

Review: Oral glycoprotein IIb/IIIa inhibitors increase mortality and myocardial infarction

Newby LK, Califf RM, White HD, et al. **The failure of orally administered glycoprotein IIb/IIIa inhibitors to prevent recurrent cardiac events.** *Am J Med.* 2002 Jun 1; 112:647-58.

QUESTION

What is the efficacy and safety of oral glycoprotein (GP) IIb/IIIa inhibitors?

DATA SOURCES

Studies were identified by searching MEDLINE (1998 to 2001); reviewing abstracts from American College of Cardiology, European Society of Cardiology, and American Heart Association scientific sessions (1998 to 2001); and contacting investigators in the field.

STUDY SELECTION

Studies were selected if they were published, phase 3, randomized, controlled trials that included > 1000 patients, compared oral GP IIb/IIIa inhibitors (with or without aspirin), and had planned follow-up \geq 30 days.

DATA EXTRACTION

Data were extracted on patient numbers, interventions (e.g., agents and doses used and treatment duration), and primary outcomes.

MAIN RESULTS

5 studies met the selection criteria, and 4 studies provided efficacy data. Of 33 438 total patients enrolled, 33 326 patients

(99.7%) were included in the efficacy analysis. Oral GP IIb/IIIa inhibitors (xemilofiban, orbofiban, sibrafiban, and lotrafiban) were assessed for percutaneous coronary intervention (PCI), postacute coronary syndrome, and secondary prevention. Data from studies of xemilofiban, orbofiban, and sibrafiban were analyzed by meta-analysis using a random-effects model. Follow-up durations ranged from 90 days to 10 months. Treatment with oral GP IIb/IIIa inhibitors was associated with greater mortality than treatment with aspirin control (Table), and oral GP IIb/IIIa inhibitors plus aspirin were associated with greater mortality than aspirin

alone (Table). In patients with the acute coronary syndrome, oral GP IIb/IIIa inhibitors were associated with greater risk for myocardial infarction (MI) than aspirin control (Table).

CONCLUSION

Oral glycoprotein IIb/IIIa inhibitors increase mortality and myocardial infarction.

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Oral glycoprotein IIb/IIIa inhibitors (GP) with or without aspirin (ASA) vs ASA at 90 days to 10 months*

| Outcomes | Comparisons (number of studies) | Pooled odds ratio (95% CI) |
|---|---------------------------------|----------------------------|
| Mortality | GP alone or GP + ASA vs ASA (4) | 1.31 (1.12 to 1.53) |
| | GP alone vs ASA (2) | 1.37 (1.00 to 1.86) |
| | GP + ASA vs ASA (3) | 1.31 (1.12 to 1.53) |
| Myocardial infarction among patients with acute coronary syndrome | GP alone or GP + ASA vs ASA (3) | 1.16 (1.03 to 1.29) |

*Odds ratios and CIs were calculated using a Bayes random-effects model.

COMMENTARY

The results of the meta-analysis by Newby and colleagues are consistent with other summaries (1–3). Oral GP IIb/IIIa inhibitors have not only failed to reduce late ischemic events, they are associated with a consistent excess in death and MI. In contrast, substantial evidence exists that prolonged platelet inhibition with aspirin and clopidogrel can reduce the risk for death, MI, or stroke (4). Further, use of intravenous GP IIb/IIIa inhibitors for coronary artery instability has provided reductions in death and MI (4), particularly among patients with non–ST-segment-elevation acute coronary syndrome and high-risk features and those having PCI.

Given the potential of orally active GP IIb/IIIa inhibitors to target the final common pathway of platelet aggregation and extend the benefit of the short-term intravenous GP IIb/IIIa antagonism, why did the oral agents fail? Several possible mechanisms have been proposed, including the variability in the pharmacokinetics and pharmacodynamics of the oral GP IIb/IIIa inhibitors, paradoxical prothrombotic antagonist-induced platelet activation, and proinflammatory effects (1–3, 5). Nevertheless, Newby and colleagues highlight the importance of the more “proximal” or “upstream” inhibitors aspirin and clopidogrel, which irreversibly decrease the process of platelet activation; the GP

IIb/IIIa inhibitors reversibly affect platelet aggregation only. Intravenous GP IIb/IIIa inhibitors should continue to play a key, complementary role to aspirin and clopidogrel in patients having PCI and in high-risk patients with non–ST-segment-elevation acute coronary syndrome.

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