

## Editorial Comment

# Conservative Management After Thrombolysis: The Strategy Of Choice\*

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**Development of thrombolytic therapy.** During the past decade thrombolytic therapy of acute myocardial infarction has been studied extensively and its efficacy has been proved unequivocally. It has been demonstrated that several agents induce patency of previously occluded coronary arteries when administered either directly into the coronary artery or into a peripheral vein (1). Prolongation of life has been recorded in several large clinical trials of thrombolytic agents administered intravenously (2-5).

As the efficacy of thrombolytic therapy has been established, investigators have intensified studies of techniques designed to enhance the rapid achievement of vascular patency and the maintenance of the benefits achieved initially because reocclusion and reinfarction during the initial hospitalization are not infrequent (1). Accordingly, cardiac catheterization, coronary angiography and coronary angioplasty have been studied as techniques employed early in the course of the care of patients with myocardial infarction either by performing primary angioplasty or utilizing these techniques to consolidate the benefits of thrombolysis (6-10). Despite the obvious logic that a widely patent vessel must provide better initial salvage and lower reocclusion rates, randomized studies (6-10) have not shown that early aggressive management of myocardial infarction has any clear long-term benefits compared with thrombolysis alone with respect to survival, reinfarction or preservation of myocardial function.

As thrombolytic therapy of acute myocardial infarction has evolved, initially it was studied and used primarily in academic and tertiary medical centers, in part because of the expertise of the investigators and in part because of the necessity for immediate access to angiography for the administration of thrombolytic agents by the intracoronary

route and for the documentation of the efficacy of thrombolytic therapy. As intravenous thrombolytic therapy gained acceptance, the feasibility and safety of performing thrombolytic therapy in community hospitals was established, at least when rapid transport to tertiary medical centers was available and employed routinely (11-14).

The present study on thrombolytic therapy in community hospitals, A "conservative management strategy" has evolved in which coronary angiography and subsequent revascularization are employed after thrombolysis only if recurrent ischemia is detected. This approach has proved useful in an environment in which access to invasive procedures was readily available and was used relatively frequently (cardiac catheterization was performed in 32.7% of patients in the conservative management arm during the first 14 days in the Thrombolysis in Myocardial Infarction [TIMI] IIB study [15,16]). However, a report in this issue of the Journal (17) indicates that, although access to invasive procedures must be established, it need not be available instantaneously to maintain the benefits of thrombolysis. In the community hospitals that enrolled patients in this TIMI IIB study (17), access to invasive procedures at a regional hospital was established before the initiation of the study. Access to catheterization was available in <4 h in only 64% of the community hospitals and in <6 h in 76% of these institutions. Despite what some might consider relatively long delays in access to a catheterization laboratory, outcomes in community hospitals (without angiographic facilities) and in tertiary hospitals (with angiographic facilities, presumably available on very short notice) were comparable at 42 days and 1 year after infarction with respect to mortality, reinfarction and frequency of angina. Patients randomized at tertiary and community hospitals also had comparable outcomes with regard to rest and exercise ejection fraction and the percentage of patients with an abnormal exercise test when each was performed before hospital discharge and 6 weeks after infarction. These findings should allay fears that some might have that high quality care for patients with myocardial infarction can only be delivered at tertiary "high tech" medical centers. It must be recognized, however, that the community hospitals that enrolled patients in the National Institutes of Health-sponsored TIMI IIB study were carefully evaluated before being accepted as centers that enrolled patients in this research protocol. Therefore, these "community hospitals" may only represent the most academically oriented of community hospitals that have close ties to tertiary medical centers.

Perhaps surprisingly, comparable clinical outcomes were observed in the two types of institutions despite the longer potential time required to initiate urgent or emergent cardiac catheterization in patients randomized in community hospital-

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tals and, importantly, despite a more aggressive invasive approach to patient care at tertiary medical centers. A higher percentage of patients enrolled in tertiary centers underwent catheterization (46% versus 31%), received coronary angioplasty (18% versus 10.9%) and coronary artery bypass surgery (11.8% versus 7.8%), even though all patients included in the report of Feit et al. (17) were assigned to a "conservative strategy."

**Possible limitations of the study.** Although the TIMI IIB protocol specified the conditions under which patients could have invasive procedures performed in the "conservative management arm," substantial physician judgment was required to determine the frequency and severity of chest pain after infarction; the severity, extent and duration of new electrocardiographic abnormalities; and the severity of other clinical events that were sufficient to warrant the initiation of invasive procedures. The perception of what constitutes an indication for clinically indicated catheterization was different between physicians in TIMI IIB enrolling patients in tertiary as opposed to community hospitals. The finding that long-term outcomes were comparable in patients enrolled in both types of institutions underscores the fact that currently there are no good criteria for deciding when patients "need" angiography early after infarction and emphasizes our inability to identify clearly patients where postinfarction chest pain is ischemic, as opposed to due to pericarditis or other causes.

Although major demographic characteristics were comparable between patients enrolled in TIMI IIB in community and tertiary hospitals, there could have been differences between patients admitted to the two types of institutions based on self-selection or referral practices. There might also have been differences in monitoring equipment, staffing patterns or hospital procedures that might have enhanced the detection of ischemic episodes in tertiary hospitals, thereby precipitating the aggressive course taken at these institutions. Alternatively, as suggested by Feit et al. (17), investigators at tertiary centers might simply have had a "lower threshold" for angiography (16), perhaps due in part to the obvious availability of this technique. Once angiography was performed, comparable percentages of such patients proceeded to coronary angioplasty or coronary artery bypass surgery, or both, regardless of the type of hospital in which patients were initially randomized.

**Clinical implications.** If one extrapolates from the TIMI IIB experience to a pattern of care across the United States, the economic impact of even the moderately more aggressive strategy employed in tertiary centers in the "conservative management arm" would be substantial. With an estimated instance of acute myocardial infarction of 1.6 to 1.7 million annually in the United States and an estimated utilization of thrombolysis of 15% to 20%, one can estimate that nearly 250,000 patients will receive thrombolytic therapy in the United States in 1990. If catheterization were

performed in 47% (as in the tertiary hospitals) compared with the 31% (performed in the community hospitals), then nearly 40,000 extra cardiac catheterizations would be performed because of the "lower threshold" for performing these procedures. Employing similar logic and the frequency of coronary artery angioplasty and bypass operations performed in the two types of centers in the report by Feit et al. (17) (in the "conservative management arm"), one would expect an extra 17,750 angioplasties and 14,250 bypass grafting procedures. The economic cost of these extra procedures (catheterization, angioplasty and surgery) would be between \$550 and \$600 million per year. Furthermore, there would be additional costs due to prolonged hospitalization, unavoidable bleeding complications and increased requirements for transfusion with their potential for further complications and costs. If the "invasive approach" of TIMI IIB were employed, angiography, angioplasty and coronary artery bypass surgery would be even more frequent and costs would increase even more drastically. Despite this enormous cost, there would be no measurable difference in short- or long-term outcome (10, 15-17).

**Conclusions.** The data presented in the report of Feit et al. (17) in this issue of the Journal underscore the importance of the findings of the overall TIMI IIB study in which the efficacy of conservative management strategy after thrombolytic therapy has been demonstrated clearly (15-17). Although some may have had concerns that measurable delays between the detection of ischemic events and the performance of angiography and angioplasty might have impaired short- and long-term prognosis, this clearly has not been the case. In fact, the conservative management of patients in the community hospitals in TIMI IIB appears to generate as favorable an outcome as that which is experienced in patients treated somewhat more aggressively in the tertiary medical centers of this country. Many, perhaps most, physicians treating patients with myocardial infarction with thrombolytic agents feel a "need to know the anatomy" and have a desire to have unequivocal evidence of the presence or absence of recanalization of the infarct-related artery. Nevertheless, it is the fervent hope of many physicians that more effective antithrombotic therapy currently under development ultimately may reduce the incidence of reocclusion and that the implementation of better noninvasive markers of recanalization and reocclusion will reduce the pressure to perform predischARGE angiography to define the vascular anatomy. There is now compelling evidence that an aggressive invasive approach to the management of patients receiving thrombolytic therapy and the resultant "oculostenotic reflex" (Topol E, personal communication) leads to an increased frequency of revascularization procedures that do not appear to influence long-term prognosis favorably in the absence of spontaneous or exercise-induced ischemia.

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