Articles

# Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials

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## Summary

**Background** Platelet glycoprotein IIb/IIIa inhibitors have been shown to reduce cardiac complications in patients undergoing percutaneous coronary intervention. The clinical efficacy of these drugs in acute coronary syndromes, however, is still unclear. We did a meta-analysis of all large randomised trials designed to study the clinical efficacy and safety of glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes who were not routinely scheduled to undergo early coronary revascularisation.

**Methods** Inclusion criteria were: randomisation of patients with acute coronary syndromes but without persistent ST elevation; comparison of a glycoprotein IIb/IIIa inhibitor with placebo or control therapy; non-recommendation of early coronary revascularisation during study-drug infusion; and enrolment of at least 1000 patients. Data on individual patients were obtained from all participants in these trials.

**Findings** Six trials, enrolling 31 402 patients, fulfilled the inclusion criteria. 30 days after randomisation, 3530 (11·2%) patients died or developed a myocardial infarction. At 30 days, a 9% reduction in the odds of death or myocardial infarction was seen with glycoprotein IIb/IIIa inhibitors compared with placebo or control (10·8% [1980/18 297] *vs* 11·8% [1550/13 105] events; odds ratio 0·91 [95% CI 0·84–0·98]; p=0·015). The relative treatment benefit was similar in subgroups of patients according to important clinical baseline characteristics; hence, the absolute treatment benefit was largest in high-risk patients. An unexpected and significant interaction was seen between sex and allocated treatment, with a treatment benefit in men (0·81 [0·75–0·89] but not in women (1·15 [1·01–1·30]). However, once patients were stratified according to troponin concentration, there was no evidence of a sex difference in treatment response, and a risk reduction was seen in men and women with raised troponin concentrations. Major bleeding complications were increased by glycoprotein IIb/IIIa inhibitors (2·4% [445/18 297] *vs* 1·4% [180/13 105]; p<0·0001), but intracranial bleeding was not (16 [0·09%] *vs* 8 [0·06%]; p=0·40).

**Interpretation** Glycoprotein IIb/IIIa inhibitors reduce the occurrence of death or myocardial infarction in patients with acute coronary syndromes not routinely scheduled for early revascularisation. The event reduction is greatest in patients at high risk of thrombotic complications. Treatment with a glycoprotein IIb/IIIa inhibitor might therefore be considered especially in such patients early after admission, and continued until a decision about early coronary revascularisation has been made.

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## Introduction

Disruption of atherosclerotic plaque, which either occurs spontaneously in patients with acute coronary syndromes or during a percutaneous coronary intervention (PCI), triggers platelet aggregation and intracoronary thrombus formation, and can result in myocardial infarction or death. Activation of the platelet glycoprotein IIb/IIIa receptor is the final common pathway in the process leading to platelet aggregation, and inhibitors of this receptor have been shown to protect against periprocedural death or myocardial infarction in patients undergoing PCI for various indications.[1–4]

Randomised clinical trials have indicated that glycoprotein IIb/IIIa inhibitors reduce the occurrence of these events by 38% compared with placebo or control therapy.[5,6] However, the results of trials in acute coronary syndromes in which coronary revascularisation during study-drug infusion was not part of the protocol, have been less conclusive. Glycoprotein IIb/IIIa inhibitors did reduce cardiac endpoints in most of these trials,[7–11] but not in all.[12] In the trials with a positive trend, the event reduction was often lower than expected, and significance was not always reached. In fact, most trials in acute coronary syndromes were powered for the detection of a large treatment effect (>20% risk reduction), but were underpowered for more modest, but potentially clinically important, effects. In this situation, a meta-analysis of the combined trial data can be useful to estimate more reliably the overall effect of glycoprotein IIb/IIIa inhibitors. If based on data from individual patients, such meta-analyses can also provide reliable estimates of treatment effects in clinically meaningful subgroups of patients.[13] In case of an overall beneficial effect, analysis of subgroups can help identify the target population to be treated preferentially. We did a meta-analysis of all large randomised trials designed to study the clinical efficacy and safety of glycoprotein IIb/IIIa

| | PRISM[7] | PRISM-PLUS[8] | PARAGON-A[9] | PURSUIT[10] | PARAGON-B[11] | GUSTO-IV ACS[12] |
|---|---|---|---|---|---|---|
| **Enrolment period** | 1994–96 | 1994–96 | 1995–96 | 1995–97 | 1998–99 | 1998–2000 |
| **Number of patients** | 3232 | 1915 | 2282 | 10 948 | 5225 | 7800 |
| **Last episode of chest pain** | ⩽24 h | ⩽12 h | ⩽12 h | ⩽24 h | ⩽12 h | ⩽24h |
| **Indicator of myocardial ischaemia** | | | | | | |
| ST depression or | ⩾1·0 mm | ⩾1·0 mm | ⩾0·5 mm | >0·5 mm | >0·5 mm | ⩾0·5 mm |
| ST elevation or | ⩾1·0 mm (<20 min duration) | ⩾1·0 mm (<20 min duration) | ⩾0·5 mm (<30 min duration) | >0·5 mm (duration not specified) | >0·5 mm (<30 min duration) | ⩾0·5 mm (<30 min duration) |
| T-wave inversion or | Yes; extent not specified | ⩾3·0 mm | Yes; extent not specified | >1 mm | Yes; extent not specified | No |
| Creatine kinase MB elevation and/or | Yes; extent not specified | Yes; extent not specified | No | Above local ULN | Above local ULN | No |
| Other conditions | Evidence of CAD based on cardiac history, stress-test, or CAG | No | No | No | Troponin T/I elevation above local ULN | Troponin T/I elevation above local ULN |
| **Study medication** | | | | | | |
| Glycoprotein IIb/IIIa inhibitor | Tirofiban | Tirofiban | Lamifiban | Eptifibatide | Lamifiban | Abciximab |
| Regimen | a) 0·6 μg/kg bolus + 0·15 μg/kg/min infusion + placebo heparin<br>b) placebo + heparin | a) 0·4 μg/kg bolus + 0·1 μg/kg/min infusion + heparin<br>b) 0·6 μg/kg bolus + 0·15 μg/kg/min infusion + placebo heparin<br>c) placebo + heparin | a) 300 μg bolus + 1 μg/min infusion + random assignment to heparin or heparin-placebo<br>b) 750 μg bolus + 5 μg/min infusion + random assignment to heparin or heparin-placebo<br>c) placebo + heparin | a) 180 μg/kg bolus + 1·3 μg/kg/min infusion<br>b) 180 μg/kg bolus + 2·0 μg/kg/min infusion<br>c) placebo | a) 500 μg bolus + 1·0–2·0 μg/min infusion (depending on creatinine clearance)<br>b) placebo | a) 250 μg/kg bolus + 0·125 μg/kg/min infusion (maximum 0·10 μg/min) for 24 h<br>b) a) 250 μg/kg bolus + 0·125 μg/kg/min infusion (maximum 0·10 μg/min) for 48 h<br>c) placebo |
| Infusion duration | 48 h | 48–96 h | 72–120 h | 72–96 h | 72–120 h | 24 or 48 h |
| **Additional management** | | | | | | |
| CAG | Discouraged <48 h after randomisation | Recommended 48–96 h after randomisation | Discouraged <24 h after randomisation | On discretion of treating physician | On discretion of treating physician | Discouraged <48 h after randomisation |
| PCI | Not scheduled | If indicated by angiography | On discretion of treating physician | On discretion of treating physician | On discretion of treating physician | Not scheduled |
| Aspirin | 300–325 mg | 325 mg | 75–325 mg | 80–325 mg | 150–325 mg | 150–325 mg |
| Heparin | Heparin part of study regimen; initial dose 5000 U bolus + 1000 U/h infusion | Heparin part of study regimen; initial dose 5000 U bolus + 1000 U/h infusion | Heparin part of study regimen; initial dose weight-adjusted: maximum 5000 U bolus + 1000 U/h infusion | Initial dose 5000 U bolus + 1000 U/h infusion | Initial dose weight-adjusted: maximum 5000 U bolus + 1000 U/h infusion, aiming for aPTT of 50–70 s | Initial dose weight-adjusted: maximum 5000 U bolus + 800 U/h infusion, aiming for aPTT of 50–70 s; dalteparin maximum 10 000 U |
| **Efficacy endpoints** | | | | | | |
| Primary | Death, MI, or refractory ischaemia at 48 h | Death, MI, or refractory ischaemia at 7 days | Death or MI at 30 days | Death or MI at 30 days | Death, MI, or severe, recurrent ischaemia at 30 days | Death or MI at 30 days |
| Required level of creatine kinase or creatine kinase MB elevation in MI definition | 2×ULN | 2×ULN; in relation to PCI: 3×ULN | 2×ULN | 1×ULN; in relation to PCI: 3×ULN; in relation to CABG: 5×ULN | 2×ULN; in relation to PCI: 3×ULN; in relation to CABG: 5×ULN | 3×ULN |
| **Safety endpoints** | | | | | | |
| Major bleeding complications | Intracranial haemorrhage; bleeding leading to decrease in haemoglobin concentration of at least 50 g/L; or cardiac tamponade | Intracranial haemorrhage; bleeding leading to decrease in haemoglobin concentration of at least 40 g/L; bleeding requiring transfusion of at least 2 units blood; or bleeding requiring corrective surgery | Intracranial haemorrhage; or bleeding leading to haemodynamic compromise requiring intervention | Intracranial haemorrhage; or bleeding leading to haemodynamic compromise requiring intervention | Intracranial haemorrhage; or bleeding leading to haemodynamic compromise requiring intervention | Intracranial haemorrhage; or bleeding leading to a decrease in haemoglobin concentration of at least 50 g/L |

ACT=activated clotting time; aPTT=activated partial thromboplastin time; CAD=coronary-artery disease; CAG=coronary angiography; MI=myocardial infarction; PCI=percutaneous coronary intervention; CABG=Coronary-artery bypass graft; ULN=upper limit of normal.

Table 1: **Design characteristics of trials on glycoprotein IIb/IIIa inhibitors in acute coronary syndrome without persistent ST-segment elevation**

inhibitors in patients with acute coronary syndromes who were not routinely scheduled for early coronary revascularisation.

## Methods

The methodological principles that lie behind a meta-analysis of randomised clinical trials based on data from

individual patients have been described in detail.[13] We therefore only briefly describe the applied methods of trial selection, data-management, endpoint definitions, and statistical analysis.

*Trial selection*

We intended to include all trials reported since 1990 with the following characteristics: randomisation of patients with acute coronary syndromes without persistent ST-segment elevation; comparison of a glycoprotein IIb/IIIa inhibitor with placebo or control therapy; non-recommendation of early (<48 h) coronary revascularisation during study-drug infusion; and enrolment of at least 1000 patients. To identify eligible trials, we did a MEDLINE search using the keywords "unstable angina", "myocardial infarction", and "platelet aggregation inhibition". Furthermore, we examined the reference lists of identified articles, as well as the scientific sessions abstracts in *Circulation*, the *Journal of the American College of Cardiology*, and the *European Heart Journal*.

Six trials were identified that fulfilled the inclusion criteria: PRISM,[7] PRISM-PLUS,[8] PARAGON-A,[9] PURSUIT,[10] PARAGON-B,[11] and GUSTO-IV ACS.[12] Table 1 summarises the design features of these trials with regard to entry criteria, study medication, and management of patients.

*Data management*

We compiled an electronic database consisting of data from individual patients in all eligible trials. Data included baseline characteristics regarded as important determinants of outcome (age, sex, cardiac history, cardiac medication, blood pressure, heart rate);[14,15] the allocated trial medication; and dates and times of randomisation, death, myocardial infarction, coronary-artery bypass surgery (CABG), PCI, stroke, intracranial haemorrhage, major bleeding, and 30-day follow-up. Data were checked for completeness, for internal consistency of patients' records, and for consistency with the published reports.

*Definitions of efficacy and safety endpoints*

The primary efficacy endpoint was a composite of death or non-fatal myocardial infarction. Myocardial infarction was part of the composite efficacy endpoint of all trials, but the applied myocardial infarction definitions were different, especially with regard to the required level of increased creatine kinase or creatine kinase MB concentrations (table 1). Still, since we know that heterogeneity in an endpoint definition will not lead to invalid results,[16] we applied the trial-specific definition of myocardial infarction for practical reasons.

There were also between-trial differences with regard to the definition of major bleeding, which was the primary safety endpoint. Again the trial-specific definitions were retained.

*Data analysis*

In the primary analysis, we intended to assess event rates at the end of study-drug infusion. There were, however, important between-trial differences in the duration of study-drug infusion as required per protocol, and analyses of event rates at different points in time across the studies might have resulted in heterogeneous estimates of treatment effect. We therefore decided to assess early event rates 120 h (5 days) after randomisation, since study-drug infusion should have stopped at that point in each trial (table 1). Events were further assessed at 30 days, since this point was the most common among trials.

We assessed differences between glycoprotein IIb/IIIa inhibitors and placebo or control within each trial, and reported odds ratios and corresponding 95% CI. The pooled odds ratio was calculated by the Cochrane-

| Trial | Study drug | Heparin | Number of patients | Death or myocardial infarction at 5 days | | Death or myocardial infarction at 30 days | |
|---|---|---|---|---|---|---|---|
| | | | | Number of patients | Odds ratio (95% CI) | Number of patients | Odd ratio (95% CI) |
| PRISM | Tirofiban | No | 1616 | 49 (3·0%) | 0·77 (0·53–1·13) | 94 (5·8%) | 0·80 (0·60–1·06) |
| | Placebo | Yes | 1616 | 63 (3·9%) | 1·00 | 115 (7·1%) | 1·00 |
| PRISM-PLUS | Low-dose tirofiban | Yes | 773 | 32 (4·1%) | 0·56 (0·36–0·87) | 67 (8·7%) | 0·70 (0·50–0·98) |
| | High-dose tirofiban | No | 345 | 29 (8·4%) | 1·19 (0·75–1·90) | 47 (13·6%) | 1·17 (0·80–1·70) |
| | Placebo | Yes | 797 | 57 (7·2%) | 1·00 | 96 (12·0%) | 1·00 |
| PARAGON-A | Low-dose lamifiban | No | 378 | 24 (6·3%) | 1·07 (0·64–1·79) | 41 (10·8%) | 0·91 (0·62–1·35) |
| | Low-dose lamifiban | Yes | 377 | 23 (6·1%) | 1·03 (0·61–1·73) | 39 (10·3%) | 0·87 (0·58–1·29) |
| | High-dose lamifiban | No | 396 | 18 (4·5%) | 0·75 (0·43–1·32) | 46 (11·6%) | 0·99 (0·68–1·44) |
| | High-dose lamifiban | Yes | 373 | 23 (6·2%) | 1·04 (0·62–1·75) | 46 (12·3%) | 1·06 (0·72–1·55) |
| | Placebo | Yes | 758 | 45 (5·9%) | 1·00 | 89 (11·7%) | 1·00 |
| PURSUIT | Low-dose integrelin | Yes | 1487 | 117 (7·9%) | 0·76 (0·61–0·94) | 200 (13·4%) | 0·83 (0·70–0·99) |
| | High-dose integrelin | Yes | 4722 | 404 (8·6%) | 0·83 (0·72–0·95) | 672 (14·2%) | 0·89 (0·79–1·00) |
| | Placebo | Yes | 4739 | 480 (10·1%) | 1·00 | 745 (15·7%) | 1·00 |
| PARAGON-B | Lamifiban | Yes | 2628 | 150 (5·7%) | 0·93 (0·74–1·17) | 278 (10·6%) | 0·92 (0·77–1·09) |
| | Placebo | Yes | 2597 | 159 (6·1%) | 1·00 | 296 (11·4%) | 1·00 |
| GUSTO-IV ACS | Abciximab 24 h | Yes | 2590 | 83 (3·2%) | 0·85 (0·63–1·15) | 212 (8·2%) | 1·02 (0·83–1·24) |
| | Abciximab 48 h | Yes | 2612 | 90 (3·4%) | 0·92 (0·69–1·23) | 238 (9·1%) | 1·15 (0·94–1·39) |
| | Placebo | Yes | 2598 | 97 (3·7%) | 1·00 | 209 (8·0%) | 1·00 |
| All | Any glycoprotein IIb/IIIa | Yes/no | 18 297 | 1042 (5·7%) | 0·84 (0·77–0·93)* | 1980 (10·8%) | 0·91 (0·85–0·98)* |
| | Placebo | Yes | 13 105 | 901 (6·9%) | 1·00 | 1550 (11·8%) | 1·00 |
| Glycoprotein IIb/IIIa additional to heparin† | Any glycoprotein IIb/IIIa | Yes | 15 562 | 922 (5·9%) | 0·84 (0·76–0·92)* | 1752 (11·3%) | 0·91 (0·85–0·99)* |
| | Placebo | Yes | 11 489 | 838 (7·3%) | 1·00 | 1435 (12·5%) | 1·00 |
| Glycoprotein IIb/IIIa as against heparin‡ | Any glycoprotein IIb/IIIa | Yes | 2735 | 120 (4·4%) | 0·91 (0·72–1·16)* | 228 (8·3%) | 0·93 (0·77–1·11)* |
| | Placebo | Yes | 3171 | 165 (5·2%) | 1·00 | 300 (9·5%) | 1·00 |
| Small-molecule glycoprotein IIb/IIa trials§ | Any glycoprotein IIb/IIIa | Yes/no | 13 095 | 869 (6·6%) | 0·84 (0·76–0·92)* | 1530 (11·7%) | 0·88 (0·82–0·95)* |
| | Placebo | Yes | 10 507 | 804 (7·7%) | 1·00 | 1341 (12·8%) | 1·00 |

Glycoprotein IIb/IIIa=glycoprotein IIb/IIIa receptor blocker. *Odds ratio represents pooled trial-specific odds ratios by the Cochrane-Mantel-Haenszel method. †Including the PRISM-PLUS and PARAGON-A glycoprotein IIb/IIIa groups with heparin, the placebo glycoprotein IIb/IIIa groups in these trials, and PURSUIT, PARAGON-B, and GUSTO-IV. ‡Including PRISM, the PRISM-PLUS and PARAGON-A glycoprotein IIb/IIIa groups without heparin, and the placebo glycoprotein IIb/IIIa groups of these trials. §All data, excluding GUSTO-IV.

Table 2: **Incidence of death or myocardial infarction by allocated treatment**

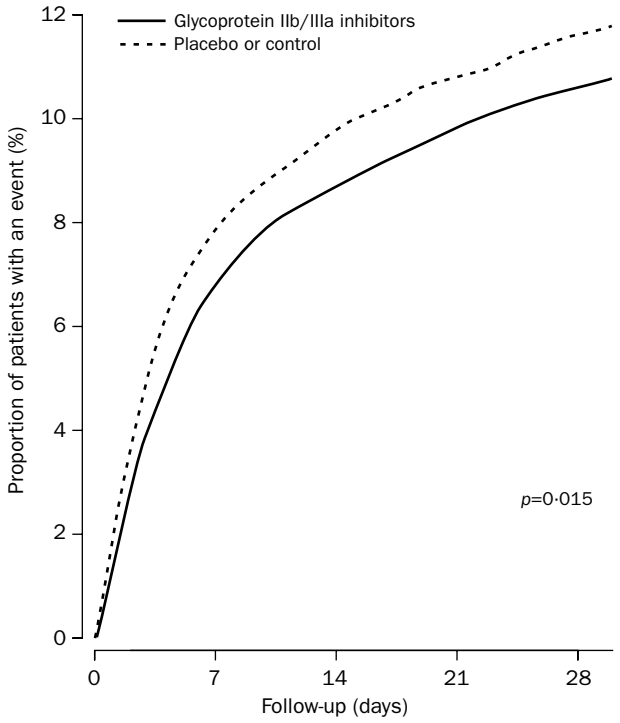


Figure 1: **Kaplan-Meier estimates of cumulative occurrence of death or myocardial infarction within 30 days after randomisation**

Mantel-Haenszel method, whereas the Breslow-Day test was used to examine the statistical evidence of heterogeneity between the trial-specific odds ratios. The frequency of events over time was studied by the Kaplan-Meier method. Simple Cox's proportional hazard regression models were used to assess differences between glycoprotein IIb/IIIa inhibitors and placebo or control in the frequency of events over time. The reported hazard ratios and 95% CI are adjusted for between-trial outcome differences. An estimate of the effect of glycoprotein IIb/IIIa inhibitors during medical management was obtained by time-to-event analyses, with events counted until the moment of a PCI or CABG, if any such procedure was done.

Subsequent analyses were done in subgroups of patients defined by baseline determinants of adverse cardiac outcome that were revealed by analyses of large datasets of patients with acute coronary syndromes.[14,15] Treatment effects in these subgroups were assessed by simple logistic regression models (which included a subgroup-allocated treatment interaction term), with adjustment for between-trial outcome differences. Adjustment for predictive baseline characteristics, even when largely balanced, can lead to different estimates of the treatment effect.[17] Therefore, more extensive multivariable logistic regression models were applied to estimate adjusted treatment effects.

*Role of the funding source*

The trials included in this analysis were sponsored by several pharmaceutical companies, which are mentioned in the main trial reports[7–12] and in the acknowledgments. This meta-analysis was initiated by the authors, and was designed, conducted, interpreted, and reported independently of these sponsors. No separate industrial or non-industrial grant was obtained for this investigation.

## Results

*Patients' characteristics*

The six trials altogether enrolled 31 402 patients in 41 countries. There were no important differences in baseline characteristics between patients randomly assigned glycoprotein IIb/IIIa inhibitors (n=18 297) and those assigned placebo or control (n=13 105). The mean age of the population was 64 years, 65% were men, and 76% had a history of cardiovascular disease. 56% of the patients presented with ST-segment depression, 46% with raised creatine kinase MB concentrations, and 80% with either one of these features.

*Efficacy endpoints*

Data with respect to the occurrence of death or myocardial infarction were complete for all patients. 5 days after randomisation, 389 (1·2%) patients had died. The 5-day composite endpoint of death or myocardial infarction was reached in 1943 (6·2%) patients. At 30 days, 1116 (3·6%) patients had died, and the composite endpoint was reached in 3530 (11·2%) patients.

Glycoprotein IIb/IIIa inhibitors were associated with a highly significant 16% relative reduction in the odds of death or myocardial infarction at 5 days after randomisation (p=0·0003; table 2). The absolute risk reduction with glycoprotein IIb/IIIa inhibitors was largely maintained until 30 days' follow-up, but no additional risk reduction was seen between 5 and 30 days (figure 1). The relative risk reduction in the odds of

| | Glycoprotein IIb/IIIa (n=18 297) | Control (n=13 105) | Odds ratio (95% CI)* | p for treatment effect† | p for homogeneity‡ |
|---|---|---|---|---|---|
| **Outcome events at 5 days** | | | | | |
| Death | 221 (1·2%) | 168 (1·3%) | 0·93 (0·76–1·14) | 0·48 | 0·36 |
| Non-fatal MI§ | 821 (4·5%) | 733 (5·6%) | 0·83 (0·75–0·92) | 0·0003 | 0·54 |
| Death or MI | 1042 (5·7%) | 901 (6·9%) | 0·84 (0·77–0·93) | 0·0003 | 0·81 |
| CABG | 875 (4·8%) | 676 (5·2%) | 1·01 (0·91–1·12) | 0·82 | 0·97 |
| PCI | 2421 (13·2%) | 1957 (14·9%) | 0·94 (0·88–1·00) | 0·049 | 0·68 |
| CABG or PCI | 3251 (17·8%) | 2596 (19·8%) | 0·95 (0·90–1·01) | 0·11 | 0·86 |
| Death, MI, CABG, or PCI | 3904 (21·3%) | 3088 (23·6%) | 0·95 (0·90–1·00) | 0·060 | 0·99 |
| **Outcome events at 30 days** | | | | | |
| Death | 631 (3·4%) | 485 (3·7%) | 0·91 (0·81–1·03) | 0·14 | 0·53 |
| Non-fatal MI¶ | 1349 (7·4%) | 1065 (8·1%) | 0·92 (0·85–1·00) | 0·063 | 0·30 |
| Death or MI | 1980 (10·8%) | 1550 (11·8%) | 0·91 (0·85–0·98) | 0·015 | 0·34 |
| CABG | 2713 (14·9%) | 1980 (15·1%) | 1·01 (0·95–1·08) | 0·70 | 0·73 |
| PCI | 4272 (23·3%) | 3210 (24·5%) | 0·97 (0·92–1·03) | 0·35 | 0·42 |
| CABG or PCI | 6862 (37·5%) | 5103 (38·9%) | 0·99 (0·94–1·03) | 0·53 | 0·21 |
| Death, MI, CABG, or PCI | 7820 (42·7%) | 5803 (44·3%) | 0·98 (0·93–1·02) | 0·33 | 0·39 |

CABG=coronary artery bypass grafting; glycoprotein IIb/IIIa=glycoprotein IIb/IIIa receptor blocker; MI=myocardial infarction; PCI=percutaneous coronary intervention. *Pooled trial-specific odds ratios by the Cochrane-Mantel-Haenszel method. †Cochrane-Mantel-Haenszel test for general association between allocated treatment and the outcome event. ‡Breslow-Day test for homogeneity between trial-specific odds ratios. §Patient survived at least 5 days. ¶Patient survived at least 30 days.

Table 3: **Summary of efficacy results by allocated treatment**

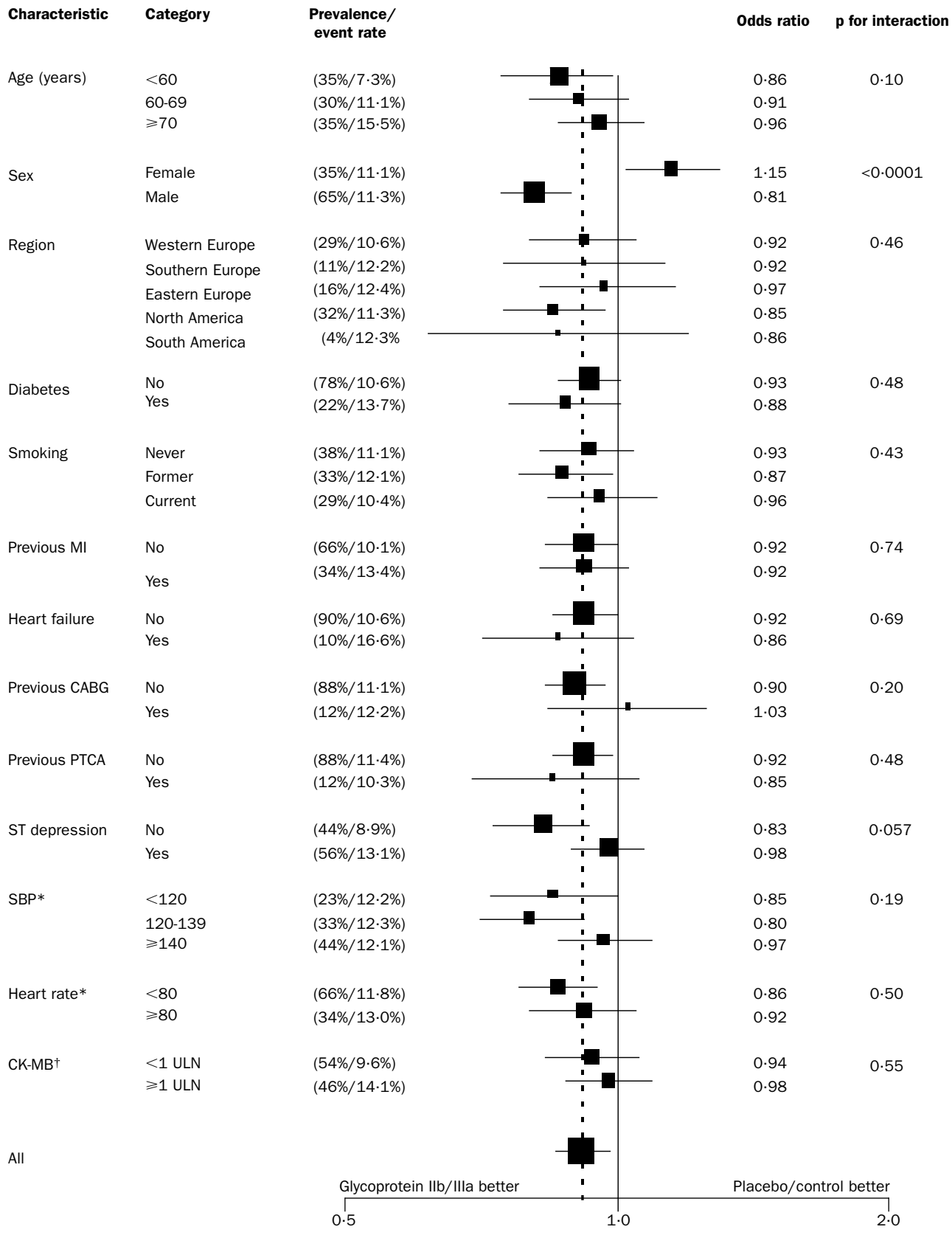


Figure 2: **Odds ratio of 30-day death or myocardial infarction in subgroups of patients according to important clinical baseline characteristics**

MI=myocardial infarction; CABG=coronary-artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty; SBP=systolic blood pressure; CK=creatine kinase. Odds ratio represents pooled trial-specific odds ratios by the method of Cochrane-Mantel-Haenszel. Data are presented on a logarithmic scale. p value corresponds with subgroup×treatment interaction term in a logistic regression model, with adjustment for between-trial outcome differences. *Blood pressure and heart rate not recorded in GUSTO-IV. †Data on creatine kinase MB missing in 7469 patients.

| | Men | | | Women | | | p for heterogeneity* |
|---|---|---|---|---|---|---|---|
| | Glycoprotein IIb/IIIa | Control | Odds ratio (95% CI)† | Glycoprotein IIb/IIIa | Control | Odds ratio (95% CI)† | |
| **All patients** | | | | | | | |
| Total | 11 886 | 8502 | | 6410 | 4603 | | |
| Death | 379 (3·2%) | 321 (3·8%) | 0·83 (0·71–0·96) | 252 (3·9%) | 164 (3·6%) | 1·08 (0·89–1·33) | 0·030 |
| Death or MI | 1242 (10·4%) | 1070 (12·6%) | 0·81 (0·75–0·89) | 738 (11·5%) | 480 (10·4%) | 1·15 (1·01–1·30) | 0·0001 |
| **Patients with missing data on baseline cardiac troponin** | | | | | | | |
| Total | 7617 | 5769 | | 3923 | 3033 | | |
| Death | 241 (3·2%) | 224 (3·9%) | 0·81 (0·67–0·98) | 158 (4·0%) | 101 (3·3%) | 1·20 (0·93–1·55) | 0·011 |
| Death or MI | 881 (11·6%) | 825 (14·3%) | 0·78 (0·70–0·86) | 523 (13·3%) | 350 (11·5%) | 1·18 (1·02–1·36) | 0·0001 |
| **Patients with data on baseline cardiac troponin‡** | | | | | | | |
| Total | 4269 | 2733 | | 2487 | 1570 | | |
| Death | 138 (3·2%) | 97 (3·5%) | 0·85 (0·65–1·11) | 94 (3·8%) | 63 (4·0%) | 0·91 (0·66–1·27) | 0·83 |
| Death or MI | 361 (8·5%) | 245 (9·0%) | 0·93 (0·78–1·11) | 215 (8·6%) | 130 (8·3%) | 1·07 (0·85–1·35) | 0·38 |
| **Patients with baseline cardiac troponin T or I <0·1 μg/L** | | | | | | | |
| Total | 2095 | 1449 | | 1548 | 1003 | | |
| Death | 48 (2·3%) | 30 (2·1%) | 1·07 (0·67–1·71) | 36 (2·3%) | 20 (2·0%) | 1·20 (0·69–2·10) | 0·84 |
| Death or MI | 159 (7·6%) | 100 (6·9%) | 1·10 (0·84–1·43) | 96 (6·2%) | 53 (5·3%) | 1·29 (0·91–1·83) | 0·65 |
| **Patients with baseline cardiac troponin T or I ⩾0·1 μg/L** | | | | | | | |
| Total | 2174 | 1284 | | 939 | 567 | | |
| Death | 90 (4·1%) | 67 (5·2%) | 0·75 (0·54–1·04) | 58 (6·2%) | 43 (7·6%) | 0·80 (0·53–1·21) | 0·88 |
| Death or MI | 202 (9·3%) | 145 (11·3%) | 0·82 (0·65–1·03) | 119 (12·7%) | 77 (13·6%) | 0·93 (0·68–1·28) | 0·48 |

Data represent outcome at 30 days. Information on sex was not available for one patient. Glycoprotein IIb/IIIa=glycoprotein IIb/IIIa receptor blocker; MI=myocardial infarction. *Represents level of statistical evidence for heterogeneity in treatment effect between men and women; p corresponds with sex×treatment interaction term in a logistic regression model, with adjustment for between-trial outcome differences. †Pooled trial-specific odds ratios by the method of Cochrane-Mantel-Haenszel. ‡Cardiac troponin data were available in 69% of patients enrolled in PRISM, 6% in PRISM-PLUS, 4% in PURSUIT, 23% in PARAGON-B, and 91% in GUSTO-IV. In PRISM, these data were not strictly baseline values, but were obtained a median of 8 h after randomisation.

Table 4: **Efficacy results according to sex and baseline cardiac troponin concentration**

death or myocardial infarction at 30 days was 9% (p=0·015; table 2, figure 1). There was no statistical evidence of heterogeneity in treatment effect among the separate trials at either time point (p=0·81 and p=0·34). Similar results were seen in analyses that were restricted to trial groups that assessed the efficacy of glycoprotein IIb/IIIa inhibitors additional to heparin, or when tested against heparin (table 2).

An event reduction was seen in both components of the composite endpoint. Glycoprotein IIb/IIIa inhibitors were associated with a non-significant reduction in the odds of 30-day death, and in the odds of 30-day non-fatal myocardial infarction (table 3). Again, there was no statistical evidence of heterogeneity in event reduction among the trials (table 3).

### *Treatment effects in subgroups of patients*

The benefits of glycoprotein IIb/IIIa inhibitors were consistent across various prognostically important subpopulations, including those grouped by age, status with regard to diabetes mellitus and history of cardiac disease, and condition on admission (figure 2). The treatment effect seemed larger in patients with ST-segment depression than in those without, but the difference did not reach significance. Baseline cardiac troponin data were available in 69% of the patients enrolled in PRISM, 6% in PRISM-PLUS, 4% in PURSUIT, 23% in PARAGON-B, and 91% in GUSTO-IV (in PRISM, these data were not strictly baseline values, but were obtained a median of 8 h after randomisation). No cardiac troponin data were available in PARAGON-A. Thus, information on baseline cardiac troponins were available in a selected subset of 11 059 patients (35% of the entire population). In the 45% of patients with positive troponins (troponin T or I concentration ⩾0·1 μg/L), glycoprotein IIb/IIIa inhibitors were associated with a 15% reduction in the odds of 30-day death or myocardial infarction compared with placebo or control (10·3% [321/3113] *vs* 12·0% [222/1851] events; 0·85 [0·71–1·03]). In patients with negative troponins, no risk reduction was seen (7·0% [255/3643] *vs* 6·2% [153/2452] events; 1·17 [0·94–1·44]). This differential treatment effect was significant (p=0·045).

A highly significant interaction with respect to cardiac events was seen between sex and allocated treatment. In men, glycoprotein IIb/IIIa inhibitors were associated with a 19% reduction in the odds of 30-day death or myocardial infarction compared with placebo or control (table 4). By contrast, in women, the point estimate and 95% CI of treatment effect were compatible with a risk increase. There were important differences between men and women with regard to age (mean age 62 years in men *vs* 66 years in women), diabetes mellitus (20% [3987/20 368] *vs* 26% [2875/10 995]), history of myocardial infarction (37% [7581/20 324] *vs* 28% [3068/10 985]), history of heart failure (9% [1822/20 346] *vs* 12% [1336/10 989]), history of coronary revascularisation (23% [4750/20 378] *vs* 15% [1690/11 008]), ST-segment depression on admission (54% [10 844/20 088] *vs* 60% [6573/10 868]), and increased creatine kinase MB concentrations on admission (50% [7703/15 524] *vs* 38% [3226/8409]).

The sex difference in treatment effect remained (p<0·0001) after adjustment for these differences in baseline characteristics by multivariable regression analysis. Men more often presented with positive baseline troponins than women (49% [3458/7002] *vs* 37% [1506/4057]). There was no statistical evidence of a differential treatment effect between men and women if patients were stratified according to their baseline troponin concentration (table 4). A reduction in the 30-day rate of death or myocardial infarction by glycoprotein IIb/IIIa inhibitors was seen in men and women with positive baseline troponins, whereas no risk reduction was seen in patients with negative troponins, irrespective of sex. The sex difference in treatment effect disappeared (p=0·44) if troponin status was added to the multivariable regression equation (but more than 65% of patients were excluded from this analysis due to missing data).

| | Glycoprotein IIb/IIIa | Control | Odds ratio (95% CI)* | | Glycoprotein IIb/IIIa | Control | Odds ratio (95% CI)* |
|---|---|---|---|---|---|---|---|
| **Patients undergoing PCI within 5 days** | | | | **Patients not undergoing PCI within 5 days** | | | |
| Total | 2421 | 1957 | | Total | 15876 | 11148 | |
| MI before† | 141 (5·8%) | 157 (8·0%) | 0·70 (0·55–0·89) | MI before† | .. | .. | .. |
| 30-day death | 42 (1·7%) | 39 (2·0%) | 0·83 (0·53–1·29) | 30-day death | 589 (3·7%) | 446 (4·0%) | 0·91 (0·81–1·04) |
| 30-day death or MI | 285 (11·8%) | 284 (14·5%) | 0·77 (0·64–0·92) | 30-day death or MI | 1695 (10·7%) | 1266 (11·4%) | 0·95 (0·87–1·02) |
| **Patients undergoing PCI or CABG within 5 days** | | | | **Patients neither undergoing PCI nor CABG within 5 days** | | | |
| Total | 3251 | 2596 | | Total | 15046 | 10509 | |
| MI before† | 257 (7·9%) | 266 (10·2%) | 0·76 (0·63–0·91) | MI before† | .. | .. | .. |
| 30-day death | 82 (2·5%) | 68 (2·6%) | 0·94 (0·67–1·30) | 30-day death | 549 (3·6%) | 417 (4·0%) | 0·90 (0·79–1·03) |
| 30-day death or MI | 464 (14·3%) | 450 (17·3%) | 0·79 (0·68–0·91) | 30-day death or MI | 1516 (10·1%) | 1100 (10·5%) | 0·97 (0·89–1·05) |
| **Patients undergoing PCI or CABG within 30 days** | | | | **Patients neither undergoing PCI nor CABG within 30 days** | | | |
| Total | 6871 | 5115 | | Total | 11426 | 7990 | |
| 30-day death | 186 (2·7%) | 157 (3·1%) | 0·87 (0·70–1·08) | 30-day death | 445 (3·9%) | 328 (4·1%) | 0·93 (0·80–1·08) |
| 30-day death or MI | 1022 (14·9%) | 850 (16·6%) | 0·89 (0·80–0·98) | 30-day death or MI | 958 (8·4%) | 700 (8·8%) | 0·95 (0·86–1·05) |

Patients are selected for revascularisation partly on the basis of their response to study medication, and the timing of revascularisation might depend on that response as well. The data in this table therefore do not represent strictly randomised comparisons, and estimates of treatment effect might be biased. CABG=coronary-artery bypass grafting; glycoprotein IIb/IIIa=glycoprotein IIb/IIIa receptor blocker; MI=myocardial infarction; PCI=percutaneous coronary intervention. *Pooled trial-specific odds ratios by the method of Cochrane-Mantel-Haenszel. †MIs occurring before the intervention (in patients undergoing PCI or CABG only).

Table 5: **Rate of death or myocardial infarction by allocated treatment according to early use of coronary revascularisation**

*Cardiac procedures, medical therapy, and outcomes*

7482 (24%) patients underwent a PCI within 30 days of randomisation, and 11 965 (38%) underwent either PCI or CABG. The use of cardiac revascularisation was related to sex and to baseline cardiac troponin concentration, with a higher use in men than in women (42% [8609/20 388] *vs* 31% [3877/11 013]), and a higher use in patients with positive troponins than in those with negative troponins (35% [1756/4964] *vs* 30% [1847/6095]). Glycoprotein IIb/IIIa inhibitors were associated with a lower use of cardiac revascularisation (especially PCI) within 5 days of randomisation than placebo or control (table 3). Therefore, data on rate of cardiac endpoints by allocated treatment in subgroups of patients according to the use and timing of coronary revascularisation (as presented in table 5) do not represent strictly randomised comparisons.

Glycoprotein IIb/IIIa inhibitors were associated with a significant reduction in death or myocardial infarction until PCI or 30-day follow-up, whichever came first (hazard ratio 0·92 [95% CI 0·86–0·99], p=0·030). A similar reduction in this composite endpoint by glycoprotein IIb/IIIa inhibitors was seen until the moment of either a PCI or CABG procedure, if any (0·91 [0·84–0·99], p=0·027). Cardiac endpoints were reduced by glycoprotein IIb/IIIa inhibitors compared with placebo or control in patients undergoing, and those not undergoing, early cardiac revascularisation (table 5).

*Safety endpoints*

Glycoprotein IIb/IIIa inhibitors were associated with an increased risk of major bleeding complications compared with placebo or control (p<0·0001; table 6). The increase in major bleeding complications was somewhat higher in women (3·0% [192/6410] *vs* 1·4% [65/4603] events; odds ratio 2·2 [95% CI 1·6–2·9]) than in men (2·1% [253/11 886] *vs* 1·4% [115/8502] events; 1·6 [1·3–2·0]), but there was no evidence of heterogeneity (p=0·10). Intracranial haemorrhage was a rare complication, occurring in only 24 (0·08%) patients. Glycoprotein IIb/IIIa inhibitors were not associated with a significantly higher rate of intracranial haemorrhage, nor with an increased incidence of total stroke (table 6). Safety results were similar in patients treated with or without heparin (table 6).

## Discussion

Inhibitors of the platelet glycoprotein IIb/IIIa receptor were associated with an absolute reduction in the 30-day rate of death or myocardial infarction of 1% compared with control therapy. This risk reduction was achieved after completion of study medication, and was maintained throughout 30-day follow-up. The treatment benefit was seen in patients treated with and without heparin. Sex differences were apparent, with a treatment benefit in men (two-thirds of the population), but not in women. However, no sex difference in treatment effect was seen in a selected subgroup of patients with raised cardiac troponin concentrations. Glycoprotein IIb/IIIa inhibitors were associated with an increased risk of bleeding complications. Importantly, the risk of intracranial haemorrhage or stroke was not significantly increased, although differences might have been missed due to a lack of statistical power.

This meta-analysis assumed a class effect of glycoprotein IIb/IIIa inhibitors. The validity of this concept was not challenged by formal statistical tests on heterogeneity of treatment effects among the trials. Still, differences between drugs might exist but are missed due to lack of statistical power. In the six trials under consideration, 12 different regimens were investigated (which included four different glycoprotein IIb/IIIa inhibitors), and the number of patients allocated to either of these strategies was relatively small, varying from 345 (PRISM-PLUS high-dose tirofiban) to 4722 (PURSUIT high-dose eptifibatide). Indeed, disappointing and divergent findings were seen in GUSTO-IV ACS with abciximab, with the point estimate of treatment effect in the 48-h infusion group compatible with a 15% increased risk of cardiac events.[12] Our findings should therefore be interpreted in relation to the pharmacological properties of the applied agents, and in relation to evidence that exists from other investigations. The results of the TARGET trial[18] showed that abciximab was more effective in protecting against cardiac events during PCI than tirofiban; however, whether the separate agents in

| Trial | Study drug | Heparin? | Number of patients | Major bleed | | Intracranial haemorrhage | Stroke | |
|---|---|---|---|---|---|---|---|---|
| | | | | Number of patients | Odds rario (95% CI) | | Number of patients | Odds ratio (95% CI) |
| PRISM | Tirofiban | No | 1616 | 27 (1·7%) | 1·36 (0·76–2·43) | 2 (0·12%) | 13 (0·80%) | 0·92 (0·43–1·98) |
| | Placebo | Yes | 1616 | 20 (1·2%) | 1·00 | 2 (0·12%) | 14 (0·87%) | 1·00 |
| PRISM-PLUS | Low-dose tirofiban | Yes | 773 | 23 (3·0%) | 1·50 (0·78–2·86) | 0 | 8 (1·03%) | 1·66 (0·54–5·09) |
| | High-dose tirofiban | No | 345 | 14 (4·1%) | 2·06 (1·00–4·28) | 0 | 4 (1·16%) | 1·86 (0·50–6·96) |
| | Placebo | Yes | 797 | 16 (2·0%) | 1·00 | 0 | 5 (0·63%) | 1·00 |
| PARAGON-A | Low-dose lamifiban | No | 378 | 5 (1·3%) | 2·01 (0·58-7·02) | 0 | 4 (1·06%) | 2·69 (0·59–12·1) |
| | Low-dose lamifiban | Yes | 377 | 5 (1·3%) | 2·02 (0·58–7·03) | 0 | 4 (1·06%) | 2·70 (0·60–12·1) |
| | High-dose lamifiban | No | 396 | 4 (1·0%) | 1·53 (0·41–5·76) | 1 (0·25%) | 3 (0·76%) | 1·92 (0·39–9·56) |
| | High-dose lamifiban | Yes | 373 | 4 (1·1%) | 1·63 (0·44–6·12) | 0 | 2 (0·54%) | 1·36 (0·23–8·15) |
| | Placebo | Yes | 758 | 5 (0·7%) | 1·00 | 0 | 3 (0·40%) | 1·00 |
| PURSUIT | Low-dose integrelin | Yes | 1487 | 17 (1·1%) | 1·33 (0·75–2·34) | 1 (0·07%) | 6 (0·40%) | 0·50 (0·21–1·19) |
| | High-dose integrelin | Yes | 4722 | 71 (1·5%) | 1·75 (1·19–2·57) | 3 (0·06%) | 33 (0·70%) | 0·87 (0·55–1·39) |
| | Placebo | Yes | 4739 | 41 (0·9%) | 1·00 | 3 (0·06%) | 38 (0·80%) | 1·00 |
| PARAGON-B | Lamifiban | Yes | 2628 | 45 (1·7%) | 1·79 (1·10–2·93) | 2 (0·08%) | 28 (1·07%) | 1·85 (0·99–3·49) |
| | Placebo | Yes | 2597 | 25 (1·0%) | 1·00 | 2 (0·08%) | 15 (0·58%) | 1·00 |
| GUSTO-IV ACS | Abciximab 24 h | Yes | 2590 | 123 (4·7%) | 1·72 (1·28–2·32) | 4 (0·15%) | 18 (0·69%) | 1·13 (0·57–2·22) |
| | Abciximab 48 h | Yes | 2612 | 107 (4·1%) | 1·48 (1·09–2·00) | 3 (0·11%) | 14 (0·54%) | 0·87 (0·42–1·79) |
| | Placebo | Yes | 2598 | 73 (2·8%) | 1·00 | 1 (0·04%) | 16 (0·62%) | 1·00 |
| All | Any glycoprotein IIb/IIIa | Yes/no | 18 297 | 445 (2·4%) | 1·62 (1·36–1·94)§ | 16 (0·09%) | 137 (0·75%) | 1·11 (0·84–1·45)* |
| | Placebo | Yes | 13 105 | 180 (1·4%) | 1·00 | 8 (0·06%) | 91 (0·69%) | 1·00 |
| Glycoprotein IIb/IIIa additional to heparin† | Any glycoprotein IIb/IIIa | Yes | 15 562 | 395 (2·5%) | 1·64 (1·36–1·97)§ | 13 (0·08%) | 113 (0·73%) | 1·11 (0·83–1·49)* |
| | Placebo | Yes | 11 489 | 160 (1·4%) | 1·00 | 6 (0·05%) | 77 (0·67%) | 1·00 |
| Glycoprotein IIb/IIIa as against heparin‡ | Any glycoprotein IIb/IIIa | No | 2735 | 50 (1·8%) | 1·61 (1·06–2·46)§ | 3 (0·11%) | 24 (0·88%) | 1·27 (0·71–2·29)* |
| | Placebo | Yes | 3171 | 41 (1·3%) | 1·00 | 2 (0·06%) | 22 (0·69%) | 1·00 |
| Small-molecule glycoprotein IIb/IIIa trials§ | Any glycoprotein IIb/IIIa | Yes/no | 13 095 | 215 (1·6%) | 1·64 (1·30–2·07) | 9 (0·07%) | 105 (0·80%) | 1·14 (0·84–1·53) |
| | Placeco | Yes | 10 507 | 107 (1·0%) | 1·00 | 7 (0·07%) | 75 (0·71%) | 1·00 |

Glycoprotein IIb/IIIa=glycoprotein IIb/IIIa receptor blocker. *Odds ratio represents pooled trial-specific odds ratios by the method of Cochrane-Mantel-Haenszel. †Including the PRISM-PLUS and PARAGON-A GP IIb/IIIa groups with heparin, the placebo glycoprotein IIb/IIIa groups of these trials, and PURSUIT, PARAGON-B, and GUSTO-IV. ‡Including PRISM, the PRISM-PLUS and PARAGON-A glycoprotein IIb/IIIa groups without heparin, and the placebo glycoprotein IIb/IIIa groups of these trials. §All data, excluding GUSTO-IV.

Table 6: **30-day safety endpoints by allocated treatment**

the dosing regimens tested produce equivalent benefit among indications (as acute coronary syndromes and PCI) is questionable. Clinicians should preferably use agents that have been proven to be effective in specific indications.

With the exception of sex, no significant interactions were seen between baseline clinical determinants of cardiac risk and allocated treatment. Thus, the relative treatment benefit was similar in all prognostically important subgroups, implying that the absolute treatment benefit is largest in high-risk patients. This implication should be borne in mind when determining the target population to be treated preferentially, especially if the allocation of glycoprotein IIb/IIIa inhibitors is hampered by budget constraints. Application of a clinical risk score for non-ST-elevation acute coronary syndromes can be useful in this respect.

The serum cardiac troponin T or troponin I concentration is regarded as a marker for necrosis due to microvascular obstruction, presumably from thrombosis, and provides important prognostic information.[19–21] Since baseline cardiac troponins were not systematically measured in five of the six trials included in our analysis, data were only available in a small, non-randomly-selected subset of patients. The available data confirmed that patients with raised troponin concentrations are at increased risk of adverse cardiac complications. Moreover, increased troponin concentrations identified a subgroup of patients in whom treatment with glycoprotein IIb/IIIa inhibitors was particularly beneficial. In fact, no benefit was apparent in patients with a negative troponin value.

There is overwhelming evidence that glycoprotein IIb/IIIa inhibitors reduce thrombotic cardiac complications in patients with acute coronary syndromes undergoing PCI.[1–4,21] A relevant question from a clinical point of view is whether or not glycoprotein IIb/IIIa inhibitors also reduce cardiac complications in patients with acute coronary syndromes who do not undergo PCI. This question cannot be answered from the current data. By design, coronary revascularisation was not recommended (and often discouraged) during study-drug infusion in the trials included in this meta-analysis. Yet, 14% of patients underwent PCI within 5 days of randomisation, and most of these procedures were done during drug infusion. Since patients treated with glycoprotein IIb/IIIa inhibitors less often underwent early PCI than patients on placebo or control, the use and timing of revascularisation was apparently related to the patient's response to study medication. Estimates of treatment effect in subgroups of patients according to the use and timing of revascularisation might therefore be biased. Still, the current data do not contradict the suggestion that glycoprotein IIb/IIIa inhibitors reduce cardiac complications during medical management. First,

among patients undergoing (early) revascularisation, glycoprotein IIb/IIIa inhibitors reduced the occurrence of preprocedural myocardial infarction. Second, in the entire population, patients treated with glycoprotein IIb/IIIa inhibitors had fewer events until a revascularisation procedure, if any, was done. One might argue that the event reduction in patients not undergoing revascularisation is less pronounced than in patients undergoing revascularisation, and is not relevant from a clinical perspective. However, besides allocated treatment, the propensity to revascularise also depends on factors that interfere with the treatment effect by glycoprotein IIb/IIIa inhibitors. Women and patients with negative troponins were particularly less likely to undergo revascularisation. Therefore, the most appropriate interpretation of the current data is that glycoprotein IIb/IIIa inhibitors reduce cardiac complications in patients with acute coronary syndromes who are not routinely scheduled for early revascularisation.

The observed differential treatment effect between men and women was unexpected, although a significant interaction between sex and allocated treatment was reported in PURSUIT.[10] Should this therefore be regarded as a chance finding? Probably not, since the observed interaction was highly significant, and since the results were not particularly driven by those of any one trial. To explain these observations, one might speculate about sex differences in platelet function and response to antiplatelet agents, but no such difference was reported with regard to eptifibatide by the PURSUIT investigators.[22] However, whether both sexes were similar with regard to the significance and instability of the underlying coronary-artery disease is questionable. Most probably, the trials included in our analysis enrolled two different groups of patients. One group presented with plaque rupture and intracoronary thrombus formation. Such patients respond favourably to intensive antiplatelet therapy, irrespective of sex. This response is compatible with the observed treatment benefit in patients with raised cardiac troponin concentrations, and in patients subsequently referred for coronary revascularisation. It is also in agreement with the absence of a sex difference in PCI trials of glycoprotein IIb/IIIa inhibitors.[23,24]

A second group of patients probably had a different pathology that was not related to platelet aggregation. In such patients, antiplatelet therapy will not be beneficial, and possibly harmful because of an increased bleeding risk, or perhaps induction of an inflammatory response.[12] The differential treatment effect between men and women could therefore be explained by an over-representation of the second type of patients among women. Indeed, in our data, women presented less often with raised cardiac troponin concentrations than men, and underwent coronary revascularisation less often. This suggestion is in agreement with a PURSUIT report, in which female sex was the second most important determinant of non-significant coronary-artery disease.[25] Since glycoprotein IIb/IIIa inhibitors reduced cardiac complications in men and women with a definite diagnosis of coronary-artery disease and raised troponin concentrations, a differential treatment strategy between men and women presenting with definite acute coronary syndromes is not recommended at present.

Several effective antiplatelet and antithrombotic drugs are available for patients with acute coronary syndromes, including aspirin,[26] glycoprotein IIb/IIIa inhibitors (current data), unfractionated or low-molecular-weight heparin,[27] direct thrombin inhibitors,[28] and thienopyridines.[29] One of the challenges for clinical cardiologists is to implement these agents in clinical practice, in the appropriate patients at the appropriate time. Notably, we found that the absolute benefit of early intensive therapy with a glycoprotein IIb/IIIa inhibitor (additional to aspirin and heparin) became apparent during the first days, and was largely sustained during follow-up. By contrast, the benefit of long-term treatment with the oral agent clopidogrel became apparent gradually during therapy.[29] This finding suggests that combined early intensive therapy with aspirin, heparin, and a glycoprotein IIb/IIIa inhibitor, followed by long term oral therapy with a thienopyridine, might be appropriate and beneficial to the patient.

Glycoprotein IIb/IIIa inhibitors reduce the occurrence of death or myocardial infarction in patients with acute coronary syndromes who are not routinely scheduled for early revascularisation. The event reduction is clinically most meaningful in patients at high risk of intracoronary thrombotic complications. In a cost-cautious environment, treatment with a glycoprotein IIb/IIIa inhibitor might therefore be considered early after admission in high-risk patients, and continued until a decision about whether to revascularise has been made. This policy is in harmony with recent guidelines.[30,31]

*Contributors*

E Boersma, R A Harrington, R M Califf, and M L Simoons were responsible for the study concept and design; E Boersma, A De Torbal, and M L Simoons collected data; E Boersma, R A Harrington, H White, P Théroux, F Van de Werf, P W Armstrong, L C Wallentin, R G Wilcox, J Simes, R M Califf, E J Topol, and M L Simoons analysed and interpreted data; E Boersma and M L Simoons drafted the paper; E Boersma, R A Harrington, D J Moliterno, H White, P Théroux, F Van de Werf, A De Torbal, P W Armstrong, L C Wallentin, R G Wilcox, J Simes, R M Califf, E J Topol, and M L Simoons were responsible for critical revision of the paper; E Boersma and A De Torbal provided statistical expertise; and H White, P Théroux, F Van de Werf, P W Armstrong, L C Wallentin, R M Califf, E J Topol, and M L Simoons supervised the study.

*Conflict of interest statement*

R A Harrington is a consultant for Schering-Plough, and has received honoraria from Schering-Plough, COR, Merck, Centocor, Lilly, and Roche. D J Moliterno is a consultant for Merck, Centocor, and Eli Lilly, and has received honoraria from the same, as well as from Roche. H White is a consultant for and has received honoraria from Merck. P Théroux was principal investigator and chairman of the Steering Committee for the PRISM-PLUS trial. P W Armstrong has received research grants and honoraria from Eli Lilly and Schering-Plough. R M Califf has worked with Centocor, Lilly, COR, Schering-Plough, and Merck. M L Simoons is a consultant for Merck, Centocor, and Lilly, and has provided paid expert testimony to Schering-Plough.

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