EDITORIAL COMMENT

Early Glycoprotein IIb/IIIa Inhibitors in Patients With Non–ST-Segment Elevation Myocardial Infarction*

Are We Ready to Open the Floodgates?

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Over the last few years, recent advances in antiplatelet and anticoagulant therapies have significantly altered the management strategies and outcomes of patients presenting with unstable angina (UA) and non–ST-segment elevation myocardial infarction (NSTEMI). These and other evolving therapies led to formulation of the American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines in 2000 (1), and a recent revision was published in 2002 (2). As these new therapies have become available, our challenge is to fully understand the value of these agents, both singly and in the inevitable combinations associated with the varied treatments and strategies used in this diverse group of patients, and to enhance their utilization in the medical community.

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The value of glycoprotein (GP) IIb/IIIa inhibitors in patients with acute coronary syndromes (ACS) who undergo percutaneous coronary interventions (PCIs) is well established. In a pooled analysis of the GP IIb/IIIa inhibitors in PCI trials, a statistically significant 33% relative risk reduction in the composite end points of death, non-fatal myocardial infarction (MI), and urgent revascularization at 30 days was reported, favoring the use of these agents versus placebo (7.8% vs. 11.6%) (3). This benefit was almost entirely achieved within the first 48 h and persisted for at least one year. Although there were significant increases in minor bleeding (3), there were no increases in major bleeding. The most recent revisions of the ACC/AHA guidelines consider the use of these agents in patients with UA/NSTEMI undergoing PCI a Class I indication (2).

The use of GP IIb/IIIa inhibitors in patients with UA/NSTEMI not routinely scheduled to undergo early coronary revascularization has also been studied, but in a less uniform manner and with less consistent results. A meta-analysis of the six major randomized clinical trials conducted between 1994 and 2000 addressing this issue involving 31,402 patients in 41 countries was recently reported (4). Clinical trials were included if the patients presented with an ACS without persistent ST-segment elevation, if a GP IIb/IIIa inhibitor was compared with placebo or control therapy, and if avoidance of early (<48 h) coronary revascularization was recommended. A variety of GP IIb/IIIa inhibitors was used in these trials (tirofiban, lamifiban, epifibatide, and abciximab) for a variable duration of therapy, and the protocol recommendations concerning invasive management were also quite variable. In some studies revascularization was discouraged for at least 48 h; in others it was encouraged after 48 h if indicated by angiography; and in others it was at the discretion of the treating physician. Revascularization procedures were performed in these studies in approximately 18% of patients by five days after randomization and in 38% by 30 days (no significant difference in revascularization between those treated with GP IIb/IIIa inhibitors and those not). The specific indications for revascularization in those patients who underwent revascularization are not provided. The meta-analysis found a 16% relative risk reduction of the odds of death or MI at five days with the use of GP IIb/IIIa inhibitors compared with placebo (5.7% vs. 6.9%, p = 0.0003) and a 9% reduction in these odds at 30 days (10.8% vs. 11.8%, p = 0.015). The absolute treatment benefit was largest in the subset of patients with positive troponins (≥0.1 μg/l), in whom a 15% reduction in the odds of death or MI was noted compared with control (10.3% vs. 12.0%), whereas no risk reduction was seen in patients with negative troponins.

The treatment effect seemed larger in patients with ST-segment depression than in those without, but the difference did not reach significance. The benefit of GP IIb/IIIa inhibitors was consistent in men, but women exhibited a worse outcome than men when treated with GP IIb/IIIa inhibitors, a difference that appeared to resolve after adjustment for differences in baseline troponin values. Death or MI at 30 days was reduced by GP IIb/IIIa inhibitors in the group undergoing PCI or coronary artery bypass surgery (odds ratio 0.89, 95% confidence interval [CI] 0.80 to 0.98) but not in the patients who did not undergo revascularization (odds ratio 0.95, 95% CI 0.86 to 1.05). Concerning safety, GP IIb/IIIa inhibitors were associated with increased risk of major bleeding complications (p < 0.0001), which was not dependent on concomitant treatment with heparin. Intracranial hemorrhage was rare and was not related to GP IIb/IIIa inhibitor use. Clearly the heterogeneity of patient characteristics in the different trials (unstable angina vs. non–ST-elevation MI), different agents used with different regimens, and the vague and variable indications and timing for revascularization make it difficult to extract definitive conclusions concerning the value of GP IIb/IIIa inhibitors in patients who are managed with an early conservative strategy.
The only randomized trial to specifically address the value of routine GP IIb/IIIa inhibitor therapy for high-risk patients with ACS who were treated with an early conservative strategy was the GUSTO IV-ACS trial, reported in 2001, which enrolled 7,800 patients with chest pain and either ST-segment depression or elevated troponin concentrations (5). Patients were treated with abciximab bolus and 24-h infusion, abciximab bolus and 48-h infusion, or placebo in addition to aspirin and either unfractionated heparin or dalteparin, a low molecular weight heparin. Surprisingly, there was no significant treatment effect with abciximab on the development of death or MI up to 30 days (8.0% of placebo patients, 8.2% of patients with the 24-h infusion, and 9.1% of patients with the 48-h infusion). In fact, the mortality at 48 h was lower in the placebo-treated patients than in the abciximab-treated patients (0.3%, 0.7%, and 0.9%, respectively, p = 0.008). Abciximab was associated with significantly increased minor bleeding in both dosage regimens and increased major bleeding in the 48-h infusion regimen (p < 0.05), excluding bleeding associated with cardiac surgery.

The initial ACC/AHA guidelines in September 2000 recommended GP IIb/IIIa therapy in all patients with positive cardiac markers (Class I) (1); however, on the basis of these emerging data over the past two years, the most recent revised ACC/AHA guidelines have given a Class IIa recommendation to the use of eptifibatide or tirofiban in patients with continuing ischemia, an elevated troponin, or with other high-risk features in whom an invasive therapy is not planned. A Class III recommendation is given to the use of abciximab in this setting.

In the current issue of the Journal, Peterson et al. (6) report the patient and hospital characteristics and subsequent outcomes for 60,770 patients with NSTEMI treated between July 2000 and July 2001 at 1,189 hospitals in the U.S. according to whether they received GP IIb/IIIa inhibitors within 24 h of admission, as suggested by the ACC/AHA 2000 guidelines. This enormous observational study was based on data from the National Registry of Myocardial Infarction 4 (NRMI 4). Their goal was to determine whether these new agents were being used in community practice nationwide in a manner recommended by the guidelines and to determine their safety and efficacy in this broad range of hospitals. They employed extensive and multiple adjustment and analytical techniques to avoid potential causes of treatment selection bias. In an effort to determine the value of early GP IIb/IIIa inhibitor therapy in conservative medical management, they repeated the analyses after excluding those who received PCI within the first 24 h, after excluding all PCI patients, and after excluding all patients who underwent cardiac catheterization.

Their results are impressive and quite compelling for a number of reasons. Perhaps most important—and disturbing—is the remarkably low use of these powerful and effective agents in the community. They observed that despite the published guidelines, only 25% of eligible patients were in fact treated with these agents. It is possible that some explanation for the lack of use of these agents is that some physicians may not have been convinced at the time that the use of GP IIb/IIIa inhibitors was justified for patients with NSTEMI unless they were to undergo cardiac catheterization and PCI. The knowledge base for appropriate use of GP IIb/IIIa inhibitors was clearly evolving during this period, as evidenced by the GUSTO IV-ACS study, as previously noted. If patients were treated in a community hospital or by non-cardiologists, then the lack of appropriate use of these agents may also be due to unfamiliarity with the use and indications of these therapies. Lack of use by cardiologists may reflect the perception that GP IIb/IIIa inhibitors should generally be reserved as a last resort medical therapy in cases where patients continue to have symptoms despite treatment with conventional approaches such as heparin, nitrates, calcium-channel blockers, and beta-blockers.

It is particularly disturbing that only 9% of the high-risk patients received GP IIb/IIIa inhibitor therapy, compared with 45% of low-risk patients with NSTEMI. What could have led to such a paradoxical use of GP IIb/IIIa inhibitors? One reason might be the selection bias of this observational study. It may be that more of the high-risk patients were referred for cardiac catheterization and that GP IIb/IIIa inhibitors were started during/after PCI after 24 h. These patients would have all been classified under the “no therapy” group by Peterson et al. (6). Physicians in the community may also not have considered all of the ostensibly “eligible” patients to be sufficiently high-risk to warrant these potentially high-risk medications. Although these patients had positive cardiac markers, <25% presented with ST-segment depression, and among the patients not treated with GP IIb/IIIa inhibitors, barely 50% presented with chest pain (7).

Another striking observation from this large-scale study is that those patients who were treated with GP IIb/IIIa inhibitors consistently experienced an improved outcome compared with those not so treated, an effect that persisted despite all adjustments. The overall unadjusted mortality rate (3.3% vs. 9.6%, p < 0.001) and the rates of death or MI (4.5% vs. 10.3%, p < 0.001) both favored the group treated with early GP IIb/IIIa inhibitors. The greatest absolute benefit was observed in patients with high-risk features on presentation, but even low-risk patients fared better with early use of these agents, by contrast with results from the previous meta-analysis (4). Patients appeared to benefit if they were managed with either an initial invasive or conservative strategy. In regard to safety, patients receiving GP IIb/IIIa inhibitors had a slight but significantly increased risk of major bleeding compared with controls (10% vs. 9.5%, p = 0.04) but had a similarly low risk of intracranial hemorrhage (0.1%).

Although the results of the Peterson study strongly favor early GP IIb/IIIa inhibitor therapy for all NSTEMI patients, the observational nature of this study cannot be
overestimated. There are important features that suggest that not all of the benefit in the patients who received GP IIb/IIIa inhibitor therapy was a result of administration of the drug alone. Those hospitals that had the highest use of early GP IIb/IIIa inhibitor treatment (treatment of 30% to 85% of eligible patients) had nearly 50% lower mortality rates than the centers with the least use. Those patients treated early with GP IIb/IIIa inhibitors were more likely to be treated by a cardiology consultant, to be treated with optimal routine medications such as aspirin and beta-blockers, and to undergo in-hospital catheterization and PCI. Those hospitals in which early GP IIb/IIIa therapy was administered were larger, more frequently offered angioplasty and bypass surgery facilities, and were teaching hospitals. Early treatment with GP IIb/IIIa inhibitor agents appears to be a surrogate for better care by cardiologists in a more experienced treatment facility.

Despite these caveats, the results remain impressive. The main message of the study (i.e., that patients with NSTEMI have been undertreated) cannot be overemphasized. This message underscores the urgent need for campaigns within the medical community, such as the AHA’s “Get With the Guidelines” program, to enhance dissemination of important therapeutic advances to the medical community and thereby improve patient outcomes.

The results from the Peterson study, however, cannot be construed at this time to indicate that all patients with NSTEMI should now be treated early with GP IIb/IIIa inhibitors. Certainly for those patients with NSTEMI who are intended to undergo coronary angiography and PCI, early treatment with GP IIb/IIIa inhibitors is clearly indicated. The group that remains most problematic at this time, however, consists of those patients who appear to be at low risk and who can be managed with an initial conservative medical approach. As the experience from GUSTO IV–ACS illustrates, a focused randomized clinical trial may not support the results of meta-analyses or subgroup analyses from other trials. It will be important to pursue randomized clinical trials with GP IIb/IIIa inhibitors other than abciximab, particularly in lower risk patients, to determine if these agents have a role in primary medical management.

The issue of concomitant medications will also need to be addressed carefully with appropriate clinical investigations before GP IIb/IIIa inhibitors are given to all NSTEMI patients, including those at low risk. The risks and benefits of newer combinations of anticoagulant and antiplatelet therapies will need to be assessed in the setting of GP IIb/IIIa inhibitor use in ACS patients, including low molecular weight heparins, direct thrombin inhibitors, clopidogrel, and tissue factor inhibitors.

This important study by Peterson et al. serves to illustrate both how valuable new forms of therapy may be, with the caveat of the observational nature of the study, and how unacceptably slow the medical community can be to incorporate such therapies into routine care. For patients with NSTEMI who are undergoing PCI, the floodgates are wide open for routine GP IIb/IIIa inhibitor use. For lower-risk patients who are to be treated with a conservative strategy, more randomized trials are necessary before their widespread use can be uniformly recommended.

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REFERENCES


