Does pre-treatment with aspirin and loading dose clopidogrel obviate the need for glycoprotein IIb/IIIa antagonists during elective coronary stenting? A focus on peri-procedural myonecrosis

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Aims Although full platelet inhibition with aspirin and thienopyridines before coronary stenting has significantly reduced the risk of acute stent thrombosis, peri-procedural myonecrosis still occurs frequently and is associated with increased death rate. Whether further inhibition of platelet aggregation by a glycoprotein IIb/IIIa antagonist may provide an additional cardioprotection is unknown.

Methods and results A total of 200 patients pre-treated with aspirin and a loading dose of clopidogrel (450 mg) were randomized just before coronary intervention (percutaneous coronary intervention, PCI) to treatment with or without abciximab. Platelet aggregation was assessed in samples collected during the procedure and the degree of platelet aggregation inhibition was correlated with cardiac enzyme release post-PCI. Abciximab treatment achieved a more complete inhibition of aggregation than dual oral antiplatelet therapy alone (median value of 1 vs. 50%, normal 100%). Any pathological increase in creatinine kinase-MB (CK-MB) post-PCI was present in 21% of the abciximab group (P = 0.9). Also the occurrence of clinically relevant myonecrosis [myocardial infarction (MI) ≥ CK-MB upper limit of normal] was not significantly influenced by treatment assignment: 9 vs. 10% (P = 0.9). In a multiple logistic regression model including clinical, angiographic, and procedural characteristics, post-PCI myonecrosis was not correlated with the degree of platelet aggregation inhibition but with procedural features (such as long inflation time) and with the presence of multi-vessel disease. There were no cases of acute or sub-acute stent thrombosis. At 6 months, major adverse cardiac events, including cardiac death, non-fatal MI, or target lesion revascularization occurred in 13% of abciximab patients and in 16% of the control patients (P = 0.6).

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Conclusions In the studied patients scheduled for elective coronary stenting and pre-treated with aspirin and a loading dose of clopidogrel, further inhibition of platelet aggregation by abciximab does not afford additional cardioprotection. Our data suggest that distal athero-embolization rather than thrombo-embolization is involved in the phenomenon of myonecrosis post-elective stenting.

Introduction

Intracoronary stenting is widely used to treat coronary artery stenotic disease. Although enthusiasm for stenting was initially tempered by a high rate of subacute stent thrombosis (>15%), this technique enjoyed explosive growth once the major risks were eliminated by appropriate stent expansion and adequate deployment, and by enhanced antiplatelet therapy. Indeed, randomized clinical trials have evidently shown that addition of thienopyridines to standard aspirin results in a significant reduction of reocclusions after stent implantation in patients with both stable and unstable coronary syndromes. More recent studies with the more powerful glycoprotein (GP) IIb/IIIa receptor antagonists have shown that these new drugs superiorly prevent ischaemic complications after percutaneous coronary interventions (PCIs), compared with standard antiplatelet therapy with aspirin and ticlopidine or clopidogrel (risk reduction up to 50%). Ischaemic complications were mainly driven by myonecrosis which occurred in the peri-procedural period. In these studies, however, ticlopidine or clopidogrel was mostly given close to the procedure indicating that the level of platelet aggregation inhibition was insufficient at the time of the intervention. Previous studies with thienopyridines have emphasized that an optimal level of platelet inhibition at the time of intervention is a pre-requisite for optimal cardioprotection during coronary stenting. The issue arises of whether further inhibition of platelet aggregation by GP IIb/IIIa antagonists during elective coronary stenting is still beneficial if patients were optimally pre-treated with dual oral antiplatelet.

Therefore we designed a study to evaluate whether addition of abciximab to a pre-treatment regimen with aspirin and a loading dose of clopidogrel provides additional cardioprotection in patients undergoing elective coronary stenting. We especially focused on the correlation between the level of platelet aggregation inhibition, as assessed by ex vivo aggregation tests and the occurrence of ischaemic complications in terms of peri-procedural myonecrosis.

Methods

Study population

Between October 2001 and November 2003 a total of 200 patients [median age 67 (interquartile range 59, 73) years] who were scheduled for elective coronary stenting were prospectively enrolled into this single-centre open-label controlled randomized trial.

Exclusion criteria were acute coronary syndromes requiring urgent coronary intervention or early treatment with GP IIb/ IIIa receptor antagonists, recent myocardial infarction (MI), intervention of lesions located in bypass grafts or near major side branches, and the presence of an angiographically visible intracoronary thrombus. Also, patients with creatinine value >2.0 mg%, with haemostatic disorders, or with a history of intolerance to thienopyridines or to abciximab were excluded.

The study protocol was approved by the Institutional Ethics Committee of the Antwerp University Hospital and all patients provided written informed consent.

Study protocol and study medication

All 200 patients were pre-treated with 450 mg clopidogrel and 160 mg aspirin and randomized for no addition (n = 100) or addition (n = 100) of abciximab. Patients received 300 mg clopidogrel in the evening preceding the coronary intervention and 150 mg on the morning of the intervention. We previously have shown that administration of this loading dose of 450 mg (300 + 150 mg) more efficiently accelerates the inhibition of adenosine diphosphate (ADP)-induced platelet aggregation at the time of the intervention compared with the conventional dosing regimen of 375 mg (300 + 75 mg) clopidogrel.

According to the randomization protocol, abciximab was administered in 100 patients just before intervention as an intravenous bolus (0.25 μg/kg) followed by a 12-h infusion (10 μg/min). Clopidogrel 75 mg/day was continued for 4 weeks in all patients. Unfractionated heparin was given at the beginning of the procedure and titrated in order to obtain activated clotting time (ACT) levels between 300 and 350 s for procedures without abciximab and between 200 and 250 s for procedures under treatment with abciximab.

Coronary angioplasty and stenting procedure were performed using low osmolar, non-ionic contrast agents (iopromid) with standard percutaneous techniques by highly experienced operators (individual operator volume of >250 angioplasty procedures per year). The inflation and stent protocol was left to the discretion of the operator. No drug-eluting or coated stents were applied in this study. For patients allocated to the no-abciximab group, bail-out GP IIb/IIIa inhibitor use was allowed in case of abrupt vessel closure, no reflow, or visible thrombus formation during PCI.

Platelet aggregation test

Ex vivo platelet aggregation was measured on blood samples taken at the end of the intervention by classical optical aggregometry (Aggrecorder II; DIC, Kyoto, Japan) after stimulation with 20 μmol/L ADP and by rapid platelet function assay (PFA) (PFA-100, Dade-Behring) as has been previously described. A PFA test was also performed in the morning after the intervention. Blood samples were collected in Becton-Dickinson vacutainer tubes containing 0.129 M trisodium citrate and were measured within 30 min of collection. Results of optical aggregometry were expressed as percentage of platelet aggregation.
ranging from 100 (=normal aggregation) to 0 (=complete inhibition of aggregation) and were available in 143 patients. In 57 patients optical aggregometry could not be performed for logistical reasons. Results of the PFA test were expressed as a closure time (time in seconds until blood flow stopped) ranging from 70 (=normal aggregation) to 300 s (complete inhibition of aggregation) and were available in 199 patients.

Cardiac enzyme release and myonecrosis

Blood samples for analysis of cardiac enzyme release were collected at the time of the intervention and 16–22 h after the intervention. Creatinine kinase MB (CK-MB) mass and cardiac troponin I (cTnI) levels were obtained according to standard enzymatic procedures. Laboratory upper limits of normal (ULN) were 2.37 ng/mL for CK-MB and 0.08 ng/mL for cTnI. Clinically relevant myonecrosis post-PCI was defined as CK-MB elevation >3 × ULN.

Angiographic data analysis

Digital coronary angiographic recordings were quantitatively analysed with a computer-based cardiovascular angiography analysis system (CAAS II, Pie Medical Data, The Netherlands). Stenosis severity was calculated from the minimal luminal diameter (MLD) and a computer-estimated reference diameter and expressed as percentage diameter stenosis. The empty catheter was used as a scaling device. Multivessel disease was defined as the presence of a lesion with >50% diameter stenosis in at least two coronary arteries. Lesion morphology was assessed using the ABC stenosis morphology classification of the American College of Cardiology/American Heart Association and a B2 or C type lesion was defined as a complex lesion.

Thrombosis in myocardial infarction TIMI (TIMI) frame count in the vascular region distal to the target lesion was measured according to previously published methods and was applied to assess integrity of microvascular circulation post-intervention.

Clinical outcome and complications

Patients were followed up for 6 months with data being recorded from clinic visits and/or telephone calls. Major adverse cardiac events (MACEs) encompassed a composite endpoint of cardiac death, MI, and revascularization of target lesion and could be obtained in 198 patients. One event, the most serious in the above order, was tabulated for each patient. MI in the peri-procedural period was defined as CK-MB release of more than 3 × ULN. Outside the peri-procedural period MI was defined as the presence of new electrocardiographic signs of MI together with typical rise and fall of cardiac biomarkers or with newly documented occlusion of the infarct-related vessel.

Bleeding was defined as any clinically overt sign of haemorrhage that was associated with a fall in haemoglobin of >3 g/dL or the occurrence of intracranial bleeding. Vascular access complications were defined as the presence of a large (>3 cm) pseudo-aneurysm or a major haemorrhage requiring surgical drainage.

Statistical analysis

The primary endpoint of the study was the occurrence of myonecrosis post-PCI defined as CK-MB release of >1 × ULN. The study was initially designed to have 90% power to detect a 50% reduction in the incidence of post-PCI myonecrosis with abciximab treatment assuming an event rate of 25% in the control group. On this basis, a total of 400 patients had to be randomized. After 200 patients, interim analysis revealed a less than 10% effect of abciximab on myonecrosis (instead of the expected 50%). It was decided to stop enrolment as type II error would remain present even if 400 patients were recruited.

Comparison between study groups was performed using the Mann–Whitney U test for continuous variables and the χ² test for discrete variables. Two-way analysis of variance for repeated measurements was used to evaluate interaction between study groups for cardiac enzyme release. Two-way analysis of variance was applied to compare post-PCI TIMI frame count between the two study groups for the three different coronary arteries.

Regression analysis was carried out to correlate the level of platelet aggregation inhibition with the extent of cardiac enzyme release post-PCI. To identify determinants of myonecrosis multiple logistic regression analysis was performed including clinical (age, sex, cardiac history, diabetes, intake of lipid-lowering therapy and beta-blocking agents, treatment assignment), angiographic (lesion characteristics, multi-vessel disease, post-PCI angiographic result), procedural (balloon inflation duration and pressure, stent to reference diameter ratio), and laboratory variables (ACT, PFA). Results are reported as median with 25th and 75th percentiles. A two-sided P-value of less than 0.05 was considered significant.

Results

Population characteristics

Clinical and procedural variables are comparable among both study populations (see Table 1) except for slightly longer lesions and less lipid-lowering therapy in the abciximab group. One-third of the patients were admitted with unstable angina pectoris and underwent elective coronary intervention after initial medical stabilization. Three no-abciximab patients received bail-out treatment with abciximab. In the abciximab study population bail-out conditions occurred in two patients.

Abciximab patients achieved almost complete inhibition of platelet aggregation [median of 1% (0, 5) with aggregometry test and median of 280 s (237, 300) with PFA test] whereas no-abciximab patients achieved an intermediate level of suppression as a result of dual oral antiplatelet therapy [median of 50% (38, 63) with aggregometry test and median of 124 s (98, 238) with PFA test]. The level of anti-aggregation in the morning after the intervention was lower than at the time of intervention: PFA value of 258 s (215, 300) for abciximab patients and 90 s (69, 170) for no-abciximab patients (P = 0.004). Because of protocol-related differences in heparin regimen, ACT levels were lower in the abciximab patients [median value of 247 s (208, 294) vs. 312 s (260, 358)]

Post-interventional myonecrosis

Post-interventional CK-MB and troponin levels increased slightly but significantly in both study groups but without interaction effect of treatment assignment (P = 0.4 and P = 0.9, respectively). The net cardiac
enzyme increase did not differ between the two study groups: \( \Delta \text{CK-MB} \) of 0 (0, 1.2) ng/mL and \( \Delta \text{TnI} \) of 0 (0, 0.12) ng/mL in abciximab patients vs. 0.2 (0, 1.3) and 0 (0, 0.18) ng/mL in no-abciximab patients (\( P = 0.5 \) and \( P = 0.4 \), respectively) (see also Table 2).

Any pathological increase (>1 × ULN) in CK-MB was present in 21 abciximab patients and in 22 no-abciximab patients (\( P = 0.9 \)). Any pathological increase (>1 × ULN) in cTnI was observed in 30 abciximab patients and in 39 no-abciximab patients (\( P = 0.2 \)).

There was also no significant difference in incidence of clinically relevant myocardial necrosis (CK-MB > 3 × ULN): 9 abciximab patients vs. 10 no-abciximab patients (\( P = 0.9 \)). All peri-procedural infarctions were non-Q-wave infarctions and occurred in the absence of acute or subacute stent thrombosis.
Abciximab treatment had no affect on myocardial flow post-PCI as assessed by TIMI frame count (cf Table 2).

Abciximab treatment also had no effect ($P = 0.9$) on post-PCI myonecrosis if study groups were stratified according to intake of lipid-lowering therapy or lesion length.

The correlation between cardiac enzyme release post-PCI and the level of platelet aggregation inhibition is depicted in Figure 1. There was a wide range in the degree of platelet aggregation inhibition in the total study population but there was no correlation at all between $\Delta$CK-MB and the degree of platelet aggregation inhibition measured by PFA (see Figure 1A) or by optical aggregometry (Figure 1B) ($r^2 = 0.001$, $P = 0.7$ for both measurements).

To elaborate further upon the importance of the level of platelet aggregation inhibition in the occurrence of myonecrosis, multiple logistic regression analysis was performed which also included clinical, angiographic, and procedural variables. Treatment assignment (abciximab vs. no abciximab) and the degree of platelet aggregation inhibition did not influence the incidence of myonecrosis as defined by any pathological increase in cardiac enzyme or by CK-MB release $\geq 3 \times$ ULN ($P > 0.5$). The occurrence of clinically relevant myonecrosis was mainly related to long inflation duration ($P = 0.01$), to high balloon inflation pressure ($P = 0.03$), to the absence of lipid lowering therapy or beta-blocking agents ($P = 0.04$), and to the presence of multi-vessel disease ($P = 0.05$) (see Table 3).

### Clinical outcome

During the clinical follow-up period of 6 months, a total of 29 patients suffered from at least one major adverse cardiac event. There were three cardiac deaths, 20 non-fatal MIs, and 10 revascularizations of the target lesion.

MI was related to peri-procedural myonecrosis in 19 patients. One no-abciximab patient developed a silent Q-wave infarction due to stent occlusion during the follow-up period as was documented on a control angiography. One no-abciximab patient underwent urgent surgical revascularization because of the impossibility of implanting a stent. The MACE rate was comparable between the two study groups: at 1 month, 9 in the abciximab group vs. 11 in the no-abciximab group ($P = 0.7$), at 6 months, 13 in abciximab group vs. 16 in the no-abciximab group ($P = 0.6$, see Figure 2).

The difference between 1 and 6 months was mainly related to revascularization of the target lesion.

There were four bleeding complications and seven vascular complications. Bleeding or vascular complications tended to occur more frequently in the abciximab group (8 vs. 3, $P = 0.1$). Three patients (all in the abciximab group) showed transient thrombocytopaenia ($<100,000 \, \text{mL}$) during index hospitalization.

### Discussion

Coronary stenting has been shown to induce prolonged platelet activation and surface expression of adhesive GPs. The recognition that these platelet-mediated mechanisms contribute to the pathogenesis of thrombotic complications post-coronary stenting led to the development of more powerful antiplatelet regimens such as thienopyridines and GP IIb/IIIa antagonists on top of aspirin. The combination of aspirin and thienopyridines not only inhibits arachidonic acid- and ADP-induced platelet activation but also reduces collagen- and thrombin-induced platelet activation. GP IIb/IIIa antagonists completely block the final common pathway for platelet aggregation and achieve even stronger antiplatelet effects during coronary stenting compared with

<table>
<thead>
<tr>
<th>Table 2 Post-Intervention myonecrosis and myocardial flow</th>
<th>Abciximab (n = 100)</th>
<th>No abciximab (n = 100)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myonecrosis</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CK-MB Post-PCI, ng/mL</td>
<td>0.7 (0.3, 2.5)</td>
<td>0.9 (0.5, 2.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>$\Delta$CK-MB, ng/mL</td>
<td>0 (0, 1.2)</td>
<td>0.2 (0, 1.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>cTnI Post PCI, ng/mL</td>
<td>0.06 (0.04, 0.3)</td>
<td>0.1 (0.04, 0.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>$\Delta$cTnI, ng/mL</td>
<td>0 (0, 0.12)</td>
<td>0 (0, 0.18)</td>
<td>0.4</td>
</tr>
<tr>
<td>Number of patients, %</td>
<td></td>
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<tr>
<td>with cTnI post-PCI $&gt;1 \times$ ULN</td>
<td>30</td>
<td>39</td>
<td>0.2</td>
</tr>
<tr>
<td>with CK-MB post-PCI $&gt;1 \times$ ULN</td>
<td>21</td>
<td>22</td>
<td>0.9</td>
</tr>
<tr>
<td>with CK-MB post-PCI $&gt;3 \times$ ULN (=clinically relevant myonecrosis)</td>
<td>9</td>
<td>10</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>TIMI frame count</strong></td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>LAD</td>
<td>31 (21, 37)</td>
<td>38 (26, 45)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>18 (13, 26)</td>
<td>19 (14, 25)</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>26 (19, 32)</td>
<td>25 (18, 31)</td>
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</tr>
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</table>

Continuous variables are presented as median with 25th and 75th percentiles.

$\Delta$, net cardiac enzyme increase.
In the present randomized clinical study, pre-treatment with a loading dose of clopidogrel (450 mg) plus aspirin resulted in almost 50% inhibition of platelet aggregation during the PCI procedure compared with more than 90% inhibition of platelet aggregation by abciximab on top of a loading dose of clopidogrel plus aspirin. (According to our own historical database, aspirin intake alone induces only a 25% inhibition of platelet aggregation inhibition.) Under these conditions we could not demonstrate an additional cardioprotective effect from abciximab in terms of death, MI, or target lesion revascularization. Myonecrosis post-PCI (that is, any pathological CK-MB release) occurred in about 20% in both study groups. There was no correlation between the degree of platelet aggregation inhibition and cardiac enzyme release post-PCI. The results of the present study concur with the recently published data from the Intra-coronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment (ISAR-REACT) study.\textsuperscript{18} In the ISAR-REACT study, patients scheduled to undergo coronary stenting received a high loading dose of 600 mg clopidogrel at least 2 h before the procedure and were then randomized to receive either abciximab and reduced-dose heparin or standard-dose heparin and placebo. Treatment with abciximab had no beneficial effect on major cardiac events at 1 month with an MI rate of 4% in each group. In the ISAR-REACT study, MI was defined as an increase of CK-MB $>3 \times$ ULN in at least two samples whereas in the present study MI diagnosis was made on one sample post-PCI. This may explain the higher observed rate of MI (9%) in the present study. In addition, differences in study population (the present study also included patients with stabilized acute coronary syndromes, which was an exclusion criterion in ISAR-REACT) may account for the
observed differences in MI rate. The lack of beneficial effect of abciximab in both studies is probably related to an optimal pre-treatment with a loading dose of clopidogrel. In ISAR-REACT this was achieved by administering an early high dose (600 mg) before intervention. In the present study a loading dose of 300 mg in the evening preceding the intervention plus 150 mg in the morning of the procedure was able to achieve sufficient inhibition of platelet aggregation. Recent studies have indeed found that 6 h or longer are needed with a 300-mg loading dose, or larger doses in the range of 600 mg are necessary to achieve maximal effects more rapidly.\textsuperscript{9,19}

In view of these findings it is tempting to try to find out why the ex vivo superiority of platelet aggregation inhibition by abciximab, compared with dual oral antiplatelet therapy, did not translate into a clinical benefit, especially with regard to prevention of peri-procedural myonecrosis. Rise in CK-MB is actually the most common post-PCI adverse event and current evidence supports its negative prognostic value, particularly for larger increases in CK-MB ($>3 \times \text{ULN}$).\textsuperscript{14} The mechanism of post-PCI cardiac enzyme release is due either to angiographic epicardial coronary complications (e.g. side branch occlusion) or to impairment of the microcirculation. Cardiac magnetic resonance imaging has shown localized myonecrosis (hyper-enhancement) in patients with post-PCI CK-MB elevation without side branch occlusion, suggesting micro-embolization of atherogenic and/or thrombogenic material.\textsuperscript{20} Antiplatelet therapy (both with thienopyridines and GP IIb/IIIa antagonists) has been associated with reduction in peri-procedural MIs especially in patients undergoing otherwise uneventful coronary stent implantation, presumably by prevention of thrombo-embolization.\textsuperscript{21,22} In our study population, there was no correlation between CK-MB release and the degree of aggregation inhibition, suggesting that thrombo-embolization was already sufficiently prevented by dual oral antiplatelet therapy and could not be further

\begin{table}
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 & \textbf{MI (n = 19)} & \textbf{No MI (n = 181)} & \textbf{RR (95\%CI)} & \textbf{P} \\
\hline
\textbf{Age, years} & 70 (64, 76) & 66 (59, 73) & 1.04 (0.96–1.13) & 0.3 \\
\textbf{Male, n (\%)} & 14 (73) & 125 (69) & 1.02 (0.19–5.4) & 0.9 \\
\textbf{Unstable angina, n (\%)} & 5 (27) & 63 (35) & 0.38 (0.05–2.7) & 0.3 \\
\textbf{Diabetes, n (\%)} & 4 (22) & 29 (16) & 2.6 (0.4–16.7) & 0.3 \\
\textbf{Lipid-lowering therapy, n (\%)} & 4 (21) & 67 (37) & 0.1 (0.01–0.93) & 0.04 \\
\textbf{Beta-blocking agent, n (\%)} & 11 (57) & 130 (72) & 0.19 (0.04–0.93) & 0.04 \\
\textbf{Abciximab therapy, n (\%)} & 9 (47) & 91 (50) & 0.66 (0.07–6.3) & 0.7 \\
\textbf{Multi-vessel disease, n (\%)} & 13 (68) & 72 (40) & 4.3 (1.01–18.5) & 0.05 \\
\textbf{Lesion length, mm} & 9 (7, 12) & 11 (8, 16) & 0.96 (0.86–1.08) & 0.6 \\
\textbf{Complex lesion, n (\%)} & 6 (32) & 89 (49) & 0.8 (0.2–3.9) & 0.8 \\
\textbf{Post-PCI DS \%} & 13 (4, 18) & 10 (4, 15) & 1.04 (0.94–1.14) & 0.5 \\
\textbf{Balloon inflation} & & & & \\
\textbf{Total duration, s} & 33 (12, 93) & 27 (16, 41) & 1.013 (1.003–1.022) & 0.01 \\
\textbf{Maximal pressure, atm} & 20 (16, 20) & 16 (12, 19) & 1.34 (1.03–1.76) & 0.03 \\
\textbf{Stent/ref. diameter} & 1.04 (0.95, 1.13) & 1.06 (1.0, 1.14) & 0.994 (0.986–1.002) & 0.12 \\
\textbf{Contrast quantity, mL} & 170 (134, 200) & 130 (100, 180) & 1.01 (0.996–1.027) & 0.15 \\
\textbf{ACT, s} & 294 (235, 365) & 280 (230, 330) & 1.008 (0.999–1.017) & 0.1 \\
\textbf{PFA, s} & 231 (123, 277) & 236 (122, 300) & 0.998 (0.986–1.010) & 0.7 \\
\hline
\end{tabular}
\caption{Determinants of post-PCI myonecrosis}
\end{table}

Continuous variables are presented as median with 25th and 75th percentiles.

Figure 2 Box plot showing the incidence of MACEs during 6 months’ follow-up including cardiac death (D), non-fatal MI, and target lesion revascularization (TLR) for abciximab patients (grey box) and no-abciximab patients (white box). There were no significant differences between groups.
attenuated by GP IIb/IIIa antagonists. Embolization of ruptured atherosclerotic plaque material may account for the observed myonecrosis post-PCI in our study population. Additional evidence for this argument comes from the observation that myonecrosis occurred more frequently in patients with multi-vessel disease and during procedures with high pressure and/or long balloon inflation reflecting situations of increased plaque burden. These situations are unlikely to be responsive to aggressive antiplatelet therapy with GP IIb/IIIa antagonists as was also shown in studies dealing with venous graft interventions. Protection of the microcirculation by distal emboli protection devices or by using lipid-lowering therapy might be more effective in these situations.

Some limitations of the present study deserve further consideration. Due to the small observed differences in event rate, a type II error may affect the interpretation of the results. We have tried to overcome this issue by correlating incidence of myonecrosis with level of platelet aggregation and with other potentially confounding factors.

Platelet aggregation was assessed by classical aggregometry after addition of 20 μmol/L adenosine and by a rapid platelet function test (PFA-100). We did not use other agonists of platelet activation such as thrombin, and we did not look for expression of platelet membrane adhesive receptors. In view of the well-known variability in the platelet inhibitory response to clopidogrel, further studies relating the degree of platelet aggregation inhibition to the prevention of ischaemic complications post-PCI are keenly welcome and should clarify whether on-site measurement of platelet function is required to adjust antiplatelet therapy in patients receiving only dual antiplatelet therapy for elective coronary stenting.

In conclusion, in patients scheduled for elective coronary stenting and pre-treated with aspirin plus loading-dose clopidogrel, further inhibition of platelet aggregation by abciximab does not afford additional cardioprotection. Our data suggest that myonecrosis post-PCI in those patients is related more to distal athero-embolization than to thrombo-embolization.

Acknowledgements

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References