EDITORIAL COMMENT

Combination Therapy for Acute Myocardial Infarction

Will it Survive?*

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Three years ago, the combination of a fibrinolytic agent given in a reduced dose, and a glycoprotein (GP) IIb/IIIa antagonist was trumpeted as a “great equalizer,” with the potential to bring the success rates for pharmacologic reperfusion regimens into line with those observed for mechanical reperfusion regimens. The promise was obvious. More rapid restoration of coronary flow and more stable reperfusion could be obtained. Consequently, myocardium could be preserved and lives could be saved. In fact, shortly after the presentations of the Thrombolysis In Myocardial Infarction (TIMI) 14 pilot study (1), many institutions began using combination therapy, even before data were available to indicate that patients benefited from this combination. Unfortunately, the clinical data to date have failed to support the pilot data.

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Shortly after the description of platelet GP IIb/IIIa (integrin \(\alpha_{IIb}\beta_3\)) antagonists to the receptor were developed. It is worth noting that the initial therapeutic application was to be augmentation of thrombolysis. A basic model was partially in place. Patients with acute myocardial infarction, particularly those receiving thrombolytic drugs, have evidence of increased platelet activation and increased platelet aggregation. One pathologic study from the National Heart, Lung, and Blood Institute has indicated that patients who manifest thrombolytic failure (death) are three times as likely to have platelet-rich thrombi as patients who die but who have not received thrombolytic therapy (2). Subsequently, a variety of animal models, particularly those studied by Gold and others (3,4), took this concept one step forward. A canine model of thrombosis was constructed, and thrombolysis was achieved using multiple boluses of tissue-type plasminogen activator (t-PA). Administering an antibody directed at platelet GP IIb/IIIa [7E3F(ab')2, a precursor of abciximab] allowed patency to be achieved and sustained using fewer boluses of t-PA and was particularly effective when thrombi proved to be t-PA resistant (5).

These observations led to two important concepts. First, platelets exhibited a threshold response to the GP IIb/IIIa antagonist (approximately 80% receptor blockade was required to limit thrombosis), and second, when this threshold was achieved, the total dose of fibrinolytic agent, measured as the number of boluses of t-PA required to achieve patency, could be reduced.

The first clinical studies of this principle followed the experimental observations by nearly a decade. Currently, five small studies (1, 6–9), six including the current one, have been published. All but one indicate increases in that favorite surrogate end point, TIMI grade 3 flow, in patients receiving combination therapy compared with those receiving a standard dose of a fibrinolytic agent. Unfortunately, the large clinical trials have not supported the enthusiasm engendered by these findings. One large trial, GUSTO V (10), revealed no reduction in mortality by a combination of reduced dose reteplase and abciximab at 30 days, although there was a substantial reduction in the rate of reinfarction among patients receiving combination therapy. However, at the end of one year, the mortality rates were absolutely identical (odds ratio 1.000). A smaller study, ASSENT III (11), compared a combination of reduced dose tenecteplase (TNK) with abciximab. Similarly, no mortality benefit was present.

Where, then, do these findings leave us? The theoretical basis for this therapeutic approach has been established; the experimental evidence supporting it is secure, and the clinical principle has been confirmed in pilot studies. Unfortunately, the acid test has not been passed. Although we may never know the reason, there are multiple potential explanations. From a clinical point of view, safety concerns may at least in part offset efficacy gains. Patients in pilot studies of new therapeutic regimens are usually selected very carefully. Consequently, risks are underestimated compared with in larger trials, which are directed at broader patient bases. In both GUSTO V and ASSENT-3, the risk of bleeding was significantly increased, particularly in elderly patients.

In addition to considering the balance between risk and benefit, the paradigm of inhibiting platelet aggregation deserves a careful look for several reasons. First, the effect of thrombolytic agents on platelet function is not clear. There is little doubt that platelet activation increases when fibrinolytic agents are administered; however, the degree and time course over which platelet aggregation is affected are controversial. Both increases as well as decreases in aggregability have been reported, and varying effects of fibrinolytic agents and their indirect mediator, plasmin, also have been noted (12). Other effects also may be important. Although combination therapy clearly decreases platelet aggregation, it has little if any effect on platelet activation. Platelets activated during the fibrinolytic and reperfusion processes may continue to secrete a variety of vasoconstrictor and inflammatory mediators that may affect the distal vascula-
ture and/or the myocardium. Furthermore, an important under-recognized fact is the role that white blood cells may play in the thrombotic process (13). Glycoprotein IIb/IIIa antagonists may or may not alter cross talk between activated platelets and white blood cells. Finally, distal embolization of fragmented thrombus may occur, as well.

The current manuscript by Giugliano et al. (14) in this issue of the Journal should be viewed in this light. The investigators of the INTEGRITI trial performed a careful dose-finding study in which eptiﬁbatide was combined with reduced-dose tenecteplase. In the dose conﬁrmation phase of the trial, 249 patients received either monotherapy with TNK or combination therapy with half-dose TNK and eptiﬁbatide given as dual 180 μg/kg boluses and a 2 μg/kg/min infusion. It is worth noting that of all the combination regimens that have been tested, this dose of eptiﬁbatide provides the greatest degree of inhibition of platelet aggregation, at least when standard turbidimetric measures of platelet aggregation are used (15). Perhaps the most telling result of the trial lies in the last portion of the last ﬁgure within the paper. Sixty minutes after beginning treatment, there were important trends toward increased frequency of TIMI ﬂow grade 3, TIMI myocardial perfusion grade 3, and complete ST resolution among patients receiving combination therapy compared with those receiving TNK monotherapy. However, the authors very astutely asked in how many patients all three indicators of reperfusion were present—in only 23% of patients were all three indicators of restoration of ﬂow to the myocardium found. Although better than that observed in patients receiving TNK monotherapy, this ﬁgure is still disappointing. Looked at another way, reperfusion fails to occur in three-fourths of patients receiving combination therapy and nearly 90% of those receiving monotherapy. In other words, even with the most aggressive of pharmacologic regimens, early complete reperfusion is rare.

Where are we left, then? Based on the studies done, it seems unlikely that combination therapy alone will offer much advantage over thrombolytic monotherapy. Perhaps it was naive to expect that it would. Based on ﬁndings from the ﬁrst GUSTO study, Simes et al. (16) calculated that a 20% improvement in TIMI grade 3 ﬂow resulted in a 1% improvement in all-cause mortality, given a baseline mortality of 7.3%. Perhaps it has been naive to expect a second reduction of equivalent proportions. It is not known whether the curve relating improvement in TIMI grade 3 ﬂow with mortality is linear. That is, a further 20% increment in TIMI grade 3 ﬂow may or may not result in an additional 1% decrement in mortality. The observed increment in TIMI grade 3 ﬂow for combination therapy is closer to 10% to 15%. Furthermore, this model does not account for potential increases in the hazard of treatment when more aggressive reperfusion regimens are studied.

Does all this mean that combination therapy is moribund and that GP IIb/IIIa antagonists will never be useful for reperfusion in patients with acute myocardial infarction? Hardly. It may well be that immediate mechanical revascularization emerges as the “savior” of combination therapy. Early restoration of coronary ﬂow using combination therapy may facilitate primary percutaneous intervention (PCI). Although nearly every comparison between primary PCI and ﬁbrinolysis has indicated that the former treatment (without ﬁbrinolytic or GP IIb/IIIa adjunct) is superior, one wonders what the ﬁndings would be if the same analysis used in Giugliano’s Figure 4 were performed in patients undergoing primary PCI. How many patients undergoing primary PCI would have TIMI grade 3 ﬂow, TIMI perfusion grade 3, and complete ST segment resolution? Observational data from both the PACT trial (17) as well as the PAMI studies (18) have indicated that, among patients who undergo successful primary PCI, left ventricular function and survival appear to be improved when TIMI grade 3 ﬂow is present before the intervention begins. Reasons likely include improved myocardial salvage as well as technically easier aspects of the intervention. These observations, coupled with the track record of GP IIb/IIIa antagonists during nonemergent PCI, lend theoretical support to the concept of “facilitated” angioplasty. Currently, only a single observational study of facilitated angioplasty has been reported (19), although several trials evaluating this approach are currently either underway or in planning stages. Perhaps in the coupling of these two strategies, the initial enthusiasm surrounding GP IIb/IIIa antagonists in combination with ﬁbrinolytic drugs will ultimately be justiﬁed.

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REFERENCES

7. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. Strategies for Pencyce Enhancement in the