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GUSTO V: Should it affect clinical practice?

YOU WOULD EXPECT a combination of drugs to be better than single-drug therapy for treating acute myocardial infarction.¹

Unfortunately, this remains to be seen.

The idea is attractive. Fibrinolytic agents, given intravenously, achieve suboptimal rates of epicardial coronary artery reperfusion.² Giving a potent intravenous antiplatelet agent such as a platelet glycoprotein (GP) IIb/IIIa inhibitor along with a reduced dose of a fibrinolytic agent *ought* to facilitate thrombus dissolution and therefore improve clinical outcomes.

But when the GUSTO V trial (Global Use of Strategies to Open Occluded Coronary Arteries)³ tested this hypothesis, the results were equivocal and should not, in our opinion, lead physicians to change their practice.

■ GUSTO V: RESULTS

No difference in mortality

The GUSTO V investigators³ compared the combination of abciximab (a GP IIb/IIIa inhibitor) plus half-dose reteplase (a fibrinolytic agent) vs reteplase in full doses and found that the combination led to no statistically significant reductions in:

- 30-day mortality (the primary end point) (5.6% with combination therapy vs 5.9% with reteplase alone)
- Nonfatal disabling stroke (0.3% vs 0.2%)
- Nonhemorrhagic stroke (0.3% vs 0.3%)
- Eleven other complications of acute myocardial infarction.

Some end points reduced

However, a number of secondary end points were significantly less common with combination therapy, including:

- In-hospital reinfarction (2.3% vs 3.5%, $P < .0001$)
- Recurrent ischemia (11.3% vs 12.8%, $P = .003$)
- Sustained ventricular tachycardia (2.2% vs 2.8%, $P = .02$)
- Ventricular fibrillation (2.7% vs 3.5%, $P = .008$)
- Second-degree or third-degree atrioventricular block (2.7% vs 3.3%, $P = .018$).

Some bleeding complications increased

The rate of intracranial hemorrhage was not increased with combination therapy (0.6% vs 0.6%, $P = .79$). But the rates of several other major bleeding complications were markedly increased with combination therapy, including:

- Any bleeding (24.6% vs 13.7%, $P < .0001$)
- Severe or moderate spontaneous nonintracranial bleeding (4.3% vs 1.9%, $P < .0001$)
- Severe bleeding (1.1% vs 0.5%, $P < .0001$)
- Need for blood transfusion (5.7% vs 4.0%, $P < .0001$).

■ ENTHUSIASM IS PREMATURE

The GUSTO V investigators concluded that combination therapy is safe and effective and may reduce the incidence of a number of mechanical and electrical complications of acute myocardial infarction. Furthermore, they and others have suggested that such combination therapy might be particularly attractive if an early invasive management strategy is preferred.

We contend that this enthusiasm is premature and not supported by the data.

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■ BLEEDING RISK SHOULD NOT BE IGNORED

The results of the GUSTO V³ and ASSENT-3 (Assessment of the Safety and Efficacy of a New Thrombolytic Regimen)⁴ trials indicate that the combination of potent fibrinolytic and antiplatelet agents increases the incidence of major bleeding.

Although it is reassuring that the incidence of intracranial hemorrhage, the most feared complication of fibrinolytic therapy, was not increased by combination therapy in the overall population of patients, other major bleeding complications cannot and should not be ignored.

The clinical importance of a major bleeding event in any particular patient is hard to predict and somewhat obscured by the reporting of aggregate estimates of incidence and severity in a selected clinical trial population.

For example, bleeding from a vascular access site in a patient with a large anterior myocardial infarction (and therefore a high risk of early and late complications) may be a very acceptable price to pay for significant reductions in the incidence of recurrent non-fatal myocardial infarction, recurrent ischemia, and mechanical and electrical complications of acute myocardial infarction. But ocular bleeding that causes blindness in a patient with an uncomplicated inferior wall myocardial infarction (and therefore a very good cardiac prognosis) is more difficult to justify.

■ WE SHOULD NOT COMPLICATE EMERGENCY CARE

In subgroup analysis, elderly patients had a higher incidence of intracranial bleeding with combination therapy, with a significant ($P = .033$) interaction of treatment by age (< 75 or ≥ 75 years).³ The ASSENT-3 investigators⁴ also reported a significant increase in intracranial bleeding among elderly patients receiving combination fibrinolytic and GP IIb/IIIa inhibitor therapy.

Small incremental changes in the risk-to-benefit ratios associated with new therapeutic strategies increase the opportunity to tailor treatments to a particular clinical profile and

to a particular patient. However, they also increase the risk of confusing health care providers, many of whom are emergency room physicians, internists, family practitioners, and other noncardiologists who cannot keep up with the results of substudies from major trials as easily as those recommending such tailored treatment.

And most importantly, attempting to tailor fibrinolytic therapy will undoubtedly increase time-to-treatment in the overall population, a critical determinant of outcome.⁵

For example, if we recommend one therapy for young patients with an anterior infarction (perhaps combination therapy), another for patients with an inferior infarction (perhaps full-dose fibrinolytic therapy with a fibrin-specific agent), and a third for elderly patients (perhaps streptokinase, with its lower risk of intracranial bleeding), it seems unlikely that the benefits that might arise from such tailored regimens would outweigh the confusion and delay caused by implementing them. Furthermore, it seems unlikely that these sorts of recommendations are good policies for the real world.

■ DOES COMBINATION THERAPY FACILITATE ANGIOPLASTY?

The GUSTO V authors and others have suggested that combination therapy may be most beneficial when angiography and angioplasty are performed early after pharmacologic reperfusion therapy is given. GUSTO V did not address this strategy (termed “facilitated angioplasty”), nor has any other randomized controlled clinical trial to date.

Although GP IIb/IIIa inhibitors reduced the incidence of periprocedural complications and improved outcomes in some (though not all) trials of primary angioplasty, we should not assume that giving a half-dose fibrinolytic along with a IIb/IIIa inhibitor will also be beneficial. Nor should we assume that it will be more beneficial than fibrinolytic therapy alone or, for that matter, more beneficial than pharmacologic therapy followed by a strategy of watchful waiting for signs of spontaneous or exercise-induced ischemia before performing angioplasty.⁶

In fact, an important body of work sug-

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gests that giving a fibrinolytic agent (which can expose clot-bound thrombin and have other effects on the coagulation cascade and platelet activation) predisposes patients to thrombotic complications during and after percutaneous coronary intervention (primarily balloon angioplasty) early after acute myocardial infarction.⁷ And in the GUSTO V trial, patients who underwent percutaneous coronary intervention within 6 hours of randomization had a *higher* mortality rate if they had received combination therapy than if they had received fibrinolytic therapy alone.

Such an analysis is inherently biased; indeed, the apparent harm associated with early percutaneous coronary intervention after combination therapy disappeared when multivariate analysis with a propensity analysis was performed. However, there are no data from GUSTO V or any other study to suggest that combination therapy routinely followed by percutaneous coronary intervention is beneficial.

■ GP IIb/IIIa INHIBITORS ARE COSTLY

The cost of health care continues to rise. We believe that if one therapy is shown to be beneficial compared with another, cost is a secondary consideration (albeit an important one). However, until an expensive regimen such as reteplase followed by abciximab (the most expensive GP IIb/IIIa inhibitor) is proven to be superior, it should not be routinely used in place of equally effective, better-studied, and less-expensive regimens.

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■ CONCLUSIONS

GUSTO V is an important, well-designed clinical trial that included more than 16,000 patients. It tested a reasonable hypothesis regarding the optimal treatment of acute myocardial infarction. However, it failed to show a statistically significant decrease in the primary end point of death within 30 days. Furthermore, there was a statistically significant increase in the incidence of nonintracranial hemorrhage, including severe hemorrhage and the need for blood transfusion. Intracranial hemorrhage was increased in the elderly.

Five of 16 predefined secondary end points were reduced to a statistically significant degree, suggesting a beneficial impact of combination therapy on the incidence of recurrent ischemic events and the mechanical and electrical complications of acute myocardial infarction.

However, the investigators' enthusiasm for the significance of these reductions needs to be kept in check until 1-year outcome data are available that reveal greater benefit from combination therapy than were seen at 30 days. We need a better understanding of who will benefit and who will suffer as a result of this novel regimen, the impact of combination therapy on early percutaneous coronary intervention, and the cost of such a management strategy. Until we have this understanding, we do not believe that combination therapy should replace full-dose fibrinolytic therapy in clinical practice.



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Pending more data, combination therapy should not replace full-dose fibrinolytic therapy