

# Deaths associated with platelet glycoprotein IIb/IIIa inhibitor treatment

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**Background:** The glycoprotein (GP) IIb/IIIa inhibitors are potent antagonists of platelet aggregation that are approved to prevent thrombotic complications of percutaneous coronary intervention and for medical treatment of patients with acute coronary ischaemic syndromes. From safety data obtained from clinical trials, these agents appear to be associated with a definite but well tolerated increase in non-fatal bleeding complications. However, the bleeding risk of patients enrolled in clinical trials may not be representative of the population actually being treated with these agents.

**Objective:** To conduct a review of the adverse events related to GP IIb/IIIa inhibitors reported to the Food and Drug Administration (FDA).

**Methods:** 450 reports of death related to treatment with GP IIb/IIIa inhibitors were submitted to the FDA between 1 November 1997 and 31 December 2000. These were reviewed and a standard rating system for assessing causation was applied to each event.

**Results:** Of the 450 deaths, 44% were considered to be definitely or probably related to the use of GP IIb/IIIa inhibitors. The mean age of patients who died was 69 years and 47% of deaths occurred in women. All of the deaths deemed to be definitely or probably related to GP IIb/IIIa inhibitor treatment were associated with excessive bleeding. The central nervous system was the most common site of fatal bleeding.

**Conclusions:** Treatment with GP IIb/IIIa inhibitors may result in fatal bleeding complications in some patients. These findings suggest that patients treated in normal clinical practice may be at greater risk than those treated in clinical trials. Judicious use of these agents is therefore appropriate.

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Agents that block the platelet glycoprotein (GP) IIb/IIIa receptor are powerful inhibitors of thrombosis as well as of normal haemostasis.<sup>1</sup> Three parenteral GP IIb/IIIa inhibitors have been approved for use in the USA in coronary artery disease settings characterised by excessive platelet dependent thrombosis.<sup>2</sup> Abciximab is approved as an adjunctive treatment for patients undergoing percutaneous coronary intervention, eptifibatid is approved for medical treatment of acute coronary ischaemic syndromes and as an adjunct to percutaneous coronary intervention, and tirofiban is approved for treatment of acute ischaemia. The use of each of these agents has been associated with reductions in ischaemic complications and an increase in major bleeding complications in placebo controlled trials.<sup>3-12</sup> However, the clinical benefit associated with GP IIb/IIIa treatment has been felt to justify the increased risk of haemorrhagic complications.<sup>13</sup>

Because of the generally low risk of patients treated in randomised clinical trials of cardiovascular disease<sup>14</sup> and the sporadic reports of serious adverse outcomes following treatment with GP IIb/IIIa inhibitors,<sup>15-17</sup> I conducted an in depth review of 450 reports of adverse events involving GP IIb/IIIa inhibitors as the primary suspect resulting in death that were submitted to the Food and Drug Administration (FDA) between 1 November 1997 and 31 December 2000. The objective of the study was to determine the likelihood that GP IIb/IIIa inhibitor treatment caused the deaths reported to the FDA. A standardised rating system for assessing causation was applied to the reports.<sup>18</sup>

## METHODS

I requested, under the Freedom of Information Act, all adverse event reports filed with the FDA listing abciximab, eptifibatid, or tirofiban as the primary suspect drug. The Medwatch reports for the 450 adverse events resulting in

death were then requested for further analysis. Causation was assessed using the following: an evaluation of the timing of the event in relation to the dose and duration of GP IIb/IIIa inhibitor treatment; an assessment of the pattern of response to determine whether it constituted a recognised reaction to GP IIb/IIIa inhibitor treatment; and determination of the contribution of any concomitant diseases, medical conditions, or other treatments.<sup>18</sup>

In general, a death was considered *definitely related* to GP IIb/IIIa use when the precipitating causes of death coincided with the expected mechanism and duration of action of drug and no other drug likely to produce the same complication was being given. A death was defined as *probably related* to the use of GP IIb/IIIa inhibitors when the majority of the evidence supported the existence of a causal link but one or more aspects of the case were unknown or there was a minor inconsistency in the supporting evidence. Death was designated as *possibly related* to the use of GP IIb/IIIa inhibitors when it was equally likely that the death was not related to the GP IIb/IIIa inhibitor. Adverse event reports that included scant medical history and incomplete information about the drugs involved were considered to have insufficient evidence to assess causality. When the clinical course was highly inconsistent with known effects of GP IIb/IIIa inhibitors, the death was considered *definitely unrelated*.<sup>19</sup>

## RESULTS

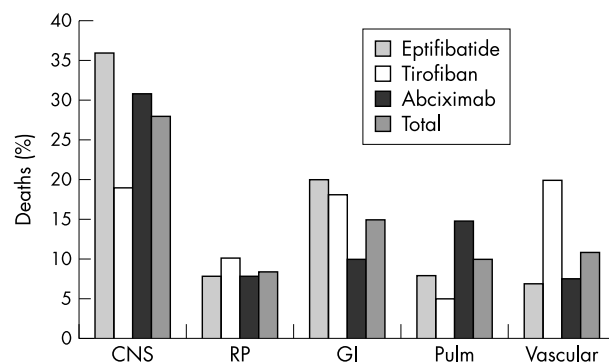
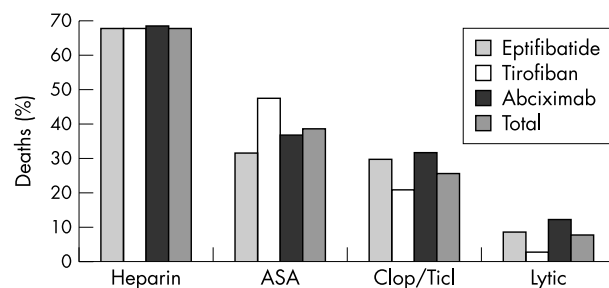
The age and sex of the patients who died following treatment with each of the GP IIb/IIIa inhibitors are given in table 1. Of the 450 deaths, 103 (23%) were associated with eptifibatid treatment, 143 (32%) with tirofiban, and 207 (46%) with abciximab. The median age of the patients who died was 70 years, with a range from 23-97 years. Women comprised 47% of patients who died. Overall, 27 deaths (6%) were thought to

**Table 1** Characteristics of patients who died during treatment with GP IIb/IIIa inhibitors

	Eptifibatide	Tirofiban	Abciximab	Total
Deaths	103	143	207	450
Female (%)	38	51	45	47
Age (years)				
Range	39–90	30–97	23–96	23–97
Median	70	72	68	70
Mean	70	71	67	69
Haemorrhage (%)	85	72	82	80
Myocardial infarction (%)	16	24	17	19
Thrombocytopenia (%)	6	18	14	13

be definitely related to GP IIb/IIIa inhibitor treatment, 170 (38%) probably related, 118 (26%) possibly related, and 126 (28%) unrelated. In nine cases (2%) there was insufficient information to make an assessment.

The clinical events associated with the deaths are presented in table 1. Haemorrhage was a significant factor in 80% of all deaths and in 100% of deaths definitely or probably attributable to GP IIb/IIIa inhibitor treatment. Myocardial infarction was present in 19% of patients who died and thrombocytopenia in 13%. Figure 1 shows the sites of bleeding among patients who died following GP IIb/IIIa treatment. The most common site of bleeding was the central nervous system (28%), followed by the gastrointestinal tract (15%). Pulmonary haemorrhage was noted in 10% of patients who died, retroperitoneal haemorrhage in 8%, and vascular bleeding in 11%. Other drugs given to patients who died are shown in fig 2. Heparin treatment was used in 68% of patients, aspirin in 39%, clopidogrel or ticlopidine in 25%, and a thrombolytic agent in 8%.

**Figure 1** Sites of haemorrhage among patients who died while being treated with GP IIb/IIIa inhibitors. CNS, central nervous system; GI, gastrointestinal; pulm, pulmonary; RP, retroperitoneal.**Figure 2** Concomitant pharmacotherapy among patients who died while being treated with GP IIb/IIIa inhibitors. ASA, aspirin; Clop, clopidogrel; Lytic, thrombolytic agent; Ticl, ticlopidine.

## DISCUSSION

Although GP IIb/IIIa inhibitors have been found to reduce thrombotic complications among patients undergoing percutaneous coronary intervention, and to reduce myocardial infarction in patients treated for acute ischaemic syndromes, individual clinical trials have not shown a reduction in mortality associated with GP IIb/IIIa treatment.<sup>3–12, 20</sup> Thus any potentially fatal complication of a treatment that does not reduce mortality is a cause for concern. Using standardised methodology for assessment of causality,<sup>18</sup> the current analysis shows that 44% of 450 deaths associated with GP IIb/IIIa treatment were definitely or probably caused by this treatment. These deaths were a result of bleeding complications associated with the GP IIb/IIIa inhibitors. The most common site of bleeding associated with death was the central nervous system. Placebo controlled randomised clinical trials of the GP IIb/IIIa inhibitors have not shown an excessive mortality associated with this treatment, though there is a consistent increase in the risk of major bleeding.<sup>3–12</sup> Furthermore, a review of four placebo controlled studies of the use of abciximab in percutaneous coronary interventions did not find an increased risk of stroke compared with the use of heparin or aspirin.<sup>21</sup>

There are at least three possible explanations for the relative absence of treatment related deaths in clinical trials, while numerous deaths outside the context of clinical trials have been reported to the FDA.

First, in clinical trials of treatments for coronary artery disease, women and elderly people—who may be at greater risk of complications from GP IIb/IIIa inhibitors—are commonly under represented relative to the disease prevalence in those populations.<sup>22</sup> In the current study the mean age of the patients was 69 years compared with approximately 60 years in the various randomised studies of GP IIb/IIIa inhibitors. Furthermore, women accounted for 48% of the patients who died in this study, whereas in the randomised studies they comprise approximately 27% of the subjects. Thus it is reasonable to question whether the safety results reported in clinical trials involving relatively few women and elderly patients are generalisable to these populations. In fact, a recent meta-analysis of randomised trials involving GP IIb/IIIa inhibitors in acute coronary syndromes documented a significant increase in bleeding complications among women.<sup>23</sup>

Second, the risk of treatment related death may be so low that the 30 000 patients enrolled in randomised trials was not sufficient for the risk to be clinically manifest.

Third, it is possible that the deaths outside the context of clinical trials are related to the use of GP IIb/IIIa inhibitors in an unapproved manner. For example, in the current dataset, 8% of patients who died were also being treated with thrombolytic agents. The combination of GP IIb/IIIa inhibitors and thrombolytic agents for the treatment of acute myocardial infarction is associated with significant risk of haemorrhage.<sup>24</sup>

Thrombocytopenia was documented in 13% of the patients who died but it has been found in only around 1% of patients following initial administration of abciximab and at even lower rates with eptifibatide and tirofiban.<sup>25</sup> The development of thrombocytopenia has been associated with increased mortality, primarily because of an increase in bleeding complications.<sup>26</sup>

A limitation of the use of reports of adverse events as an indicator of a drug's safety is that the population at risk is difficult to determine. Each year in the USA, over 500 000 angioplasty procedures are undertaken and over 1.5 million persons are admitted to hospitals with the diagnosis of acute ischaemic coronary syndromes. It is not clear what proportion of these patients is treated with GP IIb/IIIa inhibitors. Furthermore, reporting of adverse events is voluntary, resulting in a reporting rate that may be less than 15%.<sup>19</sup> Thus the frequency of deaths associated with the use of GP IIb/IIIa inhibitors cannot be determined accurately.

## Conclusions

Because of the large number of deaths potentially caused by the use of GP IIb/IIIa inhibitors outside the setting of randomised clinical trials, the use of these agents should be confined to the population most likely to benefit from their action. Although the incidence of deaths related to GP IIb/IIIa inhibitor use cannot be determined from this analysis, the findings raise concern about the risks of these agents and suggest the benefit/harm ratios reported in clinical trials may not be applicable to the population at large. Finally, these findings indicate the need for a better understanding of the individual susceptibility to bleeding following treatment with GP IIb/IIIa inhibitors and reinforce the view that these agents should be used for approved indications only.

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