

**EBEM Commentators**

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Use of Platelet  
Glycoprotein IIb/IIIa  
Inhibitors in Patients With  
Unstable Angina and  
Non–ST-Segment Elevation  
Myocardial Infarction

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SYSTEMATIC REVIEW  
SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Bosch X, Murrugat J. Platelet glycoprotein IIb/IIIa blockers for percutaneous coronary revascularization, and unstable angina and non–ST-segment elevation myocardial infarction (Cochrane Review). In: *The Cochrane Library*. Issue 2. Oxford, United Kingdom: Update Software; 2002.

The *Annals'* EBEM editors prepared the abstract of this Cochrane systematic review as well as the

Evidence-Based Medicine Teaching  
Points.

OBJECTIVE

To determine whether intravenously administered platelet glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors are effective and safe in the management of patients with unstable angina (UA) and non–ST-segment myocardial infarction (NSTEMI) who are not routinely scheduled to undergo early percutaneous coronary intervention (PCI). This systematic review also examined the benefit of these agents in all patients undergoing PCI, but those results are not the focus of this abstract.

DATA SOURCES

Broad searches of MEDLINE (1966 to 2001), EMBASE (1980 to 1999), and the Cochrane's CENTRAL register (Issue 2000) were conducted. The authors also hand searched abstracts from the proceedings of cardiology conferences. A number of online resources were searched, and information was sought from principal investigators of identified trials and other experts in the field. Trials published in French, Spanish, and English were retrieved; no stud-

ies in any other language were identified. The review was updated in August 2001.

#### STUDY SELECTION

Randomized controlled trials enrolling patients with UA/NSTEMI who are initially managed medically were included in the review. Studies were included if they examined the use of a GP IIb/IIIa inhibitors in comparison with standard care (aspirin and heparin). The primary outcomes were 30-day and 6-month mortality, as well as the development of myocardial infarction (MI); the main secondary end point was major hemorrhage.

#### DATA EXTRACTION

From a list of potentially eligible studies, 2 reviewers selected trials; discordance was resolved through discussion. Two authors conducted data abstraction using a standardized form. Data were collected on methodologic criteria and patient characteristics that pertain to baseline risk and treatment features. Data were reported as odds ratios (ORs) for individual and composite end points using a fixed-effect model; if the test for heterogeneity was statistically significant, a random-effects model was used. All analyses are presented as intention-to-treat.

#### MAIN RESULTS

A highly sensitive search yielded 1,312 publications, which was then narrowed to 97 potentially eligible studies. Eight high-quality trials involving a total of 30,006 patients with UA/NSTEMI were included in this part of the review. Studies involved 4 different GP IIb/IIIa inhibitors: lami-

fiban (3 trials), eptifibatid (2 trials), tirofiban (2 trials), and abciximab (1 trial). The proportion of patients in the entire patient pool with UA ranged from 43% to 86%, whereas those with NSTEMI comprised 14% to 57% in the included studies. Thirty-two percent to 80% of patients had ST-segment depression at enrollment. Depending on the study, 1.6% to 25% of patients underwent urgent PCI during drug infusion (ie, within 24 to 72 hours after enrollment; in 14% to 31%, non-urgent PCI was performed during hospitalizations).

There was no difference in deaths at 30 days between the treatment groups (3.6% versus 3.3%; OR 0.90, 95% confidence interval [CI] 0.80 to 1.02). Patients receiving GP IIb/IIIa inhibitors experienced fewer deaths or MI at 30 days (10.4% versus 11.7%; OR 0.91, 95% CI 0.85 to 0.98). In absolute terms, this amounts to 77 patients who would need to be treated with GP IIb/IIIa inhibitors to prevent one death or MI at 30 days. This absolute benefit is sustained and remains unchanged at 6 months.

GP IIb/IIIa inhibitors appear to slightly increase the risk of major bleeding (3.7% versus 3.6%; OR 1.37, 95% CI 1.12 to 1.44), which translates into one additional major bleed for every 1,000 patients treated. There was no evidence of heterogeneity among the 8 trials examining patients with UA/NSTEMI.

#### CONCLUSIONS

The authors of this review conclude that, in patients with UA/NSTEMI who are managed without early PCI, GP IIb/IIIa agents do not reduce mortality, only slightly reduce the risk of death or MI at 30 days and at 6 months, and slightly increase the risk for severe bleeding.

#### Cochrane Systematic Review

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#### COMMENTARY: CLINICAL IMPLICATION

GP IIb/IIIa inhibitors are a new class of antiplatelet drugs that have been proposed as an important treatment for patients with acute coronary syndromes.<sup>1</sup> There is now strong evidence that GP IIb/IIIa inhibitors reduce mortality in patients who undergo both urgent and elective PCI, with only a small increase in bleeding complications. However, whether these agents should be given to patients with UA/NSTEMI or whether they even need to be given in the emergency department at any time remains controversial.

When viewed as having a uniform class effect, GP IIb/IIIa agents used in patients with UA/NSTEMI who are not immediately being referred for PCI do not reduce mortality and produce only modest gains in terms of the subsequent development of MI. This benefit comes at the expense of a small but definite increase in the risk of major bleeding. Although the eligibility criteria for most of these studies necessitated the presence of ST-segment changes or positive biological markers of myocardial injury, this review did not perform any subgroup analysis to examine differential benefits. As a result, it is unclear whether a particular category of patient or a particular agent or class of agent (large or small molecule GP IIb/IIIa inhibitor) can be associated

with an excess benefit or risk. Another meta-analysis provides some insight in this regard.<sup>2</sup>

Based on this review, the modest reduction in the composite end point (death or the development of MI) would not justify the use of GP IIb/IIIa agents in patients not scheduled for early PCI (usually <48 hours), especially in light of cost and bleeding risk. Although the ideal timing for providing these agents is uncertain, patients with UA/NSTEMI who do undergo early PCI should receive treatment with GP IIb/IIIa inhibitors. Some authors have also suggested that GP IIb/IIIa inhibitors should be considered when patients experience refractory pain or demonstrate other high-risk features even if PCI is unavailable.<sup>1</sup> Treating these patients mandates an integrated approach between emergency physicians and cardiologists responsible for PCI referrals.

#### TAKE HOME MESSAGE

Patients with UA/NSTEMI who do not undergo early PCI derive no mortality benefit from the administration of GP IIb/IIIa inhibitors. They do, however, obtain a modest benefit in the risk of going on to develop MI both at early (30 days) and 6-month follow-up. This benefit comes at the expense of a small increase in serious bleeding complications. This systematic review did not distinguish between the benefit that might be attributable to either low-risk or high-risk subgroups, nor did it attempt to distinguish between different GP IIb/IIIa inhibitors.

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#### EVIDENCE - BASED MEDICINE TEACHING POINT

##### Fixed versus random effects model.

When selecting an analytic model to pool the results of the constituent studies, researchers choose between a fixed or random effects approach. The fixed-effects (FE) model is based on the assumption that the results being presented represent the entire population of studies included in the meta-analysis. A random-effects (RE) model presupposes that the studies under consideration are merely a sample of the trials (in existence or to come) that address the question. FE models include only within-study variation while RE models include both within- and between-study variation. As a result, analyses conducted with the FE model yield measures of effect that are generally less conservative (narrower CIs) than those yielded with an RE model. The choice of model selected for analysis is a complex one, but in general, the FE model can be justified when the meta-analysis in question is composed of several large trials that together pass the test for homogeneity.<sup>3</sup>

#### REFERENCES

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