Relationship Between the Door-to-TIMI-3 Flow Time and the Infarct Size in Patients Suffering From Acute Myocardial Infarction

— Analysis Based on the Fibrinolysis and Subsequent Transluminal (FAST-3) Trial —

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Background The purpose of this study was to use the findings of a fibrinolysis and subsequent transluminal trial (FAST-3) to evaluate the association between the target time for obtaining a thrombolysis in myocardial infarction (TIMI)-3 flow after arrival at the emergency room with acute myocardial infarction (AMI) and the degree of myocardial salvage.

Methods and Results The FAST-3 trial was administered to 100 patients suffering from AMI. Ranges in the door-to-TIMI-3 flow time (D-T3-time: TIMI-3 flow after arrival at the emergency room) according to quartile were as follows: 30–54 min (quartile 1), 55–77 min (quartile 2), 78–120 min (quartile 3) and 121–330 min (quartile 4). Peak creatine kinase (CK), peak CK-MB, and peak troponin-T values increased in a stepwise fashion across the increasing quartiles of D-T3-time. The left ventricular enddiastolic volume index at 30 days after the start of treatment showed low values for quartile 1. In multiple logistic regression analyses for independent predictors of myocardial damage, the adjusted odds ratios for myocardial damage (peak CK >3,000 U/L) in quartiles 3 and 4 of the D-T3-time were 4.0 (95% CI: 1.0–16.1) and 7.0 (95% confidence interval (CI): 1.4–36.0), respectively.

Conclusions These findings suggest that physicians should monitor the D-T3-time for at least 55 min. (*Circ J* 2004; 68: 280–285)

Key Words: Acute myocardial infarction; Thrombolysis; TIMI-3 flow time

The most significant advance in the treatment of cardiovascular disease in the past decade has been reperfusion therapy for acute myocardial infarction (AMI) and the reperfusion era has now come of age. The major determinants of myocardial salvage and long-term prognosis are a short time to reperfusion, early and sustained patency of the infarct-related artery with thrombolysis in myocardial infarction (TIMI) flow grade 3, and the presence of normal microvascular perfusion.^{1–3} A protocol for fibrinolysis and subsequent transluminal (FAST) therapy was prepared to establish a strategy for reperfusion therapy that complies with the 1996 ACC/AHA guidelines for the management of patients with AMI.⁴ The goal of FAST therapy is to achieve a TIMI-3 flow in the infarct-related-artery (IRA) as soon as possible after arriving at the emergency room. The FAST-1 trial⁵ which used either tissue-type plasminogen activator (t-PA) agents or mutant t-PA, and the FAST-2 trial⁶ proved that the early restoration of TIMI-3 flow by FAST therapy decreased the degree

of myocardial damage with a low risk of complications. Although the target time for reperfusion therapy after arrival at the emergency room has been shown to provide prognostic information for AMI patients with ST-segment elevation,⁷ the target time for achieving TIMI-3 flow after arrival at the emergency room is unknown. Therefore the purpose of this study was use the findings of a FAST-3 trial to evaluate the association between the target time for obtaining TIMI-3 flow after arrival at the emergency room and the degree of myocardial salvage.

Methods

Study Subjects

The FAST-3 trial was a prospective study conducted in the departments of Emergency and Critical Care Medicine and Cardiology at Surugadai Nihon University Hospital. The study enrolled patients who presented after 30 min of continuous symptoms but within 12 h of the onset of AMI symptoms, and who had ST-segment elevation of at least 0.1 mV in 2 or more limb leads, or a ST-segment elevation of at least 0.2 mV in the precordial leads based on 12-lead electrocardiography (ECG) recordings. Patients were excluded from the FAST-3 trial according to the following criteria: age 75 years or older, a history of stroke or central nervous system damage, bypass surgery, active bleeding or bleeding diathesis, recent trauma or major surgery, or a systolic blood pressure greater than 180 mmHg or diastolic

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Fig 1. The FAST-3 protocol. On arrival at the emergency room, patients with ischemic-type chest discomfort are evaluated immediately by electrocardiography. If the patient is considered eligible for the FAST-3 trial, single-bolus intravenous fibrinolysis using monteplase or pamiteplase is immediately initiated, followed by emergency coronary angiography. If TIMI-3 flow is observed in the infarct-related artery, angiography is discontinued and urokinase is administered in the coronary care unit for 12h. If TIMI-0, -1 or -2 flow is observed in the infarct-related artery, then rescue percutaneous coronary intervention (PCI) is immediately performed.

blood pressure greater than 110mmHg on arrival at the emergency room. In addition, the exclusion criteria for this study included: patients who lapsed into cardiogenic shock on arrival at the emergency room, whose ECG on arrival at the emergency room demonstrated a bundle branch block (BBB), whose creatine kinase concentration before the administration of fibrinolytic agents increased more than the normal upper limit, patients whose IRA at the time of final angiography revealed TIMI-0, -1 or -2 flow, or whose IRA reoccluded within 30 days from disease onset. In addition, any patients who refused to give their written informed consent to participate in the study were also excluded.

Study Methods

The FAST-3 protocol is shown in Fig 1. Patients who presented in the emergency room with ischemic-type chest discomfort were evaluated using a 12-lead ECG. Intravenous coronary fibrinolysis with aspirin (100–200mg po) was initiated immediately if the patient was considered eligible to undergo FAST-3 therapy. Patients were then assigned to receive a single bolus injection, at the optimal dose for Japanese, of either monteplase (27.5 kIU/kg) or pamiteplase (6.5 kIU/kg). Emergency coronary angiography was performed after fibrinolysis. If TIMI-3 flow was achieved then urokinase (500 U·kg⁻¹·h⁻¹) was administered for 12h. If TIMI-0, -1 or -2 flow was observed in the IRA, then an adjuvant coronary intervention procedure was immediately performed. The adjuvant intervention was selected according to whether or not there was clear thrombosis (ie, contrast medium flowed into the thrombus). If it was evident, then intracoronary fibrinolysis using prourokinase at doses of up to 3,000 units was selected; if not, then percutaneous transluminal coronary angioplasty (PTCA) was selected. When a refractory abrupt closure occurred during such an intervention, a bail-out stent or a SUNK rescue catheter was used. Heparin (60 U/kg) was administered as a single bolus injection before the initial angiography. The activated coagulation times were then measured at regular intervals (every 2–8h) and heparin was administered by continuous intravenous infusion for 2 days with a target activated coagulation time of 150–200s. Coronary angiography was evaluated by the cineangiography research group of the Nihon University School of Medicine.

Study Endpoints

The primary endpoint of this study was the degree of

myocardial damage based on the peak creatine kinase (CK), peak CK-MB and peak cardiac troponin-T concentrations. CK, CK-MB and troponin-T were measured in blood samples obtained every 3–12h after arrival at the emergency room for at least 4 days. The CK, and CK-MB concentrations were measured using an enzyme immunoassay method. The secondary endpoints assessed were the cardiac function, ie, ejection fraction (EF) and left ventricular enddiastolic volume index (LVEDVI) at 30 days after administration, mortality during the 30-day follow up, and any complications reported during the 30-day follow up.

Statistical Analysis

The patients were divided into quartiles of the time interval from arrival at the emergency room until they achieved TIMI-3 flow (Door-to-TIMI-3 time: D-T3-time). The mean values and proportions of the baseline variable were compared among the quartiles by one-way factorial analysis for continuous variables and the χ^2 distribution or the Kruskal-Wallis test for categorical variables. A one-way factorial analysis and post hoc tests was used to evaluate the association between the primary endpoint and the quartiles of the D-T3-time. The χ^2 distribution test was used to evaluate the association between the secondary endpoints and the quartiles of the D-T3-time. Finally, a multiple logistic-regression model, which we adjusted for other independent predictors of both the prognosis and myocardial damage, including age, gender, systolic blood pressure, and the heart rate on arrival at the emergency room, and the time interval from onset of AMI until achieving TIMI-3 flow, was used to evaluate the association between the primary endpoint of the peak CK and the quartiles of the D-T3-time.

Results

Patient Characteristics

From October 1999 to July 2002, 194 AMI patients met the inclusion criteria for the FAST-3 trial. A total of 94 patients (48.5%) were excluded from the study and as a result 100 patients were enrolled. The D-T3-time ranged from 30 to 330min, with a mean ($\pm$ SD) of 93 $\pm$ 56min, a median of 77 min, and 25th and 75th percentile values of 54 and 120 min, respectively. The ranges according to the quartile of D-T3-time were follows: 30–54 min (quartile 1), 55–77 min (quartile 2), 78–120 min (quartile 3), 121–

Table 1 Baseline Characteristics According to the Quartile of Door-to-TIMI-3 Flow Time

	Quartile 1 (n=24)	Quartile 2 (n=26)	Quartile 3 (n=25)	Quartile 4 (n=25)	p value
Age (years)	59.4±9.8	58.7±10.3	55.4±9.8	57.3±8.9	0.39
Male sex (%)	87.1	93.5	90.6	83.3	0.65
Time from onset to emergency room (min)	145.5±118.0	132.4±99.0	177.3±165.9	149.8±150.6	0.61
Killip class 1 (%)	67.7	61.3	68.7	62.5	0.91
Preinfarction angina (%)	58.1	51.6	65.6	70.8	0.47
Infarct related artery (%)					
LAD/RCA/CX	48.4/41.9/9.7	54.8/38.7/6.5	62.5/31.3/6.2	58.3/20.9/20.8	0.39
Multivessel disease (%)	54.8	58.1	37.5	37.5	0.23
Risk factors (%)					
Hypertension	61.2	51.6	56.3	41.7	0.52
Diabetes	16.1	32.3	50.0	41.7	0.03
Smoker	71.0	67.7	78.1	87.5	0.34
Hyperlipidemia	74.1	51.6	75.0	75.0	0.12
Fibrinolytic agents (%)					
Monteplase/pamiteplase	54.5/45.5	48.3/51.7	56.3/43.7	41.0/59.0	0.64
Rescue PCI (%)	16.1	19.4	65.6	85.3	<0.0001

Values are expressed as the mean±SD. LAD, left anterior descending; RCA, right coronary artery; CX, circumflex.

Fig 2. Association between the quartile of the door-to-TIMI-3 time and the myocardial damage (peak CK, peak CK-MB and peak troponin-T). Values are expressed as the mean±SD.

Table 2 Secondary Endpoints

	Quartile 1 (n=24)	Quartile 2 (n=26)	Quartile 3 (n=25)	Quartile 4 (n=25)	p value
30-day mortality (%)	0	3.3	0	8.3	0.18
Intracerebral bleeding (%)	0	0	0	0	—
Non-intracerebral bleeding (%)	6.4	3.2	6.2	4.2	0.92
Blood transfusion (%)	0	0	0	0	—

330 min (quartile 4). Table 1 shows the baseline characteristics according to the quartiles of the D-T3-time. There were no significant differences among the quartiles in terms of age, sex, time interval from the onset of AMI to arrival at the emergency room, Killip classification, the frequency of pre-infarction angina, the site of the IRA, multivessel disease, coronary risk factors, and fibrinolytic agents.

Study Outcomes

The primary endpoints of the peak CK, peak CK-MB and peak troponin-T concentrations increased in a stepwise fashion across the increasing quartiles of the D-T3-time (Fig 2). Although the 30-day mortality rate and the rate of a

bleeding complications at the 2nd endpoint did not show any significant differences between the quartiles of the D-T3-time (Table 2), LVEDVI at 30 days after administration showed a significantly low value for quartile 1 (Fig 3).

In the multiple logistic regression analyses for independent predictors of the myocardial damage, including age, sex, the systolic blood pressure and the heart rate on arrival at the emergency room, and time interval from onset of the AMI until achieving a TIMI-3 flow, the increasing quartiles of the D-T3-time remained significantly associated with an increased risk of myocardial damage. The adjusted odds ratios for myocardial damage (peak CK >3,000 mIU) in the third and fourth quartiles of the D-T3-time were 4.0 (95% confidence interval (CI), 1.0–16.1) and 7.0 (95% CI, 1.4–

Fig 3. Association between the quartile of the door-to-TIMI-3 time and the cardiac function (ejection function, LVEDVI) at 30 days. The values are expressed as the mean ± SD.

Fig 4. Multiple logistic regression analyses for independent predictors of myocardial damage (peak CK >3,000 mIU).

36.0), respectively (Fig 4).

Discussion

Time to Treatment With Reperfusion Therapy

The importance of rapid reperfusion has been established in experimental models and clinical studies.⁸ Several studies of fibrinolytic therapy have shown that mortality is higher with an increasing time interval from the onset of symptoms until treatment,⁹⁻¹¹ and the relative low mortality rate for both t-PA and streptokinase is believed to be related to the more rapid achievement of early patency in the IRA (ie, at 60 min and 90 min, respectively).¹² Angiographic studies of fibrinolytic therapy have supported the link between a 90-min (but not 180-min) time to IRA patency and improved survival.¹³ A study of more than 27,000 patients treated with primary PTCA has shown that mortality did not increase significantly with an increasing delay from the onset of symptoms until the first balloon inflation, but the mortality significantly increased with door-to-bal-

loon times of more than 2 h.⁷ The difference in the outcome between fibrinolytic therapy and primary PTCA with an increasing time from symptom onset may be related to the high rates of TIMI-3 flow achieved by primary PTCA. In 1996, the second edition of the ACC/AHA guidelines for the management of patients with AMI proposed an emergency care system with initial recognition and management in the emergency department and subsequent administration of reperfusion therapy.⁴ The emergency treatment team and coronary intervention team of the present institution cooperated with each other in establishing a protocol for the FAST therapy when the first trial was initiated in 1997. In the FAST-1⁵ and -2⁶ trials, the FAST therapy was effective for ischemic myocardium in patients who underwent fibrinolysis alone after presenting with TIMI-3 flow at initial angiography, but had no adverse effects on patients treated with adjuvant intervention who had presented with a TIMI-0, -1 or -2 flow at initial angiography. The PACT trial, which used the same procedure as FAST, has shown that early TIMI-3 flow produced by fibrinolysis alone was

effective in preserving left ventricular function!¹⁴ The mean time differences in the achievement of TIMI-3 flow with and without adjuvant intervention was similar in both trials (42 min for PACT; 45 min for FAST) However, few data are available regarding the target time for achieving a TIMI-3 flow after arrival at the emergency room.

Time to Achieving TIMI-3 Flow

Since 1999, we have conducted a FAST-3 trial using mutant t-PA, comparing alteplase with tenecteplase. The TIMI-3 flow rate at initial angiography and at final angiography after adjuvant intervention were similar in both groups of mutant t-PA and no significant differences were observed in either the degree of myocardial damage, the 30-day mortality or the incidence of complications. We therefore evaluated the association between the target time for achieving a TIMI-3 flow after arrival at the emergency room (D-T3-time) and the degree of myocardial salvage. We selected patients who did not have serious cardiogenic shock on arrival at the emergency room, BBB on the first ECG finding, spontaneous recanalization before the administration of fibrinolytic agents, or a reocclusion of the IRA during the first 30 days after presentation, because it was necessary to limit the eligibility of the subjects in this study in order to clarify the D-T3-time. We demonstrated that the D-T3-time provides valuable information on myocardial salvage in patients with ST-segment elevation AMI. A delay in the D-T3-time was predictive of an increased risk of myocardial damage, and the optimal cut-off point was 55 min. A D-T3-time less than 55 min was found to be a strongly independent factor for myocardial salvage in the multiple logistic-regression analysis.

The characteristics of the thrombi induced in the process of AMI development probably affects a patient's susceptibility to thrombolytic drugs and determines the extent of infarction. An association has been shown between patients with a history of smoking and the achieving of TIMI-3 flow with thrombolytic drugs.^{16,17} However, in the present study, there was no significant difference in D-T3-time among patients with or without a history of smoking and because that factor could not be an independent predictor in the multivariate logistic regression analysis, the present investigation did not prove the association with smoking.

We think that the patient group may have included those in whom spontaneous recanalization occurred. However, because the CK values on admission were within the criterion, 95% or more of the patients are empirically considered to have had thromboembolism. Pre-infarction angina, which has a pre-conditioning effect, could not be an independent predictor of infarction extent in the multivariate logistic regression analysis.

Interestingly, the time from the onset of the disease to TIMI-3 cannot be an independent predictor (Fig 4). Therefore, we compared the 4 groups from the time of the onset of the disease to TIMI-3 and found that the time caused a significant difference in peak CK-MB, but not in chronic EF and LVEDVI.

Therefore, the relationship between increased myocardial damage and a delay in the D-T3-time of more than 55 min suggests that physicians and health care systems should work to reduce the D-T3-time.

Study Limitations

This study was an observational study and did not randomize patients into rapid versus slow D-T3-times. How-

ever, the Fast-1⁵ and -2⁵ and PACT trials¹⁴ have reported that early TIMI-3 flow at initial angiography in patients treated by fibrinolysis alone resulted in a reduction in myocardial damage and preserved ventricular function, in comparison with patients treated by fibrinolysis plus intervention.

The results of the present study do not apply to patients who are older than 75 years, who have contraindications for fibrinolytic agents or who have lapsed into serious cardiogenic shock or cardiac arrest. However, the 80% of the patients who arrived at the emergency room with ST-segment elevation and a time before therapy of 12 h or less from the onset of AMI, and who did not lapse into cardiac arrest prior to hospital arrival were considered to be eligible for FAST therapy.

In a recent randomized study of primary PTCA versus prehospital fibrinolysis in AMI, primary PTCA was no better than prehospital fibrinolysis with an accelerated t-PA followed by transfer for possible emergency PTCA in patients presenting within 6 h of AMI, and the frequency of cardiac shock between randomization and hospital admission in patients treated with primary PTCA was significantly higher than for treatment by prehospital fibrinolysis.¹⁹ These findings suggest that prehospital fibrinolysis is able to reduce the number of patients who develop cardiac shock. It is therefore imperative to establish an emergency care system by which a single bolus of mutant t-PA can be administered to patients eligible for FAST therapy, not only in the emergency room, but also at all primary facilities. Adjuvant intervention can be added at the coronary care unit if needed. Reperfusion-induced arrhythmia is a well-known phenomenon;²⁰ but clinical research has shown it cannot be used as an independent prognostic factor in patients undergoing prehospital fibrinolysis.⁷ Moreover, in our previous study²¹⁻²³ the emergency angiograms of the acute coronary syndrome related artery revealed TIMI-0 or -1 flow in 84% of all patients who lapsed into ventricular fibrillation outside the hospital. We also reported that most cases of out-of-hospital ventricular fibrillation complicating the AMI were induced by ischemic myocardium caused by an occluded IRA.

Conclusions

A D-T3-time of longer than 55 min was found to be an important factor related to myocardial damage, which suggests that physicians should aim to reduce it to less than 55 min whenever possible.

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