News and Views from the Literature

Interventional Cardiology

Results of the GUSTO V Trial

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The results of the important GUSTO V Trial evaluating the safety and efficacy of combination abciximab with half-dose reteplase have recently been published. The following is a review of the study results and its potential implications.

Reperfusion Therapy for the Acute Myocardial Infarction with Fibrinolytic Therapy and Platelet Glycoprotein IIb/IIIa inhibition; The GUSTO V Randomized Trial

The GUSTO Investigators.
Lancet. 2001;357:1905–1914

The GUSTO V (Global Use of Strategies to Open Occluded Arteries in Acute Myocardial Infarction) Trial was a randomized, double-blind, open-label comparison of full-dose abciximab (ReoPro®) combined with half-dose reteplase (RPA®) to standard full-dose reteplase in 16,600 patients presenting with acute transmural myocardial infarction (AMI). The purpose of this trial was to expand and confirm the findings of the previously performed pilot trial (Strategies for Patency Enhancement in the Emergency Department, or SPEED) of a potential therapeutic benefit and safety of a combined anti-platelet/fibrinolytic approach. The primary endpoint of GUSTO V was 30-day mortality with a variety of preselected secondary endpoints.

In the SPEED trial, a trend toward achievement of increased thrombolysis in myocardial infarction (TIMI) 3 flow at about 60 minutes was observed with combination therapy versus retaplase alone (47% vs 54%). Trends were also observed in favor of combination therapy for the endpoints of death, myocardial infarction, and urgent revascularization. A trend toward more major bleeds but not intracranial hemorrhage was also observed.[1]

GUSTO V enrolled patients from 20 countries who met inclusion criteria of at least 30 minutes and less than 6 hours of continuous chest discomfort from onset to time of randomization with electrocardiographic criteria of ST-elevation myocardial infarction. Major exclusion criteria included severe hypertension, recent stroke, thrombocytopenia, and weight greater than 120 kg. Those patients for whom a catheter-based therapy was planned were also excluded. Patients were randomized to receive reteplase at the standard dose of two 10-unit boluses 30 minutes apart or the combination regimen of standard abciximab (0.25 mg/kg bolus and 0.125 μg/kg/min infusion for 12 hours) with two half doses (5 mg) of reteplase given 30 minutes apart. There were no significant demographic differences between the two study groups. All patients received aspirin and heparin dosing, depending on randomization group. In the standard reteplase group, all patients received a 5,000-unit bolus of heparin with an infusion at 1000 units/hour for those weighing at least 80 kg and 800 units/hour for those weighing less. Patients randomized to combination therapy received heparin based on a nomogram to achieve a partial thromboplastin time of 50 to 70 seconds. Decisions on proceeding with coronary angiograpy and interventions were left to the discretion of the investigator based on the patient's clinical course.

Abciximab was permitted in those patients undergoing interventions in the reteplase-only group within 24 hours of randomization and recommended for those patients undergoing intervention more than 24 hours post-randomization.

All-cause mortality at 30 days was slightly but not significantly reduced in the combination therapy compared to the reteplase-alone group (5.6% vs 5.9%, $P = .43$). There was a significant reduction of "any complication" (28.6% vs 31.7%, $P < .0001$), reinfarction (2.3% vs 3.5%, $P < .0001$), and recurrent ischemia (11.3% vs 12.8%, $P = .004$). A small but significant reduction of the composite endpoints of death or nonfatal myocardial infarction was also seen with combination therapy (7.4% vs. 8.8%, $P = .033$).

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The data on the safety of combination therapy, particularly concerning the incidence of intracranial hemorrhage (ICH), is comforting, with no difference seen compared to standard reteplase treatment. However, there was a trend toward an increase ICH in the patients > 75 years of age (2.1% vs 1.1%, $P = .069$). There was a small increase in the incidence of severe thrombocytopenia (platelet count < 50,000) in the combination group (1.2% vs. 0.1%, $P < .001$). Our surgical colleagues should be relieved that the rate of bleeding associated with coronary artery bypass surgery was not higher in the combination therapy group.

GUSTO V successfully addresses the issue of the safety of combination full-dose abciximab and half-dose reteplase for treatment of acute myocardial infarction. It seems to be safely administered to patients, particularly if they are 75 years of age and younger. Adverse event rates of bleeding and thrombocytopenia are within acceptable ranges.

In terms of efficacy, those who felt that adding antiplatelet therapy to a modified dose of a lytic agent would represent a clear enhancement to standard lytic therapy may be disappointed by the lack of a robust mortality benefit. However, the significant reduction of important secondary endpoints, including reinfarction, recurrent ischemia, ventricular fibrillation, and sustained ventricular tachycardia with combination therapy is noteworthy. Possible explanations for not reaching this primary 30-day mortality endpoint benefit include the very low mortality in the control (standard reteplase) group, which makes a significant enhancement difficult to achieve. In fact, this is the lowest 30-day mortality rate seen so far in any trial of a lytic agent. Excluding patients for whom catheter-based interventions were planned may have minimized the potential benefit of adding abciximab to the treatment regimen by excluding patients who would have benefited the most. It is clear from the Munich Experience and ADMIRAL (Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up) trials that the use of abciximab as an adjuvant to coronary interventions in patients with AMI provides significant benefit, with 30-day mortality rates of 2.0% and 3.2%, respectively.[2,3] This compares favorably to the rates seen in both groups of patients in GUSTO-V.

The impact of GUSTO V remains to be seen and will be affected by the continued analysis of the data collected. Important questions remain, including the impact of combination therapy on patients who underwent urgent primary coronary interventions (PCI) in this trial. Will it lead to any of the following?

1. Encourage the substitution of combination therapy for standard lytic therapy in medical centers not predisposed or prepared for performing PCI for AMI?
2. Use of combination therapy to "facilitate" PCI in patients with AMI?
3. Increase utilization of combination therapy for AMI among cardiologists currently predisposed to performing PCI?

We know from previous trials that there are important pharmacologic differences between individual lytic agents and IIb/IIIa inhibitors. Before other combinations of these agents are used, their effects need to be carefully studied, rather than simply extrapolated from the safety and efficacy results of GUSTO V. Until these data are presented, those who wish to use combination therapy for the treatment of AMI based on GUSTO V data should restrict their selection to the agents and doses used in this study. ■

References

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