Journal of Thrombosis and Thrombolysis 13(3), 147–153, 2002.

Feasibility and Timing of Prehospital Administration of Reteplase in Patients with Acute Myocardial Infarction

Donald G. Rosenberg MD, FACC,[1,2] Esther Levin MD,[1] Ana Lausell,[2] Allen Brown,[2] John Gardner,[2] Esther Perez,[2] Mark Veenendaal MD,[3] Yee S.C. Ong MD,[4] Mary Gunn MD[4]

[1]University of Miami, Miami, Florida, USA; [2]Miami-Dade Fire Rescue, Miami, Florida, USA; [3]Michigan State Thoracic Cardiovascular Institute Foundation, Lansing, Michigan, USA; [4]Cardiovascular Clinic at Muskogee, Muskogee, Oklahoma, USA

Abstract. ***Background:*** **In myocardial infarction patients undergoing thrombolysis, treatment delays negatively impact outcomes. This pilot study was conducted to determine the feasibility and timing of field administration of intravenous double bolus reteplase in patients with ST-elevation myocardial infarction.** ***Methods:*** **Sixty three patients with symptoms and EKG changes consistent with acute myocardial infarction of less than six hours duration received the first bolus of reteplase before arriving at the emergency department. A second bolus of reteplase was given in the emergency department. Subsequent resolution of ST-segment elevation was measured. Mean time from symptom onset to paramedic dispatch, and paramedic arrivals to first bolus of reteplase were measured. The mean time from the first bolus of reteplase to heparin bolus in an emergency department was also measured. All patients with evidence of ST-elevation and suspected acute myocardial infarction gave consent for the thrombolytic therapy. There were no refusals of therapy among those candidates eligible for thrombolysis.** ***Results:*** **The mean times from the first bolus of reteplase to heparin bolus in the emergency department was substantially longer than the in-field times. Resolution of ST-segment elevation was recorded in 52 of the 63 patients and the times of resolution ranged from five minutes after the first bolus dose to 190 minutes after the second bolus of reteplase. Resolution of ST-segment elevation and relief of pain occurred almost simultaneously.** ***Conclusions:*** **These results demonstrated that in-field administration of thrombolytic therapy is a viable option to reduce the delay from symptom onset to initiation of thrombolysis. They demonstrated that satisfactory resolution of ST-segment elevation can be recorded in the field. The reduction in mortality observed in this study is comparable to previously published studies on inpatients.**

Abbreviated Abstract. **This open-label pilot study was conducted to determine the feasibility and timing of field administration of intravenous double-bolus reteplase and to measure subsequent resolution of ST elevation in 63 patients with symptoms and ECG changes consistent with acute myocardial infarction for less than 6 hours. These results demonstrated that in-field administration of thrombolytic therapy is a viable option to reduce the delay from symptom onset to initiation of thrombolytic therapy.**

Key Words. **thrombolytic therapy, electrocardiography, emergency medical services, reteplase**

Introduction

The goal of thrombolytic therapy following acute myocardial infarction (AMI) is rapid, complete restoration of patency in the occluded artery, with the ultimate objective of preserving myocardial tissue and ventricular function [1–4]. It is well established that the initiation of thrombolytic therapy in the first 1 or 2 hours after the onset of AMI symptoms dramatically improves clinical outcomes and that the emphasis of thrombolytic therapy during AMI should be on treating patients earlier rather than later [5,6]. Prehospital administration has been investigated as a means of reducing delays and thus facilitating earlier initiation of lysis.

The objective of this pilot study was to determine the feasibility and timing of field administration of fibrinolytic therapy in patients with AMI. Reteplase, with its lack of antigenicity, longer half-life than alteplase, and double-bolus dosing regimen, was selected as an optimal agent for prehospital thrombolytic therapy administration in this trial. Reteplase, which does not require weight-adjusted dosing, has been shown to be equivalent to alteplase from a mortality standpoint, with a similar safety profile [7]. When compared with standard alteplase treatment, administration of double-bolus reteplase versus alteplase resulted in an earlier,

Address for correspondence: Donald G. Rosenberg, MD, FACC, Division of Cardiology (D-1), University of Miami School of Medicine, University of Miami, Suite 4011, 1475 Northwest 12th Avenue, Miami, Florida 33101, USA. Tel.: 305-243-7242; Fax: 305-243-7244.

significantly higher Thrombolysis In Myocardial Infarction (TIMI) 3 flow rate at 60 minutes of 51% versus 33% ($p = 0.009$) and at 90 minutes of 62.7% versus 49.3% ($p < 0.019$) without an increase in bleeding risk [8].

Methods

Inclusion/exclusion criteria

Informed, consenting patients over 18 years of age with diagnosed or suspected AMI were eligible to participate in the study. Diagnosis was confirmed by at least 20 minutes of chest pain characteristic of AMI, persistent ST-segment elevation $\geq$1 mm in at least two of three contiguous leads, regardless of AMI location, and no relief with nitroglycerin. Only patients who received thrombolytic therapy within 6 hours from onset of ischemic chest pain were included in the study. Excluded were patients with known contraindications to thrombolytic therapy, such as active internal bleeding; history of cerebrovascular accident; recent intracranial/intraspinal surgery or trauma; known intracranial neoplasm, arteriovenous malformation, or aneurysm; known bleeding diathesis; or severe, uncontrolled hypertension.

Study design

This was an open-label pilot study conducted in three centers in the United States. Two centers were major metropolitan teaching hospitals. The third was a smaller private cardiovascular care center. Initial patient care provided by paramedics conformed to the current Advanced Cardiac Life Support Recommendations for the Treatment and Evaluation of Suspected AMI Patients [9], using standard protocols and standing orders for treatment of patients who needed immediate stabilization of any life-threatening dysrhythmia.

Paramedics obtained a 12-lead ECG, brief history, and vital signs and evaluated the patient for life-threatening conditions (Fig. 1). This information, including an inclusion and exclusion criteria checklist

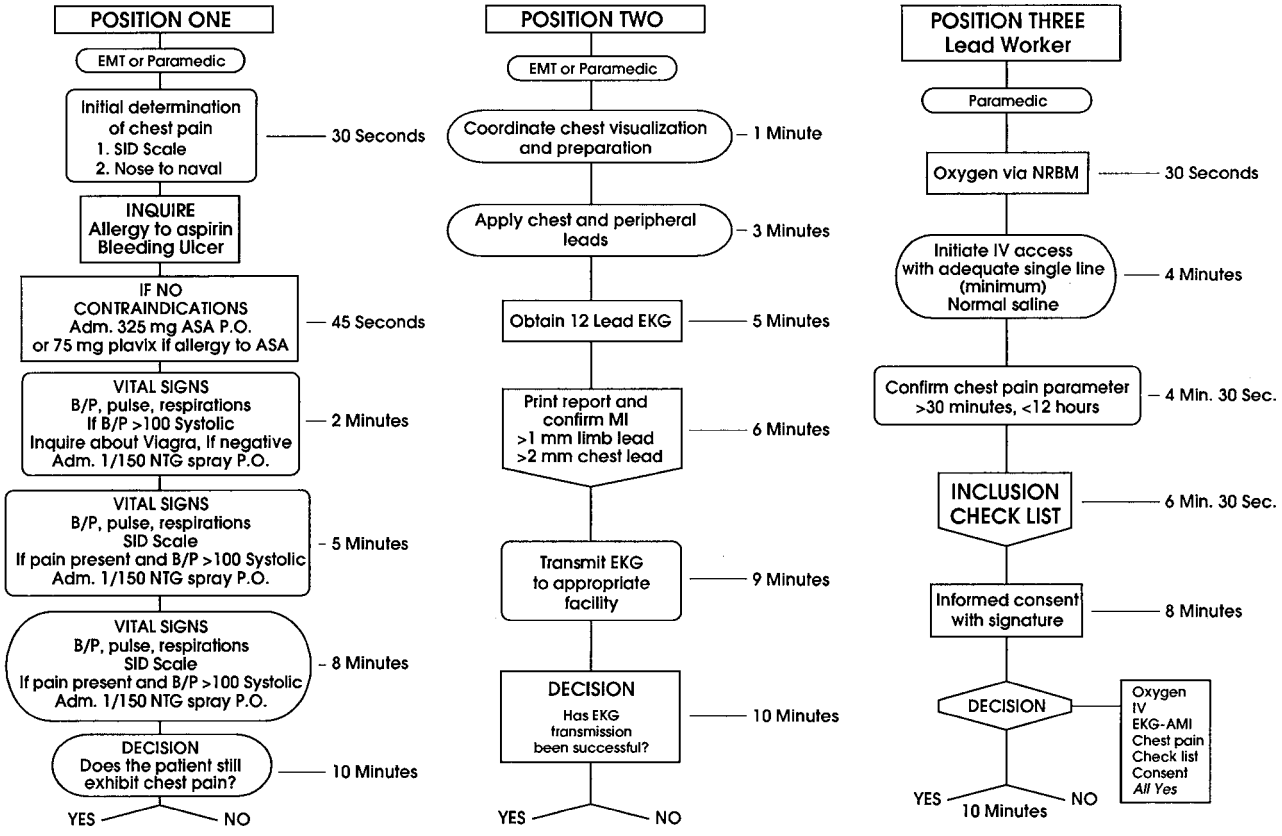

Fig. 1. *The functions of the three paramedics in each rescue vehicle helped eliminate prejudices and maintain the standard of care. Position One (A) determined chest pain, administered aspirin or clopidogrel, and took vital signs. If the patient was not using sildenafil, vital signs were taken again and nitroglycerin spray administered. Simultaneously, Position Two (B) applied the ECG 12-lead, confirmed ST elevation, and transmitted the ECG to the ED physician. Position Three (C), the leadworker, began oxygen, obtained IV access, and confirmed the duration of chest pain. The thrombolysis inclusion checklist was filled out and patient consent obtained. By this time, the decision from the ED physician was received.*

and the informed written consent of the patient, was then transmitted via 800-MHz radio to the emergency department (ED) physician. If the ED physician determined that the patient was a candidate for thrombolysis, treatment was instituted according to package insert instructions. If the patient declined participation, the protocol allowed for standard treatment with aspirin, nitroglycerin, oxygen, and intravenous pain medication. Paramedics gave eligible patients their first bolus dose of reteplase. ECGs were continuously monitored for reperfusion dysrhythmias, and patients were treated as necessary. Patients were transported to the closest appropriate facility, where the ED physician directed established treatment protocols. Another 12-lead ECG was obtained 5 minutes after the first bolus of reteplase and 30, 60, 90, and 180 minutes after the second bolus. If required, the ECG was obtained at the ED upon the patient's arrival. If the transport was taking longer than 30 minutes following the first bolus infusion and no complications (e.g., bleeding) had occurred, the protocol allowed the ED physician to order administration of the second reteplase bolus dose in the field; otherwise, this second bolus dose was administered in the ED.

The study was conducted in accordance with the United States Food and Drug Administration guidelines and in accordance with the sponsor's guidelines for ensuring data quality and monitoring. Investigators obtained institutional review board approval.

Study medication

Patients received two bolus doses (each 10 U [10 ml]) of reteplase administered intravenously over 2 minutes, separated by 30 minutes. Therapy with aspirin (250 to 350 mg on day 0) was strongly recommended prior to initiation of thrombolysis and was continued (75 to 350 mg/day on day 1 until hospital discharge and beyond) according to the investigator's routine practice. Intravenous heparin was administered as a 5000-U bolus as soon as possible after arrival at the hospital, followed by a continuous intravenous infusion of 1000 U/hour for patients $\geq$80 kg and 800 U/hour for patients $<$80 kg. Intravenous infusion of standard unfractionated heparin was continued for at least 24 hours and titrated to keep activated partial thromboplastin time (aPTT) in the target range (between 50 and 75 seconds for most standard aPTT reagents).

Efficacy parameters

The primary efficacy end point was the time sequence from onset of symptoms to field administration of reteplase. For each patient, the difference between the time of first reteplase bolus in the field and the time of heparin bolus in the ED was also calculated as a means of approximating the amount of time saved had lytic treatment been first initiated in the ED. The secondary efficacy variable was the time interval to ST-segment elevation resolution up to 3 hours after the start of thrombolysis.

ST-segment elevation resolution was evaluated based on criteria established by the TIMI 14 study group [10]. Standard 12-lead ECGs were performed prior to enrollment, upon arrival in the emergency department, and 90 minutes after the first bolus of reteplase. All available ECGs were sent to the TIMI ECG Core Laboratory (Boston, MA) for quantitative ST-segment analysis. The sum of ST deviation on the ECGs from baseline, hospital arrival, and 90 minutes was determined, and the percent ST resolution (STRES) from baseline to ED arrival and baseline to 90 minutes was calculated for all patients with both tracings available. ST resolution for each patient was categorized by two well-described classification schemes: (1) ^{3}50% STRES vs. $<$50% STRES; and (2) complete (^{3}70%), partial (30–70%), or none ($<$30%).

All study participants who received reteplase were evaluated. Descriptive statistics were used to summarize the primary and secondary end points.

Safety evaluations

Patients were followed for 30 days after study initiation for survival status and the reporting of serious adverse events. An adverse event was considered serious if it met one of the following criteria: fatal or acutely life-threatening, complications necessitating prolonged hospitalization, or events resulting in persistent or significant disability or incapacity. Adverse events were judged by the investigator to be either related or unrelated to study medications. Treatment-related adverse events were defined as those assessed as probably or possibly related to the study drug. Adverse events were reported by patients or observed by the investigator. All adverse events were reported regardless of causality.

Results

Of 63 patients who were enrolled in the trial and who received at least one dose of study medication, 39 (61.9%) were male and 24 (38.1%) were female and they ranged in age from 43.2 to 87.5 years. Sixty-two patients received a second bolus dose of reteplase. This second bolus was delayed by more than 35 minutes in one patient because the ED physician needed to confirm radiological data in order to rule out the possibility of a dissecting aneurysm of the aorta after the patient had arrived in the ED. Although eligible patients were given an option about whether they wanted to receive thrombolysis, none refused the field administration of thrombolytic therapy.

Primary efficacy parameters

The mean times from AMI symptom onset to paramedic dispatch, dispatch to paramedic arrival, and paramedic arrival to first bolus dose of reteplase were 123, 7.5, and 30 minutes, respectively. Total mean time from symptom onset to first bolus dose of reteplase was 160.5 minutes, and mean time from first reteplase bolus to heparin bolus in the ED was 64.8 minutes. Heparin therapy was administered by the ED physician's orders only, not by fire rescue.

Secondary efficacy parameters

Standard 12-lead ECGs were performed before thrombolytic therapy and again 5 minutes after each bolus infusion of reteplase and at 30, 60, 90, and 180 minutes after the second bolus dose. Overall resolution of ST-segment elevation (Fig. 2) was recorded in 52 patients (82.5%), at times ranging from 5 minutes after the first bolus dose to 190 minutes after the second. Efficacy end points are presented in Table 1.

Safety evaluations

Overall, 12.7% of patients (8 of 63) experienced one or more adverse events, with 6 patients (9.6%) reporting serious adverse events that resulted in death. Only one adverse event, a cerebral hemorrhage occurring 2 days after reteplase administration, was assessed as related to study medication. This event occurred in an 84-year-old male with a history of a cerebrovascular accident 20 years previously. An ED physician gave the order despite administration of a thrombolytic to this patient being a contraindication in this study. Other serious adverse events that resulted in death were cardiogenic shock (3 patients), respiratory distress (1 patient), and recurrent myocardial infarction (1 patient); nonserious adverse events were upper GI bleed (1 patient) and bilateral breast hematomas (1 patient). At the 30-day follow-up, 49 of the original 63 patients were alive, 6 had died (3 died in cardiogenic shock, which was a presenting symptom), and 8 were lost to follow-up.

Table 1. *Study end points of patients receiving at least one bolus dose of reteplase*

Time from symptom onset to paramedic dispatch (min) ($n = 63$)	
Mean ± SD	122.90 ± 157.88
Range	1–855
Time from dispatch to arrival (min) ($n = 63$)	
Mean ± SD	7.46 ± 4.73
Range	1–25
Time from paramedic arrival to first bolus of reteplase (min) ($n = 63$)	
Mean ± SD	30.48 ± 10.15
Range	9–63
Resolution of ST-segment elevation ($n = 52$, 82.5%)	
≤5 min after 1st bolus dose	2 (3.2%)
<30 min after 2nd bolus dose	9 (14.3%)
<60 min after 2nd bolus dose	19 (30.2%)
<90 min after 2nd bolus dose	31 (49.2%)
<180 min after 2nd bolus dose	40 (63.5%)
>180 min after 2nd bolus dose	10 (15.9%)

Discussion

Several factors can contribute to delays in treatment time from AMI symptom onset to initiation of thrombolytic therapy. The National Heart Attack Alert Program Coordinating Committee has identified the following three areas as sources of delay in initiating thrombolytic therapy: (1) patient/bystander, (2) prehospital, and (3) in-hospital [11]. Despite concerted efforts to educate the public, perhaps the most pervasive source of delay (and the most difficult area in which to effect positive change) is patient delay in seeking medical attention. Once the patient (or bystander) determines that medical attention is needed, however, the medical community can have a positive impact by deploying strategies for rapid mobilization and effective, early treatment.

This pilot study has demonstrated that prehospital administration of reteplase by paramedics is feasible and can effectively reduce time to treatment of AMI with fibrinolytic therapy.

Previous studies of delays in AMI treatment time have reported averages as long as 5.5 hours, with more than two thirds of patients presenting at the hospital up to 4 hours after symptom onset [12] and 25% delayed more than 5.2 hours [13]. Subgroups such as older patients, nonwhite patients, and women are at even higher risk of delay.

Gonzalez et al. [14] found that 210 AMI patients whose treatment was initiated in the hospital experienced a mean delay of 50 minutes from arrival in the ED to thrombolytic administration and a mean interval of 177 minutes from symptom onset to thrombolysis. In contrast, in this pilot study, the mean time from paramedic arrival to first reteplase bolus was 30 minutes, and the overall time from symptom onset to fibrinolysis was 160.5 minutes, a savings of 16.5 minutes. This timely treatment was effective in stopping or reversing AMI (based upon ST-segment resolution) in more than 80% of patients, all but one of whom experienced ST-segment resolution within 180 minutes.

In a series of 63 consecutive historical patients at the institutions where this pilot study was performed who did not receive the prehospital protocol, the mean time from paramedic arrival to first dose of thrombolytic agent was 56.2 ± 25.8 minutes, showing a savings of 26.2 minutes with prehospital administration.

Other studies have shown similar benefits for prehospital fibrinolytic therapy. Investigators for the Grampian Region Early Anistreplase Trial (GREAT)

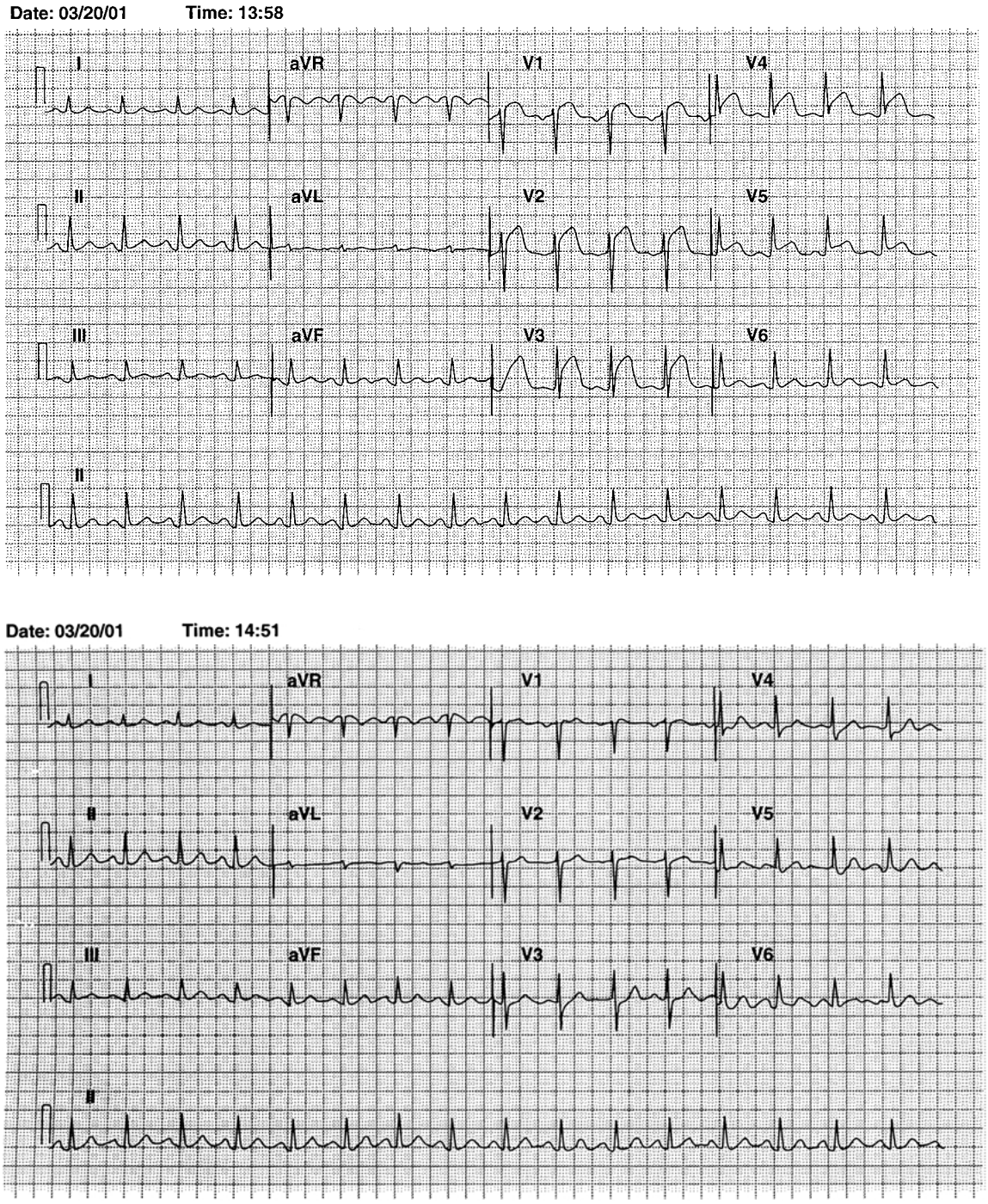

Fig. 2. *Representative ECGs showing ST elevation and resolution. ECG 1 (3/20/01, 13:58 hours) demonstrates an ST elevation V1–V5 showing epicardial injury current of the anterior wall; ECG 2 (3/20/01, 14:51 hours) shows ST resolution.*

reported that patients receiving anistreplase at home were treated about 130 minutes sooner than those who were treated in the hospital. Eighty-seven minutes of delay for the latter group occurred at the hospital. This time difference was associated with a significantly lower 1-year mortality rate (10.4% for home-treated versus 21.6% for hospital-treated, $p = 0.007$). Moreover, fewer Q-wave infarcts and better left ventricular function were seen in patients receiving prehospital treatment [15].

The European Myocardial Infarction Project Group study reported that the median time gained

with prehospital anistreplase administration by mobile emergency staff was 55 minutes [16]. Thirty-day cardiac mortality was significantly less frequent in the prehospital group (8.3%) than in the hospital group (9.8%, $p = 0.049$). Several meta-analyses of prehospital thrombolytic therapy studies have shown significant reductions in overall short-term mortality among patients who received prehospital thrombolytic treatment [5,16–20]. In the Myocardial Infarction Triage and Intervention (MITI) trial, patients randomized to prehospital thrombolytic therapy received treatment about 33 minutes faster than patients randomized to hospital therapy [5,21]. Previously reported MITI results showed that treatment of patients in the first 70 minutes of AMI symptom onset resulted in smaller infarct size, better systolic left ventricular function, and lower mortality than did later treatment.

Reteplase's half-life of 13 to 16 minutes, compared with native alteplase's half-life of 3 to 6 minutes [6], allows fast, convenient double-bolus intravenous dosing. Using reteplase in the field allows paramedics to give only one dose, with no need for weight-based calculations. This simple dosing regimen not only reduces door-to-needle time but also lowers the risk of medication errors. In a report by Hilleman et al. [22], only 1% of patients did not receive the full dose of reteplase—compared with 4% who did not receive the full dose of alteplase ($p = 0.03$). In GUSTO-I, 12% of patients had medication errors [23], resulting in significantly higher 30-day mortality rates (7.7% versus 5.5%, $p < 0.001$).

Conclusion

In this study, in-field administration of thrombolytic therapy was found to be a safe and feasible approach to improving time to thrombolysis, although the small size of the study limits our ability to draw conclusions about clinical outcomes. These results will be confirmed and expanded by the Early Retavase (ER)-TIMI 19 trial, a phase IV open-label trial in some 20 emergency medical systems in the United States and Canada, with an enrollment of 300 patients. Preliminary results from this study suggest that exceedingly long transport times or door-to-drug times may be improved significantly with the implementation of prehospital thrombolysis protocols [24].

Acknowledgment

This study was supported by Centocor, Inc.

References

1. Braunwald E. The open-artery theory is alive and well-again. *N Engl J Med* 1993;329:1650–1652.
2. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;1:397–402.
3. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673–682.
4. Zeymer U, Tebbe U, vonEssen R, Haarmann W, Neuhaus KL. Influence of time to treatment on early infarct-related artery patency after different thrombolytic regimens. ALKK-Study Group. *Am Heart J* 1999;137:34–38.
5. Weaver WD, Cerqueira M, Hallstrom AP, et al. Prehospital-initiated vs hospital-initiated thrombolytic therapy. The Myocardial Infarction Triage and Intervention Trial. *JAMA* 1993;270:1211–1216.
6. Smalling R. Molecular biology of plasminogen activators: what are the clinical implications of drug design? *Am J Cardiol* 1996;78(Suppl 12A):2–7.
7. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 1997;337:1118–1123.
8. Smalling R, Bode C, Kalbfleish J, et al. More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. RAPID Investigators. *Circulation* 1995;91:2725–2732.
9. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Part I. Introduction. *JAMA* 1992;268:2171–2183.
10. de Lemos JA, Antman EM, Guigliano RP, et al. ST-Segment resolution and infarct-related artery patency and flow after thrombolytic therapy. *Amer J Cardiol* 2000;85:299–304.
11. National Heart Attack Alert Program Coordinating Committee, 60 Minutes to Treatment Working Group. Emergency department: rapid identification and treatment of patients with acute myocardial infarction. *Ann Emerg Med* 1994;23:311–329.
12. Goldberg RJ, Gurwitz JH, Gore JM. Duration of, and temporal trends (1994–1997) in, prehospital delay in patients with acute myocardial infarction: the second National Registry of Myocardial Infarction. *Arch Intern Med* 1999;159:2141–2147.
13. Goff DC Jr, Feldman HA, McGovern PG, et al. Prehospital delay in patients hospitalized with heart attack symptoms in the United States: the REACT trial. Rapid Early Action for Coronary Treatment (REACT) Study Group. *Am Heart J* 1999;138:1046–1057.
14. Gonzalez ER, Jones LA, Ornato JP, Bleecker GC, Strauss MJ. Hospital delays and problems with thrombolytic administration in patients receiving thrombolytic therapy: a multicenter prospective assessment. Virginia Thrombolytic Study Group. *Ann Emerg Med* 1992;21:1215–1221.
15. Rawles J. Halving of mortality at 1 year by domiciliary thrombolysis in the Grampian Region Early Anistreplase Trial (GREAT). *J Am Coll Cardiol* 1994;23:1–5.
16. The European Myocardial Infarction Project Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. *N Engl J Med* 1993;329:383–389.
17. Castaigne AD, Herve C, Duval-Moulin AM, et al. Prehospital use of APSAC: results of a placebo-controlled study. *Am J Cardiol* 1989;64:30A–33A.

18. Schofer J, Buttner J, Geng G, et al. Prehospital thrombolysis in acute myocardial infarction. *Am J Cardiol* 1990;66:1429–1433.
19. GREAT Group. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampian region early anistreplase trial. *BMJ* 1992;305:548–553.
20. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. *JAMA* 2000;283:2686–2692.
21. Brouwer MA, Martin JS, Maynard C, et al. Influence of early prehospital thrombolysis on mortality and event-free survival (the Myocardial Infarction Triage and Intervention [MITI] Randomized Trial). MITI Project Investigators. *Am J Cardiol* 1996;78:497–502.
22. Hilleman DE, Shara M. Advances in the use of thrombolytic therapy in acute myocardial infarction. Pharmacist 1998:HSA41–HSA54.
23. Vorchheimer DA, Baruch L, Thompson TD, Kukin ML. North American vs Non-North American streptokinase use in GUSTO-I: impact of protocol deviation on mortality benefit of TPA. *Circulation* 1997;96(Suppl I):I-535.
24. Morrow DA, Antman EM, Sayah A, et al. Should your hospital consider a prehospital thrombolysis program? Observations from ER-TIMI 19. *Circulation* 2001;104(17): II-726.