Differential Treatment Benefit of Platelet Glycoprotein IIb/IIIa Inhibition With Percutaneous Coronary Intervention Versus Medical Therapy for Acute Coronary Syndromes

Exploration of Methods

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Background—Although many believe that platelet glycoprotein IIb/IIIa inhibitors should be used only in acute coronary syndrome patients undergoing percutaneous coronary intervention, supporting data from randomized clinical trials are tenuous. The assumption that these agents are useful only in conjunction with percutaneous coronary intervention is based primarily on inappropriate subgroup analyses performed across the glycoprotein IIb/IIIa inhibitor trials.

Methods and Results—we describe the problems with these analytical techniques and demonstrate that different approaches to the question can result in opposing answers.

Conclusions—Clinical-practice decisions and practice guidelines should be based on overall trial results and not analyses of post-randomization subgroups. (Circulation. 2004;109:641-646.)

Key Words: trials ■ glycoproteins ■ coronary disease

One of the more interesting questions arising from the results of large trials of platelet glycoprotein (GP) IIb/IIIa inhibitors in non–ST-elevation acute coronary syndromes (ACS) is the issue of which patients benefit the most from treatment. From each trial, various subgroups have been analyzed to determine the categories of patients who will benefit most from the new treatment. One of the more controversial categorizations focuses on patients receiving percutaneous coronary intervention (PCI) versus medical therapy alone.1–5 The GP IIb/IIIa inhibitors have been shown to be effective in reducing ischemic events in patients with ACS who undergo PCI,6–10 but debate continues over whether these drugs also benefit patients who do not undergo PCI.

The purpose of the present study is not to provide insight into the relative treatment effect in these PCI groups but rather to evaluate the techniques used in the literature in drawing conclusions about this treatment difference. More importantly, we will discuss problems with some of the analytical approaches described in the literature to address this question and how conclusions can widely vary, according to the approach.

Improper Subgroups

Definition
In clinical trials, patients are randomly assigned to receive the treatment of interest to alleviate concerns about selection bias. Neither study enrollment personnel nor perceived clinical events can influence which patients receive active drug and which receive placebo when treatments are randomly assigned. Without randomization, we cannot know whether differences in outcomes reflect differences in treatment received or differences in the baseline risks of the treatment groups. Thus, randomization of treatment is critical for causal inferences to be made.

Several articles have been written about the pros and cons of subgroup analyses.11–19 This discussion focuses on comparisons of the randomized treatment effect between subgroups. In the examination of randomized treatment differ-

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TABLE 1. Baseline Demographic Characteristics in PURSUIT

<table>
<thead>
<tr>
<th></th>
<th>Early PTCA (n=1228)</th>
<th>No Early PTCA (n=8233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60 (51, 68)</td>
<td>64 (55, 71)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82 (72, 92)</td>
<td>77 (68, 87)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>28% (344)</td>
<td>33% (2720)</td>
</tr>
<tr>
<td>History of CHF</td>
<td>6% (70)</td>
<td>12% (977)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>23% (278)</td>
<td>11% (934)</td>
</tr>
<tr>
<td>Prior peripheral vascular disease</td>
<td>5% (59)</td>
<td>9% (723)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>33% (403)</td>
<td>28% (2274)</td>
</tr>
<tr>
<td>North American</td>
<td>75% (917)</td>
<td>35% (2910)</td>
</tr>
<tr>
<td>Female</td>
<td>31% (378)</td>
<td>36% (2979)</td>
</tr>
<tr>
<td>ST depression</td>
<td>31% (360)</td>
<td>39% (3135)</td>
</tr>
</tbody>
</table>

Values are median (25th and 75th percentiles) or frequency (percentages).

CHF indicates congestive heart failure.

Adapted from Kleiman et al, with permission.

ferences, the improper subgroup represents a special case. The improper subgroup is based on a characteristic measured after randomization, and the randomized treatment may influence whether the patient enters the subgroup. In the cardiovascular literature, improper subgroups themselves can represent end points of 2 types: (1) clinical complications such as congestive heart failure, arrhythmias, stroke, or myocardial infarction (MI), and (2) end points based on physician discretion. These include procedures or therapies such as PCI, coronary artery bypass grafting (CABG), concomitant medications, or blood transfusions. Special care needs to be taken when interpreting results from this sort of subgroup.

Issues

For this analysis, we will define the PCI group as anyone who undergoes PCI during the time specified by the protocol in which the randomized treatment is to be administered. We will define the medical therapy group as anyone not undergoing PCI during the time of randomized therapy.

The randomized treatment undertaken in the trial may affect how assignments are made to study groups. For example, the use of a GP IIb/IIIa inhibitor may reduce early ischemic events, making PCI unnecessary. Conversely, ischemic events may trigger angiography and subsequent intervention (PCI or CABG); thus, the placebo patients might be more likely to undergo PCI than treated patients.

Many of these patients, particularly in the United States, would likely have received angiography routinely in any event. Angiographic appearances may be changed by the active treatment, and these findings can determine procedure decisions. The patients without coronary disease will not receive a PCI, potentially creating lower risk for the medical arm and diluting the absolute treatment effect.

The 2 treatment arms within the PCI subgroup may not be comparable (Table 1). Demographics of PCI and medically treated patients are rarely similar. The patients in the PCI group may be different from the medically treated patients for the same treatment arm. The PCI may have been more event driven in the placebo group. Comparing differences between treatment and placebo arms in the medically treated subgroup with differences between treatment and placebo arms in the PCI subgroup would be inappropriate.

In the above scenario, an additional problem is that of not giving consideration to the timing of events relative to PCI. If the end point for the trial is death or MI and the early ischemic event driving the PCI is an MI, then an end point is assigned to the PCI group before the patient has even undergone the procedure. The event actually occurred during the time of medical management.

The timing of events has been disregarded in many analyses, leading to the incorrect assumption that any patient who undergoes PCI during randomized therapy belongs in the PCI group and all others are medically treated. Randomized treatment comparisons are made within the PCI and medically treated groups separately. The absolute or relative treatment differences and associated P values also are compared between PCI and medically treated patients. This is the most problematic analytical method. Adding to this are the problems of selection bias, assignment of events to the wrong group, different timing of the PCI relative to the randomized treatment, inadequate statistical power, and multiple-comparison issues.

A slightly better approach is the same-assignment method but excluding any event occurring before PCI. This solves the problem of events during medical therapy being assigned to PCI patients, but it does not correctly assign these events to the medical group. To do that, one can apply survival-modeling techniques using all of the patients and censoring on PCI. Patients are followed up until a PCI is performed, an event occurs, or the end of the study, whichever occurs first. In this way, one estimates the treatment effect during the medical management period across all patients.

One also can make the PCI a time-dependent covariate to account for its timing relative to the start of randomized treatment. The time-dependent covariate considers each patient to be in the no-PCI group until PCI is performed. From then on, according to the model, the patient is considered part of the PCI group. The PCI patients are considered to be medically managed from randomization until the PCI is started, and they are compared with patients who have already undergone PCI during this time. Once a patient undergoes PCI, that patient is moved to the PCI group and then is compared with patients who have not yet undergone PCI.

These methods do not allow for direct comparisons of treatment effects between the 2 groups, nor do they correct for selection biases. For selection bias, one must adjust for differences in baseline characteristics, for the propensity to receive a PCI, or both.

A propensity score represents the likelihood that a patient will undergo PCI based on his or her baseline profile. If the score can fully explain this decision process, then the bias of patient selection for PCI is removed when the propensity score is added into the model. If the assumptions hold, then inferences actually can be made from the subgroups. Similarly, if one adjusts for all baseline factors associated with selection bias and outcomes, then valid inferences also can be made. If data needed to determine the appropriateness for PCI are unavailable, then the propensity score will not adequately
control for selection bias. Similarly, if confounders are not available, adjusting only for baseline factors collected will not allow for valid inferences. It is likely that this problem will exist, because all factors that cause a physician to refer to PCI and factors that are associated with bad outcomes cannot be collected.

An interaction test of PCI with treatment can be used in these models to evaluate whether the treatment effect is statistically different for PCI patients than for medically treated patients. With this, one can make direct comparisons of the treatment effects between the 2 groups, but the test has only limited statistical power.

Example
The Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial was an international study of patients with ACS but without persistent ST-segment elevation on hospital arrival. Its primary results showed that eptifibatide was more effective than placebo in reducing death or MI in these patients at 30 days (P = 0.042). This study involved a heterogeneous population representing 726 hospitals in 28 countries. Many of these patients did not undergo PCI during the treatment period. The study was designed to answer the question of whether eptifibatide was beneficial for all patients with ACS, but the results did not convince many cardiologists that eptifibatide should be used outside of PCI.

Kleiman et al evaluated the question of differential treatment effect between patients who underwent PCI <72 hours after randomization (the expected duration of randomized treatment) and those who did not. Disregarding timing, treatment outcomes were more favorable for patients who underwent PCI (Table 2).

Table 2. Outcomes by Early Use of PCI in PURSUIT*

<table>
<thead>
<tr>
<th>Interval</th>
<th>Death or Adjudicated MI, n (%)</th>
<th>Eptifibatide</th>
<th>Placebo</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early PCI*</td>
<td>(n=606)</td>
<td>(n=622)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>96 h</td>
<td>57 (8.4)</td>
<td>95 (15.3)</td>
<td>0.002</td>
<td>0.576 (0.406 to 0.817)</td>
<td></td>
</tr>
<tr>
<td>30 d</td>
<td>70 (11.6)</td>
<td>104 (16.7)</td>
<td>0.010</td>
<td>0.650 (0.469 to 0.901)</td>
<td></td>
</tr>
<tr>
<td>No early PCI</td>
<td>(n=4116)</td>
<td>(n=4117)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>96 h</td>
<td>302 (7.3)</td>
<td>334 (8.1)</td>
<td>0.188</td>
<td>0.897 (0.763 to 1.055)</td>
<td></td>
</tr>
<tr>
<td>30 d</td>
<td>602 (14.6)</td>
<td>641 (15.6)</td>
<td>0.232</td>
<td>0.929 (0.823 to 1.048)</td>
<td></td>
</tr>
</tbody>
</table>

*PCI <72 hours after randomization; events are those occurring both before and after PCI.

In patients with PCI, the incidence of the primary end point (death or MI at 30 days) was 11.6% for patients receiving eptifibatide versus 16.7% for placebo-treated patients (P = 0.010). In patients not undergoing early PCI, the treatment effect was minimal, 14.6% versus 15.6% (P = 0.232).

Table 3 provides insight into this difference. Far more patients in the placebo arm of the trial had an early MI and then underwent PCI (5.5% in the placebo group versus 1.7% in the eptifibatide group; P < 0.001). Although these events were attributed to the PCI arm in Table 1, they actually occurred during medical management. The treatment effect considering events that occurred only after PCI was no longer statistically significant (12.4% for placebo versus 10.2% for eptifibatide; P = 0.235).

The censored analysis results were that eptifibatide was again effective during medical management (P = 0.035 censoring on PCI alone; P = 0.058 censoring on PCI or CABG). A Cox proportional hazard model with PCI as a time-dependent covariate was also considered. The interaction term for a different treatment effect with PCI versus medical management was not statistically significant (P = 0.635), even after also including a propensity-score adjustment (P = 0.634), indicating no statistical basis for concluding that treatment effects differed between patients who underwent early PCI and those who did not.

Results from this one study show a wide variation—from a strong treatment effect only in the early-PCI patients to no statistically significant difference in treatment effect between PCI and non-PCI patients. Addressing selection biases and properly assigning outcomes to subgroup categories made a significant difference in the results.

An Alternative Approach
No clinical trial has randomized patients in a factorial design to (1) receive a GP IIb/IIIa inhibitor versus placebo and (2) undergo early PCI versus medical management. A placebo–no PCI arm would be unethical, given the knowledge that PCI with a GP IIb/IIIa inhibitor is more effective than a PCI with placebo. Trials of applying an early invasive strategy conferred better clinical outcomes than those applying a conservative strategy. These trials all used a 1-drug treatment strategy, however, so the drug effects between the 2 strategies could not be evaluated. The C7E3 Fab AntiPlatelet Therapy in Unstable REfractory angina (CAPTURE) study was the one study that randomly assigned patients to placebo versus a GP IIb/IIIa inhibitor and studied the treatment effect in the 24 hours before a procedure, as well as in the period after the PCI.

Given the literature to date, when should a GP IIb/IIIa inhibitor be given? Clinicians who believe that such treatment has little effect without PCI might choose to wait until a procedure has been planned to consider using the treatment. Those who believe that a treatment benefit exists even without PCI might choose to give it on the patient’s arrival to the hospital. With this approach, the patient would already be receiving a GP IIb/IIIa inhibitor if PCI becomes necessary but still would benefit if PCI were not performed.

Example
The design of a clinical trial testing this question. Patients with ACS would be randomized to receive...
either a GP IIb/IIIa inhibitor as soon as possible after hospital arrival (early-treatment arm) or receive placebo and be switched to a GP IIb/IIIa inhibitor once PCI is planned (delayed-treatment arm). Treatment with angiography or a procedure would occur at the discretion of the physician for both treatment arms. In the delayed-treatment arm, a GP IIb/IIIa inhibitor would be started if and when the physician decided to perform PCI. Otherwise, the patient would continue placebo treatment until the end of the treatment period. Note that some patients will have an event before the PCI can occur.

Although such a trial has not been performed, other existing trial results provide insight. The patients who were randomly assigned to receive eptifibatide in PURSUIT would be similar to patients in the arm of the proposed study for whom active treatment would be administered on hospital arrival. The patients who were randomized to receive placebo would be similar to those in the delayed arm of the proposed study, except when a PCI was given. For these PCI patients, we can estimate how many events would have been avoided had a GP IIb/IIIa inhibitor been used.

Figure 2 shows the results of the proposed study using data from the PURSUIT trial. The overall event rate in the delayed-treatment arm was 15.7% versus 14.2% in the early-treatment arm. Most of the patients in the delayed-treatment arm did not undergo an early PCI—only 561 of the 4739 placebo-treated patients. An additional 61 patients experienced an event before PCI. Boersma et al.26 found a 23% reduction in odds in the PCI arm across all of the GP IIb/IIIa inhibitor trials. Assuming 25% of the 43 post-PCI events would have been prevented with GP IIb/IIIa inhibition before the PCI, the overall event rate for the delayed-treatment arm would barely change (15.5%). Although the assumption is somewhat unrealistic, had all 43 events been prevented, the event rate in this arm would still have been slightly higher (14.8%) than that of the early-treatment group.

Figure 3 illustrates the proposed study results using data from a recent meta-analysis of all of the trials.26 Again, even if 25% of the events had been prevented by giving a GP IIb/IIIa inhibitor before PCI, the early-treatment arm would still have had a lower event rate than the delayed-treatment arm (10.8% versus 11.6%).

**Discussion**

Roffi et al.27 recently published a meta-analysis of all large randomized trials of intravenous GP IIb/IIIa inhibitors in patients with ACS. Patients were defined according to the procedure received, and although timing was not discussed, it...
appears that the timing of the events relative to the procedure was disregarded. Across all trials, the rates of death or MI at 30 days for placebo versus active drug were as follows: 12.7% versus 10.7% for patients undergoing PCI during the hospitalization; 13.6% versus 10.5% for patients undergoing PCI while receiving study drug; and 9.7% versus 9.3% for patients treated medically. The authors concluded that although their findings were not based on a randomized assessment and were derived from a post-hoc analysis, “this observation suggests that maximal efficacy of platelet glycoprotein IIb/IIIa inhibition in unstable patients may be achieved if pharmacological and mechanical stabilization occur simultaneously, whereas the benefit conferred by pharmacological stabilization may decrease if both therapy modalities occur sequentially, and only a modest benefit may be observed if sole aggressive platelet inhibition is pursued” (p 1446).

Antman, in an editorial response to this study, concurred with the authors: “If a patient with an ACS is treated only medically using a GP IIb/IIIa inhibitor, the number of events prevented per 1000 patients treated is less than a quarter of that attained when the GP IIb/IIIa inhibitor is used in association with PCI” (p 1409). Both Roffi et al and Antman overlook the fact that all events occurring before the PCI were attributed to the PCI arm. Therefore, a large treatment benefit seen during the early hours of treatment was erroneously attributed to the PCI group and not the medical therapy group to which they actually belonged.

Antman’s editorial additionally acknowledges the results of a previous meta-analysis of these same trials (Figure 3). The authors of this meta-analysis had noted important differences between patients chosen to undergo early PCI and those not chosen. First, they showed that, compared with the placebo patients, significantly fewer patients assigned to the active treatment arms had undergone early PCI (14.9% versus 13.2%; P = 0.049). Among patients who did undergo early PCI, those treated with placebo (compared with active treatment) experienced significantly more MIs before the procedure occurred (OR, 0.70; 95% CI, 0.55 to 0.89). For the subgroup of patients who did not undergo an early PCI, the treatment difference was not statistically significant (OR, 0.95; 95% CI, 0.87 to 1.02). However, if all patients in the study were included, using the information during the medical management of each patient, then the treatment difference was statistically significant (OR, 0.92; 95% CI, 0.86 to 0.99).

Boersma et al had previously performed more extensive evaluations of this question by combining 2 of the trials from the meta-analysis, PURSUIT and the Platelet Receptor Inhibition in ischemia Syndrome Management in Patients Limited by Unstable Signs and symptoms (PRISM-PLUS) trial with the CAPTURE study. They found a 34% reduction in events during the medical-therapy phase (2.5% for active treatment versus 3.8% for placebo) and a 41% reduction during the first 48 hours after PCI (4.9% versus 8.0%).

Conclusions

Many analytical approaches have been taken, resulting in very divergent answers to the question of differential GP IIb/IIIa treatment effect with versus without PCI. The evidence does not support the use of glycoprotein IIb/IIIa inhibition only in conjunction with PCI, even though practice guidelines include such a recommendation. The true answer cannot be found using postrandomization PCI decisions. The trial to answer this question has not been performed, and the biases in the data currently available are so strong that one cannot know what the true answer is. The only way to answer the question raised by these analyses is through a randomized trial—one that randomly assigns patients to both the procedure and the treatment. Such studies may be impossible. It may be unethical to withhold certain concomitant medications, even though some patients still do not receive them. Randomization to a no-PCI arm in United States hospitals also may be impossible. Finally, it is impossible to know at hospital admission which patients will later undergo PCI. The best one can do is to strive to combine medical therapy with an early-angiography strategy.

There should always be heavy reliance on the overall results of a trial. After careful evaluation of the data, including consideration of timing and bias issues, any other results should be discussed in terms of being hypothesis-
generating only. Clinical-practice decisions and practice guidelines should not be based on analyses of postrandomization subgroups.

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References
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