GP IIb/IIIa receptor antagonists in unstable angina: troponin level-based patient selection

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Troponins T and I are biochemical markers for thrombotic microembolization and minor myocardial injury and have proven to be sensitive prognostic indicators in patients with unstable angina. An analysis of data from the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial has shown that troponin-negative patients had a low incidence of cardiac events and did not benefit from glycoprotein (GP) IIb/IIIa receptor blockade. Abciximab significantly reduced both the short- and long-term risks of death or acute myocardial infarction in patients with baseline elevations in troponin. This has been confirmed in retrospective analyses of other trials. The combination of pre-treatment with a GP IIb/IIIa receptor antagonist with early invasive management was shown to provide the best outcome in the Thrombolysis and Counterpulsation to Improve Cardiogenic Shock Survival (TACTICS) study. Troponin measurements represent a practical and simple tool for risk stratifying patients with unstable angina and selecting those most likely to benefit from potent platelet inhibitor therapy.

Key Words: Troponin, GP IIb/IIIa, unstable angina, classification, risk stratification, myocardial infarction.

Introduction

In the weeks and months following an episode of unstable angina, the risk of progression to acute myocardial infarction (MI) is precariously increased. Platelet glycoprotein (GP) IIb/IIIa receptor antagonists have been applied in this setting in the expectation that interrupting the key pathophysiological events of platelet aggregation and the formation of platelet-rich thrombi might prevent the development of life-threatening ischaemic complications.

An analysis of a subgroup of patients with unstable angina who had been enrolled in the Evaluation of c7E3 for the Prevention of Ischaemic Complications (EPIC) trial, the first large-scale trial of a GP IIb/IIIa receptor antagonist, revealed that treatment with the monoclonal antibody abciximab in conjunction with percutaneous intervention dramatically reduced the risk of death and acute MI over the first 30 days. This benefit, which was markedly greater than that observed in patients with stable angina, was sustained for as long as 6 months. Since that time, a number of large-scale trials have been conducted that were specifically designed to confirm the efficacy of abciximab and the synthetic GP IIb/IIIa receptor blockers tirofiban and eptifibatide in patients with unstable angina undergoing percutaneous intervention or being managed medically. However, the results were less striking than those reported in the EPIC subgroup. In these studies, the clinical benefits of GP IIb/IIIa receptor antagonism were of marginal statistical significance, evident only with the use of composite end-points or with the use of short-term results. For example, the early reductions in the rate of death, acute MI or ischaemic complications observed with tirofiban in the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) and Platelet Receptor Inhibition in Ischaemic Syndrome Management (PRISM) trials dissipated within 30 days. In the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) study, the benefits of abciximab in preventing death, acute MI or the need for urgent revascularization were maintained for 30 days but were lost after 6 months of follow-up.

One of the chief limitations in evaluating new approaches to improving the outcome of patients with unstable angina is that the syndrome of unstable angina is defined on the basis of clinical signs and symptoms, not by objective criteria. This raises the possibility that the modest benefits observed in the trials of GP IIb/IIIa receptor inhibitors resulted from the inadvertent inclusion of low-risk patients in the study populations. There is a clear need for objectively measurable biochemical parameters that would distinguish between low- and high-risk patients, thereby permitting early intervention to prevent myocardial damage. Several recent reports have indicated that elevated levels of the myocyte regulatory proteins troponin I and troponin T may signal minor myocardial injury and thereby define a high-risk subgroup of patients with unstable angina. The combination of troponin-negative patients has a low incidence of cardiac events and did not benefit from glycoprotein (GP) IIb/IIIa receptor blockade. Abciximab significantly reduced both the short- and long-term risks of death or acute myocardial infarction in patients with baseline elevations in troponin. This has been confirmed in retrospective analyses of other trials. The combination of pre-treatment with a GP IIb/IIIa receptor antagonist with early invasive management was shown to provide the best outcome in the Thrombolysis and Counterpulsation to Improve Cardiogenic Shock Survival (TACTICS) study. Troponin measurements represent a practical and simple tool for risk stratifying patients with unstable angina and selecting those most likely to benefit from potent platelet inhibitor therapy.

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unstable angina\textsuperscript{[9–12]}. These findings suggest that such high-risk patients might represent the most appropriate target group for treatment with a GP IIb/IIIa receptor antagonist.

This article reviews the role of troponins in defining risk strata and predicting outcome in patients with unstable angina. It also discusses evidence in support of the hypothesis that GP IIb/IIIa receptor inhibitors are most effective in patients with elevated levels of troponins. The value of C-reactive protein (CRP) as a prognostic indicator also is addressed.

**Predictive value of troponins in acute coronary syndromes**

The prognostic significance of cardiac troponin levels has been established in numerous studies. The first evidence of troponin T as a marker of increased risk of death or MI in unstable angina during hospitalization was reported from a small group of patients\textsuperscript{[13]}. The Fragmin During Instability in Coronary Artery Disease (FRISC) study group confirmed the value of troponin T elevations in predicting the risk of major cardiac events in 976 patients with unstable coronary artery disease during 5 months of follow-up\textsuperscript{[14]}. They found that the risk of acute MI or cardiac death within 5 months of the index episode was only 4.3% in patients with troponin T levels <0.06 µg.1\textsuperscript{-1}, that it rose to 10.5% in patients with levels between 0.06 and 0.18 µg.1\textsuperscript{-1} and that it reached as high as 16.1% in those with levels ≥0.18 µg.1\textsuperscript{-1}. The 5-month risk of mortality alone was zero in patients with troponin levels <0.06 µg.1\textsuperscript{-1}, compared with 8.6% in patients with levels ≥0.18 µg.1\textsuperscript{-1}. A subsequent study of the FRISC population revealed that troponin T as a predictor of risk is at least as useful in women with unstable coronary artery disease as in their male counterparts\textsuperscript{[15]}. Furthermore, the combination of the troponin T test with a predischarge exercise test represents an excellent risk assessment of unstable coronary disease\textsuperscript{[16]}. The findings for troponin T were confirmed for troponin I in 1404 patients with unstable angina or non-Q-wave MI in the Thrombolysis in Myocardial Ischaemia phase IIIB (TIMI IIIB) trial\textsuperscript{[17]}. In 41% of patients who had elevated troponin I levels, 6-week mortality was nearly four times higher than in individuals with undetectable troponin I levels (3.7% versus 1.0%, \(P<0.001\)) (Fig. 1). In patients who presented more than 6 h after the onset of symptoms, elevated troponin I levels were associated with a tenfold greater risk of mortality at 6 weeks (4.0% versus 0.4%, \(P<0.001\)). The predictive value of troponin I elevations remained significant even in the absence of increased creatine kinase (CK)-MB levels. Moreover, the risk of dying within 6 weeks rose with increasing levels of troponin I, reaching 7.5% in patients with levels ≥0.9 ng. ml\textsuperscript{-1} (Fig. 2). This study established that troponin I is sufficiently sensitive and specific...
as a marker of minor myocardial necrosis to serve as an independent predictor of early mortality in patients with unstable angina or non-Q-wave MI.

A prospective trial showed that risk stratification based on a protocol that scheduled rapid testing of troponin upon the patient’s arrival in the emergency room and another 4–6 h later is more reliable than the more time-consuming earlier protocols. A single test value on admission is inappropriate for a reliable diagnosis. The prognostic value was independent of electrocardiographic (ECG) findings and was superior to CK-MB measurements. The risk of MI or death in 30 days is approximately 20% in patients with positive evidence of troponins. These patients represent a high-risk group who should be hospitalized and evaluated further. In contrast, when, as indicated by sequential testing, troponins are not elevated, the risk of death or MI within 30 days is <1%. However, it must be emphasized that the absence of elevated troponins does not exclude coronary artery disease in these patients.

In patients who present with chest pain but no ischaemic ECG abnormalities, troponin T has recently been proved useful for identifying those who are most likely to have extensive coronary artery disease and a poor long-term prognosis. In a study of 414 consecutive patients referred to a chest pain unit, the incidence of angiographically documented coronary artery disease was 90% among patients who had positive troponin T assays (>0.1 ng.ml\(^{-1}\)) but only 23% among troponin-negative patients (P<0.01). Multivessel involvement was present in nearly two thirds of troponin-positive patients and in only 12.5% of troponin-negative patients (P<0.01). After a mean follow-up period of nearly 1 year, 34% of patients with a positive troponin T test had had a major cardiac event, versus only 13% of troponin-negative patients (P=0.0004).

**Figure 2** Progressive increases in 6-week mortality according to increasing baseline levels of troponin I in the TIMI IIIB trial. Increasing levels of cardiac troponin I were associated with statistically significant increases in mortality (P<0.001). Six-week mortality was as high as 7.5% in patients with the highest levels of troponin I (≥9.0 ng.ml\(^{-1}\)). (Adapted with permission[17].)

New troponin-based subclassification of unstable angina

For more than a decade, unstable angina has been stratified according to the Braunwald classification system, which is based on clinical history and circumstances, ECG changes and the intensity of anti-ischaemic therapy. Recently, a new subclassification was suggested for assessing risk in patients who have unstable angina with rest pain occurring within the past 48 h in the absence of a recent infarction (Braunwald class IIIB[21]). The proposal is to subdivide class IIIB patients according to whether they are troponin-positive, in which case they face a 15–20% risk of death or acute MI within 1 month, or troponin-negative, in which case their short-term risk of a major cardiac event is <2%[11].

Such risk stratification must be based on at least two measurements of either troponin T or troponin I, with the last test performed ≥6 h after the first episode of acute chest pain (Fig. 3). Although combining troponin measurements with measurements of other biochemical markers, such as CRP, might afford even more precise risk stratification, the advantage of using troponin by itself is that this marker can be qualitatively assessed in only 15–20 min using a hand-held device at the patient’s bedside. Incorporation of troponin measurements into the clinical classification of unstable angina provides a simple, quick and reliable method of identifying high-risk patients. In practice, these measurements may also serve as a guide to selecting patients likely to benefit from more intense treatment, such as with a GP IIb/IIIa receptor inhibitor.

Troponins as predictors of response to GP IIb/IIIa receptor inhibitors

**Rationale for use of GP IIb/IIIa receptor inhibitors in acute coronary syndromes**

The pathophysiological event that precipitates the clinical syndrome of unstable angina is erosion or rupture of the fibrous cap of an unstable atherosclerotic plaque; exposure of the thrombogenic contents of the plaque leads to platelet activation and adhesion which, in turn, promote the formation of thrombus at the site of injury[21–25]. According to angioscopic studies, the thrombus that triggers unstable angina is usually a white, platelet-rich thrombus, not the red, fibrin-rich thrombi more commonly seen in acute MI[26]. The platelet-rich thrombus usually does not completely occlude the artery, in contrast to the total occlusion that characterizes acute MI. However, parts of the thrombus may embolize downstream, culminating in focal cell necrosis in the myocardium supplied by the involved artery[21]. The resulting minor myocardial injury is usually undetectable by routine CK or CK-MB measurements but is reflected by elevations in troponin T or
troponin I levels, shown in up to 40% of patients with unstable angina\[13,17\]. If troponins are a surrogate marker for thrombotic microembolization, platelet GP IIb/IIIa receptor inhibitors, which are potent blockers of platelet aggregation, might be the treatment of choice for unstable angina patients with elevated troponin levels. This hypothesis was first evaluated in patients in the CAPTURE trial\[27\].

**Troponins and therapeutic efficacy in CAPTURE**

The CAPTURE trial investigators retrospectively sought to determine whether baseline troponin T levels could be used to define risk strata and whether they would forecast the response to abciximab treatment in 890 of 1265 trial participants with unstable angina who were undergoing percutaneous intervention\[27\]. Baseline demographic, clinical and treatment characteristics of these 890 patients were comparable to those of the total study population.

In the 372 (41.8%) patients who were negative for troponin T (serum level ≤0.1 ng.m \(^{-1}\)) before PTCA and thereafter by 71% (from 10.8% to 2.9%, \(P=0.007\)) in the 72 h after randomization (Fig. 4). It should be noted that the benefit of abciximab in patients with elevated troponin T levels was maintained for the entire 6 months of the CAPTURE study. Abciximab reduced the cumulative 6-month rate of death or MI by 68% (to 9.5%) versus 23.9% with placebo (\(P=0.002\)) (Fig. 5). This means that treatment with abciximab reduced the 6-month risk of cardiac events in troponin T-positive patients to a level comparable with that documented in the lower-risk troponin T-negative population.

Although it was noted that elevations in CK-MB levels were important markers of increased cardiac risk in patients in the CAPTURE trial, investigators observed no significant relationship between CK-MB levels and response to abciximab treatment at any time\[27\]. Likewise, ECG indicators of unstable angina, such as ST-segment depression and T-wave inversion, had no independent predictive value. Thus, in the CAPTURE study, a troponin T level >0.1 ng.m \(^{-1}\) was the only significant independent predictor of benefit after abciximab treatment in the 6 months of follow-up.

An analysis of data from 853 patients in the CAPTURE trial for whom baseline and post-treatment angiograms were available revealed complex type B2+ or C lesions in 72% of troponin T-positive patients but only 54% of troponin T-negative patients\[10\]. Moreover, three
abciximab-treated patients with elevated troponin T levels or patients with low troponin T levels. (Adapted with permission.)

The 6-month incidence of cardiac events in patients with elevated troponin T levels who were treated with abciximab approached that of patients with low troponin T levels. (Adapted with permission.)

Further support for the value of troponin measurements in identifying patients with unstable angina who are most likely to benefit from GP IIb/IIIa receptor inhibitor treatment has come from an analysis of data from 2222 of 3232 patients enrolled in the PRISM study. Tirofiban treatment lowered the 30-day incidence of death and MI from 13.0% to 4.3% (P < 0.001) in troponin I-positive patients and from 13.7% to 3.5% (P < 0.001) in troponin T-positive patients. In contrast, patients who were negative for troponin I or troponin T had low event rates and obtained no significant benefit from tirofiban treatment. In contrast to the CAPTURE study, not all patients enrolled in the PRISM trial underwent coronary revascularization. The benefits of GP IIb/IIIa receptor inhibitor therapy were more dramatic in, but not limited to, PRISM study participants who were treated with interventional or surgical revascularization. As in the CAPTURE report, neither CK-MB elevations nor ECG changes provided any independent predictive information about the therapeutic efficacy of GP IIb/IIIa receptor blockade. Data from the PRISM trial also pointed to a significant reduction in the length of hospital stay in patients with elevated troponin levels who were treated with tirofiban. The mean duration of hospitalization fell from 15 days to 8 days in this group, which was comparable to the 6- to 7-day length of stay documented for troponin-negative patients. These findings suggest that the use of GP IIb/IIIa receptor inhibitors in the management of selected patients with unstable angina is not only clinically beneficial but also cost-effective.

Newer studies

The troponin hypothesis has been tested prospectively in the Global Use of Strategies to Open Occluded Arteries (GUSTO)-IV–ACS Study. Troponins were used as entry criteria for the first time and indicated elevated risk but did not predict the benefit of abciximab treatment. However, there was also no benefit in any other subgroup. The explanation is subject to speculation and could be related to the duration of treatment or the selection of patients. It is also possible that there are differences
between the GP IIb/IIIa receptor antagonists. Alternatively, a full effect of GP IIb/IIIa receptor antagonists may appear only in conjunction with a coronary intervention. This conclusion is supported by the recent results of the Thrombolysis and Counterpulsation to Improve Cardiogenic Shock Survival (TACTICS)-TIMI 18 study, which demonstrated that an early invasive approach incorporating GP IIb/IIIa receptor blockade with tirofiban results in a better 6-month outcome than a conservative approach. Further studies are needed to understand fully all mechanisms involved.

Conclusions

Recent years have witnessed the evolution of the role of the troponins from laboratory markers of myocardial cell injury to predictors of short- and long-term prognosis and, finally, to practical indicators from which patients with unstable angina will benefit most in GP IIb/IIIa receptor inhibitor treatment. The CAPTURE and PRISM studies have shown retrospectively that GP IIb/IIIa receptor inhibitors enhance clinical outcome in troponin-positive patients, while exerting little or no impact in troponin-negative patients. The benefits of potent platelet inhibition in these high-risk subgroups with elevated troponin levels were durable over long-term follow-up and were demonstrable both in patients undergoing coronary revascularization and in patients managed conservatively. These findings suggest that troponins may represent a surrogate marker for active thrombus formation and that this process and its associated complications can be successfully interrupted by GP IIb/IIIa receptor inhibitor therapy. However, this concept has recently been challenged by the results of the GUSTO-IV–ACS study. More evidence is necessary to understand fully all the mechanisms involved.

References


