Risk of thrombocytopenia with glycoprotein IIb/IIIa inhibitors across drugs and patient populations: a meta-analysis of 29 large placebo-controlled randomized trials

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Aims
Glycoprotein IIb/IIIa inhibitors (GPIs) reduce myocardial infarction and peri-procedural thrombotic complications in patients undergoing percutaneous coronary intervention (PCI); however, they may cause bleeding and thrombocytopenia, which are associated with poor clinical outcomes. Although the risk of bleeding has been well characterized, the extent of the risk of thrombocytopenia remains uncertain. In this meta-analysis, we aim to evaluate the risk of thrombocytopenia associated with GPI compared with placebo across drugs and patient populations.

Methods and results
Risk ratios were calculated for thrombocytopenia (<100,000 platelets/mm³) and severe thrombocytopenia (<50,000 platelets/mm³) in 29 randomized large trials (>1000 patients) of GPI vs. placebo involving a total of 123,419 patients. We used meta-analysis techniques to estimate the summary effect across all trials, in pre-specified sub-groups, and in sensitivity analyses to assess the robustness of the data. Glycoprotein IIb/IIIa inhibitor use increases the rate of thrombocytopenia [risk ratio (RR) = 1.62, 95% confidence interval (CI) 1.48–1.78] and severe thrombocytopenia (RR = 3.52, 95% CI 2.87–4.30) compared with placebo. These findings are consistent by route of administration (oral vs. intravenous). Patients with ST-segment elevation myocardial infarction (RR 2.66, 95% CI 2.12–3.34) and elective PCI (RR 2.78, 95% CI 1.76–4.40) treated with a GPI had higher risks of thrombocytopenia than patients with non-ST-segment elevation acute coronary syndrome (RR 1.41, 95% CI 1.25–1.58; P < 0.001 for heterogeneity by sub-group).

Conclusions
The administration of GPI compared with placebo was associated with a 63% increased risk of thrombocytopenia (<100,000 platelets/mm³), and >3-fold increased risk of severe thrombocytopenia (<50,000 platelets/mm³). This corresponds to an average of 10–20 additional cases of thrombocytopenia per 1000 patients given GPIs, of which 6–7 cases are severe.

Keywords
Glycoprotein IIb/IIIa inhibitor • Thrombocytopenia • Meta-analysis

Introduction
The past three decades have given rise to numerous studies supporting the use of anti-platelet therapy in the treatment and prevention of thrombotic events in acute coronary syndromes. Glycoprotein IIb/IIIa receptor inhibitors (GPIs) block the final common pathway leading to platelet aggregation that occurs via the cross-linking of fibrinogen and von Willebrand factor upon exposure to the activated GP IIb/IIIa receptor, and have demonstrated efficacy in clinical trials and meta-analyses for the prevention of MI and reduction of peri-procedural complications in percutaneous coronary intervention (PCI).1–4 The introduction of the three intravenous GPIs—abciximab, eptifibatide and tirofiban—represents an important new development in the field of cardiovascular pharmacotherapeutics; however, two major safety concerns have emerged with the use of these agents: bleeding and thrombocytopenia.5 Although thrombocytopenia is infrequent in most clinical trials (<5%) and the majority of cases are mild (50,000–100,000 platelets/mm³), the development of thrombocytopenia is associated with higher rates of mortality and poor clinic outcomes, and should therefore be evaluated thoroughly.6–9

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Several factors that are intricately related to the use of GPIs potenti- ate the morbidity of thrombocytopenia beyond what might be expected with an isolated reduction in platelet count. First, by design GPIs cause a qualitative platelet dysfunction that leaves the few platelets remaining after drug-induced thrombocytopenia poorly functioning.10 Second, GPIs are commonly co-administered with aspirin, heparin, and occasionally thrombolytic therapy, each of which carries an independent risk of bleeding and thrombocytopenia.11–13 Finally, the use of invasive procedures such as catheterization, PCI, and intra-aortic balloon counterpulsation in patients frequently treated with GPIs further augments the risk of thrombocytopenia.14,15

In this review, we report the results of a meta-analysis of the risk of thrombocytopenia associated with GPI compared with placebo, with particular attention to quantifying the extent and characteristics of this risk across different drugs and patient populations.

Methods

Identification of trials
Details of the search strategy, including trial selection and evaluation can be found in the Supplementary material online, Appendix. Clinical trials of GPI in the treatment of coronary artery disease were identified through a computerized literature search using PUBMED of articles from 1986 through March 2014. In addition, references of all retrieved articles were examined and information regarding ongoing and completed clinical trials was sought from experts in the field. Reviews, meta-analyses, editorials, sub-studies, and follow-up analyses were searched for relevant references. All reviewed articles were maintained in a master log, and reasons for exclusion were documented in a log of rejected trials.

Inclusion and exclusion criteria
Only original placebo-controlled Phase II or III clinical trials comparing a GPI to placebo for patients with coronary artery disease that were publicly presented (final results only) were included in the meta-analysis. Studies with fewer than 1000 patients were excluded due to small event numbers. Studies of multiple GPIs within the same trial and publications reporting on extended follow-up after completion of the study protocol were excluded. Studies with different anti-coagulant agents used in each study group (i.e. heparin vs. bivalirudin in REPLACE-2) were excluded.16 The PARAGON trial was treated as two separate studies owing to a protocol in which half of the patients randomized to GPI were randomly assigned to heparin and the other half did not receive heparin.17 Both PARAGON groups (designated PARAGON-I and PARAGON-II) were compared with the same placebo group. In the GUSTO-JV trial, the two different abciximab groups (24 h vs. 48 h infusions) were combined and compared with placebo as neither the dose nor length of drug administration were identified as a priori hypotheses.18 After meeting all inclusion and exclusion criteria, data from 29 trials were included in the meta-analysis.16–42 Study- and outcome-level assessments of bias were performed for each trial, which revealed low risk of bias in each of the following domains for each included trial: randomization, allocation concealment, blinding, and outcome reporting.

Data extraction
We collected the following information for each trial from the primary publication: treatment assignment, population studied, route of treatment administration, definition of thrombocytopenia, definition of severe thrombocytopenia when applicable, number of patients with and without thrombocytopenia for each treatment group, number of patients with and without severe thrombocytopenia when applicable (Table 1). When available, the number of patients who actually received the treatment (safety cohort) was used instead of the number of patients randomized (intention-to-treat cohort) since the former is a better estimate of the incidence of thrombocytopenia associated with actual drug exposure. When more than one dose of the GPI was administered, results were pooled since available evidence does not suggest that thrombocytopenia is related to the dose of GPI. When data were missing or unclear, additional evidence was sought from subsequent publications of the trial results or direct written communication with the study investigators.

Main outcome measure
The main outcome measured was the risk ratio (RR) with 95% confidence interval (CI) of thrombocytopenia associated with GPI use compared with placebo. The threshold of 100 000 platelets/mm3 was used to define thrombocytopenia, as this is considered the standard definition of thrombocytopenia and was the value most commonly reported in the literature. We also performed a secondary analysis of severe thrombocytopenia using the threshold of 50 000 platelets/mm3 which is considered a clinically more relevant level of thrombocytopenia (i.e. severe). In trials that used thrombocytopenia thresholds other than those above, results were classified by category (i.e. thrombocytopenia or severe thrombocytopenia). Data were analysed for all trials first, with a second analysis restricted to trials that investigated the three currently available intravenous GPIs: abciximab, eptifibatide, and tirofiban.

Sub-group analyses
All trials were analysed together as well as divided into four sets of predefined sub-groups based on a priori hypotheses regarding factors that might influence thrombocytopenia rates. Sub-groups that were analysed threshold of thrombocytopenia, study drug, route of administration (intravenous vs. oral), and patient population based on diagnosis [i.e. STEMI vs. non-ST-segment elevation acute coronary syndrome (NSTEACS) vs. elective PCI].

Statistical analysis
The Mantel–Haenszel fixed-effects model was used with 95% CIs for all estimation of all RRs.43 Fixed-effects modelling was used given the relative similarities of the populations of the included large clinical trials. When there were no cases of thrombocytopenia in either treatment group, 0.5 was added to all cells for that study in order to prevent undefined or zero-value RRs. Sensitivity analyses were performed using odds ratios instead of RRs, risk differences instead of RRs, and 99% CIs instead of 95% CIs. All analyses were performed using Review Manager 5.0 from the Cochrane Collaboration.44

Results

Heterogeneity of trials
This study included 29 randomized large trials involving 123 419 patients. There were eight different GPIs studied, of which four were intravenous and four were oral agents. Four of the trials were not specific for a single GPI. Five trials investigated GPI use in patients with STEMI, 12 trials investigated GPI use in NSTEACS, and six trials investigated GPI use with elective PCI; the other five trials studied a combined population of patients with coronary artery disease. The three currently available intravenous GPIs were studied in 22 of the trials involving 90 881 patients. Nearly, all (24/29) trials used standard
definitions of thrombocytopenia; however, four of the trials reported only results for severe thrombocytopenia. The absolute rates of thrombocytopenia observed in the individual 29 trials ranged from 0.5 to 10.8% with GPI and from 0 to 4.9% with placebo. This degree of heterogeneity among the trials supports the use of meta-analytic technique rather than an unweighted pooling of results, since the underlying rates of thrombocytopenia cannot be assumed to be the same across all trials.

**Overall risk of thrombocytopenia**

There were 2297 cases of thrombocytopenia (< 100 000 platelets/mm³) in 68 967 patients receiving GPI (3.3% unweighted incidence) compared with 1123 cases of thrombocytopenia in 52 230 patients receiving placebo (2.2% unweighted incidence). This degree of heterogeneity among the trials supports the use of meta-analytic technique rather than an unweighted pooling of results, since the underlying rates of thrombocytopenia cannot be assumed to be the same across all trials.

**Risk of thrombocytopenia with glycoprotein IIb/IIIa inhibitors**

(Figures 1 and 2). Using data from trials studying available GPs only, the RR for thrombocytopenia with GPI use compared with placebo was 1.61 (95% CI 1.46–1.78) for thrombocytopenia (< 100 000 platelets/mm³) and 3.90 (95% CI 3.08–4.95) for severe thrombocytopenia (< 50 000 platelets/mm³).

**Sub-group analyses**

When trials were grouped by specific agent, abciximab, tirofiban, xemilofiban, orbofiban, and lotrafiban demonstrated significantly increased rates of thrombocytopenia compared with placebo. The point estimates and 95% CIs of the RRs for currently available agents are as follows: abciximab 2.93 (2.43–3.52), eptifibatide 1.05 (0.86–1.29), and tirofiban 2.79 (1.17–6.63) (Figure 3). When trials were grouped by route of administration, both intravenous and orally administered GPs demonstrated similar rates of thrombocytopenia compared with placebo (RR (95% CI) for IV 1.61 (1.46–1.78) and oral 1.71 (1.29–2.26)) (Figure 4). In contrast, the RR for thrombocytopenia with GPI varied according to patient population, with patients undergoing treatment for STEMI (RR 2.66, 95% CI 2.12–3.34) and elective...
Figure 1  Thrombocytopenia (<100,000 platelets/mm$^3$) for glycoprotein IIb/IIIa inhibitor vs. placebo.

Figure 2  Severe thrombocytopenia (<50,000 platelets/mm$^3$) for glycoprotein IIb/IIIa inhibitor vs. placebo.
PCI (RR 2.78, 95% CI 1.76–4.40) exhibiting higher rates of thrombocytopenia than patients with NSTEACS (RR 1.41, 95% CI 1.25–1.58; \( P < 0.001 \) for heterogeneity by sub-group) (Figure 5).

Sensitivity analyses

Sensitivity analyses were performed using absolute risk differences instead of RRs. The absolute risk difference of GPI compared with control remained significant for thrombocytopenia (<100 000 platelets/mm\(^3\), risk difference (95% CI) 1.32 (1.08, 1.56) per 100 patients treated) and severe thrombocytopenia (<50 000 platelets/mm\(^3\), risk difference (95% CI) 0.59 (0.48, 0.70) per 100 patients treated). These sensitivity analyses exhibited consistent findings across route of administration, patient population, and specific drug (Table 2).

Discussion

This meta-analysis of 29 randomized large trials involving 123 419 patients with coronary disease shows that the use of GPIs is associated with a 63% relative increase in the risk of thrombocytopenia (<100 000 platelets/mm\(^3\)) compared with placebo. This risk is amplified for severe thrombocytopenia (<50 000 platelets/mm\(^3\)) where it was >3-fold. Assuming an underlying rate of thrombocytopenia of ~2%, these findings amount to an average of 10–20 additional cases of thrombocytopenia per 1000 patients, of which 6–7 cases
are severe, although generalizations of these findings differ according to specific to different patient populations in which the underlying rates of thrombocytopenia are different from the overall pooled rate observed in this meta-analysis. These results were consistent in analyses of all trials and also in analyses restricted to the currently available three intravenous GPIs only.

Thrombocytopenia following GPI therapy has been strongly associated with poor clinic outcomes, including death, MI, major hemorrhage, and prolonged hospitalization.45–49 Although the majority of thrombocytopenia cases in these trials were mild–moderate with platelet counts between 50 000 and 100 000, the risk of thrombocytopenia was increased with GPI use when thresholds of severe thrombocytopenia were used. While mild cases of GPI-induced thrombocytopenia can be managed conservatively with serial observation and consideration of GPI discontinuation, severe cases are associated with elevated risk of haemorrhage that often require active intervention.50

The findings of this analysis, that risk of thrombocytopenia is increased in patients with coronary disease treated with GPI compared with placebo, are consistent with previous reports and similar to the well-described association between the commonly used anti-thrombotic agent heparin and thrombocytopenia.7,11,51

The timing of GPI-associated thrombocytopenia is similar to that of heparin-induced thrombocytopenia, occurring in a bimodal distribution either 1–4 h or 7–14 days after GPI administration. Although the mechanism remains incompletely understood, possible mechanisms include presence of pre-existing or GPI exposure-dependent antibodies that increase platelet destruction, inhibition of megakaryocytes that express GP IIb/IIIA receptors, and heightened platelet microaggregation secondary to activation of the inflammatory system.52 GPI-induced thrombocytopenia is notably distinct from thrombotic thrombocytopenic purpura in the absence of systemic thrombotic microangiopathy that is characteristic of the latter syndrome.

**Figure 4** Thrombocytopenia (<100 000 platelets/mm³) by route of administration (intravenous vs. oral (PO)).
Sub-group analysis of the pooled trial data demonstrated significant increases in thrombocytopenia risk for two of the three currently available agents, abciximab, and tirofiban, while eptifibatide exhibited non-significant increases in thrombocytopenia risk compared with placebo. The risk did not significantly differ according to route of administration, and patients with STEMI and elective PCI had higher risk of thrombocytopenia than patients with NSTEACS. These findings suggest that different routes of administration, which yield increased exposure to oral agents due to longer periods of administrations compared with intravenous drugs, do not appear to effect risk of thrombocytopenia, whereas the chemical structure and mechanism of action of specific agents may alter subsequent thrombocytopenia risk. Specifically, the non-significant risk observed with eptifibatide as compared with other agents may be related to reduced inhibition of pro-coagulant activity that has been reported in cyclic heptapeptide agents. Meta-analysis results comparing specific drugs, however, should be interpreted with caution, as prospective comparison trials of different agents within the same population would be needed to establish confirmation of differences in thrombocytopenia risk. This is supported by the variation in risk across different populations, indicating that the underlying patient diagnosis may modify ensuing risk of thrombocytopenia. Finally, sensitivity analyses using differences in absolute rates (as opposed to odds ratios) demonstrated qualitatively similar results to the primary analyses in the entire dataset, when analysing only severe thrombocytopenia, and across different specific drugs, routes of administration, and various patient populations. These sensitivity analyses support the robust nature of the primary and sub-group findings.

This meta-analysis has several limitations that constrain its interpretability beyond a systemic review of data. The analysis of thrombocytopenia across various clinical trials and with different GPIs is...
Table 2  Sensitivity analyses using absolute risk differences

<table>
<thead>
<tr>
<th>Sub-group</th>
<th>No. of trials</th>
<th>No. of patients</th>
<th>Pooled thrombocytopenia rates (%)</th>
<th>Absolute risk difference (per 100 patients) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia (&lt;100K platelets/mm³)</td>
<td>24</td>
<td>121197</td>
<td>3.3</td>
<td>1.32 (1.08, 1.56)</td>
</tr>
<tr>
<td>Severe thrombocytopenia (&lt;50K platelets/mm³)</td>
<td>23</td>
<td>111028</td>
<td>0.8</td>
<td>0.59 (0.48, 0.70)</td>
</tr>
<tr>
<td>Intravenous</td>
<td>20</td>
<td>85322</td>
<td>4.2</td>
<td>1.60 (1.29, 1.92)</td>
</tr>
<tr>
<td>Oral</td>
<td>4</td>
<td>35875</td>
<td>1.5</td>
<td>0.60 (0.31, 0.89)</td>
</tr>
<tr>
<td>STEMI</td>
<td>5</td>
<td>27 643</td>
<td>3.2</td>
<td>2.04 (1.60, 2.49)</td>
</tr>
<tr>
<td>NSTEACS</td>
<td>10</td>
<td>48797</td>
<td>4.6</td>
<td>1.41 (0.95, 1.87)</td>
</tr>
<tr>
<td>Elective PCI</td>
<td>4</td>
<td>18147</td>
<td>1.5</td>
<td>0.99 (0.60, 1.37)</td>
</tr>
<tr>
<td>Abciximab</td>
<td>11</td>
<td>44540</td>
<td>3.8</td>
<td>2.44 (2.07, 2.86)</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>2</td>
<td>14676</td>
<td>4.5</td>
<td>0.23 (−0.67, 1.12)</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>2</td>
<td>4801</td>
<td>1.4</td>
<td>0.89 (0.17, 1.61)</td>
</tr>
</tbody>
</table>

STEMI, ST-segment elevation myocardial infarction; NSTEACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention.

difficult owing to the low incidence of thrombocytopenia, the non-standard definitions of thrombocytopenia utilized in various trials (ranging from <20 000 to <150 000 platelets/mm³) and the lack of uniform clinical settings of GPI administration (i.e. elective PCI, NSTEACS, and STEMI). Additionally, variations in route of administration (intravenous vs. oral) and concomitant medication administration (i.e. heparin, thienopyridines, and thrombolitics) may confound the causal relationship between GPI use and thrombocytopenia. However, the use of these drugs is likely to have been equally distributed between placebo and GPI treatment groups, since the dataset includes a selection of large randomized trials. Our analysis is additionally subject to selection and publication bias; however, we used clear pre-specified criteria that could be easily discerned from the trial metrics and we believe it is unlikely that large trials in excess of 1000 patients would be unpublished in the literature. Finally, the pooling of heterogeneous data across studies has the potential to limit results; however, the use of two fixed-effects models, the Mantel–Haenszel and inverse–variance methods, account for both between trial and within trial variance that reduces the effects of heterogeneity for these dichotomous trial data. Furthermore, sensitivity analyses enhance the robustness of the findings, although some of the sub-groups evaluated had a small number of trials and were limited by low numbers of thrombocytopenia cases.

Two further points limit the interpretability of this study. First, although the relative change in platelet count is a more useful measure of clinically significant thrombocytopenia owing to the fact that patients with lower platelet count at baseline are more likely to develop thrombocytopenia, this measure was unavailable in the majority of studies analysed. Although most studies used exclusion criteria of platelet count <100 000 platelets/mm³ at baseline, not all studies included this measure for exclusion and it therefore remains unknown. Second, GPI treatment is known to increase the risk of bleeding, which in turn can cause thrombocytopenia distinct from the direct effect of the drug. A complete dissociation of patients with thrombocytopenia but not experiencing bleeding would be needed to assess this relationship, data that unfortunately were unavailable for this meta-analysis. Finally, it is important to note that although a priori hypotheses were evaluated in this study, the lack of a published review protocol prior to performing this meta-analysis represents an important limitation in the interpretability of these sub-group analyses.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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**References**


