Editorial Comment

TIMI IIb Follow-up
Lessons for Clinicians and Investigators

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The 1-year follow-up from the Thrombolysis in Myocardial Infarction (TIMI) Phase II Trial adds an important perspective to the growing body of knowledge about the impact of treatment on the outcome of acute myocardial infarction. Placed in the context of other recently completed as well as ongoing clinical trials, this new information provides substantial knowledge that clinicians can use to make therapeutic decisions. Simultaneously, areas in need of further understanding and definition are identified by the results of this trial. Some of these areas of needed investigation concern the development of pharmacological and mechanical interventions to manage the thrombus and the disrupted atherosclerotic plaque, whereas others involve the methods of design and analysis of clinical trials.

The 1-year follow-up data of TIMI II, reported in this issue of Circulation,1 further solidifies the knowledge that after thrombolysis, routine mechanical intervention to the reperfused artery does not lead to markedly improved outcomes in terms of survival and major cardiac events,2-4 bleeding complications,5 or cost.6 In fact, in the relatively young (less than age 76) and low-risk population selected for entry into the TIMI Trial, clinical event rates are low, regardless of whether intervention is applied routinely. The impecable data collection and protocol adherence of the TIMI group allow considerable comfort for the physician favoring the conservative route of careful observation of the patient after thrombolysis, with intervention relegated to those with recurrent ischemia or mechanical complications of infarction.

Why did the aggressive approach not do better? Several issues in the protocol design remain unresolved in terms of their possible impact on outcomes. The following points have evolved from data that have become available since the TIMI design was conceived, and rational counterarguments have been mounted by the TIMI group to each of them.7 Therefore, discussion of these issues should not imply an invalidation of the TIMI results but rather provide a basis for discussion of the application of the results to current practice and for the design of further investigation.

No effort was made to identify patients who failed to reperfuse so that they might have mechanical recanalization. Data from an earlier TIMI report8 and others9-11 have stressed the importance of the open infarct artery after thrombolysis. In fact, the protocol design specifically recommended no angioplasty in patients with totally occluded arteries in the absence of recurrent ischemia. Despite some evidence that “rescue” angioplasty may be beneficial,12,13 evidence to the contrary has been produced by the TIMI IIA14 and ECGS I Trials.3 An improvement in the mechanical techniques and pharmacological milieu for mechanical rescue could alter the balance toward acute intervention. Recent results from the Thrombolysis in Acute Myocardial Infarction 5 Trial15 and aggregated data16 indicate that selective use of rescue angioplasty in the setting of nonspecific fibrinolytic therapy can be a successful strategy.

The timing of cardiac catheterization, at a mean of 32.5 hours, may have been too early to avoid the increased risk of early postinfarction angioplasty and too late to take advantage of the possible benefit of rescue angioplasty.

Aspirin was withheld until the second day after thrombolytic therapy in response to concern about bleeding risk and then begun at a dosage of 80 mg/day, a dosage that may be insufficient.17 Subsequently, aspirin has been shown to have a substantial effect on mortality and reinfarction reduction18 and a pivotal role in the prevention of abrupt closure after angioplasty.19 Although the majority of TIMI patients were treated with aspirin shortly before angioplasty, one must wonder whether the 0.6% mortality and 4.5% reinfarction rates associated with the angioplasty procedure could have been reduced with more vigorous aspirin therapy. Considerable additional knowledge has also been gained about the need for aggressive use of heparin during interventional procedures,20,21 leading to the hope that the high early event rate in the aggressive arm of the trial could be reduced.

Coronary artery bypass grafting was not routinely recommended for patients with multivessel disease and
impaired left ventricular function. Accumulated clinical trial and observational data clearly demonstrate a surgical benefit in these patients, and the TIMI experience when surgery was chosen was excellent.

Another intriguing issue in the analysis of trials of aggressive intervention is that of duration of follow-up in the analysis of primary end points. If analysis was confined to the first day, almost all interventional approaches, including bypass surgery, would appear to be detrimental. In fact, recent evidence has demonstrated that intravenous thrombolysis itself appears to increase mortality on the first day of treatment. Advocates of the aggressive approach to the treatment of acute myocardial infarction have postulated that early intervention would lead to better long-term outcomes because of the patent infarct artery. A very slight trend in this direction occurred in one year TIMI II follow-up with a point estimate of a 7% reduction in mortality and a 12% reduction in severe ischemic events. The magnitude of the observed differences is small, however, and even to the optimistic interventionalist does not support an aggressive approach in every patient. Nevertheless, the accumulated follow-up data change the flavor of the results from an overall impression that early intervention is detrimental when the 42-day follow-up data were reported to a more favorable impression that combined ischemic events over time may be mildly reduced, even with the limitations of the TIMI protocol mentioned above. The observation that patients with previous infarction compose a high-risk group who may benefit more from an early invasive strategy is consistent with the possibility that an invasive strategy offers benefit, albeit difficult to demonstrate in a short period of time in low-risk patients.

Our extrapolation of the TIMI results in the context of other clinical trials has led us to the following clinical practices. Early reperfusion is stressed as the cornerstone of therapy. Patients with hemodynamic instability, recurrent ischemia, or a high probability of failure to reperfuse based on clinical criteria undergo immediate cardiac catheterization. Anticoagulation and antiplatelet therapy are used in a setting of careful observation and monitoring for recurrent ischemia. Decisions about angiography in patients without clinical ischemia are made on an individual basis, but our general tendency is to recommend angiography to establish the extent of disease and left ventricular dysfunction. When a patient’s values and preferences lead away from determining the extent of disease, the TIMI results allow comfort that early clinical outcomes will not be greatly affected by a conservative approach. Decisions about patient management are then made in the overall context of the clinical findings, exercise test results, and catheterization findings. In general, patients with one-vessel disease are treated conservatively unless exercise testing shows evidence for ischemia. The tradeoff is made clear by the TIMI II results: Early intervention with current technology increases the risk of in-hospital events, but after discharge more events requiring additional hospitalization occur when conservative therapy is elected. Proponents of aggressive diagnostic catheterization must make every effort to use the information to reduce costs in other areas by discharging low-risk patients early and minimizing unnecessary testing in other areas.

New developments are needed in the technology and pharmacology associated with the use of percutaneous intervention. The 15% 1-year event rate is low compared with previous outcomes, but this target leaves substantial room for demonstrating an effect of intervention. New regimens designed to more effectively antagonize platelet function and thrombus formation hold the most promise in the pharmacological realm, whereas percutaneous devices using less-thrombogenic materials or technology to deliver high concentrations of inhibitors of thrombosis to the vascular wall also may be effective in the near future. The noninvasive identification of failure to reperfuse, coupled with more effective approaches to open these refractory arteries, also should be aggressively pursued. Substantial progress is currently being made in the area of noninvasive detection using continuous ST segment monitoring and cardiac enzyme analysis.

Because of the fluent nature of the practice of cardiology engendered by the rapid development of new technology and the increasingly cost-conscious environment, a single “definitive” clinical trial will not be possible. The questions raised by the TIMI Trial emphasize the need for ongoing groups of investigators who can rapidly answer questions about clinical practice. Hopefully, any therapy will be viewed with skepticism until clinical trials show a reduction in mortality, nonfatal reinfarction, or other important clinical end points. Particularly after lessons learned from experience with antiarrhythmic therapy leading to increased mortality in patients with nonsustained ventricular arrhythmia and with calcium channel blockers increasing mortality in heart failure, clinicians will appreciate the necessity to rigorously test therapies to prove their benefit.

Given the remarkable strides leading to the low overall event rates in the TIMI Trial, future advances are likely to lead to only modest (10–20%) further reductions in event rates. Detection of such reductions will require large sample sizes and simple protocols to improve efficiency and reduce cost. The International Study of Infarct Survival Group has set an admirable example with voluntary efforts by thousands of physicians and hospitals around the world. Through the implementation of a treatment algorithm incorporating lessons from the past with expert clinical opinion, the conservative arm of TIMI has set a rigorous standard against which new approaches to treatment must be compared.

References


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KEY WORDS: Editorial Comments • clinical trials • myocardial infarction
TIMI IIIB follow-up. Lessons for clinicians and investigators.
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Circulation. 1992;85:839-841
doi: 10.1161/01.CIR.85.2.839

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