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Issues in early risk stratification for UA/NSTEMI

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North American and European task forces representing the ACC/AHA and the ESC have recently developed new treatment guidelines for the management of unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI). At the 4th Annual Experts' Meeting of the International Cardiology Forum, workshops were held to review the new recommendations. In the discussion of risk stratification, the most debated topic was the role assigned to the cardiac-specific troponins (cTnI and cTnT). Although the importance of these indicators in an integrated risk stratification scheme was well accepted, some participants felt that they received undue emphasis in the new guidelines, and the implication that troponin status should determine use of a glycoprotein IIb/IIIa inhibitor and early catheterization was debated. The value of continuous versus serial ECG monitoring was also discussed, but no consensus was reached. Although many were encouraged by the data on C-reactive protein (CRP) as a prognostic indicator, it was generally agreed that it is too soon to recommend its routine measurement in ACS. Finally, risk stratification is a complex, ongoing process that is impossible to reduce to a simple treatment algorithm.

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Overview of the new guidelines

General classification scheme

The basic elements of risk stratification, as outlined in both the ACC/AHA[1] and ESC[2] guidelines for UA/NSTEMI, have not changed significantly from the 1994 AHCPR[3] guidelines. The nature and duration of the presenting symptoms, the cardiovascular elements of the physical exam, electrocardiographic findings, and biochemical markers of myocardial damage remain important prognosticators in the work-up of an acute coronary syndrome. Both sets of recommendations take these elements into account (see Tables 1 and 3) and the definitions of risk categories include elements from each of these areas (see Tables 2 and 4). These tables will be referred to more extensively below.

Clinical aspects of risk stratification

Although there is significant discussion of biomarkers in both sets of guidelines, both guidelines emphasize that traditional risk factors are still the most important prognosticators. In the ACC/AHA guidelines, the five most important risk factors are given as: nature of symptoms, history of CAD, age, sex, and number of traditional risk factors present (such as hypercholesterolaemia). Similarly, the discussion of risk assessment in the ESC guidelines begins with a discussion of age and sex, as well as the other traditional risk factors, before focusing on the ECG and laboratory testing.

There is little controversy that, once traditional risk-factors are assessed, the ECG becomes crucial to both diagnosis and prognosis. Both guidelines make ECG findings central to risk assessment, along with biochemical markers. Because the ECG is useful in determining continuing ischaemia, the ACC/AHA guidelines suggest that: 'Patients should undergo continuous [ECG] monitoring during their initial ED evaluation and early hospitalization phase' although this recommendation is assigned only level of evidence C. Similarly, the ESC guidelines recommend that if a patient has suspected ACS, one should initiate continuous ST-segment monitoring, but give as an alternative 'frequent ECGs where monitoring is unavailable'.

It should be emphasized that risk stratification begins in the emergency room, based on the clinical history and ECG findings, prior to obtaining the results of serum markers.

The troponins

The most striking advance in the recommendations for early risk stratification is the central role given to the measurement of the cardiac-specific troponins (cTnI and

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Table 1 ACC/AHA recommendations for early risk stratification

Recommendation	Level of evidence
Class I	
1. A determination of the likelihood (high, intermediate, or low) of acute ischaemia caused by CAD should be made in all patients with chest discomfort.	C
2. Patients who present with chest discomfort should undergo early risk stratification that focuses on anginal symptoms, physical findings, ECG findings, and biomarkers of cardiac injury.	B
3. A 12-lead ECG should be obtained immediately (within 10 minutes) in patients with ongoing chest discomfort and as rapidly as possible in patients who have a history of chest discomfort consistent with ACS but whose discomfort has resolved by the time of evaluation.	C
4. Biomarkers of cardiac injury should be measured in all patients who present with chest discomfort consistent with ACS. A cardiac-specific troponin is the preferred biomarker, and if available, it should be measured in all patients. CK-MB by mass assay is also acceptable. In patients with negative cardiac markers within 6 h of the onset of pain, another sample should be drawn in the 6– to 12-h time-frame (e.g. at 9 h after the onset of symptoms).	C
Class IIa	
1. For patients who present within 6 h of the onset of symptoms, an early marker of cardiac injury (e.g. myoglobin or CK-MB subforms) should be considered in addition to a cardiac troponin.	C
Class IIb	
1. C-reactive protein (CRP) and other markers of inflammation should be measured.	B
Class III	
1. Total CK (without MB), aspartate aminotransferase (AST, SGOT), β-hydroxybutyric dehydrogenase, and/or lactate dehydrogenase should be a marker for the detection of myocardial injury in patients with chest discomfort suggestive of ACS.	C

Table 2 ACC/AHA recommendations for short-term risk of death or nonfatal MI in patients with unstable angina

Feature	High risk (at least one)	Intermediate risk (at least one and no high-risk)	Low risk
History	Accelerating tempo of ischaemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use	
Character of pain	Prolonged ongoing (>20 min) rest pain	Prolonged (>20) min rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (<20 min or relieved with rest or sublingual NTG)	New-onset CCS III or IV angina in the past 2 wk with moderate or high likelihood of CAD
Clinical findings	Pulmonary oedema, most likely related to ischaemia New/worse MR murmur S_3 or new/worsening rales Hypotension, bradycardia, tachycardia Age >75 years	Age >70 years	
ECG findings	Angina at rest with transient ST-segment changes >0·05 mV Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave inversions >0·2 mV Pathological Q waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	Markedly elevated (e.g. TnT or TnI >0·1 ng/ml)	Slightly elevated (e.g. TnT >0·01 but <0·1 ng/ml)	Normal

cTnT). The emphasis on troponin testing in the new guidelines is not unexpected. Numerous clinical studies have found a high correlation between elevated troponin levels and the incidence of such hard end-points as death and myocardial infarction, at both early and delayed time-points. Some of these studies are based on dichotomous troponin testing, that is, labeling patients as either 'troponin-positive' or 'troponin-negative', and

Table 3 ESC recommendations for risk stratification: 'Risk assessment should be precise, reliable and, preferably, easily and rapidly available at low cost. The following methods are recommended'

(A) Markers of thrombotic risk, i.e. acute risk:
(a) Recurrence of chest pain
(b) ST-segment depression
(c) Dynamic ST-segment changes
(d) Elevated level of cardiac troponins
(e) Thrombus on angiography
(B) Markers of underlying disease, i.e. long-term risk:
(B1) Clinical markers
(a) Age
(b) History of prior MI
(c) History of severe angina
(d) Diabetes
(B2) Biological markers
(a) Level of C-reactive protein
(B3) Angiographic markers
(a) LV dysfunction
(b) Extent of coronary artery disease

Level evidence for all markers: A

Table 4 ESC criteria for high and low risk for progression to myocardial infarction or death

High risk
• Patients with recurrent ischaemia (either recurrent chest pain or dynamic ST segment changes, in particular ST segment depression, or transient ST segment elevation)
• Patients with elevated troponin levels
• Patients who develop haemodynamic instability within the observation period
• Patients with major arrhythmias (repetitive ventricular tachycardia, ventricular fibrillation)
• Patients with early post-infarction unstable angina
Low risk
• Patients who have no recurrence of chest pain within the observational period
• Patients without elevation of troponin or other biochemical markers of myocardial necrosis
• Patients without ST-segment depression or elevation but rather negative T waves, flat T waves or normal ECG

some studies find a continuity of risk associated with quantitative increases in troponin level. Troponin emerges consistently as an independent risk factor, when symptoms, ECG changes, and other traditional risk factors are all taken into account.

Studies have also demonstrated that troponins are more sensitive and specific for myocardial damage than the old 'gold standard' CK-MB. As structural proteins with isoforms that are highly specific for the myocardium, troponins enter the bloodstream when cellular damage has occurred. The cardiac isoforms of troponin I and troponin T have an amino acid sequence that is distinct from skeletal muscle forms. This has made possible immunological assays that are highly sensitive to the presence of these cardiac biomarkers. Although the level of CK-MB in serum rises roughly at the same tempo as that of troponin, troponin levels indicative of myocardial damage can be detected in many patients with a 'normal' CK-MB. Also, the presence of CK-MB in the bloodstream of some patients without myocardial damage (particularly those with skeletal muscle pathology) make the diagnosis of infarction more difficult than with troponins.

Troponin testing accomplishes diagnosis and prognosis at the same time. Just prior to the issue of both the North American and European guidelines, a joint taskforce of the ACC and ESC published a consensus document[5] redefining myocardial infarction. This document defined MI from many perspectives, among them laboratory testing and pathology. From the standpoint of laboratory testing, cardiac damage was defined as 'a [troponin] measurement exceeding the 99th percentile of a reference control group'. If the mechanism of injury is ischaemic, regardless of whether this value was obtained in the emergency room, in a cardiac care unit, or after an interventional procedure, an MI is diagnosed. The rationale behind this definition, once again, is that troponins are so easily detected in the bloodstream, and yet so specific to myocardial damage, that another biomarker is not required to confirm the diagnosis. And because of their specificity for myocardial tissue, peak quantitative measures of cTnI or cTnT should correlate with the amount of damage to the myocardium.

In the ACC/AHA document, the Class I recommendations for early risk stratification (Table 1) begin with an assessment of the likelihood that the patient is presenting with ischaemia due to coronary artery disease. The recommendations then focus on electrocardiography and testing of biochemical markers of injury. It is stated that 'a cardiac-specific troponin is the preferred biomarker' and that 'CK-MB is also acceptable'. The guidelines include a table comparing the four most commonly available biomarkers CK-MB, CK-MB isoforms, myoglobin, and cardiac troponins, together with their strengths and weaknesses. It is recommended that serum troponin is useful 'as a single test to efficiently diagnose NSTEMI . . . with serial measurements' and that clinicians familiarize themselves with the test in their own institutions. Thus, troponin testing is given a more central role than as merely a supplement to CK-MB.

The ACC/AHA guidelines also define a role for CK-MB. Apart from being 'also acceptable' as an initial biomarker, CK-MB is more useful than troponin in detecting late reinfarction. Indeed, the two weaknesses of troponin listed in the guidelines include: a low sensitivity prior to 6 h (a weakness shared with CK-MB); and possibly a low sensitivity for late reinfarction, because of the long time it takes troponin levels to become undetectable after the index event. A CK-MB may thus be helpful in determining whether a troponin elevation found after the initial presentation represents new or pre-existing damage. The guidelines also recognize that troponin testing may be a relatively new addition to a given institution's armamentarium; as such, an additional role of CK-MB may be to supplement

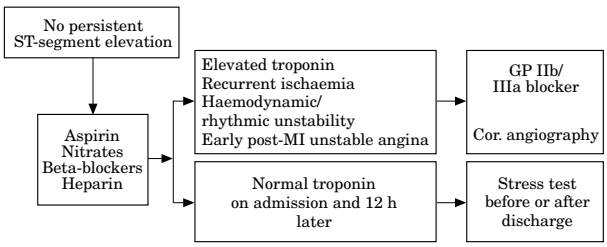

Figure 1 **ESC recommended strategy in ACS.**

troponin testing during the 'transition' period, while physicians familiarize themselves with troponin testing and its nuances. In this case, CK-MB testing may not actually add any diagnostic or prognostic information; thus, eventually, these patients would be expected to undergo only troponin testing.

The contribution of troponin testing to overall risk stratification is described in the ACC/AHA Table 2. Here there are three risk categories delineated, with quantitative troponin levels adding to the determination of high, intermediate, or low risk. Example cutoff points are given for cTnT as 0·01 and 0·1 ng/ml for entry into the intermediate- and high-risk categories, respectively. In the ESC guidelines, the emphasis on troponin testing is equally strong. In the recommendations for diagnosing NSTEMI, troponin is presented as the biomarker of choice. Again, there is only a limited role assigned to CK-MB: for the diagnosis of late reinfarction, when troponin levels would still be elevated from the initial episode of infarction. In the section on risk stratification, troponin is the only biomarker mentioned (Table 3). In a later section entitled 'Management strategy in acute coronary syndromes', the ESC guidelines present a flowchart entitled 'Recommended strategy in acute coronary syndromes' (Fig. 1). The diagram implies a dichotomous risk stratification scheme centred on troponin testing. Once ACS without ST-elevation is suspected, there are only two pathways represented: a high-risk pathway, defined by a positive troponin or some evidence for ongoing ischaemia; or a low-risk pathway, defined by serially negative troponins.

In both the North American and European guidelines, there is a connection, either implied or explicitly stated, between an elevated troponin and use of a glycoprotein IIb/IIIa inhibitor. In the ACC/AHA guidelines, the rationale for risk stratification is that:

'[A]n estimation of risk is useful in (1) selection of the site of care (coronary care unit, monitored step-down unit, or outpatient setting) and (2) selection of therapy, especially platelet glycoprotein (GP) IIb/IIIa inhibitors . . . and coronary revascularization.'

In the full-length ACC/AHA guidelines document, there is further discussion of troponin testing which links troponin elevations and IIb/IIIa inhibition even more explicitly. When discussing the interpretation of troponin levels, the guidelines state that serial testing may be more valuable than a single test, because a positive Δ value (an increase in troponin concentration over time) will reflect ongoing myocardial damage. The section concludes with the comment: 'Thus, by relying on Δ values, patients without ST-segment elevation can be selected for therapy with GP IIb/IIIa inhibitors, and those with negative Δ values can be considered for early stress-testing'.

Also in the ESC document, as seen in Figure 1, 'high-risk' is linked to the recommendation to administer a IIb/IIIa inhibitor. Once a patient is found to have an elevated troponin, the first intervention mentioned is, 'introduction of GP IIb/IIIa receptor blocker'. Following this, the physician is directed to perform coronary intervention during the initial hospitalization. While a full discussion of the management of UA/NSTEMI will be left to later sections, it is interesting to note the tight association illustrated here between risk stratification and management decisions.

The link between troponin testing and IIb/IIIa inhibition follows from subgroup analyses of clinical trials in which IIb/IIIa inhibitors were found to have a benefit when compared to placebo. In the PRISM-PLUS trial, for example, tirofiban reduced the rate of death or myocardial infarction at 30 days from 21·7% to 6·9% in patients defined to have elevated troponin levels, but only reduced death/MI from 12·8% to 7·9% in patients with a 'normal' troponin[2]. Similar results were seen in trials of other agents within this class, such as the CAPTURE trial[6] of abciximab. Other therapeutic options have similarly been shown to have an increased benefit in troponin-positive patients, such as low-molecular-weight heparin (as in TIMI 11B[7] and FRISC II[8]); nevertheless, the association between troponin levels and IIb/IIIa inhibitors is the most heavily emphasized in these guidelines.

Neither the ACC/AHA nor the ESC guidelines discuss in detail the issue of which troponin test should be performed. There are numerous studies comparing the sensitivity, specificity, and reliability of cTnI and cTnT, but no definitive case has been made for preferring one marker to the other[9]. It should be noted that there can be variability from one cTnI test to another, because the various antibodies used in the available assays recognize different epitopes on the circulating cTnI complexes; in contrast, there is a single, well-characterized antibody used to detect circulating cTnT. This underscores the need to standardize each cTnI test differently. It has also been suggested that there are more false-positives associated with cTnT, particularly in patients with skeletal myopathy or advanced renal insufficiency. As concluded in the ACC/AHA guidelines:

'With currently available assays, cTnI and cTnT are of equal sensitivity and specificity in the detection of cardiac damage. The choice should be made on the basis

of cost and the availability of instrumentation at the institution.'

Other biochemical markers

Both sets of guidelines do mention other markers of cardiac damage, but such markers are not emphasized. The ACC/AHA guidelines give a Class IIa recommendation ('usefulness less well established') to markers such as myoglobin and certain CK-MB isoforms that appear earlier in the bloodstream, and thus can detect necrosis before a troponin test would be revealing. As stated, however, the 'field performance' of CK-MB isoforms remains to be established, because their use has been limited to dedicated centres. Similarly, the ESC guidelines recommend measuring a myoglobin level in patients who present within 6 h of the onset of symptoms. Neither guidelines document includes these earlier markers in its overall risk stratification scheme.

Although C-reactive protein (CRP) has long been recognized as an acute-phase reactant, its precise role in the work-up of coronary artery disease has yet to be defined. CRP was not discussed in the 1994 AHCPR guidelines for UA, and since then there has been much interest in it as both a marker of inflammation and a possible causal agent for ACS.

Multiple studies of ACS patients have demonstrated that CRP levels correlate well with risk, independent of troponin levels, particularly when the CRP is markedly elevated. In addition, the presence of two positive tests — that is, elevations in both CRP and troponin — identifies the highest-risk group, indirectly confirming the importance of underlying pathophysiologic mechanisms such as inflammation and thrombosis[10]. However, there are some issues surrounding the use of CRP as a marker of risk. For example, underlying disease states can contribute to an elevated CRP, independent of coronary artery disease, making an interpretation of the results difficult. In addition, there have been problems with some of the commercially available tests for CRP, but, newer high-sensitivity (hsCRP) assays appear to be more reliable. Given this information, how would CRP fit into a risk stratification algorithm? For example, is an elevated CRP sufficient to move a patient into a higher-risk category? Also, it remains to be demonstrated how CRP measurements would best be used to guide therapy, such as relying more heavily on antiinflammatory agents, or else prolonging therapy because of the underlying state of inflammation.

Although the North American guidelines do not recommend the routine measurement of CRP, it is stated that this and other markers of inflammation can make a meaningful contribution to the analysis. The ESC document assigns a level of evidence of A to CRP as a risk stratification tool, but cautions that risk stratification tools in general should be 'easily and rapidly available at low cost'. Whether CRP currently meets these criteria is a matter for debate.

Areas where the guidelines differ

General

The ACC/AHA and ESC guidelines for risk stratification are mostly concordant, and the two task forces have developed fairly similar risk stratification schemes based upon the tools and data available. In general, the ESC guidelines are more concise, and include a less detailed discussion of the tools for risk stratification, even when compared to the ACC/AHA executive summary. Although brevity has its advantages, questions arise in practice that are only addressed by the full-length version of the North American guidelines. For example, as described above, there are numerous laboratory tests available for the cardiac-specific troponins, and while it is ultimately the responsibility of the practicing physician to become acquainted with the assays available at his or her institution, some would argue that there should be at least a mention of the distinction between cTnI and cTnT.

Number of risk categories

The most notable difference is the absence of an intermediate-risk category in the ESC guidelines. Although there is no formally presented table defining risk groups in the document, the flowchart illustrating a general approach to ACS (Fig. 1) gives a graphical representation of a dichotomous scheme. The text accompanying the flowchart reinforces this concept, including discussion only of 'high-risk' patients and 'low-risk' patients, with no defined category in between (Table 4).

Arguably, upon a closer reading of the text of the ESC guidelines, one could infer an intermediate-risk category, similar to that contained in the ACC/AHA guidelines. A patient who has no high-risk characteristics, for example, but who not yet been observed for the entire 'observation period' free of chest pain, is technically not yet a low-risk patient either. Similarly, a patient who has not yet undergone a second troponin test is not yet 'low-risk' by definition, even if no high-risk criterion has been met. A third example would be a patient with resolved ST-segment depressions: there is no 'recurrent ischaemia' and yet the ECG upon presentation is not compatible with the 'low-risk' definition. Without this more detailed analysis, however, the document presents a decidedly dichotomous scheme.

It is interesting to note that the numerous risk stratification schemes developed over the years have incorporated any number of different risk categories. For example, the oft-cited Braunwald classification scheme, published in 1989, involved a 3×3 analysis in which there were three possible levels of severity of symptoms (such as 'new onset severe angina'), and three possible 'clinical circumstances' in which the angina occurred (such as 'occurring within 2 weeks of an acute MI'), leading to nine basic risk categories (e.g. 'IIIB'). These

categories, in turn, could be modified by the subscripts 1, 2, or 3 (e.g. $IIIB_3$), depending on three additional clinical characteristics. Finally, the patients would then be further subdivided depending on the presence or absence of ST-T wave changes[11]. In 1994, the AHCPR guidelines included a risk stratification scheme with the three risk categories — high, intermediate and low — upon which the current ACC/AHA guidelines are based. More recently, the TIMI (Thrombolysis in Myocardial Infarction) Group used a multivariate regression analysis to isolate seven clinical characteristics that independently vary with risk; the TIMI Risk Score is simply a number between 0 and 7 representing the number of these risk factors present[4]. These various classification schemes serve to illustrate that risk is a continuum, and that the number of divisions specified is determined by what corresponds best to the aetiology of disease, as well as what would be most useful in practice.

What are the implications, then, of specifying two versus three risk categories? The answer depends upon the ultimate function of risk stratification. A dichotomous classification scheme may be desired in cases of triage, where, for example, there are a limited number of CCU beds; or when deciding whether or not to admit a patient. Conversely, a classification scheme with more categories may be appropriate when there are multiple levels of patient care to be considered. In either case, the distinction is not a trivial one, as assigning a patient to a particular risk level has implications when justifying a specific therapy, or designing a clinical trial.

Other differences

Because serum troponin takes time to reach its peak (rising at roughly the same rate as CK-MB), the ACC/AHA guidelines recommend a repeat measurement for patients who test within normal limits during the first 6 h of presentation. The ESC guidelines recommend such repeat measurements on all patients. Even if an initial test is 'positive', a second test performed later may document a much higher quantitative level. In our own workshop we found both approaches represented; that is, of those who routinely measure serum troponin level on admission, some routinely obtain a second measurement and some choose to defer additional testing if the initial troponin is already elevated.

One last difference: the ACC/AHA guidelines assign level of evidence B or C to the risk stratification recommendations, whereas the European guidelines assign a level of evidence A to all recommendations, including the measurement of CRP. The difference is most likely one of semantics: there is ample evidence that each clinical parameter varies directly with the risk of adverse events (thus, evidence level A), and yet it is a matter of opinion which tests are most crucial to incorporate into patient care (thus, evidence level C).

Commentary

We found overall that the ACC/AHA guidelines provide a comprehensive guide to risk stratification. The ESC guidelines, while less comprehensive, offer a dichotomous classification scheme that incorporates the basic elements of risk stratification into a concise approach to the management of ACS. Both classifications are largely consistent with existing evidence; in addition, the full text of the ACC/AHA guidelines includes a comprehensive description of the tools available.

Most of our discussion centred on troponin testing, because this represented the greatest change from previous guidelines. We had some discussion of the value of continuous ECG monitoring but reached no overwhelming consensus, although most felt that serial ECG tracings every 6–8 h during the first 24 h was an acceptable method of following acute ischaemia. It was acknowledged that, ultimately, resource limitations would continue to dictate who gets continuous monitoring. We also discussed the role of CRP, and while there was enthusiasm over CRP as a marker of inflammation, it was generally agreed that it was too early to consider this a regular part of our prognostic armamentarium.

In general, our discussion reinforced several cautionary notes for implementing either risk stratification scheme. First, it is necessary to learn the subtleties and limitations of troponin testing — as with any new diagnostic tool — as it replaces CK-MB as the gold standard for diagnosing MI. Second, risk is a continuum, and thus all clinical parameters should be integrated when deciding on a particular therapeutic option. Third, risk is evolving over time, and a continual reassessment is required throughout the acute phase of management.

Limitations of troponin testing

Although the data linking troponin levels with risk are impressive, an initial risk assessment should focus first and foremost on elements of the presenting complaint, history, and physical exam. Even when testing, such as electrocardiography and biochemical assays, has been performed, parameters such as age, gender, history of coronary artery disease, and other comorbidity continue to be of utmost importance when assessing risk.

There are data suggesting that, in the absence of other risk factors, an elevated troponin identifies a higher-risk subset of patients. For example, it was demonstrated that among patients with chest pain and no ECG changes suggestive of ischaemia, patients who had a positive cTnT (>0·1 ng/ml) had a higher cardiac event rate at 1-year follow-up[12]. There are other data, however, suggesting that the serum troponin level is just one of many contributors to a patient's risk. For example, when calculating the TIMI Risk Score (introduced above) an elevated troponin is given equal weight to six other parameters. The investigators who developed the system found a linear correlation between the TIMI

Risk Score and prospectively measured risk, thus supporting a classification scheme in which biomarkers are not heavily emphasized. In addition, the ACS patient without an elevated troponin (by definition an unstable angina patient) is not without risk, and thus a negative troponin in patients with other risk-factors should not offer a false sense of security. As stated in the ACC/AHA guidelines, 'troponins should not be relied on as the *sole* markers for risk, because patients without troponin elevations may still exhibit a substantial risk of an adverse outcome.' Taking this principle further, we must exercise caution not to withhold treatment from patients deemed to be 'low risk' simply because an initial troponin test is negative.

Although the full significance of the GUSTO IV ACS trial is still being debated, a brief look at the trial further illustrates this principle. Patients were enrolled in this trial with rest angina and either ST-segment depressions, an elevated troponin level, or both. Additionally, patients who were scheduled to undergo angiography were not enrolled; thus, it was a trial of medical management. Patients were randomly assigned to receive either abciximab or placebo in addition to a regimen containing aspirin and either UFH or LMWH. The study population in this trial met the criteria for 'high risk' according to either set of guidelines, and yet there was no benefit found to the addition of abciximab to their treatment regimen, even in the subset of patients who presented with an elevated troponin level. Both guideline documents imply a one-to-one correlation between elevated troponin and IIb/IIIa inhibition (particularly the ESC guidelines); although a complete analysis of GUSTO IV ACS is beyond the scope of this discussion, we can at least conclude that risk stratification is a complex task.

Troponin testing is valuable, of course, and this value is augmented by good communication and instruction between the laboratory and the physician interpreting the test. Cardiologists have had years of experience developing and implementing algorithms for serial CK and CK-MB testing, but much more limited experience with the troponins. The subtleties of troponin testing may not be as well understood. For example, a troponin level above that found in 99% of the normal population may define an NSTEMI, but virtually any level above zero, if accurate, represents myocardial damage. In addition, for some assays, there may be less accuracy at lower levels[13]. Given these uncertainties, what is the significance of a slightly elevated troponin level? There are also issues specific to each troponin. As stated above, there is less standardization among the tests available for cTnI; on the other hand, there may be less specificity of cTnT for cardiac ischaemia, particularly among patients with renal insufficiency.

As hospitals and physicians switch to troponin testing, it is important to keep these subtleties in mind, and to know the information that can be expected from a given troponin assay. It is similarly important to know when to repeat a troponin test, or to supplement the results with testing of other biomarkers, such as myoglobin or CK-MB. An expanded discussion of the issues surrounding troponin testing can be found in an editorial published by the biochemistry panel of the joint ACC/ESC task force on redefining myocardial infarction[13].

Risk as a continuum

In general, we must take care not to oversimplify risk stratification into an inflexible algorithm dictating triage and therapy. As stated appropriately in the ACC/AHA guidelines, in the legend to the table of short-term risk: 'An estimation of the short-term risks of death and nonfatal cardiac ischaemic events in UA is a complex multivariable problem that cannot be fully specified in a table such as this', and therefore, the classification scheme, 'is meant to offer general guidance and illustration rather than rigid algorithms'. Risk is a continuum, and it is the integration of all known variables, together with the clinical expertise of the treating physician, that should determine therapy.

The concept of risk as a continuum applies to each individual tool used in risk stratification. For example, the depth of T-wave inversions, as well as the number of leads in which they occur, are important parameters when interpreting their significance. Similarly, as mentioned above, the quantitative level of a troponin test conveys more information than a simple 'positive' or 'negative', as troponin levels have been demonstrated in multiple studies to correlate with a spectrum of risk[14]. Although a level of 0·1 ng/ml has frequently been used as a cutoff for 'high risk', there is a difference between troponin levels of 0 and 0·05 ng/ml, just as there is a difference between 0·5 and 1·0 ng/ml. Thus, while point-of-care ('bedside') troponin tests can be valuable tools for triage in an emergency care setting, a quantitative level ultimately conveys more meaningful information.

Risk as changing over time

Just as risk is a continuum, an estimation of risk is subject to change over time, whether because new information has been added to the equation, or else because the patient is farther on from the presenting event. While factors such as age are largely immutable, electrocardiography is the clearest example of a test that bears repeating. It is important to know the duration of ischaemic ST-T changes in order to assess the likelihood of significant myocardial compromise, as well as to monitor the response to therapy. While there was relatively little enthusiasm for *continuous* ECG monitoring in our workshop, the importance of at least serial ECG monitoring cannot be underestimated. Similarly, as discussed above, it is important to repeat a quantitative troponin test, especially if the patient presents early in the course of their syndrome. What is the timing of the infarct? If

the infarct is evolving, how large will it be? As with other biochemical markers, troponins rise and fall with time, and a sense of the troponin 'curve' may be more valuable than a single data-point. Studies confirm that two tests separated in time have more sensitivity than one for cardiac ischaemia[15], and while a single troponin test may be adequate for diagnosing NSTEMI, multiple tests may be more valuable in an ongoing risk assessment. In general, however, nothing should replace the continued assessment of the patient by a physician at the bedside.

Country or setting-specific issues

There are locations and situations in which not all the tools mentioned in the guidelines are available, or where resources are limited and cannot be used in each patient. In cases where beds are limited, risk stratification may be especially important to determine which patients need intense monitoring, such as in a coronary care unit, and which patients do not require admission at all.

In our workshop, we found that some institutions do not yet have troponin testing available. We encourage all institutions to adopt troponin testing, for several reasons: (1) Troponins are more sensitive for myocardial damage than CK-MB; (2) As troponins become the new standard for diagnosing NSTEMI, troponin testing will become necessary in order to compare patients from centre to centre, and to determine the pertinence of clinical trial results to a given patient; and (3) Troponins are a valuable tool for triage in a busy urgent care environment.

In centres where troponin testing is performed regularly, it may be that continuing to measure multiple cardiac markers is no longer an efficient use of resources. In these centres, physicians should learn to rely on quantitative troponin levels, and to supplement them only as needed, in order to minimize redundant testing. However, during this transition period, and while we learn more about the prognostic value of serial troponin testing, we should not be too quick to abandon determinations of CK-MB.

Areas where more data or guidance would be useful

As troponins become the standard of care for diagnosing myocardial damage, we anticipate more studies in which troponin levels are measured at enrolment, and in which patients are analyzed prospectively according to troponin level. At present, cutoff values for a positive or negative troponin are somewhat arbitrary, in that they mostly depend on retrospective analyses, and these studies should therefore include graded troponin levels, and not simply 'positive' or 'negative' values. In addition, we have yet to define optimal management of the patient with elevated troponin levels and negative cardiac enzymes, the 'minimal myocardial damage' patient. It is hoped that further studies will concentrate on these patients, at least in subgroup analysis.

We need better algorithms to diagnose re-infarction. Both guidelines emphasize that, at present, CK-MB is more useful than troponin in detecting further damage, as troponin levels remain elevated for some time. We need to develop simple, comprehensive models for using the available tests to diagnose recurrent ischaemia and infarction, and guidelines for using those protocols efficiently.

There are some details of ECG testing that are also not fully understood. For example, the precise significance of T-wave inversions has yet to be determined, and while the ACC/AHA guidelines list T-wave inversions of >0·2 mV as a criterion for intermediate risk, more studies to examine the significance of specific ECG changes would be helpful. Along the same lines, the value of continuous ECG monitoring has not fully been explored. Studies have demonstrated that continuous monitoring identifies patients with otherwise silent recurrences of ischaemia, and that these patients are indeed at greater risk of future events[16]; however, large studies evaluating the efficacy of continuous monitoring in guiding therapy and reducing event rates would be useful.

Lastly, are there other biochemical markers that would be useful in directing therapy? A more direct marker of platelet activation, for example, could be helpful in the decision to use a IIb/IIIa receptor antagonist, regardless of the overall level of risk. Similarly, measuring individual components of the coagulation cascade could prove useful in shaping optimal antithrombin therapy. More research into these areas is warranted.

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