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EDITORIAL COMMENT

Risk Stratification With Cardiac Troponin I in Acute Coronary Syndromes*

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Recent years have shown a rapidly growing interest among clinical chemists, clinical cardiologists and emergency physicians in the use of new biochemical markers for risk stratification of patients with acute coronary syndrome (ACS). It was demonstrated across a wide range of ACS patient populations (including low-, intermediate-, and high-risk) that evidence of myocardial injury upon presentation is a strong, independent prognostic indicator for short- and long-term adverse outcomes (1–6). The cardiac troponins T (cTnT) and I (cTnI) are especially useful in detecting (small amounts of) myocardial damage because of their cardiac specificity and the availability of new, rapid, and highly sensitive assays. Cardiac troponin becomes elevated in plasma early after the onset of symptoms (7).

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The cardiac troponins are virtually absent in plasma of healthy subjects; therefore, even small elevations are indicative of myocardial necrosis. In addition, false positive troponin results are rare: an abnormal cardiac troponin may be present only in patients with a readily recognizable clinical entity such as muscular dystrophy, and false positive results in patients with renal failure are less frequent with new-generation assays in the case of cTnT (8). As a consequence, the National Academy of Clinical Biochemists and "the joint ESC-ACC working group for the redefinition of myocardial infarction" have recommended that an elevated troponin become part of the definition of acute myocardial infarction (AMI) (8,9). Redefining AMI to include patients with very small amounts of myocardial injury as detected with the new immunoassays may have important socioeconomic (and legal and financial) consequences (10). It will also have consequences with respect to the AMI definition in large epidemiological studies. However, the definition for the clinical diagnosis of AMI should not be dependent on local reimbursement practices or national psychology, and problems with the epidemiological definition can be overcome. There is no clear (patho)physiological or clinical distinction between "minor myocardial damage," "microinfarct" and "infarctlet" characterized by a biochemical marker peak value below or equal to a predetermined cut-off value versus "true AMI" with a peak value just above the cut-off level. There is on the other hand a clear difference in risk between patients with, and patients without, evidence of myocardial injury. Moreover, an incremental risk exists: the higher the troponin concentrations, the higher the prospective risk (3,5), indicating that using the dichotomy between the classic AMI and non-AMI is clinically not meaningful. Finally, with troponin as the gold standard, with its superior sensitivity and specificity, an abnormal troponin in the setting of an ACS will eventually become equivalent to "myocardial damage" or AMI according to the revised definition. Patients presenting with typical chest pain can thus be classified *upon admission* as presenting with an ACS either with ST elevation or with no ST elevation on the electrocardiogram and, subsequently, be *risk-stratified in the following hours* as either with or without evidence of myocardial injury (as assessed by a combination of serial CK-MB_{mass} and cardiac troponin measurements) (8).

The early establishment of evidence of myocardial damage in patients presenting with non–ST elevation ACS is important: such patients more often have significant coronary artery disease (CAD), and they more often have complex lesions and visible thrombus formation on their coronary angiogram (11). In patients with unstable angina, cTnT identified patients with increased procoagulant activity and was closely related to plasma levels of molecular markers of hemostatic activation (12).

Can we now decide on the optimal treatment for patients with non–ST elevation ACS and an abnormal troponin, as opposed to patients with a normal troponin?

It was shown in post-hoc subgroup analyses from the PRISM study (which evaluated the treatment with of tirofiban for non–ST elevation ACS patients), the CAPTURE study (which evaluated the effect of abciximab in patients with refractory unstable angina, scheduled to undergo a percutaneous intervention) and the FRISC-I study (which evaluated the use of low-molecular-weight heparin in unstable angina patients) that non–ST elevation ACS patients with an abnormal troponin are likely to benefit from treatment with glycoprotein IIb/IIIa inhibitors and/or treatment with low-molecular-weight heparin, whereas in patients with a normal troponin, no treatment effect was seen (13–16). Indirectly, this apparent effect of treatment directed against platelet aggregation and trombin formation in patients with an abnormal troponin corroborates the hypothesis of embolization of micro-trombi as the explanation of troponin release in non–ST elevation ACS patients (17).

These analyses have to be put in a new perspective however, in light of the results of the GUSTO-IV ACS

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study that was recently presented at the European Society of Cardiology meeting in Amsterdam. GUSTO IV ACS tested medical treatment with abciximab, in addition to aspirin and heparin, and risk stratification with troponins was tested prospectively. To the surprise of many, although 60% of the patients had an abnormal troponin, 30-day incidence of death/MI was only 8.0% in the placebo group. Moreover, treatment with abciximab provided no benefit. These results indicated that, at present, routine treatment with a glycoprotein IIb/IIIa inhibitor in non–ST elevation ACS patients cannot be recommended solely on the basis of an abnormal troponin. Whether routine early revascularization is beneficial to these patients, as was shown in one randomized clinical trial, the FRISC-II trial, is a matter of ongoing debate (18). Early angiography and subsequent revascularization for high-risk non–ST elevation ACS patients, such as patients with an abnormal troponin, are now included in the recommendations of the European Society of Cardiology Task Force report (19).

The next question to be answered is: "What is the optimal strategy for patients presenting with suspected non–ST elevation ACS, but *without* evidence of myocardial injury? It has become increasingly clear that, depending on patient selection and a priori likelihood of disease, major cardiac events do occur in troponin-negative patients. It was demonstrated by Hamm et al. (20), in low-risk patients triaged in the emergency room, that a normal troponin T or I can identify patients that have a very low incidence of adverse cardiac events in the following months. The authors suggested that these patients may be safely discharged. However, the majority of intermediate-risk patients presenting with chest pain that subsequently have major complications during short-term follow-up do not have an elevated troponin. Although physicians are under pressure because of financial constraints to avoid unnecessary admissions and reduce hospital length of stay, they should be aware of this apparent inability of a normal cardiac troponin to exclude a large proportion of patients who either have significant disease or will develop complications, depending on the patient population studied. The study by Kontos et al. (21) in this issue of the *Journal* is welcome in that respect, as it emphasizes that a normal cardiac troponin I does not by itself exclude trouble. The study comprised a large cohort of 1,929 consecutive patients admitted to the hospital from the emergency department for possible AMI. The investigators performed serial sampling as part of an 8 h rapid diagnostic protocol, using a previously published cardiac troponin I assay. The cut-off value chosen for an abnormal troponin I in this study was 1.0 ng/ml (to maximize sensitivity) on the basis of ROC analysis, instead of using the information provided by the manufacturer. The study confirms that sensitivity of a positive troponin I for AMI (evolving AMI on admission) is high (96%). Patients without AMI but with an abnormal troponin I were more likely to have complications (43% vs. 12%) or significant disease (41% vs. 17%). An important finding however, was that sensitivity for complications or significant disease was low (14% and 21%, respectively), which remained unchanged when patients with ischaemic electrocardiograms were excluded from the analysis. The study by Kontos et al. (21) is consistent with, and extends, prior studies that reported the negative predictive value of cardiac troponins for the occurrence of major complications in patients with moderate risk. In a previous report from a relatively small study, no deaths (0%) and four AMIs (5.8%) occurred at 30 days in the 69 patients with normal cTnI, compared with two deaths (9.1%) and four AMIs (18.2%) in the 22 patients with elevated cTnI (22). In a more recent study that included 1,047 patients, Polanczyk et al. (4) reported that among patients that did not meet the criteria for AMI, cTnI was elevated in only 26% who had major cardiac complications within the first 72 h. The definition of "major complications" was identical to that used in the study by Kontos et al. (21) and the cTnI assay used was from the same manufacturer. In another study by Johnson et al. (23) among patients who did not meet criteria for AMI, cardiac troponin T was elevated within the first 24 h in 31% of patients who had major complications. The study by Kontos et al. (21) is welcome in another respect: until adequate cTnI standardization is available, thresholds established for individual assays from specific manufacturers should not be generalized, and the clinical efficacy of each cTnI assay at a given decision limit should be established in a carefully conducted study (24).

An important limitation of the study by Kontos et al. (21) was that cTnI results were available to the attending clinicians, as were the results of nuclear myocardial perfusion imaging, all of which may have affected subsequent care. The composite outcome measure used by Kontos et al. (21) is somewhat confusing: significant CAD may of course be present without plaque instability or intracoronary thrombus, and a normal cTnI in the majority of these patients is not surprising. Clinical sequelae related to arrhythmias or congestive heart failure were included in the definition of "significant complications," which may be unrelated to the presence of an ACS. Furthermore, although Kontos et al. (21) demonstrated in a multivariate analysis that a positive troponin was the most important predictor of AMI, death or significant coronary disease, readily available clinical variables upon admission that are important prognostic indicators, such as heart rate, systolic blood pressure or signs of heart failure (25), were not included in the analysis.

Further prospective studies are needed to test strategies for early risk stratification and tailored treatment in non–ST elevation ACS patients—a statement that seems even more true, now that the results of the GUSTO-IV ACS study are available. Low-, intermediate- and high-risk patient populations can be identified, using simple risk stratification that includes clinical and electrocardiographic variables obtained upon admission and an observation period of 6 h to 12 h during which the presence and extent of myocardial damage

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can be assessed. Low-risk patients who do not have evidence of myocardial damage and who show an uneventful observation period can be safely discharged and managed at the outpatient clinic. By contrast, intermediate- and high-risk patients should be admitted even in the absence of evidence of myocardial injury. Future studies may also confirm recent evidence that an elevated C-reactive protein concentration in the blood of patients presenting with a non–ST elevation ACS may have important prognostic information, in addition to the prognostic information contained in the patients troponin levels.

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