Mechanisms Behind the Prognostic Value of Troponin T in Unstable Coronary Artery Disease: A FRISC II Substudy

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OBJECTIVES
This study was designed to elucidate possible mechanisms for the prognostic value of troponin T (tnT).

BACKGROUND
The reasons for the adverse prognosis associated with elevation of troponins in unstable coronary artery disease are poorly understood.

METHODS
Patients enrolled in the Fast Revascularization during InStability in CAD (FRISC-II) trial were included. Clinical characteristics, findings at echocardiography and coronary angiography, and prognosis were evaluated in relation to different tnT levels.

RESULTS
Absence of significant coronary stenosis was more frequent and three-vessel disease or left main stem stenosis was less frequent in patients without, compared with, detectable tnT. The occurrence of visible thrombus increased with rising levels of tnT. In the group with the highest levels of tnT, occlusion of the left circumflex artery was more common than in the other tnT groups, as was a left ventricular ejection fraction below 0.45. The one-year risk of death in the noninvasive arm of the study increased by increasing levels of tnT (1.6% to 4.6%), whereas the risk of myocardial infarction showed an inverted U-shaped curve and was lower in the lowest (5.5%) and highest (8.4%) tnT groups than in the two intermediate groups (17.5% and 16.2%).

CONCLUSIONS
Any detectable elevation of tnT raises the probability of significant coronary stenosis and thrombus formation and is associated with an increased risk of reinfarction and death. However, at a more pronounced elevation of troponin, a higher proportion of patients has a persistent occlusion of the culprit vessel and reduced left ventricular function, associated with a high mortality but a modest risk of reinfarction. (J Am Coll Cardiol 2001;38:979–86) © 2001 by the American College of Cardiology

The value of troponin T (tnT) or I for risk stratification in unstable coronary artery disease (CAD), that is, non–ST-segment elevation myocardial infarction (MI) and unstable angina, is well established (1–3). However, the reasons for the adverse prognosis associated with elevations of troponin are not fully understood. The troponins are sensitive and specific markers for myocardial necrosis (4), which might occur in unstable CAD as a result of persistent or transient thrombotic vessel occlusion at the site of plaque rupture or erosion (5). Furthermore, small areas of myocardial necrosis caused by microembolizations from the thrombus, occluding arterioles and capillaries downstream, might be an alternative or contributory cause of minor elevations of troponin in unstable CAD (6). Recently, it has been shown (7,8) that patients with unstable CAD and elevated tnT or I had more widespread CAD than those without elevated tnT or I and more often had complex lesion characteristics and visible thrombus in the culprit vessel (7,9,10). The aim of the present study was to further elucidate the mechanisms behind the prognostic value of tnT in a large cohort of patients with unstable CAD.

METHODS

Patients and study design. The present study was a substudy of the FRISC-II (Fast Revascularization during InStability in CAD) trial (11,12). In brief, the FRISC-II was a prospective, multicenter trial in which 2,457 patients were randomized to a noninvasive or an invasive strategy. Furthermore, within each arm patients were randomized to 90 days treatment with low molecular weight heparin, dalteparin or placebo.

Inclusion criteria were symptoms of myocardial ischemia associated with ST-depression, T-wave inversion or elevation of available cardiac markers. Major exclusion criteria were raised risk of bleeding, angioplasty performed within past six months, waiting list for coronary revascularization procedure, previous open-heart surgery, other severe cardiac disease, renal insufficiency (serum creatinine >150 µg/l) or other severe illness.

Written consent was obtained from all patients and the protocol was approved by all local ethics committees.

Randomized treatment. All patients were initially treated with either subcutaneous dalteparin or by intravenous infu-
The patients were randomized within 48 h after the start of open-label dalteparin or standard heparin. From randomization all patients received dalteparin subcutaneously (120 U/kg) twice daily until the early invasive procedure and for at least five days in the noninvasive arm. After this initial treatment, patients received twice-daily subcutaneous injections of either dalteparin in a dose adjusted for weight and gender (5,000 to 7,500 U) or placebo for three months.

The early invasive strategy required coronary angiography and, if appropriate, revascularization within seven days from start of open-label dalteparin. The noninvasive strategy included coronary angiography only in patients with refractory symptoms, severe ischemia at a predischarge symptom-limited exercise test, or severe angina or MI during follow-up.

The patient flow in the present substudy is outlined in Figure 1.

Blood samples for biochemical markers. At randomization ethylenediamine tetraacetate-plasma samples were obtained from 2,329 patients (95%) and stored frozen at −70°C for central analysis of tntT with a third-generation tntT assay on an Elesys 2010 (13). The analytical range extends from 0.01 to 25 μg/l and the upper reference level, defined as the 99th percentile of healthy controls, is below the lower limit of the analytical range. At our laboratory the intra-assay CV was 7.9% (n = 19) and interassay CV was 11.2% (n = 8) at the low end of the analytical range (tntT = 0.037 μg/l).

The patients were divided in four groups based on tntT levels: the first group consisted of all patients without measurable tntT (<0.01 μg/l, n = 623) and the others of the first, second and third tertile, respectively, of the remaining patients (0.01 to 0.17 μg/l, n = 570; 0.18 to 0.63 μg/l, n = 569; and >0.63 μg/l, n = 567).

ECG and echocardiogram. The admission (qualifying) 12-lead electrocardiograms (ECGs) were evaluated at a core laboratory. Rhythm, presence and location of pathological Q-waves, ST-segment depression (≥0.05 mV) and T-wave inversion were recorded.

Echocardiograms were obtained in 1,867 (80%) of the patients before discharge and always before any invasive procedure. All echocardiograms were evaluated centrally and the left ventricular ejection fraction was visually assessed. A depressed systolic left ventricular function was considered present when the ejection fraction was below 0.45.

Coronary angiogram. In 1,142 (98.4%) of the 1,161 patients randomized to an invasive policy and with tntT determined at randomization, a coronary angiogram was performed at a median of four days (25th to 75th percentile; 3 to 5 days) from admission (Fig. 1). The coronary angiograms were evaluated locally according to a detailed protocol and without knowledge of tntT status. The coronary vessels were divided in 16 segments (14) and degree of stenosis, Thrombolysis In Myocardial Infarction (TIMI) flow grade and any visible thrombus were noted in each of these segments. A ≥50% diameter obstruction in at least one of

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**Figure 1.** Patient flow in the present substudy.
the segments in the respective vessel area (right coronary, left anterior descending and left circumflex artery) was considered significant in respect of the traditional one-, two- or three-vessel disease. Also for the left main artery, a 50% diameter stenosis was considered significant. The evaluator of the coronary angiogram was urged to identify and localize the culprit lesion to a single segment, which was possible in 652 patients (56%).

Clinical end points. The relation between tnT levels and clinical outcome at 12 months was evaluated in the noninvasive arm of the study (Fig. 1). The noninvasive arm was chosen because of the marked influence of an invasive strategy on subsequent events (11,12). The randomization to three months of dalteparin versus placebo was not considered, as it did not influence the long-term outcome (11). The clinical end points used in the present analysis were total death, MI and revascularization (due to incapacitating or recurrent symptoms or severe ischemia at the exercise test). Details about the follow-up and evaluation procedures and definitions have been published elsewhere (11,12).

Statistics. Differences in proportions were evaluated by chi-square test. The Kruskal-Wallis one-way analysis of variance was used to test the equality of distributions in the four tnT groups.

Adjusted relative risk ratios and 95% confidence intervals in relation to tnT levels were calculated for occurrence of depressed left ventricular ejection fraction and findings at coronary angiography, respectively, by multiple logistic regression analysis. To identify independent predictors of death and MI, respectively, multiple logistic regression analyses were applied, forcing all the tested variables into the models.

For all statistical analyses a significant difference was considered to exist at the p < 0.05 levels. All calculations were done with the SPSS system 10.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Clinical data, echocardiogram and tnT. The blood sample for analysis of tnT was obtained at randomization, which took place in median 38.6 h (25th to 75th percentile, 26.8 to 54.0 h) from onset of last episode of chest pain. Seventy-three percent, 58% and 47% of the patients had a tnT level <0.01, 0.01–0.17 and >0.17 mg/l, respectively.

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increased with increasing levels of tnt. There was no significant association between tnt levels and traditional risk factors (except for cholesterol level), previous MI, pharmacologically treated congestive heart failure or chest pain at rest.

A left ventricular ejection fraction below 0.45 was significantly more common, also after adjusting for several possible confounders, in the group with the highest levels of tnt ($>0.63 \mu g/l$) compared with every other tnt group (Table 2A and B).

Coronary angiography and tnt in the invasive arm. The proportion of patients without significant stenosis was higher and the proportion of three-vessel disease or left main stem stenosis was lower in patients without, compared to with, detectable tnt. However, among patients with detectable tnt there was no relation between severity of CAD and the level of tnt. In contrast, the occurrence of visible thrombus and TIMI flow 0 to 1 in at least one vessel gradually increased by rising levels of tnt (Table 3A). The same patterns were found irrespective of gender, although the absolute numbers differed; that is, among men and women with tnt $<0.01 \mu g/l$, no significant stenosis could be demonstrated in 26% and 43%, respectively, and among those with tnt $\geq 0.01 \mu g/l$ in 4.4% and 14.3%, respectively. The demonstrated associations between the tnt level and the severity of CAD, occurrence of visible thrombus and TIMI flow grade were consistent also after adjusting for several possible confounders (Table 3B).

Among those with tnt $<0.01$, 0.01 to 0.17, 0.18 to 0.63 and $>0.63 \mu g/l$, the proportions of patients with total or subtotal occlusion (TIMI flow 0 or 1) of a culprit lesion in the left circumflex artery territory, were 4%, 4%, 12% and 22% ($p = 0.001$), respectively. The corresponding figures for the left anterior descending artery territory were 8%, 10%, 12% and 12% ($p = 0.62$) and for the right coronary artery territory 7%, 5%, 8% and 9% ($p = 0.48$).

Prognosis and tnt. The frequency of death, MI, revascularization and the combined end point death/MI at 12

Table 2. Findings at Echocardiography (n = 1,867) in Relation to Troponin T Levels

<table>
<thead>
<tr>
<th>Troponin T</th>
<th>LVEF $&lt;0.45$</th>
<th>$0.01$–$0.17$</th>
<th>$0.18$–$0.63$</th>
<th>$&gt;0.63 \mu g/l$</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF $&lt;0.45$</td>
<td>8.5</td>
<td>11.8</td>
<td>11.8</td>
<td>20.4†</td>
<td>$&lt; 0.001$</td>
</tr>
</tbody>
</table>

*Global chi-square; †p $\leq 0.001$ group 4 compared with each of the other three groups; ‡Adjusted for gender, age, diabetes, chronic angina, previous myocardial infarction, hypertension, any medication for angina on admission, any medication for congestive heart failure at admission, ST-segment depression on admission and Q-wave on admission.

LVEF = left ventricular ejection fraction.

Table 3. Findings at Coronary Angiography in the Invasive Cohort (n = 1,142) in Relation to Troponin T Levels

<table>
<thead>
<tr>
<th>Troponin T</th>
<th>0-vd</th>
<th>3-vd/mss</th>
<th>Visible thrombus</th>
<th>TIMI 0–1 (n = 1,137)</th>
<th>TIMI 3 (n = 1,137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;0.01$</td>
<td>32.4</td>
<td>8.7</td>
<td>2.9</td>
<td>21.3</td>
<td>66.8</td>
</tr>
<tr>
<td>$0.01$–$0.17$</td>
<td>22.8</td>
<td>38.8</td>
<td>8.0</td>
<td>31.3</td>
<td>52.7</td>
</tr>
<tr>
<td>$0.18$–$0.63$</td>
<td>2.9</td>
<td>11.7</td>
<td>8.0</td>
<td>38.7</td>
<td>49.5</td>
</tr>
<tr>
<td>$&gt;0.63 \mu g/l$</td>
<td>66.8</td>
<td>15.7</td>
<td>47.6</td>
<td>39.6</td>
<td>39.6</td>
</tr>
</tbody>
</table>

B. Adjusted* odds ratio (95% confidence interval) for the different angiographic findings

<table>
<thead>
<tr>
<th>Troponin T</th>
<th>0-vd</th>
<th>3-vd/mss</th>
<th>Visible thrombus</th>
<th>TIMI 0–1</th>
<th>TIMI 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;0.01$</td>
<td>1</td>
<td>0.20 (0.12–0.33)</td>
<td>0.21 (0.13–0.35)</td>
<td>0.06 (0.03–0.13)</td>
<td></td>
</tr>
<tr>
<td>$0.01$–$0.17$</td>
<td>1</td>
<td>1.84 (1.23–2.74)</td>
<td>1.75 (1.16–2.62)</td>
<td>1.97 (1.31–2.97)</td>
<td></td>
</tr>
<tr>
<td>$0.18$–$0.63$</td>
<td>1</td>
<td>2.90 (1.30–6.46)</td>
<td>4.23 (1.96–9.13)</td>
<td>5.70 (2.67–12.2)</td>
<td></td>
</tr>
<tr>
<td>$&gt;0.63 \mu g/l$</td>
<td>1</td>
<td>1.54 (1.02–2.30)</td>
<td>2.58 (1.73–3.83)</td>
<td>3.80 (2.54–5.67)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.59 (0.41–0.85)</td>
<td>0.46 (0.32–0.66)</td>
<td>0.30 (0.21–0.43)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for gender, age, ST-segment depression, diabetes, chronic angina, previous myocardial infarction, hypertension, chest pain at rest, current smoking, aspirin treatment on admission and time from start of open label dalteparin to angiography.

0-vd = no significant stenosis; 3-vd/mss = 3-vessel disease of left main stem stenosis; TIMI = Thrombolysis In Myocardial Infarction.
Table 4. Clinical End Points at 12 Months in the Noninvasive Cohort in Relation to Troponin T Levels (n = 1,168)

<table>
<thead>
<tr>
<th>Troponin T</th>
<th>&lt;0.01</th>
<th>0.01–0.17</th>
<th>0.18–0.63</th>
<th>&gt;0.63 µg/l</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.6</td>
<td>3.8</td>
<td>4.6</td>
<td>4.5</td>
<td>0.17</td>
</tr>
<tr>
<td>MI</td>
<td>5.5</td>
<td>17.5</td>
<td>16.2</td>
<td>8.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Death/MI</td>
<td>6.8</td>
<td>20.3</td>
<td>17.6</td>
<td>11.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Revascularization</td>
<td>38.8</td>
<td>51.9</td>
<td>46.1</td>
<td>34.3</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

MI = myocardial infarction.

months in relation to the different tnT levels in the noninvasive group are shown in Table 4. The risk of death showed a trend to a gradual increase by increasing levels of tnT. However, the risk of MI, revascularization and the composite of death and MI were lowest in the lowest, modest in the highest and highest in the two intermediate tnT groups (Fig. 2).

The prognostic value of tnT regarding death and MI, respectively, was evaluated in models using multivariate logistic regression analysis (Table 5). After adjustment for age, gender, diabetes, hypertension, a history of stable angina or previous MI and ST-segment depression, patients with a tnT ≥ 0.17 µg/l had an approximately tripled risk of death compared with patients without any myocardial damage, and there was a trend to increased risk also among those with only a minor myocardial damage (tnT 0.01 to 0.17 µg/l). Somewhat differently, the relative risk of MI was also significantly and substantially elevated in patients with tnT 0.01 to 0.17 µg/l as tnT 0.18 to 0.63 µg/l. However, the risk of MI in patients with the largest myocardial damage (tnT > 0.63 µg/l) was not significantly higher than in patients without detectable myocardial damage.

The influence of the left ventricular ejection fraction on the predictive values of any tnT elevation (tnT ≥ 0.01 µg/l) was studied in the subgroup of 961 patients with an echocardiogram obtained. The relative risk ratio for death at 12 months decreased from 2.01 to 1.73 after adjustment for the left ventricular ejection fraction (≥ / < 0.45), whereas the relative risk ratio for MI was virtually unchanged after adjustment (from 2.52 to 2.45).

**DISCUSSION**

The unique design of the present study gave specific advantages in attempts to further elucidate the possible mechanisms for the prognostic value of troponin concerning mortality and myocardial (re-)infarctions in unstable CAD. The relation between tnT and baseline characteristics, ECG findings and left ventricular ejection fraction could be reliably evaluated in the large cohort of the whole trial. The relation between the tnT level and the coronary lesions and blood flow could be evaluated in the half of the population randomized to an early coronary angiogram. Finally, the prognostic information in tnT and other factors could be evaluated without the influence of early revascularization procedures in the other half of the population randomized to the noninvasive arm of the study, which mainly reflected the “natural course” of the coronary lesions and their consequences in unstable CAD.

**Prognosis and tnT.** The mortality among patients without elevation of tnT was low, in accordance with previous studies (2,3). The one-year mortality of 1.6% in patients without any measurable tnT elevation was close to the
annual mortality of 1.7% found in patients with stable angina pectoris (15). However, at any sign of myocardial damage there was a strong trend to an increased mortality in accordance with previous findings (2). The relation between the troponin T level and the risk of subsequent MI showed a somewhat different pattern. The one-year risk of MI was lowest in the group without detectable troponin T, 5.5%, which is approximately twice as high as the annual rate of MI found in patients with stable angina pectoris (15). In the two intermediate troponin T groups the rate of MI during follow-up was substantially higher, 16.2% to 17.5%, indicating a severely unstable coronary lesion as the underlying condition. However, rather unexpectedly, the rate of re-MI in those with the highest levels of troponin was only 8.4%, which was only marginally higher than in those without any troponin elevation. The one-year rate of reinfarction in this group resembles the one-year reinfarction rate of 6.4% after a Q-wave infarction in the Framingham heart study (16). Thus, the risk of myocardial (re-)infarction in relation to troponin T level showed an inverted U-shaped curve in the present study (Fig. 2), that has not previously been described. However, in retrospect, the same association between troponin T level and risk of MI could be seen in the FRISC-1 trial (2). The proportion of patients requiring a revascularization procedure during follow-up in the four troponin T groups showed a similar inverted U-shaped curve. This finding supports the concept of a more unstable coronary lesion in the two intermediate groups than in the lowest and highest troponin T groups.

Clinical characteristics, troponin T and risk of future events. Several baseline variables known to be associated with an increased risk of new coronary events differed in relation to troponin T levels. Patients without elevation of troponin T were somewhat younger, more often women and less likely to have ST-segment depression at the admission ECG. However, there was no consistent pattern that indicated that patients with elevated troponin T constituted a more sick population; on the contrary, several factors known to be associated with an increased risk of adverse events, such as previous angina, antianginal medication and higher cholesterol levels, were more common in patients without elevation of troponin T, in accordance with some (10), but not all, previous studies (17). Thus, it is unlikely that the relation between the troponin T levels and baseline characteristics is a major determinant of the prognostic value of troponin T, especially as troponin T remained an independent prognostic factor in multivariate analysis.

Coronary angiogram, troponin T and risk of future events. The extent of CAD is a major determinant of the prognosis in unstable CAD, with a very low risk of cardiac events in patients without significant obstructions (18) and the highest risk in those with three-vessel or left main disease (19). Furthermore, complex lesions, occurrence of visible thrombus and decreased TIMI flow grade have been associated with the risk of death and MI (20). Only a few studies have evaluated findings at coronary angiography in relation to troponin levels in patients with unstable CAD (7–10). In the present study, the largest so far, there were significant relations between the troponin T level and the extent and type of coronary lesions and coronary blood flow. In this large cohort it was possible to demonstrate that these relations remained after adjustment for differences in baseline variables, excluding the possibility that these relations were merely a reflection of such differences. Despite a clinical diagnosis of unstable CAD in all patients, 26% of the men and 43% of the women without any measurable elevation of troponin T (<0.01 μg/l) did not have significant coronary stenosis. In contrast, in men and women with troponin T elevation and thus myocardial damage, 4% and 14%, respectively, had no significant obstruction, which is close to the figures in patients with non–ST-elevation MI in the GUSTO IIb study, 4.2% and 9.1%, respectively (21). The gender difference might be explained by differences in thrombotic activity as well as in the underlying substrate of coronary thrombosis between the sexes (22,23). Patients with any sign of myocardial damage more often had three-vessel disease or left main stem stenosis (35% to 40%) than did those without detectable troponin T (23%). These findings are in accordance with previous smaller studies showing more frequent triple-vessel and left main coronary artery involvement in patients with elevated troponin (7,8). Thus, the relation between the troponin T levels and the extent of CAD
Coronary thrombus, tnt and risk of future events. By increasing levels of tnt there was a graded rise, from 3% to 16%, in occurrence of visible intracoronary thrombus, in accordance with the study of Heeschen et al. (10). The incidences of visible intracoronary thrombi in patients with tnt <0.01 µg/l were very low (<3%) in our study as well as in their study (10), and comparable to patients with stable angina pectoris (29%) (24). However, it should be emphasized that visual evaluation of coronary angiograms from patients with unstable CAD is associated with a substantial underestimate of the occurrence of intracoronary thrombi in comparison to intracoronary angiography (25). Therefore, the occurrence of intracoronary thrombi at increasing tnt levels probably is considerably larger than apparent in the current study. Thus, the relation between tnt and remaining thrombi at the coronary lesions might be one explanation for the relation between tnt level and risk of early (re-)infarction.

Coronary occlusion, tnt and risk of future events. In the present study there was also a relation between the tnt level and impairment of coronary blood flow, in accordance with Heeschen et al. (10). This was due mainly to a rise in occurrence of total or subtotal occlusions by increasing levels of tnt. The high incidence of total or subtotal occlusions, especially of the circumflex artery or its branches, in the group with the highest tnt levels suggests that many of the patients in this group might have had a “transmural” infarction that was undetected by the standard 12-lead ECG on admission (26). The higher rate of completed infarctions at the highest tnt levels might explain the lower risk of reinfarction and lower need for revascularization, in analogy with the lower risk of reinfarction in patients after a Q-wave compared with a non-Q-wave infarction (17).

Left ventricular ejection fraction, tnt and risk of future events. The left ventricular function has a major impact on mortality (27). The tnt level has been shown to correlate with infarct size (28) and left ventricular ejection fraction (29). A depressed left ventricular ejection fraction at the echocardiogram was significantly more common in the group with the highest tnt levels (>0.63 µg/l) in the present study (Table 2A). This relation also remained after adjustment for baseline variables possibly associated with a depressed left ventricular function (Table 2B), indicating that the lower ejection fraction in the group with the highest tnt levels was indeed a result of the myocardial damage associated with the index event. Thus, the increased mortality found at a tnt level >0.63 µg/l might be a consequence of myocardial damage large enough to cause a decreased left ventricular function. However, left ventricular dysfunction was no explanation for the increased risk of death in patients with only minor elevations of tnt. Thus, the association between a minor tnt elevation and future mortality probably is related to the raised risk of reinfarction.

Study limitations. One limitation of the present study is that tnt was determined only at randomization, at a median of 38.6 h from onset of last episode of chest pain. However, because tnt levels remain elevated for 10 to 14 days in patients with myocardial necrosis (30), very few false negative results should have occurred. It is also important to recognize that tnt was determined with the new third-generation assay, which has slightly different properties, such as a lower upper reference level, compared with the second-generation assay.

Another limitation of the study is that the coronary angiograms were not assessed centrally. However, the evaluation was performed according to a predefined protocol. The striking similarities regarding the occurrence of coronary thrombus and TIMI flow grade in the present study, as in the previous study by Heeschen et al. (10) with central evaluation, corroborate our results.

Conclusions and clinical implications. These results, together with previous experiences, suggest that much of the prognostic value of troponins in unstable CAD can be attributed to underlying severe coronary stenosis, culprit lesion thrombosis, downstream embolization with microinfarction and, in some patients, total coronary occlusion and a large MI. The group without any tnt elevation consists partly of patients without significant atherosclerotic CAD, whose symptoms often have noncardiac causes, and partly of patients with CAD, whose symptoms might be caused by an increase of oxygen demand or a decrease in oxygen supply unrelated to coronary thrombosis. At any detectable elevation of tnt the probability of significant coronary stenosis is considerably raised, and there is an increased likelihood of an unstable plaque with thrombus and downstream microembolization and impairment of coronary flow, all factors associated with a raised risk of reinfarction and death. However, with a more pronounced elevation of troponin, a higher proportion of patients will have a persistent occlusion of the culprit coronary vessel associated with reduced left ventricular function, resembling a Q-wave infarction with a high mortality but lower risk of reinfarction.

These results also give a reasonable explanation of why treatment with coagulation or platelet inhibition, which reduces the risk of thromboembolic events, is protective mainly in patients with elevated troponin (31–33).

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