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Review

The Role of Cardiac Troponin-I (cTnI) in Risk Stratification of Patients with Unstable Coronary Artery Disease

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Summary: In patients with chest pain at rest but no ST-segment elevation on the electrocardiogram, the diagnoses of unstable angina and non-Q-wave myocardial infarction (MI) are usually considered together because they cannot be differentiated clinically or angiographically. Since the extent of myocardial necrosis is an important determinant of the risk of death, it is important to identify serum markers with which to predict prognosis, in order to initiate appropriate medical treatment and/or invasive procedures in these patients. Cardiac troponin-I (cTnI), one of the subunits of the troponin regulatory complex, binds to actin and inhibits interactions between actin and myosin. The presence of elevated cTnI in serum is a significant prognostic indicator in patients with unstable angina and non-Q wave MI. Its independent prognostic potential persists even after adjustment for independent baseline variables known to be significantly associated with an increased risk of cardiac events. The use of cTnI in the triage of patients with unstable coronary disease may identify those at greater risk for adverse cardiac events.

Key words: cardiac troponin-I (cTnI), cardiac troponin-T, creatine kinase-MB (CK-MB), risk stratification, myocardial infarction, unstable angina, non-Q-wave myocardial infarction

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Introduction

Patients with unstable coronary artery disease (CAD) are a heterogeneous group whose risk of death is intermediate between the risk in chronic stable exertional angina and the risk in Q-wave myocardial infarction (MI).[1] Postmortem examinations in patients who die suddenly of ischemic causes after presenting with unstable angina often reveal layers of thrombus material of varying ages in the culprit coronary vessel and evidence of the embolic occlusion of small intramyocardial arteries with microinfarcts.[2] Since the extent of myocardial necrosis is an important determinant of the risk of death,[3] it is important to develop simple noninvasive techniques with which to predict prognosis in order to initiate appropriate medical treatment and/or invasive procedures.

Although the electrocardiographic (ECG) changes are valuable for the risk stratification of patients with unstable CAD, they are nondiagnostic or absent in the majority of these patients.[4] Therefore, in patients with chest pain at rest but no ST-segment elevation on the ECG, the diagnoses of unstable angina and non-Q-wave MI are usually considered together because they cannot be differentiated clinically or angiographically.[1, 5] These conditions are usually differentiated by demonstrating elevations in serum levels of creatine kinase (CK)-MB, when non-Q-wave MI is present. However, the independent prognostic value of elevated CK-MB in the absence of elevated total CK has been difficult to demonstrate. Another serious limitation of the CK-MB measurement is its nonspecificity, since CK-MB is present in tissues other than the myocardium. It is therefore desirable to identify a serum marker that is more sensitive and specific and the serum levels of which are more directly related to the extent of myocardial injury than the conventionally employed CK-MB.

Cardiac troponin-I (cTnI), one of the subunits of the troponin regulatory complex, binds to actin and inhibits interactions between actin and myosin. It has a molecular mass of approximately 24 kDa and it is therefore released rapidly from the injured myocardium. The initial time course of cTnI is very similar to that of CK-MB, with elevations above normal between 4 and 6 h and peak levels between 12 and 18 h after the estimated time of infarction. Cardiac troponin-I, however, remains elevated for up to 6–8 days, allowing improved sensitivity for diagnosis of MI in patients who are admitted late to the hospital.[6] Monoclonal antibody-based immunoassays

have shown that no cTnI is expressed in human skeletal muscle during fetal development, after skeletal muscle trauma, or during the regeneration of skeletal muscle.[7] Unlike CK-MB, cTnI levels are undetectable in serum from patients without cardiac disease and apparently healthy individuals. Consequently, cTnI is helpful in clinical settings where the specificity of CK-MB is in doubt, such as chest trauma, acute and chronic skeletal muscle trauma, and perioperative MI. Moreover, patients maintained on chronic dialysis without evidence of myocardial injury often have chronically increased CK-MB and cardiac troponin-T (cTnT), without increased cTnI levels. A recent study demonstrated that predialysis levels of CK-MB were elevated in 7 of 24 (30%) and cTnT levels were elevated in 3 of 18 (17%) patients without evidence of ischemic heart disease.[8] In contrast, only a single patient (4%), who had no clinical evidence of myocardial injury, exhibited increased serum cTnI. Thus, cTnI appears to have a diagnostic advantage over CK-MB and cTnT in patients with chronic renal failure. Because cTnI does not normally circulate in the blood and is 13 times more abundant in the myocardium than CK-MB on a weight basis,[9] the signal-to-noise ratio associated with cTnI is much more favorable to the detection of minor amounts of cardiac necrosis.

Given these favorable characteristics of cTnI, several recent studies have examined its prognostic potential for risk stratification of patients with unstable CAD. The focus of this article is to examine the clinical value of cTnI in this setting through review of the available literature.

Review of the Literature

In the largest multicenter study to date, Antman *et al.*[10] studied the prognostic role of cTnI for early identification of patients with unstable angina or non-Q-wave MI with an increased risk of death. Operating under the hypothesis that detection of any cTnI in the blood is abnormal, the authors sought to determine whether elevated levels of cTnI in these patients predict an increased risk of mortality and whether the quantity of cTnI detected correlates with the degree of mortality risk. The database for this study was the Thrombolysis in Myocardial ischemia (TIMI) IIIB Trial, a randomized, double-blind study that used a two-by-two factorial design to compare tissue plasminogen activator with placebo in a double-blind analysis, and to compare an early, invasive management strategy with an early, conservative strategy in patients with unstable angina and non-Q-wave MI. Specimens from 1,404 patients were analyzed for cTnI and CK-MB, using the Stratus II fluorimetric enzyme immunoassay (Dade Behring, Inc., Newark, Del., USA) with a minimal detectable concentration of cTnI of 0.4 ng/ml. The relation between mortality at 42 days and the level of cardiac cTnI in the specimen obtained on enrollment was determined both before and after adjustment for baseline characteristics.

Those patients with detectable cTnI (i.e., cTnI of at least 0.4 ng/ml) at enrollment were less likely to have a history of prior angina, hypertension, MI, or a prior coronary angiogram showing substantial stenosis. These patients were also less likely to have received nitrates, beta blockers, calcium antagonists, or aspirin prior to the qualifying episode of ischemic discomfort. However, they had a significantly longer qualifying episode of pain and were significantly more likely to present with ST-segment deviation (either depression or transient elevation) compared with patients whose cTnI was not detected at enrollment.

The mortality rate at 42 days was significantly higher (2.4–4.0%) in those with detectable cTnI levels than in those with undetectable (< 0.4 ng/ml) cTnI levels (0.5–1.7%) (Fig. 1). The magnitude of the relative difference between the mortality rate in the group with and without detectable cTnI was greatest in the subset of patients presenting at least 6 h from onset of pain, as evidenced by the approximately 2- to 3-fold increase in the odds ratio for mortality. Moreover, when compared with patients whose troponin I level was not detected at presentation, there was a statistically significant progressive increase in mortality with increasing levels of cTnI (Fig. 2). In the overall study population, each increase of 1 ng/ml in the cTnI level was associated with a significant increase in the risk ratio for death after adjustment for the baseline characteristics that were independently predictive of mortality (i.e., ST-segment depression and age ≥ 65 years). The correlation between cTnI and the risk of mortality was even stronger among the patients presenting more than 6 h after the onset of chest pain.

It is interesting that the levels of cTnI of at least 0.4 ng per ml in a single plasma specimen at presentation appear to be associated with an increased risk of mortality even in patients whose CK-MB measurements are not considered abnormally elevated (Fig. 1). This increased sensitivity of cTnI was probably due to the fact that cTnI does not normally circulate in the blood and that it is 13 times more abundant in the myocardium than CK-MB, rendering the signal-to-noise ratio much more favorable for cTnI for detection of minor myocardial injury.

The findings from the TIMI IIIB study indicate that the elevated level of cTnI, when a patient with unstable angina is first evaluated, predicts an increased risk of short-term mortality, probably because it permits the diagnosis of non-Q-wave MI that one might otherwise have overlooked by sampling only for CK-MB. With progressively higher levels of cTnI, the risk of mortality increases, presumably because the amount of myocardial necrosis increases. The prognostic information conveyed by cTnI was evident even in a group of patients with a low overall mortality rate (2.1% at 42 days). Of importance, the prognostic potential of cTnI persisted even after adjustment for independent baseline variables known to be significantly associated with an increased risk of cardiac events, such as age ≥ of 65 years and ST-segment depression on the ECG.

Similar findings were observed by Galvani *et al.*,[11] who prospectively studied a cohort of 91 patients with the clinical diagnosis of unstable angina, showing chest discomfort at rest within 48 h of admission, accompanied by objective evidence of ischemia on the qualifying ECG, total CK activity ≤ 200 IU/l on serial determinations performed during the first 16 h, and absence of elevated CK-MB mass concentration measured during the same 16-h time period. The patients were fol-

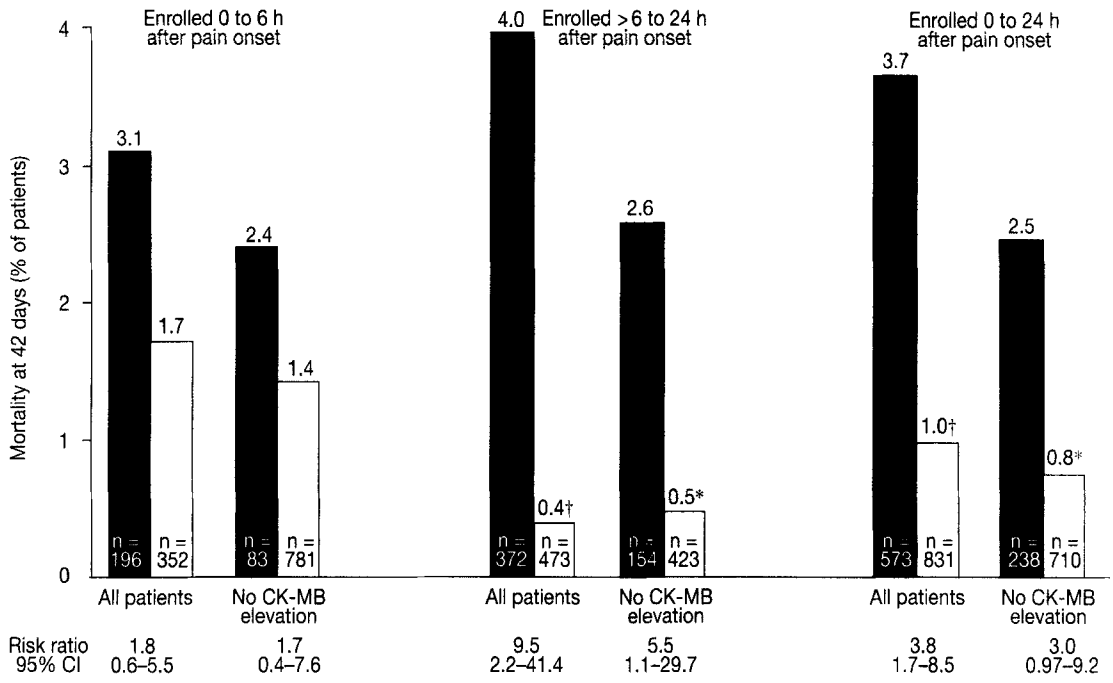

FIG. 1 Mortality rates at 42 days (without adjustment for baseline characteristics) and risk ratios and comparative 95% confidence intervals (CI) are shown for the study patients according to the time from the onset of chest pain to enrollment. n = Number of patients. ■ = troponin I > 0.4 ng/ml, □ = troponin I < 0.4 ng/ml, * = $p < 0.05$, † = $p < 0.0001$. Reprinted from Ref. No. 10 with permission.

lowed for 30 days after admission to determine the primary end point of a composite of death from cardiac causes and nonfatal MI. Secondary end points included the frequency of myocardial ischemia, the need for revascularization procedures (coronary angioplasty or bypass surgery) within 30 days of hospitalization, and the 1-year rates for cardiac mortality and nonfatal MI. In this study, cTnI was measured using a preliminary research application of the assay employed in TIMI IIIB.[10] Studies performed with this earlier version of the assay on samples of hospitalized patients without known cardiac disease have defined the upper limit of the cTnI reference range to be ≥ 3.1 ng/ml, with a lower limit of detection of 1.5 ng/ml. In contrast to TIMI IIIB, Galvani *et al.*[11] elected to use the upper limit of the reference range (i.e., 3.1 ng/ml), as opposed to the lower limit of detection of the assay of 1.5 ng/ml as a diagnostic cutoff. The limitations of this approach, using a higher diagnostic cutoff for cTnI, is the potentially decreased diagnostic sensitivity for the primary and secondary end points of the study. In addition, significant elevations in cTnI in the range between 0.4 and 1.5 ng/ml could not be discerned by the research assay employed in this study, further contributing to the potential loss of diagnostic sensitivity.

Of the patients studied, 24% had increased levels of cTnI with normal values of CK-MB. Patients with cTnI levels > 3.1 ng/ml had a significantly longer duration of chest discomfort before admission and more ST-segment shifts. The clinical outcomes during the first 30 days of follow-up were significantly different between patients with and without elevations of cTnI. At 30 days, no deaths and four acute MIs occurred in the 69 patients with normal cTnI compared with two deaths and four MIs in the 22 patients with elevated cTnI. The combined incidence of death and nonfatal MI was 5.8 and 27.3%, respectively ($p < 0.02$). In a multivariate logistic regression model, including patients' age and the presence of T-wave inversion on the qualifying ECG in addition to cTnI, the presence of T-wave inversion and cTnI levels > 3.1 ng/ml were identified as independent predictors of cardiac events. The relative risk of cardiac events at 30 days among patients with

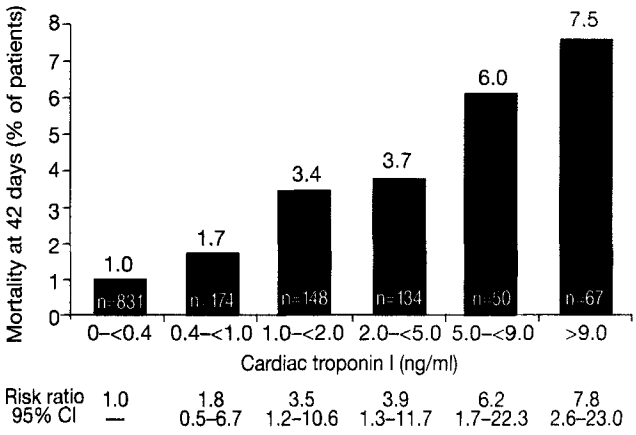

FIG. 2 Mortality rates at 42 days (without adjustment for baseline characteristics) are shown for ranges of cardiac troponin I levels measured at baseline. $P < 0.001$ for the increase in the mortality rate (and the risk ratio for mortality) with increasing levels of cardiac troponin I at enrollment. n = Number of patients. Reprinted from Ref. No. 10 with permission.

cTnI levels > 3.1 ng/ml and T-wave inversion was 8.6 compared with the remaining study population. Moreover, the prognostic value of cTnI > 3.1 ng/ml levels persisted at 1-year follow-up. At 1 year, only 68% of patients with cTnI elevations were free of cardiac events, compared with 90% of those without elevation of cTnI ($p < 0.01$). The relative risk of death or MI at 1 year in patients with cTnI > 3.1 ng/ml was 2.6.

Luscher *et al.*[12] compared the prognostic value of cTnT and cTnI in a cohort of 516 patients suspected of having unstable coronary artery disease, as part of the Thrombin Inhibition in Myocardial Ischemia (TRIM) study. The study population was categorized as having either unstable angina (n = 309), non-Q-wave acute MI (n = 190), or other diseases (n = 17), on the basis of the clinical course, ECG changes, and plasma levels of cardiac markers. Follow-up was done after 30 days, and the occurrences of cardiac death, acute MI, refractory angina, and recurrent angina were noted.

Cardiac troponin I was measured with an Opus Magnum device (Dade Behring, Inc.), and a diagnostic cutoff of 2.0 ng/ml was used as recommended by the manufacturer of the assay. The patients were considered "positive" for cTnI if the highest value on inclusion or 6 h after enrollment exceeded the chosen discriminator values of 2.0 ng/ml for cTnI. The cTnI assay in the TRIM study differs from the one used in TIMI IIIB and the study by Galvani *et al.* in that it employs polyclonal antibodies to recognize epitopes unique to cTnI.[12] In contrast, the Stratus fluorimetric immunoassay employed in TIMI IIIB and the study by Galvani *et al.*, employs two monoclonal antibodies that recognize two different epitopes on the cTnI molecule.[13]

A total of 214 patients (41%) had a highest cTnI value within 6 h, exceeding the cutoff value for cTnI of > 2.0 ng/ml. These patients had a significantly higher risk of cardiac death than those with normal levels, that is, 3.2 versus 0.7% ($p < 0.026$). The 3.2% mortality rate found in the " cTnI positive" (> 2.0 ng/ml) group in the study by Luscher *et al.* is comparable with the 3.7% mortality rate at 42 days in patients with detectable (≥ 0.4 ng/ml) cTnI in the study by Antman *et al.*[10] Elevated levels of both cardiac troponins within the first 6 h after inclusion were significantly associated with increased mortality rates at 30 days. Furthermore, both markers identified patients with an increased risk of the composite end point of cardiac death/acute MI. Multivariate analysis indicated that both cTnT and cTnI were strong independent prognostic factors with regard to cardiac death/acute MI, and the inclusion of ECG changes provided no additional information about the clinical outcome.

Conclusions

The results of the studies reviewed here indicate that the presence of elevated cTnI is a significant prognostic indicator in patients with unstable angina and non-Q-wave MI. It appears that the cTnI elevations in the absence of increased levels of CK-MB may detect a minor level of myocardial necrosis, signifying higher risk for cardiac adverse events. Moreover, the independent prognostic potential of cTnI persists even after adjustment for independent baseline variables known to be significantly associated with an increased risk of cardiac events.

It can therefore be concluded that the use of cTnI in the triage of patients with unstable coronary disease may identify those at greater risk for adverse cardiac events. Several ongoing TIMI trials (TIMI 11B, OPUS-TIMI 16, and TACTICS-TIMI 18) are investigating whether a particular mode of treatment (antithrombotic regimens or an invasive vs. conservative strategy) could improve the clinical outcome in patients classified as "high risk" by cTnI elevations.

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