SELECTED ARTICLES

Inhibition of platelet aggregation in unstable angina

Article chosen
The PURSUIT investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998;339:436-43.

Reviewers: Layton D. Burkart, MD; Michael J. Bullard, MD
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Objective
To determine if early platelet inhibition with eptifibatide will provide incremental benefit beyond that of heparin and ASA in preventing adverse outcomes for patients with acute coronary syndromes who do not have persistent ST-segment elevation.

Background
Acute myocardial infarction (AMI) and unstable angina result from the rupture of atherosclerotic plaque, which leads to platelet aggregation, thrombin generation and intracoronary thrombus formation. Randomized controlled trials have shown that platelet glycoprotein IIb/IIIa receptor inhibitiors (in addition to heparin and ASA) reduce ischemic complications among patients undergoing percutaneous coronary revascularization (PCR).[1,2]

Population studied
10,948 patients who presented to 726 participating hospitals in 28 countries were enrolled. All patients had ischemic pain at rest, lasting 10 minutes or longer, within the previous 24 hours. In addition, patients required transient ST-segment elevation more than 0.5 mm, transient or persistent ST-segment depression more than 0.5 mm, T-wave inversion more than 1 mm, or an elevated creatinine kinase MB isoenzyme. Exclusion criteria included: persistent ST elevation more than 1 mm, a bleeding diathesis or active bleeding, hypertension (systolic BP >200 mm Hg or diastolic BP >110 mm Hg), major surgery within 6 weeks, an ischemic stroke within 30 days, or any history of hemorrhagic stroke, renal failure, pregnancy, and the planned or actual administration of thrombolytic therapy within the preceding 24 hours.

Study design
In this double-blind, randomized, placebo-controlled trial, 1487 patients received low-dose eptifibatide (180 µg/kg bolus followed by a 1.3 µg/kg/min infusion), 4722 received high-dose eptifibatide (180 µg/kg bolus followed by a 2 µg/kg/min infusion) and 4739 received placebo bolus and infusion. All study drugs were infused for 72 hours or until hospital discharge, whichever came first. Percutaneous revascularization was performed at the discretion of the treating physician and, if PCR was performed, the infusion could be continued for an additional 24 hours. An interim analysis concluded that high-dose eptifibatide was safe, so the low-dose arm was stopped.

Outcomes measured
The primary (composite) end point was all-cause mortality or nonfatal AMI at 30 days. Secondary end points included death or nonfatal AMI at 96 hours and 7 days, as well as safety, based on bleeding complications and thrombocytopenia. Nonfatal AMI was determined by a masked clinical events committee. A subgroup analysis looked specifically at patients undergoing PCR.

Results
Overall, eptifibatide was associated with a 1.5% absolute reduction in the frequency of the composite end point at 30 days. In patients undergoing early (<72 hours) PCR, there was a 31% relative reduction (16.7% vs. 11.6%, $p = 0.01$); in patients not undergoing PCR there was a 7% relative reduction (15.6% vs. 14.5%, $p = 0.23$). Number-needed-to-treat (NNT) to prevent one 30-day outcome event was 48 in the PCR group and 72 in the non-PCR group. Subgroup analyses favoured eptifibatide over placebo in all groups except women, and patients from Latin America or Eastern Europe.

Stroke occurred in 0.7% of eptifibatide recipients and 0.8% of placebo recipients (p = NS). Bleeding events were more common in eptifibatide recipients, and more eptifibatide patients required red cell transfusions (11.6% vs. 9.2%; relative risk [RR] = 1.3). The incidence of thrombocytopenia was similar (6.8% vs. 6.7% for eptifibatide and placebo respectively), but more eptifibatide-treated patients had profound thrombocytopenia, with <20,000 platelets/mm^3 (0.2% vs. <0.1%; RR = 5.0).

Study conclusion
Platelet inhibition with eptifibatide reduced the incidence of

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the composite end point (death or nonfatal AMI) in patients with acute coronary syndromes who did not have persistent ST-segment elevation.

Comments

Glycoprotein IIb/IIIa inhibitors are an exciting new class of antiplatelet drugs, but their role in emergency department (ED) practice remains unclear. The 3 most relevant trials, PURSUIT, PRISM-PLUS and PARAGON (the "3-P" trials), studied, respectively, eptifibatide, tirofiban and lamifiban. These trials enrolled similar patients with unstable angina or non ST-elevation AMI.[1,2] PURSUIT and PRISM-PLUS reported 1.5% and 3% absolute reductions in the composite end point at 2–4 days that were sustained to 30 days (PURSUIT) and 6 months (PRISM-PLUS). Of interest, these studies did not show significant mortality reductions. The outcome differences reported were primarily due to differing rates of nonfatal AMI or, in PRISM-PLUS, different rates of refractory and unstable angina.

In PURSUIT, the largest of the 3, only North American (primarily US) sites showed clear benefit for patients in the IIb/IIIa study arm. Western European eptifibatide recipients experienced a small and statistically insignificant benefit, and Latin American and Eastern European eptifibatide recipients fared worse than controls. Of interest, these findings precisely paralleled regional variations in cardiac intervention rates, which were 79% in North America, 58% in Western Europe, 46% in Latin America and 20% in Eastern Europe. It is tempting to use these findings as evidence of non-benefit, but retrospective subgroup analysis is hazardous and they may merely represent random variation.

On the surface, the 3-P studies appear to support the administration of IIb/IIIa inhibitors (plus ASA and heparin) to patients with unstable angina and non ST-elevation AMI; however, a close inspection of the data reveals that the greatest benefit occurred in patients who underwent percutaneous coronary intervention. It is also important to note that these studies enrolled only high-risk patients with rest pain and CK-MB elevations or objective ECG changes. There is no evidence to suggest that similar benefits would extend to lower-risk patients without objective evidence of ischemia.

The bottom line is that glycoprotein IIb/IIIa inhibitors are of benefit for patients who undergo percutaneous coronary revascularization and of less benefit for those who don't. Unfortunately, at the time of ED assessment it is not always clear who will and will not undergo PCR within 72 hours. Future studies may define a high-risk group of ED patients likely to benefit from these agents independent of PCR. As yet, it is premature to recommend their routine use in "non-interventional" patients.

References

1. The PRISM-PLUS Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. N Engl J Med 1998;338: 1488-96.
2. The PARAGON Investigators. International randomized controlled trial of lamifoban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. Circulation 1994;97:2386-95.

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Helical CT in the diagnosis of pulmonary embolism

Reviewer: Richard Lee, MD
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Date studied: November 1999

Clinical question

What is the utility of contrast-enhanced helical CT of the chest in the diagnosis of pulmonary embolism?

Article chosen

Drucker EA, Rivitis SM, Shepard JAO, Boiselle PM, Trotman-Dickenson B, Welch TJ, et al. Acute pulmonary embolism: assessment of helical CT for diagnosis. Radiology 1998;209:235-41.

The search

MEDLINE: 1990 to present
MeSH headings: pulmonary embolism/di [diagnosis] AND tomography, x-ray computed
Yield: 106 citations. Exclusion of reviews, editorials, comments and letters and including a hand search of the references of the remaining articles yielded 4 citations prospectively comparing helical CT to pulmonary angiography.

Clinical bottom line

Some previous studies have suggested that contrast-enhanced helical CT of the chest is a sensitive and specific test for acute pulmonary embolism (PE).[1,2] This study by

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