Editorial Comment

Acute Coronary Syndromes: Is a Unified Management Strategy Emerging?*

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Albert Einstein spent the last 30 years of his career in an unsuccessful attempt to develop a unified field theory encompassing all areas of physics. If he had been a cardiologist working at the end of the 20th century, he might have tried to develop a unified management strategy for the acute coronary syndromes. He would have been encouraged to learn that the pathophysiologic basis of unstable angina and myocardial infarction are thought to be similar: rupture or erosion of a vulnerable coronary atherosclerotic plaque with overlying thrombus formation severe enough to reduce regional coronary flow and cause myocardial ischemia or infarction (1,2). But how would he have sifted through the evidence related to treatment? The article by Betriu et al., for the Global Utilization of Streptokinase and t-PA [tissue plasminogen activator] for Occluded Coronary Arteries (GUSTO-I) Investigators (3), in this issue of the Journal would be as good a place as any to start.

Angina after thrombolysis for myocardial infarction. In GUSTO-I, >40,000 patients presenting with ST elevation within 6 h of the onset of chest pain were randomized to different forms of thrombolytic therapy. The present study describes postinfarction angina in GUSTO-I, a complication that occurred in one-fifth of the patients. Postinfarction angina greatly increased the risk of reinfarction within 30 days, particularly when accompanied by transient ST segment abnormalities. However, the mortality rate was increased only in patients whose angina was accompanied by hemodynamic changes, a combination that fortunately occurred in <2% of the GUSTO patients.

Postinfarction angina was a marker of more severe underlying coronary disease, as had been shown in older studies before the thrombolytic era (4). Non-Q wave infarctions now account for ~50% of all in-hospital myocardial infarctions, but are greatly underrepresented in GUSTO-I because the selection criteria included ST elevation. Non-Q wave infarction has previously been shown (4) to be a marker for postinfarction angina and reinfarction.

What should these findings from GUSTO-I teach us about treatment? 1) As shown in Table 4 of the present study, the time from the onset of postinfarction angina to reinfarction was very short. Treatment instituted at this point, whether medical or revascularization, might have an effect on mortality, but is too late to prevent reinfarction. 2) Treating all patients prophylactically for postinfarction ischemia will be inefficient, because four patients will be treated unnecessarily for every one who will develop symptoms. 3) Intravenous heparin use for a longer duration was associated with less postinfarction angina. Platelet glycoprotein IIb/IIIa inhibitors and hirudins may prove to have a profound impact on the incidence of postinfarction angina.

Currently, the best approach to postinfarction angina after thrombolytic therapy appears to be to avoid the problem altogether, by opting for primary angioplasty instead of thrombolysis. Primary angioplasty not only leads to higher patency rates in the culprit artery, but also permits early identification of the patient with precarious coronary anatomy who is at high risk for ischemia and reinfarction. Unfortunately, within the first few hours after the onset of symptoms, most patients with a Q wave myocardial infarction will not be in the care of an interventional cardiologist whose experience meets American Heart Association/American College of Cardiology guidelines (5).

Postinfarction ischemia. Although the GUSTO-I Investigators use the term ischemia, they note in their discussion that their study did not address the issue of silent ischemia. Postinfarction ischemia detected by Holter monitoring has been shown (6) to be a strong risk factor, irrespective of whether the patient received thrombolytic therapy. The asymptomatic patients in GUSTO-I may have had even better outcomes if those with silent ischemia were excluded.

Postinfarction patients usually undergo some form of a stress test, and those with myocardial ischemia are considered for revascularization, particularly if other high risk markers are present. This approach has recently been validated by the findings of the Danish Trial in Acute Myocardial Infarction (DANAMI) (7), where 1,008 patients with inducible myocardial ischemia after thrombolytic therapy for myocardial infarction were randomized to early angiography, with revascularization where possible, or to conservative treatment. After 2.4 years of follow-up, the invasive strategy was associated with a lower incidence of reinfarction (5.6% vs. 10.5%, p = 0.0038) and admission for unstable angina (17.9% vs. 29.5%, p < 0.0001).

If an invasive approach improves outcomes after thrombolytic therapy in patients with myocardial ischemia, might it not do so in patients without ischemia as well? As summarized by Michels and Yusuf (8), an overview of the relevant trials shows that neither early nor delayed angioplasty adds benefit when applied routinely after thrombolytic therapy.
Non-Q wave myocardial infarction. Patients with a non-Q wave myocardial infarction usually undergo coronary arteriography during the hospital period, with a view to revascularization because their risk of reinfarction over the ensuing year is high. This approach was compared with a conservative strategy of noninvasive risk stratification in the Veterans Affairs Non-Q Wave Infarction Strategies In-Hospital (VANQWISH) Trial (9). A total of 920 patients were enrolled. Conservatively managed patients were referred for angiography only if testing revealed high risk features, such as >2-mm ST depression on exercise testing or multiple redistribution defects on their stress nuclear images. Most patients in the invasive group, and very few in the conservative group, underwent coronary bypass surgery or angioplasty. All patients were followed up for 1 year.

The primary end point, death or nonfatal reinfarction, occurred during the hospital period in 7.8% of the invasive group and 3.3% of the conservative group (p = 0.01); at 30 days these rates were 10.4% and 5.7%, respectively (p = 0.03), and at 1 year they were 24.0% and 18.6%, respectively. We can conclude from the VANQWISH study not only that a conservative strategy is at least as good as an invasive strategy in the management of patients with a non-Q wave infarction, but that the event rate for this syndrome remains very high, despite current therapy. As with the situation after thrombolytic therapy, it appears wise to restrict revascularization to patients with evidence of ischemia; and better thrombin inhibitors or antiplatelet drugs, perhaps given for longer periods, might reduce the high event rate over the ensuing year.

Unstable angina. The problem of recurrent coronary events due to continuing instability of the culprit lesion has recently been well characterized in unstable angina. Investigators from St. George’s Hospital in London described a series of 85 consecutive patients with unstable angina whose symptoms stabilized on medical treatment, and who were scheduled for elective coronary angioplasty (10). During an average wait of 8 months for the procedure, 1 patient died and 25 had nonfatal coronary events; these events, 4 myocardial infarctions and 21 recurrences of unstable angina, were usually related to documented progression of the culprit lesion.

Most cardiologists believe that early angioplasty would reduce this high event rate, but clinical trial results to substantiate this belief are lacking. In the Thrombolysis in Myocardial Ischemia (TIMI) IIIB trial (11), where two-thirds of patients had unstable angina and one-third had a non-Q wave infarction, an early invasive strategy did not reduce the rate of death or infarction at 6 weeks compared with a strategy of reserving coronary angiography for patients with recurrent symptoms or inducible ischemia.

A unified management strategy. Einstein said that all science requires faith in the inner harmony of the world, but his ordered world of theoretical physics was not subject to the biologic vagaries of clinical cardiology. A formulaic approach to the treatment of acute coronary syndromes is not possible, but the following conclusions seem clear. Patients with acute coronary syndromes are at increased risk for subsequent coronary events if spontaneous or stress-induced myocardial ischemia complicates their course. Patients with myocardial ischemia have been shown to benefit from revascularization. The GUSTO-I population teaches us that prevention is the best approach to ischemia after thrombolytic therapy, because the interval between the onset of ischemic symptoms and reinfarction is often very short. Newer antiplatelet and antithrombotic agents are likely to prove helpful in this regard. A strategy of coronary angiography and revascularization whenever possible should not be applied indiscriminantly to all patients with acute coronary syndromes. The presence of ischemia, either spontaneous or induced with low levels of stress, should be a prime criterion for selecting patients for an invasive approach.

Einstein’s statement in an entirely different context seems curiously relevant: “Perfection of means and confusion of goals seem—in my opinion—to characterize our age.”

References