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, 143 (32%) with eptifibatide as the primary suspect drug, 103 (23%) with abciximab, the median age of the 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.

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 eptifibatide 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
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%.

### DISCUSSION

Although GP IIb/IIIa inhibitors have been found to reduce thrombotic complications among patients undergoing percutaneous coronary interventions, 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. 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, 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 frequency of deaths associated with the use of abciximab in percutaneous coronary interventions did not find an increased risk of stroke compared with the use of heparin or aspirin.

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. 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.

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.

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. The development of thrombocytopenia has been associated with increased mortality, primarily because of an increase in bleeding complications.

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%. Thus the frequency of deaths associated with the use of GP IIb/IIIa inhibitors cannot be determined accurately.

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

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Deaths</th>
<th>Female (%)</th>
<th>Death</th>
<th>Median</th>
<th>Range</th>
<th>Haemorrhage (%)</th>
<th>Myocardial infarction (%)</th>
<th>Thrombocytopenia (%)</th>
</tr>
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<tr>
<td>39–90</td>
<td>103</td>
<td>38</td>
<td>143</td>
<td>70</td>
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<td>70</td>
<td>68</td>
<td>72</td>
<td>17</td>
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</tbody>
</table>

### 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; Clap, clopidogrel; Lytic, thrombolytic agent; Ticl, ticlopidine.
Conclusions
Because of the large number of deaths potentially caused by the use of GP IIb/IIIa inhibitors outside the setting of randomized 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.

REFERENCES