Initial Therapy for Acute Myocardial Infarction*

Socioeconomic Implications and Limitations

Rami Khouzam, MD; David Apgar, PharmD; and Brendan Phibbs, MD

Background: **The optimal therapeutic approach for acute myocardial infarction (AMI) is still evolving; however, many would consider one of two basic options: "medical"-only thrombolysis or reperfusion, or an early (invasive), percutaneous coronary intervention (PCI). The decision about which is most appropriate depends (perhaps unfortunately) on more than just medical factors. That is, the choice for some patients is also limited by payor source and the technical capabilities at the site of the initial treatment. Practically speaking, a significant portion of the US population simply does not have the option of (at least, initial) PCI.**
Methods and results: **Kino Community Hospital in Tucson, AZ, serves primarily an indigent population in southern Arizona, near the border with Mexico. This facility does not have in-house capability for PCI. Therefore, shortly after the publication of the original Thrombolysis in Myocardial Infarction (TIMI) 14 study (June 1999), we implemented their combination reperfusion protocol for the initial therapy of eligible patients admitted to the hospital with AMI. This report documents our experience with this medical reperfusion regimen in 42 patients over a span of almost 3 years. A retrospective chart review was conducted to evaluate outcome in 42 patients with ST-segment elevation myocardial infarction given the TIMI-14 reperfusion regimen. Complete resolution of ST-segment changes occurred in 30 patients (71.4%), with major bleeding complicating the therapy of only 3 patients (7.1%). After stabilization in our facility, 28 patients (66.6%) needed PCI.**
Conclusion: **This report summarizes the experience of a small county hospital where medical thrombolysis is the only immediate therapy available.** ***(CHEST 2004; 126:457–460)***

Key words: acute myocardial infarction; Thrombolysis in Myocardial Infarction 14; thrombolytics

Abbreviations: AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction

Current treatment of an acute myocardial infarction (AMI) includes two possibilities: thrombolysis or early invasive intervention. The choice of treatment is dictated in part by the availability of resources that, for the early invasive intervention option, would include a catheterization laboratory, an interventional cardiologist, and a cardiothoracic surgeon as a back-up. In pragmatic terms, however, invasive therapy is not available for some 42 million US inhabitants. These individuals comprise the "notch group," *ie*, those whose income is too large to permit funding of care by Medicaid but too small to cover private medical care.

Medicaid standards define "poverty" as an annual income of ≤ $15,500. Anyone making even a few dollars per year above this amount is not eligible for

For editorial comment see page 331

government-funded care. Thus, for the large category of "working poor" in the United States, invasive intervention is not a possibility. The Emergency Medical Treatment and Active Labor Act regulations, however, mandate care for anyone who presents to an emergency department regardless of source of funding. Since thrombolysis can be administered in any emergency setting, it is the only mode of treatment for a large percentage of the population.

Kino Community Hospital is a small county hospital in southern Arizona, near the Mexican border. Predictably, many of the patients who present to this

*From the Tucson Hospitals Medical Education Program (Dr. Khouzam), Kino Community Hospital (Drs. Apgar and Phibbs), The University of Arizona, Tucson, AZ.
Manuscript received September 16, 2003; revision accepted January 6, 2004.

Correspondence to: Rami Khouzam, MD, 699 Hotchkiss, Memphis, TN 38104, e-mail: ramisamia@hotmail.com

facility with myocardial infarction fall into the "notch" group or are foreign nationals; in other words, realistically these patients are candidates for thrombolytic therapy only.

Following the Thrombolysis In Myocardial Infarction (TIMI) 14 report,[1] the combination of thrombolytic agents described in that study was used in all appropriate cases in the Kino Hospital emergency department. This report therefore details the early results of this protocol, the number of cases referred for invasive therapy, and the results in those with and without invasive intervention.

Materials and Methods

Inclusion criteria for the chart review were as follows: (1) a clinical diagnosis of AMI (acute chest pain, ST-segment elevation, elevation in enzyme markers), and (2) treatment with thrombolytics using the TIMI 14 protocol. The regimen consisted of aspirin, 325 mg po, followed by three IV administered drugs in the order listed (each in a separate IV line): abciximab, 250 μg/kg as an IV bolus injection over at least 1 min, followed by an infusion of abciximab at 0.125 μg/kg/min over 12 h; then, as soon as possible, alteplase, 15 mg, as an IV bolus injection over at least 1 to 2 min, followed by an infusion of alteplase at 35 mg over 60 min; then, as soon as possible, heparin, 30 U/kg, as an IV bolus injection, followed by an infusion of heparin, 4 U/kg/h continued for 72 h. The specific order of administration was followed, as the original publication made a point of its importance.

Results

During the period of investigation (November 1999 through May 2002), a total of 42 patients with a discharge diagnosis of AMI received the TIMI 14 protocol. Within this study group of 42 patients, 29 were men and 13 were women. The age range for men was 34 to 87 years (average, 57.3 years); for women, the age range was 32 to 75 years (average, 62.4 years).

Twenty-seven patients had inferior (inferolateral and inferoposterior myocardial infarction), while 15 patients had anterior myocardial infarction manifested by ST-segment elevations, and rise of one or more of the following cardiac enzymes including troponin, creatinine kinase, creatinine kinase-MB, and myoglobin. Eight of 42 patients (19%) had no health insurance and were therefore "self-pay" (Table 1).

Complete resolution of ST-segment changes, defined as $> 70\%$, occurred in 25 patients (59.5%) within the first 90 min of the administration of the TIMI 14 protocol; 5 patients (11.9%) had a slower and incomplete ST-segment changes resolution, defined as $< 30\%$; while no change in ST segments or any other sign of reperfusion occurred in 12 patients (28.5%).

Table 1—*Demographics of 42 Patients Included in the TIMI 14 Protocol

Variables	Data
Male gender	29 (69.04)
Age, yr	
Range	34–87
Average	57.3
Female gender	13 (30.9)
Age, yr	
Range	32–75
Average	62.4
Inferior myocardial infarction (inferolateral or inferoposterior)	27 (64.2)
Anterior	15 (35.7)
No Insurance	8 (19)

*Data are presented as No. (%) unless otherwise indicated.

Major bleeding occurred in one patient (2.38%) in the form of intracranial hemorrhage.[1] Minor bleeding complications occurred in eight patients (19.04%) in the form of hemoptysis (n = 2), GI bleeding (n = 2), disseminated intravascular coagulopathy (n = 2) and hematuria (n = 1), and oozing from a femoral venous site (n = 1) [Table 2]. Criteria specified in the original TIMI 14 publication for the definition of major hemorrhage were invoked. This was described as any intracranial, retroperitoneal, or intraocular hemorrhage, or any clinically overt hemorrhage associated with a drop in hemoglobin ≥ 5 g/dL.[2]

After stabilization of the patients in our facility (which ranged from few hours to few days), 14 patients (33.3%) needed a therapeutic percutaneous coronary intervention (PCI), 2 patients (4.7%) only had a diagnostic catheterization without the need for an intervention, 12 patients (28.5%) were sent for a possible later intervention when stable, 9 patients (21.4%) were stable medically, 2 patients (4.7%) needed coronary artery bypass grafting, and 3 patients (7.1%) died (Table 3). The duration of follow-up was only for the in-hospital duration of stay.

Table 2—*Bleeding Complications Following the Use of TIMI 14 Protocol in 42 Patients*

Complications	Events, No.	%
Major bleeding	1	2.38
Intracranial hemorrhage	1	
Minor bleeding	8	19.04
Hemoptysis	2	
GI bleeding	2	
Disseminated intravascular coagulopathy	2	
Hematuria	1	
Oozing from a femoral venous site	1	

Table 3—*Outcome of 42 Patients Following the Use of TIMI 14 Protocol*

Outcomes	Patients, No. (%)
Need for a therapeutic PCI	14 (33.3)
Need for a diagnostic catheterization only (no therapeutic intervention)	2 (4.7)
Possible catheterization when stable	12 (28.5)
Stable with medical reperfusion only	9 (21.4)
Need for coronary artery bypass graft	2 (4.7)
Death	3 (7.1)

Discussion

The management of AMI was altered dramatically with the introduction of intracoronary thrombolytic therapy in the late 1970s by Rentrop and others.[3] After the publication of several randomized clinical trials of intracoronary and IV thrombolytic therapy, reperfusion of acutely occluded coronary artery beds with such thrombolytic therapy became a standard treatment of AMI by the mid 1980s.[4]

While thrombolytic therapy was gaining early acceptance as a means to achieve reperfusion, a parallel pathway for achieving reperfusion was developing with catheter-based techniques. Reports of percutaneous transluminal coronary angioplasty for the management of AMI first appeared in 1983.[5]

The most important difference between thrombolytic therapy and emergent percutaneous transluminal coronary angioplasty had to do with the achievement of an acceptable rate of reperfusion. From the earliest days of thrombolytic trials, it was known that the best clinical outcomes were associated with prompt restoration of normal or near-normal blood flow in the infarct-related artery.[6]

By the early 1990s, achievement of TIMI 3 (complete or normal) flow through the infarct-related artery became universally recognized as the goal of reperfusion therapy because of the survival benefit associated with its occurrence.[7] Most recently, mechanical reperfusion techniques have been further buttressed by the use of coronary stents, which appear to provide an additional benefit compared with balloon angioplasty alone in terms of achieving complete reperfusion of the infarct-related artery bed.[8] Although controversy persisted for a while,[9,10] the playing field for these two competing reperfusion therapies had definitely shifted by the mid-1990s to favor mechanical techniques if the resources and technical skills that are its prerequisites were in place.[1]

The TIMI 14 trial was conducted between March 1997 and July 1998 at 63 enrolling centers in the United States, Canada, United Kingdom, Belgium, the Netherlands, France, and Germany. The study ultimately included a total of 888 patients. The original publication in June of 1999 concluded that the combination of abciximab with low-dose tissue plasminogen activator increased the rate of angiographic patency of the infarct-related vessel following drug delivery, compared to using full-dose tissue plasminogen activator alone (76% vs 57%, respectively, $p = 0.001$). Combination therapy also improved both myocardial (microvascular) reperfusion, as reflected in greater ST-segment resolution, and epicardial flow. These findings may translate into improved clinical outcomes by enhancing myocardial salvage.[11]

Moreover, the TIMI 14 investigators have provided new data that indicate that the combination of "half"-dose thrombolytic agent alteplase, plus full-dose long-acting platelet glycoprotein IIb/IIIa inhibitor abciximab, plus low-dose or very-low-dose heparin infusions can achieve rates of TIMI 3 reperfusion at 60 min and 90 min that are similar to those achieved with primary angioplasty. In addition, their results, although based on small numbers of patients in the individual dosing groups, were associated with low rates of serious bleeding and intracranial hemorrhage.[2]

In the same issue of *Circulation* in which the original study was published, there was also an editorial article, in which Kennedy and Stadius[1] state:

> While further studies are being planned and executed, we believe that it is time for some major centers to embrace combination pharmacological reperfusion therapy and reserve primary angioplasty for patients with contraindications to its use. We believe that the TIMI 14 investigators have made a major contribution to the management of AMI. They have identified a combined pharmacological therapy for reperfusion that, with and without some modification, will likely prove to be equivalent or superior to mechanical reperfusion therapy.

Based on the above evidence, and in view of both the lack of a catheterization laboratory in our facility, and the characteristics of the patient population encountered in our community hospital, we decided to adopt what appeared to be this promising regimen from the TIMI 14 trial. The efficacy and relatively low incidence of serious adverse events are documented in our experience with this regimen. A question arose, during our experience, relative to the optimum follow-up management of our patients after having received the protocol regimen in our facility. In this setting, what is the role of mechanical intervention?

The data suggest that the degree of ST-segment resolution may be an effective, simple, and inexpensive means of identifying candidates for adjunctive intervention after combination therapy with abcix-

imab and reduced-dose thrombolysis. Patients with complete ST-segment resolution at 90 min have a very high likelihood of a patent infarct artery and a very low mortality rate; early adjunctive PCI is unlikely to improve outcomes in this subset of patients because they appear to have complete epicardial and tissue level reperfusion. However, patients with incomplete ST-segment resolution at 90 min have approximately 40% probability for an occluded infarct-related artery. Those with persistent ST-segment elevation and an occluded infarct artery should clearly undergo "rescue" PCI. It would be reasonable, therefore, to consider early coronary angiography and PCI in patients with persistent ST-segment elevation 90 min after treatment with TIMI 14 regimen.[12]

Conclusion

We conclude from our study that primary angioplasty continues to offer a small but significant advantage over "medical"-only thrombolysis or reperfusion regimens, in terms of early and late death, stroke, and reinfarction. However, what may be the optimal mode of therapy is not available to a large part of the US population, either because of lack of funding or remoteness from a center where truly early intervention can be carried out. For that large segment, we believe medical-only thrombolysis remains the only viable option for a significant portion of the population, either as definitive treatment or as a bridge to later intervention. It would therefore seem imperative to continue to investigate different regimens of medical-only reperfusion to discover alternatives or optimal agents and doses, since this mode of therapy for AMI will be the only source for millions in the United States for many years to come.

References

1 Kennedy J-W, Stadius ML. Combined thrombolytic and platelet glycoprotein IIb/IIIa inhibitor therapy for acute myocardial infarction: will pharmacological therapy ever equal primary angioplasty? Circulation 1999; 99:2714–2716

2 Antman EM, Giugliano RP, Braunwald E, et al, for the TIMI 14 investigators. Abciximab facilitates the rate and extent of thrombolysis: results of the Thrombolysis in Myocardial Infarction TIMI 14 trial. Circulation 1999; 99:2720–2732

3 Rentrop P, Blanke H, Karsch KR, et al. Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina. Circulation 1981; 63:307–317

4 Martin GV, Kennedy JW. Management of acute myocardial infarction. In: Julian D, Braunwald E, eds. Choice of thrombolytic agent. Philadelphia, PA:WB Saunders, 1994

5 Hartzler GO, Rutherford BD, McConahay DR, et al. Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. Am Heart J 1983; 106:965–973

6 Kennedy JW, Ritchie JL, Davis KB, et al. Western Washington Randomized Trial of Intracoronary Streptokinase in Acute Myocardial Infarction: a 12-month follow-up report. N Engl J Med 1985; 312:1073–1078

7 Stadius ML. Angiographic monitoring of reperfusion therapy for acute myocardial infarction: TIMI grade 3 perfusion is the goal. Circulation 1993; 87:2055–2057

8 Stone GW, Brodie BR, Griffin JJ, et al, for the Primary Angioplasty in Myocardial Infarction (PAMI) Stent Pilot Trial Investigators. Prospective, multicenter study of the safety and feasibility of primary stenting in acute myocardial infarction: in-hospital and 30-day results of the PAMI Stent Pilot Trial. J Am Coll Cardiol 1998; 31:23–30

9 Lange RA, Hills LD. Should thrombolysis or primary angioplasty be the treatment of choice for acute myocardial infarction? N Engl J Med 1996; 335:1311–1312

10 Grines CL. Primary angioplasty: the strategy of choice. N Engl J Med 1996; 335:1313–1317

11 De Lemos JA, Antman EM, Braunwald E, et al. Abciximab improves both epicardial and myocardial reperfusion in ST-elevation myocardial infarction: observations from the TIMI 14 trial. Circulation 2000; 101:239–243

12 De Lemos JA, Gibson CM, Braunwald E, et al. Abciximab and early adjunctive percutaneous coronary intervention are associated with improved ST-segment resolution after thrombolysis: observations from the TIMI 14 trial. Am Heart J 2001; 141:592–598