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Angiographic Findings in Patients With Refractory Unstable Angina According to Troponin T Status

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Background—The CAPTURE (C7E3 fab AntiPlatelet Therapy in Unstable REfactory angina) trial enrolled patients with refractory unstable angina and documented a therapeutic benefit for abciximab, a platelet glycoprotein IIb/IIIa receptor antagonist, that was particularly evident in patients with elevated troponin T (TnT) levels. In the current study, we related the angiographic data to the TnT status of the CAPTURE patients.

Methods and Results—In 853 patients, angiographic data at baseline and 18 to 24 hours after treatment were available and assessed by an Angiographic Committee with respect to TIMI flow, lesion severity, and visibility of thrombus. TnT levels >0.1 μg/L were found in 30.9% of the patients. Before randomization, thrombus was visible in 14.6% of TnT-positive patients (TnT levels >0.1 μg/L) and 4.2% of TnT-negative patients ($P=0.004$). Complex lesion characteristics B2+/C (72.0% versus 53.9%; $P<0.001$) and TIMI flow <2 (15.6% versus 5.1%; $P<0.001$) were more frequent in TnT-positive patients. Abciximab was effective with respect to reduction of visible thrombus, increase of TIMI flow, and reduction of cardiac events in TnT-positive patients only. Multivariate analysis identified TnT status, but not angiographic findings, as an independent predictor for both outcome and efficacy of treatment with abciximab.

Conclusions—Complex lesion characteristics and visible thrombus formation at baseline were significantly linked to TnT elevation. However, TnT status was a more powerful predictor of increased cardiac risk and efficacy of treatment with abciximab than either. Relative to the angiogram, TnT can thus be considered a more sensitive marker for the underlying pathology, identifying patients with unstable angina who will particularly benefit from antiplatelet treatment. (***Circulation***. 1999;104:1509-1514.)

Key Words: angina, unstable ■ abciximab ■ thrombus ■ troponin T

Unstable angina is a critical phase of coronary heart disease that is defined mainly by clinical symptoms[1]; an increased risk of myocardial infarction and death exists, particularly 72 hours after the onset of symptoms.[2–4]

Postmortem studies in patients with unstable angina have identified erosion or rupture of the fibrous cap of the atherosclerotic plaque as the initial event.[5,6] Exposure of plaque contents, collagen, and other components of the vascular wall lead to increased vascular tone and platelet activation.[7] Intracoronary thrombus formation and systemic activation of coagulation have been demonstrated in these patients with unstable angina pectoris.[8,9]

In about one-third of patients with unstable angina pectoris, elevated troponin T (TnT) levels (>0.1 μg/L) can be observed. This subgroup of patients has a particularly high risk of death and acute myocardial infarction (AMI).[3,4] Even when enzyme activity of creatine kinase remains within the normal range, TnT-positive patients have a 5- to 10-fold higher incidence of cardiac events during 30-day follow-up.[3,4,10–15] Currently, it is suggested that TnT elevation is related to the focal cell necrosis caused by thrombotic embolization from friable thrombus formation.[5,8]

The database of the CAPTURE study (C7E3 AntiPlatelet Therapy in Unstable REfractory angina) provides a unique opportunity to test this hypothesis because both angiographic information and TnT status are available for the majority of patients. The CAPTURE study was designed to assess outcome in patients with refractory angina who received either abciximab or placebo up to 24 hours before scheduled percutaneous transluminal coronary angioplasty (PTCA). We investigated the relationship between angiographic lesion characteristics and TnT release. Additionally, we compared the predictive value of TnT and angiographic findings regarding both cardiac events and the salutary effects of abciximab.

Methods

Patients

In the CAPTURE trial, 1265 patients (61% were men; all were aged 61 ± 10 years) were prospectively enrolled between May 1993 and

December 1995.[2] All patients had chest pain at rest associated with electrocardiographic changes, despite treatment with intravenous heparin and glyceryl trinitrate for ≥2 hours. All patients underwent coronary angiography before randomization, which indicated significant coronary artery disease with a culprit lesion suitable for angioplasty. Coronary intervention was scheduled 1 day later, 18 to 24 hours after the start of study medication. The patients were randomly assigned to receive abciximab or placebo, which was started within 2 hours of allocation and continued until 1 hour after completion of the procedure. For cardiac events (defined as death and nonfatal myocardial infarction), 4 time horizons were considered in this study:

- ≤36 hours before PTCA
- ≤72 hours after randomization
- 30-day follow-up
- 6-month follow-up

Myocardial infarction during the index hospital stay was defined by a creatine kinase enzyme activity value >3 times the upper limit of normal in at least 2 samples. Myocardial infarction after discharge was defined as a creatine kinase enzyme activity value >2 times the upper limit of normal.[2]

Coronary Angiogram

Initial coronary angiography was performed before randomization, and angiography was repeated 18 to 24 hours after the start of treatment (placebo or abciximab). All angiograms were assessed centrally for TIMI flow and characteristics of the culprit lesion by the Angiographic Committee at Cardialysis, Rotterdam, the Netherlands. The lesions were classified according to the American Heart Association/American College of Cardiology grading system.

Additional data regarding collateral flow and visibility of thrombus formation were collected at the time of randomization and after pretreatment but before intervention, respectively. Thrombus formation was strictly defined as either a filling defect or haziness without calcification near the lesion visible on at least 2 orthogonal views or as an embolus in the distal territory of the related artery. The responsible operator at each center documented the necessity of stent implantation and PTCA-related complications.[2]

Analytical Techniques

Serum samples were collected in 1088 patients at the time of allocation and stored centrally at −80°C. All analyses in the samples were performed at the research laboratory of the University of Hamburg; analysts were blinded regarding patient history, angiographic data, and allocated treatment. We used a 1-step enzyme immunoassay with electrochemiluminescent technology and magnetic microparticles carrying second-generation monoclonal capture antibodies (Elecsys 2010, Boehringer Mannheim). A diagnostic threshold value of 0.1 μg/L was used to classify patients as TnT-positive.[16–18] The applied internal controls interassay precision was 6.7% at 0.12 μg/L and 4.1% at 0.56 μg/L.

In addition, creatine kinase MB mass was measured in parallel on the Elecsys 2010 system. The detection limit of this test was 0.15 μg/L, and a diagnostic threshold level of 5 μg/L was used. The interassay coefficient of variation obtained was 8.4% at 8.2 μg/L and 7.2% at 14.7 μg/L, with internal controls.

Statistical Methods

Continuous variables are expressed as means±SD. Comparison between groups was performed with Mann-Whitney U tests (2-sided). Comparisons of categorical variables were performed by Fisher's exact test. We set the level of statistical significance at $P<0.05$.

The treatment effect of abciximab in terms of odds ratios (OR), including 95% confidence intervals (CI), was assessed by logistic regression analysis for different subgroups of patients regarding angiographic findings and TnT status. TnT status and angiographic findings of the patients were encoded as dichotomous variables. All variables documented to be associated with short- or long-term cardiac risk were used for reverse stepwise logistic regression analysis to identify variables of independent predictive value.[19,20] Variables that were not significantly associated with adverse outcome in this regression model ($P<0.05$) were dropped. All calculations were done with SPSS 8.0.1 (SPSS Inc) or StatXact-3 (Cytel Software Corp) software.

Results

We obtained complete data, including angiograms at baseline and before coronary intervention and TnT determination, from 90% of the 1265 patients randomized in the CAPTURE study data. In this subset, 183 patients were excluded from the analysis due to an AMI ≤14 days before enrollment because TnT levels may remain elevated for up to 14 days after such an event. In these patients, TnT elevation does not necessarily reflect acute myocardial injury before enrollment. The baseline characteristics of the remaining subset of the study population (n=853 patients) were not different than the total study population with respect to age, sex, cardiovascular risk profile, and concomitant treatment before and after randomization.

In the subset population, 5.4% of patients receiving abciximab suffered from major cardiac events (death or nonfatal AMI) during the 30-day follow-up period versus 9.4% of placebo-treated patients ($P=0.008$). This benefit of treatment is comparable to the results achieved in the complete study population (4.8% versus 9.0%, respectively; $P=0.003$). This absolute difference in event rates of 4.2% was largely maintained during the 6-month follow-up, although it was no longer statistically significant (12.3% versus 8.8%; $P=0.14$).

Angiographic Findings and Treatment Efficacy

Lesion Characteristics

The baseline angiogram revealed no differences in lesion characteristics and TIMI flow between the placebo and abciximab groups. Lesion characteristics were predictive of both adverse outcome and efficacy of treatment with abciximab. At the 30-day follow-up, patients with type A or B1 lesions had an incidence of death or AMI of 3.5% when allocated to abciximab and of 5.1% when given placebo ($P=0.59$). In contrast, for patients with more complex lesions, abciximab significantly reduced cardiac risk. For patients with type B2+ lesions, event rates were 4.9% when treated with abciximab versus 11.7% for placebo ($P=0.04$), and for patients with type B2+ or C lesions, the rates were 5.6% and 12.4%, respectively ($P=0.05$). Thus, patients in the placebo group with more complex lesion characteristics (types B2/C) were at highest cardiac risk for death and AMI (OR, 2.5; 95% CI, 1.3 to 3.1; $P=0.03$). This increased risk was reduced in patients with less complex lesions who were treated with abciximab (OR, 1.4; 95% CI, 0.7 to 1.9; $P=0.43$).

TIMI Flow

TIMI flow did not increase significantly from baseline to the pre-PTCA angiogram, independent of allocated treatment. In 69.8% of patients receiving placebo, TIMI 3 flow was documented at baseline, and incidence was unchanged before coronary intervention (69.6%; $P=1.00$). For patients allocated to abciximab, TIMI 3 flow was observed in 68.5% of patients at baseline versus 72.4% before angioplasty ($P=0.35$). In patients with TIMI 0 and 1 flow, improvement

TABLE 1.   Baseline Characteristics According to TnT Status

	TnT-Positive		TnT-Negative	
	Abciximab	Placebo	Abciximab	Placebo
n	131	132	295	294
Male sex	75.7%	66.9%	70.1%	73.6%
Age, y	62.4±10.6	62.7±10.5	60.1±9.3	60.9 ±10.2
History of				
Angina >4 wk	41.9%	39.6%	53.9%	64.5%
Infarction 14–30 d	2.9%	2.2%	4.2%	3.2%
Infarction >30 d	19.1%	15.8%	20.5%	22.8%
PTCA	11.8%	8.6%	15.9%	18.6%
CABG	1.5%	3.6%	1.3%	3.3%
Risk factors				
Diabetes	13.2%	11.5%	13.3%	9.4%
Hypertension	35.3%	35.9%	37.3%	37.1%
Current smokers	41.2%	41.0%	39.6%	41.7%
Medication before enrollment				
Aspirin	91.9%	94.2%	86.4%	93.2%
Heparin IV	98.5%	97.1%	98.7%	99.4%
Nitrates IV	100.0%	98.6%	100.0%	100.0%
β-Blockers	66.2%	62.6%	60.7%	63.2%
Ca antagonists	40.4%	43.2%	48.4%	59.9%
Medication after enrollment				
Aspirin	97.1%	97.2%	94.2%	97.4%
Ticlopidin	5.1%	3.6%	3.4%	4.9%
Heparin IV	96.3%	97.1%	95.8%	97.7%
Nitrates IV	96.3%	97.1%	94.5%	98.4%
β-Blockers	66.9%	64.0%	63.0%	60.6%
Ca antagonists	42.6%	43.2%	50.6%	58.6%

CABG indicates coronary artery bypass grafting.

of vessel patency just missed statistical significance ($P=0.08$) for treatment with abciximab.

Thrombus
Visible thrombus was documented in 7.4% of initial angiograms. No difference was observed regarding mean duration of the preceding heparin therapy between patients with and without a visible thrombus (12.4 versus 11.9 hours; $P=0.61$). During the 18 to 24 hours of treatment before scheduled angioplasty, thrombus resolved in 26.5% of patients treated with placebo and 49.5% of patients treated with abciximab ($P=0.02$). Regardless of study group, no patient under treatment with aspirin and intravenous heparin developed new thrombus formations.

TnT Subgroup Analysis
A TnT concentration >0.1 μg/L at baseline (TnT-positive) was documented in 30.9% of the patients with refractory unstable angina. The baseline characteristics of the 264 patients above (positive) and the 589 patients below (negative) the threshold level of 0.1 μg/L are shown in Table 1; no significant differences existed between the subgroups.

Lesion Characteristics
Patients with elevated TnT levels had more complex lesion characteristics in baseline coronary angiograms. In 72.0% of

patients with a TnT concentration >0.1 μg/L, type B2+ or C lesions were documented (Figure 1). In contrast, only 28.0% of the patients with TnT values >0.10 μg/L had type A or B1 lesions compared with 46% of patients with TnT concentrations ≤0.1 μg/L ($P<0.001$).

TIMI Flow
TIMI flow at baseline was normal in 59.4% of the TnT-positive patients and 74.5% of the TnT-negative patients
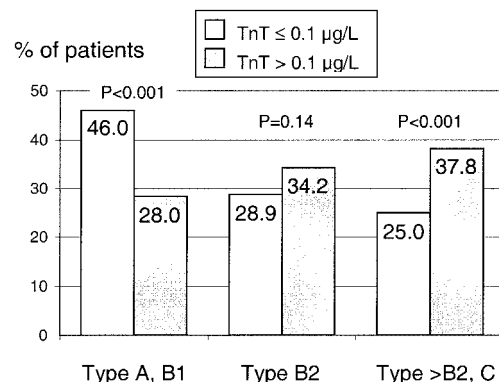

Figure 1. Lesion characteristics at baseline according to TnT status.

TABLE 2.   TIMI Flow After 18 to 24 Hours of Allocated Treatment According to TnT Status

TnT-Positive (n=263)				TnT-Negative (n=589)			
TIMI Flow at Baseline	Abciximab	Placebo	P	TIMI Flow at Baseline	Abciximab	Placebo	P
TIMI 0 (n=19)	−1	+2	0.64	TIMI 0 (n=10)	+1	−1	0.59
TIMI 1 (n=22)	−5	+1	0.13	TIMI 1 (n=20)	−1	equal	0.87
TIMI 2 (n=65)	−3	+1	0.16	TIMI 2 (n=119)	+2	−1	0.43
TIMI 3 (n=157)	+9	−4	<0.001	TIMI 3 (n=440)	−2	+2	0.06

($P<0.001$; Figure 2). TIMI flow ≤ 1 was documented for 15.6% of TnT-positive patients but only 5.1% of patients with a TnT level ≤ 0.1 μg/L ($P<0.001$). For 22.4% of TnT-positive patients, impaired TIMI flow was significantly improved by treatment with abciximab (incidence of TIMI flow ≤ 1, 16.1% versus 12.5%; $P=0.01$). In contrast, for TnT-positive patients in the placebo group, the incidence of impaired TIMI flow increased from 14.9% to 17.1% ($P=0.02$). For TnT-negative patients, no significant differences were observed between the first and second angiogram, independent of treatment group (Table 2).

Thrombus

At the time of randomization, 14.6% of the TnT-positive patients had a visible thrombus versus 4.2% of TnT-negative patients ($P<0.001$; Figure 3). Resolution of thrombus during the treatment period before PTCA was particularly evident in TnT-positive patients allocated to abciximab, with a relative reduction of 63% (placebo, −24%; $P<0.001$; Figure 4). Thrombus in TnT-negative patients was infrequent. No significant reduction was achieved with placebo ($P=0.42$) or abciximab ($P=0.54$).

Predictive Value of Angiogram and TnT Levels

Complex lesion characteristics (types B2+/C) were linked to a more adverse outcome (death or nonfatal AMI) for all investigated time periods: before PTCA (OR, 1.7; 95% CI, 0.8 to 2.9; $P=0.05$); ≤ 72 hours after coronary intervention (OR, 2.1; 95% CI, 1.4 to 3.5; $P=0.008$); at 30-day follow-up (OR, 2.5; 95% CI, 1.3 to 3.1; $P=0.03$), and at 6-month follow-up (OR, 1.7; 95% CI, 0.9 to 2.8; $P=0.04$) (Figure 5). In contrast, detection of thrombus formation on baseline angiograms was not associated with significantly increased cardiac risk at any time period: before PTCA (OR, 1.2; 95% CI, 0.4 to 3.7; $P=0.15$), ≤ 72 hours of treatment (OR, 1.3; 95% CI, 0.3 to 3.5; $P=0.39$), at 30-day follow-up (OR, 1.2; 95% CI, 0.2 to 2.8; $P=0.52$), and at

6-month follow-up (OR, 1.2; 95% CI, 0.1 to 2.7; $P=0.56$). Only failed resolution of thrombus before PTCA was significantly predictive of PTCA-related complications (OR, 1.7; 95% CI, 1.2 to 3.5; $P=0.03$). TnT was a powerful predictor of increased cardiac risk at all assessment time points: before PTCA (OR, 4.9; 95% CI, 1.1 to 12.2; $P=0.005$); at 72 hours after PTCA (OR, 3.6; 95% CI, 1.5 to 8.2; $P<0.001$); at 30-day follow-up (OR, 3.2; 95% CI, 1.4 to 6.8; $P<0.001$), and at 6-month follow-up (OR, 2.3; 95% CI, 1.3 to 5.2; $P<0.001$).

When both TnT status and angiographic findings were included in a stepwise logistic regression model, neither complex lesion characteristics nor visibility of thrombus had independent prognostic value for short- or long-term outcomes. TnT status was identified as the only independent prognostic marker for increased cardiac risk for all investigated time periods.

Complex lesion characteristics (OR, 0.56; 95% CI, 0.11 to 1.05; $P=0.02$) and TnT levels (OR, 0.23; 95% CI, 0.12 to 0.49; $P<0.001$) but not visibility of thrombus (OR, 0.67; 95% CI, 0.25 to 1.25; $P=0.39$) were predictive of efficacy of abciximab treatment. Using multivariate analysis, only TnT determination had independent predictive value. When TnT level was forced into the model first, the introduction of lesion characteristics did not improve the predictive value of the statistical model ($P=0.49$).

Discussion

The present analysis of this rather homogenous high-risk population enrolled in the CAPTURE trial demonstrates a significant relationship between angiographic lesion complexity, presence of thrombus, and a TnT level >0.1 μg/L. Lesion types of B2+/C were documented in 72.0% of the patients with TnT levels >0.10 μg/L. Classification according to lesion morphol-
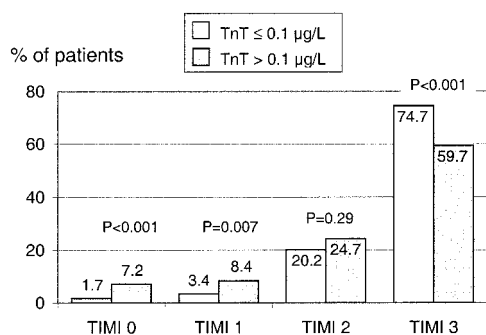

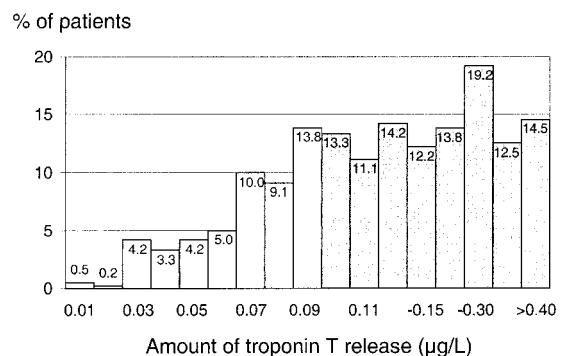**Figure 2.** TIMI flow at baseline according to TnT status.

Figure 3. Percent of patients with visible thrombus on qualifying angiogram as related to TnT concentration measured at baseline. Shaded bars indicate elevated TnT levels (≥ 0.1 μg/L).
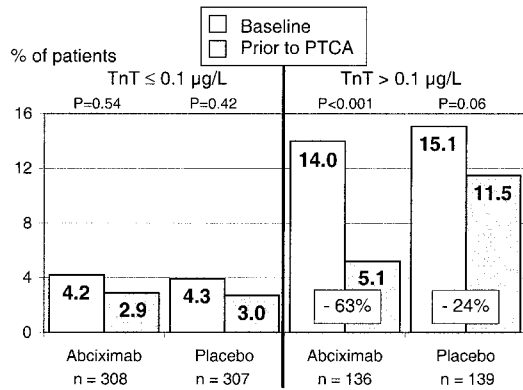
Figure 4. Share of patients with detectable thrombus at baseline and after 24 hours of allocated treatment according to TnT status.

Figure 5. Predictive value of TnT and angiographic findings: adjusted ORs and 95% CIs regarding AMI-free survival at 6-month follow-up.

ogy provided important prognostic information for estimating patients' short-term cardiac risk, particularly the risk associated with the PTCA procedure (OR, 2.1; 95% CI, 1.4 to 3.5; $P=0.008$). However, TnT status was a stronger predictor of cardiac risk relative to the angiographic findings. Patients with elevated TnT concentrations were at increased risk for progression to myocardial infarction or death during the first 24 hours before coronary intervention (OR, 4.9; 95% CI, 1.1 to 12.2; $P=0.005$); these patients were also at increased risk for thrombotic complications associated with the procedure (OR, 3.6; 95% CI, 1.5 to 8.2; $P<0.001$).

A further finding of our study was support for the hypothesis that TnT might be a surrogate marker for microembolization from liable thrombus formation.[5,8] A significantly greater accumulation of angiographically detectable thrombus was observed in patients with elevated TnT levels. Patients with TnT values >0.10 μg/L had a 4-fold higher incidence of visible thrombus in the qualifying angiogram before randomization (14.6% versus 4.2%; $P<0.001$).

In the present study, there was a low incidence of thrombus, even in TnT-positive patients (14.3%). However, when strict criteria are applied, as in the present study, angiography is not a very sensitive method for the detection of thrombus. The criterion "filling defect surrounded on 3 sites by contrast" precluded detection of a thrombus adhering to the vessel wall. Neither intravascular ultrasound nor angioscopic evaluation was performed in the CAPTURE trial; these methods might have provided a higher sensitivity for the detection of thrombus formation. However, despite its low sensitivity for the detection of mural thrombus, angiography remains highly specific for larger luminal thrombi.[21,22]

Additionally, qualifying angiograms in the CAPTURE trial were obtained after patients had been treated with intravenous heparin for a mean time of 12 hours (range, 2 to 48 hours).[2] In the placebo group with another 18 to 24 hours of treatment with heparin, thrombus formation resolved in 26.5% of the patients. This finding demonstrates the treatment efficacy of heparin alone with respect to the resolution of thrombus formation. Accordingly, treatment with heparin in this study population is likely to have reduced the incidence of thrombus even before the qualifying angiograms were obtained. Given that TnT release is detectable for >7 days after myocardial cell necrosis, the causal thrombus formation
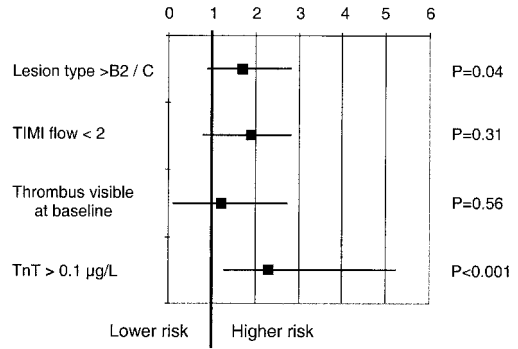
might have already been resolved by heparin therapy before study enrollment in several patients. Thrombi still visible at the time of randomization might have been larger or more resistant to the treatment with heparin and aspirin.

The angiographic findings of this study support the hypothesis that TnT release in patients with unstable angina is related to coronary thrombosis and consecutive embolization leading to minor myocardial damage. In patients with unstable angina, inflammatory reactions promote plaque fissuring or erosion, followed by exposure of thrombogenic contents such as collagen to the circulation. Platelet activation and adhesion result in formation of liable thrombus. Pathohistological studies have disclosed focal cell necroses distal in the myocardium supplied by the culprit artery; they were attributed to repetitive embolization from such liable thrombi. Our findings are consistent with the hypothesis that TnT release might be a surrogate marker for microembolization from liable thrombus formation. The increased cardiac risk of TnT-positive patients may be related less to detected minor myocardial damage than to causal high complexity of coronary morphology in the culprit lesion.

Using multivariate analysis, including both angiographic findings and patients' TnT status, TnT elevation remained the only independent and powerful predictor of increased cardiac risk (Figure 5). Relative to the angiogram, determination of cardiac TnT (and, presumably, likewise cardiac troponin I) must be considered the superior marker, with a higher sensitivity for the detection of probable unstable thrombus formation or high-risk lesion morphology. Because angiograms are a poor descriptor of true lesion complexity, it may be preferable to look at the consequences of the lesion in terms of elevated TnT levels rather than to assess angiographic characteristics.[23–26]

With regard to the efficacy of treatment with abciximab varying in different subgroups of the CAPTURE trial, we recently demonstrated that the documented treatment benefit of abciximab was largely obtained among patients having TnT concentrations >0.1 μg/L.[27] Both thrombus resolution and increase of TIMI flow, potential indicators for the efficacy of treatment, were more pronounced in patients receiving abciximab. Again, this was particularly evident in those patients with TnT elevation. Thrombi that did not resolve during pretreatment with heparin before randomization were no longer detectable in 63.6% of patients with

elevated TnT levels after infusion therapy with abciximab (placebo, 23.8%; $P<0.001$). In TnT-negative patients, incidence of visible thrombus was low, and no difference was documented for treatment with abciximab versus placebo. However, treatment with abciximab was effective with respect to the reduction of death and nonfatal AMI at 30-day follow-up in both patients with and without visible thrombus formation. This might, at least in part, be due to the relatively low incidence of angiographically detectable thrombus formation. In contrast, complex lesion characteristics served as a significant predictor for benefit of treatment with abciximab. Cardiac risk was elevated in patients with type B2 and C lesions when patients were allocated to placebo (OR, 2.5; 95% CI, 1.3 to 3.1; $P=0.03$), but it did not significantly differ from patients with less complex lesions when they were given abciximab (OR, 1.4; 95% CI, 0.7 to 1.9; $P=0.43$). In multivariate analysis, however, only TnT, not complex lesion characteristics, provided a significant predictive way to identify the subgroup of patients who received the highest benefit from treatment with abciximab (OR, 0.23 for TnT-negative versus 1.26 for TnT-positive; $P<0.001$). Regarding the predictive value of lesion morphology, these findings contrast with results from the more heterogeneous population enrolled in the EPILOG (Evaluation in PTCA to Improve Long-term Outcome by C7E3 GP IIb/IIIa receptor blockade) trial, indicating a reduction of early adverse ischemic events by abciximab that was mainly independent of lesion morphology.[28]

In conclusion, the data presented here indicate that TnT elevation was significantly linked to morphological complexity of the target lesion and to visibility of thrombus formation, even after prolonged treatment with heparin. We further suggest that troponin release can be interpreted as a surrogate marker for more complex lesion characteristics and for microembolization from liable thrombus formation. Although failed resolution of thrombus and complex lesion characteristics provide important prognostic information, our data suggest that TnT determination represents the independent and most powerful marker for the prediction of cardiac risk. TnT, but not angiographic findings, was predictive for efficacy of treatment with abciximab in patients with unstable angina.

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