Prospective Evaluation of Clinical Outcomes After Acute ST-Elevation Myocardial Infarction in Patients Who Are Ineligible for Reperfusion Therapy: Preliminary Results From the TETAMI Registry and Randomized Trial

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Background—Treatment with lytics or primary percutaneous coronary interventions (PCI) reduces the mortality rate of patients with ST-elevation myocardial infarction (STEMI) presenting within 12 hours. Patients presenting >12 hours are generally considered to be ineligible for reperfusion therapy, and there are currently no specific treatment recommendations for this subgroup.

Methods—All patients with STEMI <24 hours were included in the Treatment with Enoxaparin and Tirofiban in Acute Myocardial Infarction (TETAMI) randomized trial or registry. Those patients who were ineligible for acute reperfusion, had no cardiogenic shock, and were not planned for revascularization within 48 hours were randomized to 1 of 4 antithrombotic regimens involving enoxaparin or unfractionated heparin (UFH), in combination with tirofiban or placebo for 2 to 8 days. A concurrent registry tracked STEMI patients coming in within <12 hours, and who underwent reperfusion. This registry also tracked the remaining STEMI patients who neither received reperfusion nor were enrolled in the TETAMI randomized trial. The demographics and clinical outcomes of all three groups (received reperfusion therapy, too late for reperfusion and enrolled in the randomized trial, neither received reperfusion therapy nor were enrolled in the randomized trial) were prospectively tracked.

Results and Conclusion—There were 2,737 patients who presented with STEMI or a new left branch bundle block (LBBB), of which 1,654 (60%) presented ≤12 hours. There were 1,196 (72%) of 1,654 patients who received reperfusion therapy. There were 458 (28%) of the 1,654 patients deemed “ineligible” for reperfusion, mostly because of a contraindication to lytics or for being “too old.” In contrast, 1,083 (40%) of 2,737 patients presented >12 hours. Apart from 34 of these patients who had a stuttering infarction and were referred for reperfusion, the remaining patients did not receive reperfusion therapy.

Registry patients who received reperfusion therapy, compared with TETAMI randomized patients (all of whom received antithrombotic therapy) and registry patients who did not receive reperfusion, were younger (61 years versus 63 years and 67 years), were more likely to be male (78% versus 73% and 63%), and had persistent ST-segment elevation as opposed to LBBB or Q waves. Registry patients who received reperfusion therapy had better clinical outcomes, even after adjusting for admission Killip class, compared with TETAMI randomized patients and registry patients who did not receive reperfusion therapy. TETAMI randomized patients had better outcomes than registry patients who did not receive reperfusion therapy.

The major obstacle to expanding the delivery of reperfusion therapy to patients with STEMI is the large fraction of patients who present too late for reperfusion therapy. Examination of prospectively gathered data on STEMI patients who are ineligible for reperfusion may help optimize their treatment. (Circulation. 2003;108[suppl III]:III-14-III-21.)

Key Words: acute myocardial infarction reperfusion

The demonstration of the benefit of early reperfusion with fibrinolytic agents was a major advance leading to a reduction in morbidity and mortality in patients with acute STEMI. The development of primary PCI for acute myocardial infarction (MI) has extended the benefit of early reperfusion to include some patients ineligible for thrombolysis. Despite the increasing use of primary PCI, the proportion of eligible patients undergoing early reperfu-
sion with either fibrinolytic agents or primary PCI remained constant, at about 70%, from 1994 through 1999,7 with roughly 30% of patients receiving neither reperfusion therapy.8 Furthermore, in Global Registry of Acute Coronary Events (GRACE), 21% of patients with STEMI or LBBB were ineligible for reperfusion because of contraindications or presentation >12 hours from symptom onset.8

The optimal therapy for the patient who does not receive reperfusion therapy remains to be defined. The most recent practice guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) recommend routine use of aspirin in all patients with acute coronary syndromes (ACS) without contraindications,1,2,9 but only suggest that it may be helpful to use subcutaneous UFH or low-molecular-weight heparin (LMWH) (eg, enoxaparin) in all patients not treated with thrombolytic therapy who do not have a contraindication to heparin.2 In practice, a combined antithrombotic strategy including both aspirin and heparin is widely used in the treatment of acute STEMI.

The TETAMI randomized trial and registry were established to get a better understanding of the characteristics and outcomes of STEMI patients who are deemed ineligible for standard reperfusion.10 The TETAMI randomized trial identified a nonsignificant trend favoring enoxaparin over UFH, with and without tirofiban, in STEMI patients who were not eligible for reperfusion therapy.11 The aim of the TETAMI registry was to concurrently enroll and track the patients admitted to the same institutions who met criteria for, but did indeed receive, reperfusion, as well as those who neither received reperfusion nor were enrolled in the randomized trial. The objective of the TETAMI registry was to prospectively characterize the patient population that does not receive reperfusion with regard to risk factors and outcomes, relative to the patients who came in on time and received reperfusion therapy. Here, we describe the baseline characteristics and 30-day outcomes of patients who did not receive reperfusion therapy enrolled in the TETAMI registry and randomized trial compared with their counterparts who did receive reperfusion therapy.

Methods

TETAMI was an international, multicenter trial conducted in 91 centers in 14 countries from July 1999 to July 2002. The randomized trial was a parallel-group, double-blind, double-dummy trial with a 2×2 factorial design.10,11 Centers were instructed to concurrently enroll into the registry all patients with acute STEMI or new LBBB, and registry based on the presumption that these patients would be candidates for the TETAMI randomized trial or, if he refused, the registry. All patients presenting within 6 hours of symptom onset and who were not offered reperfusion, unless they had a major contraindication. Major exclusion criteria for the TETAMI randomized trial and registry were cardiogenic shock, planned revascularization within 48 hours, contraindications to any of the study drugs, thrombocytopenia, current treatment with an anticoagulant or glycoprotein (GP) IIb/IIIa receptor antagonist, renal insufficiency, and lack of informed consent.

Patient Selection

All patients ≥18 years of age with suspected acute STEMI considered eligible or ineligible for thrombolysis or primary PCI according to the published ACC/AHA and European Society for Cardiology (ESC) guidelines, were eligible for enrollment (Figure I).1,2 Patients were required to have ischemic symptoms of ≥30 minutes duration within the previous 24 hours, accompanied by sustained ST-segment elevation of >0.2 mV in at least two precordial leads or of >0.1 mV in limb leads, or a new LBBB or new Q waves plus elevated levels of creatine kinase-MB, creatine kinase, or serum troponin. Killip class I, II, or III

Endpoints

The primary efficacy endpoint was the occurrence of the composite of all-cause death, myocardial infarction, and recurrent angina at 30 days. Secondary efficacy endpoints were the composite of death and reinfarction, the incidence of each component of the primary

Figure 1. Among the 458 patients who presented within 12 hours of symptom onset and who were not offered reperfusion, reasons for nonreperfusion included absence of residual ST-segment elevation and contraindications to fibrinolysis.
endpoint, and the incidence of invasive cardiac procedures. Recurrent infarction was determined on the basis of symptoms, ECG changes, and serum cardiac markers using predefined criteria. Recurrent angina was defined as either one episode of angina at rest of at least 20 minutes’ duration or two episodes of at least 10 minutes’ duration occurring within 24 hours, accompanied by new ST-segment changes, or angina associated with invasive cardiac procedures, or rehospitalization for unstable angina. All efficacy endpoints and major hemorrhagic events were adjudicated by an independent committee blinded to treatment allocation.

Statistical Methods
Statistical analyses were performed using the Statistical Analysis System (SAS) software package. The incidence of the composite triple endpoint at 30 days was compared among groups (registry patients who received reperfusion, randomized trial patients who did not receive reperfusion, and registry patients who did not receive reperfusion) using a chi-squared test. “Time-to-first-event” analyses were performed using the Kaplan-Meier method, and the log-rank test was used to compare groups. Odds ratios and 95% confidence intervals were also calculated for the main comparisons. All tests were performed at a 5% alpha level. In the TETAMI randomized trial, the primary efficacy analyses were performed on the intention-to-treat population, which included all patients randomized to treatment irrespective of whether they received study medication. The incidence of the composite triple endpoint at 30 days was compared between treatment groups (enoxaparin versus UFH; tirofiban versus placebo) using a chi-squared test after checking that there was no interaction between enoxaparin/UFH and tirofiban/placebo.

Results

Patients and Baseline Characteristics
A total of 2,737 patients were enrolled in the TETAMI registry and randomized trial (Figure 1, Table). Of the 2,737 patients, 1,654 (60%) presented ≤12 hours, and of the 1,654, 1,196 (72%) received reperfusion therapy. Lytics were used in 71% of patients, primary PCI was used in 25%, and a combination of a lytic and PCI was used in 4%. Of the 1,654 patients presenting ≤12 hours, 458 (28%) were deemed “ineligible” to receive reperfusion therapy, mostly because of a contraindication to lytics (eg, previous stroke), or for being “too old.” In contrast, of the 2,737 patients, 1,083 (40%) presented >12 hours. Except for 34 patients with a stuttering infarction who were referred for reperfusion, the remaining patients did not receive reperfusion therapy. Of the 1,682 total patients who did not receive reperfusion therapy, 1,224 were enrolled in the TETAMI randomized trial and received one of four antithrombotic regimens. The remaining 283 patients received neither reperfusion nor, for one reason or another, were entered into the randomized trial; 59% of these patients presented within 12 hours of symptom onset.

The majority of patients enrolled in TETAMI were not offered thrombolytic therapy because they presented >12 hours after onset of symptoms (Figure 2A, B). Fewer than 5% of patients were considered to be ineligible for thrombolytic therapy because of contraindication. Late arrival was also a major reason for not performing PCI, although for approximately two-thirds of patients in the TETAMI randomized trial, direct PCI was not considered because there was no catheterization laboratory available.

Selected baseline characteristics of patients in the three groups are shown in the Table. Patients who received reperfusion therapy, compared with TETAMI randomized patients (all of whom received antithrombotic therapy) and registry patients who did not receive reperfusion therapy, were younger (61 years versus 63 years and 67 years), more likely to be male (78% versus 73% and 63%), and had persistent ST-segment elevation as opposed to LBBB or Q waves. Almost all reperfused patients had ST-segment elevation at baseline, and <20% had new Q waves. New Q waves were found in 70% of patients enrolled in the TETAMI randomized trial, and a slightly greater proportion of this group did not exhibit ST-segment elevation. Of the patients who did not receive reperfusion therapy, those who were not enrolled in the randomized trial were older and more likely to be female. In this group, a larger number of patients were in Killip classes II or III, relative to what was observed in either the TETAMI randomized group or in patients who received reperfusion therapy.

Outcomes
The incidence of the primary endpoint in the TETAMI trial, the composite of death, myocardial reinfarction, or recurrent angina, was lowest in the registry patients who received reperfusion therapy and highest in registry patients who did not receive reperfusion therapy (Figure 3). A similar trend
was seen for the composite of death or myocardial reinfarction. Patients enrolled in the TETAMI randomized trial were more likely to undergo late revascularization procedures than registry patients. Registry patients who did not receive reperfusion therapy had the lowest rates of revascularization. The time to death for the three groups is depicted in Figure 4. Overall mortality at 30 days was very low in patients who received early reperfusion, and highest in patients who did not receive reperfusion therapy and who were not enrolled in the randomized trial. Within Killip class I and II, the registry patients who received reperfusion therapy had consistently lower mortality rates, compared with TETAMI randomized patients, and registry patients who did not receive reperfusion therapy. TETAMI randomized patients had better outcomes than registry patients who did not receive reperfusion therapy. Regardless of treatment group, Killip class III patients had significantly higher mortality rates.

**Discussion**

**Rationale**

Early treatment with lytics or primary PCI reduces the mortality rate of STEMI patients. However, a significant fraction of STEMI patients do not receive reperfusion therapy, for various reasons. French et al. found that only 56.3% of patients with a discharge diagnosis of acute MI, in New Zealand, presented within 12 hours of symptom onset and were eligible for reperfusion. Eighty percent of those that were eligible received reperfusion therapy. In the National Registry of Myocardial Infarction (NRMI) and GRACE registries roughly 60% to 70% of all STEMI patients received immediate reperfusion therapy. The results of the prospective TETAMI registry are consistent with these observations: 1,146 (45%) of TETAMI patients received early reperfusion therapy. TETAMI, in addition to testing more aggressive antithrombotic regimens in patients ineligible for reperfu-
tion,\textsuperscript{12} provided an opportunity to compare the baseline characteristics and outcomes of STEMI patients who did and did not receive early reperfusion.

**Patient Characteristics**

Patients in the TETAMI registry who received reperfusion were more likely to be male and tended to be younger than patients who did not receive reperfusion therapy. This is consistent with previous observations that female\textsuperscript{8,13–15} and elderly patients\textsuperscript{8,16–18} are less likely to receive reperfusion. Less frequent use of reperfusion therapies in female and elderly patients can be partly explained by a greater tendency for these patients to have atypical symptoms\textsuperscript{19} and present late.\textsuperscript{12} They also are more likely to present with coexisting conditions which might be viewed as relative contraindications.\textsuperscript{20} Data from STEMI patients in GRACE indicated that multiple factors were associated with lack of reperfusion, including age $>75$ years, female sex, and presentation without residual chest pain, although in this study, female sex was no longer an independent predictor of lack of reperfusion after multivariate logistic regression analysis.\textsuperscript{8} Patients $>75$ years were underrepresented in clinical trials of thrombolytic agents, and the benefit of pharmacological reperfusion in this population is less certain than for younger patients.\textsuperscript{21–23} The Fibrinolytic Therapy Trialists (FTT) performed a meta-analysis of the large randomized trials of these agents and concluded that thrombolysis was of net benefit in this subgroup of patients, although the magnitude of the benefit was diminished relative to that observed in younger patients and was not statistically significant.\textsuperscript{24} White relooked at the FTT analysis, including only elderly patients with ST-segment elevation within 12 hours of symptom onset, and demonstrated a highly significant benefit.\textsuperscript{25}

The use of PCI, particularly in patients who are ineligible for thrombolysis because of increased risk of stroke like the elderly, could extend the benefits of early reperfusion to greater numbers of patients.\textsuperscript{4–6} In a study of 500 consecutive, unselected patients with acute MI, Juliard et al. found that $<3\%$ of patients were ineligible for both thrombolysis and emergency percutaneous transluminal coronary angioplasty.\textsuperscript{26} Comparison of angioplasty versus thrombolytics in elderly, reperfusion-eligible patients has indicated that primary PCI may be beneficial.\textsuperscript{27,28} However, availability of catheterization facilities continues to be a limiting factor—in TETAMI, lack of PCI capability was a contributing reason for not offering reperfusion therapy in 65\% of patients.

**Late Presentation**

The majority of patients in the TETAMI randomized trial did not receive reperfusion because, in the opinion of the treating physician, they presented too late to be considered for either thrombolysis (84\%) or primary PCI (70\%). Less than 5\% of patients were considered ineligible for thrombolysis because of contraindications, suggesting that in TETAMI, the disproportionate representation of older, female patients among patients who did not receive reperfusion therapy was not primarily because of a higher rate of contraindications, but is more likely explained by an increased likelihood of delayed presentation.\textsuperscript{15} In the group that received neither reperfusion nor TETAMI treatment, 59\% presented within 12 hours of symptom onset, necessitating additional explanations for lack of reperfusion in many of these patients.

There has been conflicting evidence regarding the impact of delayed opening of the infarct-related artery. The basis for considering late reperfusion depends less on the construct of reducing infarct size, but rather on the possibility that late reperfusion may improve healing of the myocardium and thereby reduce adverse remodeling.\textsuperscript{29} The FTT overview found a nonsignificant trend toward mortality reduction in patients treated between 12 and 24 hours after symptom

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure4.png}
\caption{Time to death at 30 days by reperfusion status.}
\end{figure}
onset, although the estimated magnitude of the benefit, if any, was small. Specific clinical trials of late thrombolytic therapy with streptokinase or alteplase found no significant effect of these agents on inhospital or 35-day mortality, respectively, although there may have been inadequate power to definitely exclude a benefit in these trials. Late reperfusion using PCI may be able to salvage chronically ischemic, or hibernating, myocardium. Some studies of late angioplasty have reported positive outcomes. In contrast, Yousef et al. randomized 66 symptom-free patients with persistent occlusion to angioplasty or medical therapy approximately 1 month after MI in a rigorously controlled, prospective trial. They found that late angioplasty was associated with improved quality of life and increased exercise tolerance, although left ventricular remodeling was worse in the group receiving late intervention. The National Institutes of Health-sponsored Occluded Artery Trial (OAT), which is substantially larger than previous trials, is underway looking
at the same question. Current guidelines for primary PCI in acute MI patients do not recommend intervention >12 hours after symptom onset unless there is evidence of ongoing myocardial ischemia.1,2

Outcomes
Patients with acute MI who do not receive reperfusion are a heterogeneous group, including some of the highest-risk patients.36,37 We found that patients in the TETAMI registry who received early reperfusion had lower clinical event rates at 30 days, compared with patients who did not receive reperfusion therapy. In particular, 30-day mortality was only 4.4% in patients who received reperfusion therapy, compared with 12% in non-TETAMI patients who did not receive reperfusion therapy. Mortality in the TETAMI randomized study group was intermediate. The trend to better outcomes in registry patients who received reperfusion therapy persisted when outcomes were stratified by Killip class I or II. Patients in Killip class III tended to have worse outcomes, regardless of treatment group. It has previously been observed that the presence of congestive heart failure on admission is a predictor of poor outcome in patients with MI, yet ironically, patients with heart failure are less likely to receive reperfusion.36,37

The incidence of the triple endpoint in the combined TETAMI arms was 19%. This is considerably lower than the 25.5% incidence at 43 days observed in the Q-wave MI patients treated with enoxaparin in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) and Thrombolysis in Myocardial Infarction (TIMI) 11B trials.38

Lessons Learned and Outlook
TETAMI highlights the fact that a large fraction of patients with STEMI (40%) present too late for reperfusion therapy by current criteria. These late-presenting patients are often older and female with significant comorbidities. The use of thrombolytics in the elderly in actual practice may not be optimal. While efforts to motivate the public to seek help earlier remain warranted, the experience to date has been disappointing. Despite a massive 18-month education intervention program, the Rapid Early Action for Coronary Treatment (REACT) investigators were unable to shorten the time from onset of symptoms to hospital arrival in their community.39 Other educational campaigns to reduce the delay to presentation have not been very effective either.40 The overall picture points to the need for further studies to identify the optimal treatment of patients with STEMI who are ineligible for reperfusion, particularly those who present more than 12 hours after symptom onset.

Limitations
Some patients with STEMI may not have been enrolled in either the TETAMI registry or the randomized trial. Therefore, we cannot precisely estimate the percentage of all acute MI patients who received reperfusion based on our data.

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