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Mortality Reduction with Administration of Abciximab during Primary PCI is Confined to STEMI Patients with Complex Lesions

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Abstract

Aim: The optimal timing of abciximab administration (´up-stream´/´in-cath-lab´) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI) is unclear. Data suggest that patients with high-risk profiles benefit from abciximab the most. Complex lesion on coronary angiography (CAG) implies a high-risk profile. Thus, we aimed to investigate whether lesion type (complex/simple) predicted the effect of abciximab in STEMI-patients undergoing pPCI.

Methods and results: 2,935 STEMI-patients treated with pPCI were retrospectively stratified according to lesion type on CAG (complex/simple) and use of abciximab. Endpoints at 1 year were mortality, target vessel revascularization (TVR), myocardial infarction (MI), and the combination of these. Forty-seven percent had complex lesion on CAG. Among those, abciximab reduced one year mortality in both the univariate (from 12.7% to 7.8%, p=0.006) and the adjusted analysis (HR 0.62, CI 0.42-0.91, p=0.015). Patients with simple lesions had no mortality benefit of abciximab. Effect of abciximab on TVR or MI was neutral. Regarding the combined endpoint, abciximab treatment conferred a risk reduction in patients with complex lesions.

Conclusion: Benefit of abciximab in STEMI-patients undergoing pPCI was confined to those with complex lesions on CAG. Consequently, early abciximab treatment without knowledge of the lesion type may not be recommended.

Keywords: Abciximab; STEMI; Primary PCI; Complex coronary artery disease; Simple coronary artery disease

Introduction

In numerous randomized clinical trials (RCTs) the glycoprotein IIb/IIIa inhibitor (GPI), abciximab, has proved effective in reducing major adverse cardiac events (MACE) among patients with high-risk acute coronary syndrome (ACS) such as ST-segment elevation myocardial infarction (STEMI) [1-5]. The rationale of aggressive platelet inhibition with GPIs in patients with myocardial infarction (MI) is widely accepted. Since activation and aggregation of platelets is one of the pivotal and earlier events in acute MI, and since GPIs are potent inhibitors of platelet aggregation, it has been speculated that early administration of a GPI might confer an even more pronounced reduction in MACE. Field triage, which is becoming more common, has made it possible to diagnose STEMI in patients with chest pain much earlier [6] and initiate treatment with abciximab as early as in the pre-hospital setting [7]. However; results from prior studies evaluating the effect of ´upstream´ abciximab administration are inconsistent. Still, some centres routinely use abciximab in high-risk ACS patients scheduled for coronary angiography (CAG), hence before the coronary anatomy and nature of the lesion is known. However, the most marked benefits of abciximab are observed among patients with high-risk ACS, such as STEMI, and even more among those with high-risk coronary lesions [8,9].

If the ´upstream´ strategy (in which case abciximab is administered as soon as possible) was to be preferred over ´downstream´ (in which case the decision whether to use abciximab is made in the catheterization laboratory) one would by nature not know the result of the diagnostic angiography. Post hoc analyses from the large EUROTRANSFER Registry showed a marked reduction in mortality among STEMI patients receiving early abciximab [10,11]. This effect was, however, confined to patients with the highest risk profile [12]. In contrast, the FINESSE study showed no effect of early abciximab on the clinical endpoints [13]. However, a subsequent subgroup analysis evaluating the impact of risk stratification, revealed some effect of early abciximab among patients with the highest risk score [14]. Consequently, if the risk stratification, including lesion type, predicts the effect of abciximab in STEMI patients treated with primary percutaneous coronary intervention (pPCI), diagnostic CAG is mandatory before making the decision on the optimal anti-platelet therapy.

In this study we assess if the efficacy of abciximab in STEMI patients treated with pPCI is dependent on the type of coronary artery lesion found on CAG.

Methods

Study population

Copenhagen University Hospital Gentofte, Denmark, is a high-volume invasive center with a catchment population of 1.2 million citizens, i.e., more than 20% of the total Danish population, and is the invasive hub for 10 non-invasive cardiology departments. More than 1,500 PCI procedures are performed annually (approximately 500 pPCI), with each individual PCI operator performing approximately 300 PCIs and 100 pPCIs per year. From January 2003 to November

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2008 we identified 2,938 STEMI patients treated with pPCI. STEMI was defined as presence of chest pain for >30 minutes and <12 hours and cumulative persistent ST-segment elevation >4 mm in at least 2 contiguous pericardial ECG-leads, or >2 mm in at least two or more contiguous limb ECG-leads. These were the general accepted criteria for STEMI in this period [15]. Complex lesions were defined as either 1) type C lesions such as: diffuse (>2 cm length), excessive tortuosity of proximal segment, extremely angulated segments (>90°), bifurcation lesions with major side branch, or 2) type B2 lesions such as: tubular, eccentric, moderate tortuosity of proximal segment, moderately angulated segment (>45° <90°), irregular contour, moderate to heavy calcification, or ostial in location [16]. Lesions not fulfilling one or more of the above criteria were defined as simple lesions. Pre-treatment consisted of loading with 300-500 mg acetyl salicylic acid, 300-600 mg Clopidogrel, and 10,000 IU of unfractionated heparin, which was supplemented if ACT was less than 250 seconds during the procedure. The glycoprotein IIb/IIIa inhibitor abciximab (Reo-Pro® Eli Lilly, Denmark) was used at the discretion of the operator in complex cases such as type C/B2 lesions, large visible thrombus, dissection, and as bail-out in case of no/slow-reflow. The regimen used was an intravenous bolus of 0.25 mg/kg body weight followed by a 12-hour intravenous infusion of 0.125 μg/kg body weight per minute. Subsequent medical treatment included anti-ischemic, lipid-lowering and anti-thrombotic drugs according to current treatment guidelines (including 75 mg Clopidogrel daily for 12 months and 75 mg acetyl salicylic acid life-long). Baseline data were prospectively collected from all patients and entered in a dedicated PCI-registry. Diabetes mellitus was defined as use of anti-diabetic medication (oral and/or insulin) on admission. Hypertension was defined as use of blood pressure-lowering drugs on admission. Hyperlipidemia was defined as use of lipid-lowering drugs on admission. Multivessel disease was defined as 2 or 3 vessel disease.

Follow-up and study endpoints

The primary study endpoints were all-cause mortality, target vessel revascularization (TVR), and MI. The combined endpoint was the patients-oriented endpoint: all-cause mortality, TVR or MI as proposed by the Academic Research Consortium (ARC) [17]. All patients were followed for a maximum of 1 year. Follow-up data on all-cause mortality were collected from The National Person Identification Registry which holds information on vital status (alive, dead or emigrated), while follow-up data on MI and any kind of revascularization initially were collected from the well validated Danish National Board of Health's National Patient Registry, using ICD-10 codes [18]. If an event was registered, it was subsequently validated by cross-checking with hospital source data. In case of more than one PCI-procedure within the study period, the first procedure was defined as the index-procedure and subsequent procedures as new revascularizations. MI was defined as recurrent chest pain combined with significant increases in cardiac biomarkers. The study was approved by The Danish Data Protection Agency, and complied with the 2nd Declaration of Helsinki.

Statistics

Baseline characteristics were compared using χ^2–test for frequencies and Students unpaired t-test or Mann-Whitney test for continuous variables. Tests for interaction between lesion type and abciximab treatment for outcome were significantly positive, and therefore the study population was subsequently divided into 2 groups according to lesion type: simple lesion and complex lesion. Unadjusted Kaplan-Meier plots stratified by groups according to lesion type and abciximab treatment were compared using log rank test. Hazard Ratios (HR) were calculated using Cox proportional hazard regression analyses. In order to maintain a robust model only 1 variable per each 10 events was allowed in the multivariable Cox analyses of each endpoint. In the statistical tests, p-values <0.05 were considered of statistical significance. SPSS for Windows version 17.0 (Chicago, Illinois, USA) was used.

Results

Patient population and baseline characteristics

A total of 2,935 STEMI patients treated with pPCI were identified in our registry. Complex lesions comprised 47% (n=1.382) of the population. Overall, abciximab was used in 28% of the procedures. Baseline characteristics are shown in table 1. In summary, comparing patients by their lesion type, those with complex lesions were older and more likely to suffer from hypertension and hyperlipidemia. On angiography left anterior descending artery (LAD) was more frequently the culprit lesion. Patients with complex lesions also showed higher prevalence of multivessel disease, were more frequently treated in more than one lesion during the index procedure, and were more likely to be treated with a drug eluting stent (DES) and abciximab. Looking at the groups stratified by lesion type (complex or simple) separately and stratified by the use of abciximab (Table 2), the patients with complex lesions who received abciximab were younger and more likely to be of male gender and suffer from diabetes compared to those who were not treated with abciximab. Also, use of DES was more prevalent in the abciximab treated group. Among patients with simple lesions, those treated with abciximab were also more likely to be of male gender, to suffer from diabetes and obesity, and more often showed multivessel disease on CAG. Due to the differences between those who received abciximab and those who did not, as described above, we adjusted for all the variables shown in the baseline tables in our Cox proportional hazard regression analyses.

Clinical endpoints

Looking at the crude event rates we found that in STEMI patients with complex lesions on CAG, treatment with abciximab conferred a 30% relative reduction (from 20.4% to 14.3%; p=0.006 by χ^2-test) in the combined endpoint of mortality, TVR, and MI. This difference was

	Simple lesion (n=1.553)	Complex lesion (n=1.382)	p-value
Demographic data			
Age, years, median (IQR)	66 (56-75)	68 (58-75)	0.04*
Age ≥ 70 years, %	40.2	42.5	0.22
Male gender, %	71.5	73.2	0.34
Diabetes mellitus, %	9.2	10.4	0.29
Hypertension, %	30.1	36.3	<0.0001
Hyperlipidemia, %	16.0	19.5	0.01
Smoking, %	53.3	56.2	0.13
BMI, kg/m^2, mean (SD)	26.6 (± 4.4)	26.5 (± 6.4)	0.94*
Prior PCI, %	6.1	7.7	0.08
Procedural data			
Use of DES, %	66.3	71.3	0.002
LAD culprit, %	44.3	48.4	0.03
Multivessel disease, %	2.8	6.6	<0.0001
> 1 vessel treated, %	12.9	21.9	<0.0001
Use of abciximab, %	23.2	33.4	<0.0001

*Using Mann-Whitneys test. Otherwise data are compared using χ^2 test.

IQR: Interquartile Range; BMI: Body Mass Index; SD: Standard Deviation; PCI: Percutaneous Coronary Intervention; DES: Drug Eluting Stent; LAD: Left Anterior Descending Artery.

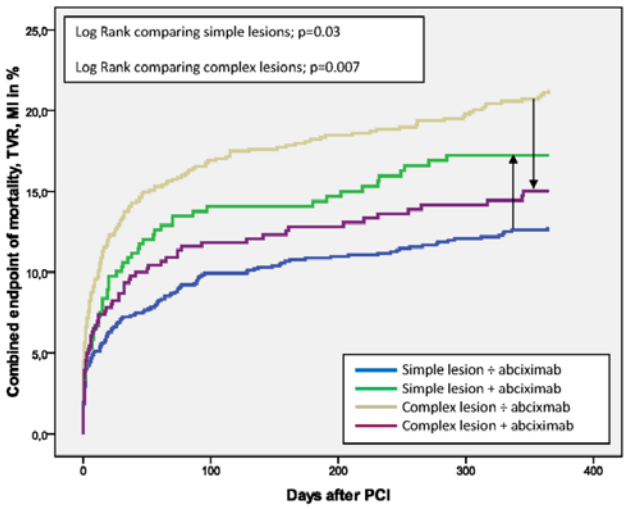
Table 1: Baseline data compared by lesion type.

	÷ Abciximab	+ Abciximab	p-value
Simple lesion (n=1.553)	(n=1.193)	(n=360)	
Demographic data			
Age, years, median (IQR)	66 (57-76)	66 (56-74)	0.07*
Age ≥ 70 years, %	41.3	36.7	0.13
Male gender, %	69.8	77.2	0.006
Diabetes mellitus, %	7.5	15.0	<0.0001
Hypertension, %	30.5	28.6	0.512
Hyperlipidemia, %	16.5	14.4	0.37
Smoking, %	53.3	53.3	1.00
BMI, kg/m^2, (SD)	26.3 (± 6.8)	27.4 (± 4.9)	0.006*
Prior PCI, %	5.6	7.5	0.21
Procedural data			
Use of DES, %	65.5	68.9	0.25
LAD culprit, %	44.8	42.5	0.47
Multivessel disease, %	2.3	4.4	0.04
> 1 vessel treated, %	13.7	10.0	0.07
Complex lesion (n=1.382)	(n=921)	(n=461)	
Demographic data			
Age, years, median (IQR)	68 (60-77)	65 (56-74)	<0.0001*
Age ≥ 70 years, %	44.1	39.5	0.11
Male gender, %	71.6	76.4	0.06
Diabetes mellitus, %	8.8	13.7	0.007
Hypertension, %	37.7	33.6	0.16
Hyperlipidemia, %	19.8	19.1	0.83
Smoking, %	56.4	55.7	0.86
BMI, kg/m^2, mean (SD)	26.5 (± 4.4)	26.7 (± 4.6)	0.37*
Prior PCI, %	8.1	6.9	0.46
Procedural data			
Use of DES, %	68.7	76.6	0.002
LAD culprit, %	49.5	46.2	0.25
Multivessel disease, %	6.4	6.9	0.73
> 1 vessel treated, %	22.0	21.7	0.95

*Using Mann-Whitneys test. Otherwise data are compared using χ^2 test.

IQR: Interquartile Range; BMI: Body Mass Index; SD: Standard Deviation; PCI: Percutaneous Coronary Intervention; DES: Drug Eluting Stent; LAD: Left Anterior Descending Artery.

Table 2: Baseline data compared by lesion type and use of abciximab.

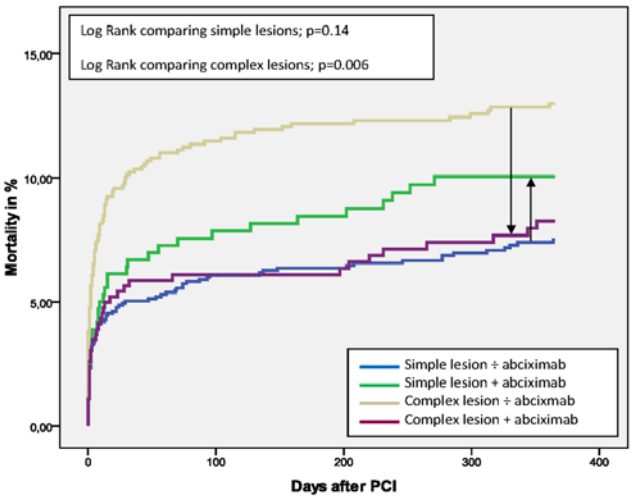


Kaplan-Meier plots for the combined endpoint showing the groups stratified according to lesion type and abciximab treatment. Arrows indicate the trend described by the Log Rank test.

Figure 1a: Kaplan-Meyer plots showing the combined endpoint.

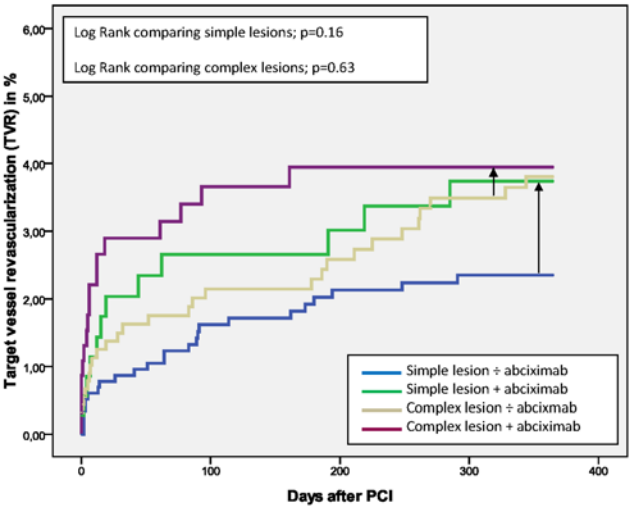
driven by an almost 40% relative risk reduction (from 12.7% to 7.8%; p=0.006 by χ^2-test) in mortality (and a neutral effect on TVR and MI). Among patients with simple lesions no significant effect of abciximab was observed for the individual endpoints, but a 27% relative increase (from 12.2% to 16.7%; p=0.03 by χ^2-test) in the combined endpoint. In (Figures 1a-1d) the time course of the unadjusted event rates are shown by Kaplan-Meyer plots and differences compared by log rank tests.

However, due to the differences in risk factors and angiographic findings we also performed a Cox proportional hazard regression analysis in which all the baseline variables were included. Importantly, as shown in figure 2, also after adjustment for baseline variables abciximab conferred a significant reduction in mortality (HR 0.62, CI 0.42-0.91, p=0.015) and the combined endpoint (also including TVR



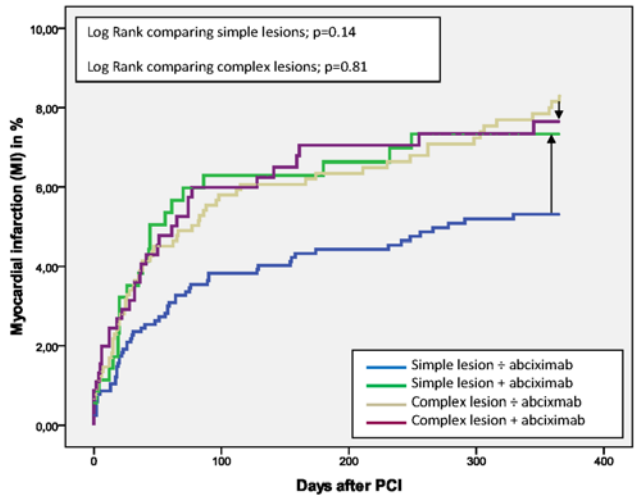
Kaplan-Meier plots for mortality showing the groups stratified according to lesion type and abciximab treatment. Arrows indicate the trend described by the Log Rank test.

Figure 1b: Kaplan-Meyer plots showing mortality.



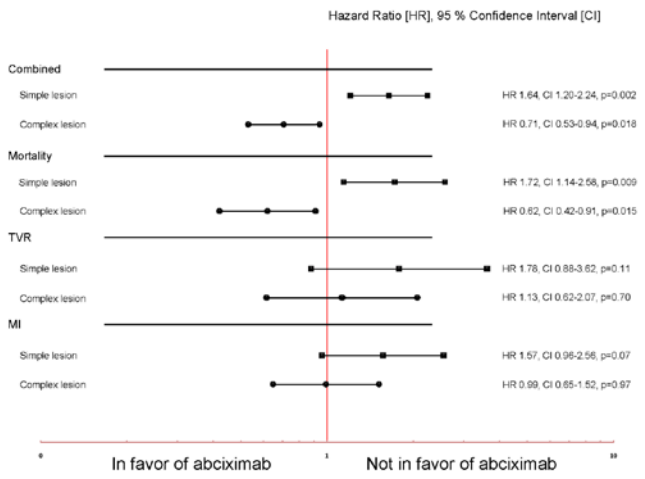
Kaplan-Meier plots for target vessel revascularization (TVR) showing the groups stratified according to lesion type and abciximab treatment. Arrows indicate the trend described by the Log Rank test.

Figure 1c: Kaplan-Meyer plots showing target vessel revascularization (TVR).



Kaplan-Meier plots for myocardial infarction (MI) showing the groups stratified according to lesion type and abciximab treatment. Arrows indicate the trend described by the Log Rank test.

Figure 1d: Kaplan-Meyer plots showing myocardial infarction (MI).



Harzard ratios (HR) and corresponding 95% Confidence intervals (CI) for the three individual endpoints mortality, target vessel revascularization (TVR), and myocardial infarction (MI), and the combination of those.

Figure 2: Harzard ratio plot for the endpoints stratified by type of lesion.

and MI) (HR 0.71, CI 0.53-0.94, p=0.018) among the patients with complex lesions. The opposite effect was seen among patients with simple lesions (mortality: HR 1.72, CI 1.14-2.58, p=0.009; combined endpoint: HR 1.64, CI 1.20-2.24, p=0.002). In the adjusted analyses no significant effect of abciximab was observed for any of the groups with regards to TVR and MI.

Discussion

In this large observational study on STEMI patients treated under real-life conditions we have assessed whether the efficacy of abciximab depends on the lesion type defined on CAG. The main findings from our study are the following: firstly, patients with complex coronary lesions who were treated with abciximab had a significantly lower mortality after one year, which was similar to those with simple lesions. This was the case even though patients with complex lesions had more severe risk factor profile and worse angiographic findings and hence an a priori higher risk of adverse outcome. Secondly, patients with simple coronary lesions treated with abciximab showed an increased mortality after one year. The effect on TVR an MI was neutral in both groups.

Several aspects of our study and results need to be addressed. Surprisingly, we found a significant increased mortality among patients with simple lesions who were treated with abciximab. At our institution abciximab is used in the complex lesions, in lesions with high thrombus burden or in bail-out situations that are complicated by peri-procedural dissection in the coronary artery, post-procedural microvascular obstruction due to microembolization or no/slow-reflow phenomenon. Hence, in cases where patients with initially simple lesions were treated with abciximab, the procedure turned out to be complicated and abciximab was used as bail-out or due to development of large thrombus during the procedure. These patients might have benefitted from the abciximab treatment and would have had an even worse outcome, had they not been treated. This might explain the excess mortality seen in this group of patients, and there may not be a cause relationship with use of abciximab. A more likely cause relationship exists among patients with complex lesions as these patients were treated with abciximab because of their high-risk lesion and in this population we found a marked lower mortality among those treated with abciximab. This implies that initiation of abciximab treatment should be reserved for patients with complex lesions, which by nature can only be known if a diagnostic CAG has been performed prior to PCI. This is an important aspect in the discussion of ´upstream´ versus ´downstream´ administration of abciximab (and GPIs in general).

With the introduction of field triage the symptom-to-balloon time has decreased significantly and STEMI patients referred for pPCI are loaded with aspirin and heparin at an early stage [6,19]. In addition, loading with a thienopyridines is considered standard care in most countries. Since the waiting period between diagnosis and treatment has shortened the time for abciximab to work is correspondingly short. Since the action of abciximab relies mainly on inhibition of thrombus formation and propagation [20-22], and possibly also exhibits some degree of thrombus disaggregation [23-25], only in the cases were thrombus is actually present, one can expect an effect of abciximab. If thrombus is not present the effect will be absent and the treatment might even be harmful, since the side effects of abciximab, that is bleeding, will outweigh the potential benefit. Also, several studies have shown intracoronary administration of abciximab to be superior to intravenous administration [26,27]. If indeed the administration route of choice in the future is intracoronary, abciximab can by nature only be administered when the patient is in the catheterization laboratory as a peri-procedural treatment.

Our findings do not support unselected use of abciximab in STEMI patients treated with pPCI.

Results from the EUROTRANSFER Registry showed improved mortality in patients treated early with abciximab [10,11]. However, this beneficial effect was confined to patients with high-risk profile defined as TIMI risk score ≥ 3, and no data on impact of lesion type were presented. Also, in a post hoc subgroup analysis of the large FINESSE study, only patients with the highest risk scores benefited from early abciximab [12]. One could speculate that the effect seen in the above studies was driven by an effect on the patients with complex lesions (and that a negative effect in patients with simple lesion confers an overall neutral result). This is supported by results from the BRAVE-3 trial in which STEMI patients were randomized to abciximab or placebo upstream. No effect of early abciximab was found on clinical endpoints

[28]. In summary, trials evaluating early versus late administration of abciximab have detected some effect on clinical endpoint, but only in patients with the highest risk scores. Having a complex lesion on CAG implies a high risk of adverse outcome. Our data suggest that only those STEMI patients with complex lesions benefit from abciximab. Consequently, the nature and profile of the coronary artery lesion should be known, before the decision whether to use abciximab or not can be made.

In conclusion, administration of the glycoprotein IIb/IIIa inhibitor abciximab in STEMI patients treated with pPCI was associated with lower one year mortality in patients with complex, but not with simple lesions. In order to include this parameter in the risk assessment of the patient, before initiating treatment with abciximab, such initiation may be recommended withheld until the coronary anatomy and type of lesion has been assessed by CAG.

Study limitations

The risk of residual confounding exists in a non-randomized trial. This is particularly important in a registry study where the treatment-strategy is decided at the operator's discretion as it is the case with abciximab (and GPIs in general). In the present analyses use of abciximab could be confounded by indication, e.g. the PCI-operator may have assumed that the overall coronary pathology combined with other co-morbidities and risk factors, would influence the use of abciximab. The choice of usage of any GPI is based on relatively complex considerations, not only the type of lesion as has been of interest in the present analysis. Such considerations may have been missed in our adjustment. On the other hand, the present study represents patients from our daily practice which may not always resemble patients from RCTs [29,30].

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