Concurrent Antiplatelet and Fibrinolytic Therapy
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In patients who have myocardial infarction with ST-segment elevation, rupture of an atherosclerotic plaque leads to platelet adhesion, activation, and aggregation, with subsequent vessel occlusion due to thrombus formation. In these circumstances, the most effective pharmacologic reperfusion regimen is concurrent fibrinolytic therapy and platelet inhibition. The marked benefit of such a combination was first established in the Second International Study of Infarct Survival, in which 35-day mortality among patients with suspected myocardial infarction was 13.2 percent for those receiving neither streptokinase nor aspirin, approximately 10.5 percent for those given one or the other, and 8.0 percent for those receiving both agents.1

Although aspirin, administered with or without fibrinolytic therapy, reduces mortality among patients with myocardial infarction, it has limitations. First, it is a relatively weak antiplatelet agent. It reversibly inhibits platelet cyclooxygenase, thereby blocking the synthesis of thromboxane A₂, a powerful promoter of platelet activation, but it exerts no effect on thromboxane-independent mediators of platelet activation, such as adenosine diphosphate, thrombin, or serotonin. Second, in up to 30 percent of persons with coronary artery disease, the condition is relatively resistant or unresponsive to aspirin, as assessed by the extent to which platelet activation and aggregation are inhibited, bleeding time is prolonged, or treatment is deemed to be clinically effective.2

All mediators of platelet activation cause conformational changes in the platelet-surface glycoprotein IIb/IIIa receptor, allowing it to bind to circulating fibrinogen and to form platelet–fibrin aggregates. As a result, inhibitors of the glycoprotein IIb/IIIa receptor are the most potent antiplatelet agents, since they block the final common pathway for platelet aggregation. In pilot studies, patients who had myocardial infarction with ST-segment elevation who were given aspirin and fibrinolytic therapy had earlier and more complete coronary arterial reperfusion when a glycoprotein IIb/IIIa inhibitor was administered concomitantly than when it was not.3,4 Subsequently, several trials showed that concomitant administration of reduced-dose fibrinolytic therapy, aspirin, and a glycoprotein IIb/IIIa inhibitor decreased the incidence of in-hospital reinfarction by 1 to 2 percent as compared with full-dose fibrinolytic therapy and aspirin.5,6 However, this modest reduction in the incidence of reinfarction was offset by a concomitant increase in the incidence of nonintracranial bleeding. In short, the addition of very potent antiplatelet therapy (in the form of glycoprotein IIb/IIIa inhibitors) to fibrinolytic therapy (even at a reduced dose) lessened the risks of reocclusion and recurrent infarction after successful reperfusion, but it did so at the expense of an increase in the frequency of bleeding complications.

Clopidogrel is a more potent platelet inhibitor than aspirin, but it is less potent than the glycoprotein IIb/IIIa inhibitors. It inhibits platelets by selectively and irreversibly binding to the P2Y₁₂ receptor, thereby blocking the adenosine diphosphate–dependent pathway of glycoprotein IIb/IIIa–receptor activation. As is the case with aspirin, the response of platelets to clopidogrel is heterogeneous, and resistance to therapy has been reported.7 In patients with stable angina, dual therapy with aspirin and clopidogrel exerts greater inhibitory effects on platelet activation and aggregation than therapy with either agent alone. In patients with myocardial infarction without ST-segment elevation, an aspirin–clopidogrel combination improved cardiovascular outcomes, as compared with aspirin alone.8 Unfortunately, those treated with combina-
tion therapy had a greater risk of bleeding than those treated with aspirin alone, and this finding was particularly noteworthy among those in whom clopidogrel was discontinued within five days before coronary-artery bypass grafting.

In this issue of the *Journal*, Sabatine et al. report that patients with myocardial infarction with ST-segment elevation who were treated with fibrinolytic therapy and aspirin derived further benefit if clopidogrel was administered concomitantly, in that their coronary arterial patency improved. At the same time, the addition of clopidogrel to full-dose fibrinolytic therapy, aspirin, and heparin did not appear to increase the incidence of bleeding complications — a finding in clear contrast to those of the previously mentioned studies of combination therapy with reduced-dose fibrinolytic therapy, aspirin, and a glycoprotein IIb/IIIa inhibitor. The fact that clopidogrel is easier to administer and is less expensive and safer than a glycoprotein IIb/IIIa inhibitor further adds to its attractiveness for use in patients receiving fibrinolytic therapy.

Of the individual components of the primary end point assessed by Sabatine et al. (i.e., death, recurrent myocardial infarction, and occlusion of the infarct-related artery), clopidogrel exerted its greatest effect in reducing the rate of occlusion of the infarct-related artery. The mechanism by which clopidogrel exerted this effect is unknown; it may have enhanced early reperfusion, prevented reoclusion, or improved late reperfusion. The clinical benefit associated with the use of clopidogrel (i.e., a reduction in the risk of recurrent myocardial infarction) suggests that its primary mechanism of action is the prevention of reoclusion.

Several caveats concerning the study reported by Sabatine et al. are worthy of mention. First, the patient population appears to have been highly selected and at very low risk: both treatment groups had a 30-day mortality of less than 3 percent, which is among the lowest reported for any study of patients who have myocardial infarction with ST-segment elevation. Whether unselected patients with myocardial infarction with ST-segment elevation will benefit from clopidogrel without having an increased incidence of bleeding is unknown. Second, because patients who were elderly or thin and treated with a standard, non-weight-based dose of heparin (i.e., those at increased risk of bleeding) and those who had previously undergone coronary-artery bypass grafting were not enrolled, it is unknown whether such patients should receive clopidogrel in combination with full-dose fibrinolytic therapy and aspirin.

Third, because few patients in the study underwent coronary-artery bypass grafting while receiving clopidogrel, the safety of that procedure during clopidogrel therapy is unknown. As noted, previous studies have shown that persons undergoing bypass grafting who recently received clopidogrel are at increased risk for substantial perioperative bleeding.

Fourth, in many centers, coronary angiography is performed promptly after fibrinolytic therapy in order to evaluate the adequacy of that therapy and to perform revascularization, if indicated. Patients undergoing early angiography promptly after successful fibrinolysis are less likely to have coronary arterial reoclusion, with recurrent myocardial ischemia or infarction as a result, than those in whom angiography is routinely delayed after fibrinolytic therapy, as it was in this study. Whether clopidogrel is beneficial when an early invasive strategy is routinely used is unknown.

Fifth, the timing of clopidogrel administration in the patients who underwent percutaneous coronary revascularization may have affected the study outcome. Previous studies have shown that clopidogrel must be administered at least four to six hours before percutaneous intervention in order for it to be effective in preventing adverse cardiovascular events. In the current study, treatment with placebo or clopidogrel was continued until the day of angiography, which was performed a median of 3.5 days after enrollment; if percutaneous coronary intervention was performed, use of open-label clopidogrel thereafter was recommended. Thus, patients who were randomly assigned to receive clopidogrel had adequate serum concentrations of the drug at the time of percutaneous intervention, whereas those who were assigned to placebo did not. This aspect of the study may explain, at least in part, why the rate of the composite end point of death, recurrent myocardial ischemia, or recurrent myocardial infarction was similar in the clopidogrel and placebo groups before angiography (8.3 and 9.3 percent, respectively; P=0.27) but favored clopidogrel therapy after percutaneous intervention, at the 30-day follow up.

Because many patients are resistant to the effects of a single oral antiplatelet agent, therapy with multiple agents with different mechanisms of action is conceptually attractive, provided that it can be ad-
ministered without an increased risk of bleeding. For patients who are receiving fibrinolytic therapy, a combination of clopidogrel and aspirin appears, in fact, to be effective and safe.

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