Prognostic Implications of myocardial injury around percutaneous coronary interventions

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Chapter 3

Pre-treatment with clopidogrel and postprocedure troponin elevation after elective percutaneous coronary intervention

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ABSTRACT

**Background:** Elevated troponin after elective percutaneous coronary intervention (PCI) has been associated with a worse prognosis. Pre-treatment with clopidogrel may be beneficial in patients undergoing PCI. Therefore, a prospective observational study was conducted to address the potential role of clopidogrel in reducing troponin release after elective PCI.

**Methods:** Troponin T was measured 12 hours after elective PCI in 656 patients without elevated troponin before PCI. To assess the independent association between pre-treatment with clopidogrel and increased troponin, multivariate analyses were performed.

**Results:** Mean age of the 656 patients was 63.5 years (SD 10.2), 194 patients (30%) were female and 114 patients (17.4%) had diabetes. In 217 patients (33%) troponin was increased after PCI. Of the 330 patients who were not pre-treated with clopidogrel, 118 patients (34%) had increased troponin after the PCI compared to 99 patients (30%) of the 326 patients who were treated with clopidogrel longer than 24 hours before the procedure (p=0.14). Stratified analyses showed that patients with older age (p=0.03), previous PCI (p=0.013), angina CCS 4 (p=0.03) and multivessel disease (p=0.04) had a significantly lower risk of troponin increase after pre-treatment with clopidogrel compared to patients without pre-treatment. After adjusting for differences in the other variables, patients who were pre-treated with clopidogrel had a significant lower risk of post-PCI increase of troponin T (odds ratio 0.69, 95% confidence interval 0.49-0.99).

**Conclusion:** Pre-treatment with clopidogrel is associated with a significantly lower incidence of increased troponin after elective PCI. Combined with results of other studies, pre-treatment should be advised in patients waiting for elective PCI.
Introduction

Intensive antiplatelet therapy is the cornerstone of pharmacological treatment of patients undergoing percutaneous coronary intervention (PCI) and may consist of aspirin, GP IIb/IIIa inhibitors and the ADP antagonist clopidogrel [1-3]. In addition to postprocedural treatment with clopidogrel, treatment with clopidogrel before PCI may also be beneficial [4-8], although a small study could not confirm this observation [9]. However, these data are based on selected patients included in randomised clinical trials, and the results may be not comparable to these observed in daily practice.

Postprocedural rise of troponin levels has been associated with an increased incidence of cardiac events during follow-up [10,11]. Troponin release occurs in approximately 30% of patients and has been related to complications during the procedure, including sapheneous vein graft interventions, multistent use, glycoprotein IIb/IIIa use, and a history of hypercholesterolemia [12]. We studied the potential association between pre-treatment with clopidogrel on the postprocedural troponin levels in consecutive, unselected patients undergoing elective PCI in daily practice.

Methods

Study population

A prospective, observational study was performed. The patient cohort included unselected patients who underwent elective PCI between June 2002 and August 2003 in a single centre (Isala klinieken, Zwolle, the Netherlands). All patients had symptomatic coronary artery disease with objective signs of ischemia. Patients with PCI for ST-segment elevation MI were excluded, as well as patients with urgent PCI for severe unstable coronary artery disease. The remaining patients consisted of outpatients with stable angina and patients referred from other hospitals with more severe or progressive angina. At the time when the study was performed, routine use of clopidogrel before PCI was not advised, leaving it at the discretion of the referring treating cardiologist. Use of clopidogrel before PCI was defined as starting clopidogrel more than 24 hours before PCI. All patients who were not treated with clopidogrel before the PCI received a loading dose of 300 mg clopidogrel just before the procedure. All patients were treated with clopidogrel 75 mg once daily for at least 28 days after the procedure.
Pre-treatment with clopidogrel

Procedure and laboratory testing
Routine care before and after the procedure was undertaken for all patients, including the preprocedural use of aspirin and a bolus of intravenous heparin (5000 U) at the beginning of the procedure. Use of stents or GP IIb-IIIa inhibitors was left at the discretion of the interventional cardiologist.

A blood sample was routinely obtained from all patients just before the interventional procedure in the catheterisation room. The second sample was taken the day after, 12-16 hours after the procedure. All samples were prepared and stored locally in our core laboratory at -70°C until analysis.

Troponin T was analysed using the third generation troponin T test (Roche diagnostics, Mannheim, Germany) with a threshold of 0.01 ng/ml, which was used in our study as the cut-off value.

Statistical analysis
Differences in baseline characteristics between patients with and without clopidogrel pre-treatment and those with and without increased troponin after the PCI procedure were compared by means of the Chi-square test or Fisher’s exact test for proportions and Student’s t test for continuous variables. Multivariate analysis (logistic regression analysis) was performed to assess the independent association between pre-treatment with clopidogrel and increased troponin level after the procedure. A two-tailed p value of <0.05 was considered statistically significant. All analyses were performed with SPSS statistical software (SPSS Inc., Chicago, Illinois).

Results
Of 745 patients enrolled in the study, data on treatment with clopidogrel before admission was available in 714 patients (96%). Of these 714 patients, a total of 656 patients (92%) had no elevated troponin T (<0.01 ng/ml) before the PCI and these patients represent the final study group. Mean age was 63.5 years (SD 10.2), 194 patients (30%) were female and 114 patients (17.4%) had diabetes. Multivessel disease was present in 314 patients (48%), and 101 patients (15%) had CCS class 4 angina.
In a total of 326 patients (50%), clopidogrel was started 24 hours or more before PCI. Differences between patients with and without pre-treatment with clopidogrel are summarised in table 1. Patients who were pre-treated with clopidogrel were younger, were more often waiting in a referring hospital for the PCI and had less often diabetes or a history of PCI. Patients with angina class 4 more often had clopidogrel started 24 hours or more before the PCI.

**Table 1.** Baseline clinical and target lesion characteristics of 656 patients with elective PCI, data on preprocedure start of clopidogrel and without increased troponin T before the procedure.

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel Pretreatment (n=326)</th>
<th>No Clopidogrel Pretreatment (n=330)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs (sd)</td>
<td>62.6 (±10.6)</td>
<td>64.4 (±9.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female</td>
<td>105 (32)</td>
<td>89 (27)</td>
<td>0.14</td>
</tr>
<tr>
<td>Waiting in hospital for PCI</td>
<td>47 (15)</td>
<td>29 (9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>46 (14)</td>
<td>68 (21)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>182 (71)</td>
<td>186 (66)</td>
<td>0.23</td>
</tr>
<tr>
<td>Smoking</td>
<td>121 (38)</td>
<td>88 (28)</td>
<td>0.01</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>113 (38)</td>
<td>123 (40)</td>
<td>0.54</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>144 (44)</td>
<td>139 (42)</td>
<td>0.60</td>
</tr>
<tr>
<td>PCI</td>
<td>69 (21)</td>
<td>103 (31)</td>
<td>0.004</td>
</tr>
<tr>
<td>Coronary bypass grafting</td>
<td>28 (9)</td>
<td>44 (13)</td>
<td>0.05</td>
</tr>
<tr>
<td>Stroke</td>
<td>26 (8)</td>
<td>21 (6)</td>
<td>0.42</td>
</tr>
<tr>
<td>Use of stent</td>
<td>235 (72)</td>
<td>227 (69)</td>
<td>0.35</td>
</tr>
<tr>
<td>Angina CCS 4</td>
<td>81 (25)</td>
<td>20 (6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Multivessel Disease</td>
<td>155 (48)</td>
<td>159 (48)</td>
<td>0.87</td>
</tr>
<tr>
<td>RCA</td>
<td>98 (30)</td>
<td>81 (25)</td>
<td>0.16</td>
</tr>
<tr>
<td>LAD</td>
<td>155 (48)</td>
<td>128 (39)</td>
<td>0.02</td>
</tr>
<tr>
<td>Multivessel PCI</td>
<td>63 (19)</td>
<td>69 (21)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

All in n (%), except when is indicated else

In 217 patients (33%), troponin was increased after the PCI. Differences between patients with and without increased troponin after the PCI are shown in table 2. Patients with increased troponin more often had multivessel disease, all other variables were not significantly different. Of the 330 patients who were not pre-treated with clopidogrel, 118 patients (34%) had increased troponin after the PCI compared to 99 patients (30%) of the 326 patients who were treated longer than 24 hours before the PCI with clopidogrel (p=0.14). During hospital admission, there were no patients with intracerebral hemorrhage or signs of stroke.
Pre-treatment with clopidogrel

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Troponin not increased (n=439)</th>
<th>Troponin increased (n=217)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>37 (17)</td>
<td>77 (18)</td>
<td>0.87</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>248 (68)</td>
<td>116 (68)</td>
<td>0.98</td>
</tr>
<tr>
<td>Smoking</td>
<td>139 (33)</td>
<td>70 (33)</td>
<td>0.86</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>161 (39)</td>
<td>75 (38)</td>
<td>0.66</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>193 (44)</td>
<td>121 (56)</td>
<td>0.004</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>187 (43)</td>
<td>96 (44)</td>
<td>0.67</td>
</tr>
<tr>
<td>PCI</td>
<td>124 (28)</td>
<td>48 (22)</td>
<td>0.10</td>
</tr>
<tr>
<td>Coronary bypass grafting</td>
<td>53 (12)</td>
<td>19 (9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Stroke</td>
<td>26 (6)</td>
<td>21 (10)</td>
<td>0.08</td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>129 (29)</td>
<td>50 (23)</td>
<td>0.09</td>
</tr>
<tr>
<td>LAD</td>
<td>187 (43)</td>
<td>96 (44)</td>
<td>0.69</td>
</tr>
<tr>
<td>Multivessel PCI</td>
<td>69 (16)</td>
<td>63 (29)</td>
<td>0.001</td>
</tr>
<tr>
<td>Clopidogrel pre-treatment</td>
<td>227 (52)</td>
<td>99 (46)</td>
<td>0.14</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor pre-treatment</td>
<td>27 (6)</td>
<td>9 (4)</td>
<td>0.29</td>
</tr>
<tr>
<td>Stent</td>
<td>308 (70)</td>
<td>154 (72)</td>
<td>0.70</td>
</tr>
<tr>
<td>Angina CCS4</td>
<td>63 (14)</td>
<td>38 (18)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

All in n (%), except when is indicated else

A stratified analysis was performed to assess whether specific subgroups had more benefit of pre-treatment with clopidogrel (Figure 1). There was a consistent reduction of the risk of troponin elevation after PCI after pre-treatment with clopidogrel in all subgroups. It was demonstrated that particularly patients at older age (p=0.03), with previous PCI (p=0.013), with angina CCS 4 (p=0.03) and multivessel disease (p=0.04) had a significantly lower risk of troponin increase after pre-treatment with clopidogrel.
Figure 1. Stratified analyses of risk of increased troponin after pre-treatment with clopidogrel in several subgroups (no pre-treatment is the reference group).
Pre-treatment with clopidogrel

Since there were several significant differences between patients with and without pre-treatment with clopidogrel, multivariate analysis was performed to assess the independent association between pre-treatment with clopidogrel and troponin increase after the PCI. The results of multivariate analyses are presented in table 3. After adjusting for differences in the other variables, patients who were pre-treated with clopidogrel had a significant lower risk of post-PCI increase of troponin T (odds ratio 0.69, 95% confidence interval 0.49-0.99; p=0.04).

Table 3. Predictors of increased troponin (>0.01 ng/ml) after elective PCI in 656 patients without increased troponin (<0.01 ng/ml) before the PCI and with data on clopidogrel use, multivariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (/year)</td>
<td>1.01</td>
<td>0.99-1.03</td>
<td>0.30</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.96</td>
<td>0.66-1.41</td>
<td>0.85</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.89</td>
<td>0.56-1.41</td>
<td>0.62</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>0.67</td>
<td>0.44-1.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Angina CCS 4</td>
<td>1.37</td>
<td>0.85-2.2</td>
<td>0.20</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.15</td>
<td>0.78-1.70</td>
<td>0.48</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.46</td>
<td>1.0-2.1</td>
<td>0.04</td>
</tr>
<tr>
<td>PCI of LAD</td>
<td>1.24</td>
<td>0.87-1.76</td>
<td>0.24</td>
</tr>
<tr>
<td>Multivessel PCI</td>
<td>2.07</td>
<td>1.37-3.15</td>
<td>0.001</td>
</tr>
<tr>
<td>Clopidogrel pretreatment</td>
<td>0.69</td>
<td>0.49-0.99</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Discussion

Our study shows that in patients undergoing elective PCI, pre-treatment with clopidogrel was associated with a decreased risk of elevated troponin after the PCI. Several subgroups, including older age and those with multivessel disease, CCS class 4 angina or previous PCI had particular benefit of pre-treatment with clopidogrel.

The results of our study are consistent with observations from randomised trials. In the TARGET study, 4809 patients undergoing elective or urgent PCI were randomised to tirofiban or abciximab. A sub-analysis of patients with clopidogrel pre-treatment showed a lower incidence of cardiovascular events at 30 days and a lower mortality at 1 year [4]. The beneficial effect of pre-treatment with clopidogrel was also suggested in the PCI-CURE study, involving patients with an acute coronary syndrome without ST-segment elevation [5]. Furthermore, Berglund et al found a significant beneficial effect of clopidogrel pre-treatment in
reducing myocardial infarction and percutaneous reintervention after PCI. However, this concerned a non-randomised study in patients with unstable coronary syndromes [6].

The Clopidogrel for the Reduction of Events During Observation (CREDO) study, including 2116 patients, has shown that pre-treatment with clopidogrel has no beneficial effects. However, when subgroup analysis was performed with regard to duration of pre-treatment, its seemed that a longer duration of pre-treatment (>6 hours) is beneficial [7]. In ISAR-REACT there was no difference in the 30 days outcome between those pre-treated with clopidogrel 2-3 hours versus >12 hours. However, this trial had many exclusion criteria, resulting in inclusion of a very low risk population [8]. In another small study in 203 patients undergoing elective stent implantation, clopidogrel pre-treatment of 3 days did reduce neither the post-procedural release of troponin I and CK-MB nor cardiovascular events during 6 months follow-up [9].

Several studies have been conducted to address platelet aggregation inhibition and the timing of clopidogrel administration. It has been shown that a 300 mg clopidogrel loading dose, given 3 to 24 hours before stenting, is associated with a better platelets inhibition and a reduced poststent activity, when compared to a 75 mg dose given at the time of the procedure [13]. In a non-randomized, observational study, the effects of a 600 mg loading dose of clopidogrel at different time periods before elective PCI were studied [14]. After 2 hours, the level of platelet aggregation and the surface expression of P-selectin and activated glycoprotein IIb/IIIa did not further change with time after clopidogrel administration. Furthermore, they could not demonstrate any difference in clinical endpoints at 30 days. The large inter-individual variability in the platelet inhibitory response from clopidogrel [15] and the inclusion of low-risk patients, in small studies, may possibly explain the failure to show significant differences between achieved platelet aggregation in patients with or without pre-treatment with clopidogrel [16,17].

Apart from direct effects on platelet aggregation, clopidogrel may also have effects on the inflammatory response. It has been demonstrated that clopidogrel pre-treatment (longer than 24 hours before PCI) reduces platelet inflammatory marker expression in patients undergoing PCI compared to patients without pre-treatment [18]. Although a high loading dose of 600 mg clopidogrel may optimise platelet inhibitory effects early after intervention and may provide a more effective protection against early thrombotic complications [14,19], the question remains
whether this has comparable effect on the inflammatory response. Therefore, further research on this topic might be necessary.

Our study confirms earlier reports that a relatively high number of patients with elective PCI develop elevated troponin, even if the procedure is successful and uncomplicated. These elevations, even when minor, have been associated with an increased incidence of repeat revascularisations, acute myocardial infarction and death [10,20-23].

Limitations
Our study has several limitations. We present data from a prospective, observational study, without randomisation. Because pre-treatment with clopidogrel was left to the discretion of the cardiologist, the decision for pre-treatment may have introduced confounding. Probably, patients who were pre-treated with clopidogrel may represent a more unstable group. It is therefore not surprising that significant differences could be observed between patients with and without pre-treatment with clopidogrel (table 1). Nevertheless, after correction for these confounding variables, a significantly lower risk of post PCI troponin rise was demonstrated in patients pre-treated with clopidogrel. We did not perform a sample size calculation. Because the sample size of the study was not very large, the number of patients in the subgroups were small. The study was not designed and powered to assess potential association between clopidogrel pre-treatment, troponin release and outcome. With our sample size and a low-risk population, a significant difference in events during follow-up can not be expected. Another limitation is that we had neither data on levels of platelet aggregation inhibition nor data on angiographic causes of troponin elevation, including loss of side branches, distal embolization or no-reflow. Also, we didn’t collect data on bleeding complications (although there were no patients with intracerebral hemorrhage).

Conclusion
Clopidogrel pre-treatment before elective PCI is associated with a decreased risk of post-PCI troponin rise. Combined with results of several randomised trials, pre-treatment with clopidogrel before elective PCI should be strongly considered.
References


Pre-treatment with clopidogrel


