics are first identified as associated with the likelihood for the event. These characteristics are then compiled into a composite score that functions as a mathematical representation of the probability of the clinical event's occurrence [1].

As an example of an RSS, the development of the TIMI risk score (TIMI RSS) for UA/NSTEMI is discussed. The purpose of the TIMI RSS is to assist in the identification of the patients at highest risk for further adverse events such as death and recurrent ischemia or infarction. Given the variability of potential adverse outcomes, the primary endpoint (within follow up for 14 days) was chosen as a composite of all-cause mortality, new or recurrent MI, or recurrent ischemia leading to urgent revascularization. The creation of the TIMI RSS included two stages of production, the initial development of the system using one cohort of patients and a subsequent validation of the system with a different set of patients. The initial patient population used for the development of the system, defined as the "derivation cohort," consisted of the 1957 patients in the TIMI 11B trial who were randomly assigned to receive standard treatment including aspirin and unfractionated heparin (UFH) [20]. Study subjects were enrolled between August 1996 and March 1998, with an adjustment in inclusion criteria after the first 10 months. Initial parameters for enrollment included the presence of ischemic discomfort at rest for at least 5 minutes and additional evidence of ischemic heart disease including history of CAD, ST-segment deviation, or elevated serum cardiac markers. After 10 months of enrollment, the criteria were adjusted to focus on higher-risk patients who have evidence of ischemic heart disease and was limited to only those with ST-segment deviation or elevated serum cardiac markers. The study subjects had a mean age of 66 years, and 64% were male. CAD risk factors within the patient population included family history (34%), hypertension (50%), hypercholesterolemia (32%), diabetes mellitus (20%), and current smoking (27%). Prior cardiac history was also present in many patients, such as previous MI (32%), history of coronary artery bypass graft surgery (CABG) (13%), and history of percutaneous transluminal coronary angioplasty (12%). ECG abnormality, including ST-segment deviations or T-wave inversion, was present in 83% of the patients, and elevated serum cardiac markers were present at enrollment in 40% of the patients. The majority of patients were ultimately diagnosed as having UA (58%), but 34.5% of the patients had a non–Q-wave MI, and 3.8% had a Q-wave MI. Through the full 14-day follow-up period, 16.7% of the patients experienced the composite endpoint.

The choice of potential predictor variables was completed with the goal of producing an easily applicable stratification system with useful predictive capacity. The number of predictors for the model was thus critical, because too few variables might limit predictive capacity, but too many variables would make the system cumbersome and hamper clinical utility. Thus the potential predictor variables selected were those that were easily identifiable as a baseline characteristic and previously demonstrated to be predictive of outcome. Twelve variables were chosen as potential contributors to the scoring system:

1. Age greater than 65 years
2. Presence of more than three CAD risk factors (including family history of CAD, hypertension, hypercholesterolemia, diabetes, current smoking)
3. Prior coronary stenosis greater than 50%
4. Prior MI
5. Prior CABG
6. Prior percutaneous transluminal coronary angioplasty
7. ST-segment deviation greater than 0.5 mV
8. Severe anginal symptoms (two anginal events in the prior 24 hours)
9. Use of aspirin in last 7 days,
10. Use of intravenous UFH within 24 hours of enrollment
11. Elevated serum cardiac markers (creatine kinase myocardial band or troponin)
12. Prior history of congestive heart failure

These 12 variables were then analyzed by univariate logistic regression, and the variables with a significant correlation ($P < .20$) were subjected to multivariate logistic regression analysis. The seven variables found to correlate significantly with the endpoint were chosen subsequently for the risk stratification model (Fig. 1) [21].

Two additional statistical tests, the C-statistic and the Hosmer-Lemeshow statistic, were applied to the final variable set to assess the model's performance in terms of discrimination and calibration. The C-statistic measures a stratification model's predictive capacity by assessing discriminative ability to classify an individual to the

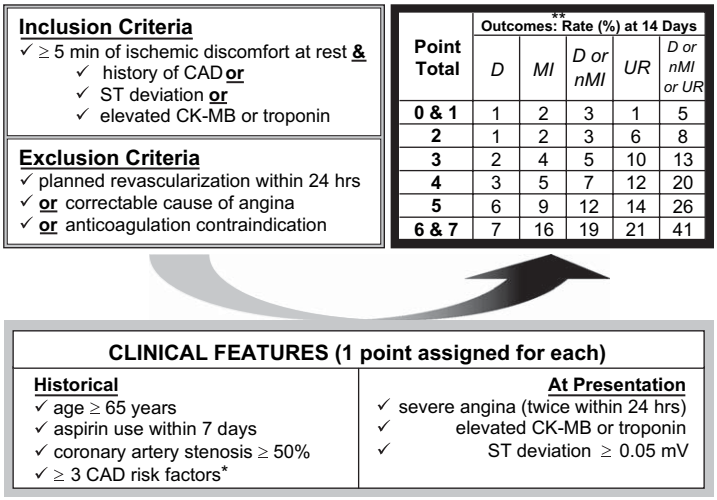

Fig. 1. The TIMI risk score for UA/NSTEMI was derived from the TIMI 11B patient cohort. Multivariate logistic regression identified seven clinical features, which provide equally weighted prognostic information. One point is assigned for each present feature, and points are summed to derive the patient's TIMI risk score. The risk scores of 0 and 1 and the risk scores of 6 and 7 are combined to derive six TIMI risk levels. Rates of individual events and composite outcomes were determined from the entire TIMI 11B patient population, including both the unfractionated heparin and enoxaparin arms. Likelihood of death, MI, or urgent revascularization increases with each risk level ($P < .001$). Risk factors for coronary artery disease are a family history of coronary artery disease, hypertension, hypercholesterolemia, diabetes mellitus, active smoking. D, all-cause mortality; MI, myocardial infarction; nMI, nonfatal myocardial infarction; UR, urgent revitalization. (*From* Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835.)

appropriate risk level. The Hosmer-Lemeshow statistic assesses a model's "goodness of fit" or calibration by comparing rates of actual events with predicted events within each risk group. The C-statistic and Hosmer-Lemeshow statistic showed the TIMI RSS to be well balanced for discriminatory capacity and calibration (Hosmer-Lemeshow statistic: 3.56, 8 degrees of freedom, $P = 0.89$; C-statistic: 0.65 with 0.83 the best balance of discrimination and calibration) [21].

Although a multivariate logistic regression model could provide a weighted score for each variable to be used in predicting a risk score, it would require complex calculations probably requiring computer assistance. Given the desire to produce an easily applicable bedside tool, each of the seven significant variables was weighted equally because the seven variables had similar prognostic significance (odds ratio). Thus the TIMI RSS was produced as a summed score of one point for each of the seven variables, making eight possible scores, ranging from 0 to 7. The summed scores of 0 and 1 were combined, as were those of 6 and 7, to make a final total of six levels of risk (Fig. 1).

When examining the clinical applicability of the TIMI RSS, several favorable characteristics were identified, each adding to the overall utility of the model. The six risk levels were found to have a normal distribution within the derivation cohort. In addition, each subsequent risk level correlated with significantly increased rates of clinical endpoints, producing a wide range of risk across the six levels. The risk of experiencing death (from any cause), new or recurrent MI, or urgent revascularization secondary to recurrent ischemia within 14 days of presentation ranged from 4.7% (at the 0–1 risk level) to 40.9% (at the 6–7 risk level.) Finally, the trend of 14-day risk for each of the individual components of the composite endpoint increased in parallel with the composite endpoint.

Once set in its final form, the risk stratification model was retrospectively applied to three additional cohorts for validation, including the patients receiving enoxaparin in TIMI 11B (n = 1953) [11] and both the UFH (n = 1564) and enoxaparin (n = 1564) arms of the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial [22]. Both discriminatory capacity and calibration were maintained within these additional patient cohorts.

Application of the Thrombolysis In Myocardial Infarction risk score for unstable angina/ non–ST-segment elevation myocardial infarction

The purpose of identifying high-risk patients is to alter management to mitigate risk. The TIMI RSS was assessed for the ability to predict which patients gained benefit from the choice of enoxaparin over UFH. Patients within the TIMI 11B and ESSENCE trials were stratified by their TIMI RSS to test retrospectively for improved outcome with enoxaparin (Fig. 2). When assessing patients within each TRS, enoxaparin was shown to provide greater benefit than UFH to patients who had a TRS of 4 or higher. A superior outcome in the high-risk groups with enoxaparin is conceptually plausible, because bolus subcutaneous dosing may reach therapeutic levels faster than the slowly titrated UFH continuous intravenous infusion. Unlike UFH, however, the degree of anticoagulation with enoxaparin is not monitored. If the presence of low molecular weight heparin delays a needed cardiac catheterization and revascularization, the benefit for high-risk patients may not

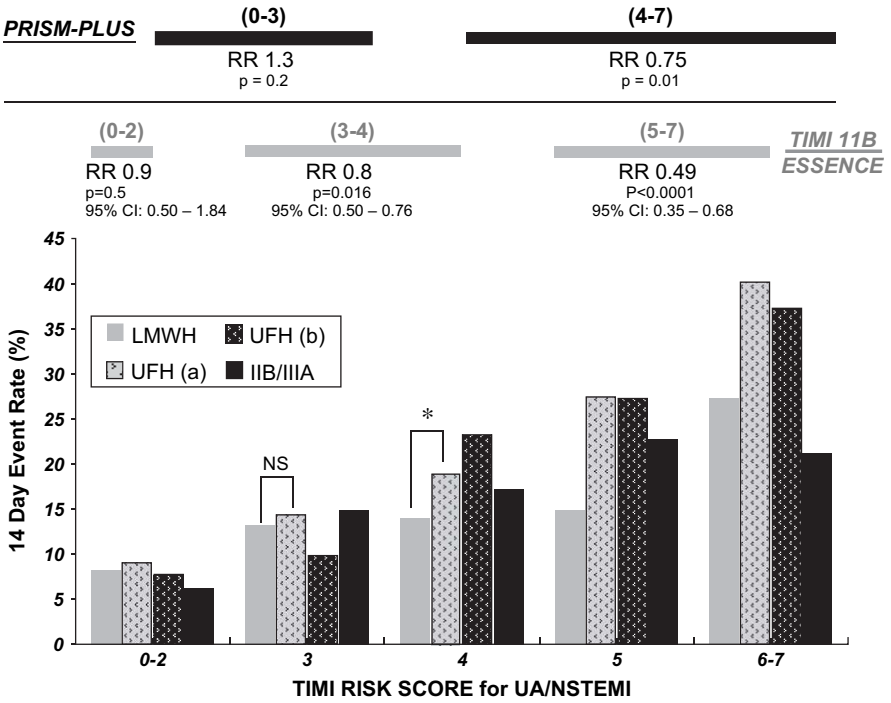

Fig. 2. Clinical outcomes as a function of TIMI risk scores. Efficacy of strategies for antithrombotic therapy in patients with NSTE ACS following stratification with the TIMI risk score (TRS) for UA/NSTEMI. All strategies included aspirin and determined composite endpoint event rates at 14 days. LMWH, patients receiving enoxaparin in the TIMI 11B and ESSENCE trials; UFH (a), patients receiving unfractionated heparin in the TIMI 11B and ESSENCE trials; UFH (b), patients receiving unfractionated heparin in the PRISM-PLUS trial; IIb/IIIa, patients receiving unfractionated heparin and the glycoprotein IIb/IIIa receptor antagonist tirofiban in the PRISM-PLUS trial. Compared with UFH alone, patients receive greater benefit with UFH and tirofiban if their TRS is 4 or higher (TRS 0–3: relative risk [RR], 1.3; $P = .2$; TRS 4–7: RR, 0.75; $P = .01$). When risk scores are further grouped into low-risk (TRS 0–2), intermediate-risk (TRS 3–4), and high-risk (TRS 5–7) groups, patients with intermediate or high risk have greater benefit with enoxaparin (TRS 0–2: RR, 0.91; 95% CI, 0.67–1.22; $P = .5$; TRS 3–4: RR, 0.8; 95% CI 0.67–0.96; $P = .016$; TRS 5–7: RR, 0.49; 95% CI 0.35–0.68; $P < 0.0001$). In analysis of clinical benefit within individual TIMI risk scores, however, there is greater benefit with enoxaparin than with UFH if the TRS is 4 or higher (TRS 3: RR, 0.91; 95% CI, 0.71–1.16; $P = .43$; TRS 4: RR, 0.71; 95% CI, 0.54–0.93; $P = .009$). (*Data from* Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835; Morrow DA, Antman EM, Snapinn SM, et al. An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes. Application of the TIMI Risk Score for UA/NSTEMI in PRISM-PLUS. Eur Heart J 2002;23:223.)

be fully realized. Since the publication of the consensus guidelines, no randomized clinical trial has prospectively assessed the relative benefit of enoxaparin over UFH in high-risk patients. On the other end of the risk spectrum, therapeutic anticoagulation with heparin (UFH or enoxaparin) can increase the risk of hemorrhage, stroke, and thrombocytopenia [22,23]. No randomized clinical trial has examined the benefit of heparin (UFH or enoxaparin) anticoagulation in low-risk NSTE ACS.

In addition to medical management of NSTE ACS with antianginal and antithrombotic therapy, the treating clinician must decide whether invasive cardiac catheterization is indicated. Two general strategies for approaching cardiac catheterization are generally used: an invasive approach in which patients routinely undergo catheterization within 48 hours of admission, or a conservative approach in which catheterization is completed if recurrent ischemia occurs spontaneously or is provoked through noninvasive testing. Between December 1997 and December 1999, 2220 patients were enrolled into the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI 18 trial and were randomly assigned to one of these two strategies [24]. Medical antithrombotic therapy consisted of aspirin, UFH, and tirofiban. Over a 6-month follow-up period, patients who underwent routine early catheterization experienced significantly less recurrent ischemia but suffered higher rates of protocol-defined bleeding (5.5% versus 3.3%; $P < .01$). Stratification with the TIMI RSS demonstrated patients who have intermediate risk (3–4) or high risk (5–7) benefited from the routine early catheterization. Patients at low risk (0–2) did not obtain greater benefit from one strategy over the other (Fig. 3). The benefit of routine early catheterization in the intermediate-risk group of patients was barely significant ($P = .048$; upper bound of 95% CI, .999). Whether analysis of patient groups within individual scores (3 versus 4; Fig. 2) or redefining the bounds of the intermediate risk group would enhance predictive capacity remains unclear. Current consensus guideline class I recommendations call for an early invasive strategy if any of the following high-risk indicators are present:

1. Recurrent angina/ischemia with rest or low-level exertion in setting of intense anti-ischemic therapy

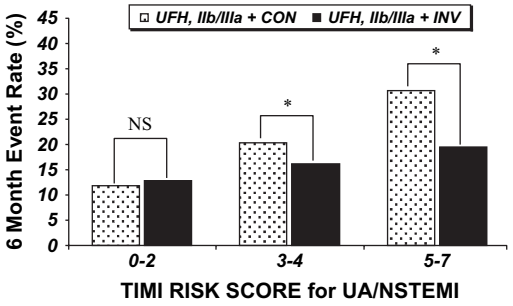

Fig. 3. Assessment of cardiac catheterization strategies in addition to aspirin, unfractionated heparin (UFH), and tirofiban (IIb/IIIa) in the TACTICS-TIMI 18 trial. Rates of a composite endpoint (death, nonfatal MI, or rehospitalization for ACS) at 6 months were compared between conservative (CON: selective catheterization) and invasive (INV: routine catheterization) strategies. Risk levels were stratified as low (TIMI risk score 0–2), intermediate (TIMI risk score 3–4) and high (TIMI risk score 5–7). Although there was no difference between strategies in the low-risk group, routine catheterization was beneficial in the intermediate-risk ($P = .048$) and high-risk ($P = .018$) groups. (*From* Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879.)

2. Elevated troponin (I or T)
3. New ST-segment depression
4. Recurrent angina/ischemia with signs or symptoms of congestive heart failure
5. High-risk results from noninvasive stress testing
6. Left ventricular ejection fraction less than 0.40
7. Hemodynamic instability
8. Sustained ventricular tachycardia
9. PCI within 6 months
10. Prior CABG

Either the early invasive strategy or early conservative strategy is recommended if none of these findings are present. Risk stratification by multivariate RSS has not yet been addressed in consensus guidelines. Likewise, the best combination of medical and invasive management for NSTE ACS is likely to remain undetermined. As new therapies and equipment continue to arise, the time required to complete a clinical trial to assess a specific combination of therapies will persist as a barrier to this goal. Nonetheless, stratified trials to assess benefit from routine early

catheterization with drug-eluting stents, a different antithrombotic regimen (enoxaparin in place of UFH), or additional therapeutic agents such clopidogrel [25] have not been completed.

Other risk stratification systems

Because risk stratification is a multivariable issue with continuously evolving risk factors and management options, current consensus guidelines describe specific clinical features independently associated with various risk levels rather than endorsing one single RSS. Multiple tables are used to illustrate how specific factors derived from the Duke Cardiovascular Databank are associated with risk of clinical events such as true ACS from CAD, death, and nonfatal MI [26]. With this system, patients are assessed as being at high, intermediate, or low risk with the presence of any one factor in that risk level grouping [27].

In efforts to maximize the predictive capacity in risk stratification during the initial time period of an ACS presentation, the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy Trial (PURSUIT) investigators examined both dichotomous and continuous baseline characteristics for prognostic utility [6]. Outcomes (30-day rates of mortality and nonfatal MI) were assessed in 9461 patients randomly assigned to receive the Gp IIb/IIIa inhibitor eptifibatide or placebo upon presentation with NSTE ACS. After univariate and subsequent multivariate logistic regression analysis, an equation was derived to calculate the probability of 30-day mortality, including 23 weighted clinical variables. Because information on all 23 variables and use of a computer would be required to complete this calculation, this model is not easily applicable at the bedside. A simplified model was then developed by removal of the 16 least informative features and subsequent placement of the remaining seven variables into a weighted point system. To estimate risk of 30-day mortality or nonfatal MI, or mortality alone, the sum of points is then applied against a curve. Although the discriminatory capacity of the mortality model is excellent (C-statistic 0.814), the complexity of the model reduces its applicability at the bedside.

To assess the risk of death across the entire ACS spectrum (UA, NSTEMI, and STEMI) and to allow application to a more generalized patient population, the Global Registry of Acute Coronary Events (GRACE) RSS was more recently developed from patients who had ACS sampled from 94 hospitals located in 14 different countries [7]. A nomogram was developed to facilitate risk assessment by summing eight weighted variables, including Killip class, systolic blood pressure, heart rate, age, creatinine level, presence of cardiac arrest at admission, ST-segment deviation, and elevated cardiac enzyme levels. Discriminatory ability was again demonstrated to be excellent (C-statistic 0.83). A comparison of the GRACE RSS and the PURSUIT RSS was recently completed with application to the Canadian ACS Registry, comprising 4627 patients who had ACS enrolled between September 1999 and June 2001 [28]. Again, both models were found to have excellent predictive capacity (C statistic: 0.84 for PURSUIT, 0.83 for GRACE). Although the GRACE RSS was found to be well calibrated (Hosmer Lemeshow $P = .40$), the PURSUIT RSS calibration was suboptimal (Hosmer Lemeshow $P < .001$). This observation demonstrates the potential for differences between clinical trial populations and real-world patients and reinforces the appropriateness of validation among diverse patient populations before widespread use of an RSS. In an effort to maximize predictive capacity, large numbers of variables with associated weighting for attributable risk are employed in the PURSUIT and GRACE systems. These systems, however, are too complex to be used easily straight from memory, and their complexity detracts from their clinical applicability. Alternatively, the TIMI RSS employs seven equally weighted variables to allow improved applicability but at the cost of predictive capacity (C statistic 0.65). With greater ease of use, the TIMI RSS has been more routinely tested for ability to assist in medical decision making, but as hand-held computers become more available to clinicians, the more complicated systems are likely to be more useful.

Future developments in risk stratification

The goal of developing optimal management for NSTE ACS will remain a moving target. Improvements in risk stratification tools and their appropriate use are needed to guide clinicians through the complicated options for management. As such, methods and tools for risk stratification will continue to evolve. Since the development of the RSS discussed here, additional variables have been recognized as prognostically important and subsequently have been shown to provide additional stratification potential. These new risk factors are likely to be spliced into existing

systems or used in the creation of new scoring systems. As one example of an attempt to improve stratification beyond that by existing systems, Bazzino and colleagues [9] assessed numerous molecular markers in conjunction with clinical features for predictive capacity, including N-terminal probrain natriuretic peptide (NT-proBNP), high sensitivity C-reactive protein, troponin T, and myoglobin. Predictive capacity for 6-month mortality improved with additional stratification with NT-proBNP level, beyond that provided by the TIMI risk score for UA/NSTEMI (Fig. 4) and the American College of Cardiology/American Heart Association classification system. Other clinical variables are frequently examined for independent prognostic utility and hence qualify for future RSS. Features associated with the pathophysiologic processes involved in ACS, including markers of inflammation (white blood cell count) [13] and myocardial injury (myoglobin) [10], as well as comorbidities such as anemia (hemoglobin) [12] and renal insufficiency (creatinine clearance) [29], have been shown to predict adverse clinical outcomes independently. How to best use this additional information within the perspective of clinical decision making and future risk models remains to be determined.

Although molecular markers that are directly reflective of cardiomyocyte death, such as troponin I (and T), provide prognostic information, the delay in achieving elevated levels significant enough for detection can be prevent their use as a variable for early risk stratification. Biomarkers of underlying processes leading to cellular death have potential for providing early prognostic information, because they will potentially reach clinically significant elevated levels earlier within the course of an ACS presentation. Some potential upstream biomarkers with early promise include myeloperoxidase, metalloproteinase-9, soluble CD-40 ligand, pregnancy-associated plasma protein A, choline, ischemia-modified unbound free fatty acids, placental growth factor, and glycogen phosphorylase isoenzyme BB [30]. Although the many clinical and biomarker factors currently used in stratification systems account for the majority of variance in outcomes, molecular markers have potential to differentiate risk more quickly and accurately. As this field continues to develop with newly recognized biomarkers and organization of biomarker panels, more precise stratification within the intermediate-risk group may allow improved delivery of optimized care.

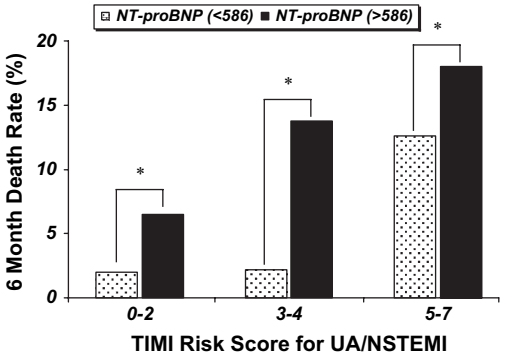

Fig. 4. Risk stratification for 6-month mortality is enhanced when N-terminal probrain natriuretic peptide (NT-proBNP levels) are checked within 7 hours of admission for NSTE ACS. Within each TIMI risk level, likelihood of the composite death or nonfatal MI, or of death alone, was higher with the NT-proBNP level greater than 586 pg/mL ($P < .001$ for interaction test). (*From* Bazzino O, Fuselli JJ, Botto F, et al. Relative value of N-terminal probrain natriuretic peptide, TIMI risk score, ACC/AHA prognostic classification and other risk markers in patients with non-ST-elevation acute coronary syndromes. Eur Heart J 2004;25:859.)

Summary

Simple RSS allow for rapid decision making in the emergency department. The data presented in this article suggest that for patients at the highest risk and the lowest risk for complications of NSTE ACS, the scoring systems work well and allow effective triage and treatment. For patients at intermediate risk (30%–40% of all patients who have ACS), however, it is not clear whether early aggressive treatment with cardiac catheterization or routine conservative management should be the standard of care. The consensus guidelines are vague, and the scoring systems discriminate less well for these patients. The authors think that patients at intermediate risk are best served by initial screening with an RSS like the TRS (with risk scores of 3–4), followed by a multimarker strategy to define risk better. They also think that the next step is to design clinical trials to test strategies of care defined prospectively by risk. This step would, in the authors' opinion, begin the next round of the cycle of clinical therapeutics [31]. The treatment of patients who have NSTE ACS has been characterized in the past 2 decades by care based on evidence from many excellent clinical trials. The consensus panels have convened and guide patient management. Quality-improvement initiatives such as CRUSADE and GRACE give

feedback to improve compliance with guidelines. The understanding of risk is developing with the help of these scoring systems. Discovery is ongoing. The next decade of acute cardiac care will focus on early identification of patients at high risk and on matching the most intensive treatments to the patients most in need. Excessive testing and care promotes cost inefficiency and, perhaps, increased hazard for some patients. New trials are needed to move these new hypotheses back into practice.

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